Section 1. Introduction

1.1 Overview of Section 1

This section contains specifics of study conduct and describes sources of procedural information for the HPTN 084 protocol version 4.0 and version 5.0 (the Open Label Extension [OLE] components of the study). Information in this section is intended for study site staff and outlines responsibilities of the site Investigators.

1.2 Source of Procedural Information

All study procedures must be conducted in accordance with the study protocol currently approved for implementation by the site’s local Institutional Review Board (IRB)/Ethic Committee (EC), etc., as is appropriate (either version 4.0 or version 5.0 of the protocol), and this study-specific procedures (SSP) manual. In the event that this manual is inconsistent with the protocol, follow the protocol. Please alert the HPTN Leadership and Operations Center (LOC) of any inconsistencies.

In instances where there is an urgent need for a change to the SSP manual, and when a full revision of the SSP is not imminent, the LOC may distribute an email containing a “Notification of Interim Change” to the current version of the SSP manual. These interim changes will be considered an official part of the SSP manual and should be considered official by any monitoring agents.

Study site staff members should use the following email alias when they have study-related questions: 084mgmt@hptn.org. Staff members of the HPTN LOC, HPTN Statistical and Data Management Center (SDMC), and HPTN Laboratory Center (LC) will receive the email. Emails with questions will be responded to by the most appropriate HPTN representative.
### Table 1-1: HPTN Staff and Contact Information

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPTN LOC Project Managers</td>
<td>Jennifer Farrior</td>
<td>Tel: +1 919-321-3517, <a href="mailto:jfarrior@fhi360.org">jfarrior@fhi360.org</a></td>
</tr>
<tr>
<td></td>
<td>Scott Mitchell Rose</td>
<td>Tel: +1 919 768-2067 (Mobile), <a href="mailto:srose@fhi360.org">srose@fhi360.org</a></td>
</tr>
<tr>
<td>HPTN LOC Clinical Trials Assistant</td>
<td>Jill Stanton</td>
<td>Tel: +1 919-321-3413, <a href="mailto:jistanton@fhi360.org">jistanton@fhi360.org</a></td>
</tr>
<tr>
<td>HPTN LOC Community Program Managers</td>
<td>Rhonda White</td>
<td>Tel: +1 919-321-3598, <a href="mailto:RWhite@fhi360.org">RWhite@fhi360.org</a></td>
</tr>
<tr>
<td>HPTN SDMC Clinical Data Manager</td>
<td>Stephanie Orme</td>
<td>Tel: +1 206-667-7109, Email: <a href="mailto:sbeigelo@scharp.org">sbeigelo@scharp.org</a></td>
</tr>
<tr>
<td>HPTN LC Representatives</td>
<td>Estelle Piwowar-Manning</td>
<td>Tel: +1 410-614-6736, Email: <a href="mailto:epiowa@jhmi.edu">epiowa@jhmi.edu</a></td>
</tr>
<tr>
<td></td>
<td>Yaw Agyei</td>
<td>Tel: +1 410-614-6736, Tel: 27-813766180, Email: <a href="mailto:yagyei1@jhmi.edu">yagyei1@jhmi.edu</a></td>
</tr>
<tr>
<td>Laboratory Data Management System (LDMS)</td>
<td></td>
<td>Tel: +1 716-834-0900, Ext. 7311, Email: <a href="mailto:ldmshelp@fstrf.org">ldmshelp@fstrf.org</a></td>
</tr>
<tr>
<td>DAIDS Protocol Pharmacist</td>
<td>Katie Shin</td>
<td>Tel: +1 240-627-3047, Email: <a href="mailto:Kashi@niaid.nih.gov">Kashi@niaid.nih.gov</a></td>
</tr>
</tbody>
</table>

Contact information for all HPTN 084 team members is found in the electronic HPTN directory at www.hptn.org.

### 1.3 Sites Participating in HPTN 084

Clinical Research Sites (CRSs) that are participating in HPTN 084 OLE are listed in Table 1-2.
<table>
<thead>
<tr>
<th>CRS ID</th>
<th>CRS Name</th>
<th>City</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Baylor Uganda CRS</td>
<td>Kampala</td>
<td>Uganda</td>
</tr>
<tr>
<td>2</td>
<td>Blantyre CRS</td>
<td>Blantyre</td>
<td>Malawi</td>
</tr>
<tr>
<td>3</td>
<td>Botha’s Hill CRS</td>
<td>Botha’s Hill</td>
<td>South Africa</td>
</tr>
<tr>
<td>4</td>
<td>Desmond Tutu TB Centre - Stellenbosch University CRS</td>
<td>Cape Town</td>
<td>South Africa</td>
</tr>
<tr>
<td>5</td>
<td>Emavundleni CRS</td>
<td>Cape Town</td>
<td>South Africa</td>
</tr>
<tr>
<td>6</td>
<td>Gaborone CRS</td>
<td>Gaborone</td>
<td>Botswana</td>
</tr>
<tr>
<td>7</td>
<td>Isipingo CRS</td>
<td>Durban</td>
<td>South Africa</td>
</tr>
<tr>
<td>8</td>
<td>Kisumu CRS</td>
<td>Kisumu</td>
<td>Kenya</td>
</tr>
<tr>
<td>9</td>
<td>Malawi CRS</td>
<td>Lilongwe</td>
<td>Malawi</td>
</tr>
<tr>
<td>10</td>
<td>MU-JHU Research Collaboration CRS</td>
<td>Kampala</td>
<td>Uganda</td>
</tr>
<tr>
<td>11</td>
<td>Milton Park CRS</td>
<td>Harare</td>
<td>Zimbabwe</td>
</tr>
<tr>
<td>12</td>
<td>Seke South CRS</td>
<td>Chitungwiza</td>
<td>Zimbabwe</td>
</tr>
<tr>
<td>13</td>
<td>Soweto HPTN CRS</td>
<td>Soweto</td>
<td>South Africa</td>
</tr>
<tr>
<td>14</td>
<td>Spilhaus CRS</td>
<td>Harare</td>
<td>Zimbabwe</td>
</tr>
<tr>
<td>15</td>
<td>St Mary’s CRS</td>
<td>Chitungwiza</td>
<td>Zimbabwe</td>
</tr>
<tr>
<td>16</td>
<td>Eswatini Prevention Center</td>
<td>Mbabane</td>
<td>Eswatini</td>
</tr>
<tr>
<td>17</td>
<td>UVRI-IAVI</td>
<td>Entebbe</td>
<td>Uganda</td>
</tr>
<tr>
<td>18</td>
<td>Verulam CRS</td>
<td>Verulam</td>
<td>South Africa</td>
</tr>
<tr>
<td>19</td>
<td>Ward 21</td>
<td>Johannesburg</td>
<td>South Africa</td>
</tr>
<tr>
<td>20</td>
<td>Zengeza CRS</td>
<td>Chitungwiza</td>
<td>Zimbabwe</td>
</tr>
</tbody>
</table>
1.4 Investigator Responsibilities

HPTN 084 must be conducted in accordance with the US Code of Federal Regulations (CFR) and the International Council on Harmonization (ICH) Consolidated Guidelines for Good Clinical Practice (GCP). Copies of the regulations governing the conduct of this study (45 CFR 46 and 21 CFR 11, 50, 54, 56, and 312) and the ICH guideline can be requested from the HPTN LOC or found online at https://www.gpo.gov/fdsys/browse/collectionCfr.action?collectionCode=CFR and http://www.ich.org/home.html respectively. DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual describes operational requirements for Clinical Research Sites (CRSs) implementing DAIDS-sponsored clinical research within the DAIDS Clinical Trials Networks and can be downloaded from https://www.niaid.nih.gov/research/daids-score-manual

HPTN 084 must be conducted in accordance with all local regulations, policies, and guidelines applicable to human subjects research in general and/or the conduct of study procedures in particular. The Investigator of Record (IoR) at each site is responsible for the conduct of the clinical trial at the CRS. The IoR is the signatory for the FDA Form 1572. (Note: Since the HPTN 084 OLE components are amendments to the original, double-blinded HPTN 084 component, a new Form 1572 is not required.) Additionally, site investigators must promptly report to the IRBs/ECs any changes in the study and must comply with the requirements of 45 CFR 46.108(a)(4) and 21 CFR 56.108(b) for promptly reporting the following: unanticipated problems involving risks to participants or others; serious or continuing noncompliance with applicable regulations or the requirements or determinations of their IRBs/ECs; and any suspension or termination of IRB approval.

IoRs may delegate the work involved in study conduct to other site staff members; however, delegation does not relieve the IoR of ultimate responsibility for all study procedures performed and all study data collected. Additional guidance can be found in the US FDA’s Information Sheet Guidance: Information Sheet Guidance for Institutional Review Boards (IRBs), Clinical Investigators, and Sponsors available at https://www.fda.gov/science-research/guidance-documents-including-information-sheets-and-notices/information-sheet-guidance-institutional-review-boards-irbs-clinical-investigators-and-sponsors

1.5 Study Activation Process

Prior to undertaking any study procedures under either the v4.0 or v5.0 protocol amendments, each study site must obtain approval to conduct the amendment from all responsible US and local IRB/ECs and any other appropriate local regulatory bodies. Sites must complete Protocol Registration with the DAIDS Regulatory Support Center (RSC) according to the timeline requirements in the Protocol Registration Manual.

Note: Before sites could implement the v3.0 protocol amendment, a Site-Specific Activation Notice from the HPTN LOC was required. However, no activation notices are being issued for Protocol Amendment V5.0 (OLE2). Sites may implement v5.0 once all approvals are in place.
1.5.1 Protocol Distribution

The HPTN 084 OLE Project Managers (PMs) or Clinical Trials Assistant (CTA) will distribute approved protocol amendments electronically to the study sites.

1.5.2 Development and HPTN LOC Review of Site-Specific Informed Consent Forms: English Language Versions

Site staff will adapt the sample informed consent forms (ICFs) appended to the study protocol (either v4.0 or 5.0, as is appropriate) to reflect local procedures and IRB/EC requirements. If the site wishes to, it may forward the site-specific ICFs to the HPTN LOC Project Managers (PMs) for review prior to submission to local review bodies. The HPTN LOC PMs are not required to review the site-ICFs for subsequent Letters of Amendment (LOA)or Clarification Memos (CMs); however, the PMs are available for assistance.

Note: The ICF for original, double-blinded portion of the study are irrelevant to the open-label protocol amendments. Sites should implement the ICFs associated with the amendments.

1.5.3 Development and HPTN LOC Review of Site-Specific Informed Consent Forms: Local Language Version(s) and Back-translation(s)

For the protocol amendments of v4.0 and v5.0, site staff will translate the ICFs into all applicable local languages. Sites are not required to submit the translated forms, back-translations of the forms, and a certificate of translation for review to the HPTN LOC. Please note back-translations are not required if local language is Spanish. The back-translation need not be completed by a certified translator; however, it is recommended that two different individuals translate the document(s) and then review each other’s work to prepare a composite. The back-translation should be completed by an individual who did not participate in the translation process.

1.5.4 IRB/EC Review

Site staff will submit the study protocol, site-specific ICFs, and any other study-related materials as applicable for protocol amendments for review by all responsible local and US-based IRBs/ECs (as is appropriate to the site). Any participant information sheets, flip charts, promotional materials, or advertisements used during the study must be reviewed and approved by all responsible IRBs/ECs prior to site use.

In the event that either the site and/or local IRBs/ECs request changes to the submitted ICFs, it is the responsibility of the IoR to incorporate all such comments into a single final version of the study ICFs, and to obtain approval of this final version from all responsible IRBs/ECs. This may require multiple submissions to the responsible IRBs/ECs. The final English back translation of the ICFs submitted to the DAIDS RSC must accurately and entirely reflect the approved local-language ICFs that will be used at the site.
An overview of IRB/EC submissions required before and during HPTN 084 and its amendments are included in Table 1-3.
Table 1-3: IRB/EC Submissions, Source and IRB/EC Approval Required

<table>
<thead>
<tr>
<th>Document</th>
<th>Source</th>
<th>IRB/EC Approval Required*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol, Version 1.0 and higher</td>
<td>LOC</td>
<td>yes</td>
</tr>
<tr>
<td>Protocol amendments (including full amendments and Letters of Amendment [LOAs])</td>
<td>LOC</td>
<td>yes</td>
</tr>
<tr>
<td>Protocol Clarification Memos (CMs)</td>
<td>LOC</td>
<td>no**</td>
</tr>
<tr>
<td>Protocol deviations</td>
<td>site</td>
<td>no**</td>
</tr>
<tr>
<td>Site specific ICFs, Version 1.0 and any subsequent updates</td>
<td>site</td>
<td>yes</td>
</tr>
<tr>
<td>Current CV for IoR (and subsequent updates)</td>
<td>site</td>
<td>no</td>
</tr>
<tr>
<td>Participant recruitment materials (posters, advertisements, etc.) and any subsequent updates</td>
<td>site</td>
<td>yes</td>
</tr>
<tr>
<td>CASI-based assessments</td>
<td>site</td>
<td>yes</td>
</tr>
<tr>
<td>Printed copies of the e-case report forms as required by the IRB/EC</td>
<td>site</td>
<td>yes, if required</td>
</tr>
<tr>
<td>Cabotegravir Investigator’s Brochure (December 2016) and any subsequent updates</td>
<td>RSC</td>
<td>no</td>
</tr>
<tr>
<td>Truvada® (TDF/FTC) Package Insert (December 2016) and subsequent updates</td>
<td>RSC</td>
<td>no</td>
</tr>
<tr>
<td>Intralipid® 20% Fat Emulsion Package Insert (April 2016) and subsequent updates</td>
<td>RSC</td>
<td>no</td>
</tr>
<tr>
<td>Other written information for study participants and any updates</td>
<td>LOC/sites</td>
<td>yes</td>
</tr>
<tr>
<td>Study Monitoring Committee (SMC) summaries</td>
<td>LOC</td>
<td>no</td>
</tr>
<tr>
<td>Document</td>
<td>Source</td>
<td>IRB/EC Approval Required*</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Data and Safety Monitoring Board (DSMB) summaries</td>
<td>LOC</td>
<td>no</td>
</tr>
<tr>
<td>Other documentation required or requested by the IRB/EC</td>
<td>site</td>
<td>yes</td>
</tr>
<tr>
<td>Study status reports/updates (at least annually); this approval documents continuing review***</td>
<td>site</td>
<td>yes</td>
</tr>
<tr>
<td>New information that may adversely affect the safety of study participants or the conduct of the study</td>
<td>DAIDS</td>
<td>no****</td>
</tr>
<tr>
<td>Final study report/closure report</td>
<td>site</td>
<td>no</td>
</tr>
</tbody>
</table>

DAIDS = Division of AIDS; EC = ethics committee; LOC = HIV Prevention Trials Network Leadership and Operations Center; IRB = institutional review board

* Based on US regulations and GCP guidelines. Local regulatory authorities and/or responsible IRBs/ECs may require additional approvals. If so, the required approvals must be obtained and filed.

** IRB/EC submission is not necessarily required depending on DAIDS or local regulatory requirements.

*** Guidance from the US Office for Human Research Protections (OHRP) on continuing review can be found at:

**** IRB/EC approval of the actual information is not required; local IRB/EC policies should be followed for this kind of information.

Note: All documents must be submitted to all IRBs/ECs responsible for oversight of study implementation at the performance site. Documentation of all submissions to and approvals from all responsible IRBs/ECs must be maintained in the Essential Document files at the local performance site.
1.5.5 Protocol Registration for HPTN 084 Amendments

Upon obtaining approval from all responsible IRBs/ECs, site staff will submit the following documents to the Protocol Registration Office (PRO) at the RSC. These documents may be sent electronically to protocol@tech-res.com.

- Signed and dated protocol signature page
- Documentation of approval from all responsible IRBs/ECs, and local regulatory authority if applicable, of the study protocol and the ICFs.

*Note:* Documentation of IRB/EC approval must reference the exact protocol number, title, version number, and date as listed on the cover page of the protocol.

- A copy of the approved site-specific ICFs including local language translations, back-translations (if appropriate) and a certificate of translation (if appropriate). Please note, per the DAIDS Protocol Registration Manual, no back-translations are required by DAIDS for Spanish informed consents.

*Note:* The approved ICFs must include the exact protocol number, title, version number, and date as listed on the cover page of the protocol. Pages should be numbered 1 of x, 2 of x, etc. When an IRB/EC approves an ICF that will be used at multiple sites, and the approved form contains blank spaces for site contact information, a memo specifying the relevant information for each site must be submitted together with the approved form.

Some sites may have additional site-specific documents to be included with the protocol registration package (e.g. additional information requested by DAIDS). These documents should be submitted to the DAIDS RSC and a copy should be submitted to HPTN LOC.

If the site deletes or makes any substantive change to basic and/or additional elements as presented in the ICFs, the IoR must provide written documentation to explain the deletions/change(s) at the time of initial protocol registration with the DAIDS RSC.

DAIDS regulatory staff will communicate their review findings to the site staff, who will coordinate any required re-submissions.
1.6 Continuing Review

Throughout the course of the study, all sites are required to submit annual progress reports to the IRB(s)/EC(s) overseeing study conduct and receive annual approval. Documentation of this approval must be submitted to the RSC. See https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual for more information.

The submission sent to the IRB(s)/EC(s) for annual review should include the following:

- The full protocol
- The current ICFs
- An annual report which includes:
  - The number of subjects accrued
  - A summary of SAEs and any unanticipated problems involving risks to participants
  - The number of participants who have withdrawn and any complaints about the research since the last IRB/EC review
  - A summary of any modifications or amendments since the last IRB/EC review
  - Any other relevant information, especially information about risks associated with the research

Additional information and guidance about continuing review can be found at the OHRP website: http://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-continuing-review-2010/
Section 2. Protocol

2.1 Overview of Section 2

The table below documents the history of the HPTN 084 protocol along with Clarification Memos (CMs), Letter of Amendments (LoAs), and Full Amendments. These documents are considered Essential Documents. A copy of each document must be available to staff and a copy must be maintained with study regulatory files.

<table>
<thead>
<tr>
<th>Document</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPTN 084 Protocol, Version 1.0</td>
<td>2 March 2017</td>
</tr>
<tr>
<td>HPTN 084 CM#1 to Version 1.0</td>
<td>11 May 2017</td>
</tr>
<tr>
<td>HPTN 084 LoA#1 to Version 1.0</td>
<td>15 August 2017</td>
</tr>
<tr>
<td>HPTN 084 CM#2 to Version 1.0</td>
<td>26 September 2017</td>
</tr>
<tr>
<td>HPTN 084 LoA#2 to Version 1.0</td>
<td>24 January 2018</td>
</tr>
<tr>
<td>HPTN 084 LoA#3 to Version 1.0</td>
<td>31 May 2018</td>
</tr>
<tr>
<td>HPTN 084 CM#3 to Version 1.0</td>
<td>02 August 2019</td>
</tr>
<tr>
<td>HPTN 084 Protocol, Version 2.0</td>
<td>06 November 2019</td>
</tr>
<tr>
<td>HPTN 084 CM#1 to Version 2.0</td>
<td>22 January 2020</td>
</tr>
<tr>
<td>HPTN 084 LoA#1 to Version 2.0</td>
<td>23 June 2020</td>
</tr>
<tr>
<td>HPTN 084 LoA#2 to Version 2.0</td>
<td>10 September 2020</td>
</tr>
<tr>
<td>HPTN 084 CM#2 to Version 2.0</td>
<td>16 September 2020</td>
</tr>
<tr>
<td>HPTN 084 LoA#3 to Version 2.0</td>
<td>22 October 2020</td>
</tr>
<tr>
<td>HPTN 084 LoA#4 to Version 2.0</td>
<td>16 November 2020</td>
</tr>
<tr>
<td>HPTN 084 Protocol, Version 3.0 (OLE 1)</td>
<td>16 August 2021</td>
</tr>
<tr>
<td>HPTN 084 LoA#1 to Version 3.0</td>
<td>24 September 2021</td>
</tr>
<tr>
<td>HPTN 084 CM#1 to Version 3.0</td>
<td>07 December 2021</td>
</tr>
<tr>
<td>HPTN 084 LoA#2 to Version 3.0</td>
<td>03 February 2022</td>
</tr>
<tr>
<td>HPTN 084 LoA#3 to Version 3.0</td>
<td>14 March 2022</td>
</tr>
<tr>
<td>HPTN 084 CM#2 to Version 3.0</td>
<td>21 July 2022</td>
</tr>
<tr>
<td>HPTN 084 Protocol, Version 4.0 (OLE 2)</td>
<td>02 November 2022</td>
</tr>
<tr>
<td>HPTN 084 CM#1 to Version 4.0</td>
<td>24 February 2023</td>
</tr>
</tbody>
</table>
Note: CMs and LoAs are incorporated into subsequent full versions of the protocol. A CM may also be incorporated into a subsequent LoA.
Section 3. Document Requirements

3.1 Overview of Section 3

This section contains a listing of required administrative and regulatory documentation, commonly referred to as “Essential Documents,” which each study site must maintain and keep current throughout the study, as well as procedures for establishing adequate and accurate study participant source documentation records.

3.2 Essential Documents

Refer to the Essential Documents Section of the DAIDS Score Manual.

https://www.niaid.nih.gov/research/daids-score-manual

Refer to the appendix which specifies the administrative and regulatory documents that HPTN study sites must maintain for DAIDS-sponsored studies.


Also refer to ICH E6 Good Clinical Practice: Consolidated Guidance (https://www.fda.gov/media/93884/download) specify the administrative and regulatory documents that HPTN study sites must maintain for Division of AIDS (DAIDS)-sponsored studies. Based on this DAIDS Policy, the documentation listed below must be maintained for HPTN 084. When required documents are modified or updated, the original and modified/updated versions must be maintained. Although all required
documentation must be available for inspection at any time, all documents need not be stored together in one location.

- Protocol (implementation version and any subsequent amendments, Letters of Amendment [LoAs] and Clarification Memos [CMs])

- Informed Consent Forms (ICFs) (all IRB/EC-approved versions, all signed and dated forms from screened/enrolled study participants), as well as any “Dear Participant” Letters (all IRB/EC-approved versions) for all screened/enrolled participants.

- Signed and dated Food and Drug Administration (FDA) Form 1572, original and subsequent versions

- Documentation of approved protocol registration from DAIDS, protocol registration for the original study and Version 3 (OLE) and for all subsequent protocol modifications

- Documentation of study activation from HPTN Leadership and Operations Center (LOC)

- Documentation of local regulatory authority correspondence, authorization, and/or approval of the protocol

- Federal Wide Assurance (FWA) number(s) and expiration date

- Institutional Review Board (IRB)/Ethics Committee (EC) roster(s)

- All correspondence to and from the local IRB/EC, including documentation of all submissions, reviews and approvals and copies of site-specific interim and annual reports

- All IRB-approved participant informational/educational materials and advertisements for participant recruitment, as well as subsequent updates

- Screening and enrollment logs

- Participant identification code list (if applicable)

- Study staff roster, signature sheet, and delegation of duties, including Investigator of Record (IoR) responsibilities

- Signed and dated Curriculum Vitae (CV) for each study staff member, current within the last two years

- Financial disclosure forms from all key staff listed in the FDA form 1572

- Documentation of staff members’ current human subjects training (within 3 years)
• Documentation of staff members’ study-specific training, including training on all official revisions/amendments/regulatory actions such as version 3 (OLE) related to the protocol

• Documentation of staff members’ current Good Clinical Practice (GCP) training (within 3 years)

• Documentation of appropriate laboratory staff members’ current Good Clinical Laboratory Practice (GCLP) training. Refer any questions to the HPTN Laboratory Center (LC).

• Local laboratory accreditations/certifications, if applicable

• Product Safety Information/Reports/Memos (Investigational New Drug [IND] Safety Reports provided by DAIDS)

• Current cabotegravir (CAB) (oral and injectable) Investigator Brochure (IB) and subsequent updates

• Current Truvada® (TDF/FTC) Package Insert and subsequent updates

• All study product accountability records

• Local laboratory reference intervals for protocol-specified testing

• Key study-related correspondence with the HPTN LOC, HPTN Statistics and Data Management (SDMC), HPTN Laboratory Center (LC), DAIDS Pharmaceutical Affairs Branch (PAB) and DAIDS, as well as other study-related communication

• Documentation of study-related conference calls and meetings

• Applicable local public health reporting requirements pertinent to study procedures

• Final version of each local site- and study-specific Study Operating Procedures (SOPs) that will be used for HPTN 084 and all subsequent updates

• DAIDS reference materials including:
  
  o Division of AIDS Clinical Research Policies
    
    o [https://www.niaid.nih.gov/research/daids-clinical-research-policies-and-other-information](https://www.niaid.nih.gov/research/daids-clinical-research-policies-and-other-information)
• Division of AIDS (DAIDS) Site Clinical Operations and Research Essentials (SCORE) Manual
  o https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations
  o DAIDS Protocol Registration Policy and Procedures Manual:
• Study specific procedures (SSP) manual, original versions and all updates, bulletins, clarifications, and communiqués
• Monitoring visit log, reports, and site response to visit findings (for the monitor, HPTN LOC, SDMC, LC, PAB, and other site visits). Sites should print monitoring visit reports for their files from the DAIDS website for Clinical Research Management System (https://ncrms.niaid.nih.gov/NCRMS/Main)
• A complete, blank copy of the electronic case report forms (CRFs) (original and all revisions – these will be provided by the HPTN SDMC). Sites may choose to print the forms and file as part of their essential documents or they may choose to file electronically.
• All completed CRFs, which will include electronic initials and dates per the electronic data capture system (these will be provided by the HPTN SDMC at the end of the study)
• Site specific e-CRFs as Source Documentation Table (Table 3-1a OR 3-1b) and Source Documentation for Eligibility Criteria (Table 3-2)
• Source documents
• Signed agreements related to the study (e.g., between IoR and affiliated sites/ Materials Transfer Agreements (MTAs)/ Protocol Signature Page, etc.)

3.3 Investigator Responsibilities

Study sites must maintain an accurate and complete participant research record containing all information pertinent to the study for each study participant. The research record consists of the following: original subject-signed ICF(s), participant source documents, and CRFs.

3.3.1 Concept of Source Documentation

A source document is defined as the first document on which study-related information is recorded. Study sites must adhere to the standards of source documentation specified in the DAIDS Score Manual and the standards outlined in this manual.

For HPTN 084 including OLE, participant source documents will consist of narrative chart notes, visit checklists, medical records, laboratory reports, pharmacy records and CRFs and other items as defined by each participating site. As a condition for study activation, each site must establish an SOP for source documentation that specifies the use of these documents as source documents.

HPTN 084 will use an electronic data capture system. Electronic records are any combination of text, graphics, data, audio, pictorial, or other information in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system (21 CFR 11.3). **When data are entered directly into a computer, the electronic data in the computer becomes the source document.** A paper record (printout/hard copy/“print screen”) of the electronic data is considered to be a copy. Requirements for documentation, record keeping and record retention apply to electronic records the same as they do for paper systems.

Examples of electronic records include but are not limited to:
1. Participant data, reports, and/or results
2. E-mail communications pertaining to a participant or protocol management (e.g., directives from protocol chairs, clinical management committee (CMC), Clinical Research Site (CRS) investigators to study nurses, etc.)
3. IRB/EC correspondence pertaining to a participant or the study
4. Computer-Assisted Self-Interview (CASI) questionnaires

Each electronic record needs to be associated with an originator type, otherwise known as an authorized data originator. In HPTN 084, the authorized data originator is most likely going to be a person; however, it can also be a computer system, a device, or an instrument that is authorized to enter, change, or transmit data into the electronic record. Sites must develop and maintain a list of all authorized data originators. This list must be made available for study-related monitoring, audits, IRB/EC review, and regulatory inspection by authorized individuals at each clinical research site. Examples of data originators include, but are not limited to:

1. Clinical investigator(s) and delegated clinical study staff
2. Participants or their legally authorized representatives
3. Consulting services (e.g., a radiologist reporting on a computed tomography (CT) scan)
4. Medical devices (e.g., electrocardiograph (ECG) machine and other medical instruments such as a blood pressure machine)
5. Electronic health records (EHRs)
6. Automated laboratory reporting systems (e.g., from central laboratories)
7. Other technology
3.3.2 Source Documentation

Participant source documentation should contain all of the following elements:

- Participant ID number (PTID) assignment.
- Documentation that the participant provided written informed consent to participate in the study prior to the conduct of any study procedures including an Informed Consent Assessment tool (see SSP Section 4 Tables 4-1 and 4-2) to verify comprehension.
- Documentation that the participant met the study's eligibility criteria.
- A record of all contacts, and attempted contacts, with the participant.
- A record of all procedures performed by study staff during the study.
- A record of the participant’s exposure to the study product.
- A record of any Adverse Events (AEs) and Social Impacts reported by participants.
- Study-related information on the participant’s condition before, during, and after the study, including:
  - Data obtained directly from the participant (e.g., self-report of injection reaction)
  - Data ascertained by study staff (e.g., exam and lab findings)
  - Data obtained from non-study sources (e.g., medical records)

In general, sites should apply ALCOA* to achieve data quality.

- Attributable: is it obvious who wrote it?
- Legible: can it be read?
- Contemporaneous: is the information current and in the correct time frame?
- Original: is it a copy; has it been altered?
- Accurate: are conflicting data recorded elsewhere?

3.3.3 Examples of Source Documentation

3.3.3.1 Clinic Notes

Study staff must document contacts with a study participant where data and pertinent study information are collected in a signed and dated clinic note specifying the date, type, purpose, location of the contact, and the general status of the participant. Routine study visit reminders may be documented per local site SOPs and requirements (and a site may wish to include this information in the retention SOP). Clinic notes also must be used to document the following:

- The informed consent process and/or coversheets
- Procedures performed that are not recorded on other source documents
- Pertinent data about the participant that are not recorded on other source documents
- Protocol deviations that are not otherwise captured on other source documents (such as the Protocol Deviation Form).

One way that clinic notes can be structured is by using the SOAP method. The acronym SOAP stands for Subjective, Objective, Assessment, and Plan and the following information is included in each section:

**S:** Subjective information that includes what the patient tells you about how he/she is feeling or his/her symptoms. For example, how he/she is sleeping or eating or if he/she is experiencing pain or having trouble urinating or defecating.

**O:** Objective information including vital signs, pertinent physical exam findings, and the most recent laboratory test results.

**A:** The assessment describes your diagnosis of the symptoms. The assessment also includes a summary of how the patient is doing and what has changed from the previous visit.

**P:** The plan includes how each diagnosis or problem will be addressed. This section will include information about new or changes to existing medication, laboratory tests to order, and consults to obtain.

3.3.3.2 Visit Checklists

The checklists provided in Section 6 of this SSP manual may be used as a convenient tool for study staff to ensure that all study procedures are performed at each visit. The checklists as designed may not be able to serve as source documentation – see Section 6.0 for further information about this. If a site modifies the checklists to serve partly or wholly as source documents, individual study staff members must initial only those procedures that they complete to fulfill the source documentation requirement of identifying responsibility. In addition, if procedures listed on a single checklist are completed across multiple dates or by more than one person, the date upon which each procedure is completed must be clearly noted and initialed.
Even with modification, the checklists alone may not be sufficient for documenting all procedures. For example, chart notes may be required to document procedures performed at unscheduled study visits or to explain why procedures in addition to those specified on a checklist have been performed. Chart notes may also be required to document the content of discussions with participants (e.g., issues related to study product adherence and HIV counseling). Sites are encouraged to contact the HPTN LOC with any questions about which checklists to use and/or how to modify them for site specific purposes.

3.3.3.3 Case Report Forms

As mentioned above, the study will utilize an electronic data capture system. Each study site must document the source documentation for each electronic CRF item by completing Table 3-1 (EITHER Table 3-1a OR Table 3-1b may be used; these tables may be modified to suit site needs), submitting a copy to the HPTN LOC, and maintaining the original document in the site’s administrative and regulatory files. The comments section of Table 3-1 (1a or 1b) should be modified to accurately reflect the source documentation for each CRF item at the site. Table 3-1 (1a or 1b) will be finalized and signed at each site prior to site activation. Site staff must follow the designations in Table 3-1 (1a or 1b) consistently for all study participants throughout the study.

In the event that it is not possible to record data directly onto forms designated as source documents, the following procedures should be followed:

- Record the data onto an alternative source document.
- Enter the alternative source document into the participant’s study chart.
- Transcribe the data from the alternative source document onto the appropriate case report form.
- Enter a chart note stating the relevant study, or dosing visit, date and the reason why an alternative source document was used.
Tables 3-1a and 3-1b: HPTN 084 Source Documentation TEMPLATES

**NOTE:** These tables are provided as example documents. Each site must complete either Table 3-1a or 3-1b site-specific source documentation table based on individual needs and policies. The CRFs in table 3-1b below are listed in alphabetical order and not necessarily in the order in which procedures are performed.

Table 3-1a: For each procedure listed below, add the source documents for each study procedure/evaluation. This is an EXAMPLE. Please add to this table if necessary.

<table>
<thead>
<tr>
<th>Evaluation /Procedure</th>
<th>Source Document(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADMINISTRATIVE, BEHAVIORAL AND REGULATORY</strong></td>
<td></td>
</tr>
<tr>
<td>Obtain Informed consent(s)</td>
<td>Example: Signed and Dated Informed Consent form</td>
</tr>
<tr>
<td></td>
<td>Informed Consent Coversheet (or chart note)</td>
</tr>
<tr>
<td>Locator information</td>
<td></td>
</tr>
<tr>
<td>Demographic information</td>
<td></td>
</tr>
<tr>
<td>HIV prevention counseling</td>
<td></td>
</tr>
<tr>
<td>Offer condoms</td>
<td></td>
</tr>
<tr>
<td>Acceptability assessments</td>
<td></td>
</tr>
<tr>
<td>Behavioral assessments</td>
<td></td>
</tr>
<tr>
<td><strong>CLINICAL</strong></td>
<td></td>
</tr>
<tr>
<td>Medical History contraceptive use, con meds, physical exam</td>
<td>Example: Medical History Questionnaires, Medical History eCRF, Concomitant Medications, and/or chart notes</td>
</tr>
<tr>
<td>Dispense product</td>
<td></td>
</tr>
<tr>
<td>Adherence counseling</td>
<td></td>
</tr>
<tr>
<td>Hep B vaccination</td>
<td></td>
</tr>
<tr>
<td>Blood collection</td>
<td></td>
</tr>
<tr>
<td>Urine collection</td>
<td></td>
</tr>
<tr>
<td>Vaginal swab collection</td>
<td></td>
</tr>
<tr>
<td>Injections</td>
<td></td>
</tr>
<tr>
<td>ISR evaluations</td>
<td></td>
</tr>
<tr>
<td><strong>LABORATORY</strong></td>
<td></td>
</tr>
<tr>
<td>HIV testing</td>
<td>Example: Lab result report (or other required site specific form)</td>
</tr>
<tr>
<td>Pregnancy testing</td>
<td></td>
</tr>
<tr>
<td>HBV and HCV testing</td>
<td></td>
</tr>
<tr>
<td>CBC with differential</td>
<td></td>
</tr>
<tr>
<td>Chemistry testing</td>
<td></td>
</tr>
<tr>
<td>Liver function tests</td>
<td></td>
</tr>
<tr>
<td>Fasting lipid profile</td>
<td></td>
</tr>
<tr>
<td>Syphilis serologic testing</td>
<td></td>
</tr>
<tr>
<td>GC/CT and TV testing</td>
<td></td>
</tr>
<tr>
<td>Evaluation /Procedure</td>
<td>Source Document(s)</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Urinalysis (protein and glucose)</td>
<td></td>
</tr>
<tr>
<td>Plasma storage</td>
<td></td>
</tr>
<tr>
<td>DBS storage</td>
<td></td>
</tr>
<tr>
<td>Whole blood storage</td>
<td></td>
</tr>
</tbody>
</table>
Table 3-1b Example Source Document Reference

For each form listed below, add which elements of the form serves as the source document for study procedure/evaluation.

<table>
<thead>
<tr>
<th>Form</th>
<th>Source</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional Procedures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional Procedures Y/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional Procedures – OLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Event X</td>
<td></td>
<td>Example: Form is source for Alternate etiology information. For all other items, source will be based on the type of AE, including chart notes, lab report/testing log, medical questionnaires.</td>
</tr>
<tr>
<td>Adverse Event Y/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Event - Infant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Event – Infant Y/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell Pellet Storage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4/Viral Load Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry Testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications Y/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consent - Pregnancy Infant Sub-study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contraception</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contraception - OLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Counseling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Visit- HIV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Visit - OLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Visit- Pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Visit- Pregnancy OLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Visit- Yearly Visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Visit- Open Label Truvada</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Visit – Step 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Visit – Step 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Visit – Step 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dried Blood Spot Storage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early Unblinding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Form</td>
<td>Source</td>
<td>Comments</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>--------</td>
<td>----------</td>
</tr>
<tr>
<td>Enrollment Visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting Lipid Test Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B Test Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C Test Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV Supplemental Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV Test Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV Test Results Y/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant Assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant Breastmilk Feeding Assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant Dried Blood Spot Storage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant HIV test results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant Specimen Collection - Blood (Plasma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant Specimen- Cord Blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed Consent V5.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection Administration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection Site Reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection Site Reaction Y/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interim Visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interim Visit Summary – OLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver Function Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log Revisions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long Term Consent Update</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History Y/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missed Visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open Label Truvada Log</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open Label Truvada Y/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participant Receipt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participant Transfer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pill Count – Enrollment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pill Count – Step 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pill Dispensation- Step 2 and 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma Storage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Form</td>
<td>Source</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>--------</td>
<td>----------</td>
</tr>
<tr>
<td>Plasma Storage-Contraceptive Substudy</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Pregnancy History</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Pregnancy Outcome Log</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Pregnancy Outcome Log – OLE</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Pregnancy Report</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Pregnancy Report- OLE</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test Results</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test Results- OLE</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Product Choice - OLE</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Product Hold/Discontinuation Log</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Product Hold Y/N</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Product Hold - OLE YN</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Product Hold - OLE</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Protocol Deviation Log</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Protocol Deviation Y/N</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Screening Chemistries</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Screening Liver Function Tests</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Screening Outcome</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>STI Test Results</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Social Impact Log</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Social Impact Log Y/N</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Specimen Collection - Breast Milk</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Specimen Storage-Contraceptive Sub-Study</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Study Step</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Sub-study Infant PTID</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Termination</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Ultrasound Results</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Ultrasound - OLE</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>VOICE Risk Score - Modified</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Whole Blood Storage</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>
3.3.4 Document Organization

Study staff must make every effort to keep all research records - both individual participant records as well as logs and documents pertaining to all participants – confidential and secure. All records should be securely stored in an area with access limited to authorized staff only.

All study-specific documents and biological specimens that are transmitted to an off-site location, including copies of electronic CRFs, SAE/EAE Report Forms and all biological specimens processed in any way by non-study staff or transferred to an off-site location must be identified only by the participant’s PTID to maintain confidentiality. Sites must ensure that any document sent by email or other communication methods does NOT contain any participant identifiers. If a document has participant identifiers, the identifying information must not be visible or legible prior to sending. When communicating via email between two institutions for transfers that do NOT include anyone external to the two institutions, sites must follow their local institution’s policy for transmission of confidential information (e.g., encrypted email, redacted files, etc.). Inclusion of more than one identifier on other study records that are accessible only to authorized study staff is not prohibited by DAIDS, however, such records must be stored securely with limited access. Regardless of whether the participant identifier on a particular document is the participant’s name or PTID number, the original identifier may not be obliterated or altered in any way, even if another identifier is added. When necessary to maintain confidentiality, identifiers may be obliterated or altered on copies of original source documents. For example, if supporting documentation of study eligibility is to be submitted to the HPTN LOC, such as chart notes or lab reports, contain a participant’s name, this should be obliterated on the copy transmitted off-site, but not on the original.

All local databases will be secured with password-protected access systems.

Log books, appointment books, and any other listings that link participant PTID numbers to participant names or other personal identifiers should never be left unattended or easily accessible to unauthorized individuals.

3.4 Protocol Deviations

Any deviation from the protocol must be documented in participant charts and in any other pertinent source documents, including a Master Protocol Deviation Log which must be maintained on site. Any deviation from the protocol, no matter how small, must be recorded on this Master Protocol Deviation Log. All protocol deviations must be reported into the electronic data capture system.

* NOTE: HPTN 084 is adopting a more conservative approach for protocol deviation reporting, given that this an IND study.
3.4.1 Protocol Deviation Categories

Protocol deviations must be classified into a category when they are reported. Explanations of each category are provided below along with some common examples.

3.4.1.1 Category: Informed consent process deviation

This category of deviations includes errors directly related to the informed consent. Errors include staff failure to follow proper consenting processes with participants, not confirming comprehension of the content of the consent, not documenting consent properly and nonadherence to what the participant agreed to.

Examples of these deviations include:

- A site made a mistake on the consent form. It did not correctly account for the blood volume needed for study testing. The consent form stated that 44mLs of blood would be taken. Instead the site was routinely taking 50mLs of blood for protocol testing.

- Participants have the ability to opt out of genetic testing on the consent form. Blood for genetic testing was erroneously collected from a participant who had already declined genetic testing.

- A participant was consented using an English consent form when it is clear from the chart notes that her understanding of English was very limited. The site had an approved translated consent in the participant’s native language. The site should have used the consent the participant did not have to struggle to understand.

3.4.1.2 Category: Use of non-IRB/EC-approved materials

This category of deviations includes instances where sites accidently use materials with participants or the Community without local IRB/EC body (ies) approval.

Examples of these deviations include:

- Advertisements for a study were hung up to help recruit participants, however, the advertisements had not yet been IRB-approved.

- A site with multiple levels of IRB/EC reviews received protocol/consent form approval from all review bodies except one. The site did not realize that one review was still outstanding and implemented the updated protocol/consent form on site.

3.4.1.3 Category: Inappropriate enrollment

In general, any situation where eligibility criteria are not met or randomization is performed before all criteria are confirmed must be categorized as an inappropriate enrollment protocol deviation.
Examples of these deviations include:

- A site accidently enrolled a woman into the study with a voice risk score of 2 instead of a score of 5 or more (protocol version 2).
- AST and ALP were erroneously requested instead of ALT and Total Bilirubin. The site did not catch omission of the enrollment criteria before it randomized the participant.
- A participant was enrolled based on screening results that were more than 45 days old.
- A participant was enrolled with a history of seizure; though this history was not revealed to the site during screening. The participant experienced a seizure during the study and only then explained she previously had an eclamptic seizure during pregnancy.
- On a source document, staff marked “Yes” but did not provide the number of sexual encounters the participant reported having in last 30 days. Consequently, a monitor was unable to verify that the participant met the eligibility criterion of having “vaginal intercourse on a minimum of two separate days in the 30 days prior to Screening.”
- A site accidently enrolled a woman that had a positive HBsAg result at the screening visit. All other screening lab results were not clinically significant, and HIV ELISA was negative.

3.4.1.4 Category: Failure to follow trial randomization or blinding procedures

This type of deviation is specific to problems with the randomization procedure or blinding/unblinding requests.

Examples of this type of deviations include:

- While a study clinician was handling the syringe containing injectable study product, the barrel cover shifted just enough for the participant to view the liquid. The participant later did some research and was able to determine which arm she was randomized to.
- A participant was hospitalized after experiencing significant cognitive confusion. In its haste, the site did not properly follow emergency unblinding procedures.

3.4.1.5 Category: Study product management deviation

Deviations in this category are related to the storage and shipping of study products as well as any failure to follow study product handling guidelines.
Examples of this type of deviation are as follows:

- Participant was scheduled for enrollment however the pharmacy was out of stock of study product and the participant could not be enrolled.
- Study product was stored in the pharmacy at the incorrect temperature.
- The Chain of Custody document was not properly complete for a shipment of study product arriving on site.
- Expired oral study product was administered to a participant in error.

3.4.1.6 Category: Study product dispensing error

Deviations in this category are directly related to study product dispensing/administration errors made by site staff.

Examples of these deviations include:

- A site accidentally forgot to sign and date a study product prescription. This mistake was caught during a PPD monitoring visit.
- A participant was given an injection after the permissible window of time post product preparation. An injection was prepared at 10:50am but was not administered until 13:00pm. As per the protocol the injection should have been given within two hours of preparation. This injection was administered at two hours and ten minutes after preparation.

3.4.1.7 Category: Incorrect study product given/taken

This category of Protocol Deviations is used exclusively for instances when the wrong study product is ingested by a participant. This type of error could be the result of a study staff error or could occur if a participant takes another participant’s study product.

Examples of these deviations include:

- Two participants in a waiting room were sitting next to each other. They each had oral study product bottles with them. By accident, the participants ended up switching study product bottles in the waiting room. They each took the bottles home and subsequently took the wrong oral product.
- A participant came to site for her Week 2 visit. Following the pill count, study staff accidentally returned the study product for another participant. Unfortunately, the participant took oral study product in front of study staff before the error was detected. However, the mistake was caught before the participant left the clinic and she was given her original oral study product.
- At Week 5, a participant took oral study product in the morning before she received her first injection on site later that day. If the participant was randomized to CAB
LA, she would have had an oral dose of CAB in the morning and an injectable CAB dose that afternoon.

3.4.1.8 Category: Breach of confidentiality

This category of deviations includes events where confidential information about the participant is released to other people without participant consent. Confidential information includes medical information, HIV status or even the fact that the participation is enrolled in the study.

An example of this type of deviation is as follows:

- In an effort to locate a participant, site staff erroneously contacted two individuals who were not indicated as participant contacts on the locator form.

3.4.1.9 Category: Missed procedures

This type of deviation is specifically related to a site not conducting protocol required procedures, including failure to complete physical examinations/assessments and failure to collect any lab samples (not to include laboratory-initiated errors).

Examples of these deviations include:

- Prior to injecting participants with study product, there are several mandatory processes and labs which must be completed first. A site accidently forgot to confirm a participant was actively using a long-acting contraceptive prior to injection.
- Site staff forgot to weigh a participant during a study visit.
- Sites are required to notify the CMC for participant management guidance where indicated in the protocol. A site erroneously did not contact the CMC when a participant presented with a Grade 3 weight loss AE.
- A clinician accidently did not conduct a targeted medical exam during a follow up study visit.
- Hepatitis B vaccination is scheduled for Week 2 of the study. The vaccination was accidently omitted during a Week 2 visit for a participant.
- A site accidently forgot to collect of a swab for Trichomonas vaginalis testing during a visit at Week 33.

3.4.1.10 Category: Lab assessment deviation

This category of deviations includes events where protocol procedures and lab SOPs are not properly followed by lab technicians. Lab technicians must: 1) properly process, test,
store and ship samples, 2) ensure adequate inventory of test kits and reagents to conduct timely protocol-required testing.

Examples of these type deviations include:

- A lab tech accidentally performs HBsAb testing during the Screening visit instead of HBsAg analysis. The correct test was ordered, the tech simply made a mistake.
- A lab tech did not order HIV rapid kits when the supply was low and subsequently ran out of test kits. Lack of test kits caused delayed participant visits since study product cannot be dispensed until a rapid test is completed.
- A lab ran out of hematology controls due to a stick out at the vendor. Study participants had to be rescheduled resulting in some out of window visits.
- Pregnancy test kits were ordered by lab staff but a significant temperature excursion during shipping to the site rendered the kits useless. Study visits were delayed until the kits could be obtained.

3.4.1.11 Category: Conduct of non-protocol procedure

This category of protocol deviations includes instances where a site accidently performs a procedure that is not mandated by either the protocol or based on participant management, and that does not fall under another category of PDs (for example over-collection of blood).

Examples of these deviations include:

- Hepatitis B vaccination was given in error; the participant was already immune.
- At visit 6.0 a urine sample was erroneously shipped to the local lab for NG/CT testing. NG/CT testing is not included in Week 6 protocol procedures. The sample was processed for NG/CT and results were sent to the clinic.

3.4.1.12 Physical assessment deviation

This category of deviations includes events where protocol procedures and are not properly followed leading to errors that occur with physical assessments.

Examples of these deviations include:

- Participant had her weight incorrectly recorded and the error in weight has resulted in the incorrect BMI calculation.

3.4.1.13 Other

Events that are not specific to any of the above categories will be grouped and classified as “other.”
An example of these deviations include:

- Hematology labs were not performed per study schedule. Due to COVID transport issues, reagents were not available to process the lab samples.

### 3.4.2 Protocol Deviations During the COVID-19 Pandemic

Sites must continue to report PDs into the database during the pandemic. For missed assessments within a study visit due to COVID, a protocol deviation should be added. See example under section 3.4.1.12 Other.

Once a site identifies a protocol deviation, it should be entered into the MediData Rave system.

If the site has any question as to whether an issue is a deviation, it should email the protocol deviation email alias list at 084mgmt@hptn.org for guidance. If the suspected deviation is confirmed, the site will need to complete the Protocol Deviation Log eCRF and include the deviation on the Master Protocol Deviation Log.

### 3.4.3 Protocol Deviation Log CRF

One Protocol Deviation Log CRF should be completed for each participant affected by the deviation. If the deviation occurred over a period of time, report the date the deviation first started and when it ended or if it is ongoing at the time this report is submitted, include this information as part of the description of the deviation.

Please note that there is a limit of 1,000 characters on the Protocol Deviation Log CRF; therefore, sites are asked to be concise and clear when describing the event.

When reporting a deviation trend individual eCRFs must be entered into MediData Rave for each affected PTID.

### 3.5 Record Retention Requirements

As this study is being conducted under IND, the study-related records must be maintained for two years after the marketing application is approved for the drug(s); or if an application is not approved for the drug(s), until two years after shipment and delivery of the drug(s) for investigational use is discontinued and the FDA has been notified (21 CFR 312.57). **No documents are to be destroyed without written permission from DAIDS.**

The study-related records include but are not limited to the following:

- Study management information, including the protocol, clarifications, letters of amendment, protocol amendments, the SSP manual and associated errata, addenda, study drug shipment and supply, and bulletins.
• Signed ICFs for each study participant.
• Electronic CRFs for each study participant labeled by PTID.
• Source documents such as clinic notes, pharmacy records, and laboratory result reports.

3.6 Ancillary Studies

Ancillary studies (also sometimes referred to as “sub-studies”) are those investigations, conducted in conjunction with a primary or “main” HPTN study, that address scientific questions not identified as study objectives in the primary study protocol.

Ancillary studies may involve HPTN investigators and/or non-HPTN investigators and may be initiated by the primary study team or by individuals inside or outside of the study team. They may:

1) involve all sites participating in a primary HPTN study or a subset of sites;
2) involve the use of data, biological specimens, or other information obtained through a primary HPTN study;
3) be either prospective or retrospective in nature;
4) involve surveys or focus groups among primary study participants; and
5) contain laboratory-based investigations using specimens obtained from participants in a primary HPTN study.

The administrative and regulatory requirements for the conduct of ancillary studies can be found in the HPTN MOP Section 17 (https://hptn.org/resources/manual-of-operations).

3.7 Study Publications

All manuscripts, abstracts, posters or presentations based on the results or conduct of HPTN 084 must be prepared in accordance with the HPTN MOP and HPTN 084 Protocol Publications Committee.
## Appendix 3A: Sample HPTN 084 Master Protocol Deviation Log*

<table>
<thead>
<tr>
<th>PTID</th>
<th>Date of event/visit</th>
<th>Date of site awareness</th>
<th>Issue/Description</th>
<th>Category of deviation**</th>
<th>eCRF completed? (yes/no)</th>
<th>IRB required to be notified? (yes/no)</th>
<th>Date IRB notified, if applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>333333333</td>
<td>30Oct2019 enrollment</td>
<td>20Nov2019</td>
<td>HIV RNA not done within 14 days of enrollment</td>
<td>Inappropriate enrollment</td>
<td>Yes</td>
<td>Yes</td>
<td>27Nov2019</td>
</tr>
</tbody>
</table>

(*May be adapted as needed for local use)

(** See section 3.4.1 for categories)
Section 4. Continuation in Protocol Version 5.0 (OLE)

4.1 Overview of Section 4

This section provides an overview of requirements and procedures for continuing previously enroll participants on the Open Label Extension (OLE)/ Protocol Version 4.0 and Version 5.0. Additional procedure-specific details can be found in the visit checklists in SSP Section 6, and in Section 5/ Schedule of Evaluations Appendices of the Protocol.

4.2 Continuation in Protocol during the Open-Label Portions

Participants who elected to remain in follow-up after the v2.0 amendment were offered the opportunity to remain in HPTN 084 under v3.0 protocol (OLE). Similarly, eligible participants in the version 3.0 protocol were offered the option to join the v4.0 protocol amendment. Eligible participants will now be offered the v5.0 protocol amendment.

Note: Always contact the CMC for questions related to safety and study product AEs of concern for participants interested in continuing or initiating CAB LA.

4.2.1 Informed Consent Process

After receiving notification to implement Version 5.0 of the protocol, sites will administer the addendum to the main informed consent form as participants present to the site. Participants do not need to be re-consented with the ICF used for v2.0 that is contained in the defunct, main body of the original protocol. That part of the study has concluded and the information in it is not representative of the trial or participant activities. The executed form specific to amendment v5.0 will document the participant's continued participation in the study. As part of the consent discussion, sites should explain to participants the options for ongoing study participation as outlined in the Informed Consent Appendices of the Protocol.

Contact the CMC for guidance if there are other scenarios for a discussion about choice and obtaining informed consent.

Deliver All Required Information in a Manner that is Understandable to Potential Participants. If the participant is literate, give her a copy of the ICF to read. Also provide the participant with other (IRB/EC-approved) informational materials developed to
complement the ICF, if any. If the participant is not literate, the materials may be read to her verbatim. After the participant has read the written material (or had it read to her), verbally review the information provided. A checklist or the ICF itself may serve as a useful guide for this. For example, staff may note the main points described in each paragraph of the informed consent form and ask if the participant has questions or concerns about each point. Listen carefully to the questions or concerns expressed by the participant and discuss these thoroughly. Take as much time as needed to address each question and concern.

If the participant is illiterate, **an impartial witness must be present during the entire informed consent discussion**. The witness will be asked to sign and date the ICF to attest that the information in the consent form was accurately explained to, and apparently understood by, the participant, and that informed consent was freely given by the participant. The ICH GCP guideline identifies an “impartial” witness as a person who is independent of the study, who cannot be unfairly influenced by people involved with the study. Each site must specify its procedures for obtaining informed consent from illiterate persons in its SOP for obtaining informed consent. The SOP should define who may serve as an impartial witness to the informed consent process. It is recommended that each site seek IRB/EC review and approval of these procedures. Refer to the DAIDS Score Manual for additional information on impartial witnesses.

### 4.2.1.1. Assure That Informed Consent Is Obtained in A Setting Free of Coercion and Undue Influence

During the informed consent discussion, take care to not overstate the possible benefits of the amendment, nor to understate the risks. Also emphasize to the participant that medical care and other services routinely available from the clinic or hospital associated with the site will not be affected by their decision whether or not to take part in the study. Encourage the participant to take as much time as she needs — and to talk about her potential participation with others, if she chooses — before making a decision.

### 4.2.1.2. Confirm That the Participant Comprehends the Information

The participant must not be asked to agree to continue in the v5.0 portion of the trial or to sign the ICF, until she fully understands the amendment. Study staff are responsible for implementing procedures to ensure that each participant understands the risks, benefits and goals of the amendment study prior to signing the amended ICF, respectively, and undertaking any study procedures.

One approach to assessing comprehension is to use a “quiz” (either oral or written) or other assessment tool that participants complete as part of the consent process. Another approach is to use open-ended questions to ascertain participant understanding during the informed consent discussion. It is possible to incorporate a scoring system into these assessment tools and to re-review the contents of the informed consent until the potential participant can answer a certain percentage of the questions correctly. Table 4-1 includes a sample informed consent assessment tool that sites may choose to adapt for their local use. For sites that choose to adopt tools
such as those included in this section, detailed instructions for their use must be specified in the site SOP for obtaining informed consent.

Regardless of the method used to assess comprehension, if the assessment results indicate misunderstanding of certain aspects of the study, review those aspects again until the participant fully understands them. If after all possible efforts are exhausted, the participant is not able to demonstrate adequate understanding of the amendment, do not ask her to sign the ICF. Similarly, if the participant has concerns about possible adverse impacts if she were to take part in the study or indicates that she may have difficulty adhering to the study requirements, do not ask her to sign the ICF for the amendment.

4.2.1.3. Document the Process

The DAIDS Score Manual https://www.niaid.nih.gov/research/daids-score-manual including the section on Informed Consent of Participants provides detailed requirements and suggestions for documenting the informed consent process. https://www.niaid.nih.gov/sites/default/files/score-informed-consent.pdf. All requirements listed must be met. In order to meet some of the suggestions listed, site staff may consider the use of an informed consent “coversheet” similar to the example included in this section.

4.2.1.4. Continue the Informed Consent Process throughout the Study

Given the ongoing nature of informed consent, key elements of informed consent should also be reviewed at study follow-up visits. At these visits, study staff should review key elements of informed consent with the participant, focusing on the remainder of their study participation. For example, participants should be encouraged to ask questions as they arise and recognize that poor adherence to their study drug regimen will not affect their continued participation in the trial.

4.2.1.5. ICF Requirements for Protocol Amendments (including LoAs)

According to DAIDS policy (Protocol Registration Policy and Procedure Manual), the site’s IRB/EC is/are ultimately responsible for determining whether study participants need to be re-consented for a protocol amendment. The details of re-consent for a protocol amendment will be determined based on the extent and content of the amendment, and instructions will be provided to sites in this regard, after consultation with DAIDS.
<table>
<thead>
<tr>
<th>Date:</th>
<th>Participant ID:</th>
<th>Participant’s Response</th>
<th>Correct Answer</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>My participation in this research study is voluntary</td>
<td>☐ True ☐ False</td>
<td>☑ True</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>During the blinded part of the study, CAB LA was found to be safe and effective in preventing HIV infection in women.</td>
<td>☐ True ☐ False</td>
<td>☑ True</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>The purpose of the open-label extension is to learn more about women’s HIV prevention choices including during pregnancy and breastfeeding.</td>
<td>☐ True ☐ False</td>
<td>☑ True</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>This research study is part of the regular medical care offered here at [clinic name].</td>
<td>☐ True ☐ False</td>
<td>☑ True</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>The clinic will test my blood for HIV throughout the study.</td>
<td>☐ True ☐ False</td>
<td>☑ True</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>If I join this research study amendment, I must stay in the study for as long as the study staff says.</td>
<td>☐ True ☐ False</td>
<td>☑ True</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>If I choose to continue Cabotegravir injections in the second open-label extension and I later decide to stop injections, I can switch to TDF/FTC to cover the tail.</td>
<td>☐ True ☐ False</td>
<td>☑ True</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>My participation in the second open-label extension part of the study will be for 48 weeks (unless I decide to have pregnancy follow-up which will follow me for 48 weeks after birth).</td>
<td>☐ True ☐ False</td>
<td>☑ True</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>If I fall pregnant, I will be able to choose whether I want to continue taking Cabotegravir injections.</td>
<td>☐ True ☐ False</td>
<td>☑ True</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>If I choose to have my infant followed in the study, my infant will be monitored for 48 weeks after I give birth.</td>
<td>☐ True ☐ False</td>
<td>☑ True</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>There are no risks in continuing to take part in this research study.</td>
<td>☐ True ☐ False</td>
<td>☑ True</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>If I have questions between study visits, I need to write them down and bring them with me at my next appointment.</td>
<td>☐ True ☐ False</td>
<td>☑ True</td>
<td>*no, but it’s a good idea.</td>
</tr>
</tbody>
</table>
If you have a baby and you are in the pregnancy substudy and test positive for HIV we will refer you and your baby for treatment □ True □ False □ True □ False

Table 4-2: Sample Informed Consent Coversheet for HPTN 084 OLE 2*

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant name:</td>
<td></td>
</tr>
<tr>
<td>Date of informed consent discussion:</td>
<td></td>
</tr>
<tr>
<td>Start time of informed consent discussion</td>
<td></td>
</tr>
<tr>
<td>Version number/date of informed consent form used during informed consent process/discussion</td>
<td></td>
</tr>
<tr>
<td>Name of study staff person completing informed consent discussion (and this coversheet):</td>
<td></td>
</tr>
<tr>
<td>In what language was informed consent obtained?</td>
<td>[insert local language] (note whether this was written and/ or verbal)</td>
</tr>
<tr>
<td>Were all participant questions answered?</td>
<td>□ Yes □ No ⇒ Explain in Notes/Comments. □ NA (participant had no questions)</td>
</tr>
<tr>
<td>Did the participant accept a copy of the informed consent form (circle one option)?</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>End time of informed consent process/discussion:</td>
<td></td>
</tr>
<tr>
<td>Notes/Comments (not documented elsewhere):</td>
<td></td>
</tr>
</tbody>
</table>

(* May be adapted as needed for local use)
Table 4-3: Sample HPTN 084 Screening and Enrollment Log*

<table>
<thead>
<tr>
<th>Participant ID</th>
<th>Participant Name</th>
<th>Date Screened</th>
<th>Eligible</th>
<th>Date of Enrollment (if not enrolled, note N/A)</th>
<th>If not enrolled, specify reason (include all applicable codes)</th>
<th>Did Participant Enroll in OLE Y/N</th>
<th>Staff name/Initials</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>Y</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>Y</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>Y</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>Y</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>Y</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>Y</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>Y</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td>Y</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td>Y</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td>Y</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(*May be adapted as needed for local use. Note: There is no standard screen failure code list.)
Section 5. Study Procedures Overview

5.1 Overview of Section 5

This section provides a brief overview of requirements and procedures to be conducted during study implementation of Protocol V4.0 and Protocol V5.0.

Additional procedure-specific details can be found in the HPTN 084 Protocol version 4.0 or version 5.0 (as is appropriate for the site) and relevant SSP manual sections (e.g. clinical, laboratory, data management procedures, etc.).

5.2 Study Overview

OLE 1 and OLE2 consist of the below Steps.
1) Step 4a- Procedures for Participants Initially Randomized to TDF/FTC Who Elect to Move to OL CAB LA with Optional Oral Lead-in first
2) Step 4b- Procedures for Participants Initiating or Re-starting CAB LA without the Optional Oral Lead-in; the Initial Dose Visit
3) Step 4c- Procedures for Participants on Maintenance Doses of CAB LA or TDF/FTC
4) Step 4d- Procedures for Pregnant/Breastfeeding Participants and their Infants.
5) Step 5- Procedures for Participants Taking OL TDF/FTC for 48 Weeks after Premature CAB LA discontinuation
6) Step 6- Procedures for Participants on Maintenance Doses of CAB LA, weeks 49-96

5.3 Study Visits

Protocol-required visits: Steps 4, 5 and 6 have protocol-required study visits, which are described in Appendix VIII of the Protocol: Procedures for Offering Open Label (OL) Cabotegravir- The Next Part of HPTN 084

For each required study visit, there is an allowable visit window specifying on which study days (Day 0) the visit is "allowed" to be completed. The allowable visit windows are contiguous from visit to visit, and do not overlap. Within each allowable visit window, there is a target visit window. These windows are outlined in Section 13 of the SSP. Efforts should be made to conduct study visits within the target visit window and may be conducted over multiple days within the target visit window if necessary (see below regarding Split visits); however, if it is not possible to complete the required visit
within the target visit window, the visit may be completed within the allowable visit window.

**Interim visits:**

Interim contacts and visits may take place between regularly-scheduled visits. These contacts/visits may be done at participant request (e.g., to receive further counseling or clarify any questions) or as deemed necessary by the IoR or designee at any time during the study (e.g., to follow-up on an adverse event). Procedures to be performed during these contacts/visits will be specific to the reason for the additional PPT interaction.

**Split visits:**

A split visit is defined as visits conducted over multiple days. Ideally, all procedures specified by the protocol to be performed at a visit will be completed at a single visit on a single day. In the event that all required procedures cannot be completed on a single day (e.g., because the participant must leave the study site before all required procedures are performed), the remaining procedures may be completed on subsequent day(s) within the allowable target visit window. When this occurs, the visit is considered a split visit. All case report forms completed for a split visit are assigned the same visit code (even though the dates recorded on the case report forms may be different).

Refer to Section 11.3.2 (HIV Testing) for considerations for HIV testing and split visits.

**Missed visits:**

Efforts should be made to contact any participant who does not attend a protocol-required visit prior to the end of the target window period. A Missed Visit e-CRF should be completed to document the missed visit at the end of the allowable window period.

In general, when a visit is missed altogether and a participant reports to the site in the interim or for the next scheduled visit, the procedures from the missed visit that are not also required for the current visit should be performed. In the case of a missed injection visit, the CMC should be contacted for guidance regarding whether the injection should be given at another visit (and before the next scheduled injection).

Because of the nature of study procedures, all visits must be completed at the study clinic only. Sites should contact the CMC regarding any questions about procedures performed outside of the study clinic if the situation arises (e.g., participant is incapacitated and cannot report to the clinic). Details regarding the CMC are described in SSP manual Section 9.
5.3.1 Study Visit Procedures

- Refer to Protocol Appendix VIII for the Schedule of Evaluations.

- Participants may withdraw from the study for any reason at any time. IoRs may, in consultation with the HPTN 084 CMC, withdraw participants before their scheduled termination visit to protect their safety, and/or if participants are unable or unwilling to comply with study procedures. The CMC also should be consulted regarding procedures to be performed in the case of early termination (e.g., final HIV testing, etc.), if a participant is willing to undergo such procedures.

- In general, participants should not be withdrawn from the study except in the case of a) explicit withdrawal of consent by the participant; b) death; or c) extreme/unusual circumstances to protect participant safety. Any such safety-related participant terminations should only be implemented after consultation with the Protocol Chair, Division of AIDS (DAIDS) Medical Officer, Statistical and Data Management Center (SDMC) Protocol Statistician, representatives from the Laboratory Center (LC), the Leadership and Operations Center (LOC) Clinical Research Manager (CRM), and others. Consultation is conducted through the CMC alias.

5.4 Participant Transfers

During the course of the study, participants may leave the area where they enrolled. If they move to the vicinity of another HPTN 084 study site, they should be encouraged to transfer to that study site and continue study participation. To accomplish this, study staff at both sites will complete the participant transfer process. The same process should be followed for temporary or permanent transfers.

Upon identifying the need for a participant transfer to another site, the transferring site is responsible for notifying the HPTN LOC, HPTN SDMC, the HPTN (LC) and the DAIDS Protocol Pharmacist (see Section 1.2 of the SSP manual for contact information). The transferring site is responsible for notifying the site to which the participant wishes to transfer (the “receiving site”). After the logistical details of the transfer have been agreed upon, the following steps will be completed:

- The transferring site will explain the transfer arrangements to the participant and obtain written permission for the release of information that will authorize the transfer of his study records to the receiving site.

- Both the transferring and receiving sites should follow the instructions for participant transfers within Medidata Rave and in Section 13 of the SSP manual.

- The transferring site will ship **certified copies** of all of the participant’s study records to the receiving site via courier or overnight mail service. The transferring site will track the shipment and the receiving site will confirm receipt of the shipment with the HPTN LOC, SDMC, and the transferring site. The receiving site
will verify receipt of said materials with the transferring site. At this point in time, follow-up of the participant becomes the receiving site’s responsibility.

- The transferring site will complete the Participant Transfer e-CRF.
- The transferring site will email the HPTN LC representative confirming transfer to the new site. The transferring site will retain archived samples for the participant unless otherwise instructed by the HPTN LC.
- Study drug supply should be discussed with the DAIDS Protocol Pharmacist in cases of participant transfer.
- The receiving site will establish contact with the participant, obtain a copy of the original screening and enrollment consent (and any others), along with his/her informed consent to continue in the study (have the participant sign a consent at the receiving site).
- Upon receipt of the Participant Transfer form and confirmation that the transferring IoR has signed off on the participant’s eCRF casebook, the SDMC will re-map the participant’s ID number (PTID) and any e-CRFs in the study database to reflect the change in study site follow-up responsibility. This will ensure that future questions and/or QCs will be sent to the appropriate site. The participant’s original ID number, treatment-arm assignment, and follow-up visit schedule will remain unchanged.
- The receiving site will complete a Participant Receipt eCRF to complete the transfer process.
- If the participant returns to the clinic where she/he enrolled, the same process should be followed to complete the transfer process. However, the certified copies to be sent to the enrolling site will only include those applicable to the visits conducted at the non-enrolling site. This is because the original records are at the enrolling site and the only records needed would be those for visits conducted at the non-enrolling site.

Note: If it is unlikely that the participant can return to the clinic where she enrolled and she is not close to another HPTN 084 clinic to transfer, the site should complete Missed Visit Forms for each visit the participant does not complete in case the participant is later able to rejoin the study. In cases where the site strongly suspects that the participant will never return to the study, the CMC should be contacted to discuss possible termination.

5.5 Protocol-Required and Interim Visits at Sites Other Than Where Participants Enrolled

During the course of the study, while it is likely rare, it may happen that a participant is temporarily (for a few days, or a week or more) in another location where there is an HPTN 084 clinic other than the one in which they originally enrolled (their “home clinic”). If the participant is in this temporary location during a protocol-required visit or when she requires medical attention, these protocol-required or interim visits may be conducted at the alternative clinic (“temporary clinic”) if both sites have an SOP in place to cover this situation. In addition, the local IRB/EC must have agreed to the procedures outlined in the site-specific SOP, which must cover the following areas:

- Informed consent will need to be re-administered at the temporary clinic.
- A method to transfer study information from the temporary to the home clinic.
- A standard method of communication between the two sites prior to the initiation of any procedure, for clinical information, final decision-making about primary care, and determination of the duration of time during which care and visits will be conducted at the temporary clinic.
- Procedures for the management of drug dispensation and accountability should be developed with the HPTN 084 Protocol Pharmacist.
Section 6. Visit Checklists

6.1 Overview of Section 6

This section provides a template checklist for each of the required study visits. The use of visit checklists is optional but is strongly recommended.

6.2 Visit Checklists as Source Documentation

Checklists are convenient tools, which may serve as source documentation if designed and completed appropriately. These checklists alone may not be sufficient for documenting all procedures but can be used to indicate that the procedure was completed and by whom. Additional information could be documented on the checklist comment sections and/or chart notes. It is up to each site to determine whether and how to use the visit checklists as source documentation.

It also should be noted that the visit checklists outlined below depict the visit schedule for a participant completing all protocol-specified study visits. In what is hoped to be a rare occurrence, there may be cases where a participant may have a modified study visit; in which case, any modifications to the procedures could be noted in in the comment section of the checklists.

6.3 Use of the Checklists

One checklist should be used for each participant. Checklists are commonly used for following the participant through a study visit; as activities are completed they are checked off the list. The checklists are designed so that there is one for each visit. Sites may add steps/activities/reminders to improve protocol adherence/implementation. Sites may also modify the order of procedures to maximize the efficiency with the following exceptions/considerations:

- Informed consent for the currently IRB-approved protocol at a given site must be obtained before any OLE study procedures are performed.
- Behavioral assessment and acceptability assessments must be administered prior to the delivery of HIV and adherence counseling.
- It is recommended that procedures for determining eligibility for continued product use (for example, HIV testing) be conducted early in the visit to ensure sufficient time is allowed for product to be prepared for dispensing.
When using the checklists, it is important to confirm that every item is completed - this is done by initialing and dating each step of the checklist (to show that the step was completed), or by entering ND (not done), or NA (not applicable) if a procedure is not performed. See checklist instructions for further information.

Source documentation for procedures will need to be identified for some items that are in the protocol, but not on captured on the Case Report Forms (CRFs).

A good example of this is locator information. At each visit, the protocol requires that locator information is confirmed and, if necessary, updated. Some of the ways that the “act” of confirming or updating can be documented at each visit include writing a note in the participant's chart, creating a locator information log, or having a review/revision log attached to the locator information itself. The checklist cannot serve as the source for the confirmation of locator information unless it is revised to show who confirmed the information, if changes were made to the form.

6.4 Visit Checklist Templates
**INSTRUCTIONS:** Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

**Step 4c: Procedures for participants on maintenance doses of CAB LA or TDF/FTC (Weeks 0, 8, 16, 24, 32, 40 and 48)**

*Circle applicable visit week*

<table>
<thead>
<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
<th>Comments</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Confirm participant identity and PTID</td>
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<tr>
<td></td>
<td></td>
<td>Review/update locator information</td>
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<td>Informed consent for those not part of Steps 4a or 4b</td>
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<td></td>
<td>Conduct Acceptability Assessment (Weeks 0, 24 and 48)</td>
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<td></td>
<td></td>
<td>Conduct Behavioral Assessment</td>
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<td></td>
<td>Provide HIV pre-test / prevention counseling</td>
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<td></td>
<td>Offer condoms</td>
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<td></td>
<td></td>
<td>Medical history (including concomitant medications, targeted physical exam (including pulse, temperature, BP, weight and BMI calculated at each visit)</td>
<td></td>
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</tbody>
</table>
**Step 4c: Procedures for participants on maintenance doses of CAB LA or TDF/FTC (Weeks 0, 8, 16, 24, 32, 40 and 48)**

*Circle applicable visit week*

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<thead>
<tr>
<th>Initial/date</th>
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<th>Procedures</th>
<th>Comments</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Collect blood and test for:</td>
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<td></td>
<td></td>
<td>• HIV testing</td>
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<td></td>
<td>• FDA-cleared HIV rapid test</td>
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<td></td>
<td>• Laboratory based, instrument HIV Immunoassay (HIV antigen and antibody)</td>
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<td>• HIV Viral Load (detection limit &lt;50copies/mL)</td>
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<td></td>
<td>• Pregnancy testing (if not done via urine)</td>
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<td></td>
<td></td>
<td>• CBC with differential at Week 0 if not done in Steps 4a or b; otherwise, only at Weeks 24 and 48)</td>
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<tr>
<td></td>
<td></td>
<td>• Chemistry panel (Albumin, BUN/urea, creatinine) at Week 0 if not done in Steps 4a or b; otherwise, only at Weeks 24 and 48)</td>
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<td></td>
<td></td>
<td>• LFTs (AST, ALT, total bilirubin) (Weeks 0, 24 and 48)</td>
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<td></td>
<td></td>
<td>• Fasting lipid profile (Week 48 only) total cholesterol, HDL, triglycerides, and LDL either calculated or measured</td>
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<td>• Syphilis testing (Weeks 0, 24 and 48)</td>
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<td>Collect vaginal swab (Weeks 0, 24 and 48) and test for:</td>
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<td></td>
<td></td>
<td>• GC/CT (this may be done using urine instead)</td>
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<td>• TV testing</td>
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<td></td>
<td>Collect urine and test for:</td>
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<td></td>
<td></td>
<td>• Pregnancy testing (if site using urine for Pregnancy testing)</td>
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<td></td>
<td></td>
<td>• GC/CT testing (if site using urine for this) (Weeks 0, 24 and 48) for urinalysis (protein, glucose) Weeks 0, 24 and 48)</td>
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</tr>
</tbody>
</table>
INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

Step 4c: Procedures for participants on maintenance doses of CAB LA or TDF/FTC (Weeks 0, 8, 16, 24, 32, 40 and 48)

Circle applicable visit week

<table>
<thead>
<tr>
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<th>Procedures</th>
<th>Comments</th>
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<tbody>
<tr>
<td>_____</td>
<td></td>
<td>Plasma storage</td>
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<td>_____</td>
<td></td>
<td>DBS storage</td>
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<td>_____</td>
<td></td>
<td>Provide HIV post-test counseling</td>
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<td>_____</td>
<td></td>
<td>Provide Adherence counseling</td>
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<td>_____</td>
<td></td>
<td>Dispense/provide study product</td>
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<tr>
<td>_____</td>
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<td>Provide site contact information and instructions to report symptoms and/or clarify any questions</td>
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<td>_____</td>
<td></td>
<td>Schedule next study visit, if applicable</td>
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<td>_____</td>
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<td>Provide participant reimbursement, if applicable</td>
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</tbody>
</table>

Comments:
________________________________________________________________________________________
________________________________________________________________________________________
________________________________________________________________________________________
**INSTRUCTIONS:** Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

### Procedures listed in Appendix 4d: Schedule of Evaluations for Pregnant/Breastfeeding Participants on CAB LA

**Visits:**

*Enter applicable visit week__________*

<table>
<thead>
<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>___</td>
<td>☐</td>
<td>Confirm participant identity and PTID</td>
<td></td>
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<td>___</td>
<td>☐</td>
<td>Review/update locator information, except at delivery and post-partum Weeks 2pp and 4pp</td>
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<tr>
<td>___</td>
<td>☐</td>
<td>Informed Consent, as is appropriate</td>
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<td>___</td>
<td>☐</td>
<td>Acceptability Assessment (Weeks 0, 12, 32 and Post-partum Weeks 24pp and 48pp)</td>
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<tr>
<td>___</td>
<td>☐</td>
<td>Conduct Behavioral Assessment (all visits except Delivery and Post-partum Week 2pp and Week 4pp)</td>
<td></td>
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<tr>
<td>___</td>
<td>☐</td>
<td>HIV pre-test/ prevention counseling (all visits except Delivery and Post-partum Week 2pp and Week 4pp)</td>
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<td>___</td>
<td>☐</td>
<td>Offer condoms (all visits except Delivery, Post-partum Week 2pp and Week 4pp)</td>
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<td>☐</td>
<td>Medical history, concomitant medications (including folate intake) (all visits except Delivery, Post-partum Week 2pp and Week 4pp)</td>
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<td>___</td>
<td>☐</td>
<td>Targeted physical exam including antenatal assessment per SOC (all visits during pregnancy; only Post-partum Weeks 8pp and 48pp)</td>
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<tr>
<td>___</td>
<td>☐</td>
<td>ISR assessment for PPTs taking CAB LA at Weeks 4, 12, 20, 28, 36 and beginning at Post-partum Week 8pp and all visits up to and including Week 48pp</td>
<td></td>
</tr>
</tbody>
</table>
**INSTRUCTIONS:** Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

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<th>Initial/date</th>
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<th>Procedures</th>
<th>Comments</th>
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<tr>
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<td>Ultrasound or refer for ultrasound (Ideally the ultrasound should be completed by Week 12)</td>
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<td>Collect blood and test for:</td>
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<td>☐</td>
<td>- HIV testing</td>
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<td>☐</td>
<td>- FDA-cleared HIV rapid test</td>
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<td>☐</td>
<td>- Laboratory based, instrument HIV Immunoassay (HIV antigen and antibody)</td>
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<td>- HIV Viral Load (detection limit &lt;50 copies/mL)</td>
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<td>☐</td>
<td>- Pregnancy testing (if not done via urine; beginning at Post-partum Week 8pp and all visits up to and including Week 48pp)</td>
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<td>☐</td>
<td>- CBC with differential at Week 0, 24 and 36 during pregnancy; then at Post-partum Week 8pp and 48pp</td>
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<td>☐</td>
<td>- Chemistry panel (Albumin, BUN/urea, creatinine) at Week 0, 24 and 36 during pregnancy; then at Post-partum Week 8pp and 48pp</td>
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<td></td>
<td>☐</td>
<td>- LFTs (AST, ALT, total bilirubin) at Week 0, 24 and 36 during pregnancy; then at Post-partum Week 8pp and 48pp</td>
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<tr>
<td></td>
<td>☐</td>
<td>- Syphilis testing at Week 0 and 24 during pregnancy; then at Post-partum Week 8pp and 48pp</td>
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</tbody>
</table>
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### Procedures listed in Appendix 4d: Schedule of Evaluations for Pregnant/Breastfeeding Participants on CAB LA

**Visits:**

Enter applicable visit week __________

<table>
<thead>
<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
<th>Comments</th>
</tr>
</thead>
</table>
| ____         | ☐         | Collect urine and conduct:  
• Pregnancy testing (if not done via blood; beginning at Post-partum Week 8pp and all visits up to and including Week 48pp)  
• GC/CT testing (if site using urine for this at Week 0 and 24 during pregnancy; then at Post-partum Week 8pp and 48pp  
• Urinalysis at Week 0, 24 and 36 during pregnancy; then at Post-partum Week 8pp and 48pp | |
| ____         | ☐         | Collect vaginal swab at Week 0 and 24 during pregnancy; then at Post-partum Week 8pp and 48pp and conduct:  
• GC/CT (this may be done using urine instead)  
• TV testing | |
| ____         | ☐         | Plasma storage | |
| ____         | ☐         | DBS Storage only for TDF/FCT PPTs (all antenatal visits; at Delivery and Post-partum Weeks 4pp, 8pp, 16pp, 24pp) | |
| ____         | ☐         | Adherence counseling every visit except Delivery, Post-partum Week 2 pp and Week 4pp | |
| ____         | ☐         | Contraceptive counseling beginning at Post-partum Week 8pp and all visits up to and including Week 48pp | |
| ____         | ☐         | Dispense/ administer study product as appropriate (Weeks 0, 8, 16, 24, 32, 40 and Post-partum Weeks 8pp, 16pp, 24pp, 32pp, 40pp and 48pp) | |
**INSTRUCTIONS:** Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

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<table>
<thead>
<tr>
<th>Participant ID</th>
<th>Visit Date</th>
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**Procedures listed in Appendix 4d: Schedule of Evaluations for Pregnant/Breastfeeding Participants on CAB LA**

**Visits:**

Enter applicable visit week _________

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<thead>
<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
<th>Comments</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Breast milk collection Post-partum Weeks 2pp, 4pp, 8pp, 16pp, 24pp (Breast milk collection does not need to be performed if the mother is not breastfeeding or producing milk)</td>
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<tr>
<td></td>
<td></td>
<td>Breast milk storage at Post-partum Weeks 2pp, 4pp, 8pp, 16pp, 24pp</td>
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<td></td>
<td></td>
<td>Pregnancy outcome assessment including abbreviated infant exam (Post-partum weeks 8 and 48)</td>
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<td>Infant feeding history (Post-partum weeks 8, 16 and 24)</td>
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<td>Infant AE assessment (Delivery and all Post-partum visits)</td>
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<td>Cord blood collection at Delivery</td>
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<td></td>
<td></td>
<td>Infant blood collection at Delivery and all subsequent visits</td>
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<td></td>
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<td>Infant HIV testing, if the mother has one or more reactive/positive HIV results (Delivery and all subsequent visits)</td>
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<td></td>
<td></td>
<td>Cord blood storage (Delivery)</td>
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<td></td>
<td></td>
<td>Infant DBS storage (Delivery and all subsequent visits)</td>
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<tr>
<td></td>
<td></td>
<td>Infant plasma storage (Delivery and all subsequent visits)</td>
<td></td>
</tr>
</tbody>
</table>
INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

<table>
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<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
<th>Comments</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Provide site contact information and instructions to report symptoms and/or clarify any questions</td>
<td></td>
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<td></td>
<td></td>
<td>Schedule next study visit, if applicable</td>
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<td>Provide participant reimbursement, if applicable</td>
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</tr>
</tbody>
</table>

Comments: ______________________________________________________

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Procedures listed in Appendix 4d: Schedule of Evaluations for Pregnant/Breastfeeding Participants on CAB LA

Visits: Enter applicable visit week __________
### INSTRUCTIONS:
Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

### Step 5 Visits:

**Weeks in Study Step 5 Day 0 (no later than 8 weeks after last injection), Weeks 12, 24, 36 and 48**

*Circle applicable visit week*

<table>
<thead>
<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Confirm participant identity and PTID</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Review/update locator information</td>
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<tr>
<td></td>
<td></td>
<td>Acceptability Assessment (weeks 0 and 48)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Behavioral Assessment (if done in last 4 weeks skip day 0 and start at week 12; otherwise weeks 0, 24 and 48)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>HIV prevention counseling</td>
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<td></td>
<td></td>
<td>Offer condoms</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medical history, conmeds, targeted physical exam with pulse, BP, weight and BMI calculated at each visit</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Collect blood and test for:</td>
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<td></td>
<td></td>
<td>• HIV testing</td>
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<td></td>
<td></td>
<td>• FDA-cleared HIV rapid test</td>
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<td></td>
<td></td>
<td>• Laboratory based, instrument HIV Immunoassay (HIV antigen and antibody)</td>
<td></td>
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<td></td>
<td></td>
<td>• HIV Viral Load (detection limit &lt;50 copies/mL)</td>
<td></td>
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<td></td>
<td></td>
<td>• Pregnancy (can be urine, plasma or serum)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Chemistry (Albumin, BUN/Urea, creatinine-skip day 0 if testing was in last 3 months; only perform at weeks 0, 24 and 48)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Liver function testing at weeks 0 and 48 only (AST, ALT, total bilirubin)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Syphilis testing weeks 0, 24, and 48</td>
<td></td>
</tr>
</tbody>
</table>
**INSTRUCTIONS**: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

<table>
<thead>
<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Collect urine and conduct:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pregnancy testing (if site using urine for Pregnancy testing)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• GC/CT testing (if site using urine for this) (Weeks 0, 24 and 48)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Collect vaginal swab (weeks 0, 24 and 48) and conduct:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• GC/CT (this may be done using urine instead)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• TV testing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma storage</td>
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<tr>
<td></td>
<td></td>
<td>DBS storage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Provide HIV post-test counseling</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adherence counseling</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pill dispensation (not at week 48)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Provide site contact information and instructions to report symptoms and/or clarify any questions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Schedule next study visit, if applicable (not at week 48)</td>
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<td></td>
<td></td>
<td>Provide participant reimbursement, if applicable</td>
</tr>
</tbody>
</table>

Comments:__________________________________________________________________________________________________________
__________________________________________________________________________________________________________

**Step 5 Visits:**

**Weeks in Study Step 5 Day 0 (no later than 8 weeks after last injection), Weeks 12, 24, 36 and 48**

_Circle applicable visit week_

---

**Participant ID**

**Visit Date**

---

HPTN 084 SSP Manual  
Version 5.0  
23 February 2024  
Section 6: Visit Checklists  
Page 6-12 of 6-16
**INSTRUCTIONS:** Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

### Step 6 Visits:
**Weeks in Study Step 6**
Weeks 56, 64, 72, 80, 88, 96, 104*, 112*)

*PPTs who do not have local access to CAB LA the PPT will be offered up to two additional injections on the study (Weeks 104 and 112).

*Circle applicable visit week*

<table>
<thead>
<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Confirm participant identity and PTID</td>
<td></td>
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<td></td>
<td></td>
<td>Review/update locator information</td>
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<td></td>
<td></td>
<td>Informed Consent (Weeks 0 and 104)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Acceptability Assessment (Weeks 72, 96, 112)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Behavioral Assessment (Weeks 72, 96, 104, 112)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Provide HIV pre-test/prevention counseling</td>
<td></td>
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<td></td>
<td></td>
<td>Offer condoms per local SOC</td>
<td></td>
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<td></td>
<td></td>
<td>Medical history, concomitant medications, targeted physical exam (with pulse, BP, weight and BMI calculated at each visit)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Collect blood and test for:</td>
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<tr>
<td></td>
<td></td>
<td>- HIV testing</td>
<td></td>
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<td></td>
<td></td>
<td>- FDA-cleared HIV rapid test</td>
<td></td>
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<td></td>
<td></td>
<td>- Laboratory based, instrument HIV Immunoassay (HIV antigen and antibody)</td>
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<td></td>
<td>- HIV Viral Load (detection limit &lt;50 copies/mL)</td>
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<td></td>
<td></td>
<td>- Pregnancy, if not done via urine</td>
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<td></td>
<td></td>
<td>- Chemistry (Weeks 96, 112)</td>
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<td></td>
<td></td>
<td>- Liver function testing (Weeks 96, 112)</td>
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<tr>
<td></td>
<td></td>
<td>- Syphilis testing (Weeks 72, 96, 112)</td>
<td></td>
</tr>
</tbody>
</table>
INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed.
If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

### Step 6
#### Visits:
**Weeks in Study Step 6**
Weeks 56, 64, 72, 80, 88, 96, 104*, 112*)

*PPTs who do not have local access to CAB LA the PPT will be offered up to two additional injections on the study (Weeks 104 and 112).

Circle applicable visit week

<table>
<thead>
<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>☐</strong></td>
<td>Collect vaginal swab (Weeks 72, 96, 112) and test for:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• GC/CT (this may be done using urine instead)</td>
<td></td>
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<td></td>
<td></td>
<td>• TV testing</td>
<td></td>
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<tr>
<td></td>
<td><strong>☐</strong></td>
<td>Collect urine and test for:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pregnancy testing (if site using urine for Pregnancy testing)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• GC/CT testing (if site using urine for this) (Weeks 72, 96, 112)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>☐</strong></td>
<td>Plasma storage</td>
<td></td>
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<td></td>
<td><strong>☐</strong></td>
<td>DBS storage</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>☐</strong></td>
<td>Provide HIV post-test counseling</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>☐</strong></td>
<td>Adherence counseling</td>
<td></td>
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<tr>
<td></td>
<td><strong>☐</strong></td>
<td>Administer CAB LA</td>
<td></td>
</tr>
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<td></td>
<td><strong>☐</strong></td>
<td>Provide site contact information and instructions to report symptoms and/or clarify any questions</td>
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<tr>
<td></td>
<td><strong>☐</strong></td>
<td>Schedule next study visit, if applicable</td>
<td></td>
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<tr>
<td></td>
<td><strong>☐</strong></td>
<td>Provide participant reimbursement, if applicable</td>
<td></td>
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</tbody>
</table>

Comments:
### Instructions

Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

### Schedule of additional procedures for women with reactive/positive HIV tests (HIV confirmation visit)

**Study visit week**

<table>
<thead>
<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>____</td>
<td>☐</td>
<td>Confirm participant identity and PTID</td>
<td></td>
</tr>
<tr>
<td>____</td>
<td>☐</td>
<td>Review/update locator information</td>
<td></td>
</tr>
</tbody>
</table>
| ____         | ☐         | Date of first HIV positive test/ [084HIV@hptn.org](mailto:084HIV@hptn.org)
email alias list contacted: ________ |          |
| ____         | ☐         | Confirm prior HIV results |          |
| ____         | ☐         | Provide HIV pre-test counseling |          |
| ____         | ☐         | Offer condoms |          |
| ____         | ☐         | Medical history, conmeds, physical exam (with pulse, BP, weight and BMI calculated) |          |
| ____         | ☐         | Collect blood and test for: |          |
| | | - HIV testing |          |
| | | o FDA-cleared HIV rapid test, |          |
| | | o Laboratory based, instrument HIV Immunoassay (HIV antigen and antibody) |          |
| | | o HIV viral load testing (must be 50 copies/ml or lower) |          |
| | | - CD4 cell count |          |
| | | - ART resistance (if able to conduct for local mgmt.) |          |
| | | - Chemistry (Albumin, BUN/urea, creatinine) |          |
| | | - LFTs (AST, ALT, total bilirubin) |          |
INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

Schedule of additional procedures for women with reactive/postive HIV tests (HIV confirmation visit)

<table>
<thead>
<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>____</td>
<td>☐</td>
<td>Plasma storage</td>
<td></td>
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<td>____</td>
<td>☐</td>
<td>DBS storage</td>
<td></td>
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<tr>
<td>____</td>
<td>☐</td>
<td>Provide HIV post-test counseling, as is appropriate</td>
<td></td>
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<tr>
<td>____</td>
<td>☐</td>
<td>Provide site contact information and instructions to report symptoms and/or clarify any questions</td>
<td></td>
</tr>
<tr>
<td>____</td>
<td>☐</td>
<td>Provide participant reimbursement, if applicable</td>
<td></td>
</tr>
<tr>
<td>____</td>
<td>☐</td>
<td>Link to care and confirm when the participant has achieved viral suppression on ART. Document the ART regimen in the conmeds form. Terminate from the study once suppression is achieved.</td>
<td></td>
</tr>
</tbody>
</table>

Notes for Procedures for Enrolled Participants who Seroconvert: Please refer to Appendix II of the HPTN 084 Protocol. For any questions related to the requirements for suspected or confirmed HIV infection or clinical management questions, email 084HIV@hptn.org and CMC at 084cmc@hptn.org

Comments: ____________________________________________

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Section 7. Participant Retention

7.1 Overview of Section 7

This section presents information related to participant retention definitions, requirements, and procedures. Once a participant consents for HPTN 084 Protocol v4.0 or v5.0, the study site will make every effort to retain her for the full study in order to minimize possible bias associated with loss-to-follow-up (LTFU). Successful retention begins with inclusion of participants who fully understand what study participation involves and collection of exhaustive locator information from each study participant. It also relies on development and implementation of a comprehensive retention plan.

7.2 Retention Definition

The term “retention” refers, in general, to participant attendance and completion of study visits/procedures as specified in the protocol. Participants who do not complete a particular scheduled visit within the allowable visit window, but do complete the next scheduled visit, will not be considered retained for the missed visit, but will be considered retained for the attended visit. Thus, retention rates can fluctuate over time and across study visits. Importantly, retention can be improved by ensuring that any participants who miss a visit return for the next scheduled visit.

7.3 Retention Targets

Ideally, each site should strive for 100% retention of those enrolled in the currently approved protocol. Routine retention reports for all sites are available on the Atlas portal maintained by the HPTN Statistics and Data Management Center (SDMC). The HPTN SDMC will also generate a final end-of-study retention rate for each site at study end. See SSP Section 15 for more information about Retention Reports.

7.4 Retention Plan

Sites are expected to retain eligible participants with no more than 5% annual loss to follow-up. A new SOP is not required for OLE 1 or 2, but sites may wish to modify their existing plan if necessary.
7.5 Participant Tracking Database

Due to the potential complexities that may be encountered when scheduling and completing visits, it is recommended that sites use a participant visit tracking sheet or database. This will most likely be a separate database created at your site for the OLE. Any participant tracking database that is developed is to be used for tracking purposes only. The database may not be used to record source data or to generate source documents unless specified in the site SOP for Source Documentation. All information entered into the database must be based on other source documents contained in participant study charts.

7.6 Retention Strategies

Some general strategies for maximizing participant retention are presented below:

- Dedicate adequate staff time and effort to retention efforts.
- Discuss the length of the study (48 weeks typically) and whether she will be able to meet the visit schedule during the consent process.
- Treat every participant with respect. Keep information confidential.
- Make visits as pleasant and short as possible. Do not keep participants waiting unnecessarily.
- Emphasize the value of the participant involvement in the study during the informed consent process and at subsequently visits. When participants complete scheduled visits, acknowledge and compliment their commitment, time, and effort devoted to the study.
- Whenever possible, make appointments to fit participant needs, such as offering clinic hours during the evening, weekend, or early in the morning.
- Work with Community Advisory Board members and key stakeholders to identify the most applicable contact and retention strategies for the local study population, including the type and amount of participant incentives.
- Keep participants, Community Advisory Board members, and key stakeholders up-to-date on study progress to foster a sense of partnership and ownership of the study (through the use of study newsletters, or quarterly meetings, for example).
- Inform local service providers who interact with the study population about the study and address any questions or concerns they have. Encourage them to express their support for the study and inform potential participants and key stakeholders about the study.
• Use a Tracking Database to easily identify when participant visit schedules. Establish routine mechanisms to remind both study staff and participants of upcoming scheduled visits.

• Always schedule the participant’s’ next visit before she completes the current contact or visit. During clinic visits give the participant an appointment card with the next scheduled visit date and time noted.

• Prepare a calendar of scheduled visits or input scheduled visit dates on participant’s cell phone for each enrolled participant, based on the enrollment date (or offer a planner/calendar as an incentive and note all study appointments). Note the dates of all scheduled visits in the participant’s file for easy reference.

• Consider scheduling study visits for participants at the beginning of the allowable visit window (see Section 13 of the SSP for allowable visit windows) to allow maximum time for re-contact and rescheduling if needed.

• Pay close attention to the allowable visit window and prioritize retention efforts for participants nearing the end of the window. Organize daily caseloads and work assignments based on these priorities.

• Follow-up on missed appointments with an attempt to contact and reschedule as soon as possible (preferably on the same day). Continue these efforts per the local retention plan until contact is made.

• Keep locator information up-to-date and maintain thorough documentation of all efforts to contact the participant. Keep all this information in an organized manner, so that different staff members can easily review the information and contribute to contact efforts when necessary.

• Use all information collected on the participant’s locator form while being careful to protect the participant’s privacy. Even if a locator source is not useful/ successful on one occasion, try it again later unless it is proven to be incorrect.

• Use all available contact methods the participant agreed to (e.g., phone, mail, home visits, street outreach, cell phone texts, e-mail, and social media). Also make use of other available locator information sources, such as phone and post office directories and other public registries.

• Post outreach staff at other local service organizations used by the study population, such as health care clinics. Be sure to maintain participant confidentiality in these public situations.

• Attempt contact with the participant at different times during the day and the week, including evenings and weekends.
• Assist participants in making transportation arrangements if necessary. This may be done with mass transit vouchers, site-owned vehicles, or assistance with other modes of transportation.

• If a participant dies during the study (even if that participant is LTFU), every effort should be made to locate copies of official paperwork if it exists (e.g., a death certificate) to verify this information and ascertain the cause of death.

7.7 Participant Withdrawal

Regardless of the participant retention methods described above, participants may voluntarily withdraw from the study for any reason at any time.

The Investigator of Record (IoR) or designee also may withdraw participants from the study in order to protect their safety or if they are unwilling or unable to comply with required study procedures after consultation with the Protocol Chair, Division of AIDS (DAIDS) Medical Officer, SDMC Protocol Statistician, and the HPTN Leadership and Operations Center (LOC) Clinical Research Managers (CRMs). In general, participants should not be withdrawn from the study except in the case of a) withdrawal of consent b) death; or c) extreme/unusual circumstances to protect participant safety. Any such safety-related participant terminations should only be implemented after consultation with the Protocol Chair, Division of AIDS (DAIDS) Medical Officer, Statistical and Data Management Center (SDMC) Protocol Statistician, representatives from the Laboratory Center (LC), the Leadership and Operations Center (LOC) Clinical Research Manager (CRM), and others. Consultation is conducted through the CMC alias.

Participants may be withdrawn if the study sponsor, government or regulatory authorities, or site IRBs/Ethics Committees terminate the study prior to its planned end date.

Every reasonable effort will be made to complete a final evaluation of participants who terminate from the study early, and study staff will record the reason(s) for all withdrawals from the study in participants’ study records. In such cases, the IoR or designee must contact the Clinical Management Committee (CMC) for guidance regarding final evaluation procedures.
Section 8. Study Product Considerations

8.1 Overview of Section 8
This section provides instructions to the Pharmacist of Record (PoR) and the study staff for the proper management of study products used in HPTN 084 including ordering, storage, randomization, dispensing, transport, administration, and record keeping of pharmacist-prepared, participant-specific study products. In addition to these specifications, the participating clinical research sites must adhere to the Pharmacy Guidelines and Instructions for DAIDS Clinical Trial Networks, and the site Pharmacy Establishment Plan approved by the DAIDS Pharmaceutical Affairs Branch (PAB). These specifications and the protocol take precedence over this document.

8.1.1 Chain of Custody
In addition to the requirements of the PoR for maintaining the Study Product Accountability Record and participant-specific study product accountability record, if the pharmacist is not dispensing study products directly to participants, the non-pharmacy study staff must help to ensure the chain of custody of study product by completing any applicable sections and/or the following documents in their entirety, as directed for each participant. The sites may choose to use the documents listed below for this purpose or develop their site-specific documents as long as these include all the required information.
- Record of Dispensation of Participant-Specific Study Product to Non-Pharmacy staff (Appendix 8c)
- Record of Return of Participant-Specific Study Product by Non-Pharmacy Staff (Appendix 8d)

In an instance when the participant returns their oral study products at any time during the study for reasons such as study product discontinuation, damage, spills, inappropriate storage, etc.; the return must be reconciled by documenting on the participant specific study product accountability record when applicable and by following the instructions in the DAIDS pharmacy guidelines.

Each study site must designate its dispensing method(s) in HPTN 084 Standard Operating Procedures (SOPs) for participant-specific study product supply during clinic visits. These SOPs should be developed with input from both pharmacy and clinic staff. If applicable, the chain of custody SOP must be provided to the DAIDS Protocol Pharmacist for review prior to study activation and may only be modified after consultation with the DAIDS Protocol Pharmacist.

8.1.2 Preparation of the Oral Study Product

The oral products for this study will be provided with customary two-part structure which includes a tear-off portion containing the blinded-product identification (i.e., active or placebo).

Prior to dispensing, the un-blinded portion of the tear-off label must be removed and attached to the participant specific pharmacy records such as participant prescription or participant specific study product accountability record. The permanently affixed section of the label will remain on the original container.

The site pharmacist will label the bottle with a participant specific label prior to dispensing. The participant specific label must be in accordance with the local regulations and the DAIDS Pharmacy Guidelines manual.

The pharmacist will prepare the participant-specific study product and dispense sufficient quantity to last until the next follow-up visit. Pharmacists will record dispensations on the Pharmacy Accountability Logs.

8.1.3 Short-Term Storage of Participant-Specific Study Product in the Clinic

Oral Study Product:

If the PoR is not dispensing directly to participants and participant-specific study product is stored in the clinic for a short period of time (e.g., while the participant is undergoing the study visit procedures for a particular visit), it must be stored at the conditions described per protocol in an area that is always locked and is accessible only to pharmacists and authorized study staff as specified in the site’s SOP and Pharmacy Establishment Plan.
If the participant or site staff believes that the study product storage temperature has reached outside the specified storage temperature range per protocol, the PoR at the site must be contacted immediately so that she/he can dispense the appropriate participant-specific study product again as needed. In addition, the HPTN 084 DAIDS Protocol Pharmacist must be notified by email that this occurred, the reason that it occurred, and the corrective mechanism in place to assure that it will not occur again. This email should come from the Investigator of Record or designee and should copy the PoR at the site. The PoR is responsible for ensuring that the temperature in the storage cabinet is reviewed and recorded daily. These records must be reviewed by the PoR on a monthly basis. The monthly temperature records must be provided to the PoR to be maintained in the pharmacy. These records must be available for review by site monitors.

**Injectable Study Product:**

Injectable study product will be prepared in the pharmacy and delivered to the study clinic. The product must be administered to a participant as soon as possible or **within two hours of preparation by the site pharmacist. The product must remain at controlled room temperature of 20 to 25°C from the time it is prepared to the time it is administered (within two hours).** If the injectable study product is unable to be administered within two hours from the time it was prepared, the PoR at the site must be contacted immediately so that she/he can prepare and dispense the appropriate participant-specific study product again as needed. In addition, the HPTN 084 DAIDS Protocol Pharmacist must be notified by email that this occurred, the reason that it occurred, and the corrective mechanism in place to assure that it will not occur again. This email should come from the Investigator of Record or designee and should copy the PoR at the site, as well as the HPTN 084 Clinical Management Committee (084CMC@hptn.org).

**8.1.4 Step 1: Enrollment**

The PoR will dispense the participant-specific labeled oral study product to the participant directly or will dispense it to the clinical staff to give to the participant. If the oral study product is given to the study participant by the clinical staff, the Record of Dispensation of Participant-Specific Study Product to Non-Pharmacy Staff (Appendix 8c) must be completed.

Each participant is to receive a 5-week supply of oral study product upon enrollment (and after randomization). Each bottle of oral study product contains 30 tablets per bottle. Therefore, two bottles of each oral study product (TDF/FTC or Placebo AND CAB or placebo) should be dispensed in Step 1. Dosing should begin on the day of Enrollment or no later than 24 hours of Enrollment.

**8.1.5 Weeks 2 and 4**

No additional dispensing procedures are noted for these visits unless at the Week 2 visit a participant requires additional oral study product (e.g., they lost or damaged the oral study product). Participants are to return with their bottle at the Week 2 and Week 4
visits. Any returned study product still in the bottle will be counted and that number will be captured in the participant’s study chart and on the electronic case report form (e-CRF). Returned product at the Week 5 visit will also be counted and recorded by the PoR for product accountability logs.

If there is not a greater than 50% adherence seen via pill count at Week 4, the participant should not proceed to Step 2. The IoR or designee should contact the CMC.

8.1.6 Step 2: Weeks 5, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 97+8w, 185 +/- 4-8 w

Oral Product:

The PoR will dispense the participant-specific labeled oral study product to the participant directly or will dispense it to the clinical staff to give to the participant. If the oral study product is given to the participant by the clinical staff, the Record of Dispensation of Participant-Specific Study Product to Non-Pharmacy Staff (Appendix 8c) must be completed. The site pharmacist will dispense sufficient supply of the oral study product to last until their next scheduled study visit when injectable product will be administered at two time points four weeks apart and every 8 weeks thereafter beginning at Week 5 (Time points: Weeks 5, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 97+8w, 185 +/- 4-8 w)

The site pharmacist and site study staff should maintain close communication to ensure that adequate supply of participant’s oral study products is prescribed and dispensed. The participant should have about one-month buffer oral study product supply in case the participant’s next scheduled clinic visit date is rescheduled within the allowable study visit window per protocol.

Injectable Product:

Participant-specific labeled injectable study product will be prepared by the PoR as outlined in Section 8.7.4. Syringes will be covered with an overlay by the PoR prior to dispensing to the study clinic in order to maintain the blind.

The PoR will dispense the participant-specific labeled injectable study product to the clinic where it will be administered to the participant within two hours from the time the syringe was prepared. The Record of Dispensation of Participant-Specific Study Product to Non-Pharmacy Staff (Appendix 8c) must be completed.

Injectable study product will be administered as one 3 mL (600 mg) injection in the gluteal muscle at two time points four weeks apart and every 8 weeks thereafter beginning at Week 5 (Time points: Weeks 5, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 97+8w, 185 +/- 4-8 w)
8.1.7 Step 3:

Dispense tablets only at Day 0, Weeks 12, 24, 36

The study is designed such that participants in Step 2 will continue to receive injections until the last participant enrolled in the study completes their Week 65 visit or the required number of endpoints have been met. In either case, all participants still receiving injections on Step 2 will be transitioned to Step 3. Additionally, participants who permanently discontinue receiving injections before their Step 2 participation in the study ends will transition to Step 3 at the time that it is determined that they can no longer continue to receive injections (either due to an adverse event or participant decision). Any participant transitioning to Step 3 will receive open-label TDF/FTC 300 mg/200 mg fixed dose combination daily oral tablets, provided for up to 48 weeks.

Participants in Step 1 of the study who do not transition to Step 2 (that is, they never received an injection) will no longer receive any study product, will be referred to preventive care services, and will be followed on study for annual HIV testing until the end of Step 2.

Participants will begin Step 3 approximately 4-8 weeks after final injection in Step 2.

8.2 Dispensing, Labeling, and Study Product Return

8.2.1 Study Product Labeling

Under Step 1 and Step 2, the study products are to be labeled in a blinded fashion.

Under Step 3, the study products are to be labeled in an unblinded fashion.

The site pharmacist must place a participant-specific label on the prepared study product in accordance with the local regulations and by following instructions provided in the manual, Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

8.2.2 Emergency Unblinding by CRS IoR or designee for Medical Reasons

Please see additional information in SSP Section 9 for unblinding.

If, in the judgment of the CRS IoR or designee or in the judgment of the participant’s medical provider and the CRS IoR or designee, a medical event is of sufficient extreme severity that it requires the immediate unblinding of a participant without CMC consultation, the CRS IoR or designee may ask the CRS PoR to unblind the participant. Emergency Unblinding is expected to be extremely rare, if it occurs at all. It should only occur in the setting of a potentially life threatening clinical event, and if knowing the participant’s treatment assignment would affect decisions regarding the participant’s immediate medical management. Both conditions must be satisfied.

Emergency Unblinding IoR or designee may use the unblinding feature in the Medidata system to perform emergency unblinding of a participant. If this feature is not available or the
IoR or designee is unable to perform this for any reason, the IoR or designee may ask the site pharmacist to unblind the participant.

The CRS IoR or designee must provide a written request to unblind the participant’s treatment assignment to the PoR. The PoR must then provide the participant’s treatment assignment in writing to the CRS IoR or designee.

In case of extreme medical emergency, the CRS IoR or designee may verbally request the PoR to unblind a participant’s treatment assignment. However, in such cases, the verbal request must be followed by a written request to the PoR within 24 hours of the verbal request and must include a reason why the request to unblind participant’s treatment assignment could not be provided to the PoR in writing initially.

The written request to unblind the participant’s treatment assignment from the CRS IoR or designee and a copy of the written participant’s treatment assignment provided by the PoR to the CRS IoR or designee must be filed in pharmacy records.

The CRS IoR or designee must email the HPTN 084 Clinical Management Committee (084CMC@hptn.org) and copy the PoR regarding the participant’s emergency unblinding within 24 hours of the event.

The PoR must email the HPTN 084 protocol pharmacist (kashin@niaid.nih.gov) regarding the participant’s emergency unblinding within 24 hours of the event.
Appendix 8a: Specific Updates to SSP Section 8 in relation to Unblinding and issuance of study products in when implementing Letter of Amendment 4, Protocol Version 2.0

Documentation to be Provided to the Site Pharmacist of Record and staff:

When the site has LoA # 4 to HPTN 084, Version 2.0 approved by their IRB/EC/other regulatory entities and the participant is informed of her randomized assignment, the site investigator or designated study staff must provide a written notification to the pharmacy that the participant has been informed of their randomized assignment for pharmacy record. This documentation can be in an email to the site Pharmacist of Record (PoR) from the site investigator or designee or on a prescription for un-blinded study product that is signed by an authorized prescriber. If the written notification was not provided prior to the implementation of unblinding in relation to LoA 4 for Protocol Version 2.0, then the site investigator or designee should provide retroactive written notification to the PoR of participant(s) who have been informed of their randomized assignment for pharmacy records.

Sections 8.1.2, 8.1.4, 8.1.5 and 8.1.6 Participants Assigned to the TDF/FTC Arm in Steps 1 and 2:

- When the participant has been informed of her randomized assignment to the TDF/FTC arm, a new prescription for un-blinded oral active TDF/FTC signed by an authorized prescriber must be provided to the site pharmacist.
- The pharmacist will take the following steps to prepare and dispense un-blinded active oral TDF/FTC to the participant:
  1) Retrieve oral active TDF/FTC bottle with two part-label from Step 2 supply.
  2) Retain both the un-blinded part and the blinded part of the two-part label on the TDF/FTC bottle. Do not tear off the un-blinded part of the two-part label from the bottle.
  3) Place pharmacist prepared participant-specific un-blinded label in such a way that the blinded part of the two-part label on the bottle is covered.
- The pharmacist-prepared, participant-specific, un-blinded oral active TDF/FTC bottle will have the manufacturer’s unblinded part of the two-part label and site pharmacist generated participant-specific un-blinded label visible on the prepared bottle before dispensation.
- Alternatively, retrieve open-label oral active TDF/FTC supply from Step 3 supply if the site no longer has oral active TDF/FTC bottles with a two-part label from Step 2 supply due to no further supply of oral TDF/FTC from Step 2 supply available at the CRPMC to distribute to sites. Place pharmacist prepared participant-specific un-blinded label on the open-label oral active TDF/FTC bottle from Step 3 supply and dispense.
- If a participant assigned to the TDF/FTC arm in Step 2 wishes to switch to CAB, then the authorized prescriber will write a prescription for CAB once oral CAB is available from the CRPMC for these participants.
• The participant will initiate oral CAB 30 mg tablet, one tablet orally once daily for 5 weeks. After 5 weeks of oral CAB therapy, the participant will start injectable CAB-LA 600 mg administered as one 3 mL (600 mg) IM at two times points 4 weeks apart and every 8 weeks thereafter.

Sections 8.1.2, 8.1.4 and 8.1.5- Participants Assigned to the CAB Arm in Step 1:

• When the participant has been informed of their randomized assignment to the CAB arm, a new prescription for unblinded oral active CAB signed by an authorized prescriber must be provided to the site pharmacist.

• The pharmacist will take the following steps to prepare and dispense unblinded active oral CAB to the participant:
  1) Retrieve oral active CAB bottle with two part-label from Step 1 supply.
  2) Retain both the un-blinded part and the blinded part of the two-part label on the CAB bottle. Do not tear off the un-blinded part of the two-part label from the bottle.
  3) Place pharmacist-prepared participant-specific un-blinded label in such a way that the blinded part of the two-part label on the bottle is covered.

• The pharmacist prepared, participant-specific, un-blinded oral active CAB bottle will have the manufacturer’s unblinded part of the two-part label and site pharmacist generated participant specific un-blinded label visible on the prepared bottle before dispensation.

Section 8.1.6 Participants Assigned to the CAB Arm in Step 2:

• When the participant’s treatment assignment has been unblinded and the participant is assigned to the CAB arm, a new prescription for unblinded injectable CAB-LA signed by an authorized prescriber must be provided to the site pharmacist.

• The pharmacist will take the following steps to prepare and dispense unblinded active injectable CAB-LA to the participant:
  1) Retrieve injectable CAB-LA vial(s) from storage.
  2) Prepare the injectable CAB dose in a syringe per protocol. The overlay tape that covers the syringe barrel of the prepared unblinded, injectable CAB-LAB in a syringe is not required.
  3) Place pharmacist-prepared participant-specific un-blinded label on the prepared syringe.

Section 8.1.7 Participants in Step 3:

• Participants in Step 3 will continue to take open-label TDF/FTC from Step 3 supply per protocol.
Appendix 8b: Specific Updates to SSP Section 8 in relation to issuance of unblinded study products in when implementing Appendix VIII, HPTN 084 Protocol Version 3.0

Participants in Step 4

Participants who transition from TD/FTC or re-start CAB LA may choose from two options (Step 4a or Step 4b) before starting Step 4c.

**Step 4a (Participants Initially Randomized to TDF/FTC Who Elect to Move to OL CAB LA with Optional Oral Lead-in first)**

CAB 30 mg tablet, one tablet orally once daily for 4 weeks, with or without food, prior to initiating CAB-LA injection. This is an optional oral CAB lead-in prior to receiving CAB-LA injection for participants originally randomized to TDF/FTC.

**Step 4b (Participants Initiating or Re-starting CAB LA without the Optional Oral Lead-in; the Initial Dose Visit, CAB LA Loading Dose)**

CAB-LA 600 mg administered as one 3 mL (600 mg) IM in the gluteal muscle one time at Step 4b visit. The participant will then transition to Step 4c four weeks later. This is for participants who are initiating CAB for the first time with or without oral CAB (Step 4a) or for participants who have been on cabotegravir during the study but have had a long absence of visits (>15 weeks since prior injection) and require a reload of cabotegravir injection.

**Step 4c (Participants on Maintenance Doses of CAB LA or TDF/FTC)**

**CAB LA Maintenance Doses**

CAB-LA 600 mg administered as one 3 mL (600 mg) IM in the gluteal muscle every 8 weeks for no longer than a total of 48 weeks. This is for participants transitioning from Step 4b, or for participants originally randomized to cabotegravir who choose to continue it and do not need reloading dose.

**TDF/FTC Maintenance Doses**

TDF/FTC 300 mg/200 mg fixed dose combination tablet, one tablet orally once daily, with or without food for no longer than a total of 48 weeks.
Step 4d (Participants who become pregnant in Step 4 and first 8 weeks of Step 5, who have had at least one CAB LA injection ever and Participants who are Breastfeeding)

CAB-LA 600 mg administered as one 3 mL (600 mg) IM in the gluteal muscle every 8 weeks for no longer than a total of 48 weeks.

If participant declines to continue CAB LA during pregnancy or breastfeeding will be offered OL TDF/FTC. TDF/FTC 300 mg/200 mg fixed dose combination tablet, one tablet orally once daily, with or without food for no longer than a total of 48 weeks per protocol.

Step 5 (Participants Taking OL TDF/FTC for 48 Weeks after Premature CAB LA discontinuation)

TDF/FTC 300 mg/200 mg fixed dose combination tablet, one tablet orally once daily, with or without food for no longer than a total of 48 weeks per protocol.

This is for participants who received OL CAB LA in Step 4 and who discontinue CAB-LA early for safety or other reasons will have the option to transition to Step 5.

Step 6 HPTN 084 Version 4.0 (Participants on Maintenance Doses of CAB LA in Step 4 who elect to continue CAB-LA Maintenance Doses for up to an additional 48 weeks (Week 56-96))

CAB-LA 600 mg administered as one 3 mL (600 mg) IM injection in the gluteal muscle every 8 weeks, up to an additional 48 weeks (Week 56-96).

Step 6 HPTN 084 Version 5.0

Participants on Step 6 who complete 48 weeks (Week 56-96) of CAB-LA injection may receive up to two additional CAB-LA injection doses (Week 104 -112) per protocol.

CAB-LA 600 mg administered as one 3 mL (600 mg) IM injection in the gluteal muscle every 8 weeks up to an additional 16 weeks (Week 104 -112).
Study Product Preparation:

Prescription

A prescription for all unblinded study product signed by an authorized prescriber must be provided to the site pharmacist prior to preparation of study product. The prescription must include the Step number (4a, 4b, 4c, 4d, 5 or 6) and a notation if the participant is switching between CAB arm and TDF/FTC arm.

Study Product Preparation in Steps 4a, 4b, 4c, 4d, 5 and 6

The site pharmacist must follow the study product preparation instruction in HPTN 084 protocol and comply with the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks for standard pharmacy operations.

Preparation of Unblinded Oral CAB Study Product

The pharmacist will take the following steps to prepare and dispense un-blinded active oral CAB to the participant:

1) Retrieve oral active CAB 30mg tablet bottle with two part-label from Step 1 supply.
2) Retain both the un-blinded part and the blinded part of the two-part label on the CAB bottle. Do not tear off the un-blinded part of the two-part label from the bottle.
3) Place pharmacist-prepared, participant-specific, un-blinded label in such a way that the blinded part of the two-part label on the bottle is covered.

The pharmacist prepared, participant-specific, un-blinded oral active CAB bottle will have the manufacturer’s unblinded part of the two-part label and site pharmacist generated participant specific un-blinded label visible on the prepared bottle before dispensation.

The participant specific label must be in accordance with the local regulations, and the DAIDS Pharmacy Guidelines manual.

Preparation of Unblinded Oral TDF/FTC Study Product

The pharmacist will take the following steps to prepare and dispense un-blinded active oral TDF/FTC to the participant:

1) Retrieve oral active TDF 300 mg/FTC 200 mg with two-part label from Step 2 supply.
2) Retain both the un-blinded part and the blinded part of the two-part label on the TDF/FTC bottle. Do not tear off the un-blinded part of the two-part label from the bottle.
3) Place pharmacist prepared participant-specific un-blinded label in such a way that the blinded part of the two-part label on the bottle is covered.
The pharmacist-prepared, participant-specific, un-blinded oral active TDF/FTC bottle will have the manufacturer’s unblinded part of the two-part label and site pharmacist generated participant-specific un-blinded label visible on the prepared bottle before dispensation.

Alternatively, retrieve open-label oral active TDF/FTC supply from Step 3 supply if the site no longer has oral active TDF/FTC bottles with a two-part label from Step 2 supply due to no further supply of oral TDF/FTC from Step 2 supply available at the CRPMC to distribute to sites. Place pharmacist prepared participant-specific un-blinded label on the open-label oral active TDF/FTC bottle from Step 3 supply and dispense.

The participant specific label must be in accordance with the local regulations and the DAIDS Pharmacy Guidelines manual.

**Preparation of Unblinded Injectable CAB LA 600 mg/3mL.**

The pharmacist will take the following steps to prepare and dispense unblinded active injectable CAB-LA in a syringe to the participant:

1) Retrieve injectable CAB-LA vial(s) from storage.

2) Prepare the injectable CAB LA dose in a syringe using aseptic technique under a pharmacy BSC Class 2 or better as detailed in Appendix 8 of the protocol. The overlay tape that covers the syringe barrel of the prepared unblinded, injectable CAB-LA in a syringe is not required.

3) Place pharmacist-prepared participant-specific un-blinded label on the prepared syringe.

The participant specific CAB LA label must be in accordance with the protocol, local regulations and the DAIDS Pharmacy Guidelines manual.
### Appendix 8c: HPTN 084 Record of Dispensation of Participant-Specific Study Product to Non-Pharmacy Staff

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<tr>
<th>CRS Name:</th>
<th>CRS Number:</th>
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<tr>
<th>Date Dispensed from Pharmacy (dd-MMM-yy), and Time Prepared (hh:mm)</th>
<th>Pharmacy Staff Initials</th>
<th>PTID</th>
<th>Date (dd-MMM-yy) and Time (hh:mm) Collected from Pharmacy</th>
<th>Number of oral tablet Bottles</th>
<th>Number of CAB LA/Placebo Syringes</th>
<th>Prepared Syringes Should be Administered by hh:mm (to correspond within 2 hours of preparation, outlined in first column)</th>
<th>Staff Initials</th>
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**Instructions:**
- Complete one row each time participant-specific study products are provided to a participant.
- Comments may be recorded in the designated column and, if additional space is needed, on the back of the record or chart notes.
## Appendix 8d: HPTN 084 Record of Return of Participant-Specific Study Product by Non-Pharmacy Staff

### Table: HPTN 084 Record of Return of Participant-Specific Study Product by Non-Pharmacy Staff

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<table>
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<tr>
<th>STUDY STAFF</th>
<th>COMMENTS</th>
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**Instructions:**

- Complete one row each time participant-specific study products are returned by study staff or study participants.
- Comments may be recorded in the designated column and, if additional space is needed, on the back of the record or chart notes.
## Section 9. Clinical Considerations

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### 9.1 Overview of Section 9

This section provides information on the clinical considerations for participants in HPTN 084 protocol, version 3.0, 4.0 and 5.0 of the Open Label Extension (OLE) and versions OLE. The Schedule of Evaluations (SOE) in Appendix VIII of the protocol indicates when specific clinical, counseling, and questionnaire procedures are required along with relevant laboratory testing.

Safety assessments will be obtained at every visit throughout the study. However, the IoR or designee should perform any additional symptom-directed examinations at his/her discretion at any time during any visit if s/he determines it to be clinically necessary, particularly if there are any on-going conditions which may require follow-up.
Information pertaining to participant safety monitoring and Adverse Event (AE) reporting procedures are provided in Section 10 of this SSP manual. Information on performing laboratory procedures is described in Section 11 of this manual. Further instructions for the electronic data capture systems are provided in Sections 13 and 14 of this manual.

**Steps for the HPTN 084 Versions 3.0, 4.0 and 5.0 study are listed below:**

1) Step 4a- Procedures for Participants Initially Randomized to TDF/FTC Who Elect to Move to OL CAB LA with Optional Oral Lead-in first
2) Step 4b- Procedures for Participants Initiating or Re-starting CAB LA without the Optional Oral Lead-in; the Initial Dose Visit
3) Step 4c- Procedures for Participants on Maintenance Doses of CAB LA or TDF/FTC
4) Step 4d- Procedures for Pregnant/Breastfeeding Participants and their Infants
5) Step 5- Procedures for Participants Taking OL TDF/FTC for 48 Weeks after Premature CAB LA discontinuation (this Step may also be used for participants who were pregnant on 4c, as is appropriate)
6) Step 6- Procedures for Participants on Maintenance Doses of CAB LA, weeks 49-96, and through to week 112 if additional visits are needed because local access has not yet been secured.

**Figure 1: HPTN 084, v3.0 (OLE1) non-pregnant Protocol High Level Study Flowchart**

![Flowchart](#)
Any questions regarding the safety assessments and clinical management of participants in HPTN 084 must be directed to the HPTN 084 Clinical Management Committee (CMC) (084CMC@hptn.org). Protocol-related queries should be directed to the 084 management alias (084mgmt@hptn.org). Queries about visit coding should be directed to SDMC (sc.084cdm@scharp.org).

9.2 Clinical Management Committee

As outlined in the HPTN Manual of Operations (MOP), a CMC is constituted for each HPTN study with a biomedical intervention. The HPTN 084 CMC continues to provide consultation and decision-making regarding management of toxicities and study product administration, interpretation of clinical or laboratory eligibility criteria, and other questions related to general clinical management of participants. The CMC is comprised of a designated CMC Safety medical officer and also includes the Protocol Chair and Co-Chair, pharmaceutical sponsor medical officers, DAIDS Medical Officer, DAIDS Protocol Pharmacist, and representatives from the HPTN LOC, HPTN LC, and the HPTN SDMC. The CMC has a primary responder who is “on call” and is responsible for soliciting input and responding to site queries within a 24-hour time period. The scope of the CMC is described in the CMC charter (CMC Operating Guidelines).

Sites that plan to conduct visits during off hours (nights or weekends) should notify the CMC and their local laboratories in advance so that a responder will be available, and samples will be able to be received and processed within protocol requirements.

Sites should be mindful that throughout the HPTN 084 protocol and associated protocol appendices, as well as the SSP manual, are examples of situations and AEs that require consultation with the CMC.
Queries from sites are submitted to the following email alias list: 084CMC@hptn.org.

Queries must be formatted to include the information outlined below.

- Include all of the following in the body of the email message:
  1. **Site name and number**
  2. **Name of person submitting query**
  3. **Participant Identification number (PTID) and Week on Study (Use “Screen” if pre-enrollment)**
  4. **Query submission type (choose one of the following)**
     - Initial submission
     - Follow-up submission (this pertains to the PTID, i.e., a follow-up query to the initial submission
  5. **Reason for query and case narrative**

An example of the suggested e-mail is provided here:

**Subject line of email:** 084 CMC: Participant 103-000011 – Elevated ALT Grade 3

**Body of email:**

Site name and number: Site 103 –Prevention Clinic

Person submitting query: Felicity Bones, Study Coordinator

PTID and Week on Study: 103-000011, Week 2

Query Type: Initial submission

Reason for query: 32-year-old participant week 2 on blinded oral study medication found to have Grade 4 CK elevation after cross-fit competition with Grade 3 ALT elevation. Per protocol, participant will be unable to progress to injection phase. Please advise on further work-up and follow-up schedule (unless CMC can envision a way to continue participant on-study products).

Con meds: Tylenol, Ibuprofen, Naprosyn, Isoniazid, Rifampin, PZA, Ethambutol

Denies Alcohol, other recreational drug use
Pertinent laboratory values with chronology, values, and DAIDS toxicity table grade:

<table>
<thead>
<tr>
<th></th>
<th>Reference Ranges*</th>
<th>4/6/17 W2</th>
<th>3/23/17 EntryW0</th>
<th>3/19/17 screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td>10-40 U/L</td>
<td>812 (G4 25xULN)</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>ALT</td>
<td>9-46 U/L</td>
<td>225 (G3 7xULN)</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>CK</td>
<td>21-215 U/L</td>
<td>7100 (G4 20x ULN)</td>
<td>43</td>
<td>49</td>
</tr>
<tr>
<td>creatinine</td>
<td>0.60-1.35 mg/dL</td>
<td>0.97</td>
<td>0.97</td>
<td>1.04</td>
</tr>
</tbody>
</table>

*NOTE: Reference Ranges included on this table are for example purposes only; it does not represent ranges to be used in the study.

Sites that submit queries will print and file the full CMC correspondence regarding the query and place in the relevant participant regulatory binder/participant study file. Keeping this documentation will help explain to monitors why the site followed a particular course of action.

**Note:** Any Grade 5 (Death) EAE/SAE must be reported to the CMC within 72 hours of site discovery.

**Note:** Due to the relaxed contraceptive requirements under the OLE (Protocol V3.0 and Protocol V4.0), sites will no longer need to report to the CMC cases when a participant’s LARC (Long-acting reversible contraceptives) is delayed.

### 9.3 Participant-Reported Medical History during Follow up

Medical History should include, but is not limited to, symptoms, conditions, and diagnoses that affect eligibility or participation in the study, bleeding history, concomitant medications, contraceptive methods, and a history of hospitalizations, surgeries and allergies. The medical history collects a participant’s medical information by major body systems, including a participant’s drug, tobacco and alcohol use history. The history explores any medical conditions or any medications that are deemed exclusionary for this study, including a previous history of psychiatric illness or severe cardiovascular disease. The purpose for obtaining this information is to:

- Assess and document continued participant eligibility to participate in the study.
- Assess and document the participant’s medical conditions and symptoms for comparison with signs, symptoms and conditions that may be identified or reported during follow-up.
- Monitor any potential AEs associated with the use of the study product during the course of the study.
When collecting past medical history from the participant, the clinician should ask probing questions in order to collect the most complete and accurate information possible, especially with regard to severity and frequency. Sites must have a consistent method for documenting this information. In all cases, information obtained at visits must be documented in the participant’s chart and on appropriate e-case report forms.

**Assessment of Acute HIV Infection**

During follow-up, prior to study product administration, assess for signs and symptoms of acute HIV infection. Acute HIV infection is defined as the period of rapid viral replication that immediately follows the initial establishment of infection with HIV. Symptoms of acute HIV infection may be indistinguishable from a typical viral syndrome. Symptoms of acute HIV infections are listed below.

Clinicians should assess the possible causes of these symptoms, length of time the participant has been experiencing these symptoms, and severity grade. Symptoms should be managed clinically per standard of care. If a participant has signs or symptoms consistent with acute HIV infection, or expresses a concern about recent HIV acquisition, testing will be performed per protocol.

- Signs and symptoms of acute HIV infection should be assessed:
  - Fever
  - Fatigue
  - Headache
  - Myalgia
  - Weight loss
  - Pharyngitis or sore throat
  - Lymphadenopathy,
  - Rash
  - Diarrhea
  - Oral or genital ulcers

Site staff must assess the possible causes of these symptoms, length of time the participant has been experiencing these symptoms, and severity grade.

Under the OLE, HIV RNA is required at every visit (in addition to other HIV testing). Refer to the HIV testing algorithm for follow up visits in SSP, Section 11 for details. For split visits excluding HIV confirmatory visits, the HIV viral load does not need to be repeated if the split visit occurs less than 7 days from the initial visit. See SSP, Section 11 for further procedures.

### 9.3.1 AE Review of Medical History at Follow-Up Visits

Note: baseline refers to the timepoint at which the participant enrolled in the original blinded trial. At scheduled follow-up visits, collection of interval medical history should be obtained to:
• Determine whether previously reported and/or documented conditions are ongoing or have changed with regard to severity or frequency
• Determine whether newly-identified symptoms, illnesses, or condition have occurred since the last medical history was performed

Note: For purposes of this study, “newly-identified” is defined as a condition that:

• Was not present at baseline (Enrollment)
• Was present at baseline (ongoing at Enrollment) BUT has now increased in severity grade or frequency or has resolved after Enrollment and prior to the current report;
• Has already been reported as an AE but it has increased in severity grade/frequency

At the participant’s follow-up visits, retrieve the complete medical history source document and look up the Medical History Case Report Form (CRF) for reference.

At each follow-up visit, begin the follow-up medical history by reviewing with the participant and eliciting updates (resolution, outcome date, severity grade, etc.) on those symptoms/conditions that were documented as ongoing since the participant’s last visit. Site clinicians should then probe and evaluate for any new onset conditions/symptoms since the participant’s last visit. Clinicians should use their clinical experience and judgment to elicit complete and accurate medical history information from participants.

• New onset conditions/symptoms that began since the last visit may require completion of an AE Log e-CRF. This MAY include reoccurrences of conditions/symptoms that were reported at baseline and had resolved at a prior visit (only if the condition has increased in severity grade or frequency since baseline).
• Ongoing conditions that have increased in severity grade or frequency should be recorded as new events.
• Ongoing conditions that have not changed in severity or frequency, or have improved but not yet resolved, do not warrant any changes to the AE Log e-CRF.
• Ongoing conditions that have completely resolved since the last visit should have their AE LOG updated with an “Outcome Date”.

If during follow-up, a condition is identified as being present at baseline and the participant inadvertently did not report it as part of the baseline medical history, the clinician should add the information to the Medical History documentation. A chart note should also be documented to explain why the information is recorded retrospectively.

For all abnormal conditions or symptoms identified during follow-up, the severity grade of the condition or symptom must be documented, as must onset and resolution dates, when applicable.

9.4 Targeted Physical Exam at Follow-Up Visits
A targeted physical examination is required at most visits (Refer to Appendix VIII of the Protocol). A physical exam may be conducted at the discretion of the IoR or designee during an interim visit in response to clinically indicated and/or reported symptoms.

Targeted physical exams are performed at each follow-up visit. These exams are driven by the signs and symptoms that the participant reports. At a minimum, the participant must be weighed (see instructions in Section 9.4.1 below) and vital signs recorded at each visit (including temperature, weight, body mass index [BMI], blood pressure, pulse).

As safety is one of the objectives of this study, the goal at each visit is for the clinician to be assured that through the targeted physical exam and any ensuing conversation (history) that the participant is healthy enough to continue in the study and on the study drugs. Minimally, collecting vital signs at the follow-up visits gives the clinician a rudimentary idea of the participant’s health state that may be overlooked by conversation (history) alone.

9.4.1 Instructions for Weight Collection

Collecting participants’ weight is required as part of all physical exams (complete and targeted physical exams). To ensure consistency and accuracy in weight measurements, any time weight is collected, sites should follow the steps below:

- Measurements should be made at the same time of day each time, if possible.
- Participant should remove shoes, sweaters, coats, scarves, etc. prior to weighing.
- Participants should be asked to void (urinate/empty bladder) before weight is measured.
- Whenever possible, weight should not be measured during bouts of severe diarrhea or other obvious disturbances of hydration status.
- Participants should not engage in strenuous exercise for 8 hours preceding the measurements because of its potential effect on hydration status. If the participant reports that he/she did engage in strenuous exercise for 8 or more hours preceding the measurement, weight measurement should be performed anyway and documented on participant’s record.
- The same scale should be used for all measurements performed for this protocol to the extent possible. The scale should be calibrated at minimum annually.
- Before the participant is weighed, make certain that the scale is in balance if it is a beam-balance scale or reads zero if it is an electronic scale.
- Instruct the participant to stand with both feet centered on the scale with arms at the sides. The participant should not move or hold onto anything during the measurement.
- Allow the scale to stabilize and record the weight in the units shown on the scale (lbs or kg).

Weight data will be recorded when applicable.
9.5 Additional Considerations for Medical History and Physical Exams

The following additional assessments will be made throughout the study as part of the medical history and physical exams:

9.5.1 Adverse events

All abnormal findings for adult participants (i.e., Grade 1 and higher) are to be graded and recorded in the participant’s source documentation. AE Grade 1 or higher and any AE that leads to a study product hold (temporary or permanent) will be captured on the electronic Adverse Experience (AE) Log. For each AE, an assessment must be made by a study clinician of whether the event is related to the study product. Clinicians should review the relevant study product Investigator Brochures (IBs) and Package Inserts (PIs) to help make a determination. AEs will be assessed as specified in Version 2.0, January 2010 of the DAIDS EAE Reporting Manual.

Please note, if a laboratory result cannot be graded per the DAIDS toxicity table, it will not be reported as an AE. For example, the DAIDS toxicity table does not provide grading for non-fasting lipid profile; thus, these results will not be graded or reported as an AE.

See Section 10 of the SSP for more details regarding the reporting of AEs, as well as the HPTN 084 protocol Section 6.

See section 10.7.3 for how to handle AEs detected under the V2.0 protocol where tests were performed but are not required under V3.0. Similarly, see Section 10.7.3 for managing any AEs noted while performing testing under v3.0 that is not required by the versions 4.0 or 5.0 protocol.

For infant AEs, refer to SSP Section 10

9.5.2 Neurologic Symptoms

It is not required to actively assess neurologic symptoms: seizure, trouble sleeping, vivid/strange dreams, dizziness, problems concentrating, lightheaded, tremor, vision changes, weakness, numbness/tingling, fainting. However, these symptoms will be assessed as part of the targeted physical exam as needed.

9.5.3 Injection site reaction (ISR) assessment

ISRs are captured on the Injection Site Reaction e-Log post-injection (refer to Protocol Appendix VIII Step 4). Note: Step 4d has specific ISR reporting requirements. ISR assessments are required at these visits and sites should document that ISR assessments were performed at these visits.

Please note that for data to be consistent across all sites, sites should not telephone participants the day after an injection. Instead, they should only assess any reactions at the visits specified in the SOEs UNLESS a participant contacts the site with any questions or concerns about an ISR. If a participant contacts the site, then the site may
choose to schedule an interim visit. Any ISR symptoms noted during the interim visit will be documented on the Injection Site Reaction Log.

ISR examinations will include an assessment of pain, tenderness, pruritus, warmth, purulence, rash, erythema, swelling, induration, and nodules (granulomas or cysts). Participants should be instructed that ISR discomfort can be managed symptomatically (e.g., cold/warm compress, acetaminophen, ibuprofen) as necessary. See the last bullet in Section 9.6 of the SSP (below) for instructions to the participant upon leaving the clinic following an injection.

Participants should be instructed to contact the site regarding any ISRs of concern (and they may take a picture if they wish and email it to the site or return for an interim/unscheduled visit). **Per the HPTN 084 Protocol, Modified Toxicity Management Appendix VIII, the CMC must be notified of refractory cases in extreme circumstances.** Any questions regarding assessment of ISRs should be directed to the CMC.

It is important to distinguish between signs and symptoms from the injection process itself versus an ISR. Although these definitions are somewhat arbitrary, for protocol consistency, sites should follow the following definitions: An ISR typically begins 24-48 hours after an injection. However, if for example a participant experiences pain or discomfort from the actual procedure of giving an injection, e.g., the insertion of the needle beginning at time of, during or immediately after the procedure, this is, for purposes of reporting, considered associated with the injection procedure and is **not** considered an ISR. If a participant reports that on the day after the injection or later, she experienced symptoms (e.g., pain, redness, swelling, etc.) at the injection site, this would be an ISR. If an ISR is reported, use the Injection Site Reaction eCRF, using the “Site Reactions to Injections and Infusions” category for grading as found in the DAIDS Table for Grading the Severity of Adult and Pediatric Events, Corrected Version 2.1. If a participant experiences immediate pain or discomfort or other immediate signs and symptoms due to the procedure of giving an injection, it may be reported as an AE on the AE log eCRF using the category “Estimating Severity Grade for Parameters Not Identified in the Grading Table” for grading.

Sites should document all interventions that have been attempted to mitigate injection site reactions, which should include at a minimum:

- Pre-treatment (prior to injection administration) warm compresses
- Topical or oral pre-treatment with NSAID preparations, unless contraindicated
- Immediate post-injection massage to injection location
- Post-treatment warm or cold compresses
- Post-treatment NSAID or other analgesic preparations, topically or orally

Such interventions and their outcome should be documented in the source documents and the CMC consulted.
9.5.4 Concomitant medications

Sites must document on the Concomitant Medications Log all medications/preparations (prescription and non-prescription) including alternative/complementary medications/preparations (e.g., herbs, vitamins) taken by study participants within 30 days prior to Enrollment and anytime thereafter during study participation. Contraception should be recorded on the Concomitant Medications Log as well. Participants who seroconvert and start ART need to have their ART documented in the CM log.

For infants, do not record concomitant medications on the CM log; however, they should be documented in the source documentation.

It is helpful to ascertain the baseline medication information in the context of the baseline medical history. Participants should be asked open-ended questions to elicit participant report of current medications, and use the information obtained in the medical history to probe for additional medications that the participant may otherwise forget to report. For example, if the participant reports headaches as part of their medical history but does not spontaneously list any medications taken for headaches, ask what medications they take for headaches. Similarly, if a participant reports taking a medication for a condition that she inadvertently did not report when providing medical history information, add the condition to the baseline medical history source document.

At each follow-up clinic visit, retrieve the participant’s previously completed Concomitant Medications Log, record any new medications provided to the participant by study staff, and actively ask the participant whether she is still taking all previously-recorded medications, at the same dose and frequency. Also, actively ask whether the participant has taken any new medications since the last medical history was taken. To further probe for updates, if the participant reports any intercurrent illnesses, symptoms, etc. since her last medical history, ask whether she took any medications for those. Add all new information to the Concomitant Medications Log. If a participant reports taking a new medication for a condition that they inadvertently did not report when providing follow-up medical history information, add the condition to their follow-up medical history source document. To help ensure accurate reporting of concomitant medications information, participants should be encouraged to bring all medications to all study visits.

- Consult the CMC for instructions when a participant or provider decides it is in the participant’s best interest to initiate PEP.
- Consult the CMC for guidance in the case of a participant who has used TDF/FTC as PrEP during an extended absence from the study, such as extended lost to follow-up. If the participant returns to the site, she may be allowed to continue with study participation once use of clinically (outside of the study) obtained TDF/FTC for PrEP is stopped and study visits resume.
9.5.4.1 Precautionary and Prohibited Medications

In order to avoid AEs caused by drug interactions, whenever a concomitant medication is taken, site staff must review the concomitant medication's and study product’s most recent PI for Truvada® and IB for cabotegravir to obtain the most current information on drug interactions and contraindications. Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study.

For any precautionary or prohibited drug listed in the Truvada PI or cabotegravir IB, it is required that the HPTN 084 CMC be notified for recommendations for continuing or stopping (or holding) study product.

Experimental agents not otherwise specified in the SSP Manual may not be administered. Precautionary and prohibited medications may be found in the most recent versions of the protocol, Investigator’s Brochures, and template Informed Consent Forms.

9.5.4.2 Drugs to be used with caution in people using TDF/FTC

- Co-administration of the following drugs should be clinically monitored by site clinician, as per considerations below:
  - drugs that are eliminated by active tubular secretion (e.g. drug, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose (please refer to the table below) or multiple NSAIDS), as these may increase concentrations of emtricitabine, tenofovir, and/or the co-administered drug.
  - Drugs that decrease renal function (e.g., cause nephrotoxicity) as these may increase concentrations of emtricitabine and/or tenofovir.

- **NOTE**: Please report to the CMC if a participant takes a total daily dose of NSAIDS that meets or exceeds high dose, as designated in the table below, for MORE than 72 consecutive hours.

- **NOTE**: Acyclovir and valacyclovir may be used when indicated. If needed for treatment – sites do NOT need CMC permission for the use of these products, but sites should counsel the participant to increase hydration to avoid additive nephrotoxicity; no additional laboratory monitoring is required per protocol.
### Table: Comparable NSAID Dose Levels*

<table>
<thead>
<tr>
<th>Nonselective NSAIDs</th>
<th>Low Dose</th>
<th>Medium Dose</th>
<th>High or Max Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac potassium</td>
<td>50mg bid</td>
<td>50mg tid</td>
<td>50mg qid (in OA/RA only)</td>
</tr>
<tr>
<td>Diclofenac sodium</td>
<td>50mg bid</td>
<td>75mg bid</td>
<td>50mg qid or 100mg SR bid (in RA only)</td>
</tr>
<tr>
<td>Fenoprofen</td>
<td>200-300mg qid</td>
<td>600mg tid-qid</td>
<td>800mg qid</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>50mg bid</td>
<td>50mg tid-qid</td>
<td>100mg tid</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>400mg tid</td>
<td>600mg tid-qid</td>
<td>800mg qid</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>25–50mg tid</td>
<td>75mg tid</td>
<td>IR =300mg/day (divide), SR =200mg/day</td>
</tr>
<tr>
<td>Naproxen</td>
<td>250mg tid</td>
<td>500mg bid</td>
<td>1250mg/day (divide)</td>
</tr>
<tr>
<td>Naproxen sodium</td>
<td>275mg tid</td>
<td>550mg bid</td>
<td>1375mg/day (divide)</td>
</tr>
<tr>
<td>Oxaprozin</td>
<td>600mg qd</td>
<td>1,200mg qd</td>
<td>1,200mg qd</td>
</tr>
<tr>
<td>Sulindac</td>
<td>150mg bid</td>
<td>200mg bid</td>
<td>200g bid</td>
</tr>
<tr>
<td>Proxican</td>
<td>10mg qd</td>
<td>20mg qd</td>
<td>40mg per day (not indicated for OA or RA)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Partially-selective NSAIDs</th>
<th>Low Dose</th>
<th>Medium Dose</th>
<th>High or Max Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etodolac</td>
<td>200mg tid</td>
<td>400mg bid</td>
<td>1,200mg max (IR or SR divided doses)</td>
</tr>
<tr>
<td>Meloxicam/Mobic</td>
<td>7.5mg qd</td>
<td>7.5mg qd</td>
<td>15mg qd</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>1,000mg qd</td>
<td>1,000mg bid</td>
<td>2,000mg/day (qd or divided bid)</td>
</tr>
<tr>
<td>Cox-2 inhibitors</td>
<td>Low Dose</td>
<td>Medium Dose</td>
<td>High or Max Dose</td>
</tr>
<tr>
<td>Celecoxib/Celebrex</td>
<td>200mg qd</td>
<td>200mg bid</td>
<td>200mg bid</td>
</tr>
</tbody>
</table>

COX = cyclo-oxygenase; IR = immediate release; NSAID = nonsteroidal antiinflammatory drug; OA = osteoarthritis; RA = rheumatoid arthritis; SR = sustained release

*This table does not represent exact or equivalent dosing conversions. It is based on U.S. Food and Drug Administration approved dosing ranges and comparative doses from clinical trials.

Source: [www.ashp.org/cmplibrary/NSAIDsConversionTools.pdf](https://www.ashp.org/cmplibrary/NSAIDsConversionTools.pdf)

#### 9.6 Injection Administration

As outlined in the SSP Section 8 – Study Product Considerations, injections must be administered within **two hours of study product preparation by the site pharmacy**. Therefore, coordination with the site pharmacy is important when scheduling and setting up the flow of these visits.

Instructional videos for administering IM injections in the gluteal muscle can be found on [https://hptn.org/research/studies/hptn084](https://hptn.org/research/studies/hptn084) (password is “HPTN”). These videos are provided as examples only. Sites should use their clinical judgement and be guided by participant preference regarding which approach (ventrogluteal or dorsogluteal locations) to use for injections.

Specific instructions for the injections are as follows:

- Participants should be instructed not to take their oral study product on the day of their injection visit if they opted for an oral lead-in. However, if a participant takes study product on the day of the visit, **DO NOT** defer injection and document in the participant’s file.

- Ensure appropriate supplies are on hand: alcohol wipes, gloves, and a filled syringe with the appropriate gauge and inch needle.
• An appropriate needle size (per BMI, as outlined above) should be used for each intramuscular (IM) injection. The needle should be long enough to reach the muscle mass and ensure an IM injection, but not so long as to involve underlying nerves, blood vessels, or bones. Longer needle lengths may be necessary for participants with higher body mass indexes (BMI > 30), to ensure that injections are administered intramuscularly as opposed to subcutaneously. The clinical staff should consult with the pharmacy staff regarding each participant and the appropriate needle length that should be used.

• Wash hands.

• Use alcohol to clean the area of the body to be injected.

• Use discretion as to where in the gluteus muscle each injection is given according to individual participant circumstance. If possible, injections should be spaced approximately 2 cm from one another, from the site of any previous injection or any injection site reaction.

• Hold the muscle of the injection site firmly between your thumb and fingers of one hand.

• With the other hand, hold the needle and syringe like a pencil. Using a quick dart-like motion, insert the needle at a 90-degree angle through the skin and into the muscle.

• Release your hold on the skin and muscle.

• Pull back slightly on the plunger to see if blood is present. If there is blood, remove the needle and syringe and start over with a new needle and syringe. If a new needle and syringe is needed, please discard the contaminated needle and syringe and request new participant’s study product from pharmacy. If there is no blood, inject the medicine.

NOTE: In the rare case the needle malfunctions, such that the full amount of the study product is not administered, remove the needle from the end of the syringe, place a new needle, and continue the injection with the same study product.

• Push the plunger slowly down to inject the study product into the muscle.

• Take the needle out.

• Apply pressure at the injection site and gently rub the site.

• Apply a bandage if needed.

• Discard the used needle and syringe properly.

• Check for any immediate injection site or other adverse reactions. There is no need to keep a participant in the clinic under observation after an injection.
9.6.1 Schedule of Injections

The injection schedule is included in Appendix VIII of the protocol.

Note that participants who elect to either begin or re-start CAB LA during the OLE must do so within the first 24 weeks of the OLE period. Participants initiating CAB LA will be permitted to choose between an oral run-in (4a) or a moving directly to injections (4b). Participants then move to Step 4c for 48 weeks of CAB LA injections.

9.6.2 Injection Visit Window Considerations

Timeliness of injections and adherence to visit windows must be carefully explained to participants. If participants present to the clinic outside of the visit windows (see Section 13 of this SSP for visit windows and refer to 9.7.3 below), contact the CMC for guidance. Injections may never be given with less than three weeks between them.

If participants who have delayed injections at study visits during Steps 4a, 4b and 4c, the sites must consult the CMC. Sites should also refer to all Data Communiques for visit coding.

9.6.3 Missed or Late Injections

First, CONTACT THE CMC.

Visit windows are contiguous. The following principles will be considered when advising sites on how to address missed injection visits.

- The interval between injections:
  - Injections must not be given closer together than three weeks.
  - Delays between injections may require participants to be re-loaded.
- The visit schedule: The team should attempt to get the participant back onto her visit schedule; this may require the use of interim visits.

- Instruct participants regarding how to manage any ISR at home, including:
  - If possible and if disclosure about participating in this study is not an issue, have someone look at the injection site if they cannot see/access it.
  - Note color, tenderness, any drainage. A picture should be taken if possible.
  - For pain, paracetamol, Ibuprofen/other NSAIDS, hot packs should be administered.
  - For swelling, Ibuprofen/other NSAIDS should be administered.
  - If any drainage, fever, chills, fatigue, weakness, the site should be contacted immediately.
  - Do not attempt to squeeze or drain any fluid from injection site.
  - Cover with a sterile bandage and contact clinic immediately if drainage occurs.

Questions regarding the injection instructions should be directed to the CMC.
• The availability of safety assessments: Prior to injection, a recent set of safety bloods should be available to confirm that it is safe to administer injections. At a minimum HIV testing and pregnancy testing should be performed prior to injection administration.

The site must consult the CMC regarding possible re-loading of the participant with delayed or missed visits. The CMC will use the guidance below to advise the sites:

<table>
<thead>
<tr>
<th>CAB LA Dose Delay For Any Injection (time from planned dose injection date)</th>
<th>Recommendation for All Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-7.5*+ weeks delayed</td>
<td>Give delayed dose and 600mg Q8W thereafter</td>
</tr>
<tr>
<td>≥7.5* weeks delayed</td>
<td>Give delayed dose, 600mg 4 weeks later, and 600mg Q8W thereafter (reloading required)</td>
</tr>
</tbody>
</table>

* An exception to the 7.5 week delayed interval re-load rule applies only to PPTs who were on a maintenance CAB LA dose prior to the OLE.

If the interval between the last target injection visit date and current visit is 7.5 weeks or less (52 days or less), then there is no requirement to re-load. The participant should be provided with her missed injection no matter the study week but not before confirming that all safety assessments are within normal limits. She should then return to her regular visit schedule, making sure that the subsequent injection is not less than 3 weeks after the last injection, and that safety parameters are within normal limits.

If the interval between the target visit date and the current visit is 7.5 or more weeks (53 days or more) then re-loading is required. The goal of this process is to ensure that participants are returned to steady state and target drug concentrations, which may have waned as a result of a long period without receiving injection. During re-loading participants will be required to receive the missed injection, and another 4 weeks later similar to the process observed with injections at the original study weeks 5 and 9. Thereafter there should be an attempt to ensure that participant visits return to the appropriate SOE. During the re-loading process, necessary safety assessments should be completed prior to injection.

The participant must be confirmed HIV and pregnancy negative prior to any injections being given. Once the first of the two loading dose injections is administered, the timing of subsequent injections will be adjusted to ensure that the participant is able to return to her visit schedule as soon as possible.

9.7 Specimen Collection

Blood and urine will be collected throughout the study. The protocol outlines the clinical procedures and corresponding testing to be performed according to Modified Section 5.0 of the HPTN 084 protocol. Sections 6 and 11 (checklists and lab) of the SSP also should
be consulted for further specifications. The following additional considerations should be noted:

- Since plasma samples for drug levels will be collected throughout the study, blood sample must be collected at injection visits PRIOR to the injections.
- Calculated creatinine clearance must be performed at every visit where chemistry testing is being performed. The formula is in Section 11.3.5 "Creatinine Clearance" of the SSP (Laboratory and Specimen Management Procedures Section). Note: Participants who initiated the trial on HPTN 084-01 using the Modified Bedside Schwartz equation will have creatinine clearance assessed per the Modified Schwartz equation at follow up visits.

9.8 Toxicity and Clinical Management

Sites should regularly consult the HPTN 084 Modified Protocol Appendix VIII – Toxicity Management as well as the Toxicity Management Diagrams at the end of this section, for guidance related to toxicities. It should be noted that Appendix VIII of the Protocol refers to several instances where the CMC must be contacted in the case of AE management and grading. For AEs that require CMC consultation, the CMC should be notified as soon as possible after site awareness, ideally within 72 hours.

All toxicity management must be fully documented in participant study records. When the CMC is consulted in relation to toxicity management, all communication should be filed in participant study records.

9.8.1 Suspected hepatotoxicity

In addition to the diagrams at the end of this SSP Section 9, sites should consider and investigate any potential causes leading to liver damage as proposed in the protocol.

In the event of permanent discontinuation for liver criteria, the site should consider the following tests to determine possible causes of hepatotoxicity in consultation with the CMC:

- Hep A IgM
- Hep B sAg; Hep B cAb
- Hep C RNA
- Hep E IgM
- CMV IgM
- EBV IgM
- RPR and syphilis screening
- Tox screen
- ANA; a-smooth muscle Ab; type - anti-liver kidney microsomal Ab, total IgG
- APAP (acetaminophen) level of reported use
- Review of any herbal meds and supplement use
9.9 HIV Considerations During Study Conduct

At all follow-up visits, HIV test results from previous visits and at least one HIV test result from the current visit must be available and reviewed by designated staff. All available HIV test results (results from previous visit and a current visit rapid test) must be confirmed to be negative/non-reactive prior to study product administration.

Positive/Reactive HIV Test

If a participant has a reactive or positive HIV test, product will be held. Sites should email the 084HIV@hptn.org and 084CMC@hptn.org alias lists in cases of reactive or “indeterminate” results regardless of the site interpretation (false positive, discordant, discrepant) or with questions about the HIV test algorithm. When emailing these groups, make sure to attach the template for documenting of all HIV results for the participant.

Further testing for confirmation of HIV infection will be done per Section 3.2 in Appendix VIII of the Protocol. Note: It may take several visits to confirm HIV infection. The SOE for seroconverters refers to the final steps once a participant has HIV infection confirmed and is linked to ART.

Participants who are determined not to be infected (i.e. false positive) may resume study products ONLY after CMC consultation.
**HIV testing log template for positive or indeterminate results**

**The subject line of the email:** 084 HIV: Participant 333-333-33333 – Reactive ELISA

**Body of email:**

Site name and number: 31033 Nowhere CRS
The person submitting a query: Zeb McGillicuty
PTID and Week on Study: 333-333-33333 Week 41
Query Type: Initial
Reason for query: rapid HIV positive

<table>
<thead>
<tr>
<th>Site name and number:</th>
<th>Nowhere CRS</th>
<th>31033</th>
</tr>
</thead>
<tbody>
<tr>
<td>The person submitting the query:</td>
<td>Zeb McGillicuty</td>
<td></td>
</tr>
<tr>
<td>PTID and Week on Study:</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Query Type:</td>
<td>Initial Query</td>
<td></td>
</tr>
<tr>
<td>Treatment assignment during blinded trial:</td>
<td>TDF/FTC</td>
<td></td>
</tr>
<tr>
<td>Treatment assignment during OLE</td>
<td>CAB LA</td>
<td></td>
</tr>
<tr>
<td>Reason for query:</td>
<td>Positive Rapid HIV</td>
<td></td>
</tr>
</tbody>
</table>

A 32-year-old participant's rapid HIV test for week 40 was reactive. She had flu-like symptoms 3 weeks ago and has missed taking her pills on two occasions. She denies having unprotected sex in the past 6 months. We have called the participant to stop taking the study medication, and to come next week for confirmatory lab work.

Please advise if our plan is in order.

**Summary table of relevant HIV test results**

<table>
<thead>
<tr>
<th>Date/ Visit Week</th>
<th>Date of last product</th>
<th>Rapid test 1</th>
<th>Rapid test 2</th>
<th>Laboratory based Instrumented Ag/Ab immunoassay</th>
<th>HIV RNA</th>
<th>Geenius if HIV Ag/Ab available and Instrumented test reactive</th>
<th>Other relevant test results</th>
</tr>
</thead>
</table>


Management of participants with discrepant HIV results.

Study staff should follow the guidance of the HIV alias regarding additional testing to confirm HIV status. Guidance on management of participants is provided in the Appendix I: Guidance for the Management of “Discordant/discrepant” HIV Testing Results – HPTN 083 and 084.

For some participants even with repeat testing their final HIV status may be uncertain. Investigators under guidance of CMC and HIV alias should engage participants on their options (see section 12 for counseling considerations).

For participants where treatment is recommended but in the context of atypical test results, investigators may want to explore with participants the option to start treatment to avoid the potential for emergence of INSTI resistance, with the potential for a subsequent treatment interruption 12-18 months later.

Some sites may be able to refer participants with atypical test results for enrolment and follow up in ACTG A5321. Sites should contact their CTU coordinator to determine whether this protocol is active at their CTU.

Some participants may be reluctant to start ART and may wish to wait for further test results. In this situation, participants should ideally be counselled about the potential risks for HIV infection if they are on PrEP hold and uninfected in addition to the risks for resistant infection if they are in fact HIV infected. All participant discussions should be adequately documented, and participants should be supported to make an informed choice that is appropriate to her personal circumstances.

9.10 Sexually Transmitted Infections (STIs)

As noted in the HPTN 084 protocol, treatment for STIs will be provided per local guidelines (and may include referral for treatment).

Symptomatic screening, or oropharyngeal screening for STIs beyond what is required by the protocol may be done at a site’s discretion and cost. Costs associated may come out of each site’s respective per participant study reimbursements.

9.11 Tuberculosis

As noted above in section on Concomitant Medications, rifampicin, rifapentine and rifabutin are contraindicated to concurrent use with cabotegravir. If TB treatment is required contact the CMC for guidance. For participants with suspected or confirmed tuberculosis, contact the CMC at 084cmc@hptn.org for further guidance.
9.12 Pregnancy

Prior to implementing version 3.0 or subsequent versions of the protocol, all sites should have a pregnancy management SOP in place that details how they will manage participants in terms of antenatal care, delivery and post-natal follow-up. The plan should include details about access to and recording of ultrasound information. See an example SOP attached in Appendix 9c. This SOP was loaned to 084 from a site; sites may modify/adapt it to best suit their needs as long as all 084 protocol requirements are met. Sites are not required to use the example SOP format.

- Pregnancy must be confirmed on two separate samples. Per protocol version 3.0 onwards, pregnancy can be confirmed on two separate samples on the same day.

- All participants interested in participating in Step 4d will be provided informed consent for this Step prior to any study activities. Participants cannot receive CAB LA during pregnancy without consenting to Step 4d.

- Participants with a positive pregnancy test may be ambivalent about their pregnancy. Participants can be given time within the visit window to decide about their pregnancy options and whether or not they wish to participate in the sub-study.

- Participants who are pregnant during Step 4 and Step 6 and who received at least one CAB LA injection during HPTN 084 (either blinded study, unblinded phase or during the OLE) are eligible to participate in Step 4d. In addition, participants in Step 5 who received a CAB LA injection within 8 weeks of pregnancy confirmation may join the Pregnancy and Infant Sub-Study.

- Participants who were in the TDF/FTC arm and are pregnant at the time of transition to the OLE and choose to take CAB during pregnancy are also eligible for Step 4d.
• Participants who received CAB LA and are pregnant at the transition are eligible for Step 4d.

• Sites should seek guidance from the CMC regarding study product administration procedures for participants who are pregnant at the time of the transition to the OLE.

**IN CONSULTATION WITH THE CMC, Women who are PREGNANT AT THE TIME OF TRANSITION TO THE OLE will be managed as follows:**

• Sites should consult with the CMC regarding pregnant participants transitioning to the OLE before implementing the guidance below.
• When transitioning to the 4d schedule, they will be allocated to the 4d visit week closest to gestational age. This guidance applies to participants who are pregnant at the time of transition ONLY.
• If an injection reload is required because they were on open-label Truvada, they will begin with a visit 4b prior to transitioning to the 4d schedule.
• If Estimated Gestational Age >12 weeks they should be referred for ultrasound at the time pregnancy is detected (or first pregnancy SOE visit).
• Syphilis testing should be conducted at the time pregnancy is detected (or first pregnancy SOE visit) if it has not been done as part of the step 2 pregnancy SOE. The rationale for this is that there is a 6 month gap in syphilis testing between week 0 and week 24 of the pregnancy SOE.
• GC/CT testing should be done at the time pregnancy is detected (or first pregnancy SOE visit) if there has been a > 3 month gap since last GC/CT testing and/or there is a long gap until the next scheduled GC/CT testing at the week 24 pregnancy visit. For women who present late in pregnancy (after week 24) and have not had GC/CT testing in the last three months, GC/CT testing should be done.

With respect to participants who become pregnant **AFTER** their transition to the open-label extension, the following considerations apply:

• Consult the CMC for guidance regarding product administration.
• Per above, if they require more time to consider their participation complete the visit 4c procedures for that visit up until product administration.
• Ask participant to return for a split visit within the window once she has had an opportunity to consider her pregnancy and study participation options.
• See section 12 on counseling support options.
• Participant will follow the schedule of evaluations for step 4d from week 0; participants should NOT be allocated to a visit on the SOE based on estimated gestational age.
For participants in Step 4d who experience pregnancy loss prior to 40 weeks gestational age

- Consult the CMC.
- Participants can return to either Step 4c or Step 6, whichever is appropriate, after entering 4d in these cases.
- Participants should return to the visit in the schedule of evaluations that reflects their last visit plus the period that they were on step 4d.
  - E.g. participant tested positive for pregnancy at Step 4 week 16 and had a miscarriage at step 4d week 16 would return to step 4c week 32.
- Report the pregnancy outcome on the appropriate CRF.

Ultrasound during pregnancy in all participants

All pregnant participants should have an ultrasound ideally before gestational age 12 weeks. Gestational age should ideally be calculated based on ultrasound. Ultrasound is preferred for the identification of fetal anomalies. With respect to fetal anomaly reporting, these should only be reported as an SAE/EAE at the time of delivery of the infant when surface examination can confirm the anomalies. Where there is pregnancy loss prior to delivery, the pregnancy outcome report should include comments on the fetal anomalies observed on ultrasound as part of the pregnancy outcome report. The CMC should be contacted regarding any pregnancy loss associated with fetal anomalies detected on ultrasound. Ultrasound not available contact SDMC.

Management of Participants who are pregnant but decline participation OR are not otherwise eligible for Step 4d

As noted in Protocol Section 5.14, regardless of the step a pregnant participant is followed on, first semester ultrasound findings and pregnancy outcome data (infant growth assessment at delivery and approximately 48 weeks post partum) will be collected.

Note: ALL INFANT SAEs THAT OCCUR UP TO 48 WEEKS POST PARTUM WILL BE COLLECTED AND REPORTED.

Infant assessment

- Sites should aim to ensure that mother and infant visits are coordinated.
- Infant outcomes should be reported on the appropriate CRF.
- An Infant PTID should be created in Rave for all live births. In the event of a stillbirth if it is feasible to collect cord blood samples an Infant PTID number is also required.
- When preparing for an infant exam ensure that you
  - Plan assessments in advance
  - Supplies are laid out and within reach
  - Room is warm and well lit
  - Mother is informed and comfortable
  - Provider has washed hands
- Assess for any infant danger signs
  - stopped feeding well,
  - history of convulsions,
  - fast breathing,
  - severe chest in-drawing,
- no spontaneous movement,
- temperature >37.5°C,
- temperature <35.5°C
- any jaundice in first 24 hours of life, or yellow palms and soles at any age

- Complete infant examination in a systematic, step-wise manner and assess
  - Physical appearance
  - Length
  - Weight
  - Skin
  - Head (including fontanels and circumference)
  - Face (including mouth)
  - Neck
  - Chest
  - Abdomen and anus
  - Hips and genitalia
  - Arms, legs, fingers, and toes
  - Spine
  - Auscultation of chest
  - Neurologic assessment

- The following tools may assist with infant assessments
  - Video Guide to a Stepwise Surface Examination of Newborns
    who.int/tdr/publications/videos/stepwise-surface-examination-newborns/en/
  - Global Birth Defects App for the assessment and classification of birth defects
    https://globalbirthdefects.tghn.org/download-birth-defects-surveillance-app/
  - Complete Examination of the Newborn. Effective Perinatal Care Geneva: World Health Organization
    https://apps.who.int/iris/bitstream/handle/10665/43601/9789241595070_B_eng.pdf?sequence=2&isAllowed=y
    https://www.who.int/publications/i/item/WHO-MCA-17.07

- To note only major structural congenital anomalies that per the WHO definition have significant medical, social or cosmetic consequences for the affected individual, and typically require medical intervention should be reported. E.g. cleft lip and spina bifida. Major structural anomalies are the conditions that account for most of the deaths, morbidity and disability related to congenital anomalies. In contrast, minor congenital anomalies, although more prevalent among the population, are structural changes that pose no significant health problem in the neonatal period and tend to have limited social or cosmetic consequences for the affected individual. E.g single palmar crease and
clinodactyly. See WHO Birth defects surveillance A manual for program managers 2nd edition [https://iris.who.int/bitstream/handle/10665/337425/9789240015395-eng.pdf?sequence=1] for more information

- In version 3.0, 4.0 and 5.0 all pregnant participants required follow-up of their infants until one year of age (for convenience this was linked to a week 48 visit), including those not in step 4d. In version 5, we have clarified what information we are seeking over the first 12 months of infant life. Specifically, we would like updates on any SAEs, growth parameters, and congenital anomalies. This information will be captured on the Ultrasound-OLE, Pregnancy Outcome-OLE, Infant Assessment form, for all live births in addition to the, Adverse Events- Infants form, where applicable.

- For participants in step 4d only, infant sample collection is required at visits specified in the protocol.
  - Ideally, a staff member with pediatric experience should collect infant samples to minimize discomfort and ensure adequate sample collection.

- For infants in step 4d, Infant adverse events should be discussed with CMC if these are considered related to potential product exposure. The CMC will provide guidance on product administration in these situations.

For missed injections during step 4d, consult the CMC.
Toxicity Management Diagrams (Only applies to direct recipients of study product)

General Guidance*

*General Guidance applies only to toxicities not addressed under Guidance on Toxicity Management for Specified Toxicities
General Guidance*

* General Guidance applies only to toxicities not addressed under Guidance on Toxicity Management for Specified Toxicities

↓ Any grade 3 or higher clinical or laboratory AE observed prior to their first injection of active CAB (i.e. in STEP 4b) will prompt consultation with the CMC prior to any injectable dosing.

¥ Investigator should re-evaluate the participant until resolution of the toxicity.

If study product is temporarily or permanently discontinued have participants return any pills as soon as possible.
General Guidance*

*General Guidance applies only to toxicities not addressed under Guidance on Toxicity Management for Specified Toxicities.

Any grade 4 or higher clinical or laboratory AE observed prior to their first injection of active CAB (i.e. in STEP 4b) will prompt permanent study product discontinuation.
Guidance on Toxicity Management for Specified Toxicities
Nausea, Vomiting, and Diarrhea*

*For all grade levels, treat symptomatically
Guidance on Toxicity Management for Specified Toxicities
ALT Elevations
Oral CAB

Grade ≥ 3

• Report to the CMC
• Retest every two weeks until ALT ≤ Grade 1
• The CMC may direct an alternate interval for follow-up or return to clinical care

Cannot enter the injection phase of the study. Permanently discontinue from the study
Guidance on Toxicity Management for Specified Toxicities
ALT Elevations
Oral open label TDF/FTC

Grade ≥ 3 → Consult the CMC for guidance
Guidance on Toxicity Management for Specified Toxicities
ALT Elevations
Injectable CAB

- Grade ≥ 3
- Repeat testing as soon as possible
- Retest every two weeks until ALT < Grade 1
- Report to the CMC, and the CMC may direct an alternate interval for follow-up or refer to clinical care with study termination
- Permanently discontinue study product
Guidance on Toxicity Management for Specified Toxicities
Creatinine Clearance
Only applicable to Oral label TDF/FTC

- Estimated CrCl < 60 mL/min
  - Temporarily discontinue study product
  - Consult the CMC
  - Confirm calculated clearance within 1 week of receiving test results

- Confirmed Calculated CrCl < 60 mL/min
  - Permanently discontinue study product
  - Notify the CMC

- Retesting CrCl ≥ 60 mL/min
  - Consult the CMC for guidance
  - If it’s determined that case has stabilized, frequency of follow-up testing could decrease, and study product may resume

Adverse events related to creatinine clearance should be based on examination of BOTH the absolute creatinine clearance AND the change in creatinine clearance from baseline (Enrollment/Visit 2.0).
Guidance on Toxicity Management for Specified Toxicities
Injection Site Reactions (ISRs)

- Manage ISR discomfort symptomatically (e.g., cold/warm compress, acetaminophen, ibuprofen) Recommended interventions include:
  - Pre-treatment (prior to injection administration) warm compresses
  - Topical or oral pre-treatment with NSAID preparations, unless contraindicated
  - Immediate post-injection massage to injection location
  - Post-treatment warm or cold compresses
  - Post-treatment NSAID or other analgesic preparations, topically or orally
**Guidance on Toxicity Management for Specified Toxicities: CPK**

- **Grade 3**
  - Continue study product until repeat test results are available
  - Repeat assessment within 2-4 weeks.

- **Grade 4**
  - Continue study product until repeat test results are available if the elevation is thought to be possibly related to study product
  - Repeat assessment after abstaining from exercise for more than 24 hours.
  - For persistent Grade 4 elevations possibly related to product follow on study/ off study product.
Guidance on Toxicity Management for Specified Toxicities
Allergic Reactions

1. Grade 1 or 2
   - Continue Study Product

2. Grade ≥ 3
   - Related to Study Product?
     - Yes
       - Permanently discontinue study product
     - No
       - Consult the CMC for guidance
Appendix 9a: HPTN 084 Cheat Sheet for Transitioning PPTs from V2.0 to V3.0

Note: Contact the CMC if there is any doubt whatsoever.

*Participants can choose CAB up until and including week 24, thereafter no changes to CAB allowed per protocol.

<table>
<thead>
<tr>
<th>Participant Status under v2.0 Protocol</th>
<th>Participant Options under v3.0</th>
<th>Where to Transition the Participant Under v3.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPT on TDF/FTC with no contraindications chooses between:</td>
<td>joining v3.0, staying on TDF/FTC</td>
<td>Start with Step 4c</td>
</tr>
<tr>
<td></td>
<td>joining v3.0, transitioning to CAB LA</td>
<td>Offer oral lead in (Step 4a) and straight to injection (Step 4b); Participant chooses; After completing Step 4b move to Step 4c</td>
</tr>
<tr>
<td></td>
<td>joining v3.0, does not want to take either product</td>
<td>Start with Step 4c, but without study product administration</td>
</tr>
<tr>
<td></td>
<td>not joining v3.0</td>
<td>Complete termination procedures</td>
</tr>
<tr>
<td>PPT on CAB LA with no contraindications chooses between:</td>
<td>joining v3.0, staying on CAB LA</td>
<td>Start with Step 4c</td>
</tr>
<tr>
<td></td>
<td>joining v3.0, transitioning to TDF/FTC</td>
<td>Start with Step 4c</td>
</tr>
<tr>
<td></td>
<td>joining v3.0 but does not want to take either product</td>
<td>Start with Step 4c, but without study product administration</td>
</tr>
<tr>
<td></td>
<td>not joining v3.0</td>
<td>Complete termination procedures</td>
</tr>
<tr>
<td>PPT who is confirmed HIV+ on v2.0 chooses between:</td>
<td>joining v3.0</td>
<td>Consent to v3.0. Contact the HIV alias AND the CMC. Follow their guidance for PPT management.</td>
</tr>
<tr>
<td></td>
<td>not joining v3.0</td>
<td>Complete termination procedures</td>
</tr>
<tr>
<td>PPT on the Contraceptive Sub-study chooses between:</td>
<td>joining v3.0 and continuing on contraceptive sub-study</td>
<td>Have PPT sign the ICF signature block for continuing the sub-study, Contact the CMC for PPT management</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NOTE: participants are permitted to change contraceptive method.</td>
</tr>
<tr>
<td>Participant Status under v2.0 Protocol</td>
<td>Participant Options under v3.0</td>
<td>Where to Transition the Participant Under v3.0</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>joining v3.0 and stopping the contraceptive sub-study</td>
<td>Have PPT sign the ICF signature block for declining the sub-study</td>
<td>Manage PPT as regular study PPT</td>
</tr>
<tr>
<td>not joining v3.0</td>
<td>Complete termination procedures</td>
<td></td>
</tr>
<tr>
<td><strong>PPT on Annual Testing Schedule, with no safety contraindications, chooses between:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>joining v3.0, taking TDF/FTC</td>
<td>Start with Step 4c</td>
<td></td>
</tr>
<tr>
<td>joining v3.0, wanting to take CAB LA</td>
<td>Offer oral lead in (Step 4a) and straight to injection (Step 4b); Participant chooses; After completing Step 4b move to Step 4c</td>
<td></td>
</tr>
<tr>
<td>not joining v3.0</td>
<td>Complete termination procedures</td>
<td></td>
</tr>
<tr>
<td><strong>PPT on Annual Testing Schedule, WITH SAFETY contra-indications:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participant may not join v3.0</td>
<td>Complete termination procedures</td>
<td></td>
</tr>
<tr>
<td><strong>Participant who discontinued study product during v2.0 for safety reasons and was transitioned to open-label TDF/FTC for 48 weeks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>joining v3.0</td>
<td>Consent to v3.0. Contact the CMC alias. Follow their guidance for PPT management.</td>
<td></td>
</tr>
<tr>
<td>Note: we will follow PPTs who on v2.0 are on OL TDF/FTC due to safety discontinuations according to the v3.0 protocol, Step 5. Each PPT will complete a total of 48 weeks of TDF/FTC. So, if the PPT was at Week 36 under v2.0 she still will be at Week 36 of Step 5 under v3.0.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>not joining v3.0</td>
<td>Complete termination procedures</td>
<td></td>
</tr>
<tr>
<td><strong>PPT who was on TDF/FTC (and never took CAB LA) and who is pregnant on v2.0 at the time of site transition to</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>joining v3.0, staying on TDF/FTC</td>
<td>Start with Step 4c</td>
<td></td>
</tr>
<tr>
<td>(note: This PPT is not eligible for the Pregnancy and Infant Sub-Study. She was never exposed to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participant Status under v2.0 Protocol</td>
<td>Participant Options under v3.0</td>
<td>Where to Transition the Participant Under v3.0</td>
</tr>
<tr>
<td>----------------------------------------</td>
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<td>-----------------------------------------------</td>
</tr>
<tr>
<td>version 3.0, chooses between:</td>
<td>CAB LA and elects TDF/FTC for the pregnancy on v3.0.</td>
<td>Site staff to consult CMC for initiating CAB LA relative to due date</td>
</tr>
<tr>
<td>joining 3.0, transitioning to CAB LA, agrees to Pregnancy and Infant Sub-Study</td>
<td>(note: This PPT is eligible for the Pregnancy and Infant Sub-Study since she is electing to take CAB LA on v3.0. In fact, she must agree to join the Pregnancy and Infant Sub-Study for safety monitoring if she wants to take CAB LA.)</td>
<td>Offer oral lead in (Step 4a) and straight to injection (Step 4b); After completing Step 4b move to Step 4d</td>
</tr>
<tr>
<td>joining v3.0, declines study product</td>
<td>Follow up on 4c without study product administration; collect outcomes at delivery and 48 weeks if possible</td>
<td></td>
</tr>
<tr>
<td>not joining v3.0</td>
<td>Complete termination procedures</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participant Status under v2.0 Protocol</th>
<th>Participant Options under v3.0</th>
<th>Where to Transition the Participant Under v3.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPT who was on CAB LA (and had at least one CAB LA injection) and who is pregnant on v2.0 at the time of site transition to version 3.0, chooses between:</td>
<td>joining v3.0, staying on TDF/FTC for the pregnancy, declines Pregnancy and Infant Sub-Study (note: This PPT is eligible for Pregnancy and Infant Sub-Study because she had at least one CAB LA injection on the v2.0 protocol. However, she may choose not to join the Sub-Study if she takes TDF/FTC during pregnancy.)</td>
<td>Start with Step 4c</td>
</tr>
<tr>
<td>Participant Status under v2.0 Protocol</td>
<td>Participant Options under v3.0</td>
<td>Where to Transition the Participant Under v3.0</td>
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</tbody>
</table>
| joining v3.0, staying on TDF/FTC for the pregnancy, and agrees to join the Pregnancy and Infant Sub-Study  
(\textbf{note}: This PPT is eligible for Pregnancy and Infant Sub-Study because she had at least one CAB LA injection on the v2.0 protocol.)| Start with Step 4d | |
| joining v3.0, transitioning to CAB LA and joining the Pregnancy and Infant Sub-Study  
(\textbf{note}: Any PPT who is eligible and elects to take CAB LA during pregnancy must join the Pregnancy and Infant Sub-Study for safety monitoring.)| Site staff to consult CMC for initiating CAB LA relative to due date  
Offer oral lead in (Step 4a) and straight to injection (Step 4b); After completing Step 4b move to Step 4d | |
| not joining v3.0 | Complete termination procedures; if possible, try to at least get pregnancy outcome information | |
| Participant who had a laboratory AE on either CAB or TDF/FTC and not discontinued but tests not required in new SOE | Transition to product choice | Follow up AE until grade 1; testing is acceptable under clinical care. Contact the CMC for guidance. |
Appendix 9b: HPTN 084 Cheat Sheet for PPT transitions from V3.0 to V4.0

Not all participants who were followed under the first OLE (v3.0 of the protocol) are eligible for the v4.0 protocol (OLE2).

Below are the most common scenarios sites will encounter when transitioning PPTs from the v3.0 amendment to the v4.0 amendment. Please note that sites may have participants who do not fall neatly into the below categories; when that occurs the site must contact the CMC for transition guidance.

<table>
<thead>
<tr>
<th>Participant Status under v3.0 Protocol at the Consent Visit for v4.0</th>
<th>How to Manage PPT Under v4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Pregnant, PPT on Step 4c TDF/FTC</td>
<td>Has the PPT completed 48 weeks of TDF/FTC during the first OLE?</td>
</tr>
<tr>
<td></td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>no</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Not Pregnant, in Step 4c PPT on CAB LA</td>
<td>Does the PPT wish to continue CAB LA?</td>
</tr>
<tr>
<td></td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>no</td>
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<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Pregnant, on step 5</td>
<td>Completed step 5</td>
</tr>
<tr>
<td></td>
<td>no</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Participant Status under v3.0 Protocol at the Consent Visit for v4.0</td>
<td>How to Manage PPT Under v4.0</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Not Pregnant, PPT seroconverted</td>
<td></td>
</tr>
<tr>
<td>Has participant had infection confirmed, been linked to care and evidence of viral suppression on ART confirmed</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>Release PPT from study per protocol</td>
</tr>
<tr>
<td>no</td>
<td>Consent to v4.0</td>
</tr>
<tr>
<td></td>
<td>Continue to follow up with PPT until infection status confirmed, and/or participant referred to ART and viral suppression is confirmed, then release PPT from the study.</td>
</tr>
<tr>
<td>Pregnant, on Step 4c and taking TDF/FTC</td>
<td></td>
</tr>
<tr>
<td>Step 4c visits completed?</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>Consent to v4.0</td>
</tr>
<tr>
<td></td>
<td>Once the Step 4c SOE is completed move the PPT to Step 5 for the full 48 weeks of TDF/FTC. Collect pregnancy outcome information</td>
</tr>
<tr>
<td>no</td>
<td>Continue following PPT on the appropriate week of Step 4c. Once the Step 4c SOE is completed move the PPT to Step 5 for the full 48 weeks of TDF/FTC. Collect pregnancy outcome information</td>
</tr>
<tr>
<td>Pregnant, on Step 4d taking CAB LA or TDF/FTC and being followed</td>
<td></td>
</tr>
<tr>
<td>Visits in step 4d completed?</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>Consent to v4.0</td>
</tr>
<tr>
<td></td>
<td>Consult CMC regarding continuation on step 6</td>
</tr>
<tr>
<td>no</td>
<td>Consent to v4.0</td>
</tr>
<tr>
<td></td>
<td>Continue following PPT on the appropriate week of Step 4d until 48 weeks post delivery, then consult CMC about step 6</td>
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Appendix 9c: Example SOP for the management of pregnancy

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**DOCUMENT HISTORY**

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</table>
I. Purpose
To describe the procedures regarding management of participants who become pregnant.

II. Scope
This SOP applies to all [site] staff that manage the study participants who are pregnant such as study PI’s, Coordinator, Counselors, Nurses and Clinicians. This procedure applies to all studies. Specifics for the HPTN 084 study are included below in the Addendum.

III. Responsibilities
1. **Clinicians**
   a. To correctly identify clinical situations requiring obstetric care
   b. To deliver appropriate obstetric care to the participant and refer accordingly.
   c. To inform referral facility staff of the participant’s arrival.

2. **Nurses**
   a. To perform nursing duties to facilitate the appropriate obstetric care and monitoring to the participant

3. **Community Educators**
   a. Tracing participants and tracking medical records

4. **HTS Counsellors**
   a. Providing HIV testing and counselling

5. **Clinic Aides**
   a. Sample transportation and escorting participants to [XXXXX].

IV. Allowable Exceptions
This SOP is meant to be followed without deviation. However, it is an allowable exception to follow procedures specified in a protocol or Study Specific Procedure Manual (SSP) that may supersede this SOP.

1. **BACKGROUND:**
[Site Name] CRS has extensive experience in research involving pregnant women and therefore already has existing collaborations and structures that will ensure the study participants have access to antenatal care including delivery and postnatal care. [XXX] has [XX] Obstetricians (Drs. XXXXX and XXXX) who are available to do obstetric scans for gestational age assessment as well as fetal anomaly scan [within the study site or referred to XXXX].

The study site has a memorandum of understanding and strong working relationship with staff at the referral facilities in XXXX and therefore the study team will be able to access hospital records whenever required. The site team through its community educators will closely trace all participants referred for further care to obtain copies of medical records.

V. PROCEDURES

1. **Referral of pregnant participants for antenatal care (ANC)**
   1. To ensure access to antenatal care during pregnancy, a participant with a confirmed pregnancy on 2 different samples collected will be counselled about the need to
attend antenatal care services as required per XXXX Ministry of Health Guidelines. The pregnant participant will be referred for antenatal care to their health facility of choice. The study clinic will refer the participant for all applicable pregnancy-related services and will provide participant a referral letter to the antenatal care services detailing participation in the trial; certified copy of referral letter must be kept on participant file. However, the site will not be responsible for paying for pregnancy-related care.

2. We shall encourage participants to attend antenatal care at [XXX]. These facilities are affiliated with the site and we hope this will enable the site to collect the hospital records and the required samples at delivery as per the HPTN 084 study requirements.

3. Pregnant participants will be escorted by study community educator to register for antenatal care if necessary. The community educator will confirm that participant is enrolled in antenatal care as feasibly possible.

4. Pregnant participants will be asked to share their antenatal care records and certified copies of these will be made and kept in the participant chart. In the event that the participant is unable to bring the antenatal care records, the community educator will confirm from the health facility and obtain as much information as possible. This will only be done following verbal permission from the participant.

5. The study clinician will offer early monitoring to a participant who becomes pregnant and will refer participant for an ultrasound scan and evaluation, within 12 weeks of gestation.

6. Dating ultrasound scans for participants will be conducted by [XXXX]. All enrolled participants will be booked for a review by the obstetrician and will be scanned accordingly using a standard case report form. In cases where the site Obstetrician is not available, the participant may be referred for dating ultrasound scan at [XXXX]. Study clinicians (non-specialists) who are trained and certified to provide obstetric ultrasound scans may be allowed to offer the services as long as this is allowable by the study protocol and they are listed accordingly on the delegation of duty log. The Ultrasound scan reports will be given to the study participant and a copy of these will be kept on the participant chart.

- The Ultrasound will include the following reporting capabilities and parameters:
  1. Number of fetuses
  2. Ultrasound-estimated gestational age on the date of scan*
  3. Estimated date of delivery based on the scan
  4. Viability of fetus (heartbeat)
  5. Fetal abnormality
  6. Additional comments, if applicable

  *Estimated gestational age should be measured via
    - First Trimester Crown-Rump length
    - Later Trimesters
      - Femur length
      - Abdominal circumference
      - Biparietal diameter OR Head circumference
- Trans cerebellar diameter (optional if the other biometry is present)

In the event that the participant comes to the study clinic with an ultrasound scan performed outside these providers; an ultrasound scan with all the above required parameters will be acceptable and a certified copy will be made and kept on the participant chart. A ultrasound scan will be repeated in case some parameters above are missing.

7. The study staff will discuss with the pregnant participant their delivery plan as they come for their scheduled visits. The participants will be encouraged to inform the study staff in case of any changes in their delivery plans. These delivery plans will enable the study staff to plan accordingly for the participant to ensure that the required samples at delivery are collected and the participant receives adequate care during their delivery as per the national guidelines.

8. For planning purposes, the study site will create schedules for expectant mothers with their expectant delivery dates (EDDs) and these will be shared with the community educators. The community educators will keep in contact with these participants and send reminders for required study visits and also regarding their delivery plans. Mothers will be asked to contact the study site at onset of labor or when admitted in hospital for delivery or any other complications.

9. Referral for obstetric complications will be made to [XXXX]. The site has already existing working relationship with [XXXX] team and two site Obstetricians who also provide clinical care at [XXX]. The site Obstetricians that are affiliated with [XXXX] will be contacted in case of any complications. Consultations will be done for non-study related complications of pregnancy and delivery, abnormalities on fetal ultrasound, birth outcomes and phenotyping of abnormalities etc.

10. Management of all obstetric emergencies will be done per site S.O.P on Medical and Obstetric Emergencies. Pregnant participants with obstetric complications will be escorted by the clinic aide to [XXXX] to ensure they are worked on adequately. This will also enable easy follow up of participant in the hospital and access to their medical records as per permission from the hospital and the study participant.

11. The study site will consult Dr. [XXXX] for birth outcomes and phenotyping of abnormalities noted during study follow up.

12. All efforts will be made to ensure that participants are followed up to ascertain outcome of pregnancy and appropriate study CRFs will be completed. Participants who are pregnant at the termination visit will continue to be followed until the pregnancy outcome is ascertained in consultation with the study clinical management teams.

2. Referral of pregnant participants and seroconverters for Prevention Mother To Child Transmission (PMTCT) of HIV programs
1. Refer to **SOP XXXX HIV Seroconversion** for guidance on participants who seroconverts during study follow up. A participant may be identified as being pregnant and a seroconverter (or possible seroconverter) in one of three ways.
   - A participant known to be pregnant (already off study drug) has a positive rapid HIV test.
   - A known seroconverter (already off study drug) has a positive pregnancy test.
   - A participant has a positive rapid HIV test and a positive pregnancy test at the same visit.

2. All pregnant HIV-1 positive participants will be referred by a study clinician to ANC health facilities with PMTCT services. Appropriate counseling concerning pregnancy and the importance of PMTCT will be provided at the study clinic by the study clinician and HTC counsellors.

3. The pregnancy and HIV test result information will be availed on the referral form to the health workers at the PMTCT Antenatal clinic. This will be documented on the participant’s chart and a certified copy of the referral form kept on the participants file.

4. Infant feeding counseling will be provided for HIV infected women by study clinician. As per WHO/[XXXX] Ministry of Health current guidelines, mothers known to be HIV-infected (and whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complementary foods thereafter, and continue breastfeeding for the first 12 months of life. Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast milk can be provided. The mother may still choose not to breastfeed and this is acceptable. The study counselors may also provide this counseling.

### 3.0 ADDENDUM FOR HPTN 084 STUDY

#### 3.1 Background

HPTN084/LIFE is a phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women.

During HPTN 084, women were required to be on a long-acting, reversible contraceptive (LARC). This was because we did not know how well CAB LA worked in women and a report from Botswana was released raising the possibility that a drug called dolutegravir (DTG) may have caused a very serious birth defect of the spinal cord and the brain in women who were taking DTG at the time they became pregnant for treatment of HIV. DTG is similar to CAB LA so we wanted to be careful during HPTN 084. Ever since the first Botswana report, doctors have continued to monitor babies born to mothers who have taken DTG during pregnancy. It now seems much less likely that DTG was the cause of the birth defects in babies. We now know that the difference in the rate of birth defects in mothers who took DTG and those that used other antiretrovirals for HIV treatment is essentially the same. Other studies that study large groups of pregnant women that use medications, including DTG during have not found this problem. CAB LA is not the same as DTG. CAB LA has not been shown to cause birth defects in animal studies. In blinded portion of HPTN 084 there were 50 confirmed pregnancies; none of the babies born to women in HPTN 084 had any birth defects.

Now that we know that CAB LA is safe and works to prevent HIV in women, we no longer will require study participants to use a LARC during this study.
Study staff will talk with participants about ways to avoid pregnancy if they wish to do so.

Addressing the use of CAB LA for HIV PrEP in pregnancy is important and timely. Women in high HIV prevalence settings may be at increased risk for HIV when planning to conceive, and need HIV prevention options, like PrEP that go beyond condoms. Pregnancy may also be a vulnerable period for HIV acquisition. Pregnancy and breastfeeding are periods marked by significant biological and behavioral changes that may have varying effects on the risk of HIV.

Preventing HIV in high-risk populations who are also at risk for pregnancy remains a priority for reducing both maternal and infant morbidity and mortality. As access to PrEP expands, data on the safety, acceptability and dosing requirements of PrEP agents during pregnancy are a priority.

Data on the safety and PK of CAB LA in pregnant women compared to non-pregnant women are critical. In particular, data on PK are important for informing the need for dose adjustments in pregnancy. Data on CAB LA concentrations in breastmilk are extremely limited. In pre-clinical pre- and post-natal development studies in female rats, no effect of CAB on lactation was seen at any dose. There was also no effect on rat pup growth and development, or AEs with exposure to CAB in maternal milk.

The HPTN 084 amendment provides an opportunity to offer participants the chance to reconsent to active CAB LA dosing during pregnancy and breastfeeding, while ensuring adequate monitoring of safety in both mother and infant. These data will provide important information on acceptability, tolerability, safety and PK of CAB LA during pregnancy and breastfeeding prior to wide scale implementation in demonstration projects and national programs where extensive monitoring may be limited.

### 3.2 Precautions taken to prevent pregnancy in HPTN084

#### 3.2.1 Contraceptive requirements in the Open label extension (OLE) of the study;

Pregnancy prevention in the OLE is optional. Following counselling, a participant can decide to remain on family planning or stop family planning. Participants that opt to stop family planning will continue receiving study product depending on the choice of study product they will choose during the OLE. Participants that opt for a family planning method will receive it at the study clinic where possible and in case they receive it outside the clinic, we shall request for a copy of the family planning card or documents so that we can update the concomitant med Log and contraceptive Log in Medidata appropriately.

3. **Procedures for HPTN 084 Pregnant Participants**
   1. All pregnancies that occur during the course of the study must be reported to the CMC within seven (7) days of site awareness (either upon confirmation by urine or blood pregnancy testing during a study visit or as reported by the participant between study visits). The CMC will now be contacted following the first positive pregnancy test.
   2. At the first pregnancy test positive visit, participants will have their pregnancy confirmed on a second independent sample that could be taken off on the same day.
   3. Participants should be counselled about the risks and benefits of continuing CAB through pregnancy and breastfeeding, and offered an opportunity to re-consent to receive CAB LA injections during pregnancy. Participants who need more time to consider their
decision can have their CAB LA injection temporarily deferred, within the remaining visit window.

4. Participants who decline to continue CAB LA during pregnancy and breastfeeding will be offered Open Label (OL) TDF/FTC.

5. All pregnant participants who have had at least one CAB LA injection will be followed up in accordance with the pregnancy schedule of evaluations in Step 4d. CAB LA injections will be administered every eight weeks in those that consent. Additional safety assessments and PK samples will be collected at study visits four weeks after every injection.

6. At delivery, a maternal blood sample and cord blood sample will be collected from the mother, and where feasible an infant blood sample will be collected (week 0).

7. During the post-partum period, blood and breastmilk samples will be collected from the mother, and blood samples from the infant per the Step 4d SOE. Infant outcomes will be assessed at delivery up to approximately 12 months later (Week 48 of Step 4d).

8. Participants who do not have a live birth outcome will be followed up in accordance with Step 4c visits. Pregnancy outcome data will still be collected in these participants at the time of the pregnancy outcome.

9. Participants who have never received a CAB LA injection will be followed up through Step 4c and through to pregnancy outcome. They will remain on the Step 4c SOE.

10. All participants who complete Steps 4c or d will have the option to link to a CAB LA access program or local HIV prevention program if preferred.

4.0 Tracking and documentation of pregnancy outcomes

4.1 All efforts will be made to ensure that participants are followed up to ascertain outcome of pregnancy. Participants who are pregnant at the termination visit will continue to be followed until the pregnancy outcome is ascertained or, in consultation with CMC, it is determined that the pregnancy outcome cannot be ascertained. In the event that a pregnant participant is lost to follow up, this will be documented on the CRF and source documents.

2. Data will be collected on outcomes of all participant pregnancies and recorded on appropriate study CRFs. Whenever possible, medical records documenting pregnancy outcomes will be obtained, photocopied and certified and filed in participant’s study records.

3. For all pregnancies which do not continue to term or end in stillbirth, data on the timing and nature of the loss will be recorded, including whether termination was spontaneous or elective.

4. Pregnancy outcomes meeting criteria for AE and/or EAE reporting per protocol will be reported accordingly (see HPTN084 Safety monitoring and reporting SOP).

5.0 Procedures for delivery, collection and processing of required samples at delivery

5.1 Study staff will encourage pregnant participants to deliver at XXX which is in the same facility as XXXX. XXX already has an existing MOU with XXXX allowing the conduct of several studies within the hospital. The study site will obtain clearance from the hospital to work with the HPTN084 study team on the pregnancy infant study. Each pregnant participant who consents to participate in the pregnancy infant sub study will also be asked to provide verbal permission to access her medical records at the point of consent to participate in the pregnancy infant sub study. This will be documented in the participant chart notes.

5.2 Since the management of pregnant participants will follow the standard of care, the site will on case by case support participants in need beyond the standard of care.
5.3 Part time midwives at XXX will be contracted by XXX to support pregnant participants as contact persons when participants report in for ANC or labor and deliver to inform study staff when needed. These midwives will be trained on the study prior to their addition to the Delegation of duties Log. After adequate training and delegation, they will collect the study samples as required at delivery.

5.6 Processing of samples collected at delivery; the protocol requires that the samples collected at delivery for participants in the pregnancy infant sub study are processed within 6 hours of sample collection. The samples that will be collected at XXX will be primarily processed by the XXX Lab. The samples will be transported in cooler boxes as soon as possible within the allowable protocol time by the XXX staff. These staff who transport the samples will be trained and delegated to do so on the study delegation of duties Log.

5.7 We however anticipate that some of the deliveries will be occur outside the XXX lab operational times. In such instances;

- The study staff will keep in contact with the contracted midwives at XXXX and inform the XXXX Lab about any pregnant participants in labor that will not have delivered by 5.30pm on a daily basis so that the XXXX study team can prepare accordingly and have staff available to ensure samples collected at delivery are transported to the Lab and processed within the allowable 6 hour period.
- For any participant who reports to the hospital in labor outside the XXX Lab operational time, the contracted midwives at XXX will be requested to inform the study staff as soon as possible with details on labor progress so that arrangements are made accordingly.
- Special support will be provided to the XXXX staff that will be required to deliver the samples to XXXX Lab processing staff who will ensure the samples collected are adequately processed within the required time as per SOE.

5.8 In case the site is unable to collect or process required samples at delivery for a participant as required, CMC will be informed and protocol deviation will be reported accordingly. This also applies to participants that will deliver in health facilities where we are unable to get the required samples at delivery.

5.9 Sample collection in the postpartum period; Postpartum samples will be collected at XXXXXXX clinic. Transport will be provided using the UNCPM vehicles. Mother and baby in the postpartum period will be picked up and taken back home for their scheduled visits to ease their movements.

6.0 Procedures for Infant assessments in HPTN 084

6.1 Pregnancy outcome assessment including abbreviated infant examination will be conducted at week 8 and week 48 postpartum. Whenever feasible, site will use delivery notes plus complete assessment in clinic.

6.2 Infant feeding history will also be collected at weeks 8, 16 and 24 postpartum. These will be documented in the chart notes.

6.3 Infant HIV testing will be performed if the mother is confirmed to have HIV infection. If HIV testing indicates that an infant has HIV infection, a second confirmatory visit should be conducted to confirm HIV infection in the infant. If infant infection is confirmed, resistance testing should be performed locally using a separate (additional) infant sample collected for this purpose.

6.4 Cord blood and infant plasma collection and storage will be conducted at delivery and weeks 2, 4, 8, 16, 24 and 48. Assessments on stored samples will be performed retrospectively; results will not be returned to study sites or participants, except as noted in the SSP. These samples will be used for PK analysis and may be used for other assessments, including virology testing.
6.5 In the event that an infant is sick, the site will manage the infant accordingly, document in the required CRFs. Those that need referral will be referred for care as per national guidelines.

**Training Date and Method**

Unless otherwise specified:
1. All new or revised SOPs are presented at the next study team meeting. The IoR has ultimate responsibility for study conduct, including appropriate training of study staff. The CRS Coordinator or designee is responsible for assisting the IoR in training staff that are absent from study team meetings.
2. All staff are responsible for reviewing all SOPs yearly.
3. New employees are responsible for job specific SOPs within 30 days of hire and all SOPs within 90 days of hire.
Section 10. Adverse Event Reporting and Safety Monitoring

10.1 Overview of Section 10

This section contains information related to Adverse Event (AE) reporting and safety monitoring for HPTN 084. The following resources are relevant to AE reporting:

- DAIDS Table for Grading Adult and Pediatric Adverse Events, corrected version 2.1 dated July 2017
- Current Investigational Brochure (IB) for oral and injectable cabotegravir (CAB)
- Current Truvada® (emtricitabine/tenofovir disoproxil fumarate) Package Insert (PI)
- Sections 5.0 and 6.0 and Toxicity Management (in Appendix VIII of the HPTN 084 protocol as well as any accompanying Clarification Memos (CMs) or Letters of Amendment (LoAs)).

Safety Monitoring, Review, and Oversight

Primary safety monitoring of study participants is primarily the responsibility of study staff, under the direction of the Investigator of Record (IoR). The IoR and designated study staff are responsible for submitting required e-forms to the HPTN Statistics and Data Management Center (SDMC) and Expedited Adverse Event (EAE) reports to DAIDS, to ensure relevant safety data are available in a timely manner.

Safety monitoring bodies for this study include the Clinical Management Committee (CMC), SDMC Clinical Safety Associates, Independent Safety Reviewer (ISR), DAIDS Safety Office and Medical Officer, and the Study Monitoring Committee (SMC).
Descriptions of these groups and their responsibilities can be found in Section 14 and 15 of the HPTN MOP: https://www.hptn.org/resources/manual-of-operations.

10.2 Adverse Event

AEs are defined in Appendix VIII, Section 6 of the HPTN 084 protocol. This AE definition applies to all participants from the time a participant is enrolled/randomized to the point in time when the participant terminates from the study.

10.3 Documenting Adverse Events

Site staff are responsible for documenting all AEs reported or observed in study participants, regardless of presumed attribution, seriousness or severity, in the study source documentation. All AEs will be graded according to the DAIDS Table for Grading Adult and Pediatric Adverse Events, corrected version 2.1 dated July 2017 (referred to herein in this section as the “DAIDS Toxicity Table”). This table will be used throughout the entire study, and can be downloaded at: http://rsc.technosoft.com/safetyandpharmacovigilance/gradingtables.aspx.

Laboratory results that are outside of the normal range but are not abnormal enough to reach a Grade 1, can be identified as “NCS” (not clinically significant) in the source documentation, if determined by a study clinician.

All information obtained while conducting follow-up physical examinations, review of symptoms, and laboratory tests should be recorded in the source documentation according to site Standard Operating Procedures (SOPs). This information should be reviewed after each participant visit to determine if an AE has occurred. For events captured on the Adverse Experience Case Report Form (AE CRF), whenever possible, the final diagnosis, rather than the individual signs and symptoms, should be documented (in both the source documentation and on the AE CRF). If a diagnosis is not possible, each individual sign and symptom should be reported separately. Each site should develop a system for collecting signs, symptoms and diagnoses and ensuring that these events are captured appropriately in the source documents. All signs, symptoms and diagnoses reported as AEs must be assessed as to whether they are related or not related to study drug.

If an AE meets the criteria of a Serious Adverse Event (SAE) / EAE, see Section 10.5 below for guidance on documentation and reporting.

It should be noted that injection site reactions (ISRs) will be captured in the study database using the Injection Site Reaction e-CRF and not on the AE Log. It is important to distinguish between signs and symptoms from the actual injection procedure versus an ISR. See Section 9.4.7 of the SSP for further guidance. A participant may report an ISR at any time during the study. All ISRs are reported using the Injection Site Reaction eCRF, using the “Site Reactions to Injections and Infusions” category for grading as found in the DAIDS Toxicity Table.
10.3.1 Considerations for Pregnancy Outcome and Infant AE Reporting

Regardless of the Step a pregnant participant is followed on, first trimester ultrasound findings and pregnancy outcome data (infant growth assessment at delivery and approximately 48 weeks post birth) will be collected. Regardless of the Step, all infant SAEs that occur up to 48 weeks post-delivery will be collected and reported. Grade 2 and higher AEs will be reported into the database ONLY FOR PARTICIPANTS in STEP 4d.

What should be considered for when determining relationship to study product for infants?

Pregnancy Outcome Reporting for All Participants

All pregnancy outcomes that result in live infants are reported at delivery on the Pregnancy Outcome log. Additionally, fetal losses (i.e. spontaneous abortion, elective/therapeutic abortion, and stillbirth) are to be reported as pregnancy outcomes on a Pregnancy Outcome log. Generally, these outcomes are not reported separately as an AE. However, any complications of the pregnancy outcome (i.e. excessive bleeding, infection, etc.) that meet AE reporting criteria or pregnancy outcomes that meet SAE/EAE criteria are to be reported separately as AEs.

Infant Reporting
AE reporting for participants in Step 4d ONLY

We anticipate a fair number of infant AEs; however, it is expected that very few will be product-related. Once a baby is born the only exposure mechanism is through breast milk, and study product concentration in breast milk is small.

All AEs will be graded according to the DAIDS Table for Grading Adult and Pediatric Adverse Events, corrected version 2.1 dated July 2017.

Only Grade 2 and above infant AEs need to be reported in the database on the Infant Adverse Event form up to and including 24 weeks post-partum. Grade 1 AEs should be recorded in the chart notes but do not need to be captured in the database.

SAE Reporting for ALL participants with an infant, regardless of Step

All SAE/EAEs, including deaths and congenital anomalies, must be reported throughout Week 48 post-delivery.

If a mother has concerns about her infant, study sites will refer her to a local pediatrician.

10.4 Adverse Event Severity Grading

The severity of all AEs identified in HPTN 084 will be graded per the DAIDS Toxicity Table (link above). The term “severity” is used to describe the intensity of an AE. The severity of all AEs identified in HPTN 084 must be graded on a five-point scale:

Grade 1 = Mild
Grade 2 = Moderate
Grade 3 = Severe
Grade 4 = Potentially life-threatening
Grade 5 = Death

Severity is not the same as seriousness, which is based on the outcome or action associated with an event.

AEs not listed in the DAIDS Toxicity Table should be graded according to the “estimating severity grade” row of the table:

<table>
<thead>
<tr>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE-THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild symptoms causing no or minimal interference with usual social &amp; functional activities with intervention not indicated</td>
<td>Moderate symptoms causing greater than minimal interference with usual social &amp; functional activities with intervention indicated.</td>
<td>Severe symptoms causing inability to perform usual social &amp; functional activities with intervention indicated.</td>
<td>Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death</td>
</tr>
</tbody>
</table>
If the severity of an AE falls into more than one grading category on the Toxicity Table, assign the higher of the two grades to the AE.

If a single AE term is used as a unifying diagnosis to report a cluster of signs and symptoms, and the diagnosis is not specifically listed in the Toxicity Table, assign the AE the highest severity grade among each of the associated signs and symptoms. Record the diagnosis as the AE term and record each associated sign and symptom in the AE Log comments section.

Seasonal allergies should be graded according to the “Estimating Severity Grade for Parameters Not Identified in the Grading Table” row of the Toxicity Table (not the “acute systemic allergic reaction” row).

When grading using the “Estimating Severity Grade for Parameters Not Identified in the Grading Table” row of the Toxicity Table, note that if the condition requires treatment, it must automatically be graded at Grade 2 or higher.

10.5 AE Relationship to Study Product

When assessing an AE’s relationship to study product, the site clinician should consider the study product used.

OL1:
Step 4a- Procedures for Participants Initially Randomized to TDF/FTC Who Elect to Move to OL CAB LA with Optional Oral Lead-in first
Step 4b- Procedures for Participants Initiating or Re-starting CAB LA without the Optional Oral Lead-in; the Initial Dose Visit
Step 4c- Procedures for Participants on Maintenance Doses of CAB LA or TDF/FTC
Step 4d- Procedures for Pregnant/Breastfeeding Participants and Their Infants
Step 5- Procedures for Participants Taking OL TDF/FTC for 48 Weeks after Premature CAB LA discontinuation

If an AE onset date falls in between Steps (e.g. 4a vs. 4c or 5), the site clinician should assess the AE’s relationship to the study product used during the last completed Step in which the participant received study product.

OL2:
Step 4d- Procedures for Pregnant/Breastfeeding Participants and Their Infants
Step 5- Procedures for Participants Taking OL TDF/FTC for 48 Weeks after Premature CAB LA discontinuation
Step 6- Procedures for Participants on Maintenance Doses of CAB LA during weeks 49-96
One of the following relationship categories must be assigned to each reportable AE:

**Related:** There is a reasonable possibility that the AE may be related to the study product.

**Not related:** There is not a reasonable possibility that the AE is related to the study product.

**Note:** When an AE is assessed as “not related”, an alternative etiology, or explanation should be provided in the ‘Comments’ section of the CRF. If new information becomes available, the relationship assessment of any AE should be reviewed again and updated as required.

### 10.6 Reporting AEs to the HPTN SDMC

Using the AE Log CRFs, this study database will collect:

- Grade 1 and higher AEs for adult participants
- Grade 2 and higher AEs for infants in Step 4d up to and including 24 weeks after birth
- SAEs are reported for all infants, regardless of Step, up to and including 48 weeks post delivery
- any AE that leads to study product hold/discontinuation.

Infant AEs will be collected on the Adverse Event – Infant Log. Adult AEs will be collected on the Adverse Event Log.

Medical conditions, problems, signs, symptoms, abnormal laboratory value, and findings identified before enrollment/randomization (into the original study) but not meeting protocol exclusionary criteria were documented on the Medical History eCRF (Pre-Existing Conditions). If a condition was ongoing at the time of enrollment, it is a pre-existing condition. If this condition worsens (increases in severity or frequency) after enrollment/randomization (in the original study), the worsened condition is considered an AE. If a pre-existing condition resolves after enrollment/randomization (into the original study), but then recurs at a later date, the recurrence is considered a new AE.

For any AE at any severity grade that contributes to a temporary or permanent hold of study product, regardless of the presumed relationship, study staff should submit an AE e-Log to the HPTN SDMC and mark either “held” or “permanently discontinued” on the Action Taken with Study Product AE CRF e-Log.

If an AE increases in severity or frequency (worsens) after it has been reported on an AE Log e-CRF, the “old” AE should be marked “recovered/resoled” for the Outcome variable and the new AE should be submitted. When an AE improves to a lower severity or becomes less frequent, a new AE submission is not necessary.

Each AE identified in HPTN 084 must be followed clinically through study participation until the AE resolves (returns to baseline) or stabilizes. Please consult the CMC for
guidance on when to cease or reduce follow-up on an AE, or what constitutes “stability”. AE resolution date is the date that the condition is no longer present or stabilizes. If a participant is taking a medication to manage an AE that occurs during study participation, it is not considered resolved. If an event continues at end of study participation, the status/outcome of the AE should be updated to “not recovered/resolved.” Study sites should be prepared to have a plan to manage AEs with a severity grade of Grade 3 or higher, as well as an ALT≥3xULN PLUS total bilirubin≥2xULN, and any seizure event at end of study participation for each participant. The CMC (084cmc@hptn.org) is available for consultation of these events, if needed.

The following are tips and guidelines for assigning AE terms:

- Whenever possible, a diagnosis should be reported, rather than a cluster of signs and/or symptoms.
- Do not include information on relatedness to study product or timing of study product use in the AE term/description. Limit the AE text to the medical description and anatomical location, when needed.
- When it is not possible to identify a single diagnosis to describe a cluster of signs and/or symptoms, each individual sign and symptom must be reported as an individual AE. The term can be updated later when a diagnosis becomes available.
- When reporting a laboratory event, describe the direction of the abnormality, (e.g., decreased hemoglobin, elevated ALT).
- A specific medical term should be used whenever possible (e.g., “ulcers” instead of “sores”)
- Correct spelling for all terms should be used and site should avoid using abbreviations.
- When reporting an AE that is associated with an underlying condition, include the underlying condition in the AE term or description. For example, if a participant is experiencing pain related to an underlying cancer diagnosis, include the cancer diagnosis in the AE term or description.
- If possible, try to include the anatomical location of the event, such as, pain on the right arm.
- Procedures per se should not be reported as AEs; rather the underlying condition which leads to a procedure may be considered an AE. Any associated procedures may be considered treatments for the AE. For example, while “appendectomy” would not be considered an AE, “appendicitis” would, with “appendectomy” documented as a treatment provided for the AE. In addition, any event that occurs due to a study-related procedure should be recorded as an AE. Specify in the AE text description if the AE is related to a procedure (iatrogenic). For example, if a
participant experiences dizziness from a blood draw, then “dizziness due to blood draw” should be submitted as an AE.

- HIV seroconversion is not in of itself an AE. However, symptoms related to HIV could be categorized as an AE (e.g. fever sustained for 2 days of 39.2).

10.7 Additional Adverse Event Reporting Considerations

10.7.1 Reporting Injection Site Reactions (ISRs) and Post Injection Adverse Events (AEs)

- Injection Site Reactions should only be reported on the ISR log. If the site considers an event to be related to the injection but there is no code available on the ISR form, the event should be reported on the AE log.
- If an AE location is directly at the injection site, include the term “at injection site” in the reported Event diagnosis.
- “Local” is not a defined anatomic site.
- Recording that an AE occurred at the injection site is important, as complications at the site of study product administration are grouped separately in the coding and analysis of AEs.
- The term “post-injection” should only be used for AEs related to the injection procedure, generally occurring during or immediately after the injection procedure. “Post-injection” refers to the time after the act of delivering the study product with needle and syringe. This is distinct from an AE related to the study product. See below for examples.

<table>
<thead>
<tr>
<th>REPORT as the AE term</th>
<th>DO NOT report as the AE term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site rash</td>
<td>• Rash</td>
</tr>
<tr>
<td>Post injection dizziness</td>
<td>• Dizziness</td>
</tr>
</tbody>
</table>

10.7.2 Reporting procedure-related Adverse Events (AEs)

AEs that are complications of procedures belong to a separate classification (for example, complications/consequences of surgery, biopsy, or dental work). This applies to any procedure, whether or not the procedures are a part of the study. For example, infection, pain, bleeding, or lightheadedness that is a consequence of a procedure is different from these events happening spontaneously.

For an AE related to a procedure, indicate relationship to the procedure in the AE term so that the AE is classified as a procedural complication. Example:

- For a wound infection that happens directly as a result of surgery, this should be reported as “post-operative wound infection.”
10.7.3 Reporting laboratory abnormalities as AEs

If an abnormal laboratory test result is reported as an AE per protocol requirements, separate from any clinical diagnosis associated with the result, the type of test performed and the direction of the abnormality should be reported (e.g., elevated ALT). The specific value or the severity grade of the result should not be reported as part of the AE term. Laboratory values that fall outside of a site’s normal range but are below severity Grade 1 are not considered AEs. These out of range but below Grade 1 values are not documented as pre-existing conditions or AEs unless requested by the Investigator of Record (IoR) or designee. When assigning severity grades, note that some sites may have normal reference ranges that overlap with the severity grade ranges. Thus, it is possible for a participant to have a result that falls within the site’s normal range but is still gradable per the Toxicity Table. Assign the severity grade based on the Toxicity Table severity grade ranges, regardless of whether or not the lab result falls within the site’s normal reference range.

Lab abnormalities that meet the criteria for expedited reporting to DAIDS will be reported separately on the AE Log CRF and reported to DAIDS via the DAERS Reporting System.

Note: AEs must be followed to resolution even after a site transitions to a newer protocol version, and the newer version does not specify testing for the AE in the SOE. For example, if a participant has an AE ongoing under V3.0, but under V4.0 those same labs are not protocol specified, the site should still request those labs as part of clinical care purposes to ensure the AE returns to Grade 1 or resolves.

Sites should check the Toxicity Management section in the currently approved protocol version. If toxicities are specified in the toxicity tables, then sites must follow that guidance for AE resolution. Should sites have additional questions about AE resolution, they should contact the CMC (084cmc@hptn.org).

10.7.4 Reporting Recurrent Adverse Events

If an AE previously reported on an AE Log CRF resolves and then recurs at a later date, the second occurrence must be reported as a new AE on a new AE Log CRF (new log line in the study database).

Some participants may have chronic, episodic, pre-existing conditions. In these situations, if the participant experiences an episode of the condition during follow-up that has not increased in severity or frequency from the baseline condition, it is not considered an AE. For example, if a participant reports experiencing three (3) migraines a month before the study, and they continue at the same frequency and severity during the study, these migraines should not be reported as AEs.

10.7.5 Reporting Sexually Transmitted Infections (STIs) as Adverse Events (AEs)

When reporting sexually transmitted infections, sites need to report infections diagnosed as part of protocol-required testing for GC/CT and syphilis on the STI eCRF as well as
the AE Log eCRF. All other STIs diagnosed as part of standard of care will be reported on the AE Log eCRF only. If sites only reported STIs in one place, is not required to report retroactively.

10.8 SAEs

ICH-E6 defines a serious adverse event (SAE) as any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,  
  NOTE: The term “life threatening” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. A grade 4 severity grading on the Toxicity Table does not necessarily mean that an event is life-threatening. When determining whether a grade 4 event meets the ICH definition of “life threatening”, consider the event in the context of any related symptoms the participant may have experienced.
- Requires in-patient hospitalization or prolongs an existing hospitalization. The following types of hospitalizations are not considered adverse events, serious or otherwise:
  - Any admission unrelated to an AE (e.g., for cosmetic procedures)
  - Admission for diagnosis or therapy of a condition that existed before randomization AND has not increased in severity or frequency since baseline.
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed above.

ICH guidance (E2A) also states that medical and scientific judgment should be exercised in deciding whether other adverse events not listed above should be considered serious.

SAEs are a subset of all reportable AEs. For each AE identified, an authorized study clinician must determine whether the AE meets the ICH definition of “serious”.

When assessing whether an AE meets the definition of serious, note that seriousness is not the same as severity, which is based on the intensity of the AE.

10.9 Expedited Reporting of AEs to DAIDS

Sites are responsible for reporting AEs per the Manual for Expedited Reporting of Adverse Events to DAIDS. The manual can be found at: https://rsc.niaid.nih.gov/sites/default/files/manual-exped-aes-v2_0.pdf

All AEs that meet the definition of “serious” (SAEs), regardless of relationship to study
product, are expedited adverse events (EAE).

In addition to SAEs, sites will report in an expedited manner the following results:

- ALT \( > 3\times \text{ULN} \) AND total bilirubin \( > 2\times \text{ULN} \) (must be both at the same time in order to require expedited reporting)
- Any seizure event

This reporting is required for all participants from the time they are enrolled/randomized until their participation in the study ends. After this time, sites must report to DAIDS Serious, Unexpected, clinical Suspected Adverse Reactions (SUSAR), as defined in Version 2.0 of the DAIDS EAE Manual, if the study site becomes aware of the event on a passive basis, i.e., from publicly available information.

The study agents for the purposes of EAE reporting are: Oral CAB 30 mg tablet; CAB LA injectable suspension (600 mg/mL); TDF/FTC fixed dose combination tablet containing 200 mg of FTC and 300 mg of TDF.

Each site will use the DAIDS internet-based reporting system, DAERS (DAIDS Adverse Experience Reporting System), to report all AEs that require expedited reporting to DAIDS (see section 10.7 above for definition or refer to ). DAERS can be accessed at https://ncrms.niaid.nih.gov/.

The study Chairs and LOC staff should be notified of all EAEs and SAEs when the site reports them. To do this, sites should add the following to the report Notification Recipient list within DAERS:
- Sinead Delany-Moretlwe at sdelany@whri.ac.za
- Mina Hosseinipour at mina_hosseinipour@med.unc.edu
- Scott Rose at srose@fhi360.org
- Jennifer Farrior at jfarrior@fhi360.org

In the event of system outages or technical difficulties, expedited adverse events may be submitted via the DAIDS EAE form (paper format). This form is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting. For questions about DAERS, contact DAIDS-ES at DAIDSRSCSafetyOffice@tech-res.com. Site queries may also be sent from within the DAERS application itself.

All EAEs must also be reported as AEs on the AE Log e-CRF and to be submitted to the HPTN SDMC within 72 hours of the site awareness date. When completing AE Log e-CRFs and EAE forms, study clinicians should carefully review all documentation of the event to ensure accuracy, completeness, and consistency. All AE descriptions and details (e.g., AE term, onset date, severity grade, relationship to study product) must be recorded consistently across all documents. All EAE forms received at the DAIDS Safety Office will be compared with the AE Log CRFs received at the HPTN SDMC to ensure that all key data elements are matched with consistent details.
Table 10-1: Reference Guide for Reporting AEs and EAEs

The table below is an “at a glance” reference guide for reporting AEs to the study database at the HPTN SDMC, and AEs that also meet the definition for expedited reporting to DAIDS (EAEs). HPTN 084 will follow the SAE (Serious Adverse Event) Reporting Category for adverse events that require expedited reporting (EAEs), as defined the Manual for Expedited Reporting of Adverse Events to DAIDS, January 2010. An SAE in this study is defined as: results in death, is life threatening, requires hospitalization, results in persistent or significant disabilities or incapacity, is a congenital anomaly/birth defect; is an important medical event – see below.

<table>
<thead>
<tr>
<th>AE</th>
<th>Report on AE Log</th>
<th>Report as EAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SERIOUS ADVERSE EVENT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Results in death</td>
<td>Yes</td>
<td>Yes, regardless of relatedness to study drug</td>
</tr>
<tr>
<td>Is life-threatening</td>
<td>Yes</td>
<td>Yes, regardless of relatedness but does not include all Grade 4 events (see Note 1 below)</td>
</tr>
<tr>
<td>Requires inpatient hospitalization or prolongation of existing hospitalization</td>
<td>Yes</td>
<td>Yes, regardless of relatedness to study drug (see Note 2 below)</td>
</tr>
<tr>
<td>Results in persistent or significant disabilities or incapacities</td>
<td>Yes</td>
<td>Yes, regardless of relatedness to study drug</td>
</tr>
<tr>
<td>Is a congenital anomaly/birth defect</td>
<td>Yes</td>
<td>Yes, regardless of relatedness to study drug</td>
</tr>
<tr>
<td>Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the above definition</td>
<td>Yes</td>
<td>Yes, regardless of relatedness to the study drug</td>
</tr>
<tr>
<td>IS A REPORTABLE ADVERSE EVENT TO THE HPTN SDMC, BUT MAY OR MAY NOT ALSO BE A SERIOUS ADVERSE EVENT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 and higher AEs (adult participants)</td>
<td>Yes</td>
<td>Only if it meets the definition of an SAE as outlined above</td>
</tr>
<tr>
<td>Grade 1 AEs (infant participants)</td>
<td>No</td>
<td>Only if it meets the definition of an SAE as outlined above</td>
</tr>
<tr>
<td>Grade 2 and higher AEs (infant participants)</td>
<td>Yes</td>
<td>Only if it meets the definition of an SAE as outlined above</td>
</tr>
<tr>
<td>OTHER ADVERSE EVENT IDENTIFIED FOR REPORTING</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT ≥ 3x ULN AND total bilirubin ≥ 2x ULN</td>
<td>Yes</td>
<td>Yes, regardless of relatedness to study drug</td>
</tr>
<tr>
<td>Any seizure event</td>
<td>Yes</td>
<td>Yes, regardless of relatedness to study drug</td>
</tr>
</tbody>
</table>

1: “Life-threatening” refers to an event in which the participant was at risk of death at the time of the event. It does NOT refer to an event that hypothetically might have caused death if it were more severe.

2: Per ICH SAE definition, hospitalization is NOT an adverse event (AE), but is an outcome of the event. **DO NOT REPORT:** Any admission unrelated to an AE (e.g., cosmetic surgery, administrative or social admission for temporary placement for lack of a place to sleep); protocol-specified admission (e.g., for a procedure required by protocol); admission for diagnosis or therapy of a condition that existed before receipt of study agent(s) and has not increased in severity or frequency as judged by the clinical investigator. **(NOTE:** A new AIDS-defining event in a subject already known to be HIV-infected would be considered an increase in severity of a pre-existing condition [HIV infection] and would be reportable.)

3: Clinically insignificant physical findings at births including those regarded as normal variants do NOT meet reporting criteria unless there is also a clinically significant anomaly being reported. Refer to the Manual for Expedited Reporting of Adverse Events to DAIDS for full details.
10.10 Social Impact Reporting

In addition to medical AEs, participants in HPTN 084 may experience social impacts — participant reported non-medical adverse consequences or benefits — as a result of their participation in the study. For example, participants could experience difficulties in their personal relationships with partners, family members, and friends, if they find out they are participating in the study. They also could experience stigma or discrimination from family members and members of their community. In the event that social impact occurs, study staff should fully document the issues or problems and make every effort to facilitate their resolution as described in this section. In addition, the social impact must be recorded on the Social Impact e-Log. As with medical AEs, follow all problems to resolution (until they no longer exist), or stabilization (they exist, but at a manageable level). Provide referrals as needed/appropriate to other organizations, agencies, and service providers that may be able to help address the problem.

If the reported social impact is associated with an AE, report the AE on the AE e-Log. If the social impact is associated with an AE that meets criteria for expedited reporting to DAIDS, report it on the AE e-Log and as an EAE. Also report the issue or problem to all IRBs/ECs responsible for oversight of HPTN 084, if required per IRB guidelines.

10.11 Product Safety Information

Once a site has completed protocol registration, it will begin to receive product safety information on the study product being used in the study. The information that the sites may receive is:

- Revised Investigator Brochures
- IND Safety Reports
- Safety Memos, reports or updates
- Other safety memoranda and updates

This information will be forwarded to the sites by the HPTN Leadership and Operations Center via an email alias set up for this purpose. Each site should maintain copies of each communication in their regulatory files. This information originates from the DAIDS Regulatory Support Center (RSC). Each email will indicate how the information is to be handled. In many cases, this information must be submitted to the site’s IRB/EC. Product safety information does not require IRB/EC approval; however, sites should maintain a copy of the IRB/EC submission cover letters indicating the date of submission and identifying the content of the submission in their regulatory files. Any acknowledgements from the IRB/EC should also be filed in the regulatory file. The Investigator of Record and the Study Coordinator are responsible for reviewing this information, disseminating this information to their staff and ensuring that it is submitted to the IRB/EC.
Section 11. Laboratory and Specimen Management Procedures

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11.1 Overview of Section 11

This section contains information on the laboratory procedures performed in HPTN 084. Laboratory procedures will be performed in a variety of settings, including:

1. Clinics
2. Local laboratories
3. The HPTN Laboratory Center (LC, Baltimore, MD, USA)
4. Other laboratories designated by the HPTN LC

Tables in this document list the time points, testing location(s), and specimen requirements for each test. In all settings, laboratory procedures will be performed according to the guidelines included in this section of the SSP and in addition study site Standard Operating Procedures (SOPs) that have been reviewed and approved by the LC. In addition, package insert instructions must be followed.

Ideally, one method, test kit, and/or combination of test kits will be used for each test throughout the duration of the study. If for any reason a new or alternative method, kit, or test must be used after study initiation, site laboratory staff must inform the HPTN LC to determine if any test kit validation is required.

Regardless of whether tests are performed in clinic or laboratory settings, study staff that perform the tests must be trained in proper testing and associated quality control (QC) procedures before performing the tests for study purposes; documentation of training should be available for inspection at any time.

As transmission of HIV and other infectious agents can occur through contact with contaminated needles, blood, blood products, and vaginal secretions, all study staff must take appropriate precautions when collecting and handling biological specimens. Guidance on universal precautions is available from the US Centers for Disease Control and Prevention at:

https://www.cdc.gov/niosh/topics/healthcare/default.html and https://www.cdc.gov/niosh/topics/bbp/

Additional reference information can be requested from the HPTN LC. The information provided below is intended to standardize laboratory procedures for HPTN 084 across the study sites. Adherence to the specifications detailed in this section is essential to ensure that primary, secondary and exploratory endpoint data derived from laboratory testing will be considered acceptable to regulatory authorities.

11.2 Specimen Labeling

All containers into which specimens are initially collected (e.g., blood collection tubes) will be appropriately labeled according to local practices. Participant Identification (PTID) labels will be provided by the HPTN Statistical and Data Management Center (SDMC, SCHARP) if required.
for this function. Laboratory Data Management System (LDMS) Tracking Forms will also be provided for use if required although sites may use their own specimen transport documentation. The staff member who collects the samples will ensure the visit code, specimen collection date and time as well as their initials or code is documented.

More detailed information about the labeling procedures must be provided in the site’s Chain of Custody SOP.

When specimens are tested at the laboratories, any additional labeling required for in-country specimen management or chain of custody will be performed in accordance with site-specific SOPs. Stored specimens will be entered into the LDMS and labeled with LDMS-generated labels.

11.2.1 Local Specimen Processing and Storage

For samples that are processed and stored locally, each sample will be entered into the LDMS and labeled with the LDMS generated labels. If needed, any temporary labels (e.g. during plasma processing) for samples will include at least the full PTID, in addition to any other information required by lab SOPs.

11.2.2 Local Specimen Testing

Sites will follow local testing arrangements for the collection and testing of samples, this will be described in the site SOPs. All lab results must be recorded following local guidelines.

11.2.3 Remote Specimen Testing

Samples that will be sent to the HPTN LC will be entered into the LDMS and labeled with the LDMS generated labels.

11.2.4 Use of the LDMS

LDMS must be used at all sites to track specimens that will be tested, stored, or shipped off-site for testing. Detailed instructions for use of LDMS are available in the LDMS User Manual:

https://www.ldms.org/resources/manuals/

Web (Cloud-Based) https://www.ldms.org/resources/ldms/web/

All sites are responsible for ensuring they are using the most recent version of LDMS. All sites must use the HPTN barcode label format in order to ensure that both the specimen ID and the global specimen ID assigned to each specimen are printed on LDMS-generated labels.

An example of a two-dimensional LDMS-generated barcode label is below:
Windows

Row 1: LDMS Specimen ID
Row 2: Global Specimen ID
Row 3: Patient Identifier (ID1) and Study/Protocol Identifier (ID2)
Row 4: Specimen Date or Harvest Date and Specimen Collection Time
Row 5: Primary Type, Additive Type, Derivative Type, and Sub Additive/Derivative Type
Row 6: Volume/Volume Unit and Visit/Visit Unit (VID)
Row 7: Other Specimen ID (if applicable)

Web

Row 1: Global Specimen ID
Row 2: Patient Identifier (ID1) and Study/Protocol Identifier (ID2)
Row 3: Specimen Date or Harvest Date and Specimen Collection Time
Row 4: Primary Type, Additive Type, Derivative Type, and Sub Additive/Derivative Type
Row 5: Volume/Volume Unit and Visit/Visit Unit (VID)
Questions related to use of LDMS for HPTN 084 should be directed to Yaw Agyei (yagyei1@jhmi.edu).

Technical support for the general use of LDMS is available from Frontier Science. (www.LDMS.org)

**LDMS User Support at Frontier Science**

Regular Hours: 24-hour coverage 7 days a week with the exception of Select US Holidays – Thanksgiving Day, Christmas Day, New Year’s Day, Memorial Day, Independence Day. See below for contact details.

https://www.ldms.org/contact/

Phone: +1 (716) 834-0900, extension 7311

Email: ldmshelp@fstrf.org

Fax: +1 (716) 832-8448 (should be used to fax Installation Reports only)

When you contact LDMS user support, there are certain pieces of information that you can provide to help them better respond to your question. Please provide the following information in your email support:

1. **Your name**

2. **Your laboratory’s LDMS ID number**
   This is a 3-digit number assigned by Frontier Science to uniquely identify your laboratory. It appears when you start LDMS, and can also be found in the bottom-right corner of the screen.

3. **A full explanation of the issue**
   Your explanation should include any error messages or error numbers that appeared, what you were doing in LDMS at the time the issue occurred, and steps needed to reproduce the issue. The more details that you can provide, the faster LDMS User Support can help you.

4. **How you want to be contacted**
   If you want LDMS user support to call a specific telephone number, please provide that number and extension.

5. **(If applicable) The license code or challenge code being generated by LDMS**
   Note: If you are contacting user support about a license or challenge code, do not close the window with the code. Doing so will cause LDMS to generate a new code.
Below are a few other details that can also be helpful to include in your email:

1. Have there been any recent changes to the computer with LDMS, such as new hardware installed, a firewall upgrade, a network name change, or another change?

2. Are you or another user able to repeat the issue?

3. If you have LDMS installed on multiple computers, does the issue occur on all of them or does it only occur on a specific computer?

Each site using the windows version of LDMS must export its LDMS data to Frontier Science (FSTRF) on a minimum weekly basis or whenever changes or additions are made to the LDMS database.

Exported data are used by the HPTN SDMC to generate daily Specimen Data Quality Check (SDQC) reports comparing the data from the LDMS with that entered onto the CRFs/Medidata Rave. Any discrepancies identified are included in the SDQC for each site. The HPTN SDMC reviews the discrepancy reports for critical samples (e.g., plasma needed for confirmatory HIV testing) that appear to be missing and works with the LC and site staff to undertake appropriate corrective action. All corrective action should be documented in paper-based clinic and/or laboratory records per site standards (CAPA or NTF) as appropriate and entered in the details section of LDMS. Any corrections to the LDMS need to be made following guidelines provided by FSTRF on behalf of the HPTN LC.

11.2.5 LDMS Reconciliation

All sites must follow the HPTN LC approved site-specific SOP for regular reconciliation and verification of specimens that are stored; these independent SOPs or detailed Chain of Custody procedures must be followed throughout the study. All sites must also create a monthly Primary Specimen report to submit to the HPTN LC for review. See section11.12 for directions on how to make a primary specimen report. The report will provide the HPTN LC with the primary blood draw information for each participant logged into the LDMS. In addition, all sites must create a Specimen Log report to submit weekly to the HPTN LC for review. See section 11.12 for directions on how to make a specimen log report. The report will provide the HPTN LC with the participant, primary, and aliquot information for each of the specimens logged into the site LDMS during the week. The report also provides the condition codes, comments, and shipping information (if available) for the given specimens. In the event that the required volume or number of sample aliquots based on Sections 11.3 and 11.4 is not obtained at any time point, designated site clinic and lab staff must immediately inform the HPTN LC. The LC will liaise with the LOC, and HPTN SDMC and will provide guidance on how to respond to the problem. In addition to following this guidance, designated site and lab staff will work together to document the problem, take appropriate corrective and preventive action, and document all action taken. Reconciliation must be performed for all specimen types that are received by the laboratory and stored in the LDMS. It is the originating processing LDMS laboratory responsibility to notify subsequent laboratories with changes, corrections, and modification to LDMS entries of shipped samples e.g. DBS cards, Plasma aliquots.
11.3 Protocol related testing and sample collection

Samples will be collected and processed at the screening, enrollment, and follow up visits as indicated in tables 11-1, 11-2, 11-3.

Participants who have received at least one injection and refuse further injections or discontinue due to an AE will enter Step 3 and be followed on open-label TDF/FTC according to Step 3 as indicated in table 11-3.

Participants who are unable to receive the first injection for any reason will be terminated from the study. If the reason is due to HIV infection, those participants will be referred for care and will be terminated from the study.

Collect specimens and label tubes according to manufacturer recommendations and local regulations as well as the Blood Collection, Breast milk, Cord blood, and Urine Collection SOPs. Blood collection tubes must be filled to the appropriate fill level as indicated by the tube manufacturer. After collection:

- EDTA tubes should be gently inverted at least 8 times (or as specified by manufacturer) after specimen collection, to prevent clotting.
- EDTA collections must be performed after samples collected for serum chemistry testing.
- For plasma storage, 20 mL of whole blood should be collected into spray dried EDTA tubes, e.g. BD 366643 or other, to yield 5 x 1.8mL plasma aliquots.
- For Pharmacogenomic testing, a minimum of 1mL of whole blood should be collected in an EDTA tube.
- For Cord blood, collect in a 5mL K2EDTA tube, to yield 2 X 1.0ml plasma aliquots.
- For infant collections, collect 750uL to 1ml K2EDTA to yield 300uL of plasma.
- Breast milk will be collected in sufficient quantity to store a minimum of 3 mL of whole breast milk.
Table 11-1: Schedule of Study Visits and Specimen Collection –Step 1. Screening, Enrollment, Week 2 and 4.

<table>
<thead>
<tr>
<th>Specimen Collection</th>
<th>Screening</th>
<th>Day 0 Enrollment</th>
<th>Week 2</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing¹</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy testing²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>HBV and HCV testing³</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC with Differential</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry testing (BUN/urea, creatinine, CPK, calcium, phosphorous, glucose, amylase and lipase)</td>
<td>X</td>
<td>Creatinine only</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Liver Function Test (AST, ALT, total bilirubin, alkaline phosphatase)</td>
<td>X</td>
<td>ALT and Total Bilirubin only</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Fasting Lipid Profile⁴</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis serological testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GC/CT and TV testing⁵</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinalysis (protein and glucose)⁶</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma Storage⁷</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage⁷</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Whole blood storage⁷</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Additional sample storage for participants enrolled in the Injectable Contraception Sub-Study⁷</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

¹ Following the HIV algorithms described in SSP figures 11.1 to 11.3, section 11.3. RNA testing for acute HIV must be negative and must be performed within 14 days of enrolling the participant. At least one HIV test must be available the same day as sample collection and before product is administered. HIV testing does not need to be performed after confirmation of HIV infection (based on results from samples collected on two separate dates).

² Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant.

³ At Screening: HBsAg and HCV antibody testing. At Enrollment: HBsAb and HBeAb total testing. Note: These tests can all be done at Screening at the discretion of the IOR.

⁴ At Screening: HBsAg and HCV antibody testing. At Enrollment: HBsAb and HBeAb total testing. Note: These tests can all be done at Screening at the discretion of the IOR.

⁵ The fasting lipid profile includes total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.

⁶ GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab.

⁷ Urinalysis may be performed in the clinic or the laboratory. Results from urinalysis are not needed prior to enrollment.

⁸ See section 11.4 for plasma processing and storage instructions; section 11.6 for DBS processing and storage instructions; section 11.7 for whole blood storage instructions; section 11.5 for Injectable Contraception sub-study storage instructions. Blood must be collected prior to study product administration during the visit. Also, record the date that the participant’s LARC was last injected/inserted). Whole blood collection and storage is only required for participants who consent to genetic testing.
### Table 11-2: Schedule of Study Visits and Specimen Collection – Step 2. Blinded Injections and Daily Oral Pills

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 9</th>
<th>Week 13</th>
<th>Week 17</th>
<th>Week 21</th>
<th>Week 25</th>
<th>Week 33</th>
<th>Week 41</th>
<th>Week 42</th>
<th>Week 49</th>
<th>Week 57</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing&lt;sup&gt;1&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pregnancy testing&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV antibody testing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>CBC with Differential</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry testing (BUN/urea, creatinine, CPK, calcium, phosphorous, glucose, amylase and lipase)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>LFT (AST, ALT, total bilirubin, alkaline phosphatase)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fasting Lipid Profile&lt;sup&gt;3&lt;/sup&gt;</td>
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<td></td>
<td>X</td>
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<tr>
<td>(Total Cholesterol, HDL, LDL, Triglycerides)</td>
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<tr>
<td>Syphilis serological testing</td>
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<td>X</td>
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<tr>
<td>Urine GC/CT and TV testing&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
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<td>X</td>
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<tr>
<td>Urinalysis (protein and glucose)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Plasma Storage&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>DBS storage&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td>X</td>
</tr>
<tr>
<td>Additional sample storage for participants enrolled in the injectable Contraception Sub-study&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

<sup>1</sup> Following the HIV algorithms described in SSP figures 11.1 to 11.3, section 11.3.1. At least one HIV test must be available the same day as sample collection and before product is administered. HIV testing does not need to be performed after confirmation of HIV infection (based on results from samples collected on two separate dates). Additional HIV testing may be requested by the 084HIV alias.

<sup>2</sup> Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant.

<sup>3</sup> Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.

<sup>4</sup> GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab.

<sup>5</sup> See section 11.4 for plasma processing and storage instructions; section 11.6 for DBS processing and storage instructions; section 11.5 for Injectable Contraception sub-study storage instructions. Whole blood collection and storage is only required for participants who consent to genetic testing.
Table 11-2 (Cont’d): Schedule of Study Visits and Specimen Collection – Step 2. Blinded Injections and Daily Oral Pills

<table>
<thead>
<tr>
<th>Test</th>
<th>Week 65</th>
<th>Week 73</th>
<th>Week 81</th>
<th>Week 89</th>
<th>Week 97</th>
<th>Week 105</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy testing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HCV antibody testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>CBC with Differential</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry testing (BUN/urea, creatinine, CPK, calcium, phosphorous, glucose, amylase and lipase)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>LFT (AST, ALT, total bilirubin, alkaline phosphatase)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fasting Lipid Profile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>(Total Cholesterol, HDL, LDL, Triglycerides)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Syphilis serological testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urine GC/CT testing and TV testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urinalysis (protein and glucose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Plasma Storage</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Additional sample storage for participants enrolled in the injectable Contraception Sub-study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

1 Following the HIV algorithms described in SSP figures 11.1 to 11.3, section 11.3.1. At least one HIV test must be available the same day as sample collection and before product is administered. HIV testing does not need to be performed after confirmation of HIV infection (based on results from samples collected on two separate dates). Additional HIV testing may be requested by the 084HIV alias.

2 Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant.

3 Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.

4 GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab.

5 See section 11.4 for plasma processing and storage instructions; section 11.6 for DBS processing and storage instructions; section 11.5 for Injectable Contraception sub-study storage instructions. Whole blood collection and storage is only required for participants who consent to genetic testing.
Table 11-2 (Cont’d): Schedule of Study Visits and Specimen Collection – Step 2. Blinded Injections and Daily Oral Pills

<table>
<thead>
<tr>
<th></th>
<th>Week 113</th>
<th>Week 121</th>
<th>Week 129</th>
<th>Week 137</th>
<th>Week 145</th>
<th>Week 153</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing(^1)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy testing(^2)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HCV antibody testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>CBC with Differential</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry testing (BUN/urea, creatinine, CPK, calcium, phosphorous, glucose, amylase and lipase)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>LFT (AST, ALT, total bilirubin, alkaline phosphatase)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fasting Lipid Profile(^3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Total Cholesterol, HDL, LDL, Triglycerides)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis serological testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urine GC/CT testing and TV testing(^4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urinalysis (protein and glucose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Plasma Storage(^5)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage(^5)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

\(^1\) Following the HIV algorithms described in SSP figures 11.1 to 11.3, section 11.3.1. At least one HIV test must be available the same day as sample collection and before product is administered. HIV testing does not need to be performed after confirmation of HIV infection (based on results from samples collected on two separate dates). Additional HIV testing may be requested by the 084HIV alias.

\(^2\) Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant.

\(^3\) Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.

\(^4\) GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab.

\(^5\) See section 11.4 for plasma processing and storage instructions; section 11.6 for DBS processing and storage instructions.
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Week 161</th>
<th>Week 169</th>
<th>Week 177</th>
<th>Week 185</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing&lt;sup&gt;1&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy testing&lt;sup&gt;2&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HCV antibody testing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CBC with Differential</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry testing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>(BUN/urea, creatinine, CPK, calcium, phosphorous, glucose, amylase and lipase)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>LFT (AST, ALT, total bilirubin, alkaline phosphatase)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fasting Lipid Profile&lt;sup&gt;3&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>(Total Cholesterol, HDL, LDL, Triglycerides)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Syphilis serological testing</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine GC/CT testing and TV testing&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Urinalysis (protein and glucose)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Plasma Storage&lt;sup&gt;5&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

---

1. Following the HIV algorithms described in SSP figures 11.1 to 11.3, section 11.3.1 HIV testing does not need to be performed after confirmation of HIV infection (based on results from samples collected on two separate dates). Additional HIV testing may be requested by the 084HIV alias.

2. Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant.

3. Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.

4. GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab.

5. See section 11.4 for plasma processing and storage instructions; section 11.6 for DBS processing and storage instructions.
Table 11-3: Schedule of Study Visits and Specimen Collection – Step 3. Open Label TDF/ FTC Daily Oral (Post-Last Injection)

<table>
<thead>
<tr>
<th></th>
<th>Step 3 Day 0*</th>
<th>Step 3 Week 12</th>
<th>Step 3 Week 24</th>
<th>Step 3 Week 36</th>
<th>Step 3 Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing¹</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy testing²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry testing³</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver function testing⁴</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis testing</td>
<td>X³</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GC/CT and TV testing⁵</td>
<td>X⁵</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma storage⁷</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage⁷</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

¹ Following the HIV algorithms described in SSP figures 11.1 to 11.3, section 11.3.1. At least one HIV test must be available the same day as sample collection and before product is administered. HIV testing does not need to be performed after confirmation of HIV infection (based on results from samples collected on two separate dates). Additional HIV testing may be requested by the 084HIV alias.

² Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant.

³ Chemistry testing includes: BUN/Urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.

⁴ Liver function testing includes: AST, ALT, TBili, and alkaline phosphatase.

⁵ Skip Day 0 if testing has occurred within the last 3 months of Day 0 and do only at Weeks 24 and 48.

⁶ GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab.

⁷ See section 11.4 for plasma processing and storage instructions; section 11.6 for DBS processing and storage instructions.
### Table 11-4: Additional Procedures: Participants who have a Reactive or Positive HIV test at any time after Enrollment

<table>
<thead>
<tr>
<th>Procedure</th>
<th>HIV Confirmation visit</th>
<th>Post HIV + Week 12</th>
<th>Post HIV + Week 24</th>
<th>Post HIV + Week 36</th>
<th>Post HIV + Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing&lt;br&gt;2</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 cell count.</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV viral load testing</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV resistance testing&lt;br&gt;3</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry testing (BUN/Urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, lipase)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>LFT (AST, ALT, total bilirubin, alkaline phosphatase)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Plasma Storage&lt;br&gt;4,5</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage&lt;br&gt;5</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. The week 48 visit should be timed as closely as possible to 52 weeks after the participant received their last injection.
2. The HIV confirmatory visit must be held on a different day from the visit where the participant had their initial reactive/positive HIV test. The testing algorithm for the HIV Confirmation Visit is provided in the SSP Manual. If HIV rapid testing is included in the HIV testing algorithm, this testing may be performed in the clinic or the laboratory. Additional HIV testing may be requested by the 084HIV alias.
3. Sites may collect specimens for resistance testing at a local laboratory to assist with clinical management; results from resistance testing performed at local laboratories will not be reported to the SDMC. Stored plasma may not be used real-time/local resistance testing; additional samples must be collected for this testing.
4. Stored plasma will be used for Quality Assurance testing and other assessments at the HPTN LC (see Section 9). Assessments will be performed retrospectively; results will not be returned to study sites or participants, except as noted in Section 9.0.
5. See section 11.4 for plasma processing and storage instructions; section 11.6 for DBS processing and storage instructions.

The Seroconversion Committee (084HIV@hptn.org) must be notified immediately and study drug should be discontinued if one or more reactive HIV test results are obtained on the Laboratory based test at enrollment or at any follow up visit after enrollment. The procedures listed for Weeks 12, 24, 36, and 48 apply only to participants with confirmed HIV infection during Step 2 of the study. Participants with confirmed HIV infection in Step 3 of the study may undergo similar procedures and will be determined by the members of the 084HIV@hptn.org. Note that participants who acquire HIV infection during Step 1 will permanently discontinue study product, will be terminated from the study, and referred for HIV related care. The additional blood draw for HIV testing and plasma storage at the HIV confirmation visit should be performed on a different date than the blood draw that gave the initial reactive or positive HIV test.
Table 11-5: Schedule of Study Visits and Specimen Collection: For Pregnant Participants

<table>
<thead>
<tr>
<th>WEEKS in Study</th>
<th>4 weeks after first positive pregnancy test</th>
<th>Quarterly Visit 1 (12 weeks since first positive pregnancy test)</th>
<th>Quarterly Visit 2 (24 weeks since first positive pregnancy test)</th>
<th>Quarterly Visit 3 (36 weeks since first positive pregnancy test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

**LOCAL LABORATORY EVALUATIONS & PROCEDURES**

<table>
<thead>
<tr>
<th>HIV testing(^1)</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy testing(^2)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry testing(^4)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver function testing(^5)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Syphilis testing</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal GC/CT and TV Testing(^3)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma storage(^6)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

\(^1\) The HIV testing algorithm is provided in the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory. At least one HIV test must be available the same day as sample collection and before product is administered.

\(^2\) Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant. If the confirmatory pregnancy test is positive, the participant is referred for an Ultrasound and evaluation by an obstetric specialist at about 12-14 weeks gestational age, for other testing, counseling, and management. Further biochemical blood testing may be done as indicated. All findings and outcomes will be collected and reported.

\(^3\) GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab.

\(^4\) BUN/urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.

\(^5\) AST, ALT, TBili, and alkaline phosphatase.

\(^6\) Stored plasma will be used for Quality Assurance testing and other assessments at the HPTN LC (see Section 9). Assessments will be performed retrospectively; results will not be returned to study sites or participants, except as noted in Section 9.0.

\(^7\) If not done within 4 weeks of initial positive pregnancy test.
### Table 11-6: Schedule of Evaluations - Step 2, Injectable Contraceptive Substudy ONLY

| Weeks in study | Enrollment | 5 | 6 | 13 | 17 | 21 | 25 | 33 | 41 | 42 | 46 | 57 | 65 | 73 | 81 | 89 | 97 | 105 | 113 | 121 | 129 | 137 | 145 | 153 | 161 | 169 | 177 | 185 |
|----------------|------------|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Plasma storage 1,2 | X          |   |   | X  | X  | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| DBS 1,2         | X          |   |   | X  | X  | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

1. Additional stored plasma will be used for PK evaluations and DMPA, NET-EN, Etonogestrel
2. Blood must be collected prior to study product administration during the visit. Also, record the date that the participant’s LARC was last injected/inserted.
11.3.1 Open Label (OL) Cabotegravir samples.

Table 11-7: Schedule of Evaluations - Step 4a, Participants initially randomized to TDF/FTC who elect to move to OL CAB LA with optional Oral Lead-In First.

<table>
<thead>
<tr>
<th>Test Description</th>
<th>DAY 0/ of Step 4a</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing(^2)</td>
<td>X</td>
</tr>
<tr>
<td>HIV viral load testing(^3)</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy testing(^1)</td>
<td>X</td>
</tr>
<tr>
<td>CBC with differential,</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry testing(^4)</td>
<td>X</td>
</tr>
<tr>
<td>Liver function tests(^5)</td>
<td>X</td>
</tr>
<tr>
<td>Fasting lipid profile,</td>
<td></td>
</tr>
<tr>
<td>Plasma storage(^7,8)</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage(^8)</td>
<td>X</td>
</tr>
</tbody>
</table>

\(^1\) Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant.

\(^2\) HIV rapid testing may be performed in the clinic or the laboratory. At least one HIV test must be available the same day as sample collection and before product is administered.

\(^3\) This testing will be performed for all study participants, regardless of HIV status or the results of other HIV tests. This testing must be performed with an assay with a lower limit of quantification of 50 copies/mL or lower.

\(^4\) Albumin, BUN/urea, creatinine. Additional testing may be required if abnormalities of clinical significance are detected.

\(^5\) AST, ALT, total bilirubin.

\(^6\) Total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.

\(^7\) Stored plasma may be used for Quality Assurance testing, possible HSV-2 testing and other assessments at the HPTN LC.

\(^8\) Assessments on stored samples will be performed retrospectively; results will not be returned to study sites or participants, except as noted in the SSP.
Table 11-8: Schedule of Evaluations - Step 4b, Participants initiating or re-starting CAB LA without the optional Oral Lead-In; the initial Dose Visit.

<table>
<thead>
<tr>
<th>Test</th>
<th>DAY 0/ of Step 4b</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing(^2)</td>
<td>X</td>
</tr>
<tr>
<td>HIV viral load testing(^3)</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy testing(^1)</td>
<td>X</td>
</tr>
<tr>
<td>CBC with differential, if not done in Step 4a</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry testing(^4)</td>
<td>X</td>
</tr>
<tr>
<td>Liver function tests(^5)</td>
<td>X</td>
</tr>
<tr>
<td>Fasting lipid profile, if not done in Step 4a(^6)</td>
<td>X</td>
</tr>
<tr>
<td>Plasma storage(^7,8)</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage(^8)</td>
<td>X</td>
</tr>
</tbody>
</table>

\(^1\) Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant.

\(^2\) HIV rapid testing may be performed in the clinic or the laboratory. At least one HIV test must be available the same day as sample collection and before product is administered.

\(^3\) This testing will be performed for all study participants, regardless of HIV status or the results of other HIV tests. This testing must be performed with an assay with a lower limit of quantification of 50 copies/mL or lower.

\(^4\) Albumin, BUN/urea, creatinine. Additional testing may be required if abnormalities of clinical significance are detected.

\(^5\) AST, ALT, total bilirubin.

\(^6\) Total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.

\(^7\) Stored plasma may be used for Quality Assurance testing, possible HSV-2 testing and other assessments at the HPTN LC.

\(^8\) Assessments on stored samples will be performed retrospectively; results will not be returned to study sites or participants, except as noted in the SSP.
Table 11-9: Schedule of Evaluations - Step 4c, Participants on maintenance Dose of CAB LA or TDF/FTC

<table>
<thead>
<tr>
<th>Time on OL Study Product</th>
<th>Week 0 of Step 4c</th>
<th>Week 8</th>
<th>Week 16</th>
<th>Week 24</th>
<th>Week 32</th>
<th>Week 40</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing(^2)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HIV viral load testing(^3)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy testing(^4)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CBC with differential, if not done in Step 4a or 4b</td>
<td>X(^5)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Chemistry testing,(^4)</td>
<td>X(^4)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Liver function testing(^6)</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fasting lipid profile(^7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Syphilis testing</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Vaginal GC/CT and TV testing(^8)</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Urinalysis (protein, glucose)</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Plasma storage(^8,9,10)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage(^9)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

1 Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant.

2 HIV rapid testing may be performed in the clinic or the laboratory. At least one HIV test must be available the same day as sample collection and before product is administered.

3 This testing will be performed for all study participants, regardless of HIV status or the results of other HIV tests. This testing must be performed with an assay with a lower limit of quantification of 50 copies/mL or lower.

4 Albumin, BUN/urea, creatinine. Additional testing may be required if abnormalities of clinical significance are detected.

5 Only for those who did not have this collected in steps 4a and 4b

6 AST, ALT, total bilirubin.

7 Total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.
GC/CT and TV testing to be done only if not performed in the past 3 months. GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab. If a woman is menstruating, the swab may be collected at a later visit and all testing using the swab may be performed at that later visit.

Stored plasma may be used for Quality Assurance testing, possible HSV-2 testing and other assessments at the HPTN LC.

Assessments on stored samples will be performed retrospectively; results will not be returned to study sites or participants, except as noted in the SSP.
Table 11-10: Schedule of Evaluations - Step 4d, Participants who become pregnant during step 4 and who received at least one CAB LA injection.

<p>| Time on Pregnancy and Infant Sub-study | Week 0 | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24 | Week 28 | Week 32 | Week 36 | Week 40 | Delivery | Week 2, pp | Week 4, pp | Week 8, pp | Week 16, pp | Week 24, pp | Week 32, pp | Week 40, pp | Week 48, pp |
|---------------------------------------|--------|--------|--------|---------|---------|---------|---------|---------|---------|---------|---------|----------|-----------|------------|------------|------------|------------|------------|------------|------------|-----------|
| HIV testing¹                         | X      | X      | X      | X       | X       | X       | X       | X       | X       | X       | X       | X        | X         | X          | X          | X          | X          | X          | X          | X          |
| HIV viral load testing²              | X      | X      | X      | X       | X       | X       | X       | X       | X       | X       | X       | X        | X         | X          | X          | X          | X          | X          | X          | X          |
| Pregnancy testing³                   |        |        |        |         |         |         |         |         |         |         |         | X        | X         | X          | X          | X          | X          | X          | X          | X          |
| CBC with differential                | X      |        |        |         |         |         |         |         |         |         |         |         | X         | X          | X          | X          | X          | X          | X          | X          |
| Chemistry testing⁴                   | X      | X      |        |         |         |         |         |         |         |         |         |         | X         | X          | X          | X          | X          | X          | X          | X          |
| Liver function testing⁵              | X      |        |        |         |         |         |         |         |         |         |         |         | X         | X          | X          | X          | X          | X          | X          | X          |
| Syphilis testing                     | X      |        |        |         |         |         |         |         |         |         |         |         | X         | X          | X          | X          | X          | X          | X          | X          |
| Vaginal GC/CT and TV testing⁶        | X      |        |        |         |         |         |         |         |         |         |         |         | X         | X          | X          | X          | X          | X          | X          | X          |
| Urinalysis (protein, glucose)        | X      |        |        |         |         |         |         |         |         |         |         |         | X         | X          | X          | X          | X          | X          | X          | X          |</p>
<table>
<thead>
<tr>
<th>Time on Pregnancy and Infant Sub-study</th>
<th>Week 0</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 20</th>
<th>Week 24</th>
<th>Week 28</th>
<th>Week 32</th>
<th>Week 36</th>
<th>Week 40</th>
<th>Delivery</th>
<th>Week 2, pp</th>
<th>Week 4, pp</th>
<th>Week 8, pp</th>
<th>Week 16, pp</th>
<th>Week 24, pp</th>
<th>Week 32, pp</th>
<th>Week 40, pp</th>
<th>Week 48, pp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma storage&lt;sup&gt;7,8,&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Breastmilk storage&lt;sup&gt;8,9,&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage for women on TDF/FTC only&lt;sup&gt;8,10&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Infant assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Delivery</td>
<td>Week 2, pp</td>
<td>Week 4, pp</td>
<td>Week 8, pp</td>
<td>Week 16, pp</td>
<td>Week 24, pp</td>
<td>Week 32, pp</td>
<td>Week 40, pp</td>
</tr>
<tr>
<td>Infant HIV testing, if the mother has one or more reactive/positive HIV test result&lt;sup&gt;11&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cord blood storage&lt;sup&gt;8,12&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dried Blood spot storage&lt;sup&gt;8,12&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
NOTE: PK analysis will be performed on cord blood and infant plasma samples at an offsite laboratory.

1 HIV rapid testing may be performed in the clinic or the laboratory. At least one HIV test must be available the same day as sample collection and before product is administered.

2 This testing will be performed for all study participants, regardless of HIV status or the results of other HIV tests. This testing must be performed with an assay with a lower limit of quantification of 50 copies/mL or lower.

3 Pregnancy testing may be done if indicated. Pregnancy testing may be performed in the clinic or the laboratory. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant.

4 Albumin, BUN/urea, creatinine. Additional testing may be required if abnormalities of clinical significance are detected.

5 AST, ALT, total bilirubin.

6 GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab. If a woman is menstruating, the swab may be collected at a later visit and all testing using the swab may be performed at that later visit.

7 Stored plasma may be used for Quality Assurance testing, possible HSV-2 testing and other assessments at the HPTN LC.

8 Assessments on stored samples will be performed retrospectively; results will not be returned to study sites or participants, except as noted in the SSP.

9 Breastmilk collection does not need to be performed if the mother is not breastfeeding or producing milk.

10 DBS will be stored for participants who elect to receive TDF/FTC. Processing and storage procedures will be described in detail in the SSP. Assessments will be performed retrospectively; results will not be returned to study sites or participants.

11 Perform infant HIV testing at this visit and all subsequent study visits using local infant testing algorithms if the mother has one or more reactive/positive tests, even if HIV infection in the mother is not confirmed. If HIV testing indicates that an infant has HIV infection, a second confirmatory visit should be conducted to confirm HIV infection in the infant. If infant infection is confirmed, resistance testing should be performed locally using a separate (additional) infant sample collected for this purpose.

12 Stored cord blood, DBS, and plasma samples will be used for PK analysis and may be used for other assessments, including virology testing. Results from this testing will not be returned to the study sites or participants.
### Table 11-11: Schedule of Evaluations - Step 5, Participants taking OL TDF/FTC for 48 weeks after premature CAB LA discontinuation.

<table>
<thead>
<tr>
<th>Time in Step 5</th>
<th>Step 5, Day 0*</th>
<th>Step 5, Week 12</th>
<th>Step 5, Week 24</th>
<th>Step 5, Week 36</th>
<th>Step 5, Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing¹</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HIV viral load testing²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy testing³</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry testing⁴</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Liver function testing⁵</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Syphilis testing</td>
<td>X³</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>GC/CT and TV testing⁶</td>
<td>X³</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Plasma storage⁷⁻⁸</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage⁸</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

¹ HIV rapid testing may be performed in the clinic or the laboratory. At least one HIV test must be available the same day as sample collection and before product is administered.

² This testing will be performed for all study participants, regardless of HIV status or the results of other HIV tests. This testing must be performed with an assay with a lower limit of quantification of 50 copies/mL or lower.

³ Pregnancy testing may be done if indicated. Pregnancy testing may be performed in the clinic or the laboratory. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant.

⁴ Albumin, BUN/urea, creatinine. Additional testing may be required if abnormalities of clinical significance are detected.

⁵ AST, ALT, total bilirubin.

⁶ GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab. If a woman is menstruating, the swab may be collected at a later visit and all testing using the swab may be performed at that later visit.

⁷ Stored plasma may be used for Quality Assurance testing, possible HSV-2 testing and other assessments at the HPTN LC.

⁸ Assessments on stored samples will be performed retrospectively; results will not be returned to study sites or participants, except as noted in the SSP.
Table 11-12: Schedule of Evaluations – Participants with Reactive/Positive HIV tests during OL portion of the trial

<table>
<thead>
<tr>
<th>Participants who acquire HIV infection</th>
<th>HIV Confirmation Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing(^1)</td>
<td>X</td>
</tr>
<tr>
<td>CD4 cell count</td>
<td>X</td>
</tr>
<tr>
<td>HIV viral load testing(^2)</td>
<td>X</td>
</tr>
<tr>
<td>HIV resistance testing(^3)</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry testing(^4)</td>
<td>X</td>
</tr>
<tr>
<td>Liver function testing(^5)</td>
<td>X</td>
</tr>
<tr>
<td>Plasma storage(^6,7)</td>
<td>X</td>
</tr>
<tr>
<td>DBS Storage(^7)</td>
<td>X</td>
</tr>
</tbody>
</table>

\(^1\) The HIV confirmatory visit must be held on a different day from the visit where the participant had their initial reactive/positive HIV test. The testing algorithm for the HIV Confirmation Visit is provided in the SSP Manual. If HIV rapid testing is included in the HIV testing algorithm, this testing may be performed in the clinic or the laboratory. Additional HIV testing may be requested by the 084HIV alias committee.

\(^2\) This testing must be performed with an assay with a lower limit of quantification of 50 copies/mL or lower.

\(^3\) Sites may collect specimens for resistance testing at a local laboratory to assist with clinical management; results from resistance testing performed at local laboratories will not be reported to the SDMC. Stored plasma may not be used for real-time/local resistance testing; additional samples must be collected for this testing.

\(^4\) Required chemistry testing: Albumin, BUN/urea, creatinine

\(^5\) Required LFTs: AST, ALT, total bilirubin

\(^6\) Stored plasma will be used for Quality Assurance testing and other assessments at the HPTN LC.

\(^7\) Assessments on stored samples will be performed retrospectively; results will not be returned to study sites or participants, except as noted in the SSP. Additional HIV testing may be requested by the 084 HIV alias committee.
Table 11-13: Schedule of Evaluations – Step 6, Participants on Maintenance Doses of CAB LA weeks 49-96 (or Weeks 49-112)

<table>
<thead>
<tr>
<th>Time in Step 6 **</th>
<th>Week 56</th>
<th>Week 64</th>
<th>Week 72</th>
<th>Week 80</th>
<th>Week 88</th>
<th>Week 96</th>
<th>Week 104</th>
<th>Week 112</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HIV viral load testing³</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy testing, only if indicated¹</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry testing⁴</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Liver function testing⁶</td>
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<td>X</td>
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<tr>
<td>Syphilis testing</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>GC/CT and TV testing⁵</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Plasma storage⁷,⁸</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>DBS storage⁸</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

** Participants will flow from Step 4c into Step 6.

1 Urine will only be collected when needed for pregnancy testing or for GC/CT testing. Pregnancy testing will only be conducted when clinically indicated and for participants who are either not on birth control or who have had a lapse in birth control coverage. Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant. If a participant has a positive pregnancy test, and is eligible, follow her according to the Step 4d SOE.

2 HIV rapid testing may be performed in the clinic or the laboratory. At least one HIV test must be available the same day as sample collection and before product is administered.

3 This testing will be performed for all study participants, regardless of HIV status or the results of other HIV tests. This testing must be performed with an assay with a lower limit of quantification of 50 copies/mL or lower.

4 Albumin, BUN/urea, creatinine. Additional testing may be required if abnormalities of clinical significance are detected.

5 GC/CT and TV testing to be done only if not performed in the past 3 months. GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab. If a woman is menstruating, the swab may be collected at a later visit and all testing using the swab may be performed at that later visit

6 AST, ALT, total bilirubin.

7,8 Stored plasma may be used for Quality Assurance testing, possible HSV-2 testing and other assessments at the HPTN LC.

8 Assessments on stored samples will be performed retrospectively; results will not be returned to study sites or participants, except as noted in the SSP.

### 11.3.2 HIV Testing
All HIV test results from previous visits, and at least one HIV test result from the current visit, must be available and reviewed prior to administration of study products. If any of these tests is reactive/positive, study drug should not be administered. **HIV rapid testing must be performed the same day and prior to administration of study drug.**

HIV testing will be performed using blood collected by phlebotomy (no finger-stick or oral fluid testing) at participant visits in accordance with the testing algorithms described in Figures 11.1 through 11.3.

For further help on implementing the HIV testing algorithm prior to study start, seek guidance from the HPTN LC.

Whole blood will be collected according to site-specific procedures.

Participants with one or more reactive HIV test results at the screening visit (Figure 11.1) or enrollment visit (see notes associated with Figure 11.2 regarding result review) will not be eligible for enrollment, regardless of subsequent test results.

RNA testing for acute HIV infection must be collected and performed within the 14 days prior to the Enrollment visit.

RNA testing must be collected and performed at all visits after enrollment.

Every time a blood specimen is drawn for HIV testing, additional blood must be drawn for plasma storage if it does not exceed the visit blood draw limits stated in your local consent forms. This includes split visits, interim visits, and all visits for repeat HIV testing and confirmatory testing. The amount of blood drawn if not limited by consent forms should be sufficient to yield 5 x 1.8mL (approximately) plasma aliquots. See additional testing information below for split and interim visits.

During the open-label part of this study, both the CMC (084cmc@hptn.org) and HIV alias (084HIV@hptn.org) lists should be contacted immediately about any HIV reactive or positive results or seroconversion events) at any follow-up visit after enrollment. In certain circumstances as outlined in Appendix I Discordant-Discrepent Testing Management, the Seroconversion committee may request further testing and additional sample collections on a case by case basis. Per Appendix I, participants may be placed on product hold and the additional testing results need to be communicated to the Seroconversion Committee promptly upon receipt. In addition, select samples will be requested for further testing at the HPTN LC in order to assist with the HIV diagnosis. These samples should be shipped as soon as possible per the instructions from the Seroconversion Committee.

Additional HIV testing may be performed at any time at the discretion of the site investigator/clinician.

All tests and associated QC procedures must be documented on local laboratory log sheets or other laboratory source documents. Kit lot numbers and expiry dates must also be documented. Note that US FDA-cleared HIV rapid tests are required.
All staff involved in HIV testing and verification of HIV test results should be aware of the testing time frame for the HIV test, so that all tests are performed, read, and confirmed within the specified time frame of testing. Place appropriate timekeeping devices in all test settings to ensure that each test is read and verified at appropriate time points. Documentation is required for the testing start and stop times, as well as, result confirmation and verification times (second trained staff member confirms initial reading). These must be recorded on testing log sheets.

If a participant has a reactive or positive HIV test, the participant will not receive additional doses of study products pending further direction regarding testing and continued participation in the study from designated study team members.

If a participant has a reactive or positive HIV test at any time after enrollment, additional blood draw and testing is required as detailed in Table 11-4.

HIV infection must be confirmed using two independent samples collected on different days. Plasma storage is required at every visit at which HIV testing is performed.

For split visits, excluding confirmation visits (held specifically to perform further HIV testing), the laboratory-based HIV EIA (4th Gen/5th Gen) and viral load assay does not need to be repeated if the split visit (i.e. x.1) occurs less than seven days from the initial visit (i.e. x.0). If the split visit is seven or more days from the initial visit, all HIV lab assay must be repeated. This also applies to DBS samples if regularly scheduled for that visit (i.e. if repeating HIV testing at seven or more days, repeat DBS collection and storage with that day’s visit). Keep all samples from all visits unless specifically directed to handle stored samples differently by the HPTN LC.

Participants with confirmed HIV infection during Step 1, prior to receipt of their first injection will have oral study product permanently discontinued and will be transitioned to local HIV-related care and terminated from the study.

Participants with confirmed HIV infection during Step 2 will not receive additional injections or oral study product and will be followed per the Schedule of Evaluations and Procedures in Appendix II of the protocol for approximately 48 weeks.

Participants with confirmed HIV infection during Step 3 will be followed quarterly, at least for the duration of Step 3, with possible additional assessments and follow-up to be determined by the members of CMC and HIV alias.

Additional samples from participants with confirmed HIV infection may be sent to a local laboratory for resistance testing to assist with clinical management (results from resistance testing performed in local laboratories should not be reported to the HPTN SDMC or the HPTN LC).
Figure 11.1  HIV Testing Algorithm at the Screening Visit

HIV Testing Algorithm at Screening*

All Participants

US FDA-cleared HIV Rapid Test\(^a\)

Non-reactive

Laboratory based HIV Immunoassay (Capable of detecting HIV antigen and antibody)\(^b\)

Non-reactive

HIV RNA Test for acute HIV infection\(^c\)

Reactive

Reactive

Reactive

Non-reactive

This individual is not eligible for enrollment if any HIV test is reactive/positive. Follow local testing guidelines to determine HIV infection status.

This individual is eligible to attend the Enrollment visit based on HIV status.

\(^a\) Site-specific HIV testing plans must be approved by the HPTN LC before the study opens.

\(^b\) Sites that are not able to obtain HIV rapid test kits that are cleared by the US FDA may seek approval from the HPTN LC to use an alternate kit.

\(^c\) This testing must be performed using a laboratory based, non-rapid HIV immunoassay that detects both HIV antigen and HIV antibody (either a 4th generation or 5th generation assay).

\(^c\) Screening for acute infection should be performed using an RNA test that, in the opinion of the site investigator, is able to detect early HIV infection. If possible, the site should use an assay that is FDA-cleared for this testing, such as the APTIMA HIV-1 RNA Qualitative Assay. RNA test results must be obtained from a specimen collected within 14 days prior to enrollment.
HIV Testing Algorithm at Enrollment

All Participants*

U.S. FDA-cleared HIV Rapid Test®

All prior HIV tests negative/non-reactive®
The individual is eligible for enrollment only if this result and all HIV test results from the Screening visit are available and are non-reactive/negative.

Possible HIV infection
This individual is not eligible for enrollment. Follow local testing guidelines to determine HIV infection status.

Possible HIV infection
If the individual is already enrolled, immediately consult the Seroconversion Committee at 084HIV@hptn.org. Follow local testing guidelines and consult the Seroconversion Committee to determine HIV infection status. Do not administer any further study product without approval from the Seroconversion Committee.

Laboratory based HIV Immunoassay
(Capable of detecting HIV antigen and antibody)®
The participant may be enrolled and the oral drug may be given before this result is available.

NOTES:

* If acute HIV infection is suspected, do not enroll the participant or administer study product at this time. In addition to following the algorithm above, the site should send a sample for an RNA test that, in the opinion of the site investigator, is able to detect early HIV infection. If possible, the site should use an assay that is FDA-cleared for early HIV diagnosis, such as the APTIMA HIV-1 RNA Qualitative Assay. The site should contact the Seroconversion Committee (084HIV@hptn.org) for additional guidance once all of the test results from this visit (including the HIV RNA test) are available.

® Sites that are not able to obtain HIV rapid test kits that are cleared by the US FDA may seek approval from the HPTN LC to use an alternate kit.

® This testing must be performed using a laboratory based, non-rapid HIV immunoassay that detects both HIV antigen and HIV antibody (either a 4th generation or 5th generation assay).

® Before providing study drug, the site must ensure that the HIV rapid test from the Enrollment visit, and all HIV results from the Screening visit are available and are negative or non-reactive.
Figure 11.3  HIV Testing Algorithm at the Follow up Visits

HIV Testing Algorithm for Follow up Visits

All Participants*

U.S. FDA-cleared HIV Rapid Test

Non-reactive or negative

Reactive or positive

Laboratory based HIV immunoassay (Capable of detecting antigen and antibody)* AND
HIV viral load (LOD < 50 copies/mL)
Study drug may be provided before these results are available.

Immuoassay reactive or positive, or HIV RNA detected

Possible HIV infection
Immediately consult the seroconversion committee. Follow local testing guidelines and simultaneously consult the CMC to determine HIV infection status. Do not administer any further study product without approval from the CMC.

Immuoassay non-reactive or negative and HIV RNA not detected

All HIV tests documented as Not Detected, Negative, or Non-reactive
This individual may continue study visits as planned

NOTES:

*If acute HIV infection is suspected, do not administer any further study product. Immediately consult the CMC. In addition to following the algorithm above, the site should send a sample for an RNA test that, in the opinion of the site investigator, is able to detect early HIV infection. If possible, the site should use an assay that is FDA-cleared for early HIV diagnosis, such as the APTIMA HIV-1 RNA Qualitative Assay. The site should contact the Seroconversion Committee (BMMHV@hpn.org) for additional guidance once all of the test results from this visit (including the HIV RNA test) are available.

* This testing must be performed using a laboratory based, non-rapid HIV immunoassay that detects both HIV antigen and HIV antibody (commonly referred to previously as either a 4th generation or 5th generation assay).

b At any visit where study product will be given, the site must ensure that the HIV rapid test from this visit, and all HIV results from prior study visits are negative or non-reactive or not detected.
11.3.3 Hepatitis Testing

Testing for HBV (HBsAb, HBsAg, HBcAb total) and HCV will be performed at screening, enrollment, and other time points as dictated by tables 11-1 and 11-2. Sites will follow local testing arrangements for the collection and testing of samples, this will be described in the site SOPs.

Test results are required for the enrollment visit.

Persons with a positive HBsAg and/or HCV antibody test will be excluded from the study.

11.3.4 Safety Testing

CBC, Chemistry, and LFTs will be performed at various time points throughout the study. Sites will follow local testing arrangements for the collection and testing of samples, this will be described in the site SOPs. Participants do not have to be fasting before having blood drawn for glucose.

Test results from the screening visit are required prior to enrollment.

Same day test results are not required prior to the issue of study product.

Note: Please inform the HPTN LC and SDMC before using your back-up laboratory. Use of your back up lab may result in different reference ranges used and reported via Medidata/Rave.

11.3.5 Creatinine Clearance

The calculated creatinine clearance will be performed at all visits where creatinine testing is performed, using the Cockcroft-Gault formula.

eCcr (female in mL/min = [(140 - age in years) x (actual body weight in kg)] / (72 x serum creatinine in mg/dL) x 0.85.

For participants who join from the HPTN 084-01 protocol, the calculated creatinine clearance (estimated Glomerular Filtration Rate eGFR) will be performed using the Modified Bedside Schwartz Equation (2009). HPTN 084 leadership requested that sites continue to use this equation. This equation is validated only for individuals <18yrs of age.

eGFR = (0.413 x height)/(serum creatinine)

eGFR units are mLs/minute per 1.73m², when height is by cm and serum creatinine as mg/dL

11.3.6 Fasting Lipid Profile

A fasting lipid profile (total cholesterol, HDL, triglycerides, LDL – calculated or measured) will be collected at the enrollment, week 57, and week 105 visits. Participants should be fasting for at
least 8 [preferably 12] hours prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.

Sites will follow local testing arrangements for the collection and testing of the lipid profile. This will be described in the site SOPs.

Results from the lipid profile at the enrollment visit are NOT required prior to the issue of study product.

11.3.7 Urinalysis Testing

Sites will follow local testing arrangements for the collection and testing of urine for urinalysis (only for protein and glucose). This will be described in the site SOPs.

Urinalysis results from the enrollment visit are not required prior to enrollment.

11.3.8 Pregnancy Testing

Sites will follow local testing arrangements for the collection and testing of urine, plasma, or serum for beta human chorionic gonadotropin (βHCG) pregnancy test (sensitivity of $\leq 25$ mIU/mL) performed and results known the same day and before initiating the protocol-specified study product(s) at Enrollment. Pregnancy test must be confirmed to be negative PRIOR to injection/dispensing of study products. This is a requirement at all visits at which study product is to be administered or continued. Pregnancy testing is not required at subsequent visits if a woman had a positive pregnancy test at a previous visit and this has been confirmed 4 weeks after the first test, and the participant is still pregnant.

This will be described in the site SOPs.

11.3.9 Syphilis Testing

Sites will follow local testing arrangements for the collection and testing of serum or plasma for syphilis testing. This will be described in the site SOPs.

11.3.10 Urine or Vaginal Sample for GC/CT Testing

Sites will follow local testing arrangements for the collection and testing of urine/vaginal swab sample for GC/CT nucleic acid testing. This will be described in the site SOPs.

GC/CT results from the enrollment visit are not required prior to enrollment.

11.3.11 Vaginal Sample for Trichomonas vaginalis (TV) Testing

Sites will follow local testing arrangements for the collection and testing of Vaginal swabs for TV (Rapid test) or Wet mount. This will be described in the site specific SOPs.

11.4 Plasma Processing for Storage Main Study

Approximately 20 mL of EDTA whole blood should be drawn into spray dried EDTA tubes for plasma storage at each time point at which HIV testing is performed as indicated in Tables 11-1 to 11-3. Sites are requested to store 5 x 1.8 mL aliquots of plasma if possible. HPTN LC should be informed at any time that three or fewer aliquots of 1.8mL or less are stored via a NTF (see Section 11.2.4)
An additional 20 mL (approximately) of EDTA whole blood will be drawn for plasma storage for participants with a reactive or positive HIV test at any time after enrollment as indicated in Table 11-4. This additional plasma will be stored in the same way.

Sites will follow the instructions below or may follow site specific SOPs for plasma processing which will include the following:

- Collect blood into lavender top blood collection tubes (EDTA) labeled with a SCHARP-provided PTID label. The sizes of tubes will be reviewed by the HPTN LC to ensure blood draws will yield the required number of aliquots for storage. An alternate, site-specific labeling process may be used if an SOP is in place, and HPTN LC approved, but still must use the PTID with other identifiers. Size and number of collection tubes may vary depending on local lab requirements.

- Deliver the samples to the local LDMS laboratory along with the LDMS Specimen Tracking Sheet or site-specific requisition that contains the required information.

- Using the LDMS Specimen Tracking Sheet or site-specific requisition, log the sample into LDMS (specimen type = BLD) and generate the appropriate number of LDMS cryovial labels. The lab should store plasma in labeled cryovials. Cryovial size must be 2.0 mL. We require the use of Sarstedt tube (#72.694.006) 2 mL cryovials, or cryovials of the same dimension. Reminder: Do not add more than 1.8 mL due to expansion of plasma during freezing. Other cryovial types may only be used if specifically approved by the HPTN LC.

- Blood processing and plasma storage should be performed within 6 hours of sample collection.

- Centrifuge tube at 800 - 1000 x g for 10 minutes to separate cells and plasma.

- Carefully remove plasma and avoid disturbing the cell layer. Transfer the plasma to an appropriately labelled sterile centrifuge tube.

- Centrifuge plasma again at 800 - 1000 x g for 10 minutes to remove any contaminating debris, cells, or platelets.

- Log samples into LDMS and generate LDMS labels (PL2). Each aliquot will have its own individual identification number (Global Specimen ID).

- Store plasma in aliquot number order. For example, if there is only 3 mL of plasma for storage: store 1.8 mL in aliquot 1, then store the remaining 1.2 mL of plasma in aliquot 2 and adjust the aliquot volume in LDMS to indicate 1.2 mL. The remaining aliquots (3, 4, and 5) should be entered as QNS.

- Store the aliquots in the freezer locations assigned in LDMS in a ultra-low minus 70°C to minus 90°C freezer. Aliquots may be requested as needed.

Plasma for storage will be stored on site until all protocol-related testing is complete. Note that some testing will be performed after study visits have been completed. Study sites should plan to store specimens until all of the protocol specified testing (including assessments at the HPTN LC) has been completed and the primary research paper has been published.
LDMS Entry:

PL2 aliquots from the 20mL EDTA draw as follows:

- Several possible tube combinations equaling at least 20mL (per individual site chain of custody)
- A single primary container of EDTA whole blood is created
- 5 PL2 aliquots of 1.8mL are created (adjusted to approximate aliquot volume as needed during storage)
  - Primary container and aliquot entries should have the “SHV” (short volume) condition code used as needed when incomplete volumes are obtained. Change condition code to SAT or SHV only if you store < 5 aliquots for primary tubes, and SHV for any aliquots < 1.8 mL.
  - Please remember to contact the HPTN LC when using condition codes not listed in the SSP.
- No other aliquots are created from this primary container
- See figures 11.4 and 11.5

LDMS Specimen Code for Plasma Storage

<table>
<thead>
<tr>
<th>Test</th>
<th>Primary LDMS Code</th>
<th>Additive</th>
<th>Derivative</th>
<th>Sub Add/Deriv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Storage</td>
<td>BLD</td>
<td>DPE</td>
<td>PL2</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Codes used in table:

BLD       Blood
DPE       Spray Dried EDTA
PL2       Plasma, Double Spun
N/A       Not Applicable
Other Spec ID: Not Applicable
All plasma vials are stored electronically in the LDMS and physically in an ultra-low minus 70°C to minus 90°C freezer. Selected aliquots will be shipped to HPTN Laboratory Center (LC) when requested.

All enrolled study participants must consent to collection and storage of their plasma for the duration of their study participation and until all protocol-specified testing has been completed. Participants are asked to consent separately to indefinite storage and possible future research testing of their plasma after the study is completed. Participants may refuse to consent to indefinite storage and possible future research testing and still enroll in the study. After all protocol-specified testing has been completed; the stored plasma of participants who do not consent to indefinite storage and possible future research testing must be destroyed. After all protocol-specified testing has been completed, the HPTN SDMC will provide each site with a list of participants who did not consent to indefinite storage and possible future research testing and the HPTN LC will provide detailed instructions for specimen destruction and documentation thereof.

Figure 11.4 Example LDMS Entry of Plasma (Windows LDMS)
### Figure 2 - Example Visit 4.0 (follow-up) LDMS entry

#### 2 primary containers for a 24mL EDTA collection

<table>
<thead>
<tr>
<th>Spec. Date</th>
<th>Exp. Date</th>
<th>Specimen ID</th>
<th>Additive</th>
<th>Volume</th>
<th>Time</th>
<th>Time Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-May/2027</td>
<td>13:15</td>
<td>5001-7000025</td>
<td>BLD</td>
<td>0.80 ML</td>
<td>SAT</td>
<td>EDT</td>
</tr>
<tr>
<td>11-May/2027</td>
<td>13:15</td>
<td>5001-7000026</td>
<td>BLD</td>
<td>0.80 ML</td>
<td>SAT</td>
<td>EDT</td>
</tr>
</tbody>
</table>

### Figure 3 - Example Visit 5.0 (follow-up) LDMS entry

#### 1 primary container for a 24mL EDTA collection

<table>
<thead>
<tr>
<th>Spec. Date</th>
<th>Exp. Date</th>
<th>Specimen ID</th>
<th>Additive</th>
<th>Volume</th>
<th>Time</th>
<th>Time Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-May/2027</td>
<td>13:15</td>
<td>5001-7000025</td>
<td>BLD</td>
<td>0.80 ML</td>
<td>SAT</td>
<td>EDT</td>
</tr>
</tbody>
</table>
Figure 11.5 Example LDMS Entry of Plasma (Web LDMS)

Figure 4 - Web LDMS - Example Visit 2.0 (Enrollment) 24mL EDTA collection for 2 primary containers
11.5 Plasma Processing for IC Storage

Approximately 10 mL of EDTA whole blood should be drawn into spray dried EDTA tubes for plasma storage at each time point at which IC testing is performed as indicated in Tables 11-6. Sites are requested to store 3-4 x 1.0 mL aliquots of plasma if possible. HPTN LC should be informed at any time that three or fewer aliquots of 1.0 mL or less are stored via a NTF (see Section 11.2.4).

Sites will follow the instructions below or may follow site specific SOPs for plasma processing which will include the following:

- Collect blood into lavender top blood collection tubes (EDTA) labeled with a SCHARP-provided PTID label. The sizes of tubes will be reviewed by the HPTN LC to ensure blood draws will yield the required number of aliquots for storage. An alternate, site-specific labeling process may be used if an SOP is in place, and HPTN LC approved, but still must use the PTID with other identifiers. Size and number of collection tubes may vary depending on local lab requirements.

- Deliver the samples to the local LDMS laboratory along with the LDMS Specimen Tracking Sheet or site-specific requisition that contains the required information.

- Using the LDMS Specimen Tracking Sheet or site-specific requisition, log the sample into LDMS (specimen type = BLD) and generate the appropriate number of LDMS cryovial labels. The lab should store plasma in labeled cryovials. Cryovial size must be 2.0 mL. We require the use of Sarstedt tube (#72.694.006) 2 mL cryovials, or cryovials of the same dimension. Other cryovial types may only be used if specifically approved by the HPTN LC.

- Blood processing and plasma storage should be performed within 6 hours of sample collection.

- Centrifuge tube at 1300 x g for 10 minutes to separate cells and plasma.

- Carefully remove plasma and avoid disturbing the cell layer.

- Log samples into LDMS and generate LDMS labels (PL1). Each aliquot will have its own individual identification number (Global Specimen ID).

- Store plasma in aliquot number order. For example, if there is only 2.5 mL of plasma for storage: store 2 x 1.0 mL in aliquot 1 and 2, then store the remaining 0.5 mL of plasma in aliquot 3 and adjust the aliquot volume in LDMS to indicate 0.5 mL.

- Store the aliquots in the freezer locations assigned in LDMS in an ultra-low minus 70°C to minus 90°C freezer. Starting at visit 2 (enrollment visit), and until the end of the study, all plasma aliquots for IC sub study should be stored in a separate “to be shipped” box. The LC will notify sites when to ship these aliquots.

Plasma for storage will be stored on site until all protocol-related testing.
is complete. Note that some testing will be performed after study visits have been completed. Study sites should plan to store specimens until all of the protocol specified testing (including assessments at the HPTN LC) has been completed and the primary research paper has been published.

**LDMS Entry:**

PL1 aliquots from the 10mL EDTA draw as follows:

- Several possible tube combinations equaling at least 10mL (per individual site chain of custody)
- A single primary container of EDTA whole blood is created
- 3 to 4 PL1 aliquots of 1.0 mL are created (adjusted to approximate aliquot volume as needed during storage)
  - Primary container and aliquot entries should have the “SHV” (short volume) condition code used as needed when incomplete volumes are obtained. Change condition code to SAT or SHV only if you store < 3 aliquots for primary tubes, and SHV for any aliquots < 1.0 mL.
  - Please remember to contact the HPTN LC when using condition codes not listed in the SSP.
- No other aliquots are created from this primary container
- See figures 11.4 and 11.5

**LDMS Specimen Code for Plasma Storage**

<table>
<thead>
<tr>
<th>Test</th>
<th>Primary LDMS Code</th>
<th>Additive</th>
<th>Derivative</th>
<th>Sub Add/Deriv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Storage</td>
<td>BLD</td>
<td>DPE</td>
<td>PL1</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Codes used in table:**

- **BLD** Blood
- **DPE** Spray Dried EDTA
- **PL1** Plasma, Single Spun
- **N/A** Not Applicable

All plasma vials are stored electronically in the LDMS and physically in an ultra-low minus 70°C to minus 90°C freezer. Selected aliquots will be shipped to HPTN Laboratory Center (LC) when requested.
11.6 Dried Blood Spots (DBS)

11.6.1 Supplies:

Possible vendors for DBS supplies: Thermo Fisher Scientific, VWR, Sigma Aldrich, and Market Lab. Some Whatman items may be listed as GE Healthcare Life Sciences. The following supplies may be used. Contact HPTN LC if alternate supplies are to be used.

- EDTA spray dried Blood Collection Tubes
- Whatman Protein Saver Card #903 (Whatman 10534612 or Fisher Scientific # 05-715-121). Please handle with gloves and do not touch spot areas.
- Whatman Plastic Sample Bags (Whatman 10548232 or Fisher Scientific # 09-800-16) or Whatman Foil-BARRIER Sample Bags (Whatman 10534321 or Sigma Aldrich # WHA10534321).
- Desiccant pack (GE Healthcare Life Sciences (Whatman)10548234, or P/N WB100003 or Fisher Scientific # 09-800-17).
- Humidity indicator Cards (Manufacturer # MS200032 or MS200033; ADCOA # MS20003-2 or MS20003-3; Fisher Scientific # NC9511648, or NC0281067). Or similar products with similar indicator levels, suitable for storage bag size.
- Whatman card drying rack (VWR # 89015-592 or Sigma Aldrich # WHA10539521) or other suitable drying rack.
- Gloves, preferably powder free.
- Water proof marker (Fisher Scientific# 50853571 or VWR # 95042-566)
- LDMS labels.
- A fixed 25µL, variable 10-100µl, or 20-200µl micropipette with appropriate filtered pipette tips. Sites should check with local suppliers for appropriate tips for their micropipettes.

11.6.2 DBS Preparation and Storage

Sites will follow the instructions below or may follow site specific SOPs for DBS processing and storage which will include the following:

DBS will be prepared and stored at Week 4 (not week 5 injection), multiple injection follow-up visits, and HIV positive confirmation visits. See Tables 11-1 to 11-4 for complete schedules.

DBS should be prepared from an EDTA blood tube received in the laboratory. For HPTN 084 it is acceptable to use one of the tubes received for plasma storage before it is processed for plasma storage or a sample received for HIV rapid testing after testing has been performed.

The EDTA tube should be well mixed before preparing the DBS. Pipette 25 µL of whole blood directly onto the center of each spot on the filter paper so that it is contained within the circle (Figure 11.11).

- There will be a total of 5 blood spots created
- Whole blood for DBS should be stored at room temperature (approximately 15°C to 25°C) until spots have been created.
- Samples should be processed within 6 hours of the time of collection; the actual time of collection should be recorded on the Case Report Form, and DBS creation time in LDMS.
- Ensure that both hands are gloved before handling the Protein Saver (DBS) card; Do not
touch the areas where the blood spots will be placed (the filter paper portion).

- Label each Protein Saver Card with study protocol number, PID#, Study date and time of sample collection. Use a waterproof pen or a non-removable label.
- Create an LDMS label and enter specimen information into LDMS. See Figures 11.6 to 11.8.
- Assure the blood tube has been inverted 8 times and well mixed. Remove the cap from the EDTA tube and spot 25µl of blood, using a pipette, onto the center of the designated circles on the Protein Saver Cards (see Figures 11.11 to 11.13 below). Return the cap to the tube and process for other lab tests (i.e. plasma processing).
  - Pipette tip should be held approximately 3mm above the spot location and the blood dispensed onto the card with one single dispensing from the micropipette. Do not touch, press, or smear the spots.
- Air dry the cards in a card holder or other drying rack (Figure 11.14). Overnight drying (up to 16 hours) is acceptable, otherwise minimum drying time is 2 hours.
- Keep the DBS cards away from direct sunlight. Do not dry the DBS cards with a fan in an attempt to decrease drying time. Air dry only at temperature range of 15°C to 40°C
- After DBS cards have dried, place DBS card in low gas-permeability plastic bags with humidity indicator and desiccant pack to reduce humidity. See figures 11.15 and 11.16.
  - The humidity indicator should be checked periodically as needed.
  - If the indicator indicates too much humidity (color change from blue to pink- 40% to 50% level), replace the old desiccant pack and indicator card with a new one.
- Store bag in an appropriately labeled box in an ultra-low minus 70 to minus 90°C freezer. Select DBS will be requested quarterly.

**LDMS Entry:**

**LDMS Specimen Code for DBS Storage**

<table>
<thead>
<tr>
<th>Test</th>
<th>Primary LDMS Code</th>
<th>Additive</th>
<th>Derivative</th>
<th>Sub Add/Deriv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dried Blood Spots</td>
<td>BLD</td>
<td>DPE</td>
<td>DBS</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Codes used in table:**

- **BLD** Blood
- **DPE** Spray Dried EDTA
- **DBS** Dried Blood Spot
- **N/A** Not Applicable
- **Other Spec ID:** Not Applicable
Figure 11.6  Example LDMS Entry of DBS

In addition to the illustrations below, include the date and time of specimen receipt, date and time of DBS processing (spot time), and date and time of DBS completion and storage for each aliquot. Note the primary aliquot is BLD with 5 aliquots created from the primary specimen. Each aliquot will be 25μL having its own Global Specimen ID. DBS need to be entered into LDMS and stored in appropriate location so they can be easily retrieved when necessary. Each spot will have its own Global Specimen ID.

```
<table>
<thead>
<tr>
<th>Specimen</th>
<th>Global Specimen ID</th>
<th>Primary</th>
<th>Add</th>
<th>DBS</th>
<th>Date</th>
<th>Unit</th>
<th>Spec Time</th>
<th>Time</th>
<th>Time Unit</th>
<th>Other Spec ID</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>000109037219</td>
<td>BLD</td>
<td>PRE</td>
<td>DBS</td>
<td>2016</td>
<td>05/20</td>
<td>10:30 AM</td>
<td>05/20</td>
<td>10:30 AM</td>
<td>000109037219</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>000109037219</td>
<td>BLD</td>
<td>DBS</td>
<td>DBS</td>
<td>2016</td>
<td>05/20</td>
<td>10:30 AM</td>
<td>05/20</td>
<td>10:30 AM</td>
<td>000109037219</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>000109037219</td>
<td>BLD</td>
<td>DBS</td>
<td>DBS</td>
<td>2016</td>
<td>05/20</td>
<td>10:30 AM</td>
<td>05/20</td>
<td>10:30 AM</td>
<td>000109037219</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>000109037219</td>
<td>BLD</td>
<td>DBS</td>
<td>DBS</td>
<td>2016</td>
<td>05/20</td>
<td>10:30 AM</td>
<td>05/20</td>
<td>10:30 AM</td>
<td>000109037219</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>000109037219</td>
<td>BLD</td>
<td>DBS</td>
<td>DBS</td>
<td>2016</td>
<td>05/20</td>
<td>10:30 AM</td>
<td>05/20</td>
<td>10:30 AM</td>
<td>000109037219</td>
<td></td>
</tr>
</tbody>
</table>
```
Figure 11.7 Example LDMS Entry of DBS (2)
Figure 11.8 Example LDMS Entry of DBS (3)
Figure 11.9 Example DBS LDMS Labels for each aliquot

Figure 11.10 Suggested labeling of DBS cards
Figure 11.11. Example of correctly spotted DBS card (25µl spot volume)

Note: 25µl spot volume may not completely fill target circle on DBS card.
Figure 11.12. Example of *incorrectly* spotted DBS card

![Incorrectly spotted DBS card](image)

Figure 11.13. Example of *incorrectly* spotted DBS card (continued)

![Invalid Specimens](image)

<table>
<thead>
<tr>
<th>1. Specimen quantity insufficient for testing.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Specimen appears scratched or abraded.</td>
</tr>
<tr>
<td>3. Specimen not dry before mailing.</td>
</tr>
<tr>
<td>4. Specimen appears supersaturated.</td>
</tr>
<tr>
<td>5. Specimen appears diluted, discolored or contaminated.</td>
</tr>
<tr>
<td>6. Specimen exhibits serum rings.</td>
</tr>
<tr>
<td>7. Specimen appears clotted or layered.</td>
</tr>
<tr>
<td>8. No blood.</td>
</tr>
</tbody>
</table>
Figure 11.14. Whatman card drying rack (VWR catalogue # 89015-592)

Figure 11.15 Properly labeled and packaged DBS card for storage
DBS Shipping and Packing

When shipping DBS, ensure specimens are shipped on dry ice. Check the desiccant packs and humidity indicators before shipping and replace if needed. Boxes should be placed in a watertight secondary containers (Tyvek bags) to protect from humidity while in transit. Make sure to generate an LDMS shipping manifest with each shipment including all requested information.
11.7 Whole Blood Storage for Pharmacogenomic Testing

Specimen Type: Whole blood collected in dried EDTA anticoagulant (“purple top”) tube.

Specimen volume: Minimum 1 mL whole blood

Handling Instructions: Whole blood is transferred to a suitable cryovial and frozen at minus 70°C to minus 90°C within 6 hours of collection.

Whole blood aliquot should be prepared from an EDTA blood tube received in the laboratory. For HPTN 084 it is acceptable to use one of the tubes received for plasma storage before it is processed for plasma storage or a sample received for HIV rapid testing after testing has been performed.

Sites will follow the instructions below or may follow site specific SOPs for whole blood storage which will include the following:

Procedure – Stepwise

- An appropriately labeled and filled EDTA whole blood tube will be received. Transfer a minimum of 1.0mL of the whole blood to a labeled cryovial using a transfer pipet.
- Do not fill cryovials to more than ¾ of capacity.
- Optional - Parafilm can be used to seal caps of the cryovials to prevent leakage during shipping.
- Ensure PTID, date, visit number and laboratory identifier are on the LDMS label.
- Store whole blood in an ultra-low freezer minus 70°C to 90°C until requested for shipment.
- Ship when requested on dry ice overnight for arrival on Monday through Friday only, site must follow appropriate shipping regulations.
- Batch shipment to:

  Estelle Piwowar-Manning/
  Johns Hopkins University Hospital
  Department of Pathology
  Pathology Building, Room 313
  600 North Wolfe Street
  Baltimore, MD 21287
  USA
LDMS Entry:

LDMS Specimen Code for Whole Blood Storage

<table>
<thead>
<tr>
<th>Test</th>
<th>Primary LDMS Code</th>
<th>Additive</th>
<th>Derivative</th>
<th>Sub Add/Deriv</th>
<th>Other Spec ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Blood Storage</td>
<td>BLD</td>
<td>DPE</td>
<td>BLD</td>
<td>N/A</td>
<td>PGEN</td>
</tr>
</tbody>
</table>

Codes used in table:

BLD          Blood
DPE          Spray Dried EDTA
N/A          Not Applicable
Other Spec ID: PGEN

11.8 Breast Milk collection and processing for OL participants.

Specimen Type: Breast Milk.

Specimen volume: 5 mL unspun whole breast milk processed into 3-5 x 1 mL aliquots.

Handling Instructions: Whole breast milk is transferred to a suitable cryovial and frozen at minus 70°C to minus 90°C within 6 hours of collection.

Procedure –Stepwise

- Collect 3-5 mLs of Breast Milk in an appropriately labeled 50 mL conical tube.
- Store at 4°C (2 to 8°C acceptable) within 10 minutes of collection and send to the lab on wet ice.
- Process within 6 hours of collection.
- Transfer a minimum of 1.0mL of the whole breast milk in to a labeled cryovial using a transfer pipet.
- Log specimens into LDMS and generate LDMD labels (BMK), each aliquot should have each own individual identification number (Global Specimen).
- Store breast milk in aliquot number order
- Store the aliquots in the freezer location assigned in LDMS in the ultra-low -70°C to -90°C freezer.
- Aliquots will be requested as needed.
LDMS Entry:

LDMS Specimen Code for Breast Milk Storage

<table>
<thead>
<tr>
<th>Test</th>
<th>Primary LDMS Code</th>
<th>Additive</th>
<th>Derivative</th>
<th>Sub Add/Deriv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Breast Milk Storage</td>
<td>BMK</td>
<td>Non</td>
<td>BMK</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Codes used in table:

BMK    Whole Breast Milk
NON   No-Additive
N/A   Not Applicable

11.9 Cord Blood collection and processing for OL participants.

Approximately 5 mL of whole cord blood (CRD) should be drawn into spray dried K2EDTA tube for plasma storage as indicated in Tables 11-10. Sites are requested to store 2 x 1.0 mL aliquots of plasma if possible.

Sites will follow the instructions below or may follow site specific SOPs for plasma processing which will include the following:

**Specimen volume:** 5 mL unspun whole cord blood processed into 2 x 1.0 mL plasma aliquots.

**Handling Instructions:** Whole cord blood is centrifuged and transferred to a suitable cryovial and frozen at minus 70°C to minus 90°C within 6 hours of collection.

**Procedure –Stepwise**

- Collect blood into lavender top blood collection tubes (K2EDTA) labeled with a SCHARP-provided PTID label. The sizes of tubes will be reviewed by the HPTN LC to ensure blood draws will yield the required number of aliquots for storage. An alternate, site-specific labeling process may be used if an SOP is in place, and HPTN LC approved, but still must use the PTID with other identifiers. Size and number of collection tubes may vary depending on local lab requirements.
- Deliver the samples to the local LDMS laboratory along with the LDMS Specimen Tracking Sheet or site-specific requisition that contains the required information.
- Using the LDMS Specimen Tracking Sheet or site-specific requisition, log the sample
into LDMS (specimen type = CRD) and generate the appropriate number of LDMS cryovial labels. The lab should store plasma in labeled cryovials. Cryovial size must be 2.0 mL. We require the use of Sarstedt tube (#72.694.006) 2 mL cryovials, or cryovials of the same dimension. Other cryovial types may only be used if specifically approved by the HPTN LC.

- Blood processing and plasma storage should be performed within 6 hours of sample collection.
- Centrifuge tube at 800 - 1000 x g for 10 minutes to separate cells and plasma.
- Carefully remove plasma and avoid disturbing the cell layer.
- Log samples into LDMS and generate LDMS labels (PL1). Each aliquot will have its own individual identification number (Global Specimen ID).
- Store plasma in aliquot number order. For example, if there is only 1.5 mL of plasma for storage: store 1.0 mL in aliquot 1, then store the remaining .5 mL of plasma in aliquot 2 and adjust the aliquot volume in LDMS to indicate .5 mL. The remaining aliquots (3,) should be entered as QNS.
- Store the aliquots in the freezer location assigned in LDMS in the ultra-low -70°C to -90°C freezer.
- Aliquots will be requested as needed.

LDMS Entry:

<table>
<thead>
<tr>
<th>Test</th>
<th>Primary LDMS Code</th>
<th>Additive</th>
<th>Derivative</th>
<th>Sub Add/Deriv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Cord Blood Storage</td>
<td>CRD</td>
<td>DPE</td>
<td>PL1</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Codes used in table:

- CRD     Whole Cord Blood
- DPE     No-Additive
- N/A     Not Applicable

11.10 Infant Blood collection and processing for OL participants.

Approximately 500 µL to 2 mL of whole blood (if possible) should be drawn into spray dried K2EDTA tube for plasma storage as indicated in Tables 11-10. Sites are requested to store 2 x 250 µL aliquots of plasma if possible.

Sites will follow the instructions below or may follow site specific SOPs for plasma processing which will include the following:

**Procedure –Stepwise**

- Collect blood into lavender top blood collection tubes (K2EDTA) labeled with a
SCHARP-provided PTID label. The sizes of tubes will be reviewed by the HPTN LC to ensure blood draws will yield the required number of aliquots for storage. An alternate, site-specific labeling process may be used if an SOP is in place, and HPTN LC approved, but still must use the PTID with other identifiers. Size and number of collection tubes may vary depending on local lab requirements.

- Deliver the samples to the local LDMS laboratory along with the LDMS Specimen Tracking Sheet or site-specific requisition that contains the required information.
- Using the LDMS Specimen Tracking Sheet or site-specific requisition, log the sample into LDMS (specimen type = BLD) and generate the appropriate number of LDMS cryovial labels. The lab should store plasma in labeled cryovials. Cryovial size must be 2.0 mLs. We require the use of Sarstedt tube (#72.694.006) 2 mL cryovials, or cryovials of the same dimension. Other cryovial types may only be used if specifically approved by the HPTN LC.
- Blood processing and plasma storage should be performed within 6 hours of sample collection.
- Centrifuge tube at 800 - 1000 x g for 10 minutes to separate cells and plasma.
- Carefully remove plasma and avoid disturbing the cell layer.
- Log samples into LDMS and generate LDMS labels (PL1). Each aliquot will have its own individual identification number (Global Specimen ID).
- Store plasma in aliquot number order. For example, if there is only 250 µL of plasma for storage: store .250 µL in aliquot 1 in aliquot 1. The remaining aliquots (2,) should be entered as QNS.
- Store the aliquots in the freezer location assigned in LDMS in the ultra-low -70°C to -90°C freezer.
- Aliquots will be requested as needed.

**LDMS Entry:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Primary LDMS Code</th>
<th>Additive</th>
<th>Derivative</th>
<th>Sub Add/Deriv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant Blood Storage</td>
<td>BLD</td>
<td>DPE</td>
<td>PL1</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**11.11 Required LDMS data entry scheme**

LDMS data entry is to be standardized across the sites participating in HPTN 084. This may not align with current practice or entry for other network studies.

**11.11.1 PL2 aliquots from the 20mL EDTA draw (as per protocol and SSP)**

a. Several possible tube combinations equaling at least 20mL (*per individual site chain of custody*)
b. A single primary container of EDTA whole blood is created
c. 5 PL2 aliquots of 1.8mL are created (adjusted to actual aliquot volume as needed during storage)
d. No other aliquots are created from this primary container
e. See Figures 11.4 and 11.5).
11.11.2 DBS from EDTA whole blood (example 4mL draw)
   a. A single primary container of 4mL EDTA whole blood is created
   b. 5 aliquots of 25uL each are created (1 for each spot on the DBS card)

11.11.3 Whole Blood for Pharmacogenomics (Example 4mL draw)
   a. Occurs only once at visit 2.0 (Enrollment)
   b. Single primary container
   c. Single 1mL whole blood aliquot
   d. “PGEN” entered into primary container Other Specimen ID field (Other Spec Id)

11.11.4 Blood for Injectable Contraceptive Sub-Study. (additional 10 mL draw)
   a. Plasma and DBS will be collected from selected sites at Steps 1 and 2.
   b. Follow plasma processing (see instructions above) and DBS instructions in sections 11.4 and 11.5.

11.11.5 Breast Milk
   a. 5 mLs collected in a single primary container of 50mL conical tube of whole breast milk is created.
   b. 3-5 aliquots of 1.0 mL each are created.
   c. Follow breast milk processing (see instructions above) instructions in section 11.8

11.11.6 Cord Blood
   a. A single primary container of 5mL K2EDTA whole cord blood is created.
   b. 2 aliquots of 1.0 mL each are created.
   c. Follow cord blood processing (see instructions above) instructions in section 11.9

11.11.7 Infant blood
   a. A single primary container of 500 μL to 2mL K2EDTA whole blood is created
   b. 2 aliquots of 250 μL each are created.
   c. Follow infant blood processing (see instructions above) instructions in section 11.10

11.12 Primary Specimen Report for HPTN 084 in PC-based LMDS
   a. Open the LDMS “Reports” module:
      i. Click on the “Reports” icon (under the main Menu bar) or click on the “Tasks” Menu and select “Reports” from the drop-down menu.
   b. In the Category box on the top-left of the Reports screen, highlight the “Specimen” line.
   c. In the Description box at the top of the Reports screen, highlight the “Primary Specimens Received” line.
   d. Under the “Selection Criteria” area at the bottom of the Reports screen:
      i. In the Field box, select “Group” from the drop-down menu.
      ii. In the Operator box, select “=” from the drop-down menu.
iii. In the Value box, select “HPTN” from the drop-down menu.

iv. Click on the “Add” button, to the right of the selection criteria, to save the information in the search options box to the right, for use with your search later.

e. Go back to the Selection Criteria area and repeat the process to enter protocol information:

i. In the Field box, select “Non-ACTG Prot/ID2” from the drop-down menu.

ii. In the Operator box, select “=” from the drop-down menu.

iii. In the Value box, select “084.0” from the drop-down menu.

iv. Click on the “Add” button, to the right of the selection criteria, to save the information in the search options box to the right, for use with your search later.

v. If the drop-down “Value” options include both “084.0” and “084” as a choice, instruction “e” (this section) should be repeated so that both are included in the saved search options (as in the figure below). If only one is an option, instruction “e” only needs to be performed once.

**Figure 1**

<table>
<thead>
<tr>
<th>Field</th>
<th>Operator</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>=</td>
<td>HFTN</td>
</tr>
<tr>
<td>Non ACTG Prot/ID2</td>
<td>=</td>
<td>084.0</td>
</tr>
<tr>
<td>Non ACTG Prot/ID2</td>
<td>=</td>
<td>084</td>
</tr>
</tbody>
</table>

f. Go back to the Selection Criteria area and repeat the process to enter search date information. The following are ways to search for one day or one month within a single search:

i. To search only one day:

1. In the Field box, select “Received Date” from the drop-down menu.
2. In the Operator box, select “=” from the drop-down menu.
3. In the Value box, select the date for which you would like to check the status of the primary specimens.
4. Click on “Add” box – located on to the right of the Selection Criteria.

ii. To search within one month:

1. In the Field box, select “Received Date” from the drop-down menu.
2. In the Operator box, select “>=” from the drop-down menu.
3. In the Value box, select the first day of the month for which you would like to check the status of the primary specimens.
4. Click on “Add” box – located on to the right of the Selection Criteria.
5. In the Operator box, select “<=” from the drop-down menu.
6. In the Value box, select the last day of the month for which you would like to check the status of the primary specimens.
7. Click on “Add” box – located on to the right of the Selection Criteria.
8. The figure below displays what you should see in the saved area to the right of selection criteria. Lines 4 and 5 together in the figure represent the two entries for the one-month search window.

Figure 2

<table>
<thead>
<tr>
<th>Field</th>
<th>Operator</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non ACTG Proc/ID2</td>
<td>=</td>
<td>084</td>
</tr>
<tr>
<td>Received Date</td>
<td>&gt;=</td>
<td>01/Nov/2017</td>
</tr>
<tr>
<td>Received Date</td>
<td>&lt;=</td>
<td>30/Nov/2017</td>
</tr>
</tbody>
</table>

- There will now be multiple lines of information in the box to the right of the search criteria. The minimum lines that should be present is three, but there could be up to five lines if two protocol ID’s and two date criteria have been entered. One line will be present for each of the following:
  i. The HPTN group
  ii. The protocol number (ID2)
    1. Two lines are present if the additional protocol number (ID2) is included (e.g. 084.0 and 084 will have separate lines as in figure 1)
  iii. The search date
    1. Two lines are present if a one-month window is to be searched (e.g. starting November 1st and ending November 31st will have separate lines as in figure 2)

h. In the “Valid sentence” field, write a search to use all the entered and saved criteria as needed.
   i. A simple search with only 3 lines in the saved area will look like: “1 and 2 and 3” – referring to a search for HPTN samples, protocol 084.0, and the specified date.
   ii. A search that uses two dates (for a one-month search) and two protocol ID’s (to search 084.0 and 084 entries) will look like figure 3: “1 and (2 or 3) and 4 and 5” – referring to a search for HPTN samples, any 084 or 084.0 protocol entries, and the month specified between the two dates.
Figure 3

<table>
<thead>
<tr>
<th>Add</th>
<th>3  Non ACTG Prot/D2</th>
<th>=</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modify</td>
<td>4  Received Date</td>
<td>&gt;=</td>
</tr>
<tr>
<td>Delete</td>
<td>5  Received Date</td>
<td>&lt;=</td>
</tr>
<tr>
<td>Valid Sentence Items: and, or, ( ), or a number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 and (2 or 3) and 4 and 5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

i. Click on the “Execute” icon (the lightning bolt) at the top of the screen under the main menu bar.

j. The “Primary Specimens Received” report will automatically generate and pop-up once completed. This provides a detailed description of each primary specimen entry.

k. This report can then be exported into an Excel (CSV) format.
   i. Click the “Export Report” icon in the pop-up window (figure 4).

Figure 4

ii. In the “Save As” pop-up window, create a file name for the report and select to save as a “CSV” file type. See figure 5.
Figure 5

a. Email reports to the HPTN 084 LC staff (Estelle Piwowar-Manning epiwowa@jhmi.edu and Yaw Agyei yagyei1@jhmi.edu)

Windows: Specimen Log Report
1. Click on Specimen in the Category grid at the top left of the Reports screen
2. Click on Specimen Log Report in the Description window
3. Return to Field and select Received Date
   a. Operator is ‘=’
   b. In Value, set the Current Date
   c. Click Add
4. Click the Execute button on the LDMS toolbar
**Webs: Specimen Log Report**

This report provides the user with a specific set of information for each of their logged specimens. The report will provide the user with the participant, primary, and aliquot information for each of their specimens. The report also provides the user with the condition codes, comments, and shipping information (if available) for the given specimens. Using the search criteria below will provide the user with a list of all specimens received by the lab on a particular date.

1. On the LDMS menu bar, hover over **Reports** and click **Standard Reports**.
2. Select the following:
   a. Report Categories: **Specimen**
   b. Report: **Specimen Log Report**
3. In **Filter Criteria**:
   a. **Field**: Received Date
   b. **Operator**: ‘=’
   c. **Value**=Current Date
4. Set **File Type** to PDF; Click **Generate Report**
11.13 Shipping of Samples to the HPTN Laboratory Center

Each site will ship plasma, whole blood, Cord blood, infant plasma, or DBS samples to the LC or designated laboratory upon request, or following a shipping schedule as determined by the LC. The site will batch the shipment, export the LDMS data, and notify the LC.

a. The remaining plasma aliquots should be stored as per normal site standards.

b. Other samples, such as those from Seroconverters, will also be requested on an ad-hoc basis and may be included in quarterly shipments. Separate shipping instructions will be provided at that time by LC non-protocol team members.

c. Separate LDMS batches may be required depending on the shipping request.

Contact the HPTN LC at Johns Hopkins University (Estelle Piwowar-Manning: epiwowa@jhmi.edu and Paul Richardson: pricha18@jhmi.edu, +410-614-6737) to coordinate the timing and logistics of each shipment.

Sites will ship samples to the LC using the LDMS following the LC approved Shipping SOP indicating Lab 300 as the ship to lab ID number. The site should export the data to FSTRF after a batch has been made and notify the HPTN LC with the batch number.

Personnel involved in the shipping process must be IATA trained and certified for the shipping of Category B Biological specimens UN 3373 (Diagnostic) Packing Instructions 650.
Plasma, Cord Blood, Breast Milk and Whole blood for pharmacogenomics

Include a copy of the shipping manifest and box map with the shipment. For dry ice shipments, use diagnostics packing code 650, UN 3373, and address the shipment to:

Estelle Piwowar-Manning/Susan Eshleman MD
Johns Hopkins University Hospital
Department of Pathology
Pathology Building, Room 313
600 North Wolfe Street
Baltimore, MD  21287
USA

For some shipments, an alternate address may be provided at the time of request.

Notify the HPTN LC via email (epiwowa@jhmi.edu) when the shipment has been picked up from the site by the courier/shipping company. Attach an electronic copy of the shipping manifest and LDMS batch to the email notification and include the following information in the notification: name of courier/shipping company, shipment tracking number, number of boxes shipped, date of shipment, and expected date of arrival.

Dried Blood Spot cards

Storing Dried Blood Spots by individual participant will simplify the shipment process. Lists of DBS that are required to be shipped will be uploaded to the Atlas Portal. An email will be sent directly to the sites from the SDMC.

These Dried blood spot cards should also be shipped when requested. Note: Sites can ship all samples to Johns Hopkins University, and the DBS will be forwarded to University of Colorado at Denver if indicated in the site MTA.

Sites should ship the DBS cards directly to:

Lane Bushman
C/O Pete Anderson
University of Colorado at Denver
Skaggs School of Pharmacy and Pharmaceutical Sciences
C-238-V20, Rm V20-4410
12850 East Montview Blvd
Aurora, CO 80045
USA
Phone: 303-724-6132
LDMS Number 533
11.14  HIV QA Testing

Selected plasma aliquots will be shipped to the HPTN LC for HIV QA testing according to the HPTN Manual of Operations; additional testing may be performed e.g. ABO typing.

When samples are received at the HPTN LC, the LC will perform additional QA and HIV testing. This will include:

- Quality assurance testing (to confirm results of in-country testing)
- Testing to confirm seroconversion events

Data from the HPTN LC will be submitted to the SDMC.

11.15  Pharmacology Testing

Plasma samples for drug levels will be collected throughout the study. These samples will be collected from all participants, although PK testing may be limited to a subset of the samples. At each injection visit a blood sample will be collected PRIOR to the injections. The actual date and time of each blood sample collection will be recorded, as well as the time of each injection. This information should be captured on the relevant CRF.

Specimens for pharmacology testing will be shipped following a shipping schedule as determined by the LC.

Pharmacology testing will be performed at the HPTN LC or at an outside laboratory designated by the HPTN LC. The primary pharmacologic assessments will be performed using assays that have been validated and approved by the Clinical Pharmacology Quality Assurance (CPQA) Committee. Results will not be returned to the sites or study participants.

Stored plasma may also be tested for the presence of other ARV drugs or other substances.

11.16  Pharmacogenomic Testing

Specimens for Pharmacogenomic analysis will be collected at the enrollment visit for participants who consent to Pharmacogenomic testing. Samples will be stored on site for shipment to the HPTN LC upon request. Assays will be performed at the HPTN LC. Results will not be returned to the sites or study participants.
11.17 Other Testing

The HPTN LC will perform QA testing, including testing to determine HIV infection status in selected cases. Additional assays may be performed at the HPTN LC or a laboratory designated by the HPTN LC. This testing may include the following tests for participants who acquire HIV infection: HIV viral load, HIV resistance testing, HIV subtyping, and other tests to characterize HIV viruses and/or the host response to HIV infection. Results will not be returned to the sites or study participants, with the exception of HIV testing (if results obtained at the HPTN LC do not agree with site results) and the exception for resistance test results, noted below.

Resistance testing will be performed at the HPTN LC or a laboratory designated by the HPTN LC. This testing will be performed retrospectively at the end of the study. If real-time resistance testing is needed for clinical management, that testing should be arranged by the site outside of the study; separate specimens should be collected for that testing. For sites that do not have the capacity for local resistance testing for clinical care, results from resistance testing may be provided at the end of the study at the request of the site IoR, with approval of the HPTN LC and Protocol Chair. Results from specialized resistance testing (e.g., minority variants analysis, if performed) will not be returned to study sites.

11.18 Laboratory Monitoring

LC staff will conduct periodic site visits to review in-clinic documentation, LDMS reports, specimen storage and other laboratory documentation relevant to this protocol.
## Section 12. Counseling Considerations

12.1 Overview of Section 12

This section contains guidance on HIV Pre-/Post-Test counseling and adherence counseling provided in HPTN 084.

HIV Pre-/Post-Test counseling is required at all study visits. All counseling should be provided in a non-judgmental participant-centered manner that responds to current participant needs for information, education, support, skills building, and/or referrals. Participants’ needs are likely to change over time; counseling provided should also change over time accordingly.

All counseling process outcomes should be documented in participant study records. Proper documentation may be achieved by using counseling checklists, worksheets, and other tools, as well as counselors’ chart notes. To support ongoing participant-centered counseling over time, documentation of each counseling session should include sufficient information and detail to inform and guide the participant’s next counseling session.

During counseling, a site-specific tool may be used to guide any of the counseling sessions. During the session, counselors should engage in the discussion and be client oriented rather than focusing on taking notes. A summary of the counseling session should be written once the session is completed.

12.2 HIV Pre-/Post-Test Counseling

HIV testing is required at each scheduled HPTN 084 study visit for as long as participant is not found to be HIV infected.

Each site is encouraged to develop a Standard Operating Procedure (SOP) for this counseling. It is suggested that the SOP be site-specific and the following elements be incorporated:
• Each participant should be provided with information that allows her to decide whether to be tested (informed decision with informed consent). However, if a participant elects not to undergo HIV testing she may not receive study product and the Clinical Management Committee (CMC) must be contacted for participant management. CMC guidance will then be followed by the site.

• The HIV testing procedure should be organized to maximize confidentiality.

• HIV antibody testing should be linked with information and recommendations regarding HIV.

• Adequate pre- and post-testing counseling should be provided to all individuals being tested.

• Disclosing HIV status to others should be discussed with all participants.

• The need for additional and appropriate referrals should be addressed where possible.

All HIV counseling should be provided in accordance with local counseling standards. Study staff who provide HIV counseling should be trained to do so per local practice standards. Counseling staff should also be trained on study-specific HIV testing methods and interpretation of test results per the study testing algorithms in SSP manual Section 11. Information on interpretation of screening, enrollment, and follow-up test results is provided as part of the testing algorithms. These figures should be referenced as needed when providing pre-test and post-test counseling.

Given that HIV counseling will be provided at all HPTN 084 study visits, when providing pre-test and post-test counseling, it is especially important to avoid repetition of the same information at each counseling session. Participant-centered approaches should be used to assess participant knowledge of relevant information, dispel any misconceptions, ensure participant readiness for HIV testing, and ensure participant understanding of why HIV testing is being done on every visit and understanding test results.

HIV test results should be provided in the context of post-test counseling, which should begin when the first test results (rapid test results) are available the day of testing, and continued, as results become available. If it is convenient for the participant, or it is part of a site’s standard of care, interim visits may be scheduled to give HIV test results and conduct post-test counseling.

When results from the HIV tests are discordant, participants as well as staff members may feel anxious about the ambiguity of their HIV status. While following the HIV testing algorithm, participants should also be engaged in a discussion about the pros and cons of starting ART.
Additionally, mechanisms for linking individuals to appropriate HIV specialty care who acquire HIV infection during study participation is required to be detailed in an SOP for each site. “Appropriate care” should be locally defined and include consideration of language, geography, insurance status and type, provider cultural sensitivity, and resource availability. Ideally sites should build relationships with HIV care providers ahead of time so that discussions about participants with atypical results can be easily facilitated.

Risk reduction counseling should be incorporated into the HIV counseling approach noted above. Participant-centered approaches should be used when providing risk reduction counseling. For HPTN 084, risk reduction counseling will include condom use, data on the known effectiveness of both Truvada (TDF/FTC) and long-acting cabotegravir (CAB LA) as HIV pre-exposure prophylaxis. The counselor should ask open-ended questions, actively listen to participant responses, probe as needed for further information, and guide the participant in identifying his/her risk factors and barriers to risk reduction, as well as strategies and action plans to try to address these.

### 12.2.1 Counseling consideration for participants with discrepant results

Here are some counseling messages based on the tests results. It is advisable that clinicians provide counselling support in the context of discrepant blood results so that they can provide information in response to participant questions. Counsellors can provide additional counseling support but should seek guidance from clinicians on the interpretation of the test results and appropriate counseling messages.

<table>
<thead>
<tr>
<th>First test positive</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Same day rapid test positive</td>
<td>“Your initial results indicate that you may be infected with HIV and we need to do additional testing in order to confirm this result. We will draw a new blood sample and results will be available in about XX days”</td>
</tr>
</tbody>
</table>
| Non-rapid test positive | Your HIV status is not clear to us because while your first test was negative for HIV, your second test was reactive. We would like to conduct additional testing in order to feel sure about your HIV status. 

We will draw more blood today and results will be available in about XX days.” |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subsequent test results</strong></td>
<td></td>
</tr>
</tbody>
</table>
| HIV infection status uncertain; additional testing needed | Your HIV status is not clear to us

Thank you for your patience as we continue to work to determine your HIV status. We would like to draw more blood today. Those results should be available in about XX days.” |
| Likely false positive | “We do not believe that you have HIV. Even though your very first test was reactive, no subsequent tests have indicated HIV infection. The first test was likely a false-positive.” |
| Likely infected | Based on the results from additional tests, it is likely that you have HIV infection. It is important that we get you started on ART as soon as possible. 

It is also important that we draw additional bloods for study purposes, but we do not expect these tests to show a different result.” |
In some instances, final determination of HIV status may be challenging particularly in participants with prior CAB exposure. In that situation, there may be uncertainty about whether to reinitiate PrEP or start ART. In this scenario, clinicians should engage participants in shared decision-making about the best possible treatment option based on her personal life circumstances. Clinicians should ideally address the following issues in their conversations with participants:

- **False negative:** In the context of long-acting CAB use, CAB may suppress virus replication and delay seroconversion making diagnosis with conventional diagnostics difficult.
  - Participants in this scenario may benefit from ART initiation to avoid potential emergence of INSTI resistance if they are infected and have a prolonged period of CAB monotherapy.

- **False positive:** False reactive test results are possible when testing is frequent. False reactive results can occur in the context of pregnancy, syphilis, malaria, other co-infections.
  - Participants in scenario may benefit from re-resting to exclude any lab errors.

- **Risk balance:**
  - In some scenarios it may not be possible to know for certain whether a participant has HIV infection e.g. an isolated HIV RNA result >200 copies where no other tests are positive
  - Consideration needs to be given to whether the participant needs to reinitiate PrEP to avoid ongoing HIV risk or start ART to avoid emergence of resistant infection. This decision will be influenced by available test results, and participants should be kept informed regarding the tests and timing of results so that they remain engaged in care.
  - It may be preferable to initiate ART when diagnosis is uncertain to avoid potential resistance and to plan for a treatment interruption in 12-18 months when CAB is considered cleared.
  - These decisions should be shared with participants so that the participant can make the most informed decision at that point in time. Study staff should communicate that those decisions may be revisited at a later timepoint if needs be as new information becomes available.
The decisional balance tool (Appendix 12A) can also be used as a tool to assist participants with indeterminate HIV test results to decide whether or not to start ART in the case of discrepant HIV test results where HIV diagnosis is uncertain and CAB monotherapy may be associated with the risk of emerging INSTI resistant infection.

### 12.3 Product Use Instructions and Adherence Counseling

Participants will be provided product use instructions and adherence counseling for the first time at their study enrollment visit, and per the schedule on the protocol and the adherence counseling protocol. The person providing product use instructions and adherence counseling will discuss with participants adherence to protocol requirements such as returning for study visits and not sharing product. Adequate time should be taken to explain the product use instructions thoroughly and to answer any questions the participant may have. Any questions or concerns raised by the participant should be documented in his/her study records so this information is easily available for reference at follow-up visits.

In general, adherence counseling will be provided in accordance with recommendations from PrEP clinical guidance documents and in-country implementation strategies (Centers for Disease Control [CDC], World Health Organization [WHO]). Using a participant-centered approach to frame discussions, adherence counseling for those on TDF/FTC will include education around the importance of daily pill adherence and supporting strategies that link pill taking to the participant’s daily routine (i.e., daily calendar, plans for travel, habits). For those choosing cabotegravir injections, counseling should be focused on attending study visits to receive the injections and what to expect before, during, and after injections, as well as daily adherence to oral tablets if the participant decides to take the oral lead-in.

### 12.4 Study Product Use Instructions

#### Oral Product (either CAB or TDF/FTC)

Participants will be instructed to take one tablet by mouth daily. The oral tablets should be taken as close to the same time each day as possible. If a participant misses a dose, the participant can take the missed dose within the same calendar day as soon they remember. The next dose will be taken by mouth as originally scheduled. Participants should be instructed not take two doses of the same product on the same day. Participants should be reminded to store study tablets at room temperature, in a safe place and out of reach of children. Although tablets should be kept in original container with labels intact, participants may use pill boxes or other mechanisms they find helpful to assist with adherence or protect privacy. Such containers would need to accompany participants to their visits to perform pill counts as appropriate and medication reconciliation.
If a participant reports issues swallowing the tablets due to size, they may split the tablet in half and then swallow immediately. Although a pill cutter is preferred, it’s not required for pill-splitting. *NOTE: Antacid products containing divalent cations (e.g., aluminum, calcium and magnesium) must be taken at least 2 hours before or at least 4-6 hours after the oral formulation of CAB.*

**Injection Product**

See section 8 of this manual for information.

### 12.5 Counseling Considerations

Please refer to the decisional balance worksheet in Appendix 12A which can be used in your discussions with participants about the options in the OLE. Participants who opt into the oral CAB lead-in should be counseled on the purpose of the lead-in, with an emphasis placed on the fact that it is being conducted specifically to rule out any serious side effects of the study drug prior to the administration of injections, and that therefore it is important that the study drug be taken every day. Sites should refer to the HPTN 084 protocol for side effects of oral cabotegravir (CAB) (Section 1 and the Sample Informed Consent Form Template), as well as the Investigator’s Brochure (IB) and Section 9 of this manual.

For participants choosing CAB LA, counseling conducted prior to each injection should focus mainly on what to expect before, during, and after each injection is given, including any side effects that they may experience, and that it will last in their system for a long time (a year or more after a single injection) with clear explanation why participants get more than one injection at different intervals yet the long-acting formulation drug lasts for a year or more after a single dose. Participants should be informed of the schedule of injections and the expected timeframe they will receive them (based on their enrollment date, see Protocol Section 5 and SSP manual Section 6).

Additionally, it should be explained that the injection site (the buttocks) may have localized pain, be tender to palpitation, itch, swell, bruise, be temporarily discolored, feel warm or have a pulsing sensation. Participants must be encouraged to contact site staff after they have left the study clinic if any side effects occur, including suspected injection site reactions. Participants who report injection site reactions should be assessed by a clinician. Participants can be counselled on how best to minimize injection site pain using the guidance in section 9.

While the HPTN 084 protocol provides instructions regarding when to contact the CMC about adverse events, the CMC may be contacted at any time there is a question about any side effects of the oral or long-acting study product.
Participants choosing TDF/FTC will be counseled to identify reminder cues to assist with daily dosing, including reviewing calendars for daily habits, setting phone alarms, etc. The counseling should also include clear instructions about the product, any side effects anticipated, and strategies for maintaining daily adherence. Counseling may also incorporate conversations around disclosure of study participation to supportive others (see optional tools Appendix 12b).
Appendix 12A: Decisional Balance Worksheet for OLE

| STATE | Thank you for your ongoing participation in the HPTN 084 study. In this phase of the study, there are some choices for you to make. In order for you to weigh the pros and cons for yourself, you can use something called a decisional balance worksheet. |
| HANDOUT | Decisional Balance Worksheet |
| STATE | With a decisional balance sheet, you are listing pros and cons that are very specific to you, your life, your thoughts and your feelings. This allows you to weigh the drawbacks and benefits of all of your options in order to get a clearer understanding of what is right for you. Let’s review this worksheet together. |
| DISCUSS | Decisional Balance Worksheet with participant. Help with pros and cons if needed. Examples are just for discussion if needed. |

**Choice to stay on TDF/FTC:**
Pros may include:
- Used to taking daily pill
- Don’t like injections

Cons may include
- Not long-acting
- Product storage

**Choice of oral CAB lead-in or direct-to-inject:**
Pros may include:
- Getting used to the medication
- Avoiding allergic reaction

Cons may include
- Taking a daily pill temporarily (if required)

**Choice to join the pregnancy substudy:**
Pros may include:
- Help gather valuable information for pregnant women in the future
- Monitoring of pregnancy by study staff; getting additional care

Cons may include
- Additional study procedures
- Extra time at study visits

**Choice to start ART following discordant results:**
Pros may include:
- Benefits of early treatment
- Protecting sexual partners and potential pregnancies while waiting for determination of HIV status
- Not life long, might only for a period until a treatment interruption 12-18 months later could confirm uninfected

Cons may include:
- Preparation for daily pill intake/adherence
- Disclosure and stigma concerns
- Challenges with transfer to local ART clinics

<table>
<thead>
<tr>
<th>DISCUSS</th>
<th>Any questions or concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>STATE</td>
<td><em>When making big decisions, it is important to consider who can provide you with support.</em> “Supportive others” are the people or groups of people who are most important in our lives. Supportive others may include parents, peers, family members, schools, health providers, faith communities, and dating partners. We all rely on supportive others to listen when we need to talk, give us advice, and shape our ideas about the decisions we make and the consequences of each decision. In this activity, let’s identify the people who are supportive to you.</td>
</tr>
<tr>
<td>ASK</td>
<td><em>If you could fill a room with the most important people in your life, who would be in the room?</em></td>
</tr>
</tbody>
</table>
| DISCUSS | *Who are the people/groups in the room?*
- Why are they important to you?
- Are there some that have more influence than others?
- Are these people/groups you can count on when you are in trouble or in need?
- Do they help you make good decisions? Always? Most of the time? Sometimes? Never?
- Do you feel good about the decisions they help you make? |
| REVIEW | *Who would help the participant make medical decisions – make sure that they have a qualified provider to support them if needed.* |
| STATE   | *Thank you for completing this activity. I’m glad to understand who is important to you and how they may help with decision-making for this study.* |
| DISCUSS | Any final questions or concerns |
**Appendix 12B: PrEP Disclosure Activities**

Disclosure tools should be approved by local IRB/EC prior to distributing to participants.

**ACTIVITY A: SAFE TALK- HOW DO I DISCLOSE THAT I AM ON PREP?**

<table>
<thead>
<tr>
<th>QUESTION</th>
<th>ANSWER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASK PARTICIPANT</strong></td>
<td>How do you feel about telling people that you are taking PrEP?</td>
</tr>
<tr>
<td><strong>DISCUSS</strong></td>
<td>Participants views on disclosing or not disclosing PrEP</td>
</tr>
<tr>
<td><strong>STATE</strong></td>
<td>If you are struggling with how to tell someone that you are taking PrEP, here is an acronym, T.A.L.K. that can help guide you through the process.</td>
</tr>
<tr>
<td><strong>HANDOUT</strong></td>
<td>“Safe TALK” handout.</td>
</tr>
<tr>
<td><strong>Timing</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Assertive Communication</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Know What to Say</strong></td>
<td></td>
</tr>
<tr>
<td><strong>STATE</strong></td>
<td>Timing, Assertive Communication, Location, Know What to Say.</td>
</tr>
<tr>
<td><strong>ASK</strong></td>
<td>Have the participant read text on the “SAFE Talk” handout.</td>
</tr>
</tbody>
</table>

**TIMING**

Choose an appropriate time to talk with your person. If the person that you need to talk with has a busy lifestyle, then it might be easier for you to set a meeting time. This way, each person’s attention can be focused on the issue.

**ASSERTIVE COMMUNICATION**

Clearly tell the person how you feel and what you want or need by being honest and direct. Think carefully about your relationship and pay attention to others’ responses. Depending on the specific person, you might have to address issues differently. Remember to use “I” statements, take deep breaths, keep a reasonable tone, and actively listen to the other person.

**LOCATION**

Choose a quiet place where you cannot be interrupted or overheard by others.

**KNOWING WHAT TO SAY**

Think about what you want to say in advance by sorting out your own feelings about the issue before talking with the other person. You might find that making a list or writing a letter of your thoughts and feelings will help you focus.
<table>
<thead>
<tr>
<th>DISCUSS</th>
<th>Handout and answer any questions.</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPHASIZE</td>
<td>You have control over whether you tell people, who you tell and how you tell them. Think about what is best for you and make sure YOU are ready.</td>
</tr>
<tr>
<td>STATE</td>
<td>Now we are going to practice telling someone you are on PrEP by doing some role-playing, even if you aren’t ready to tell someone yet. Choose someone who you may want to tell about PrEP in the future. Let me know who it is and provide me with some details about where the conversation is taking place. The more details you provide, the better. I will then pretend to be the person and react as I think the person might respond.</td>
</tr>
<tr>
<td>ALLOW</td>
<td>Time for participant to prepare then Conduct the role-play.</td>
</tr>
<tr>
<td>ASK</td>
<td>What was the most challenging thing about this role-play?</td>
</tr>
<tr>
<td></td>
<td>What part of this was easier than you thought it would be?</td>
</tr>
<tr>
<td></td>
<td>What surprised you going through this role-play?</td>
</tr>
<tr>
<td>ENCOURAGE</td>
<td>Participant to share one thing they liked, and one thing they wish they would do differently.</td>
</tr>
<tr>
<td>ALLOW</td>
<td>Time for discussion</td>
</tr>
</tbody>
</table>

**ACTIVITY B: ACTION PLAN: DISCLOSURE**

<table>
<thead>
<tr>
<th>NOTE</th>
<th>This activity is ONLY for participants who are interested in telling someone about being on PrEP.</th>
</tr>
</thead>
<tbody>
<tr>
<td>STATE</td>
<td>You have said that you are interested in telling someone that you are taking PrEP. Let’s develop an action plan to outline what steps you will take.</td>
</tr>
<tr>
<td>HANDOUT</td>
<td>“Action Plan: Disclosure” handout</td>
</tr>
<tr>
<td>STATE</td>
<td>Think about the specific person whom you would like to disclose your PrEP use to. Use this worksheet to think through the reasons why you want to disclose to that person. Then use this form to plan out the process. Decide when you would like to tell them, where you will have the talk, what you will say, and how you will do it. Finally, think about what the potential costs and benefits of disclosing to this person would be.</td>
</tr>
<tr>
<td>ALLOW</td>
<td>Participants time to fill out their action plan. They may leave the worksheet with the counselor or take it home if they wish.</td>
</tr>
</tbody>
</table>
ACTIVITY C: Negotiating PrEP Use in a Sexual Relationship

| STATE | You may decide that you want to talk to your husband, boyfriend or a sexual partner about using PrEP at some point. This might seem a bit difficult, but if you prepare yourself, it will be easier. Remember last time with discussed the “Safe TALK” strategy?

Show “Safe TALK” handout and review if participant hasn’t seen it or doesn’t remember it

| TIMING | Choose an appropriate time to talk with your person. If the person that you need to talk with has a busy lifestyle, then it might be easier for you to set a meeting time. This way, each person’s attention can be focused on the issue.

| ASSERTIVE COMMUNICATION | Clearly tell the person how you feel and what you want or need by being honest and direct. Think carefully about your relationship and pay attention to others’ responses. Depending on the specific person, you might have to address issues differently. Remember to use “I” statements, take deep breaths, keep a reasonable tone, and actively listen to the other person.

| LOCATION | Choose a quiet place where you cannot be interrupted or overheard by others.

| KNOWING WHAT TO SAY | Think about what you want to say in advance by sorting out your own feelings about the issue before talking with the other person. You might find that making a list or writing a letter of your thoughts and feelings will help you focus.

Tell him some of the things you have learned about STIs and HIV. It’s also important to negotiate and listen to him. Keep in mind that it’s not only your right, but also your RESPONSIBILITY to make decisions that you will help you stay healthy.

It’s very important to know what you will say in response to your partner’s questions, complaints, or efforts to change your mind. You can anticipate his reactions and responses and make the conversation a little easier for you.

<p>| STATE | Let’s practice discussing PrEP with your husband/boyfriend. |</p>
<table>
<thead>
<tr>
<th>DISPLAY</th>
<th>How to talk PrEP with your partner handout...</th>
</tr>
</thead>
<tbody>
<tr>
<td>What if your partner says...</td>
<td></td>
</tr>
<tr>
<td>• “I am faithful to you, you don’t need PrEP.”</td>
<td></td>
</tr>
<tr>
<td>• “PrEP doesn’t work.”</td>
<td></td>
</tr>
<tr>
<td>• “If you need PrEP, you must be sleeping around.”</td>
<td></td>
</tr>
<tr>
<td>• “You must have HIV and aren’t telling me.”</td>
<td></td>
</tr>
<tr>
<td>ASK</td>
<td>How would you respond to these statements by your partner? Let’s practice.</td>
</tr>
<tr>
<td>ROLE PLAY</td>
<td>Different ways to respond to the partner statements</td>
</tr>
<tr>
<td>DISCUSS</td>
<td>Alternative responses with the participant.</td>
</tr>
<tr>
<td>THANK</td>
<td>Participant for sharing her feelings and being open and honest about the process of disclosure.</td>
</tr>
</tbody>
</table>
SAFE T.A.L.K

TIMING

Choose an appropriate time to talk with your family or significant others. If the family member that you need to talk with has a busy lifestyle, then it might be easier for you to set a meeting time. This way, each person's attention can be focused on the issue.

ASSERTIVE COMMUNICATION

Clearly tell your family member or significant others how you feel and what you want or need by being honest and direct. Think carefully about your relationship and pay attention to others' responses. Depending on the specific person, you might have to address issues differently. Remember to use "I" statements, take deep breaths, keep a reasonable tone, and actively listen to your family member or significant others.

LOCATION

Choose a quiet place where you and your family member or significant others cannot be interrupted or overhead by others.

KNOWING WHAT TO SAY

Think about what you want to say in advance by sorting out your own feelings about the issue before talking with your family member or significant others. You might find that making a list or writing a letter of your thoughts and feelings will help you focus.
ACTION PLAN: DISCLOSURE

Think about one specific person to whom you would like to disclose your PrEP use. Let's use this worksheet to think through the reasons why you might want to disclose to that person. Then use this form to plan out the process.

List all the reasons WHY you want to disclose to ________________.

<table>
<thead>
<tr>
<th>WHO am I disclosing to?</th>
<th>WHAT will I say?</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHERE will I say it?</td>
<td>WHEN will I have this conversation?</td>
</tr>
<tr>
<td>HOW will I do it?</td>
<td></td>
</tr>
</tbody>
</table>

Potential Costs: Potential Benefits:
How to talk PrEP with your partner...

Your partner says:

“I am faithful to you, you don’t need PrEP.”

“PrEP doesn’t work.”

“If you need PrEP, you must be sleeping around.”

“You must have HIV and aren’t telling me.”
Section 13. Data Management

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The purpose of this document is to provide site staff with the information needed to complete electronic Case Report Forms (eCRFs) in MediData Rave.

The Statistics and Data Management Center (SDMC) for this study is the Statistical Center for HIV/AIDS Research and Prevention (SCHARP). SCHARP is located in Seattle, USA, and is in the US Pacific Time (PT) time zone.

HPTN 084 SDMC Staff

<table>
<thead>
<tr>
<th>Job Role</th>
<th>Name</th>
<th>Email Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sr. Clinical Data Manager**</td>
<td>Stephanie Beigel-Orme</td>
<td><a href="mailto:sbeigelo@scharp.org">sbeigelo@scharp.org</a></td>
</tr>
<tr>
<td>Clinical Safety Associate***</td>
<td>Sophie Hasan</td>
<td><a href="mailto:shasan@scharp.org">shasan@scharp.org</a></td>
</tr>
</tbody>
</table>

**For data management questions, contact the alias, sc.084cdm@scharp.org
***For questions about clinical queries (queries that say “To Site from Safety” or “To Site from Coder”, please contact the SDMC Clinical Safety group: sc.clinsafety@scharp.org
13.1 Medidata Rave Overview

Medidata Rave is the data management system used by SCHARP to receive and manage study data collected at study sites. Each site completes study eCRFs by entering data into the Medidata Rave study database. As specified in each site’s Source Documentation Standard Operating Procedure (SOP), data may be entered directly into the study database (i.e., electronic CRF is source), collected first on paper CRFs and then entered into the study database, and/or entered into the study database based on other non-CRF source documents (e.g., lab reports, testing logs, chart notes, etc.).

The HPTN 084 study database in Medidata Rave may be accessed at [www.imedidata.com](http://www.imedidata.com).

When using Medidata Rave, the internet browser chosen and internet connectivity quality will be the most critical factors affecting functionality, as Medidata is accessed via a URL using a web browser. Using an outdated browser will result in a warning banner on the log-in page of iMedidata. This warning will inform the user that their browser does not support security features that are being implemented in future iMedidata releases and to upgrade their browser. Users using any of the following browsers will see this banner:

- Internet Explorer – Versions older than 8.0
- Chrome – Versions older than 30.0
- Firefox – Versions older than 24.0
- Safari - Versions older than 7.0
- Opera - Versions older than 17.0

Each site’s Data Management SOP designates the site staff members responsible for entering data into the study database. SCHARP grants designated site staff access with specific user permissions to the study database. They are required to complete eLearning modules in Medidata, as assigned by SCHARP, before access is granted and data can be entered into the study database. For more detailed information, see the iMedidata Access Guide, posted on the HPTN 084 Atlas webpage.

Detailed guidance on data collection, entry, navigation and general use of Medidata Rave is provided in the Medidata Rave Electronic Data Capture (EDC) Training Manual, which is posted on the HPTN084 Atlas web page.

https://atlas.scharp.org/cpas/project/HPTN/084/begin.view?

Site staff should contact the study Clinical Data Manager(s) with any questions related to study data collection and management. A representative from Medidata Solutions may be contacted (see contact information below) anytime a site has technical questions or problems related to access or use of the Medidata Rave software.
13.2 Data Entry/Quality Control

- Once data for an eCRF is completed and saved in the study database, the following may occur:
  - A system query may be automatically triggered in Medidata Rave (e.g., denoting incomplete or inconsistent data).
  - Manual data queries may be placed by the SCHARP Clinical Data Manager (CDM) and/or Clinical Safety Associate (CSA) after review of entered forms.
  - Data queries may be placed by the site monitor (i.e., PPD) after required review for certain forms and/or fields.
  - Coding queries may be placed by the SCHARP MedDRA coder to help clarify AE data.
  - Inconsistency queries may be manually placed during AE-EAE reconciliation.

- Queries, or QCs, appear in the Medidata Rave Task Summary on the study home page of designated site users (example below). Staff members designated by the site are responsible for routinely checking the Task Summary and correcting/updating study data to resolve any outstanding queries.

Task Summary Example:

<table>
<thead>
<tr>
<th>Task Summary: Site</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requiring Signature</td>
<td>16</td>
</tr>
<tr>
<td>NonConformant Data</td>
<td>0</td>
</tr>
<tr>
<td>Requiring Coding</td>
<td>0</td>
</tr>
<tr>
<td>Requiring Translation</td>
<td>0</td>
</tr>
<tr>
<td>Open Queries</td>
<td>8</td>
</tr>
<tr>
<td>Answered Queries</td>
<td>0</td>
</tr>
</tbody>
</table>
• When site staff correct/update study data in response to a manual or coding query, SCHARP staff review the updated data and resolve the query or re-query as needed.

• When site staff correct/update study data in response to a monitoring query, the site monitor (i.e., PPD) reviews the updated data and resolves the query or re-queries as needed.

• If a site utilizes paper CRFs as source documents, any changes to the paper CRFs must be entered into the Medidata Rave study database.

**Electronic Signatures by Investigators**

Each site Investigator of Record or designee must sign off on each participant’s complete set of data, or ‘case book’ to attest that the data has been reviewed and is deemed to be accurate. Their iMedidata login credentials serve as their electronic signature. Please refer to the “Electronic Signature” section of the Medidata Rave EDC Training Manual and/or the Investigator e-Learning module for specific instructions on how to sign off on CRFs.

![Electronic Signature Image]

The SCHARP Clinical Data Manager(s) will provide directions for the timing of when the Investigator should perform the final review and sign the form pages. Please note that if an eCRF is signed off and a query is applied to the form or a change to the form occurs during the study, the electronic signature will be broken and the IoR will need to re-sign the form.

**13.3 eCRF Completion**

**13.3.1 Participant Identification number (PTID) Creation and Screening**

Each participant who provides written informed consent to be screened in HPTN084 will be assigned a Participant Identifier, or PTID. The PTID is created when site staff add a subject within their Medidata home study and site folder. Refer to the “Creating Subjects” section of the Medidata Rave EDC Training Manual and the CRF Completion Guidelines (CCGs) for specific instructions.
Each PTID is unique. It will be assigned to a single participant only at a given site and not assigned to any other participant at any site or in any study for which SCHARP is the SDMC.

PTIDs are nine digits, and formatted as “XXXYYYYYZ”. The PTID consists of three parts: the site number (XXX), the participant number (YYYYY), and a numerical check digit (Z). The check digit (Z) is a number generated by SCHARP with the participant number, and helps ensure that the correct PTID is recorded and entered.

If a participant does not enroll in the study, the following forms are required to document the Screening Visit: Screening Outcome, HIV Test Results, Plasma Storage, and VOICE Risk Score – Modified. Inclusion and exclusion criteria are documented on the Screening Outcome eCRF as well as reasons for not enrolling into the study.

If a participant returns at a later date to re-screen she must be assigned a new, unique PTID and treated as a new participant in the data management system.

### 13.3.2 Enrollment and Randomization

Prior to randomization eligibility must be confirmed, which includes a negative HIV test on a sample drawn at the Enrollment visit as well as a negative pregnancy test.

To randomize a participant, site staff mark ‘Yes’ to the question, “Is the participant ready to be randomized?” on the Randomization eCRF and click the “Save” button (see image below).

Once the Randomization eCRF is saved, a message will appear on the form that reads: “Subject successfully randomized” as shown in the image below. The Medidata Balance module will assign the participant to a treatment arm and the participant is considered successfully randomized. **A participant is considered enrolled in the study once this step takes place.**

Note that the participant’s randomly assigned treatment arm will not appear in the clinical study database, since the study is double-blinded. Rather, PAB-approved site pharmacists only (along with the study statisticians) will be provided restricted access to Medidata Balance to obtain the coded information needed to select and dispense the correct study medication.
Each time a participant is randomized an email confirmation will be sent to anyone with a Medidata account who is assigned the role of “CRC”, “IoR”, “Read only access” or “Pharmacist” to inform them of the new randomization. The randomization confirmation notice will include the following information:

Randomization Alert:
Study: HPTN084
Environment: PROD
Site Number: 12345
Subject ID: 999999990
A Subject has been randomized at 2/9/2018 9:21:17 AM Calendar Date. Pharmacists can log into the [www.imedidata.com](http://www.imedidata.com) to view the participant’s assigned treatment

All randomization notices should be kept in a secure location.

In the event the randomization confirmation email is not received, please follow the steps detailed below:

- Inform the site pharmacist that a randomization confirmation email for the randomized participant was not received (it does not mean that the participant was not randomized, just that the email did not get through to the site).
- Ask the site pharmacist to confirm the participant was successfully randomized by logging in to Balance.
- When final product preparations are to begin, provide the pharmacist with the PTID of the randomized participant and request that the pharmacist log into Medidata RTSM (Balance), locate the PTID, retrieve the treatment assignment, and prepare study product accordingly.
- Document all steps in the participant chart.
- Do not contact Medidata Support.

### 13.3.3 General Guidelines for eCRF Completion

- When completing an eCRF, refer to the CCG document, posted on ATLAS, for detailed instructions on data collection pertaining to the given form and fields on that form.
- Medidata Rave allows data to be entered directly into the study database (i.e., electronic CRF as source). Any data that is either collected first on paper CRFs or derived from non-CRF source documents (e.g., lab reports) should ideally be entered into Rave within 1-2 business days of the visit, though up to 5 days is acceptable.
- AEs should be entered within 3 days and EAEs within 24 hours.
- If some or all of the eCRFs will be completed first as paper CRFs, write the participant’s PTID and Visit Label (e.g., Week 6) or Visit code on the paper form.

Any eCRF that does not collect study data does not need to be completed as a paper form, such as all “Y/N” forms that are used as triggers for log forms (e.g., Concomitant Medications Y/N or Adverse Event Y/N):
13.3.4 Visit Codes

Most eCRFs in the study database are set up within pre-defined study visit folders, so the visit name and code automatically appear (and do not need to be entered for required study visits). Interim Visit Codes do need to be assigned. For more information see section 13.6.

Please remember: For specimen collection, the visit code and date on the eCRF must match the visit code and date in the Laboratory and Data Management System (LDMS) database.

Visit codes for required visits are listed in table 13-1.

13.4 Visit Scheduling: Target Days and Visit Windows

Table 13-1 lists the HPTN 084 visit codes, target days and visit windows for each study visit. All windows are listed in days.

13.4.1 Target Days
A target date is the day in which a visit should ideally occur. Target dates for Step 1 visits are based on the date of Enrollment into the study; target dates for Step 2 visits are based on the date the Week 5 Visit is completed; and target dates for Step 3 visits on the day that the first Step 3 visit, Day 0, is conducted. Target dates do not change even if a visit in that step takes place before or after the target date. Whenever possible, visits should be completed on the target day for that visit.

13.4.2 Visit Windows
There are two types of visit windows in HPTN084. If a visit cannot be completed on the target date, it should be completed within the target visit window in order to be counted as “on time” in the Retention Report. If it is not possible to complete the visit on within the target window, the visit still needs to be completed within the allowable (larger) visit window in order to be considered “complete” in the Retention Report. Visits conducted before the target window opens but still within the allowable window are considered “complete” but “early” in the Retention Report. Visits conducted after the target window closes but still within the allowable visit window are considered “complete” but “late” in the Retention Report. If a visit doesn’t occur within the allowable window it will be considered “missed” in the Retention Report. Medidata Rave will not query for an overdue visit (i.e. the forms for that visit) until the allowable visit window has closed.
Table 13-1: HPTN 084 Visit Codes, Target Days, and Visit Windows

<table>
<thead>
<tr>
<th>Week</th>
<th>Visit Code</th>
<th>Day allowable window opens</th>
<th>Day target window opens</th>
<th>Target Day</th>
<th>Day target window closes</th>
<th>Day allowable window closes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>1.0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0/Enrollment</td>
<td>2.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Week 2</td>
<td>3.0</td>
<td>7</td>
<td>11</td>
<td>14</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>Week 4*</td>
<td>4.0</td>
<td>21</td>
<td>25</td>
<td>28</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0/Week 5*</td>
<td>5.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Week 6</td>
<td>6.0</td>
<td>4</td>
<td>4</td>
<td>7</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Week 9</td>
<td>7.0</td>
<td>18</td>
<td>25</td>
<td>28</td>
<td>31</td>
<td>41</td>
</tr>
<tr>
<td>Week 13</td>
<td>8.0</td>
<td>42</td>
<td>53</td>
<td>56</td>
<td>59</td>
<td>69</td>
</tr>
<tr>
<td>Week 17</td>
<td>9.0</td>
<td>70</td>
<td>81</td>
<td>84</td>
<td>87</td>
<td>97</td>
</tr>
<tr>
<td>Week 21</td>
<td>10.0</td>
<td>98</td>
<td>109</td>
<td>112</td>
<td>115</td>
<td>125</td>
</tr>
<tr>
<td>Week 25</td>
<td>11.0</td>
<td>126</td>
<td>137</td>
<td>140</td>
<td>143</td>
<td>168</td>
</tr>
<tr>
<td>Week 33</td>
<td>12.0</td>
<td>169</td>
<td>189</td>
<td>196</td>
<td>203</td>
<td>224</td>
</tr>
<tr>
<td>Week 41</td>
<td>13.0</td>
<td>225</td>
<td>245</td>
<td>252</td>
<td>255</td>
<td>255</td>
</tr>
<tr>
<td>Week 42</td>
<td>14.0</td>
<td>256</td>
<td>256</td>
<td>259</td>
<td>266</td>
<td>283</td>
</tr>
<tr>
<td>Week 49</td>
<td>15.0</td>
<td>284</td>
<td>301</td>
<td>308</td>
<td>315</td>
<td>336</td>
</tr>
<tr>
<td>Week 57</td>
<td>16.0</td>
<td>337</td>
<td>357</td>
<td>364</td>
<td>371</td>
<td>392</td>
</tr>
<tr>
<td>Week 65</td>
<td>17.0</td>
<td>393</td>
<td>413</td>
<td>420</td>
<td>427</td>
<td>448</td>
</tr>
<tr>
<td>Week 73</td>
<td>18.0</td>
<td>449</td>
<td>469</td>
<td>476</td>
<td>483</td>
<td>504</td>
</tr>
<tr>
<td>Week 81</td>
<td>19.0</td>
<td>505</td>
<td>525</td>
<td>532</td>
<td>539</td>
<td>560</td>
</tr>
<tr>
<td>Week 89</td>
<td>20.0</td>
<td>561</td>
<td>581</td>
<td>588</td>
<td>595</td>
<td>616</td>
</tr>
<tr>
<td>Week 97</td>
<td>21.0</td>
<td>617</td>
<td>637</td>
<td>644</td>
<td>651</td>
<td>672</td>
</tr>
<tr>
<td>Week 105</td>
<td>22.0</td>
<td>673</td>
<td>693</td>
<td>700</td>
<td>707</td>
<td>728</td>
</tr>
<tr>
<td>Week 113</td>
<td>23.0</td>
<td>729</td>
<td>749</td>
<td>756</td>
<td>763</td>
<td>784</td>
</tr>
<tr>
<td>Week 121</td>
<td>24.0</td>
<td>785</td>
<td>805</td>
<td>812</td>
<td>819</td>
<td>840</td>
</tr>
<tr>
<td>Week 129</td>
<td>25.0</td>
<td>841</td>
<td>861</td>
<td>868</td>
<td>875</td>
<td>896</td>
</tr>
<tr>
<td>Week 137</td>
<td>26.0</td>
<td>897</td>
<td>917</td>
<td>924</td>
<td>931</td>
<td>952</td>
</tr>
<tr>
<td>Week 145</td>
<td>27.0</td>
<td>953</td>
<td>973</td>
<td>980</td>
<td>987</td>
<td>1008</td>
</tr>
<tr>
<td>Week 153</td>
<td>28.0</td>
<td>1009</td>
<td>1029</td>
<td>1036</td>
<td>1043</td>
<td>1064</td>
</tr>
<tr>
<td>Week 161</td>
<td>29.0</td>
<td>1065</td>
<td>1085</td>
<td>1092</td>
<td>1099</td>
<td>1120</td>
</tr>
<tr>
<td>Week 169</td>
<td>30.0</td>
<td>1121</td>
<td>1141</td>
<td>1148</td>
<td>1155</td>
<td>1176</td>
</tr>
<tr>
<td>Week 177</td>
<td>31.0</td>
<td>1177</td>
<td>1197</td>
<td>1204</td>
<td>1211</td>
<td>1232</td>
</tr>
<tr>
<td>Week 185</td>
<td>32.0</td>
<td>1233</td>
<td>1253</td>
<td>1260</td>
<td>1267</td>
<td>1288</td>
</tr>
</tbody>
</table>
**Step 3**

<table>
<thead>
<tr>
<th>Week</th>
<th>Visit Code</th>
<th>Day allowable window opens</th>
<th>Day target window opens</th>
<th>Target Day</th>
<th>Day target window closes</th>
<th>Day allowable window closes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0 (Step 3 only)</td>
<td>33.0</td>
<td>0</td>
<td>0</td>
<td>&lt;8 weeks from last injection</td>
<td>14</td>
<td>42</td>
</tr>
<tr>
<td>Week 12</td>
<td>34.0</td>
<td>43</td>
<td>70</td>
<td>84</td>
<td>98</td>
<td>126</td>
</tr>
<tr>
<td>Week 24</td>
<td>35.0</td>
<td>127</td>
<td>154</td>
<td>168</td>
<td>182</td>
<td>210</td>
</tr>
<tr>
<td>Week 36</td>
<td>36.0</td>
<td>211</td>
<td>238</td>
<td>252</td>
<td>266</td>
<td>294</td>
</tr>
<tr>
<td>Week 48</td>
<td>37.0</td>
<td>295</td>
<td>322</td>
<td>336</td>
<td>350</td>
<td>378</td>
</tr>
</tbody>
</table>

*Please note that the Week 4 and Week 5 Visits must be completed in order for a participant to move to Step 2. If a Week 4 or Week 5 Visit is delayed or missed, contact the CMC for further guidance.

**The target dates for all Step 2 visits are based off of the actual date of the Week 5 Visit. The target dates for all Step 3 visits are based off of the first Step 3 Visit, called “Step 3/Day 0”.

### Open Label Truvada Schedule

<table>
<thead>
<tr>
<th>Week</th>
<th>Visit Code</th>
<th>Day allowable window opens</th>
<th>Day target window opens</th>
<th>Target Day</th>
<th>Day target window closes</th>
<th>Day allowable window closes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0 (date injections permanently discontinue)</td>
<td>V201/or other*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>42</td>
</tr>
<tr>
<td>Week 12</td>
<td>202.0</td>
<td>43</td>
<td>70</td>
<td>84</td>
<td>98</td>
<td>126</td>
</tr>
<tr>
<td>Week 24</td>
<td>203.0</td>
<td>127</td>
<td>154</td>
<td>168</td>
<td>182</td>
<td>210</td>
</tr>
<tr>
<td>Week 36</td>
<td>204.0</td>
<td>211</td>
<td>238</td>
<td>252</td>
<td>266</td>
<td>294</td>
</tr>
<tr>
<td>Week 48</td>
<td>205.0</td>
<td>295</td>
<td>322</td>
<td>336</td>
<td>350</td>
<td>378</td>
</tr>
</tbody>
</table>

- Day 0 for Open Label Truvada Schedule may be a Step 2 visit code or 201. See Section 13.5 Alternate Visits.
### Pregnancy Schedule*

<table>
<thead>
<tr>
<th>Week</th>
<th>Visit Code</th>
<th>Day allowable window opens</th>
<th>Day target window opens</th>
<th>Target Day</th>
<th>Day target window closes</th>
<th>Day allowable window closes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0 (First positive Pregnancy Test)</td>
<td>XX.X</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4 weeks after first positive pregnancy test</td>
<td>Interim visit XX.X</td>
<td>21</td>
<td>--</td>
<td>28</td>
<td>--</td>
<td>35</td>
</tr>
<tr>
<td>Quarterly Visit 1 (12 weeks since first positive pregnancy test)</td>
<td>101</td>
<td>43</td>
<td>70</td>
<td>84</td>
<td>98</td>
<td>126</td>
</tr>
<tr>
<td>Quarterly Visit 2 (24 weeks since first positive pregnancy test)</td>
<td>102</td>
<td>127</td>
<td>154</td>
<td>168</td>
<td>182</td>
<td>210</td>
</tr>
<tr>
<td>Quarterly Visit 3 (36 weeks since first positive pregnancy test)</td>
<td>103</td>
<td>211</td>
<td>238</td>
<td>252</td>
<td>266</td>
<td>294</td>
</tr>
</tbody>
</table>

*Pregnancy schedule is to be followed throughout pregnancy and while participant is breastfeeding.

### Yearly/Annual Visits

<table>
<thead>
<tr>
<th>Week</th>
<th>Visit Code</th>
<th>Day allowable window opens</th>
<th>Day target window opens</th>
<th>Target Day</th>
<th>Day target window closes</th>
<th>Day allowable window closes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0 (Last visit participant at clinic HIV Test conducted)</td>
<td>XX.X</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Yearly Visit 1</td>
<td>50.0</td>
<td>182</td>
<td>358</td>
<td>365</td>
<td>372</td>
<td>548</td>
</tr>
<tr>
<td>Yearly Visit 2</td>
<td>51.0</td>
<td>547</td>
<td>723</td>
<td>730</td>
<td>737</td>
<td>913</td>
</tr>
<tr>
<td>Yearly Visit 3</td>
<td>52.0</td>
<td>912</td>
<td>1088</td>
<td>1095</td>
<td>1102</td>
<td>1278</td>
</tr>
<tr>
<td>Yearly Visit 4</td>
<td>53.0</td>
<td>1277</td>
<td>1453</td>
<td>1460</td>
<td>1467</td>
<td>1643</td>
</tr>
<tr>
<td>Yearly Visit 5</td>
<td>54.0</td>
<td>1642</td>
<td>1818</td>
<td>1825</td>
<td>1832</td>
<td>2008</td>
</tr>
</tbody>
</table>
Seroconverter Schedule

<table>
<thead>
<tr>
<th>Week</th>
<th>Visit Code*</th>
<th>Day allowable window opens</th>
<th>Day target window opens</th>
<th>Target Day</th>
<th>Day target window closes</th>
<th>Day allowable window closes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Confirmatory Visit</td>
<td>XX.X</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>42</td>
</tr>
<tr>
<td>Week 12</td>
<td>XX.X</td>
<td>43</td>
<td>70</td>
<td>84</td>
<td>98</td>
<td>126</td>
</tr>
<tr>
<td>Week 24</td>
<td>XX.X</td>
<td>127</td>
<td>154</td>
<td>168</td>
<td>182</td>
<td>210</td>
</tr>
<tr>
<td>Week 36</td>
<td>XX.X</td>
<td>211</td>
<td>238</td>
<td>252</td>
<td>266</td>
<td>294</td>
</tr>
<tr>
<td>Week 48</td>
<td>XX.X</td>
<td>295</td>
<td>322</td>
<td>336</td>
<td>350</td>
<td>378</td>
</tr>
</tbody>
</table>

*Due to unblinding considerations, there are no unique visit codes for seroconverters. The visit codes should reflect the next study visits for the participants.
### Table 13-2: HPTN 084 Open Label Extension (OLE) Visit Codes, Target Days, and Visit Windows

<table>
<thead>
<tr>
<th>Week</th>
<th>Visit Code</th>
<th>Day allowable window opens</th>
<th>Day target window opens</th>
<th>Target Day</th>
<th>Day target window closes</th>
<th>Day allowable window closes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OLE Transition 1: Steps 4a → 4b→ 4c</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4a Day 0 (Oral lead in)</td>
<td>55.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>4b Week 4 (Loading Dose)</td>
<td>56.0</td>
<td>14</td>
<td>25</td>
<td>28</td>
<td>31</td>
<td>41</td>
</tr>
<tr>
<td>4c Day 0*</td>
<td>57.0</td>
<td>42</td>
<td>53</td>
<td>56</td>
<td>59</td>
<td>69</td>
</tr>
<tr>
<td><strong>OLE Transition 2: Steps 4b → 4c</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4b Day 0 (Loading Dose)</td>
<td>56.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>4c Day 0*</td>
<td>57.0</td>
<td>21</td>
<td>25</td>
<td>28</td>
<td>31</td>
<td>63</td>
</tr>
<tr>
<td><strong>OLE Transition 3: Step 4c</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAB / TDF/FTC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>57.0 / 64.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>Week 8</td>
<td>58.0 / 65.0</td>
<td>29</td>
<td>49</td>
<td>56</td>
<td>63</td>
<td>84</td>
</tr>
<tr>
<td>Week 16</td>
<td>59.0 / 66.0</td>
<td>85</td>
<td>105</td>
<td>112</td>
<td>119</td>
<td>140</td>
</tr>
<tr>
<td>Week 24</td>
<td>60.0 / 67.0</td>
<td>141</td>
<td>161</td>
<td>168</td>
<td>175</td>
<td>196</td>
</tr>
<tr>
<td>Week 32</td>
<td>61.0 / 68.0</td>
<td>197</td>
<td>217</td>
<td>224</td>
<td>231</td>
<td>252</td>
</tr>
<tr>
<td>Week 40</td>
<td>62.0 / 69.0</td>
<td>253</td>
<td>273</td>
<td>280</td>
<td>287</td>
<td>308</td>
</tr>
<tr>
<td>Week 48</td>
<td>63.0 / 70.0</td>
<td>309</td>
<td>329</td>
<td>336</td>
<td>343</td>
<td>364</td>
</tr>
<tr>
<td><strong>OLE Step 4d- Pregnant/Breastfeeding Participants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>76.0</td>
<td>14</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Week 4</td>
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<td>25</td>
<td>28</td>
<td>31</td>
<td>41</td>
</tr>
<tr>
<td>Week 8</td>
<td>78.0</td>
<td>42</td>
<td>53</td>
<td>56</td>
<td>59</td>
<td>69</td>
</tr>
<tr>
<td>Week 12</td>
<td>79.0</td>
<td>70</td>
<td>81</td>
<td>84</td>
<td>87</td>
<td>97</td>
</tr>
<tr>
<td>Week 16</td>
<td>80.0</td>
<td>98</td>
<td>109</td>
<td>112</td>
<td>115</td>
<td>125</td>
</tr>
<tr>
<td>Week 20</td>
<td>81.0</td>
<td>126</td>
<td>137</td>
<td>140</td>
<td>143</td>
<td>153</td>
</tr>
<tr>
<td>Week 24</td>
<td>82.0</td>
<td>154</td>
<td>165</td>
<td>168</td>
<td>171</td>
<td>181</td>
</tr>
<tr>
<td>Week 28</td>
<td>83.0</td>
<td>182</td>
<td>193</td>
<td>196</td>
<td>199</td>
<td>209</td>
</tr>
<tr>
<td>Week 32</td>
<td>84.0</td>
<td>210</td>
<td>221</td>
<td>224</td>
<td>227</td>
<td>237</td>
</tr>
<tr>
<td>Week 36</td>
<td>85.0</td>
<td>238</td>
<td>249</td>
<td>252</td>
<td>255</td>
<td>265</td>
</tr>
<tr>
<td>Week 40</td>
<td>86.0</td>
<td>266</td>
<td>277</td>
<td>280</td>
<td>283</td>
<td>293</td>
</tr>
<tr>
<td>Delivery (Day 0)</td>
<td>95.0****</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Week 2, pp**</td>
<td>87.0</td>
<td>7</td>
<td>11</td>
<td>14</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>Week 4, pp</td>
<td>88.0</td>
<td>21</td>
<td>25</td>
<td>28</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Week 8, pp</td>
<td>89.0</td>
<td>32</td>
<td>49</td>
<td>56</td>
<td>63</td>
<td>84</td>
</tr>
</tbody>
</table>
### Step 5

<table>
<thead>
<tr>
<th>Week</th>
<th>Visit Code</th>
<th>Day allowable window opens</th>
<th>Day target window opens</th>
<th>Target Day</th>
<th>Day target window closes</th>
<th>Day allowable window closes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 16, pp</td>
<td>90.0</td>
<td>85</td>
<td>105</td>
<td>112</td>
<td>119</td>
<td>140</td>
</tr>
<tr>
<td>Week 24, pp</td>
<td>91.0</td>
<td>141</td>
<td>161</td>
<td>168</td>
<td>175</td>
<td>196</td>
</tr>
<tr>
<td>Week 32, pp</td>
<td>92.0</td>
<td>197</td>
<td>217</td>
<td>224</td>
<td>231</td>
<td>252</td>
</tr>
<tr>
<td>Week 40, pp</td>
<td>93.0</td>
<td>253</td>
<td>273</td>
<td>280</td>
<td>287</td>
<td>308</td>
</tr>
<tr>
<td>Week 48, pp</td>
<td>94.0</td>
<td>309</td>
<td>329</td>
<td>336</td>
<td>343</td>
<td>364</td>
</tr>
</tbody>
</table>

*Day 0 (Day 0 no later than 8 weeks after the last injection)*

<table>
<thead>
<tr>
<th>Week</th>
<th>Visit Code</th>
<th>Day allowable window opens</th>
<th>Day target window opens</th>
<th>Target Day</th>
<th>Day target window closes</th>
<th>Day allowable window closes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 12</td>
<td>71.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>42</td>
</tr>
<tr>
<td>Week 24</td>
<td>72.0</td>
<td>43</td>
<td>70</td>
<td>84</td>
<td>98</td>
<td>126</td>
</tr>
<tr>
<td>Week 36</td>
<td>73.0</td>
<td>127</td>
<td>154</td>
<td>168</td>
<td>182</td>
<td>210</td>
</tr>
<tr>
<td>Week 48</td>
<td>74.0</td>
<td>211</td>
<td>238</td>
<td>252</td>
<td>266</td>
<td>294</td>
</tr>
</tbody>
</table>

### Step 6 (OLE2)

<table>
<thead>
<tr>
<th>Week (continued from Step 4c CAB-LA Week 48 v 63)</th>
<th>Visit Code</th>
<th>Day allowable window opens</th>
<th>Day target window opens</th>
<th>Target Day</th>
<th>Day target window closes</th>
<th>Day allowable window closes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 56</td>
<td>116.0</td>
<td>365</td>
<td>385</td>
<td>392</td>
<td>399</td>
<td>420</td>
</tr>
<tr>
<td>Week 64</td>
<td>117.0</td>
<td>421</td>
<td>441</td>
<td>448</td>
<td>455</td>
<td>476</td>
</tr>
<tr>
<td>Week 72</td>
<td>118.0</td>
<td>477</td>
<td>497</td>
<td>504</td>
<td>511</td>
<td>532</td>
</tr>
<tr>
<td>Week 80</td>
<td>119.0</td>
<td>533</td>
<td>553</td>
<td>560</td>
<td>567</td>
<td>588</td>
</tr>
<tr>
<td>Week 88</td>
<td>120.0</td>
<td>589</td>
<td>609</td>
<td>616</td>
<td>623</td>
<td>644</td>
</tr>
<tr>
<td>Week 96</td>
<td>121.0</td>
<td>645</td>
<td>665</td>
<td>672</td>
<td>679</td>
<td>700</td>
</tr>
<tr>
<td>Week 104</td>
<td>122.0</td>
<td>701</td>
<td>721</td>
<td>728</td>
<td>735</td>
<td>756</td>
</tr>
<tr>
<td>Week 112</td>
<td>123.0</td>
<td>757</td>
<td>777</td>
<td>784</td>
<td>791</td>
<td>812</td>
</tr>
</tbody>
</table>

*Proceed with Step 4c*

**Additional pregnancies that also participate in 4d will be assigned visit codes in the following manner: pregnancy 2 176.0-196.0, pregnancy 3 276.0-296.0, etc. The visit windows will be as shown in the table for 4d.

***Delivery – OLE visit codes have been assigned 95.0-99.0 in the event of multiple deliveries for a single participant in the OLE.

****post-partum visit
13.5 Types of Visits

Scheduled Visits

A scheduled visit is a required visit as dictated by the protocol.

Missed Visits

A scheduled visit is considered missed if it is not completed within its allowable visit window. Missed Visits are documented by completing a Missed Visit eCRF. Do not completed a Missed Visit CRF until you are sure that the visit has been missed (i.e. once the allowable window has closed and the participant has not returned to the clinic for that visit).

Split Visits

When a participant is not able to complete all required visit evaluations on the same day, the participant may return and complete the remaining evaluations on another day, as long as all evaluations for that visit are completed within the same allowable visit window for that visit. When such a split visit occurs, case report forms completed for the visit are all assigned the same visit code (even though some forms and evaluations will have different visit dates).

If a form contains a place to record a visit date, and a visit is split, record the date of the first visit associated with the split visit. The exception is the Week 5 Visit. If a Week 5 Visit is split, the date of visit will always be considered the date that the first injection was given.

Interim Visits

All interim visits/contacts with the participant should be documented in a chart note. Additionally, if the interim contact results in at least one newly-completed Medidata Rave CRF, the interim visit is assigned an interim visit code (visit number ending in something other than “.0”) and the Interim Visit eCRF is used to document the visit. All phone contacts that result in at least one newly-completed Rave CRF are also assigned interim visit codes.

To add an interim visit in Rave, click on ‘Add Event’ while in the participant’s folder and select ‘interim’:
An interim visit folder that contains the Interim Visit CRF is then added to the participant’s casebook, or set of folders.

13.6 Interim Visit Codes

Interim visit codes are assigned using the following guidelines:

- To the left of the decimal point, record the two-digit visit code for the most recently required follow-up visit even if the visit was missed and/or if the participant is within the next visit’s window.

- To the right of the decimal point:
  - #.1 = the first interim visit after the most recently-required visit,
  - #.2 = the second interim visit after the most recently-required visit,
  - #.3 = the third interim visit after the most recently-required visit, and so on.

**Example:** A participant completes all required study procedures at Week 6 (visit code =6.0). When the lab results are available later in the week, the site clinician notices the participant has an abnormal lab result that needs to be repeated. The participant returns a few days later to get her blood re-drawn. The second visit is considered an interim visit because the participant had already completed the required study procedures for visit 6.0. Since this is the first interim visit after visit 6.0, it is assigned visit code 6.1.

If participant is on alternate schedule, the interim visit code should reflect that. For example if she is on the Pregnancy Schedule and comes in after visit 102, the interim visit code should be 102.1.
13.7 HPTN 084 Schedule of Forms

The case report forms required for each study visit are summarized in Appendix 13A at the end of this SSP section.

13.8 Completing Interviewer-administered Forms

In order to standardize interviewer-administered data collection from site to site and to maximize quality, it is important that participant interviews be conducted with a non-biased, non-judgmental approach. Study staff should help a participant feel comfortable sharing personal information and opinions while asking the study questions in a consistent manner from participant to participant.

13.9 Site Review (Quality Control) of CRFs

As described in the site’s Data Management SOP, each site must perform Quality Control (QC) review steps, especially for paper CRFs prior to their data entry into the study database. While paper CRFs are being reviewed, it is important that they are stored and tracked systematically. Below are specific review guidelines that should be followed for these QC review steps.

**QC Review Step #1**

- Review visit checklist to ensure all required procedures were completed
- Review completed paper CRFs and eCRFs based on participant responses to ensure completeness.

**QC Review Step #2 procedures for all visits:**

- Review visit checklist to ensure all required procedures were completed
- Ensure the PTID is correct, is recorded correctly on all paper source documents (including paper CRFs), and is the same on the paper source documents and the eCRFs for a given participant.
- Confirm that no participant identifiers other than the PTID are present on paper source documents, including paper CRFs.
- Ensure that the assigned visit code is correct, and is consistent between the paper source documents, including paper CRFs, the eCRFs, the LDMS Specimen Tracking Sheet, and LDMS for a given participant visit.
- If a log CRF is newly completed at a visit that is not an interim visit, make sure the corresponding “Y/N” CRF is marked “yes” for the visit. For example, if the Adverse Event CRF is completed, the Adverse Event Y/N CRF must be completed and marked “yes”.
Concomitant Medications CRF: if a medication is taken for an AE, make sure the linked AE CRF is entered and saved first; then confirm on the Con Meds CRF that the appropriate, linked AE is selected. Also confirm that ‘Medication’ is marked on the AE CRF.

Additional QC Steps for Paper CRFs
If some or all CRFs will first be completed on paper, the following review step should occur before forms are data-entered into the study database. Ideally, this review will happen once all lab results are available, so that all forms for a particular visit can be reviewed for consistency across documents. The goal is to correct data inconsistencies/errors prior to entering data into the study database, so that data is accurate, complete, and available at the time of data entry, thus minimizing the likelihood of data queries.

- Make sure a response has been recorded for each item, as required per instructions in the CCG document.
- If a response box with “other” or “specify” line is present, make sure there is text responding to that item.
- Make sure text responses are clearly recorded.
- For paper CRFs that are not source documents, make sure the data recorded on the paper CRFs matches or is consistent with the source documents.

Additional QC Steps for Electronic CRFs (eCRF)
When data is entered into the study database, and an eCRF is saved, system queries are automatically generated in response to inconsistent or incomplete data. Unlike the paper CRFs, which require manual review, eCRFs have the advantage of having the study database itself provide a real-time QC review to ensure data completeness. No additional review steps are required for eCRFs that are source (i.e., the data is directly entered into the study database, rather than entered based on a separate paper CRF or other paper source document).

Electronic CRFs that are completed based on other paper source documents (e.g., data entry of paper CRFs or lab reports) should be reviewed to ensure that the data entered matches or is consistent with the source documents. The site’s Data Management SOP provides additional details, and specifies which staff members will perform the review.

13.10 Form-Specific Completion Instructions
Detailed form completion instructions for each form are provided in the Case Report Form Completion Guidelines (CCGs) document. The instructions document skip patterns, required items, formats of variables, and include guidance on completion of the eCRF in the study database. Some items on forms are straightforward and do not require specific instructions. Therefore, you may not see all forms or form items listed in the CCG, but rather only those items needing detailed explanation.
13.11 Case Report Forms

The current version of the eCRFs can be found on the HPTN084 Atlas web page.
### Appendix 13A: HPTN084 Schedule of Forms

<table>
<thead>
<tr>
<th>STEP</th>
<th>VISIT</th>
<th>FORM</th>
</tr>
</thead>
<tbody>
<tr>
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*All Screening forms are required if a participant enrolls in the study. In addition, the Conmeds and Contraception CRFs must be completed. If a participant does not enroll in the study, please complete only those forms identified with an *.

<p>| 1    | Enrollment/Day 0 | Chemistry Testing |
|      | Visit 2.0        | Counseling |
|      |                  | Demographics |
|      |                  | Enrollment Visit |
|      |                  | Fasting Lipid Test Results |
|      |                  | Hematology |
|      |                  | Hepatitis B Test Results |
|      |                  | HIV Test Results |
| 1    | Enrollment/Day 0 | Liver Function Test Results |</p>
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*Update the Concomitant Medications Log and Medical History Log at this visit as appropriate.*

1. **Week 2**
   - Visit 3.0
     - Counseling
     - Date of Visit – Step 1 Only
     - Hematology
     - HIV Test Results
     - Pill Count – Step 1
     - Plasma Storage
     - Pregnancy Test Results

1. **Week 4**
   - Visit 4.0
     - Counseling
     - Date of Visit – Step 1 Only
     - DBS Storage
     - Hematology
     - HIV Test Results
     - Liver Function Test Results
     - Pill Count – Step 1
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*Complete the Injection Site Reaction Log if needed.*

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|      | Visit 7.0 | Counseling      |
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*Complete the Injection Site Reaction Log if needed.*

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|      |               | Injection Administration                 |
|      |               | Liver Function Test Results              |
|      |               | Pill Dispensation – Step 2 and 3        |</p>
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<td>Step 6</td>
<td>V119.0 Week 80</td>
<td>Plasma Storage</td>
</tr>
<tr>
<td>Step 6</td>
<td>V119.0 Week 80</td>
<td>Dried Blood Spot Storage</td>
</tr>
<tr>
<td>Step 6</td>
<td>V119.0 Week 80</td>
<td>Injection Administration</td>
</tr>
<tr>
<td>Step 6</td>
<td>V119.0 Week 80</td>
<td>Missed Visit</td>
</tr>
<tr>
<td>Step 6</td>
<td>V119.0 Week 80</td>
<td>Additional Procedures- OLE</td>
</tr>
<tr>
<td>Step 6</td>
<td>V119.0 Week 80</td>
<td>Contraception OLE</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 6</th>
<th>V120.0 Week 88</th>
<th>Date of Visit - OLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 6</td>
<td>V120.0 Week 88</td>
<td>Counseling</td>
</tr>
<tr>
<td>Step 6</td>
<td>V120.0 Week 88</td>
<td>HIV Test Results Y/N</td>
</tr>
<tr>
<td>Step 6</td>
<td>V120.0 Week 88</td>
<td>HIV Test Results</td>
</tr>
<tr>
<td>Step 6</td>
<td>V120.0 Week 88</td>
<td>Pregnancy Test Results - OLE</td>
</tr>
<tr>
<td>Step 6</td>
<td>V120.0 Week 88</td>
<td>Plasma Storage</td>
</tr>
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</tr>
<tr>
<td>Step 6</td>
<td>V120.0 Week 88</td>
<td>Dried Blood Spot Storage</td>
</tr>
<tr>
<td>Step 6</td>
<td>V120.0 Week 88</td>
<td>Injection Administration</td>
</tr>
<tr>
<td>Step 6</td>
<td>V120.0 Week 88</td>
<td>Missed Visit</td>
</tr>
<tr>
<td>Step 6</td>
<td>V120.0 Week 88</td>
<td>Additional Procedures- OLE</td>
</tr>
<tr>
<td>Step 6</td>
<td>V120.0 Week 88</td>
<td>Contraception -OLE</td>
</tr>
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<td>Step 6</td>
<td>V121.0 Week 96</td>
<td>Date of Visit - OLE</td>
</tr>
<tr>
<td>Step 6</td>
<td>V121.0 Week 96</td>
<td>Counseling</td>
</tr>
<tr>
<td>Step 6</td>
<td>V121.0 Week 96</td>
<td>HIV Test Results Y/N</td>
</tr>
<tr>
<td>Step 6</td>
<td>V121.0 Week 96</td>
<td>HIV Test Results</td>
</tr>
<tr>
<td>Step 6</td>
<td>V121.0 Week 96</td>
<td>Chemistry Testing</td>
</tr>
<tr>
<td>Step 6</td>
<td>V121.0 Week 96</td>
<td>Liver Function Tests</td>
</tr>
<tr>
<td>Step 6</td>
<td>V121.0 Week 96</td>
<td>STI Test Results</td>
</tr>
<tr>
<td>Step 6</td>
<td>V121.0 Week 96</td>
<td>Pregnancy Test Results- OLE</td>
</tr>
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<td>Step 6</td>
<td>V121.0 Week 96</td>
<td>Plasma Storage</td>
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<tr>
<td>Step 6</td>
<td>V121.0 Week 96</td>
<td>Dried Blood Spot Storage</td>
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<td>V121.0 Week 96</td>
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</tr>
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<td>Missed Visit</td>
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<td>Additional Procedures- OLE</td>
</tr>
<tr>
<td>Step 6</td>
<td>V121.0 Week 96</td>
<td>Contraception OLE</td>
</tr>
<tr>
<td>Step 6</td>
<td>V122.0 Week 104</td>
<td>Date of Visit - OLE</td>
</tr>
<tr>
<td>Step 6</td>
<td>V122.0 Week 104</td>
<td>Counseling</td>
</tr>
<tr>
<td>Step 6</td>
<td>V122.0 Week 104</td>
<td>HIV Test Results Y/N</td>
</tr>
<tr>
<td>Step 6</td>
<td>V122.0 Week 104</td>
<td>HIV Test Results</td>
</tr>
<tr>
<td>Step 6</td>
<td>V122.0 Week 104</td>
<td>Pregnancy Test Results - OLE</td>
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<tr>
<td>Step 6</td>
<td>V122.0 Week 104</td>
<td>Plasma Storage</td>
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<tr>
<td>Step 6</td>
<td>V122.0 Week 104</td>
<td>Dried Blood Spot Storage</td>
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<tr>
<td>Step 6</td>
<td>V122.0 Week 104</td>
<td>Injection Administration</td>
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<td>Step 6</td>
<td>V122.0 Week 104</td>
<td>Missed Visit</td>
</tr>
<tr>
<td>Step 6</td>
<td>V122.0 Week 104</td>
<td>Additional Procedures - OLE</td>
</tr>
<tr>
<td>Step 6</td>
<td>V122.0 Week 104</td>
<td>Contraception - OLE</td>
</tr>
<tr>
<td>Step 6</td>
<td>V123.0 Week 112</td>
<td>Date of Visit - OLE</td>
</tr>
<tr>
<td>Step 6</td>
<td>V123.0 Week 112</td>
<td>Counseling</td>
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<td>Step 6</td>
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<td>HIV Test Results Y/N</td>
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<td>Pregnancy Test Results - OLE</td>
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<td>Step 6</td>
<td>V123.0 Week 112</td>
<td>Chemistry Testing</td>
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<td>Step 6</td>
<td>V123.0 Week 112</td>
<td>Liver Function Tests</td>
</tr>
<tr>
<td>Step 6</td>
<td>V123.0 Week 112</td>
<td>STI Test Results</td>
</tr>
<tr>
<td>Step 6</td>
<td>V123.0 Week 112</td>
<td>Plasma Storage</td>
</tr>
</tbody>
</table>

NOTE: Some as-needed forms, such as the Adverse Event Log and the Product Hold/Discontinuation Log, can be found in the “Ongoing Logs” folder in the participant’s casebook. Other as needed forms, such as forms related to a participant’s pregnancy or early unblinding, can be added using the “Add Event” feature of Rave. Please see the CCGs for more information. The Product Choice CRF, which marks the start of the OL portion of the study is not listed along with Informed Consent V4 and V5 forms. In addition, all live births at 48 weeks, not in 4d require an Infant Assessment, this is not listed. Required CRFs for 4d apply for visit codes 176.0-194.0, 276.0-294.0, etc.
Appendix 13B: Participant Transfer and Receipt Process in Rave

Transferring Site:

1. When initiating a participant transfer to another site please contact the CDM alias ‘sc.084cdm@scharp.org’. Data managers included on the alias will facilitate the transfer process within Rave.
2. On the appropriate DOV CRF, indicate additional procedures were required to populate the Additional Procedures CRF. Then mark ‘Participant Transfer’ to populate that CRF.
3. Complete and save the Transfer form.
4. Ensure and all required eCRFs have been completed all data queries are resolved.
5. Investigator of Record (IOR) or designee must verify the data is complete and accurate by signing off on the participant’s eCRFs as follows:
   a. IoR (or designee) logs into Medidata and selects transferring PTID. On the Participant page, select “Grid View”:
   b. Grid View lists all forms completed and expected for a participant.
   c. To sign off on all completed forms for the PTID, select “All” forms while in Grid View and then click “Sign and Save”.

   ![Grid View Image]

   ![Sign and Save Image]
d. A signature prompt will display alongside a user ID and password text box. This serves as your electronic signature:

![Signature Prompt](image)

Note: The time that it takes for Medidata Rave to apply the IoR signature to all completed eCRFs will depend on the number of completed CRFs within the participant’s casebook. If there are a large number of completed eCRFs, the application of eSignatures may take up to several minutes.

IMPORTANT: When this step is complete please contact the SCHARP Clinical Data Manager so that the transfer can be completed within Rave. Please allow 1-2 days to complete this step.

**Receiving Site:**

1. Prior to the participant’s first scheduled visit at your site, confirm that the participant’s casebook is accessible within the Medidata Rave database from your site homepage. Note that the participant retains their original PTID.
2. When participant arrives for the first visit at your site, navigate to the participant’s Medidata casebook.
3. On the scheduled DOV CRF, indicate additional procedures were required to populate the Additional Procedures CRF. Then mark ‘Participant Receipt’ to populate that CRF.
4. Complete and save the Participant Receipt form.
5. Proceed with study visits in Rave.
Section 14. Computer Assisted Self-Interview (CASI)

14.1 Background

Computer Assisted Self-Interview (CASI) is a method for collecting information where a person reads questions on a computer screen and enters his or her answers directly into the computer. Many different types of electronic equipment (such as laptops, desktops, touch-screen computers or handheld devices) can be used to administer the CASI and various types of software can be used to design the data collection tool. For HPTN 084, the software used to design the survey is called REDCap Cloud (RCC). The HPTN084 Questionnaire is attached in Appendix 14A.

14.2 Technical Requirements

Device

The HPTN 084 CASI questionnaires are web-based (using RCC software) and can be taken from almost any device with a strong internet connection and a web browser. Please review RCC’s hardware and software requirements web page for more information:


In the room where the computer is located, there should be an electrical outlet and a jack for broadband connection unless a reliable wireless connection is used. If possible, the computer should be plugged into an AC power source. If a laptop is used, it is recommended that an external mouse be connected to the laptop. To minimize problems with computers, sites should avoid having food or drink nearby and keep the area where the computer is used clutter-free. An antivirus program should also be installed on the computer.

Each site is responsible for addressing issues of computer security and privacy as well as general issues such as lighting, ergonomics, and overall participant comfort. For questions about how to use a computer, sites should refer to the operations manual of the desktop or laptop. Issues such as where the computer(s) will be located and who is in charge of addressing computer-related issues should be addressed in each site’s study specific Data Management Standard Operating Procedure (SOP).
Web Browser

The following list of web browsers can be used to administer the CASI in RCC.

- Safari for macOS
- Microsoft Edge
- Google Chrome for Windows, macOS, and Linux desktops
- Mozilla Firefox for Windows, macOS, and Linux desktops

Make sure to always use the most current version of each browser to optimize the full capacity of the product’s features and functionality.

14.3 CASI Administration

The CASI will be administered to participants at many different visits. Participants are expected to complete each of the surveys. However, if the participant does not complete the survey (e.g., decides not to take it), this must be noted on the Behavioral Assessment CRF.

The questionnaire should always be administered before any HIV/STD risk reduction counseling occurs and the participant should complete the questionnaire in one sitting whenever possible.

14.3.1 Survey URL

All surveys are accessed via a single URL provided by SCHARP. The link can be bookmarked in a web browser; however, desktop shortcuts to the survey should not be created: using a desktop link to connect to the survey will result in the site always connecting to the version of the survey that was running when they originally created the link rather than the most current version of the survey. It is likely that the survey will need to be updated over time; using a desktop link or shortcut will result in the old version of the survey being administered.

14.3.2 CASI Practice for Site Staff

Staff members should be familiar with the content of the questionnaire in order to respond to participant questions. Staff members who will administer the survey should practice taking, and demonstrating how to use, the survey using test CASI Identification numbers (CASI IDs) provided by SCHARP. The staff member responsible for administering the CASI should be able to explain to the participant how to complete the survey, including how to use a computer and how to click through the questions using a mouse or touchpad.
14.3.3 Logging in to the CASI

When the participant is ready to begin the CASI, the staff member responsible for administering the survey will click on the appropriate URL. To find the surveys easily it is helpful to bookmark the URL you will be using in this study in your preferred web browser.

SCHARP will provide each site a list of CASI IDs in a link log to document the HPTN 084 PTIDs linked to each CASI ID.

Once the survey is opened, the staff member will enter a “CASI ID” from the list provided by SCHARP and the appropriate language (if applicable) and visit is selected. You will then be prompted to enter the PTID that is linked to the CASI ID.

Site staff will then answer one or more questions based on the visit; the answers to these questions will determine whether certain survey items will be included or excluded from the questionnaire.

Once these questions are answered, the participant is ready to take the survey on his or her own.

14.3.4 Navigating the Survey

Participants should navigate through the survey using the “< Prev” and “Next >” buttons that are part of the RCC software (Figure 1); they should not use the browser navigation buttons, which are the forward and back arrows usually located in the top left-hand corner of the browser (Figure 2). If the browser navigation buttons are mistakenly used, proper functioning of the survey can be disrupted, and data may be lost.

If a participant asks for help while taking the survey it is OK for a staff member to assist the participant. For example, if the Internet crashes, the survey freezes or the participant does not understand a question, it is OK for the site staff to help. For technical problems with RCC see Section 9.6.12.
14.3.5 Graphical Interface of the CASI

Most of the questions in the survey are answered by clicking on radio buttons (Figure 3), which consist of a group of circular white dots. When the participant selects one of the circles, a grey dot appears in the middle of the circle. Some of the questions in the survey are answered by clicking on check boxes (Figure 4). When the participant clicks on the check box, a blue check appears in the box. For some questions, instructions will indicate whether more than one check box may be selected.
Some questions require participants to type in a number (Figure 5). Sometimes an “other, specify” box is included as one of the response categories to capture participant responses that do not fit into one of the categories listed. When a participant’s response does not match or fit into one of the listed response categories, the participant may select “other” and type in their answer in the space provided (Figure 6).

When training the participant how to complete the survey on the computer, it can be helpful to point out the different ways they will be required to answer questions. There is also a brief (1-page) non-required section at the beginning of the survey for participants to practice entering responses, if desired.

14.3.6 Figure 3: Graphical Interface – Radio Buttons

Before we begin, would you like to answer some practice questions to make sure you understand how to complete the survey?

Yes
No

Figure 4: Graphical Interface – Check Boxes

Do you have any favorite colors? Mark all that apply.

Red
Blue
Orange
Yellow
14.3.7 Submitting the Survey

Once the participant has answered the last question and clicked the “Submit” button, there will be a “thank you” message on the screen, which indicates the survey is complete.

It is important that the staff member responsible for administering the CASI survey double check that the participant has completed the survey before closing the browser.

14.3.8 What Happens to the Data?

It is important to understand, and to tell the participant, that the data the participant enters into the computer will never be stored on that computer. Each time the “next” button is clicked and the participant moves to the next question, the answer to the previous question will automatically be transmitted to the SCHARP-specific server. Site staff cannot access these data.
14.3.9 How to Resume a Partially Completed RCC Survey

If there is an intentional or accidental closure of the browser, if internet connection is lost, if the computer crashes, or if the participant needs to pause survey completion mid-visit for any reason, site staff will need to log the participant back in to the survey – once available - to allow completion.

Re-open the survey in a web browser and re-enter the participant ID. A page will appear with the following message: “We have located a survey in-progress. Would you like to continue where you last left off or start over?” (Figure 7).

**Figure 7: Resuming a Partially Completed Survey**

We have located a survey in-progress.

Would you like to continue where you last left off or start over?

[Restore] [Start-Over]

Select the “Start-Over ” button to open the survey to where the participant stopped.

14.3.10 Making Up a Missed CASI

If a participant misses taking the CASI at a required visit, or if there is a technical problem that cannot be resolved, the participant can take the CASI at a later time, but no later than the next required visit. If the survey was not done for Week 24 visit, it can be made up no later than Week 32 visit. The original CASI ID/visit code combination for the missed survey is entered into the CASI. For example, the Week 24 visit took place on 1 July 2023 but the survey was not done; the participant returned on 8 July and completed the survey. Week 24 would be entered into the survey.

14.3.11 Reminders

Before the participants take the survey, the site should remember to do the following:

- Explain the purpose of the survey and provide general instructions regarding how to use the computer, if necessary, such as how to use a mouse and how to “click” a button.
- Emphasize that the browser navigation buttons should never be used; only the buttons that say “Previous” and “Next” in the actual RCC survey should be used when navigating the survey.
- Remind the participants that their answers are completely confidential. The answers provided by the participants will never be permanently stored on the computer (they
are sent to a server that is only accessed by the Statistical and Data Management Center); therefore, none of the site staff will ever see their answers.

- Tell the participants that at the end of the survey they will see a “thank you” message on the screen. This indicates that the participants have completed the survey and they do not have to do anything else.
- Let the participants know that they can ask a site staff member for help, if needed.

### 14.4 Problems and Questions

If a problem with the CASI occurs, or for all other questions about the CASI including technical questions regarding RCC, contact the SCHARP Clinical Data Manager alias: sc.084cdm@scharp.org.

Stephanie Beigel-Orme
sbeigelo@scharp.org

Please remember that the SCHARP office is located in the Pacific Time Zone (GMT – 7:00). Therefore, “real time” responses to emails and phone calls may not always be possible. A response can be expected, however, within 24 hours.
Section 15. Reporting Plan

15.1 Purpose of Reporting Plan

The purpose of this reporting plan is to:

- identify the content of each HPTN084 report;
- identify those responsible for production and distribution of each report;
- identify who should receive and review the reports so corrective action (if necessary) is taken.

The reporting plan is prepared by the HPTN084 Clinical Data Manager at SCHARP in conjunction with SDMC HPTN084 statisticians and programmers.

15.2 Reports

The table below provides detailed information about each report that will be produced for HPTN 084, including the distribution frequency and distribution list. The exact day of the week these reports are distributed will be determined once data collection begins.
<table>
<thead>
<tr>
<th>Report Name</th>
<th>Purpose</th>
<th>Components</th>
<th>Distribution Frequency</th>
<th>Responsibility for Preparation</th>
<th>Distribution Platform</th>
<th>Distribution List</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Summarizes screening at each site as reflected by case report form data</td>
<td>The number of participants screened, number enrolled, and reasons not enrolled for all sites individually as well as all sites combined.</td>
<td>Daily</td>
<td>SDMC Protocol Programmer and/or Statistical Programmer</td>
<td>Atlas <a href="http://scharp.atlas.org">http://scharp.atlas.org</a></td>
<td>Anyone</td>
</tr>
<tr>
<td>Enrollment</td>
<td>To monitor participant accrual as reflected by case report form data</td>
<td>Enrollment data are presented for all sites individually as well as all sites combined. Includes site activation date, dates of first enrollments, duration of accrual, and the number of participants enrolled each week compared with weekly enrollment targets.</td>
<td>Daily</td>
<td>SDMC Protocol Programmer and/or Statistical Programmer</td>
<td>Atlas <a href="http://scharp.atlas.org">http://scharp.atlas.org</a></td>
<td>Anyone</td>
</tr>
<tr>
<td>Retention</td>
<td>To monitor participant retention as reflected by case report form data</td>
<td>Retention data are presented for all sites individually as well as all sites combined. Includes the total number of participants randomized who 1) completed a visit</td>
<td>Daily</td>
<td>SDMC Statistical Programmer</td>
<td>Atlas <a href="http://scharp.atlas.org">http://scharp.atlas.org</a></td>
<td>Anyone</td>
</tr>
<tr>
<td>Report Name</td>
<td>Purpose</td>
<td>Components</td>
<td>Distribution Frequency</td>
<td>Responsibility for Preparation</td>
<td>Distribution Platform</td>
<td>Distribution List</td>
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<tr>
<td>Data Management Quality</td>
<td>To provide information on site performance with regard to key data management and data quality metrics</td>
<td>(on time, early or late) and 2) did not complete a visit (visit was missed or ppt was terminated early). Total retention is calculated as the number of enrolled participants who completed follow-up visits divided by the total number of participants expected for a visit.</td>
<td>Monthly</td>
<td>SDMC</td>
<td>Atlas</td>
<td>Anyone</td>
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<tr>
<td></td>
<td></td>
<td>Data are presented for all sites individually as well as all sites combined. Cumulative and previous-month statistics including: • Percentage of CRFs entered within 7 calendar days of study visits • Percentage of AEs entered within 3 days of date reported to site</td>
<td></td>
<td></td>
<td><a href="http://atlas.scharp.org">http://atlas.scharp.org</a></td>
<td></td>
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<tr>
<td>Report Name</td>
<td>Purpose</td>
<td>Components</td>
<td>Distribution Frequency</td>
<td>Responsibility for Preparation</td>
<td>Distribution Platform</td>
<td>Distribution List</td>
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<tr>
<td><strong>Site-Specific Specimen Monitoring</strong></td>
<td>To identify stored specimens whose information in LDMS does not match corresponding information collected on case report forms</td>
<td>Site-specific listings of all discrepancies between specimens listed as “stored” in case report forms and data entered into LDMS as well as LDMS data entry errors.</td>
<td>Bi-monthly</td>
<td>SDMC Lab Data Operations (LDO) Group</td>
<td>E-mail</td>
<td>Site Study Coordinator, Other site staff as requested, Laboratory Center Representative, SDMC Clinical Data Manager</td>
</tr>
<tr>
<td><strong>Summary Specimen Monitoring</strong></td>
<td>To provide the Laboratory Center (LC) with a summary for all sites of</td>
<td>Summary listing for all sites of all discrepancies between the case report form stored specimen data</td>
<td>Bi-monthly</td>
<td>SDMC Lab Data Management (LDM) Group</td>
<td>E-mail</td>
<td>Laboratory Center Representative,</td>
</tr>
<tr>
<td>Report Name</td>
<td>Purpose</td>
<td>Components</td>
<td>Distribution Frequency</td>
<td>Responsibility for Preparation</td>
<td>Distribution Platform</td>
<td>Distribution List</td>
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<tr>
<td><strong>Study Monitoring Committee (SMC)</strong></td>
<td>To monitor the overall progress of the study and study conduct at each site</td>
<td>information contained in the Site-Specific Specimen Monitoring Reports and data entered into LDMS.</td>
<td>Will occur after ~ 4 months of enrollment and every 6 months thereafter</td>
<td>SDMC Statistical Research Associates (SRAs) and Protocol Statistician, with assistance from SCHARP study team</td>
<td>Atlas</td>
<td>SDMC Clinical Data Manager (open and closed reports), Protocol Chairs (open report only), Selected members of HPTN LOC, SDMC, LC, DAIDS and Site IoRs, (open report only)</td>
</tr>
<tr>
<td>Report Name</td>
<td>Purpose</td>
<td>Components</td>
<td>Distribution Frequency</td>
<td>Responsibility for Preparation</td>
<td>Distribution Platform</td>
<td>Distribution List</td>
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</tr>
<tr>
<td>Data Safety Monitoring Board (DSMB)</td>
<td>To monitor efficacy and safety as well as to perform an administrative review and/or design review</td>
<td>Open report includes: all components listed for the SMC Open Report. Closed report includes: all components listed for the SMC report by treatment arm, with the addition of adverse event data and HIV-infection data.</td>
<td>Every 6 months or as determined by the DSMB</td>
<td>SDMS Statistical Research Associates and Protocol Statistician, with assistance from SCHARP study team</td>
<td>Mail or E-mail</td>
<td>DSMB members only</td>
</tr>
</tbody>
</table>
Section 16. Data Communiqués

For HPTN084, SCHARP will use “Data Communiqués” to document and communicate data decisions and procedures that are made or revised during the study.

Data Communiqués are considered official study documentation. As such, each time a Data Communiqué is distributed, please circulate it among relevant staff for their review, print the Data Communiqué, and place it in this section of each HPTN084 SSP binder in your possession. Consider each Data Communiqué an official part of the SSP.

Each Data Communiqué sent will consist of three sections: a Reminders section, used to remind sites of specific data collection or forms completion procedures; a Clarification section, used to clarify data collection or form completion procedures; and an Updates section, used to communicate when an updated version of a form is being issued or to notify the sites that an updated version of the forms instructions is about to be distributed (for example).

Note that a “Data Communiqué” does not request specific actions or corrections to a particular participant’s data - it is just a listing of general items to keep in mind when performing data collection for the study.
Section 17. COVID-19 Measures

17.1 Overview of Section 17

This section provides a brief overview of recommendations for trial conduct during the COVID Pandemic.

17.2 Conducting visits

These recommendations are made with the goal of ensuring both participant and staff safety and respecting the public health recommendations to minimize disease transmission.

Sites may choose to provide ICFs to participants ahead of visits to minimize time on site and participant/site contact and to allow participants to read, make notes, discuss with family and friends if needed. Prior to implementing such a plan, sites should develop an SOP detailing the procedures and methods for the process which should also be approved by applicable ethics/regulatory authorities. The site may also contact the potential participant telephonically to discuss the forms and any questions she may have. When contacting the participant, the site must confirm the participant identity (name, date of birth, and potentially information known to the site and the participant but not a 3rd party) and document the conversation in chart notes. This does not mean that the consent process may be entirely remote. Sites that are able may deliver, mail, WhatsApp, or share by means of other communication platforms the Informed Consent(s) to participants prior to a study visit so that they may review the form. Given that the consent form is unsigned, it gives participants an opportunity to discuss with her partner or family prior to signing and to identify any potential barriers to consent prior to participation. When the participant presents to the clinic for a visit, staff will offer a general overview of the consent form and answer any questions and sites may then obtain the wet signature and assessment of understanding. In some cases, a complete review may be necessary.

Note: Make sure that any study materials (including blank informed consents and flyers) are shared without risk of harm.

- Sites can always counsel participants to think about who they want to talk to share information with ahead of time, and if the participant indicates that she is concerned about her partner then a secure channel for communication should be identified.
- The issues of security with sending blank informed consents via WhatsApp or other communication platforms apply to participants that are already enrolled and that are re-consenting.
Follow-up visits should continue to ensure safety of the participants in alignment with local guidance and protocol where possible.

1. In the event that CRS operations are diminished or suspended entirely, and where conduct of study visits is not possible either because of staffing or operational concerns, please note the following:

   **For participants on maintenance doses of CAB LA:** Injections may be lengthened to 12 weeks (ie the full visit window) in the event of prolonged lockdowns or ongoing COVID disruption. Every effort should be made to confirm participant identity prior to initiating data collection. For example, information like name, date of birth, and responses about clinic or study information might be considered reasonable ways to confirm participant identity. Participants may be reimbursed for telephonic data collection, given that there may be costs to them associated with phone calls, and this is acceptable to the local IRB/REC. If for some reason participants cannot receive study product, they are advised to take additional measures to prevent HIV infection and exposure by all means available until they can return to study site. If they use non-study provided open-label PrEP during this period they should be encouraged to keep a log of dates of use should they use this option.

   **For participants on TDF/FTC:** Participants should continue on daily unblinded oral product. Where participants cannot report for quarterly visits, participants should continue study product and where possible sites should explore delivery of product directly to participants from site investigational pharmacies. The DAIDS guidelines for shipping product should be followed. If not feasible, participants should be counselled to use other available means to protect themselves against HIV exposure and infection and pregnancy prevention until they are able to return to study participation. IoR can use their judgement about ongoing dispensation of oral product in these extraordinary circumstances without routine HIV and creatinine testing, based on known previous renal function, risk and adherence. Self-testing for HIV may also be useful in this setting if practical. The same guidance would apply to pregnant participants.

   **For annual follow up if applicable:** Annual visits should be delayed until study conduct can be resumed at the site.

2. **PLEASE NOTE:** Notify the protocol chairs, LOC, LC, SDMC and DAIDS as soon as possible of any updates to your site-specific plan. Please note that additional guidance was issued to CTU PIs and CRS leaders regarding considerations for visits during this extraordinary time by DAIDS.

   Sites should consider procedures for symptom screening and isolation of suspected cases and linkage to testing based on national guidelines.
17.3 Incomplete or Missed Visits

Any procedures that cannot be conducted per protocol should be recorded as protocol deviations per guidance in SSP Section 3, and per the Data Communique #8. Follow Data Communique #8 Dated 2 April 2020 for instructions on Missed Visits, Telephonic Visits, Partial Visits, Product Holds or Discontinuations, Open Label Truvada Administration and guidance on Pill Count/ Dissemination CRFs (https://www.hptn.org/sites/default/files/inline-files/HPTN084_Data_Communique_8_20200402.pdf).

In addition, teams should continue to send queries to the CMC. Where possible CMC queries should be sent ahead of anticipated participant visits to ensure sufficient response time from the CMC. Where queries are sent on the same day and where an immediate response is not possible, investigators may use their discretion regarding the dispensing of study product after assessment of safety parameters.

17.4 Covid-19 vaccinations

If a participant has been vaccinated please document this on the ConMeds CRF. If the vaccine is part of a clinical trial also contact the HPTN 084 CMC when you are made aware in order to manage participant/ trial burden.
Section 1. Introduction

1.1 Overview of Section 1

This section contains specifics of study conduct and describes sources of procedural information for the HPTN 084 protocol version 4.0 and version 5.0 (the Open Label Extension [OLE] components of the study). Information in this section is intended for study site staff and outlines responsibilities of the site Investigators.

1.2 Source of Procedural Information

All study procedures must be conducted in accordance with the study protocol currently approved for implementation by the site’s local Institutional Review Board (IRB)/Ethic Committee (EC), etc., as is appropriate (either version 4.0 or version 5.0 of the protocol), and this study-specific procedures (SSP) manual. In the event that this manual is inconsistent with the protocol, follow the protocol. Please alert the HPTN Leadership and Operations Center (LOC) of any inconsistencies.

In instances where there is an urgent need for a change to the SSP manual, and when a full revision of the SSP is not imminent, the LOC may distribute an email containing a “Notification of Interim Change” to the current version of the SSP manual. These interim changes will be considered an official part of the SSP manual and should be considered official by any monitoring agents.

Study site staff members should use the following email alias when they have study-related questions: 084mgmt@hptn.org. Staff members of the HPTN LOC, HPTN Statistical and Data Management Center (SDMC), and HPTN Laboratory Center (LC) will receive the email. Emails with questions will be responded to by the most appropriate HPTN representative.
Table 1-1: HPTN Staff and Contact Information

<table>
<thead>
<tr>
<th>HPTN LOC Project Managers</th>
<th>Jennifer Farrior</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tel: +1 919-321-3517</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:jfarrior@fhi360.org">jfarrior@fhi360.org</a></td>
</tr>
<tr>
<td>Scott Mitchell Rose</td>
<td></td>
</tr>
<tr>
<td>Tel. +1 919 768-2067 (Mobile)</td>
<td><a href="mailto:srose@fhi360.org">srose@fhi360.org</a></td>
</tr>
<tr>
<td>HPTN LOC Clinical Trials Assistant</td>
<td>Jill Stanton</td>
</tr>
<tr>
<td></td>
<td>Tel: +1 919-321-3413</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:jistanton@fhi360.org">jistanton@fhi360.org</a></td>
</tr>
<tr>
<td>HPTN LOC Community Program Managers</td>
<td>Rhonda White</td>
</tr>
<tr>
<td></td>
<td>Tel: +1 919-321-3598</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:RWhite@fhi360.org">RWhite@fhi360.org</a></td>
</tr>
<tr>
<td>HPTN SDMC Clinical Data Manager</td>
<td>Stephanie Orme</td>
</tr>
<tr>
<td></td>
<td>Tel: +1 206-667-7109</td>
</tr>
<tr>
<td></td>
<td>Email: <a href="mailto:sbeigelo@scharp.org">sbeigelo@scharp.org</a></td>
</tr>
<tr>
<td>HPTN LC Representatives</td>
<td>Estelle Piwowar-Manning</td>
</tr>
<tr>
<td></td>
<td>Tel: +1 410-614-6736</td>
</tr>
<tr>
<td></td>
<td>Email: <a href="mailto:epiwowa@jhmi.edu">epiwowa@jhmi.edu</a></td>
</tr>
<tr>
<td></td>
<td>Yaw Agyei</td>
</tr>
<tr>
<td></td>
<td>Tel: +1 410-614-6736</td>
</tr>
<tr>
<td></td>
<td>Tel: 27-813766180</td>
</tr>
<tr>
<td></td>
<td>Email: <a href="mailto:vagye1@jhmi.edu">vagye1@jhmi.edu</a></td>
</tr>
<tr>
<td>Laboratory Data Management System (LDMS)</td>
<td>Tel: +1 716-834-0900, Ext. 7311</td>
</tr>
<tr>
<td></td>
<td>Email: <a href="mailto:ldmshelp@fstrf.org">ldmshelp@fstrf.org</a></td>
</tr>
<tr>
<td>DAIDS Protocol Pharmacist</td>
<td>Katie Shin</td>
</tr>
<tr>
<td></td>
<td>Tel: +1 240-627-3047</td>
</tr>
<tr>
<td></td>
<td>Email: <a href="mailto:KaShin@niaid.nih.gov">KaShin@niaid.nih.gov</a></td>
</tr>
</tbody>
</table>

Contact information for all HPTN 084 team members is found in the electronic HPTN directory at www.hptn.org.

1.3 Sites Participating in HPTN 084

Clinical Research Sites (CRSs) that are participating in HPTN 084 OLE are listed in Table 1-2.
<table>
<thead>
<tr>
<th>CRS ID</th>
<th>CRS Name</th>
<th>City</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31798</td>
<td>Baylor Uganda CRS</td>
<td>Kampala</td>
</tr>
<tr>
<td>2</td>
<td>30301</td>
<td>Blantyre CRS</td>
<td>Blantyre</td>
</tr>
<tr>
<td>3</td>
<td>31445</td>
<td>Botha’s Hill CRS</td>
<td>Botha’s Hill</td>
</tr>
<tr>
<td>4</td>
<td>31790</td>
<td>Desmond Tutu TB Centre - Stellenbosch University CRS</td>
<td>Cape Town</td>
</tr>
<tr>
<td>5</td>
<td>30346</td>
<td>Emavundleni CRS</td>
<td>Cape Town</td>
</tr>
<tr>
<td>6</td>
<td>12701</td>
<td>Gaborone CRS</td>
<td>Gaborone</td>
</tr>
<tr>
<td>7</td>
<td>31635</td>
<td>Isipingo CRS</td>
<td>Durban</td>
</tr>
<tr>
<td>8</td>
<td>31460</td>
<td>Kisumu CRS</td>
<td>Kisumu</td>
</tr>
<tr>
<td>9</td>
<td>12001</td>
<td>Malawi CRS</td>
<td>Lilongwe</td>
</tr>
<tr>
<td>10</td>
<td>30293</td>
<td>MU-JHU Research Collaboration CRS</td>
<td>Kampala</td>
</tr>
<tr>
<td>11</td>
<td>30313</td>
<td>Milton Park CRS</td>
<td>Harare</td>
</tr>
<tr>
<td>12</td>
<td>30294</td>
<td>Seke South CRS</td>
<td>Chitungwiza</td>
</tr>
<tr>
<td>13</td>
<td>31610</td>
<td>Soweto HPTN CRS</td>
<td>Soweto</td>
</tr>
<tr>
<td>14</td>
<td>30314</td>
<td>Spilhaus CRS</td>
<td>Harare</td>
</tr>
<tr>
<td>15</td>
<td>30303</td>
<td>St Mary’s CRS</td>
<td>Chitungwiza</td>
</tr>
<tr>
<td>16</td>
<td>31994</td>
<td>Eswatini Prevention Center</td>
<td>Mbabane</td>
</tr>
<tr>
<td>17</td>
<td>30924</td>
<td>UVRI-IAVI</td>
<td>Entebbe</td>
</tr>
<tr>
<td>18</td>
<td>31663</td>
<td>Verulam CRS</td>
<td>Verulam</td>
</tr>
<tr>
<td>19</td>
<td>31966</td>
<td>Ward 21</td>
<td>Johannesburg</td>
</tr>
<tr>
<td>20</td>
<td>30320</td>
<td>Zengeza CRS</td>
<td>Chitungwiza</td>
</tr>
</tbody>
</table>

Table 1-2
Participating HPTN 084 OLE Sites in Alphabetical Order
1.4 Investigator Responsibilities

HPTN 084 must be conducted in accordance with the US Code of Federal Regulations (CFR) and the International Council on Harmonization (ICH) Consolidated Guidelines for Good Clinical Practice (GCP). Copies of the regulations governing the conduct of this study (45 CFR 46 and 21 CFR 11, 50, 54, 56, and 312) and the ICH guideline can be requested from the HPTN LOC or found online at https://www.gpo.gov/fdsys/browse/collectionCfr.action?collectionCode=CFR and http://www.ich.org/home.html respectively. DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual describes operational requirements for Clinical Research Sites (CRSs) implementing DAIDS-sponsored clinical research within the DAIDS Clinical Trials Networks and can be downloaded from https://www.niaid.nih.gov/research/daids-score-manual

HPTN 084 must be conducted in accordance with all local regulations, policies, and guidelines applicable to human subjects research in general and/or the conduct of study procedures in particular. The Investigator of Record (IoR) at each site is responsible for the conduct of the clinical trial at the CRS. The IoR is the signatory for the FDA Form 1572. (Note: Since the HPTN 084 OLE components are amendments to the original, double-blinded HPTN 084 component, a new Form 1572 is not required.) Additionally, site investigators must promptly report to the IRBs/ECs any changes in the study and must comply with the requirements of 45 CFR 46.108(a)(4) and 21 CFR 56.108(b) for promptly reporting the following: unanticipated problems involving risks to participants or others; serious or continuing noncompliance with applicable regulations or the requirements or determinations of their IRBs/ECs; and any suspension or termination of IRB approval.

IoRs may delegate the work involved in study conduct to other site staff members; however, delegation does not relieve the IoR of ultimate responsibility for all study procedures performed and all study data collected. Additional guidance can be found in the US FDA’s Information Sheet Guidance: Information Sheet Guidance for Institutional Review Boards (IRBs), Clinical Investigators, and Sponsors available at https://www.fda.gov/science-research/guidance-documents-including-information-sheets-and-notices/information-sheet-guidance-institutional-review-boards-irbs-clinical-investigators-and-sponsors

1.5 Study Activation Process

Prior to undertaking any study procedures under either the v4.0 or v5.0 protocol amendments, each study site must obtain approval to conduct the amendment from all responsible US and local IRB/ECs and any other appropriate local regulatory bodies. Sites must complete Protocol Registration with the DAIDS Regulatory Support Center (RSC) according to the timeline requirements in the Protocol Registration Manual.

Note: Before sites could implement the v3.0 protocol amendment, a Site-Specific Activation Notice from the HPTN LOC was required. However, no activation notices are being issued for Protocol Amendment V5.0 (OLE2). Sites may implement v5.0 once all approvals are in place.
1.5.1 **Protocol Distribution**

The HPTN 084 OLE Project Managers (PMs) or Clinical Trials Assistant (CTA) will distribute approved protocol amendments electronically to the study sites.

1.5.2 **Development and HPTN LOC Review of Site-Specific Informed Consent Forms: English Language Versions**

Site staff will adapt the sample informed consent forms (ICFs) appended to the study protocol (either v4.0 or 5.0, as is appropriate) to reflect local procedures and IRB/EC requirements. If the site wishes to, it may forward the site-specific ICFs to the HPTN LOC Project Managers (PMs) for review prior to submission to local review bodies. The HPTN LOC PMs are not required to review the site-ICFs for subsequent Letters of Amendment (LOA) or Clarification Memos (CMs); however, the PMs are available for assistance.

Note: The ICF for original, double-blinded portion of the study are irrelevant to the open-label protocol amendments. Sites should implement the ICFs associated with the amendments.

1.5.3 **Development and HPTN LOC Review of Site-Specific Informed Consent Forms: Local Language Version(s) and Back-translation(s)**

For the protocol amendments of v4.0 and v5.0, site staff will translate the ICFs into all applicable local languages. Sites are not required to submit the translated forms, back-translations of the forms, and a certificate of translation for review to the HPTN LOC. Please note back-translations are not required if local language is Spanish. The back-translation need not be completed by a certified translator; however, it is recommended that two different individuals translate the document(s) and then review each other’s work to prepare a composite. The back-translation should be completed by an individual who did not participate in the translation process.

1.5.4 **IRB/EC Review**

Site staff will submit the study protocol, site-specific ICFs, and any other study-related materials as applicable for protocol amendments for review by all responsible local and US-based IRBs/ECs (as is appropriate to the site). Any participant information sheets, flip charts, promotional materials, or advertisements used during the study must be reviewed and approved by all responsible IRBs/ECs prior to site use.

In the event that either the site and/or local IRBs/ECs request changes to the submitted ICFs, it is the responsibility of the IoR to incorporate all such comments into a single final version of the study ICFs, and to obtain approval of this final version from all responsible IRBs/ECs. This may require multiple submissions to the responsible IRBs/ECs. The final English back translation of the ICFs submitted to the DAIDS RSC must accurately and entirely reflect the approved local-language ICFs that will be used at the site.
An overview of IRB/EC submissions required before and during HPTN 084 and its amendments are included in Table 1-3.
<table>
<thead>
<tr>
<th>Document</th>
<th>Source</th>
<th>IRB/EC Approval Required*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol, Version 1.0 and higher</td>
<td>LOC</td>
<td>yes</td>
</tr>
<tr>
<td>Protocol amendments (including full amendments and Letters of Amendment [LOAs])</td>
<td>LOC</td>
<td>yes</td>
</tr>
<tr>
<td>Protocol Clarification Memos (CMs)</td>
<td>LOC</td>
<td>no**</td>
</tr>
<tr>
<td>Protocol deviations</td>
<td>site</td>
<td>no**</td>
</tr>
<tr>
<td>Site specific ICFs, Version 1.0 and any subsequent updates</td>
<td>site</td>
<td>yes</td>
</tr>
<tr>
<td>Current CV for IoR (and subsequent updates)</td>
<td>site</td>
<td>no</td>
</tr>
<tr>
<td>Participant recruitment materials (posters, advertisements, etc.) and any subsequent updates</td>
<td>site</td>
<td>yes</td>
</tr>
<tr>
<td>CASI-based assessments</td>
<td>site</td>
<td>yes</td>
</tr>
<tr>
<td>Printed copies of the e-case report forms as required by the IRB/EC</td>
<td>site</td>
<td>yes, if required</td>
</tr>
<tr>
<td>Cabotegravir Investigator’s Brochure (December 2016) and any subsequent updates</td>
<td>RSC</td>
<td>no</td>
</tr>
<tr>
<td>Truvada® (TDF/FTC) Package Insert (December 2016) and subsequent updates</td>
<td>RSC</td>
<td>no</td>
</tr>
<tr>
<td>Intralipid® 20% Fat Emulsion Package Insert (April 2016) and subsequent updates</td>
<td>RSC</td>
<td>no</td>
</tr>
<tr>
<td>Other written information for study participants and any updates</td>
<td>LOC/sites</td>
<td>yes</td>
</tr>
<tr>
<td>Study Monitoring Committee (SMC) summaries</td>
<td>LOC</td>
<td>no</td>
</tr>
<tr>
<td>Document</td>
<td>Source</td>
<td>IRB/EC Approval Required*</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>--------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Data and Safety Monitoring Board (DSMB) summaries</td>
<td>LOC</td>
<td>no</td>
</tr>
<tr>
<td>Other documentation required or requested by the IRB/EC</td>
<td>site</td>
<td>yes</td>
</tr>
<tr>
<td>Study status reports/updates (at least annually); this approval documents continuing review***</td>
<td>site</td>
<td>yes</td>
</tr>
<tr>
<td>New information that may adversely affect the safety of study participants or the conduct of the study</td>
<td>DAIDS</td>
<td>no****</td>
</tr>
<tr>
<td>Final study report/closure report</td>
<td>site</td>
<td>no</td>
</tr>
</tbody>
</table>

DAIDS = Division of AIDS; EC = ethics committee; LOC = HIV Prevention Trials Network Leadership and Operations Center; IRB = institutional review board

* Based on US regulations and GCP guidelines. Local regulatory authorities and/or responsible IRBs/ECs may require additional approvals. If so, the required approvals must be obtained and filed.

** IRB/EC submission is not necessarily required depending on DAIDS or local regulatory requirements.

*** Guidance from the US Office for Human Research Protections (OHRP) on continuing review can be found at: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-continuing-review-2010/index.html

**** IRB/EC approval of the actual information is not required; local IRB/EC policies should be followed for this kind of information.

Note: All documents must be submitted to all IRBs/ECs responsible for oversight of study implementation at the performance site. Documentation of all submissions to and approvals from all responsible IRBs/ECs must be maintained in the Essential Document files at the local performance site.
1.5.5 Protocol Registration for HPTN 084 Amendments

Upon obtaining approval from all responsible IRBs/ECs, site staff will submit the following documents to the Protocol Registration Office (PRO) at the RSC. These documents may be sent electronically to protocol@tech-res.com.

- Signed and dated protocol signature page
- Documentation of approval from all responsible IRBs/ECs, and local regulatory authority if applicable, of the study protocol and the ICFs.

**Note:** Documentation of IRB/EC approval must reference the exact protocol number, title, version number, and date as listed on the cover page of the protocol.

- A copy of the approved site-specific ICFs including local language translations, back-translations (if appropriate) and a certificate of translation (if appropriate). Please note, per the DAIDS Protocol Registration Manual, no back-translations are required by DAIDS for Spanish informed consents.

**Note:** The approved ICFs must include the exact protocol number, title, version number, and date as listed on the cover page of the protocol. Pages should be numbered 1 of x, 2 of x, etc. When an IRB/EC approves a ICF that will be used at multiple sites, and the approved form contains blank spaces for site contact information, a memo specifying the relevant information for each site must be submitted together with the approved form.

Some sites may have additional site-specific documents to be included with the protocol registration package (e.g. additional information requested by DAIDS). These documents should be submitted to the DAIDS RSC and a copy should be submitted to HPTN LOC.

If the site deletes or makes any substantive change to basic and/or additional elements as presented in the ICFs, the IoR must provide written documentation to explain the deletions/change(s) at the time of initial protocol registration with the DAIDS RSC.

DAIDS regulatory staff will communicate their review findings to the site staff, who will coordinate any required re-submissions.
1.6 Continuing Review

Throughout the course of the study, all sites are required to submit annual progress reports to the IRB(s)/EC(s) overseeing study conduct and receive annual approval. Documentation of this approval must be submitted to the RSC. See https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual for more information.

The submission sent to the IRB(s)/EC(s) for annual review should include the following:

- The full protocol
- The current ICFs
- An annual report which includes:
  - The number of subjects accrued
  - A summary of SAEs and any unanticipated problems involving risks to participants
  - The number of participants who have withdrawn and any complaints about the research since the last IRB/EC review
  - A summary of any modifications or amendments since the last IRB/EC review
  - Any other relevant information, especially information about risks associated with the research

Additional information and guidance about continuing review can be found at the OHRP website: http://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-continuing-review-2010/
Section 2. Protocol

2.1 Overview of Section 2

The table below documents the history of the HPTN 084 protocol along with Clarification Memos (CMs), Letter of Amendments (LoAs), and Full Amendments. These documents are considered Essential Documents. A copy of each document must be available to staff and a copy must be maintained with study regulatory files.

<table>
<thead>
<tr>
<th>Document</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPTN 084 Protocol, Version 1.0</td>
<td>2 March 2017</td>
</tr>
<tr>
<td>HPTN 084 CM#1 to Version 1.0</td>
<td>11 May 2017</td>
</tr>
<tr>
<td>HPTN 084 LoA#1 to Version 1.0</td>
<td>15 August 2017</td>
</tr>
<tr>
<td>HPTN 084 CM#2 to Version 1.0</td>
<td>26 September 2017</td>
</tr>
<tr>
<td>HPTN 084 LoA#2 to Version 1.0</td>
<td>24 January 2018</td>
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<tr>
<td>HPTN 084 LoA#3 to Version 1.0</td>
<td>31 May 2018</td>
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<tr>
<td>HPTN 084 CM#3 to Version 1.0</td>
<td>02 August 2019</td>
</tr>
<tr>
<td>HPTN 084 Protocol, Version 2.0</td>
<td>06 November 2019</td>
</tr>
<tr>
<td>HPTN 084 CM#1 to Version 2.0</td>
<td>22 January 2020</td>
</tr>
<tr>
<td>HPTN 084 LoA#1 to Version 2.0</td>
<td>23 June 2020</td>
</tr>
<tr>
<td>HPTN 084 LoA#2 to Version 2.0</td>
<td>10 September 2020</td>
</tr>
<tr>
<td>HPTN 084 CM#2 to Version 2.0</td>
<td>16 September 2020</td>
</tr>
<tr>
<td>HPTN 084 LoA#3 to Version 2.0</td>
<td>22 October 2020</td>
</tr>
<tr>
<td>HPTN 084 LoA#4 to Version 2.0</td>
<td>16 November 2020</td>
</tr>
<tr>
<td>HPTN 084 Protocol, Version 3.0 (OLE 1)</td>
<td>16 August 2021</td>
</tr>
<tr>
<td>HPTN 084 LoA#1 to Version 3.0</td>
<td>24 September 2021</td>
</tr>
<tr>
<td>HPTN 084 CM#1 to Version 3.0</td>
<td>07 December 2021</td>
</tr>
<tr>
<td>HPTN 084 LoA#2 to Version 3.0</td>
<td>03 February 2022</td>
</tr>
<tr>
<td>HPTN 084 LoA#3 to Version 3.0</td>
<td>14 March 2022</td>
</tr>
<tr>
<td>HPTN 084 CM#2 to Version 3.0</td>
<td>21 July 2022</td>
</tr>
<tr>
<td>HPTN 084 Protocol, Version 4.0 (OLE 2)</td>
<td>02 November 2022</td>
</tr>
<tr>
<td>HPTN 084 CM#1 to Version 4.0</td>
<td>24 February 2023</td>
</tr>
</tbody>
</table>
Note: CMs and LoAs are incorporated into subsequent full versions of the protocol. A CM may also be incorporated into a subsequent LoA.
Section 3. Document Requirements

3.1 Overview of Section 3

This section contains a listing of required administrative and regulatory documentation, commonly referred to as “Essential Documents,” which each study site must maintain and keep current throughout the study, as well as procedures for establishing adequate and accurate study participant source documentation records.

3.2 Essential Documents

Refer to the Essential Documents Section of the DAIDS Score Manual.

https://www.niaid.nih.gov/research/daids-score-manual

Refer to the appendix which specifies the administrative and regulatory documents that HPTN study sites must maintain for DAIDS-sponsored studies.


Also refer to ICH E6 Good Clinical Practice: Consolidated Guidance (https://www.fda.gov/media/93884/download) specify the administrative and regulatory documents that HPTN study sites must maintain for Division of AIDS (DAIDS)-sponsored studies. Based on this DAIDS Policy, the documentation listed below must be maintained for HPTN 084. When required documents are modified or updated, the original and modified/updated versions must be maintained. Although all required
documentation must be available for inspection at any time, all documents need not be
stored together in one location.

- Protocol (implementation version and any subsequent amendments, Letters of
  Amendment [LoAs] and Clarification Memos [CMs])

- Informed Consent Forms (ICFs) (all IRB/EC-approved versions, all signed and
dated forms from screened/enrolled study participants), as well as any “Dear
Participant” Letters (all IRB/EC-approved versions) for all screened/enrolled
participants.

- Signed and dated Food and Drug Administration (FDA) Form 1572, original and
  subsequent versions

- Documentation of approved protocol registration from DAIDS, protocol registration
  for the original study and Version 3 (OLE) and for all subsequent protocol
  modifications

- Documentation of study activation from HPTN Leadership and Operations Center
  (LOC)

- Documentation of local regulatory authority correspondence, authorization, and/or
  approval of the protocol

- Federal Wide Assurance (FWA) number(s) and expiration date

- Institutional Review Board (IRB)/Ethics Committee (EC) roster(s)

- All correspondence to and from the local IRB/EC, including documentation of all
  submissions, reviews and approvals and copies of site-specific interim and annual
  reports

- All IRB-approved participant informational/educational materials and
  advertisements for participant recruitment, as well as subsequent updates

- Screening and enrollment logs

- Participant identification code list (if applicable)

- Study staff roster, signature sheet, and delegation of duties, including Investigator
  of Record (IoR) responsibilities

- Signed and dated Curriculum Vitae (CV) for each study staff member, current
  within the last two years

- Financial disclosure forms from all key staff listed in the FDA form 1572

- Documentation of staff members’ current human subjects training (within 3 years)
- Documentation of staff members’ study-specific training, including training on all official revisions/amendments/regulatory actions such as version 3 (OLE) related to the protocol

- Documentation of staff members’ current Good Clinical Practice (GCP) training (within 3 years)

- Documentation of appropriate laboratory staff members’ current Good Clinical Laboratory Practice (GCLP) training. Refer any questions to the HPTN Laboratory Center (LC).

- Local laboratory accreditations/certifications, if applicable

- Product Safety Information/Reports/Memos (Investigational New Drug [IND] Safety Reports provided by DAIDS)

- Current cabotegravir (CAB) (oral and injectable) Investigator Brochure (IB) and subsequent updates

- Current Truvada® (TDF/FTC) Package Insert and subsequent updates

- All study product accountability records

- Local laboratory reference intervals for protocol-specified testing

- Key study-related correspondence with the HPTN LOC, HPTN Statistics and Data Management (SDMC), HPTN Laboratory Center (LC), DAIDS Pharmaceutical Affairs Branch (PAB) and DAIDS, as well as other study-related communication

- Documentation of study-related conference calls and meetings

- Applicable local public health reporting requirements pertinent to study procedures

- Final version of each local site- and study-specific Study Operating Procedures (SOPs) that will be used for HPTN 084 and all subsequent updates

- DAIDS reference materials including:
  - Division of AIDS Clinical Research Policies
    - https://www.niaid.nih.gov/research/daids-clinical-research-policies-and-other-information
• Division of AIDS (DAIDS) Site Clinical Operations and Research Essentials (SCORE) Manual
  - https://www.niaid.nih.gov/research/daida-site-implementation-operations
  - DAIDS Protocol Registration Policy and Procedures Manual:

• Study specific procedures (SSP) manual, original versions and all updates, bulletins, clarifications, and communiqués

• Monitoring visit log, reports, and site response to visit findings (for the monitor, HPTN LOC, SDMC, LC, PAB, and other site visits). Sites should print monitoring visit reports for their files from the DAIDS website for Clinical Research Management System (https://ncrms.niaid.nih.gov/NCRMS/Main)

• A complete, blank copy of the electronic case report forms (CRFs) (original and all revisions – these will be provided by the HPTN SDMC). Sites may choose to print the forms and file as part of their essential documents or they may choose to file electronically.

• All completed CRFs, which will include electronic initials and dates per the electronic data capture system (these will be provided by the HPTN SDMC at the end of the study)

• Site specific e-CRFs as Source Documentation Table (Table 3-1a OR 3-1b) and Source Documentation for Eligibility Criteria (Table 3-2)

• Source documents

• Signed agreements related to the study (e.g., between IoR and affiliated sites/ Materials Transfer Agreements (MTAs)/ Protocol Signature Page, etc.)

3.3 Investigator Responsibilities

Study sites must maintain an accurate and complete participant research record containing all information pertinent to the study for each study participant. The research record consists of the following: original subject-signed ICF(s), participant source documents, and CRFs.

3.3.1 Concept of Source Documentation

A source document is defined as the first document on which study-related information is recorded. Study sites must adhere to the standards of source documentation specified in the DAIDS Score Manual and the standards outlined in this manual.

For HPTN 084 including OLE, participant source documents will consist of narrative chart notes, visit checklists, medical records, laboratory reports, pharmacy records and CRFs and other items as defined by each participating site. As a condition for study activation, each site must establish an SOP for source documentation that specifies the use of these documents as source documents.

HPTN 084 will use an electronic data capture system. Electronic records are any combination of text, graphics, data, audio, pictorial, or other information in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system (21 CFR 11.3). **When data are entered directly into a computer, the electronic data in the computer becomes the source document.** A paper record (printout/hard copy/“print screen”) of the electronic data is considered to be a copy. Requirements for documentation, record keeping and record retention apply to electronic records the same as they do for paper systems.

Examples of electronic records include but are not limited to:

1. Participant data, reports, and/or results
2. E-mail communications pertaining to a participant or protocol management (e.g., directives from protocol chairs, clinical management committee (CMC), Clinical Research Site (CRS) investigators to study nurses, etc.)
3. IRB/EC correspondence pertaining to a participant or the study
4. Computer-Assisted Self-Interview (CASI) questionnaires

Each electronic record needs to be associated with an originator type, otherwise known as an authorized data originator. In HPTN 084, the authorized data originator is most likely going to be a person; however, it can also be a computer system, a device, or an instrument that is authorized to enter, change, or transmit data into the electronic record. Sites must develop and maintain a list of all authorized data originators. This list must be made available for study-related monitoring, audits, IRB/EC review, and regulatory inspection by authorized individuals at each clinical research site. Examples of data originators include, but are not limited to:

1. Clinical investigator(s) and delegated clinical study staff
2. Participants or their legally authorized representatives
3. Consulting services (e.g., a radiologist reporting on a computed tomography (CT) scan)
4. Medical devices (e.g., electrocardiograph (ECG) machine and other medical instruments such as a blood pressure machine)
5. Electronic health records (EHRs)
6. Automated laboratory reporting systems (e.g., from central laboratories)
7. Other technology
3.3.2 **Source Documentation**

Participant source documentation should contain all of the following elements:

- Participant ID number (PTID) assignment.
- Documentation that the participant provided written informed consent to participate in the study prior to the conduct of any study procedures including an Informed Consent Assessment tool (see SSP Section 4 Tables 4-1 and 4-2) to verify comprehension.
- Documentation that the participant met the study's eligibility criteria.
- A record of all contacts, and attempted contacts, with the participant.
- A record of all procedures performed by study staff during the study.
- A record of the participant’s exposure to the study product.
- A record of any Adverse Events (AEs) and Social Impacts reported by participants.
- Study-related information on the participant’s condition before, during, and after the study, including:
  - Data obtained directly from the participant (e.g., self-report of injection reaction)
  - Data ascertained by study staff (e.g., exam and lab findings)
  - Data obtained from non-study sources (e.g., medical records)

In general, sites should apply ALCOA* to achieve data quality.

- **Attributable:** is it obvious who wrote it?
- **Legible:** can it be read?
- **Contemporaneous:** is the information current and in the correct time frame?
- **Original:** is it a copy; has it been altered?
- **Accurate:** are conflicting data recorded elsewhere?

*Source: “The Facts About Source Documents” by Stan W. Woollen, Presented at the 1999 DIA Annual Meeting*
3.3.3  Examples of Source Documentation

3.3.3.1 Clinic Notes

Study staff must document contacts with a study participant where data and pertinent study information are collected in a signed and dated clinic note specifying the date, type, purpose, location of the contact, and the general status of the participant. Routine study visit reminders may be documented per local site SOPs and requirements (and a site may wish to include this information in the retention SOP). Clinic notes also must be used to document the following:

- The informed consent process and/or coversheets
- Procedures performed that are not recorded on other source documents
- Pertinent data about the participant that are not recorded on other source documents
- Protocol deviations that are not otherwise captured on other source documents (such as the Protocol Deviation Form).

One way that clinic notes can be structured is by using the SOAP method. The acronym SOAP stands for Subjective, Objective, Assessment, and Plan and the following information is included in each section:

S: Subjective information that includes what the patient tells you about how he/she is feeling or his/her symptoms. For example, how he/she is sleeping or eating or if he/she is experiencing pain or having trouble urinating or defecating.

O: Objective information including vital signs, pertinent physical exam findings, and the most recent laboratory test results.

A: The assessment describes your diagnosis of the symptoms. The assessment also includes a summary of how the patient is doing and what has changed from the previous visit.

P: The plan includes how each diagnosis or problem will be addressed. This section will include information about new or changes to existing medication, laboratory tests to order, and consults to obtain.

3.3.3.2 Visit Checklists

The checklists provided in Section 6 of this SSP manual may be used as a convenient tool for study staff to ensure that all study procedures are performed at each visit. The checklists as designed may not be able to serve as source documentation – see Section 6.0 for further information about this. If a site modifies the checklists to serve partly or wholly as source documents, individual study staff members must initial only those procedures that they complete to fulfill the source documentation requirement of identifying responsibility. In addition, if procedures listed on a single checklist are completed across multiple dates or by more than one person, the date upon which each procedure is completed must be clearly noted and initialed.
Even with modification, the checklists alone may not be sufficient for documenting all procedures. For example, chart notes may be required to document procedures performed at unscheduled study visits or to explain why procedures in addition to those specified on a checklist have been performed. Chart notes may also be required to document the content of discussions with participants (e.g., issues related to study product adherence and HIV counseling). Sites are encouraged to contact the HPTN LOC with any questions about which checklists to use and/or how to modify them for site specific purposes.

### 3.3.3.3 Case Report Forms

As mentioned above, the study will utilize an electronic data capture system. Each study site must document the source documentation for each electronic CRF item by completing Table 3-1 (EITHER Table 3-1a OR Table 3-1b may be used; these tables may be modified to suit site needs), submitting a copy to the HPTN LOC, and maintaining the original document in the site’s administrative and regulatory files. The comments section of Table 3-1 (1a or 1b) should be modified to accurately reflect the source documentation for each CRF item at the site. Table 3-1 (1a or 1b) will be finalized and signed at each site prior to site activation. Site staff must follow the designations in Table 3-1 (1a or 1b) consistently for all study participants throughout the study.

In the event that it is not possible to record data directly onto forms designated as source documents, the following procedures should be followed:

- Record the data onto an alternative source document.
- Enter the alternative source document into the participant’s study chart.
- Transcribe the data from the alternative source document onto the appropriate case report form.
- Enter a chart note stating the relevant study, or dosing visit, date and the reason why an alternative source document was used.
Tables 3-1a and 3-1b: HPTN 084 Source Documentation TEMPLATES

NOTE: These tables are provided as example documents. Each site must complete either Table 3-1a or 3-1b site-specific source documentation table based on individual needs and policies. The CRFs in table 3-1b below are listed in alphabetical order and not necessarily in the order in which procedures are performed.

Table 3-1a: For each procedure listed below, add the source documents for each study procedure/evaluation. This is an EXAMPLE. Please add to this table if necessary.

<table>
<thead>
<tr>
<th>Evaluation /Procedure</th>
<th>Source Document(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADMINISTRATIVE, BEHAVIORAL AND REGULATORY</td>
<td></td>
</tr>
<tr>
<td>Obtain Informed consent(s)</td>
<td>Example: Signed and Dated Informed Consent form</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Informed Consent Coversheet (or chart note)</td>
</tr>
<tr>
<td>Locator information</td>
<td></td>
</tr>
<tr>
<td>Demographic information</td>
<td></td>
</tr>
<tr>
<td>HIV prevention counseling</td>
<td></td>
</tr>
<tr>
<td>Offer condoms</td>
<td></td>
</tr>
<tr>
<td>Acceptability assessments</td>
<td></td>
</tr>
<tr>
<td>Behavioral assessments</td>
<td></td>
</tr>
<tr>
<td>CLINICAL</td>
<td></td>
</tr>
<tr>
<td>Medical History contraceptive use, con meds, physical exam</td>
<td>Example: Medical History Questionnaires, Medical History eCRF, Concomitant Medications, and/or chart notes</td>
</tr>
<tr>
<td>Dispense product</td>
<td></td>
</tr>
<tr>
<td>Adherence counseling</td>
<td></td>
</tr>
<tr>
<td>Hep B vaccination</td>
<td></td>
</tr>
<tr>
<td>Blood collection</td>
<td></td>
</tr>
<tr>
<td>Urine collection</td>
<td></td>
</tr>
<tr>
<td>Vaginal swab collection</td>
<td></td>
</tr>
<tr>
<td>Injections</td>
<td></td>
</tr>
<tr>
<td>ISR evaluations</td>
<td></td>
</tr>
<tr>
<td>LABORATORY</td>
<td></td>
</tr>
<tr>
<td>HIV testing</td>
<td>Example: Lab result report (or other required site specific form)</td>
</tr>
<tr>
<td>Pregnancy testing</td>
<td></td>
</tr>
<tr>
<td>HBV and HCV testing</td>
<td></td>
</tr>
<tr>
<td>CBC with differential</td>
<td></td>
</tr>
<tr>
<td>Chemistry testing</td>
<td></td>
</tr>
<tr>
<td>Liver function tests</td>
<td></td>
</tr>
<tr>
<td>Fasting lipid profile</td>
<td></td>
</tr>
<tr>
<td>Syphilis serologic testing</td>
<td></td>
</tr>
<tr>
<td>GC/CT and TV testing</td>
<td></td>
</tr>
<tr>
<td>Evaluation /Procedure</td>
<td>Source Document(s)</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Urinalysis (protein and glucose)</td>
<td></td>
</tr>
<tr>
<td>Plasma storage</td>
<td></td>
</tr>
<tr>
<td>DBS storage</td>
<td></td>
</tr>
<tr>
<td>Whole blood storage</td>
<td></td>
</tr>
</tbody>
</table>
Table 3-1b Example Source Document Reference

For each form listed below, add which elements of the form serves as the source document for study procedure/evaluation.

<table>
<thead>
<tr>
<th>Form</th>
<th>Source</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional Procedures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional Procedures Y/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional Procedures – OLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Event</td>
<td></td>
<td>Example: Form is source for Alternate etiology information. For all other items, source will be based on the type of AE, including chart notes, lab report/testing log, medical questionnaires.</td>
</tr>
<tr>
<td>Adverse Event Y/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Event - Infant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Event – Infant Y/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell Pellet Storage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4/Viral Load Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry Testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications Y/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consent - Pregnancy Infant Sub-study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contraception</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contraception - OLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Counseling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Visit- HIV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Visit - OLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Visit- Pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Visit - Pregnancy OLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Visit- Yearly Visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Visit- Open Label Truvada</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Visit – Step 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Visit – Step 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Visit – Step 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dried Blood Spot Storage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early Unblinding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Form</td>
<td>Source</td>
<td>Comments</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>--------</td>
<td>----------</td>
</tr>
<tr>
<td>Enrollment Visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting Lipid Test Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B Test Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C Test Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV Supplemental Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV Test Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV Test Results Y/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant Assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant Breastmilk Feeding Assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant Dried Blood Spot Storage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant HIV test results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant Specimen Collection - Blood (Plasma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant Specimen- Cord Blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed Consent V5.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection Administration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection Site Reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection Site Reaction Y/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interim Visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interim Visit Summary – OLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver Function Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log Revisions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long Term Consent Update</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History Y/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missed Visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open Label Truvada Log</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open Label Truvada Y/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participant Receipt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participant Transfer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pill Count – Enrollment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pill Count – Step 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pill Dispensation- Step 2 and 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma Storage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Form</td>
<td>Source</td>
<td>Comments</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>--------</td>
<td>----------</td>
</tr>
<tr>
<td>Form</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Plasma Storage-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contraceptive Substudy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Outcome Log</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Outcome Log – OLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Report</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Report- OLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test Results-OLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product Choice - OLE</td>
<td></td>
<td></td>
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<tr>
<td>Product Hold/Discontinuation Log</td>
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<tr>
<td>Product Hold Y/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product Hold - OLE YN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product Hold - OLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol Deviation Log</td>
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<td></td>
</tr>
<tr>
<td>Protocol Deviation Y/N</td>
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<td></td>
</tr>
<tr>
<td>Randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening Chemistries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening Liver Function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tests</td>
<td></td>
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<tr>
<td>Screening Outcome</td>
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<tr>
<td>STI Test Results</td>
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<td>Social Impact Log</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social Impact Log Y/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specimen Collection - Breast Milk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specimen Storage-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contraceptive Sub-Study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Step</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sub-study Infant PTID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Termination</td>
<td></td>
<td></td>
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<tr>
<td>Ultrasound Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound - OLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinalysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VOICE Risk Score - Modified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole Blood Storage</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.3.4 Document Organization

Study staff must make every effort to keep all research records - both individual participant records as well as logs and documents pertaining to all participants – confidential and secure. All records should be securely stored in an area with access limited to authorized staff only.

All study-specific documents and biological specimens that are transmitted to an off-site location, including copies of electronic CRFs, SAE/EAE Report Forms and all biological specimens processed in any way by non-study staff or transferred to an off-site location must be identified only by the participant’s PTID to maintain confidentiality. Sites must ensure that any document sent by email or other communication methods does NOT contain any participant identifiers. If a document has participant identifiers, the identifying information must not be visible or legible prior to sending. When communicating via email between two institutions for transfers that do NOT include anyone external to the two institutions, sites must follow their local institution’s policy for transmission of confidential information (e.g., encrypted email, redacted files, etc.). Inclusion of more than one identifier on other study records that are accessible only to authorized study staff is not prohibited by DAIDS, however, such records must be stored securely with limited access. Regardless of whether the participant identifier on a particular document is the participant’s name or PTID number, the original identifier may not be obliterated or altered in any way, even if another identifier is added. When necessary to maintain confidentiality, identifiers may be obliterated or altered on copies of original source documents. For example, if supporting documentation of study eligibility is to be submitted to the HPTN LOC, such as chart notes or lab reports, contain a participant’s name, this should be obliterated on the copy transmitted off-site, but not on the original.

All local databases will be secured with password-protected access systems.

Log books, appointment books, and any other listings that link participant PTID numbers to participant names or other personal identifiers should never be left unattended or easily accessible to unauthorized individuals.

3.4 Protocol Deviations

Any deviation from the protocol must be documented in participant charts and in any other pertinent source documents, including a Master Protocol Deviation Log which must be maintained on site. Any deviation from the protocol, no matter how small, must be recorded on this Master Protocol Deviation Log. All protocol deviations must be reported into the electronic data capture system.

* NOTE: HPTN 084 is adopting a more conservative approach for protocol deviation reporting, given that this an IND study.
3.4.1 Protocol Deviation Categories

Protocol deviations must be classified into a category when they are reported. Explanations of each category are provided below along with some common examples.

3.4.1.1 Category: Informed consent process deviation

This category of deviations includes errors directly related to the informed consent. Errors include staff failure to follow proper consenting processes with participants, not confirming comprehension of the content of the consent, not documenting consent properly and nonadherence to what the participant agreed to.

Examples of these deviations include:

- A site made a mistake on the consent form. It did not correctly account for the blood volume needed for study testing. The consent form stated that 44mLs of blood would be taken. Instead the site was routinely taking 50mLs of blood for protocol testing.

- Participants have the ability to opt out of genetic testing on the consent form. Blood for genetic testing was erroneously collected from a participant who had already declined genetic testing.

- A participant was consented using an English consent form when it is clear from the chart notes that her understanding of English was very limited. The site had an approved translated consent in the participant’s native language. The site should have used the consent the participant did not have to struggle to understand.

3.4.1.2 Category: Use of non-IRB/EC-approved materials

This category of deviations includes instances where sites accidently use materials with participants or the Community without local IRB/EC body (ies) approval.

Examples of these deviations include:

- Advertisements for a study were hung up to help recruit participants, however, the advertisements had not yet been IRB-approved.

- A site with multiple levels of IRB/EC reviews received protocol/consent form approval from all review bodies except one. The site did not realize that one review was still outstanding and implemented the updated protocol/consent form on site.

3.4.1.3 Category: Inappropriate enrollment

In general, any situation where eligibility criteria are not met or randomization is performed before all criteria are confirmed must be categorized as an inappropriate enrollment protocol deviation.
Examples of these deviations include:

- A site accidently enrolled a woman into the study with a voice risk score of 2 instead of a score of 5 or more (protocol version 2).
- AST and ALP were erroneously requested instead of ALT and Total Bilirubin. The site did not catch omission of the enrollment criteria before it randomized the participant.
- A participant was enrolled based on screening results that were more than 45 days old.
- A participant was enrolled with a history of seizure; though this history was not revealed to the site during screening. The participant experienced a seizure during the study and only then explained she previously had an eclamptic seizure during pregnancy.
- On a source document, staff marked “Yes” but did not provide the number of sexual encounters the participant reported having in last 30 days. Consequently, a monitor was unable to verify that the participant met the eligibility criterion of having “vaginal intercourse on a minimum of two separate days in the 30 days prior to Screening.”
- A site accidently enrolled a woman that had a positive HBsAg result at the screening visit. All other screening lab results were not clinically significant, and HIV ELISA was negative.

3.4.1.4 Category: Failure to follow trial randomization or blinding procedures

This type of deviation is specific to problems with the randomization procedure or blinding/unblinding requests.

Examples of this type of deviations include:

- While a study clinician was handling the syringe containing injectable study product, the barrel cover shifted just enough for the participant to view the liquid. The participant later did some research and was able to determine which arm she was randomized to.
- A participant was hospitalized after experiencing significant cognitive confusion. In its haste, the site did not properly follow emergency unblinding procedures.

3.4.1.5 Category: Study product management deviation

Deviations in this category are related to the storage and shipping of study products as well as any failure to follow study product handling guidelines.
Examples of this type of deviation are as follows:

- Participant was scheduled for enrollment however the pharmacy was out of stock of study product and the participant could not be enrolled.
- Study product was stored in the pharmacy at the incorrect temperature.
- The Chain of Custody document was not properly complete for a shipment of study product arriving on site.
- Expired oral study product was administered to a participant in error.

3.4.1.6 Category: Study product dispensing error

Deviations in this category are directly related to study product dispensing/administration errors made by site staff.

Examples of these deviations include:

- A site accidentally forgot to sign and date a study product prescription. This mistake was caught during a PPD monitoring visit.
- A participant was given an injection after the permissible window of time post product preparation. An injection was prepared at 10:50am but was not administered until 13:00pm. As per the protocol the injection should have been given within two hours of preparation. This injection was administered at two hours and ten minutes after preparation.

3.4.1.7 Category: Incorrect study product given/taken

This category of Protocol Deviations is used exclusively for instances when the wrong study product is ingested by a participant. This type of error could be the result of a study staff error or could occur if a participant takes another participant’s study product.

Examples of these deviations include:

- Two participants in a waiting room were sitting next to each other. They each had oral study product bottles with them. By accident, the participants ended up switching study product bottles in the waiting room. They each took the bottles home and subsequently took the wrong oral product.
- A participant came to site for her Week 2 visit. Following the pill count, study staff accidentally returned the study product for another participant. Unfortunately, the participant took oral study product in front of study staff before the error was detected. However, the mistake was caught before the participant left the clinic and she was given her original oral study product.
- At Week 5, a participant took oral study product in the morning before she received her first injection on site later that day. If the participant was randomized to CAB
LA, she would have had an oral dose of CAB in the morning and an injectable CAB dose that afternoon.

3.4.1.8 Category: Breach of confidentiality

This category of deviations includes events where confidential information about the participant is released to other people without participant consent. Confidential information includes medical information, HIV status or even the fact that the participation is enrolled in the study.

An example of this type of deviation is as follows:

- In an effort to locate a participant, site staff erroneously contacted two individuals who were not indicated as participant contacts on the locator form.

3.4.1.9 Category: Missed procedures

This type of deviation is specifically related to a site not conducting protocol required procedures, including failure to complete physical examinations/assessments and failure to collect any lab samples (not to include laboratory-initiated errors).

Examples of these deviations include:

- Prior to injecting participants with study product, there are several mandatory processes and labs which must be completed first. A site accidently forgot to confirm a participant was actively using a long-acting contraceptive prior to injection.
- Site staff forgot to weigh a participant during a study visit.
- Sites are required to notify the CMC for participant management guidance where indicated in the protocol. A site erroneously did not contact the CMC when a participant presented with a Grade 3 weight loss AE.
- A clinician accidentally did not conduct a targeted medical exam during a follow up study visit.
- Hepatitis B vaccination is scheduled for Week 2 of the study. The vaccination was accidently omitted during a Week 2 visit for a participant.
- A site accidently forgot to collect of a swab for Trichomonas vaginalis testing during a visit at Week 33.

3.4.1.10 Category: Lab assessment deviation

This category of deviations includes events where protocol procedures and lab SOPs are not properly followed by lab technicians. Lab technicians must: 1) properly process, test,
store and ship samples, 2) ensure adequate inventory of test kits and reagents to conduct timely protocol-required testing.

Examples of these type deviations include:

- A lab tech accidentally performs HBsAb testing during the Screening visit instead of HBsAg analysis. The correct test was ordered, the tech simply made a mistake.
- A lab tech did not order HIV rapid kits when the supply was low and subsequently ran out of test kits. Lack of test kits caused delayed participant visits since study product cannot be dispensed until a rapid test is completed.
- A lab ran out of hematology controls due to a stick out at the vendor. Study participants had to be rescheduled resulting in some out of window visits.
- Pregnancy test kits were ordered by lab staff but a significant temperature excursion during shipping to the site rendered the kits useless. Study visits were delayed until the kits could be obtained.

3.4.1.11 Category: Conduct of non-protocol procedure

This category of protocol deviations includes instances where a site accidently performs a procedure that is not mandated by either the protocol or based on participant management, and that does not fall under another category of PDs (for example over-collection of blood).

Examples of these deviations include:

- Hepatitis B vaccination was given in error; the participant was already immune.
- At visit 6.0 a urine sample was erroneously shipped to the local lab for NG/CT testing. NG/CT testing is not included in Week 6 protocol procedures. The sample was processed for NG/CT and results were sent to the clinic.

3.4.1.12 Physical assessment deviation

This category of deviations includes events where protocol procedures and are not properly followed leading to errors that occur with physical assessments.

Examples of these type deviations include:

- Participant had her weight incorrectly recorded and the error in weight has resulted in the incorrect BMI calculation.

3.4.1.13 Other

Events that are not specific to any of the above categories will be grouped and classified as “other.”
An example of these deviations include:

- Hematology labs were not performed per study schedule. Due to COVID transport issues, reagents were not available to process the lab samples.

### 3.4.2 Protocol Deviations During the COVID-19 Pandemic

Sites must continue to report PDs into the database during the pandemic. For missed assessments within a study visit due to COVID, a protocol deviation should be added. See example under section 3.4.1.12 Other.

Once a site identifies a protocol deviation, it should be entered into the MediData Rave system.

If the site has any question as to whether an issue is a deviation, it should email the protocol deviation email alias list at 084mgmt@hptn.org for guidance. If the suspected deviation is confirmed, the site will need to complete the Protocol Deviation Log eCRF and include the deviation on the Master Protocol Deviation Log.

### 3.4.3 Protocol Deviation Log CRF

One Protocol Deviation Log CRF should be completed for each participant affected by the deviation. If the deviation occurred over a period of time, report the date the deviation first started and when it ended or if it is ongoing at the time this report is submitted, include this information as part of the description of the deviation.

Please note that there is a limit of 1,000 characters on the Protocol Deviation Log CRF; therefore, sites are asked to be concise and clear when describing the event.

When reporting a deviation trend individual eCRFs must be entered into MediData Rave for each affected PTID.

### 3.5 Record Retention Requirements

As this study is being conducted under IND, the study-related records must be maintained for two years after the marketing application is approved for the drug(s); or if an application is not approved for the drug(s), until two years after shipment and delivery of the drug(s) for investigational use is discontinued and the FDA has been notified (21 CFR 312.57). **No documents are to be destroyed without written permission from DAIDS.**

The study-related records include but are not limited to the following:

- Study management information, including the protocol, clarifications, letters of amendment, protocol amendments, the SSP manual and associated errata, addenda, study drug shipment and supply, and bulletins.
3.6 Ancillary Studies

Ancillary studies (also sometimes referred to as “sub-studies”) are those investigations, conducted in conjunction with a primary or “main” HPTN study, that address scientific questions not identified as study objectives in the primary study protocol.

Ancillary studies may involve HPTN investigators and/or non-HPTN investigators and may be initiated by the primary study team or by individuals inside or outside of the study team. They may:

1) involve all sites participating in a primary HPTN study or a subset of sites;
2) involve the use of data, biological specimens, or other information obtained through a primary HPTN study;
3) be either prospective or retrospective in nature;
4) involve surveys or focus groups among primary study participants; and
5) contain laboratory-based investigations using specimens obtained from participants in a primary HPTN study.

The administrative and regulatory requirements for the conduct of ancillary studies can be found in the HPTN MOP Section 17 (https://hptn.org/resources/manual-of-operations).

3.7 Study Publications

All manuscripts, abstracts, posters or presentations based on the results or conduct of HPTN 084 must be prepared in accordance with the HPTN MOP and HPTN 084 Protocol Publications Committee.
### Appendix 3A: Sample HPTN 084 Master Protocol Deviation Log*

<table>
<thead>
<tr>
<th>PTID</th>
<th>Date of event/visit</th>
<th>Date of site awareness</th>
<th>Issue/Description</th>
<th>Category of deviation**</th>
<th>eCRF completed? (yes/no)</th>
<th>IRB required to be notified? (yes/no)</th>
<th>Date IRB notified, if applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>333333333</td>
<td>30Oct2019 enrollment</td>
<td>20Nov2019</td>
<td>HIV RNA not done within 14 days of enrollment</td>
<td>Inappropriate enrollment</td>
<td>Yes</td>
<td>Yes</td>
<td>27Nov2019</td>
</tr>
</tbody>
</table>

(*May be adapted as needed for local use)

(** See section 3.4.1 for categories)
Section 4. Continuation in Protocol Version 5.0 (OLE)

4.1 Overview of Section 4

This section provides an overview of requirements and procedures for continuing previously enroll participants on the Open Label Extension (OLE)/ Protocol Version 4.0 and Version 5.0. Additional procedure-specific details can be found in the visit checklists in SSP Section 6, and in Section 5/ Schedule of Evaluations Appendices of the Protocol.

4.2 Continuation in Protocol during the Open-Label Portions

Participants who elected to remain in follow-up after the v2.0 amendment were offered the opportunity to remain in HPTN 084 under v3.0 protocol (OLE). Similarly, eligible participants in the version 3.0 protocol were offered the option to join the v4.0 protocol amendment. Eligible participants will now be offered the v5.0 protocol amendment.

Note: Always contact the CMC for questions related to safety and study product AEs of concern for participants interested in continuing or initiating CAB LA.

4.2.1 Informed Consent Process

After receiving notification to implement Version 5.0 of the protocol, sites will administer the addendum to the main informed consent form as participants present to the site. Participants do not need to be re-consented with the ICF used for v2.0 that is contained in the defunct, main body of the original protocol. That part of the study has concluded and the information in it is not representative of the trial or participant activities. The executed form specific to amendment v5.0 will document the participant's continued participation in the study. As part of the consent discussion, sites should explain to participants the options for ongoing study participation as outlined in the Informed Consent Appendices of the Protocol.

Contact the CMC for guidance if there are other scenarios for a discussion about choice and obtaining informed consent.

Deliver All Required Information in a Manner that is Understandable to Potential Participants. If the participant is literate, give her a copy of the ICF to read. Also provide the participant with other (IRB/EC-approved) informational materials developed to
complement the ICF, if any. If the participant is not literate, the materials may be read to her verbatim. After the participant has read the written material (or had it read to her), verbally review the information provided. A checklist or the ICF itself may serve as a useful guide for this. For example, staff may note the main points described in each paragraph of the informed consent form and ask if the participant has questions or concerns about each point. Listen carefully to the questions or concerns expressed by the participant and discuss these thoroughly. Take as much time as needed to address each question and concern.

If the participant is illiterate, **an impartial witness must be present during the entire informed consent discussion.** The witness will be asked to sign and date the ICF to attest that the information in the consent form was accurately explained to, and apparently understood by, the participant, and that informed consent was freely given by the participant. The ICH GCP guideline identifies an “impartial” witness as a person who is independent of the study, who cannot be unfairly influenced by people involved with the study. Each site must specify its procedures for obtaining informed consent from illiterate persons in its SOP for obtaining informed consent. The SOP should define who may serve as an impartial witness to the informed consent process. It is recommended that each site seek IRB/EC review and approval of these procedures. Refer to the DAIDS Score Manual for additional information on impartial witnesses.

**4.2.1.1. Assure That Informed Consent Is Obtained in A Setting Free of Coercion and Undue Influence**

During the informed consent discussion, take care to not overstate the possible benefits of the amendment, nor to understate the risks. Also emphasize to the participant that medical care and other services routinely available from the clinic or hospital associated with the site will not be affected by their decision whether or not to take part in the study. Encourage the participant to take as much time as she needs — and to talk about her potential participation with others, if she chooses — before making a decision.

**4.2.1.2. Confirm That the Participant Comprehends the Information**

The participant must not be asked to agree to continue in the v5.0 portion of the trial or to sign the ICF, until she fully understands the amendment. Study staff are responsible for implementing procedures to ensure that each participant understands the risks, benefits and goals of the amendment study prior to signing the amended ICF, respectively, and undertaking any study procedures.

One approach to assessing comprehension is to use a “quiz” (either oral or written) or other assessment tool that participants complete as part of the consent process. Another approach is to use open-ended questions to ascertain participant understanding during the informed consent discussion. It is possible to incorporate a scoring system into these assessment tools and to re-review the contents of the informed consent until the potential participant can answer a certain percentage of the questions correctly. Table 4-1 includes a sample informed consent assessment tool that sites may choose to adapt for their local use. For sites that choose to adopt tools...
such as those included in this section, detailed instructions for their use must be specified in the site SOP for obtaining informed consent.

Regardless of the method used to assess comprehension, if the assessment results indicate misunderstanding of certain aspects of the study, review those aspects again until the participant fully understands them. If after all possible efforts are exhausted, the participant is not able to demonstrate adequate understanding of the amendment, do not ask her to sign the ICF. Similarly, if the participant has concerns about possible adverse impacts if she were to take part in the study or indicates that she may have difficulty adhering to the study requirements, do not ask her to sign the ICF for the amendment.

4.2.1.3. Document the Process

The DAIDS Score Manual [https://www.niaid.nih.gov/research/daids-score-manual](https://www.niaid.nih.gov/research/daids-score-manual) including the section on Informed Consent of Participants provides detailed requirements and suggestions for documenting the informed consent process. [https://www.niaid.nih.gov/sites/default/files/score-informed-consent.pdf](https://www.niaid.nih.gov/sites/default/files/score-informed-consent.pdf). All requirements listed must be met. In order to meet some of the suggestions listed, site staff may consider the use of an informed consent “coversheet” similar to the example included in this section.

4.2.1.4. Continue the Informed Consent Process throughout the Study

Given the ongoing nature of informed consent, key elements of informed consent should also be reviewed at study follow-up visits. At these visits, study staff should review key elements of informed consent with the participant, focusing on the remainder of their study participation. For example, participants should be encouraged to ask questions as they arise and recognize that poor adherence to their study drug regimen will not affect their continued participation in the trial.

4.2.1.5. ICF Requirements for Protocol Amendments (including LoAs)

According to DAIDS policy (Protocol Registration Policy and Procedure Manual), the site’s IRB/EC is/are ultimately responsible for determining whether study participants need to be re-consented for a protocol amendment. The details of re-consent for a protocol amendment will be determined based on the extent and content of the amendment, and instructions will be provided to sites in this regard, after consultation with DAIDS.
Table 4-1: 084 OLE 2 (Version 4.0 Protocol) Sample Informed Consent Assessment Tool*  
(* May be adapted as needed for local use)

<table>
<thead>
<tr>
<th>Date:</th>
<th>Participant ID:</th>
<th>Staff name initials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Participant’s Response</td>
<td>Correct Answer</td>
</tr>
<tr>
<td>1</td>
<td>My participation in this research study is voluntary</td>
<td>□ True</td>
</tr>
<tr>
<td></td>
<td>During the blinded part of the study, CAB LA was found to be safe and effective in preventing HIV infection in women.</td>
<td>□ True</td>
</tr>
<tr>
<td>2</td>
<td>The purpose of the open-label extension is to learn more about women’s HIV prevention choices including during pregnancy and breastfeeding.</td>
<td>□ True</td>
</tr>
<tr>
<td>3</td>
<td>This research study is part of the regular medical care offered here at [clinic name].</td>
<td>□ True</td>
</tr>
<tr>
<td>4</td>
<td>The clinic will test my blood for HIV throughout the study.</td>
<td>□ True</td>
</tr>
<tr>
<td>5</td>
<td>If I join this research study amendment, I must stay in the study for as long as the study staff says.</td>
<td>□ True</td>
</tr>
<tr>
<td>6</td>
<td>If I choose to continue Cabotegravir injections in the second open-label extension and I later decide to stop injections, I can switch to TDF/FTC to cover the tail.</td>
<td>□ True</td>
</tr>
<tr>
<td>7</td>
<td>My participation in the second open-label extension part of the study will be for 48 weeks (unless I decide to have pregnancy follow-up which will follow me for 48 weeks after birth).</td>
<td>□ True</td>
</tr>
<tr>
<td>8</td>
<td>If I fall pregnant, I will be able to choose whether I want to continue taking Cabotegravir injections.</td>
<td>□ True</td>
</tr>
<tr>
<td>9</td>
<td>If I choose to have my infant followed in the study, my infant will be monitored for 48 weeks after I give birth.</td>
<td>□ True</td>
</tr>
<tr>
<td>10</td>
<td>There are no risks in continuing to take part in this research study.</td>
<td>□ True</td>
</tr>
<tr>
<td>11</td>
<td>If I have questions between study visits, I need to write them down and bring them with me at my next appointment.</td>
<td>□ True</td>
</tr>
</tbody>
</table>
If you have a baby and you are in the pregnancy substudy and test positive for HIV we will refer you and your baby for treatment

- True
- False

True

Table 4-2: Sample Informed Consent Coversheet for HPTN 084 OLE 2*

<table>
<thead>
<tr>
<th>Participant name:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of informed consent discussion:</td>
</tr>
<tr>
<td>Start time of informed consent discussion</td>
</tr>
<tr>
<td>Version number/date of informed consent form used during informed consent process/discussion:</td>
</tr>
<tr>
<td>Name of study staff person completing informed consent discussion (and this coversheet):</td>
</tr>
<tr>
<td>In what language was informed consent obtained?</td>
</tr>
<tr>
<td>Were all participant questions answered?</td>
</tr>
<tr>
<td>Did the participant accept a copy of the informed consent form (circle one option)?</td>
</tr>
<tr>
<td>End time of informed consent process/discussion:</td>
</tr>
<tr>
<td>Notes/Comments (not documented elsewhere):</td>
</tr>
</tbody>
</table>

(* May be adapted as needed for local use)
Table 4-3: Sample HPTN 084 Screening and Enrollment Log*

<table>
<thead>
<tr>
<th>Participant ID</th>
<th>Participant Name</th>
<th>Date Screened</th>
<th>Eligible</th>
<th>Date of Enrollment (if not enrolled, note N/A)</th>
<th>If not enrolled, specify reason (include all applicable codes)</th>
<th>Did Participant Enroll in OLE Y/N</th>
<th>Staff name/Initials</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>Y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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(*May be adapted as needed for local use. Note: There is no standard screen failure code list.)
Section 5. Study Procedures Overview

5.1 Overview of Section 5

This section provides a brief overview of requirements and procedures to be conducted during study implementation of Protocol V4.0 and Protocol V5.0.

Additional procedure-specific details can be found in the HPTN 084 Protocol version 4.0 or version 5.0 (as is appropriate for the site) and relevant SSP manual sections (e.g. clinical, laboratory, data management procedures, etc.).

5.2 Study Overview

OLE 1 and OLE2 consist of the below Steps.
1) Step 4a- Procedures for Participants Initially Randomized to TDF/FTC Who Elect to Move to OL CAB LA with Optional Oral Lead-in first
2) Step 4b- Procedures for Participants Initiating or Re-starting CAB LA without the Optional Oral Lead-in; the Initial Dose Visit
3) Step 4c- Procedures for Participants on Maintenance Doses of CAB LA or TDF/FTC
4) Step 4d- Procedures for Pregnant/Breastfeeding Participants and their Infants.
5) Step 5- Procedures for Participants Taking OL TDF/FTC for 48 Weeks after Premature CAB LA discontinuation
6) Step 6- Procedures for Participants on Maintenance Doses of CAB LA, weeks 49-96

5.3 Study Visits

Protocol-required visits: Steps 4, 5 and 6 have protocol-required study visits, which are described in Appendix VIII of the Protocol: Procedures for Offering Open Label (OL) Cabotegravir- The Next Part of HPTN 084

For each required study visit, there is an allowable visit window specifying on which study days (Day 0) the visit is "allowed" to be completed. The allowable visit windows are contiguous from visit to visit, and do not overlap. Within each allowable visit window, there is a target visit window. These windows are outlined in Section 13 of the SSP. Efforts should be made to conduct study visits within the target visit window and may be conducted over multiple days within the target visit window if necessary (see below regarding Split visits); however, if it is not possible to complete the required visit
within the target visit window, the visit may be completed within the allowable visit window.

**Interim visits:**

Interim contacts and visits may take place between regularly-scheduled visits. These contacts/visits may be done at participant request (e.g., to receive further counseling or clarify any questions) or as deemed necessary by the IoR or designee at any time during the study (e.g., to follow-up on an adverse event). Procedures to be performed during these contacts/visits will be specific to the reason for the additional PPT interaction.

**Split visits:**

A split visit is defined as visits conducted over multiple days. Ideally, all procedures specified by the protocol to be performed at a visit will be completed at a single visit on a single day. In the event that all required procedures cannot be completed on a single day (e.g., because the participant must leave the study site before all required procedures are performed), the remaining procedures may be completed on subsequent day(s) within the **allowable target visit window**. When this occurs, the visit is considered a split visit. All case report forms completed for a split visit are assigned the same visit code (even though the dates recorded on the case report forms may be different).

Refer to Section 11.3.2 (HIV Testing) for considerations for HIV testing and split visits.

**Missed visits:**

Efforts should be made to contact any participant who does not attend a protocol-required visit prior to the end of the target window period. A Missed Visit e-CRF should be completed to document the missed visit at the end of the allowable window period.

In general, when a visit is missed altogether and a participant reports to the site in the interim or for the next scheduled visit, the procedures from the missed visit that are not also required for the current visit should be performed. In the case of a missed injection visit, the CMC should be contacted for guidance regarding whether the injection should be given at another visit (and before the next scheduled injection).

Because of the nature of study procedures, all visits must be completed at the study clinic only. Sites should contact the CMC regarding any questions about procedures performed outside of the study clinic if the situation arises (e.g., participant is incapacitated and cannot report to the clinic). Details regarding the CMC are described in SSP manual Section 9.
5.3.1 Study Visit Procedures

- Refer to Protocol Appendix VIII for the Schedule of Evaluations.

- Participants may withdraw from the study for any reason at any time. IoRs may, in consultation with the HPTN 084 CMC, withdraw participants before their scheduled termination visit to protect their safety, and/or if participants are unable or unwilling to comply with study procedures. The CMC also should be consulted regarding procedures to be performed in the case of early termination (e.g., final HIV testing, etc.), if a participant is willing to undergo such procedures.

- In general, participants should not be withdrawn from the study except in the case of a) explicit withdrawal of consent by the participant; b) death; or c) extreme/unusual circumstances to protect participant safety. Any such safety-related participant terminations should only be implemented after consultation with the Protocol Chair, Division of AIDS (DAIDS) Medical Officer, Statistical and Data Management Center (SDMC) Protocol Statistician, representatives from the Laboratory Center (LC), the Leadership and Operations Center (LOC) Clinical Research Manager (CRM), and others. Consultation is conducted through the CMC alias.

5.4 Participant Transfers

During the course of the study, participants may leave the area where they enrolled. If they move to the vicinity of another HPTN 084 study site, they should be encouraged to transfer to that study site and continue study participation. To accomplish this, study staff at both sites will complete the participant transfer process. The same process should be followed for temporary or permanent transfers.

Upon identifying the need for a participant transfer to another site, the transferring site is responsible for notifying the HPTN LOC, HPTN SDMC, the HPTN (LC) and the DAIDS Protocol Pharmacist (see Section 1.2 of the SSP manual for contact information). The transferring site is responsible for notifying the site to which the participant wishes to transfer (the “receiving site”). After the logistical details of the transfer have been agreed upon, the following steps will be completed:

- The transferring site will explain the transfer arrangements to the participant and obtain written permission for the release of information that will authorize the transfer of his study records to the receiving site.

- Both the transferring and receiving sites should follow the instructions for participant transfers within Medidata Rave and in Section 13 of the SSP manual.

- The transferring site will ship **certified copies** of all of the participant’s study records to the receiving site via courier or overnight mail service. The transferring site will track the shipment and the receiving site will confirm receipt of the shipment with the HPTN LOC, SDMC, and the transferring site. The receiving site
will verify receipt of said materials with the transferring site. At this point in time, 
follow-up of the participant becomes the receiving site’s responsibility.

- The transferring site will complete the Participant Transfer e-CRF.
- The transferring site will email the HPTN LC representative confirming transfer to 
  the new site. The transferring site will retain archived samples for the participant 
  unless otherwise instructed by the HPTN LC.
- Study drug supply should be discussed with the DAIDS Protocol Pharmacist in 
cases of participant transfer.
- The receiving site will establish contact with the participant, obtain a copy of the 
  original screening and enrollment consent (and any others), along with his/her 
  informed consent to continue in the study (have the participant sign a consent at the 
  receiving site).
- Upon receipt of the Participant Transfer form and confirmation that the transferring 
  IoR has signed off on the participant’s eCRF casebook, the SDMC will re-map the 
  participant’s ID number (PTID) and any e-CRFs in the study database to reflect the 
  change in study site follow-up responsibility. This will ensure that future questions 
  and/or QCs will be sent to the appropriate site. The participant’s original ID 
  number, treatment-arm assignment, and follow-up visit schedule will remain 
  unchanged.
- The receiving site will complete a Participant Receipt eCRF to complete the 
  transfer process.
- If the participant returns to the clinic where she/he enrolled, the same process 
  should be followed to complete the transfer process. However, the certified copies 
  to be sent to the enrolling site will only include those applicable to the visits 
  conducted at the non-enrolling site. This is because the original records are at the 
  enrolling site and the only records needed would be those for visits conducted at the 
  non-enrolling site.

Note: If it is unlikely that the participant can return to the clinic where she enrolled and 
she is not close to another HPTN 084 clinic to transfer, the site should complete Missed 
Visit Forms for each visit the participant does not complete in case the participant is later 
able to rejoin the study. In cases where the site strongly suspects that the participant will 
never return to the study, the CMC should be contacted to discuss possible termination.

* See the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual 
  https://www.niaid.nih.gov/research/daids-score-manual for Requirements for Source 
  Documentation in DAIDS Funded and/or Sponsored Clinical Trials (listed under 
  Certified Copies) for requirement for certification. 
  https://www.niaid.nih.gov/sites/default/files/score-source-documentation- 
  requirements.pdf
5.5 Protocol-Required and Interim Visits at Sites Other Than Where Participants Enrolled

During the course of the study, while it is likely rare, it may happen that a participant is temporarily (for a few days, or a week or more) in another location where there is an HPTN 084 clinic other than the one in which they originally enrolled (their “home clinic”). If the participant is in this temporary location during a protocol-required visit or when she requires medical attention, these protocol-required or interim visits may be conducted at the alternative clinic (“temporary clinic”) if both sites have an SOP in place to cover this situation. In addition, the local IRB/EC must have agreed to the procedures outlined in the site-specific SOP, which must cover the following areas:

- Informed consent will need to be re-administered at the temporary clinic.
- A method to transfer study information from the temporary to the home clinic.
- A standard method of communication between the two sites prior to the initiation of any procedure, for clinical information, final decision-making about primary care, and determination of the duration of time during which care and visits will be conducted at the temporary clinic.
- Procedures for the management of drug dispensation and accountability should be developed with the HPTN 084 Protocol Pharmacist.
Section 6. Visit Checklists

6.1 Overview of Section 6

This section provides a template checklist for each of the required study visits. The use of visit checklists is optional but is strongly recommended.

6.2 Visit Checklists as Source Documentation

Checklists are convenient tools, which may serve as source documentation if designed and completed appropriately. These checklists alone may not be sufficient for documenting all procedures but can be used to indicate that the procedure was completed and by whom. Additional information could be documented on the checklist comment sections and/or chart notes. It is up to each site to determine whether and how to use the visit checklists as source documentation.

It also should be noted that the visit checklists outlined below depict the visit schedule for a participant completing all protocol-specified study visits. In what is hoped to be a rare occurrence, there may be cases where a participant may have a modified study visit; in which case, any modifications to the procedures could be noted in the comment section of the checklists.

6.3 Use of the Checklists

One checklist should be used for each participant. Checklists are commonly used for following the participant through a study visit; as activities are completed they are checked off the list. The checklists are designed so that there is one for each visit. Sites may add steps/activities/reminders to improve protocol adherence/implementation. Sites may also modify the order of procedures to maximize the efficiency with the following exceptions/considerations:

- Informed consent for the currently IRB-approved protocol at a given site must be obtained before any OLE study procedures are performed.
- Behavioral assessment and acceptability assessments must be administered prior to the delivery of HIV and adherence counseling.
- It is recommended that procedures for determining eligibility for continued product use (for example, HIV testing) be conducted early in the visit to ensure sufficient time is allowed for product to be prepared for dispensing.
When using the checklists, it is important to confirm that every item is completed - this is done by initialing and dating each step of the checklist (to show that the step was completed), or by entering ND (not done), or NA (not applicable) if a procedure is not performed. See checklist instructions for further information.

Source documentation for procedures will need to be identified for some items that are in the protocol, but not on captured on the Case Report Forms (CRFs).

A good example of this is locator information. At each visit, the protocol requires that locator information is confirmed and, if necessary, updated. Some of the ways that the “act” of confirming or updating can be documented at each visit include writing a note in the participant's chart, creating a locator information log, or having a review/revision log attached to the locator information itself. The checklist cannot serve as the source for the confirmation of locator information unless it is revised to show who confirmed the information, if changes were made to the form.

6.4 Visit Checklist Templates
**INSTRUCTIONS:** Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

### Step 4c: Procedures for participants on maintenance doses of CAB LA or TDF/FTC (Weeks 0, 8, 16, 24, 32, 40 and 48)

*Circle applicable visit week*

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<thead>
<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
<th>Comments</th>
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<td></td>
<td>☐</td>
<td>Confirm participant identity and PTID</td>
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<td>☐</td>
<td>Review/update locator information</td>
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<td>Informed consent for those not part of Steps 4a or 4b</td>
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<td>☐</td>
<td>Conduct Acceptability Assessment (Weeks 0, 24 and 48)</td>
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<td>☐</td>
<td>Conduct Behavioral Assessment</td>
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<td>Provide HIV pre-test / prevention counseling</td>
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<td>Offer condoms</td>
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<td>☐</td>
<td>Medical history (including concomitant medications, targeted physical exam (including pulse, temperature, BP, weight and BMI calculated at each visit)</td>
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</tbody>
</table>
**INSTRUCTIONS:** Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

### Step 4c: Procedures for participants on maintenance doses of CAB LA or TDF/FTC (Weeks 0, 8, 16, 24, 32, 40 and 48)

*Circle applicable visit week*

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<td>Collect blood and test for:</td>
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<td>• HIV testing</td>
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<td>• FDA-cleared HIV rapid test</td>
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<td>• Laboratory based, instrument HIV Immunoassay (HIV antigen and antibody)</td>
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<td>• HIV Viral Load (detection limit &lt;50copies/mL)</td>
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<td>• Pregnancy testing (if not done via urine)</td>
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<td>• CBC with differential at Week 0 if not done in Steps 4a or b; otherwise, only at Weeks 24 and 48</td>
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<td>• Chemistry panel (Albumin, BUN/urea, creatinine) at Week 0 if not done in Steps 4a or b; otherwise, only at Weeks 24 and 48</td>
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<td>• LFTs (AST, ALT, total bilirubin) (Weeks 0, 24 and 48)</td>
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<td>• Fasting lipid profile (Week 48 only) total cholesterol, HDL, triglycerides, and LDL either calculated or measured</td>
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<td>• Syphilis testing (Weeks 0, 24 and 48)</td>
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<td>Collect vaginal swab (Weeks 0, 24 and 48) and test for:</td>
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<td>• GC/CT (this may be done using urine instead)</td>
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<td>• TV testing</td>
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<td>Collect urine and test for:</td>
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<td>• Pregnancy testing (if site using urine for Pregnancy testing)</td>
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<td>• GC/CT testing (if site using urine for this) (Weeks 0, 24 and 48) for urinalysis (protein, glucose) Weeks 0, 24 and 48</td>
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</table>
**INSTRUCTIONS:** Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

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### Step 4c: Procedures for participants on maintenance doses of CAB LA or TDF/FTC (Weeks 0, 8, 16, 24, 32, 40 and 48)

*Circle applicable visit week*

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<td>____</td>
<td>☐</td>
<td>Plasma storage</td>
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<td>DBS storage</td>
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<td>____</td>
<td>☐</td>
<td>Provide HIV post-test counseling</td>
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<td>____</td>
<td>☐</td>
<td>Provide Adherence counseling</td>
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<td>☐</td>
<td>Dispense/provide study product</td>
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<td>Provide site contact information and instructions to report symptoms and/or clarify any questions</td>
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<td>☐</td>
<td>Schedule next study visit, if applicable</td>
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<td>☐</td>
<td>Provide participant reimbursement, if applicable</td>
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</tbody>
</table>

**Comments:**

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**Instructions:** Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

**Procedures listed in Appendix 4d: Schedule of Evaluations for Pregnant/Breastfeeding Participants on CAB LA**

**Visits:**

*Enter applicable visit week _________*

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<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
<th>Comments</th>
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<tr>
<td>___</td>
<td></td>
<td>Confirm participant identity and PTID</td>
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<td>___</td>
<td></td>
<td>Review/update locator information, except at delivery and post-partum Weeks 2pp and 4pp</td>
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<td>Informed Consent, as is appropriate</td>
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<td>___</td>
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<td>Acceptability Assessment (Weeks 0, 12, 32 and Post-partum Weeks 24pp and 48pp)</td>
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<td>___</td>
<td></td>
<td>Conduct Behavioral Assessment (all visits except Delivery and Post-partum Week 2pp and Week 4pp)</td>
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<tr>
<td>___</td>
<td></td>
<td>HIV pre-test/ prevention counseling (all visits except Delivery and Post-partum Week 2pp and Week 4pp)</td>
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<tr>
<td>___</td>
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<td>Offer condoms (all visits except Delivery, Post-partum Week 2pp and Week 4pp)</td>
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<td>___</td>
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<td>Medical history, concomitant medications (including folate intake) (all visits except Delivery, Post-partum Week 2pp and Week 4pp)</td>
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<td>___</td>
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<td>Targeted physical exam including antenatal assessment per SOC (all visits during pregnancy; only Post-partum Weeks 8pp and 48pp)</td>
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<tr>
<td>___</td>
<td></td>
<td>ISR assessment for PPTs taking CAB LA at Weeks 4, 12, 20, 28, 36 and beginning at Post-partum Week 8pp and all visits up to and including Week 48pp</td>
<td></td>
</tr>
</tbody>
</table>
**INSTRUCTIONS:** Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

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### Procedures listed in Appendix 4d: Schedule of Evaluations for Pregnant/Breastfeeding Participants on CAB LA

**Visits:**

*Enter applicable visit week__________*

<table>
<thead>
<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
<th>Comments</th>
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<tbody>
<tr>
<td></td>
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<td>Ultrasound or refer for ultrasound (Ideally the ultrasound should be completed by Week12)</td>
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<td>Collect blood and test for:</td>
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<td></td>
<td></td>
<td>• HIV testing</td>
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<td>• FDA-cleared HIV rapid test</td>
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<td>• Laboratory based, instrument HIV Immunoassay (HIV antigen and antibody)</td>
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<td></td>
<td>• HIV Viral Load (detection limit &lt;50copies/mL)</td>
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<td></td>
<td>• Pregnancy testing (if not done via urine; beginning at Post-partum Week 8pp and all visits up to and including Week 48pp)</td>
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<tr>
<td></td>
<td></td>
<td>• CBC with differential at Week 0, 24 and 36 during pregnancy; then at Post-partum Week 8pp and 48pp</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Chemistry panel (Albumin, BUN/urea, creatinine) at Week 0, 24 and 36 during pregnancy; then at Post-partum Week 8pp and 48pp</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• LFTs (AST, ALT, total bilirubin) at Week 0, 24 and 36 during pregnancy; then at Post-partum Week 8pp and 48pp</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Syphilis testing at Week 0 and 24 during pregnancy; then at Post-partum Week 8pp and 48pp</td>
<td></td>
</tr>
</tbody>
</table>
**INSTRUCTIONS:** Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

### Procedures listed in Appendix 4d: Schedule of Evaluations for Pregnant/Breastfeeding Participants on CAB LA

**Visits:**

*Enter applicable visit week ____________*

<table>
<thead>
<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>____________</td>
<td>__________</td>
<td>Collect urine and conduct:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>__________</td>
<td>• Pregnancy testing (if not done via blood; beginning at Post-partum Week 8pp and all visits up to and including Week 48pp)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>__________</td>
<td>• GC/CT testing (if site using urine for this at Week 0 and 24 during pregnancy; then at Post-partum Week 8pp and 48pp)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>__________</td>
<td>• Urinalysis at Week 0, 24 and 36 during pregnancy; then at Post-partum Week 8pp and 48pp</td>
<td></td>
</tr>
<tr>
<td>____________</td>
<td>__________</td>
<td>Collect vaginal swab at Week 0 and 24 during pregnancy; then at Post-partum Week 8pp and 48pp and conduct:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>__________</td>
<td>• GC/CT (this may be done using urine instead)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>__________</td>
<td>• TV testing</td>
<td></td>
</tr>
<tr>
<td>____________</td>
<td>__________</td>
<td>Plasma storage</td>
<td></td>
</tr>
<tr>
<td>____________</td>
<td>__________</td>
<td>DBS Storage only for TDF/FCT PPTs (all antenatal visits; at Delivery and Post-partum Weeks 4pp, 8pp, 16pp, 24pp)</td>
<td></td>
</tr>
<tr>
<td>____________</td>
<td>__________</td>
<td>Adherence counseling every visit except Delivery, Post-partum Week 2 pp and Week 4pp</td>
<td></td>
</tr>
<tr>
<td>____________</td>
<td>__________</td>
<td>Contraceptive counseling beginning at Post-partum Week 8pp and all visits up to and including Week 48pp</td>
<td></td>
</tr>
<tr>
<td>____________</td>
<td>__________</td>
<td>Dispense/ administer study product as appropriate (Weeks 0, 8, 16, 24, 32, 40 and Post-partum Weeks 8pp, 16pp, 24pp, 32pp, 40pp and 48pp)</td>
<td></td>
</tr>
</tbody>
</table>
INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

<table>
<thead>
<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>_____</td>
<td>☐</td>
<td>Breast milk collection Post-partum Weeks 2pp, 4pp, 8pp, 16pp, 24pp (Breast milk collection does not need to be performed if the mother is not breastfeeding or producing milk)</td>
<td></td>
</tr>
<tr>
<td>_____</td>
<td>☐</td>
<td>Breast milk storage at Post-partum Weeks 2pp, 4pp, 8pp, 16pp, 24pp</td>
<td></td>
</tr>
<tr>
<td>_____</td>
<td>☐</td>
<td>Pregnancy outcome assessment including abbreviated infant exam (Post-partum weeks 8 and 48)</td>
<td></td>
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<tr>
<td>_____</td>
<td>☐</td>
<td>Infant feeding history (Post-partum weeks 8, 16 and 24)</td>
<td></td>
</tr>
<tr>
<td>_____</td>
<td>☐</td>
<td>Infant AE assessment (Delivery and all Post-partum visits)</td>
<td></td>
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<tr>
<td>_____</td>
<td>☐</td>
<td>Cord blood collection at Delivery</td>
<td></td>
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<tr>
<td>_____</td>
<td>☐</td>
<td>Infant blood collection at Delivery and all subsequent visits</td>
<td></td>
</tr>
<tr>
<td>_____</td>
<td>☐</td>
<td>Infant HIV testing, if the mother has one or more reactive/positive HIV results (Delivery and all subsequent visits)</td>
<td></td>
</tr>
<tr>
<td>_____</td>
<td>☐</td>
<td>Cord blood storage (Delivery)</td>
<td></td>
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<tr>
<td>_____</td>
<td>☐</td>
<td>Infant DBS storage (Delivery and all subsequent visits)</td>
<td></td>
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<tr>
<td>_____</td>
<td>☐</td>
<td>Infant plasma storage (Delivery and all subsequent visits)</td>
<td></td>
</tr>
</tbody>
</table>

Procedures listed in Appendix 4d: Schedule of Evaluations for Pregnant/Breastfeeding Participants on CAB LA

Visits:

*Enter applicable visit week ___________*
INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

### Procedures listed in Appendix 4d: Schedule of Evaluations for Pregnant/Breastfeeding Participants on CAB LA

#### Visits:

*Enter applicable visit week __________*

<table>
<thead>
<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>__________</td>
<td>☐</td>
<td>Provide site contact information and instructions to report symptoms and/or clarify any questions</td>
<td></td>
</tr>
<tr>
<td>__________</td>
<td>☐</td>
<td>Schedule next study visit, if applicable</td>
<td></td>
</tr>
<tr>
<td>__________</td>
<td>☐</td>
<td>Provide participant reimbursement, if applicable</td>
<td></td>
</tr>
</tbody>
</table>

Comments: ____________________________________________

____________________________________________________________________________

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____________________________________________________________________________
### INSTRUCTIONS:
Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

### Step 5 Visits:

**Weeks in Study Step 5 Day 0 (no later than 8 weeks after last injection), Weeks 12, 24, 36 and 48**

*Circle applicable visit week*

<table>
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<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Confirm participant identity and PTID</td>
<td></td>
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<td></td>
<td></td>
<td>Review/update locator information</td>
<td></td>
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<td></td>
<td></td>
<td>Acceptability Assessment (weeks 0 and 48)</td>
<td></td>
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<td></td>
<td></td>
<td>Behavioral Assessment (if done in last 4 weeks skip day 0 and start at week 12; otherwise weeks 0, 24 and 48)</td>
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<td></td>
<td></td>
<td>HIV prevention counseling</td>
<td></td>
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<td></td>
<td></td>
<td>Offer condoms</td>
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<td></td>
<td></td>
<td>Medical history, conmeds, targeted physical exam with pulse, BP, weight and BMI calculated at each visit</td>
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<td></td>
<td></td>
<td>Collect blood and test for:</td>
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<td></td>
<td></td>
<td>- HIV testing</td>
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<td></td>
<td>- FDA-cleared HIV rapid test</td>
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<td></td>
<td></td>
<td>- Laboratory based, instrument HIV Immunoassay (HIV antigen and antibody)</td>
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<td></td>
<td>- HIV Viral Load (detection limit &lt;50 copies/mL)</td>
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<td></td>
<td>- Pregnancy (can be urine, plasma or serum)</td>
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<td></td>
<td></td>
<td>- Chemistry (Albumin, BUN/Urea, creatinine-skip day 0 if testing was in last 3 months; only perform at weeks 0, 24 and 48)</td>
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<td></td>
<td></td>
<td>- Liver function testing at weeks 0 and 48 only (AST, ALT, total bilirubin)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Syphilis testing weeks 0, 24, and 48</td>
<td></td>
</tr>
</tbody>
</table>
INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

### Participant ID

<table>
<thead>
<tr>
<th>Visit Date</th>
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</table>

INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

### Step 5 Visits:

**Weeks in Study Step 5 Day 0 (no later than 8 weeks after last injection), Weeks 12, 24, 36 and 48**

*Circle applicable visit week*

<table>
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<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
<th>Comments</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Collect urine and conduct:</td>
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<td></td>
<td></td>
<td>• Pregnancy testing (if site using urine for Pregnancy testing)</td>
<td></td>
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<td></td>
<td></td>
<td>• GC/CT testing (if site using urine for this) (Weeks 0, 24 and 48)</td>
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<td></td>
<td>Collect vaginal swab (weeks 0, 24 and 48) and conduct:</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• GC/CT (this may be done using urine instead)</td>
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<td></td>
<td></td>
<td>• TV testing</td>
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<td></td>
<td></td>
<td>Plasma storage</td>
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<td></td>
<td></td>
<td>DBS storage</td>
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<td></td>
<td></td>
<td>Provide HIV post-test counseling</td>
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<td></td>
<td></td>
<td>Adherence counseling</td>
<td></td>
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<td></td>
<td></td>
<td>Pill dispensation (not at week 48)</td>
<td></td>
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<td></td>
<td></td>
<td>Provide site contact information and instructions to report symptoms and/or clarify any questions</td>
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<td></td>
<td>Schedule next study visit, if applicable (not at week 48)</td>
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<td>Provide participant reimbursement, if applicable</td>
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</tr>
</tbody>
</table>

Comments:

___________________________________________________________________________________________
___________________________________________________________________________________________
___________________________________________________________________________________________
INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

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<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Confirm participant identity and PTID</td>
<td></td>
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<td></td>
<td></td>
<td>Review/update locator information</td>
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<td></td>
<td></td>
<td>Informed Consent (Weeks 0 and 104)</td>
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<tr>
<td></td>
<td></td>
<td>Acceptability Assessment (Weeks 72, 96, 112)</td>
<td></td>
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<td></td>
<td></td>
<td>Behavioral Assessment (Weeks 72, 96, 104, 112)</td>
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<td></td>
<td></td>
<td>Provide HIV pre-test/prevention counseling</td>
<td></td>
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<td></td>
<td>Offer condoms per local SOC</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Medical history, concomitant medications, targeted physical exam (with pulse, BP, weight and BMI calculated at each visit)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Collect blood and test for:</td>
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<td></td>
<td></td>
<td>• HIV testing</td>
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<td></td>
<td>• FDA-cleared HIV rapid test</td>
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<td></td>
<td></td>
<td>• Laboratory based, instrument HIV Immunoassay (HIV antigen and antibody)</td>
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<td></td>
<td></td>
<td>• HIV Viral Load (detection limit &lt;50 copies/mL)</td>
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<td></td>
<td></td>
<td>• Pregnancy, if not done via urine</td>
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<td></td>
<td></td>
<td>• Chemistry (Weeks 96, 112)</td>
<td></td>
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<td></td>
<td>• Liver function testing (Weeks 96, 112)</td>
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<tr>
<td></td>
<td></td>
<td>• Syphilis testing (Weeks 72, 96, 112)</td>
<td></td>
</tr>
</tbody>
</table>
INSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

---

**Step 6 Visits:**

**Weeks in Study Step 6**  
Weeks 56, 64, 72, 80, 88, 96, 104*, 112*)

*PPTs who do not have local access to CAB LA the PPT will be offered up to two additional injections on the study (Weeks 104 and 112).

Circle applicable visit week

<table>
<thead>
<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
<th>Comments</th>
</tr>
</thead>
</table>
| ____         | ☐         | Collect vaginal swab (Weeks 72, 96, 112) and test for:  
• GC/CT (this may be done using urine instead)  
• TV testing |          |
| ____         | ☐         | Collect urine and test for:  
• Pregnancy testing (if site using urine for Pregnancy testing)  
• GC/CT testing (if site using urine for this) (Weeks 72, 96, 112) |          |
| ____         | ☐         | Plasma storage |          |
| ____         | ☐         | DBS storage |          |
| ____         | ☐         | Provide HIV post-test counseling |          |
| ____         | ☐         | Adherence counseling |          |
| ____         | ☐         | Administer CAB LA |          |
| ____         | ☐         | Provide site contact information and instructions to report symptoms and/or clarify any questions |          |
| ____         | ☐         | Schedule next study visit, if applicable |          |
| ____         | ☐         | Provide participant reimbursement, if applicable |          |

Comments:
I NSTRUCTIONS: Enter staff initials next to each procedure completed. Do not initial procedures another staff member completed. If other staff members are not available to initial next to the procedure they completed, add a note on the checklist documenting who completed the procedure. If all procedures listed on a checklist are performed on the date entered in the top section of the checklist, it is not necessary to enter the date beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable. If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why (if not self-explanatory); initial and date this entry.

Schedule of additional procedures for women with reactive/positive HIV tests (HIV confirmation visit)

Study visit week __________

<table>
<thead>
<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>____</td>
<td>☐</td>
<td>Confirm participant identity and PTID</td>
<td></td>
</tr>
<tr>
<td>____</td>
<td>☐</td>
<td>Review/update locator information</td>
<td></td>
</tr>
<tr>
<td>____</td>
<td>☐</td>
<td>Date of first HIV positive test/ <a href="mailto:084HIV@hptn.org">084HIV@hptn.org</a> email alias list contacted: _________</td>
<td></td>
</tr>
<tr>
<td>____</td>
<td>☐</td>
<td>Confirm prior HIV results</td>
<td></td>
</tr>
<tr>
<td>____</td>
<td>☐</td>
<td>Provide HIV pre-test counseling</td>
<td></td>
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<tr>
<td>____</td>
<td>☐</td>
<td>Offer condoms</td>
<td></td>
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<tr>
<td>____</td>
<td>☐</td>
<td>Medical history, conmeds, physical exam (with pulse, BP, weight and BMI calculated)</td>
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<tr>
<td>____</td>
<td>☐</td>
<td>Collect blood and test for:</td>
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<tr>
<td>____</td>
<td>☐</td>
<td>• HIV testing</td>
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<tr>
<td>____</td>
<td>☐</td>
<td>o FDA-cleared HIV rapid test,</td>
<td></td>
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<tr>
<td>____</td>
<td>☐</td>
<td>o Laboratory based, instrument HIV Immunoassay (HIV antigen and antibody)</td>
<td></td>
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<tr>
<td>____</td>
<td>☐</td>
<td>o HIV viral load testing (must be 50 copies/ml or lower)</td>
<td></td>
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<tr>
<td>____</td>
<td>☐</td>
<td>• CD4 cell count</td>
<td></td>
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<tr>
<td>____</td>
<td>☐</td>
<td>• ART resistance (if able to conduct for local mgmt.)</td>
<td></td>
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<tr>
<td>____</td>
<td>☐</td>
<td>• Chemistry (Albumin, BUN/urea, creatinine)</td>
<td></td>
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<tr>
<td>____</td>
<td>☐</td>
<td>• LFTs (AST, ALT, total bilirubin)</td>
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</tbody>
</table>
Schedule of additional procedures for women with reactive/postive HIV tests (HIV confirmation visit)

<table>
<thead>
<tr>
<th>Initial/date</th>
<th>Completed</th>
<th>Procedures</th>
<th>Comments</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Plasma storage</td>
<td></td>
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<td>DBS storage</td>
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<td>Provide HIV post-test counseling, as is appropriate</td>
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<td>Provide site contact information and instructions to report symptoms and/or clarify any questions</td>
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<td>Provide participant reimbursement, if applicable</td>
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<td>Link to care and confirm when the participant has achieved viral suppression on ART. Document the ART regimen in the conmeds form. Terminate from the study once suppression is achieved.</td>
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Notes for Procedures for Enrolled Participants who Seroconvert: Please refer to Appendix II of the HPTN 084 Protocol. For any questions related to the requirements for suspected or confirmed HIV infection or clinical management questions, email 084HIV@hptn.org and CMC at 084cmc@hptn.org.

Comments: ________________________________________________
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Section 7. Participant Retention

7.1 Overview of Section 7

This section presents information related to participant retention definitions, requirements, and procedures. Once a participant consents for HPTN 084 Protocol v4.0 or v5.0, the study site will make every effort to retain her for the full study in order to minimize possible bias associated with loss-to-follow-up (LTFU). Successful retention begins with inclusion of participants who fully understand what study participation involves and collection of exhaustive locator information from each study participant. It also relies on development and implementation of a comprehensive retention plan.

7.2 Retention Definition

The term “retention” refers, in general, to participant attendance and completion of study visits/procedures as specified in the protocol. Participants who do not complete a particular scheduled visit within the allowable visit window, but do complete the next scheduled visit, will not be considered retained for the missed visit, but will be considered retained for the attended visit. Thus, retention rates can fluctuate over time and across study visits. Importantly, retention can be improved by ensuring that any participants who miss a visit return for the next scheduled visit.

7.3 Retention Targets

Ideally, each site should strive for 100% retention of those enrolled in the currently approved protocol. Routine retention reports for all sites are available on the Atlas portal maintained by the HPTN Statistics and Data Management Center (SDMC). The HPTN SDMC will also generate a final end-of-study retention rate for each site at study end. See SSP Section 15 for more information about Retention Reports.

7.4 Retention Plan

Sites are expected to retain eligible participants with no more than 5% annual loss to follow-up. A new SOP is not required for OLE 1 or 2, but sites may wish to modify their existing plan if necessary.
7.5 Participant Tracking Database

Due to the potential complexities that may be encountered when scheduling and completing visits, it is recommended that sites use a participant visit tracking sheet or database. This will most likely be a separate database created at your site for the OLE. Any participant tracking database that is developed is to be used for tracking purposes only. The database may not be used to record source data or to generate source documents unless specified in the site SOP for Source Documentation. All information entered into the database must be based on other source documents contained in participant study charts.

7.6 Retention Strategies

Some general strategies for maximizing participant retention are presented below:

- Dedicate adequate staff time and effort to retention efforts.
- Discuss the length of the study (48 weeks typically) and whether she will be able to meet the visit schedule during the consent process.
- Treat every participant with respect. **Keep information confidential.**
- Make visits as pleasant and short as possible. Do not keep participants waiting unnecessarily.
- Emphasize the value of the participant involvement in the study during the informed consent process and at subsequently visits. When participants complete scheduled visits, acknowledge and compliment their commitment, time, and effort devoted to the study.
- Whenever possible, make appointments to fit participant needs, such as offering clinic hours during the evening, weekend, or early in the morning.
- Work with Community Advisory Board members and key stakeholders to identify the most applicable contact and retention strategies for the local study population, including the type and amount of participant incentives.
- Keep participants, Community Advisory Board members, and key stakeholders up-to-date on study progress to foster a sense of partnership and ownership of the study (through the use of study newsletters, or quarterly meetings, for example).
- Inform local service providers who interact with the study population about the study and address any questions or concerns they have. Encourage them to express their support for the study and inform potential participants and key stakeholders about the study.
• Use a Tracking Database to easily identify when participant visit schedules. Establish routine mechanisms to remind both study staff and participants of upcoming scheduled visits.

• Always schedule the participant’s’ next visit before she completes the current contact or visit. During clinic visits give the participant an appointment card with the next scheduled visit date and time noted.

• Prepare a calendar of scheduled visits or input scheduled visit dates on participant’s cell phone for each enrolled participant, based on the enrollment date (or offer a planner/calendar as an incentive and note all study appointments). Note the dates of all scheduled visits in the participant’s file for easy reference.

• Consider scheduling study visits for participants at the beginning of the allowable visit window (see Section 13 of the SSP for allowable visit windows) to allow maximum time for re-contact and rescheduling if needed.

• Pay close attention to the allowable visit window and prioritize retention efforts for participants nearing the end of the window. Organize daily caseloads and work assignments based on these priorities.

• Follow-up on missed appointments with an attempt to contact and reschedule as soon as possible (preferably on the same day). Continue these efforts per the local retention plan until contact is made.

• Keep locator information up-to-date and maintain thorough documentation of all efforts to contact the participant. Keep all this information in an organized manner, so that different staff members can easily review the information and contribute to contact efforts when necessary.

• Use all information collected on the participant’s locator form while being careful to protect the participant’s privacy. Even if a locator source is not useful/ successful on one occasion, try it again later unless it is proven to be incorrect.

• Use all available contact methods the participant agreed to (e.g., phone, mail, home visits, street outreach, cell phone texts, e-mail, and social media). Also make use of other available locator information sources, such as phone and post office directories and other public registries.

• Post outreach staff at other local service organizations used by the study population, such as health care clinics. Be sure to maintain participant confidentiality in these public situations.

• Attempt contact with the participant at different times during the day and the week, including evenings and weekends.
• Assist participants in making transportation arrangements if necessary. This may be done with mass transit vouchers, site-owned vehicles, or assistance with other modes of transportation.

• If a participant dies during the study (even if that participant is LTFU), every effort should be made to locate copies of official paperwork if it exists (e.g., a death certificate) to verify this information and ascertain the cause of death.

7.7 Participant Withdrawal

Regardless of the participant retention methods described above, participants may voluntarily withdraw from the study for any reason at any time.

The Investigator of Record (IoR) or designee also may withdraw participants from the study in order to protect their safety or if they are unwilling or unable to comply with required study procedures after consultation with the Protocol Chair, Division of AIDS (DAIDS) Medical Officer, SDMC Protocol Statistician, and the HPTN Leadership and Operations Center (LOC) Clinical Research Managers (CRMs). In general, participants should not be withdrawn from the study except in the case of a) withdrawal of consent b) death; or c) extreme/unusual circumstances to protect participant safety. Any such safety-related participant terminations should only be implemented after consultation with the Protocol Chair, Division of AIDS (DAIDS) Medical Officer, Statistical and Data Management Center (SDMC) Protocol Statistician, representatives from the Laboratory Center (LC), the Leadership and Operations Center (LOC) Clinical Research Manager (CRM), and others. Consultation is conducted through the CMC alias.

Participants may be withdrawn if the study sponsor, government or regulatory authorities, or site IRBs/Ethics Committees terminate the study prior to its planned end date.

Every reasonable effort will be made to complete a final evaluation of participants who terminate from the study early, and study staff will record the reason(s) for all withdrawals from the study in participants’ study records. In such cases, the IoR or designee must contact the Clinical Management Committee (CMC) for guidance regarding final evaluation procedures.
Section 8. Study Product Considerations

8.1 Overview of Section 8

This section provides instructions to the Pharmacist of Record (PoR) and the study staff for the proper management of study products used in HPTN 084 including ordering, storage, randomization, dispensing, transport, administration, and record keeping of pharmacist-prepared, participant-specific study products. In addition to these specifications, the participating clinical research sites must adhere to the Pharmacy Guidelines and Instructions for DAIDS Clinical Trial Networks, and the site Pharmacy Establishment Plan approved by the DAIDS Pharmaceutical Affairs Branch (PAB). These specifications and the protocol take precedence over this document.

8.1.1 Chain of Custody

In addition to the requirements of the PoR for maintaining the Study Product Accountability Record and participant specific study product accountability record, if the pharmacist is not dispensing study products directly to participants, the non-pharmacy study staff must help to ensure the chain of custody of study product by completing any applicable sections and/or the following documents in their entirety, as directed for each participant. The sites may choose to use the documents listed below for this purpose or develop their site-specific documents as long as these include all the required information.
• Record of Dispensation of Participant-Specific Study Product to Non-Pharmacy staff (Appendix 8c)
• Record of Return of Participant-Specific Study Product by Non-Pharmacy Staff (Appendix 8d)

In an instance when the participant returns their oral study products at any time during the study for reasons such as study product discontinuation, damage, spills, inappropriate storage, etc.; the return must be reconciled by documenting on the participant specific study product accountability record when applicable and by following the instructions in the DAIDS pharmacy guidelines.

Each study site must designate its dispensing method(s) in HPTN 084 Standard Operating Procedures (SOPs) for participant-specific study product supply during clinic visits. These SOPs should be developed with input from both pharmacy and clinic staff. If applicable, the chain of custody SOP must be provided to the DAIDS Protocol Pharmacist for review prior to study activation and may only be modified after consultation with the DAIDS Protocol Pharmacist.

8.1.2 Preparation of the Oral Study Product

The oral products for this study will be provided with customary two-part structure which includes a tear-off portion containing the blinded-product identification (i.e., active or placebo).

Prior to dispensing, the un-blinded portion of the tear-off label must be removed and attached to the participant specific pharmacy records such as participant prescription or participant specific study product accountability record. The permanently affixed section of the label will remain on the original container.

The site pharmacist will label the bottle with a participant specific label prior to dispensing. The participant specific label must be in accordance with the local regulations and the DAIDS Pharmacy Guidelines manual.

The pharmacist will prepare the participant-specific study product and dispense sufficient quantity to last until the next follow-up visit. Pharmacists will record dispensations on the Pharmacy Accountability Logs.

8.1.3 Short-Term Storage of Participant-Specific Study Product in the Clinic

Oral Study Product:

If the PoR is not dispensing directly to participants and participant-specific study product is stored in the clinic for a short period of time (e.g., while the participant is undergoing the study visit procedures for a particular visit), it must be stored at the conditions described per protocol in an area that is always locked and is accessible only to pharmacists and authorized study staff as specified in the site’s SOP and Pharmacy Establishment Plan.
If the participant or site staff believe that the study product storage temperature has reached outside the specified storage temperature range per protocol, the PoR at the site must be contacted immediately so that she/he can dispense the appropriate participant-specific study product again as needed. In addition, the HPTN 084 DAIDS Protocol Pharmacist must be notified by email that this occurred, the reason that it occurred, and the corrective mechanism in place to assure that it will not occur again. This email should come from the Investigator of Record or designee and should copy the PoR at the site. The PoR is responsible for ensuring that the temperature in the storage cabinet is reviewed and recorded daily. These records must be reviewed by the PoR on a monthly basis. The monthly temperature records must be provided to the PoR to be maintained in the pharmacy. These records must be available for review by site monitors.

Injectable Study Product:

Injectable study product will be prepared in the pharmacy and delivered to the study clinic. The product must be administered to a participant as soon as possible or within two hours of preparation by the site pharmacist. The product must remain at controlled room temperature of 20 to 25° C from the time it is prepared to the time it is administered (within two hours). If the injectable study product is unable to be administered within two hours from the time it was prepared, the PoR at the site must be contacted immediately so that she/he can prepare and dispense the appropriate participant-specific study product again as needed. In addition, the HPTN 084 DAIDS Protocol Pharmacist must be notified by email that this occurred, the reason that it occurred, and the corrective mechanism in place to assure that it will not occur again. This email should come from the Investigator of Record or designee and should copy the PoR at the site, as well as the HPTN 084 Clinical Management Committee (084CMC@hptn.org).

8.1.4 Step 1: Enrollment

The PoR will dispense the participant-specific labeled oral study product to the participant directly or will dispense it to the clinical staff to give to the participant. If the oral study product is given to the study participant by the clinical staff, the Record of Dispensation of Participant-Specific Study Product to Non-Pharmacy Staff (Appendix 8c) must be completed.

Each participant is to receive a 5-week supply of oral study product upon enrollment (and after randomization). Each bottle of oral study product contains 30 tablets per bottle. Therefore, two bottles of each oral study product (TDF/FTC or Placebo AND CAB or placebo) should be dispensed in Step 1. Dosing should begin on the day of Enrollment or no later than 24 hours of Enrollment.

8.1.5 Weeks 2 and 4

No additional dispensing procedures are noted for these visits unless at the Week 2 visit a participant requires additional oral study product (e.g., they lost or damaged the oral study product). Participants are to return with their bottle at the Week 2 and Week 4
visits. Any returned study product still in the bottle will be counted and that number will be captured in the participant’s study chart and on the electronic case report form (e-CRF). Returned product at the Week 5 visit will also be counted and recorded by the PoR for product accountability logs.

If there is not a greater than 50% adherence seen via pill count at Week 4, the participant should not proceed to Step 2. The IoR or designee should contact the CMC.

8.1.6 Step 2: Weeks 5, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 97+8w, 185 +/- 4-8 w

**Oral Product:**

The PoR will dispense the participant-specific labeled oral study product to the participant directly or will dispense it to the clinical staff to give to the participant. If the oral study product is given to the participant by the clinical staff, the Record of Dispensation of Participant-Specific Study Product to Non-Pharmacy Staff (Appendix 8c) must be completed. The site pharmacist will dispense sufficient supply of the oral study product to last until their next scheduled study visit when injectable product will be administered at two time points four weeks apart and every 8 weeks thereafter beginning at Week 5 (Time points: Weeks 5, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 97+8w, 185 +/- 4-8 w)

The site pharmacist and site study staff should maintain close communication to ensure that adequate supply of participant’s oral study products is prescribed and dispensed. The participant should have about one-month buffer oral study product supply in case the participant’s next scheduled clinic visit date is rescheduled within the allowable study visit window per protocol.

**Injectable Product:**

Participant-specific labeled injectable study product will be prepared by the PoR as outlined in Section 8.7.4. Syringes will be covered with an overlay by the PoR prior to dispensing to the study clinic in order to maintain the blind.

The PoR will dispense the participant-specific labeled injectable study product to the clinic where it will be administered to the participant within two hours from the time the syringe was prepared. The Record of Dispensation of Participant-Specific Study Product to Non-Pharmacy Staff (Appendix 8c) must be completed.

Injectable study product will be administered as one 3 mL (600 mg) injection in the gluteal muscle at two time points four weeks apart and every 8 weeks thereafter beginning at Week 5 (Time points: Weeks 5, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 97+8w, 185 +/- 4-8 w)
8.1.7 **Step 3:**

Dispense tablets only at Day 0, Weeks 12, 24, 36

The study is designed such that participants in Step 2 will continue to receive injections until the last participant enrolled in the study completes their Week 65 visit or the required number of endpoints have been met. In either case, all participants still receiving injections on Step 2 will be transitioned to Step 3. Additionally, participants who permanently discontinue receiving injections before their Step 2 participation in the study ends will transition to Step 3 at the time that it is determined that they can no longer continue to receive injections (either due to an adverse event or participant decision). Any participant transitioning to Step 3 will receive open-label TDF/FTC 300 mg/200 mg fixed dose combination daily oral tablets, provided for up to 48 weeks.

Participants in Step 1 of the study who do not transition to Step 2 (that is, they never received an injection) will no longer receive any study product, will be referred to preventive care services, and will be followed on study for annual HIV testing until the end of Step 2.

Participants will begin Step 3 approximately 4-8 weeks after final injection in Step 2.

8.2 **Dispensing, Labeling, and Study Product Return**

8.2.1 **Study Product Labeling**

Under Step 1 and Step 2, the study products are to be labeled in a blinded fashion.

Under Step 3, the study products are to be labeled in an unblinded fashion.

The site pharmacist must place a participant-specific label on the prepared study product in accordance with the local regulations and by following instructions provided in the manual, *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

8.2.2 **Emergency Unblinding by CRS IoR or designee for Medical Reasons**

Please see additional information in SSP Section 9 for unblinding.

If, in the judgment of the CRS IoR or designee or in the judgment of the participant’s medical provider and the CRS IoR or designee, a medical event is of sufficient extreme severity that it requires the immediate unblinding of a participant without CMC consultation, the CRS IoR or designee may ask the CRS PoR to unblind the participant. Emergency Unblinding is expected to be extremely rare, if it occurs at all. It should only occur in the setting of a potentially life threatening clinical event, and if knowing the participant’s treatment assignment would affect decisions regarding the participant’s immediate medical management. Both conditions must be satisfied.

Emergency Unblinding IoR or designee may use the unblinding feature in the Medidata system to perform emergency unblinding of a participant. If this feature is not available or the
IoR or designee is unable to perform this for any reason, the IoR or designee may ask the site pharmacist to unblind the participant.

The CRS IoR or designee must provide a written request to unblind the participant’s treatment assignment to the PoR. The PoR must then provide the participant’s treatment assignment in writing to the CRS IoR or designee.

In case of extreme medical emergency, the CRS IoR or designee may verbally request the PoR to unblind a participant’s treatment assignment. However, in such cases, the verbal request must be followed by a written request to the PoR within 24 hours of the verbal request and must include a reason why the request to unblind participant’s treatment assignment could not be provided to the PoR in writing initially.

The written request to unblind the participant’s treatment assignment from the CRS IoR or designee and a copy of the written participant’s treatment assignment provided by the PoR to the CRS IoR or designee must be filed in pharmacy records.

The CRS IoR or designee must email the HPTN 084 Clinical Management Committee (084CMC@hptn.org) and copy the PoR regarding the participant’s emergency unblinding within 24 hours of the event.

The PoR must email the HPTN 084 protocol pharmacist (kashin@niaid.nih.gov) regarding the participant’s emergency unblinding within 24 hours of the event.
Appendix 8a: Specific Updates to SSP Section 8 in relation to Unblinding and issuance of study products in when implementing Letter of Amendment 4, Protocol Version 2.0

Documentation to be Provided to the Site Pharmacist of Record and staff:

When the site has LoA # 4 to HPTN 084, Version 2.0 approved by their IRB/EC/other regulatory entities and the participant is informed of her randomized assignment, the site investigator or designated study staff must provide a written notification to the pharmacy that the participant has been informed of their randomized assignment for pharmacy record. This documentation can be in an email to the site Pharmacist of Record (PoR) from the site investigator or designee or on a prescription for un-blinded study product that is signed by an authorized prescriber. If the written notification was not provided prior to the implementation of unblinding in relation to LoA 4 for Protocol Version 2.0, then the site investigator or designee should provide retroactive written notification to the PoR of participant(s) who have been informed of their randomized assignment for pharmacy records.

Sections 8.1.2, 8.1.4, 8.1.5 and 8.1.6 Participants Assigned to the TDF/FTC Arm in Steps 1 and 2:

- When the participant has been informed of her randomized assignment to the TDF/FTC arm, a new prescription for un-blinded oral active TDF/FTC signed by an authorized prescriber must be provided to the site pharmacist.
- The pharmacist will take the following steps to prepare and dispense un-blinded active oral TDF/FTC to the participant:
  1) Retrieve oral active TDF/FTC bottle with two part-label from Step 2 supply.
  2) Retain both the un-blinded part and the blinded part of the two-part label on the TDF/FTC bottle. Do not tear off the un-blinded part of the two-part label from the bottle.
  3) Place pharmacist prepared participant-specific un-blinded label in such a way that the blinded part of the two-part label on the bottle is covered.
- The pharmacist-prepared, participant-specific, un-blinded oral active TDF/FTC bottle will have the manufacturer’s unblinded part of the two-part label and site pharmacist generated participant-specific un-blinded label visible on the prepared bottle before dispensation.
- Alternatively, retrieve open-label oral active TDF/FTC supply from Step 3 supply if the site no longer has oral active TDF/FTC bottles with a two-part label from Step 2 supply due to no further supply of oral TDF/FTC from Step 2 supply available at the CRPMC to distribute to sites. Place pharmacist prepared participant-specific un-blinded label on the open-label oral active TDF/FTC bottle from Step 3 supply and dispense.
- If a participant assigned to the TDF/FTC arm in Step 2 wishes to switch to CAB, then the authorized prescriber will write a prescription for CAB once oral CAB is available from the CRPMC for these participants.
• The participant will initiate oral CAB 30 mg tablet, one tablet orally once daily for 5 weeks. After 5 weeks of oral CAB therapy, the participant will start injectable CAB-LA 600 mg administered as one 3 mL (600 mg) IM at two times points 4 weeks apart and every 8 weeks thereafter.

Sections 8.1.2, 8.1.4 and 8.1.5- Participants Assigned to the CAB Arm in Step 1:

• When the participant has been informed of their randomized assignment to the CAB arm, a new prescription for unblinded oral active CAB signed by an authorized prescriber must be provided to the site pharmacist.

• The pharmacist will take the following steps to prepare and dispense unblinded active oral CAB to the participant:
  1) Retrieve oral active CAB bottle with two part-label from Step 1 supply.
  2) Retain both the un-blinded part and the blinded part of the two-part label on the CAB bottle. Do not tear off the un-blinded part of the two-part label from the bottle.
  3) Place pharmacist-prepared participant-specific un-blinded label in such a way that the blinded part of the two-part label on the bottle is covered.

• The pharmacist prepared, participant-specific, un-blinded oral active CAB bottle will have the manufacturer’s unblinded part of the two-part label and site pharmacist generated participant specific un-blinded label visible on the prepared bottle before dispensation.

Section 8.1.6 Participants Assigned to the CAB Arm in Step 2:

• When the participant’s treatment assignment has been unblinded and the participant is assigned to the CAB arm, a new prescription for unblinded injectable CAB-LA signed by an authorized prescriber must be provided to the site pharmacist.

• The pharmacist will take the following steps to prepare and dispense unblinded active injectable CAB-LA to the participant:
  1) Retrieve injectable CAB-LA vial(s) from storage.
  2) Prepare the injectable CAB dose in a syringe per protocol. The overlay tape that covers the syringe barrel of the prepared unblinded, injectable CAB-LAB in a syringe is not required.
  3) Place pharmacist-prepared participant-specific un-blinded label on the prepared syringe.

Section 8.1.7 Participants in Step 3:

• Participants in Step 3 will continue to take open-label TDF/FTC from Step 3 supply per protocol.
Appendix 8b: Specific Updates to SSP Section 8 in relation to issuance of unblinded study products in when implementing Appendix VIII, HPTN 084 Protocol Version 3.0

Participants in Step 4

Participants who transition from TD/FTC or re-start CAB LA may choose from two options (Step 4a or Step 4b) before starting Step 4c.

Step 4a (Participants Initially Randomized to TDF/FTC Who Elect to Move to OL CAB LA with Optional Oral Lead-in first)

CAB 30 mg tablet, one tablet orally once daily for 4 weeks, with or without food, prior to initiating CAB-LA injection. This is an optional oral CAB lead-in prior to receiving CAB-LA injection for participants originally randomized to TDF/FTC.

Step 4b (Participants Initiating or Re-starting CAB LA without the Optional Oral Lead-in; the Initial Dose Visit, CAB LA Loading Dose)

CAB-LA 600 mg administered as one 3 mL (600 mg) IM in the gluteal muscle one time at Step 4b visit. The participant will then transition to Step 4c four weeks later. This is for participants who are initiating CAB for the first time with or without oral CAB (Step 4a) or for participants who have been on cabotegravir during the study but have had a long absence of visits (>15 weeks since prior injection) and require a reload of cabotegravir injection.

Step 4c (Participants on Maintenance Doses of CAB LA or TDF/FTC)

CAB LA Maintenance Doses

CAB-LA 600 mg administered as one 3 mL (600 mg) IM in the gluteal muscle every 8 weeks for no longer than a total of 48 weeks. This is for participants transitioning from Step 4b, or for participants originally randomized to cabotegravir who choose to continue it and do not need reloading dose.

TDF/FTC Maintenance Doses

TDF/FTC 300 mg/200 mg fixed dose combination tablet, one tablet orally once daily, with or without food for no longer than a total of 48 weeks.
**Step 4d (Participants who become pregnant in Step 4 and first 8 weeks of Step 5, who have had at least one CAB LA injection ever and Participants who are Breastfeeding)**

CAB-LA 600 mg administered as one 3 mL (600 mg) IM in the gluteal muscle every 8 weeks for no longer than a total of 48 weeks.

If participant declines to continue CAB LA during pregnancy or breastfeeding will be offered OL TDF/FTC. **TDF/FTC 300 mg/200 mg fixed dose combination tablet, one tablet orally once daily, with or without food for no longer than a total of 48 weeks per protocol.**

**Step 5 (Participants Taking OL TDF/FTC for 48 Weeks after Premature CAB LA discontinuation)**

**TDF/FTC 300 mg/200 mg fixed dose combination tablet, one tablet orally once daily, with or without food for no longer than a total of 48 weeks per protocol.**

This is for participants who received OL CAB LA in Step 4 and who discontinue CAB-LA early for safety or other reasons will have the option to transition to Step 5.

**Step 6 HPTN 084 Version 4.0 (Participants on Maintenance Doses of CAB LA in Step 4 who elect to continue CAB-LA Maintenance Doses for up to an additional 48 weeks (Week 56-96))**

CAB-LA 600 mg administered as one 3 mL (600 mg) IM injection in the gluteal muscle every 8 weeks, up to an additional 48 weeks (Week 56-96).

**Step 6 HPTN 084 Version 5.0**

Participants on Step 6 who complete 48 weeks (Week 56-96) of CAB-LA injection may receive up to two additional CAB-LA injection doses (Week 104 -112) per protocol.

CAB-LA 600 mg administered as one 3 mL (600 mg) IM injection in the gluteal muscle every 8 weeks up to an additional 16 weeks (Week 104 - 112).
Study Product Preparation:

Prescription
A prescription for all unblinded study product signed by an authorized prescriber must be provided to the site pharmacist prior to preparation of study product. The prescription must include the Step number (4a, 4b, 4c, 4d, 5 or 6) and a notation if the participant is switching between CAB arm and TDF/FTC arm.

Study Product Preparation in Steps 4a, 4b, 4c, 4d, 5 and 6
The site pharmacist must follow the study product preparation instruction in HPTN 084 protocol and comply with the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for standard pharmacy operations.

Preparation of Unblinded Oral CAB Study Product
The pharmacist will take the following steps to prepare and dispense un-blinded active oral CAB to the participant:

1) Retrieve oral active CAB 30mg tablet bottle with two part-label from Step 1 supply.
2) Retain both the un-blinded part and the blinded part of the two-part label on the CAB bottle. Do not tear off the un-blinded part of the two-part label from the bottle.
3) Place pharmacist-prepared, participant-specific, un-blinded label in such a way that the blinded part of the two-part label on the bottle is covered.

The pharmacist prepared, participant-specific, un-blinded oral active CAB bottle will have the manufacturer’s unblinded part of the two-part label and site pharmacist generated participant specific un-blinded label visible on the prepared bottle before dispensation.

The participant specific label must be in accordance with the local regulations, and the DAIDS Pharmacy Guidelines manual.

Preparation of Unblinded Oral TDF/FTC Study Product
The pharmacist will take the following steps to prepare and dispense un-blinded active oral TDF/FTC to the participant:

1) Retrieve oral active TDF 300 mg/FTC 200 mg with two-part label from Step 2 supply.
2) Retain both the un-blinded part and the blinded part of the two-part label on the TDF/FTC bottle. Do not tear off the un-blinded part of the two-part label from the bottle.
3) Place pharmacist prepared participant-specific un-blinded label in such a way that the blinded part of the two-part label on the bottle is covered.
The pharmacist-prepared, participant-specific, un-blinded oral active TDF/FTC bottle will have the manufacturer’s unblinded part of the two-part label and site pharmacist generated participant-specific un-blinded label visible on the prepared bottle before dispensation.

Alternatively, retrieve open-label oral active TDF/FTC supply from Step 3 supply if the site no longer has oral active TDF/FTC bottles with a two-part label from Step 2 supply due to no further supply of oral TDF/FTC from Step 2 supply available at the CRPMC to distribute to sites. Place pharmacist prepared participant-specific un-blinded label on the open-label oral active TDF/FTC bottle from Step 3 supply and dispense.

The participant specific label must be in accordance with the local regulations and the DAIDS Pharmacy Guidelines manual.

**Preparation of Unblinded Injectable CAB LA 600 mg/3mL**

The pharmacist will take the following steps to prepare and dispense unblinded active injectable CAB-LA in a syringe to the participant:

1) Retrieve injectable CAB-LA vial(s) from storage.

2) Prepare the injectable CAB LA dose in a syringe using aseptic technique under a pharmacy BSC Class 2 or better as detailed in Appendix 8 of the protocol. The overlay tape that covers the syringe barrel of the prepared unblinded, injectable CAB-LA in a syringe is not required.

3) Place pharmacist-prepared participant-specific un-blinded label on the prepared syringe.

The participant specific CAB LA label must be in accordance with the protocol, local regulations and the DAIDS Pharmacy Guidelines manual.
## Appendix 8c: HPTN 084 Record of Dispensation of Participant-Specific Study Product to Non-Pharmacy Staff

<table>
<thead>
<tr>
<th>CRS Name:</th>
<th>CRS Number:</th>
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<table>
<thead>
<tr>
<th>Date Dispensed from Pharmacy (dd-MM-yyyy), and Time Prepared (hh:mm)</th>
<th>Pharmacy Staff Initials</th>
<th>PTID</th>
<th>Date (dd-MM-yyyy) and Time (hh:mm) Collected from Pharmacy</th>
<th>Number of oral tablet Bottles</th>
<th>Number of CAB LA/Placebo Syringes</th>
<th>Prepared Syringes Should be Administered by hh:mm (to correspond within 2 hours of preparation, outlined in first column)</th>
<th>Staff Initials</th>
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**Instructions:**
- Complete one row each time participant-specific study products are provided to a participant.
- Comments may be recorded in the designated column and, if additional space is needed, on the back of the record or chart notes.
### Appendix 8d: HPTN 084 Record of Return of Participant-Specific Study Product by Non-Pharmacy Staff

<table>
<thead>
<tr>
<th>CRS Name:</th>
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</thead>
<tbody>
<tr>
<td>CRS Number:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STUDY STAFF</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date Returned by study staff or participant (dd-MM-yyyy)</strong></td>
<td><strong>PTID</strong></td>
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</table>

**Instructions:**
- Complete one row each time participant-specific study products are returned by study staff or study participants.
- Comments may be recorded in the designated column and, if additional space is needed, on the back of the record or chart notes.
Section 9. Clinical Considerations

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9.1 Overview of Section 9

This section provides information on the clinical considerations for participants in HPTN 084 protocol, version 3.0, 4.0 and 5.0 of the Open Label Extension (OLE) and versions OLE. The Schedule of Evaluations (SOE) in Appendix VIII of the protocol indicates when specific clinical, counseling, and questionnaire procedures are required along with relevant laboratory testing.

Safety assessments will be obtained at every visit throughout the study. However, the IoR or designee should perform any additional symptom-directed examinations at his/her discretion at any time during any visit if s/he determines it to be clinically necessary, particularly if there are any on-going conditions which may require follow-up.
Information pertaining to participant safety monitoring and Adverse Event (AE) reporting procedures are provided in Section 10 of this SSP manual. Information on performing laboratory procedures is described in Section 11 of this manual. Further instructions for the electronic data capture systems are provided in Sections 13 and 14 of this manual.

**Steps for the HPTN 084 Versions 3.0, 4.0 and 5.0 study are listed below:**

1) Step 4a- Procedures for Participants Initially Randomized to TDF/FTC Who Elect to Move to OL CAB LA with Optional Oral Lead-in first
2) Step 4b- Procedures for Participants Initiating or Re-starting CAB LA without the Optional Oral Lead-in; the Initial Dose Visit
3) Step 4c- Procedures for Participants on Maintenance Doses of CAB LA or TDF/FTC
4) Step 4d- Procedures for Pregnant/Breastfeeding Participants and their Infants
5) Step 5- Procedures for Participants Taking OL TDF/FTC for 48 Weeks after Premature CAB LA discontinuation (this Step may also be used for participants who were pregnant on 4c, as is appropriate)
6) Step 6- Procedures for Participants on Maintenance Doses of CAB LA, weeks 49-96, and through to week 112 if additional visits are needed because local access has not yet been secured.

**Figure 1: HPTN 084, v3.0 (OLE1) non-pregnant Protocol High Level Study Flowchart**

### Under OLE1

- **Step 4c**
- **CAB**
- **TDF/FTC**
- **If CAB d/c, then move to Step 5 complete 48 weeks TDF/FTC**

48 weeks step 4C
Any questions regarding the safety assessments and clinical management of participants in HPTN 084 must be directed to the HPTN 084 Clinical Management Committee (CMC) (084CMC@hptn.org). Protocol-related queries should be directed to the 084 management alias (084mgmt@hptn.org). Queries about visit coding should be directed to SDMC (sc.084cdm@scharp.org).

9.2 Clinical Management Committee

As outlined in the HPTN Manual of Operations (MOP), a CMC is constituted for each HPTN study with a biomedical intervention. The HPTN 084 CMC continues to provide consultation and decision-making regarding management of toxicities and study product administration, interpretation of clinical or laboratory eligibility criteria, and other questions related to general clinical management of participants. The CMC is comprised of a designated CMC Safety medical officer and also includes the Protocol Chair and Co-Chair, pharmaceutical sponsor medical officers, DAIDS Medical Officer, DAIDS Protocol Pharmacist, and representatives from the HPTN LOC, HPTN LC, and the HPTN SDMC. The CMC has a primary responder who is “on call” and is responsible for soliciting input and responding to site queries within a 24-hour time period. The scope of the CMC is described in the CMC charter (CMC Operating Guidelines).

Sites that plan to conduct visits during off hours (nights or weekends) should notify the CMC and their local laboratories in advance so that a responder will be available, and samples will be able to be received and processed within protocol requirements.

Sites should be mindful that throughout the HPTN 084 protocol and associated protocol appendices, as well as the SSP manual, are examples of situations and AEs that require consultation with the CMC.
Queries from sites are submitted to the following email alias list: 084CMC@hptn.org.

Queries must be formatted to include the information outlined below.


- Include all of the following in the body of the email message:
  1. Site name and number
  2. Name of person submitting query
  3. Participant Identification number (PTID) and Week on Study (Use “Screen” if pre-enrollment)
  4. Query submission type (choose one of the following)
     - Initial submission
     - Follow-up submission (this pertains to the PTID, i.e., a follow-up query to the initial submission
  5. Reason for query and case narrative

An example of the suggested email is provided here:

Subject line of email: 084 CMC: Participant 103-000011 – Elevated ALT Grade 3

Body of email:
Site name and number: Site 103 – Prevention Clinic
Person submitting query: Felicity Bones, Study Coordinator
PTID and Week on Study: 103-000011, Week 2
Query Type: Initial submission
Reason for query: 32-year-old participant week 2 on blinded oral study medication found to have Grade 4 CK elevation after cross-fit competition with Grade 3 ALT elevation. Per protocol, participant will be unable to progress to injection phase. Please advise on further work-up and follow-up schedule (unless CMC can envision a way to continue participant on study products).
Con meds: Tylenol, Ibuprofen, Naprosyn, Isoniazid, Rifampin, PZA, Ethambutol
Denies Alcohol, other recreational drug use
Pertinent laboratory values with chronology, values, and DAIDS toxicity table grade:

<table>
<thead>
<tr>
<th></th>
<th>Reference Ranges*</th>
<th>4/6/17 W2</th>
<th>3/23/17 EntryW0</th>
<th>3/19/17 screen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AST</strong></td>
<td>10-40 U/L</td>
<td>812 (G4 25xULN)</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td><strong>ALT</strong></td>
<td>9-46 U/L</td>
<td>225 (G3 7xULN)</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td><strong>CK</strong></td>
<td>21-215 U/L</td>
<td>7100 (G4 20xULN)</td>
<td>43</td>
<td>49</td>
</tr>
<tr>
<td><strong>creatinine</strong></td>
<td>0.60-1.35 mg/dL</td>
<td>0.97</td>
<td>0.97</td>
<td>1.04</td>
</tr>
</tbody>
</table>

*NOTE: Reference Ranges included on this table are for example purposes only; it does not represent ranges to be used in the study.

Sites that submit queries will print and file the full CMC correspondence regarding the query and place in the relevant participant regulatory binder/participant study file. Keeping this documentation will help explain to monitors why the site followed a particular course of action.

**Note:** Any Grade 5 (Death) EAE/SAE must be reported to the CMC within 72 hours of site discovery.

**Note:** Due to the relaxed contraceptive requirements under the OLE (Protocol V3.0 and Protocol V4.0), sites will no longer need to report to the CMC cases when a participant’s LARC (Long-acting reversible contraceptives) is delayed.

### 9.3 Participant-Reported Medical History during Follow up

Medical History should include, but is not limited to, symptoms, conditions, and diagnoses that affect eligibility or participation in the study, bleeding history, concomitant medications, contraceptive methods, and a history of hospitalizations, surgeries and allergies. The medical history collects a participant’s medical information by major body systems, including a participant’s drug, tobacco and alcohol use history. The history explores any medical conditions or any medications that are deemed exclusionary for this study, including a previous history of psychiatric illness or severe cardiovascular disease. The purpose for obtaining this information is to:

- Assess and document continued participant eligibility to participate in the study.
- Assess and document the participant’s medical conditions and symptoms for comparison with signs, symptoms and conditions that may be identified or reported during follow-up.
- Monitor any potential AEs associated with the use of the study product during the course of the study.
When collecting past medical history from the participant, the clinician should ask probing questions in order to collect the most complete and accurate information possible, especially with regard to severity and frequency. Sites must have a consistent method for documenting this information. In all cases, information obtained at visits must be documented in the participant’s chart and on appropriate e-case report forms.

Assessment of Acute HIV Infection

During follow-up, prior to study product administration, assess for signs and symptoms of acute HIV infection. Acute HIV infection is defined as the period of rapid viral replication that immediately follows the initial establishment of infection with HIV. Symptoms of acute HIV infection may be indistinguishable from a typical viral syndrome. Symptoms of acute HIV infections are listed below.

Clinicians should assess the possible causes of these symptoms, length of time the participant has been experiencing these symptoms, and severity grade. Symptoms should be managed clinically per standard of care. If a participant has signs or symptoms consistent with acute HIV infection, or expresses a concern about recent HIV acquisition, testing will be performed per protocol.

- Signs and symptoms of acute HIV infection should be assessed:
  - Fever
  - Fatigue
  - Headache
  - Myalgia
  - Weight loss
  - Pharyngitis or sore throat
  - Lymphadenopathy,
  - Rash
  - Diarrhea
  - Oral or genital ulcers

Site staff must assess the possible causes of these symptoms, length of time the participant has been experiencing these symptoms, and severity grade.

Under the OLE, HIV RNA is required at every visit (in addition to other HIV testing). Refer to the HIV testing algorithm for follow up visits in SSP, Section 11 for details. For split visits excluding HIV confirmatory visits, the HIV viral load does not need to be repeated if the split visit occurs less than 7 days from the initial visit. See SSP, Section 11 for further procedures.

9.3.1 AE Review of Medical History at Follow-Up Visits

Note: baseline refers to the timepoint at which the participant enrolled in the original blinded trial. At scheduled follow-up visits, collection of interval medical history should be obtained to:
• Determine whether previously reported and/or documented conditions are ongoing or have changed with regard to severity or frequency

• Determine whether newly-identified symptoms, illnesses, or condition have occurred since the last medical history was performed

Note: For purposes of this study, “newly-identified” is defined as a condition that:

• Was not present at baseline (Enrollment)

• Was present at baseline (ongoing at Enrollment) BUT has now increased in severity grade or frequency or has resolved after Enrollment and prior to the current report;

• Has already been reported as an AE but it has increased in severity grade/frequency

At the participant’s follow-up visits, retrieve the complete medical history source document and look up the Medical History Case Report Form (CRF) for reference.

At each follow-up visit, begin the follow-up medical history by reviewing with the participant and eliciting updates (resolution, outcome date, severity grade, etc.) on those symptoms/conditions that were documented as ongoing since the participant’s last visit. Site clinicians should then probe and evaluate for any new onset conditions/symptoms since the participant’s last visit. Clinicians should use their clinical experience and judgment to elicit complete and accurate medical history information from participants.

• New onset conditions/symptoms that began since the last visit may require completion of an AE Log e-CRF. This MAY include reoccurrences of conditions/symptoms that were reported at baseline and had resolved at a prior visit (only if the condition has increased in severity grade or frequency since baseline).

• Ongoing conditions that have increased in severity grade or frequency should be recorded as new events.

• Ongoing conditions that have not changed in severity or frequency, or have improved but not yet resolved, do not warrant any changes to the AE Log e-CRF.

• Ongoing conditions that have completely resolved since the last visit should have their AE LOG updated with an “Outcome Date”.

If during follow-up, a condition is identified as being present at baseline and the participant inadvertently did not report it as part of the baseline medical history, the clinician should add the information to the Medical History documentation. A chart note should also be documented to explain why the information is recorded retrospectively.

For all abnormal conditions or symptoms identified during follow-up, the severity grade of the condition or symptom must be documented, as must onset and resolution dates, when applicable.

9.4 Targeted Physical Exam at Follow-Up Visits
A targeted physical examination is required at most visits (Refer to Appendix VIII of the Protocol). A physical exam may be conducted at the discretion of the IoR or designee during an interim visit in response to clinically indicated and/or reported symptoms.

Targeted physical exams are performed at each follow-up visit. These exams are driven by the signs and symptoms that the participant reports. At a minimum, the participant must be weighed (see instructions in Section 9.4.1 below) and vital signs recorded at each visit (including temperature, weight, body mass index [BMI], blood pressure, pulse).

As safety is one of the objectives of this study, the goal at each visit is for the clinician to be assured that through the targeted physical exam and any ensuing conversation (history) that the participant is healthy enough to continue in the study and on the study drugs. Minimally, collecting vital signs at the follow-up visits gives the clinician a rudimentary idea of the participant’s health state that may be overlooked by conversation (history) alone.

9.4.1 Instructions for Weight Collection

Collecting participants’ weight is required as part of all physical exams (complete and targeted physical exams). To ensure consistency and accuracy in weight measurements, any time weight is collected, sites should follow the steps below:

- Measurements should be made at the same time of day each time, if possible.
- Participant should remove shoes, sweaters, coats, scarves, etc. prior to weighing.
- Participants should be asked to void (urinate/empty bladder) before weight is measured.
- Whenever possible, weight should not be measured during bouts of severe diarrhea or other obvious disturbances of hydration status.
- Participants should not engage in strenuous exercise for 8 hours preceding the measurements because of its potential effect on hydration status. If the participant reports that he/she did engage in strenuous exercise for 8 or more hours preceding the measurement, weight measurement should be performed anyway and documented on participant’s record.
- The same scale should be used for all measurements performed for this protocol to the extent possible. The scale should be calibrated at minimum annually.
- Before the participant is weighed, make certain that the scale is in balance if it is a beam-balance scale or reads zero if it is an electronic scale.
- Instruct the participant to stand with both feet centered on the scale with arms at the sides. The participant should not move or hold onto anything during the measurement.
- Allow the scale to stabilize and record the weight in the units shown on the scale (lbs or kg).

Weight data will be recorded when applicable.
9.5 Additional Considerations for Medical History and Physical Exams

The following additional assessments will be made throughout the study as part of the medical history and physical exams:

9.5.1 Adverse events

All abnormal findings for adult participants (i.e., Grade 1 and higher) are to be graded and recorded in the participant’s source documentation. AE Grade 1 or higher and any AE that leads to a study product hold (temporary or permanent) will be captured on the electronic Adverse Experience (AE) Log. For each AE, an assessment must be made by a study clinician of whether the event is related to the study product. Clinicians should review the relevant study product Investigator Brochures (IBs) and Package Inserts (PIs) to help make a determination. AEs will be assessed as specified in Version 2.0, January 2010 of the DAIDS EAE Reporting Manual.

Please note, if a laboratory result cannot be graded per the DAIDS toxicity table, it will not be reported as an AE. For example, the DAIDS toxicity table does not provide grading for non-fasting lipid profile; thus, these results will not be graded or reported as an AE.

See Section 10 of the SSP for more details regarding the reporting of AEs, as well as the HPTN 084 protocol Section 6.

See section 10.7.3 for how to handle AEs detected under the V2.0 protocol where tests were performed but are not required under V3.0. Similarly, see Section 10.7.3 for managing any AEs noted while performing testing under v3.0 that is not required by the versions 4.0 or 5.0 protocol.

For infant AEs, refer to SSP Section 10

9.5.2 Neurologic Symptoms

It is not required to actively assess neurologic symptoms: seizure, trouble sleeping, vivid/strange dreams, dizziness, problems concentrating, lightheaded, tremor, vision changes, weakness, numbness/tingling, fainting. However, these symptoms will be assessed as part of the targeted physical exam as needed.

9.5.3 Injection site reaction (ISR) assessment

ISRs are captured on the Injection Site Reaction e-Log post-injection (refer to Protocol Appendix VIII Step 4). Note: Step 4d has specific ISR reporting requirements. ISR assessments are required at these visits and sites should document that ISR assessments were performed at these visits.

Please note that for data to be consistent across all sites, sites should not telephone participants the day after an injection. Instead, they should only assess any reactions at the visits specified in the SOEs UNLESS a participant contacts the site with any questions or concerns about an ISR. If a participant contacts the site, then the site may
choose to schedule an interim visit. Any ISR symptoms noted during the interim visit will be documented on the Injection Site Reaction Log.

ISR examinations will include an assessment of pain, tenderness, pruritus, warmth, purulence, rash, erythema, swelling, induration, and nodules (granulomas or cysts). Participants should be instructed that ISR discomfort can be managed symptomatically (e.g., cold/warm compress, acetaminophen, ibuprofen) as necessary. See the last bullet in Section 9.6 of the SSP (below) for instructions to the participant upon leaving the clinic following an injection.

Participants should be instructed to contact the site regarding any ISRs of concern (and they may take a picture if they wish and email it to the site or return for an interim/unscheduled visit). **Per the HPTN 084 Protocol, Modified Toxicity Management Appendix VIII, the CMC must be notified of refractory cases in extreme circumstances.** Any questions regarding assessment of ISRs should be directed to the CMC.

It is important to distinguish between signs and symptoms from the injection process itself versus an ISR. Although these definitions are somewhat arbitrary, for protocol consistency, sites should follow the following definitions: An ISR typically begins 24-48 hours after an injection. However, if for example a participant experiences pain or discomfort from the actual procedure of giving an injection, e.g., the insertion of the needle beginning at time of, during or immediately after the procedure, this is, for purposes of reporting, considered associated with the injection procedure and is **not** considered an ISR. If a participant reports that on the day after the injection or later, she experienced symptoms (e.g., pain, redness, swelling, etc.) at the injection site, this would be an ISR. If an ISR is reported, use the Injection Site Reaction eCRF, using the “Site Reactions to Injections and Infusions” category for grading as found in the DAIDS Table for Grading the Severity of Adult and Pediatric Events, Corrected Version 2.1. If a participant experiences immediate pain or discomfort or other immediate signs and symptoms due to the procedure of giving an injection, it may be reported as an AE on the AE log eCRF using the category “Estimating Severity Grade for Parameters Not Identified in the Grading Table” for grading.

Sites should document all interventions that have been attempted to mitigate injection site reactions, which should include at a minimum:

- Pre-treatment (prior to injection administration) warm compresses
- Topical or oral pre-treatment with NSAID preparations, unless contraindicated
- Immediate post-injection massage to injection location
- Post-treatment warm or cold compresses
- Post-treatment NSAID or other analgesic preparations, topically or orally

Such interventions and their outcome should be documented in the source documents and the CMC consulted.
9.5.4 Concomitant medications

Sites must document on the Concomitant Medications Log all medications/preparations (prescription and non-prescription) including alternative/complementary medications/preparations (e.g., herbs, vitamins) taken by study participants within 30 days prior to Enrollment and anytime thereafter during study participation. Contraception should be recorded on the Concomitant Medications Log as well. Participants who seroconvert and start ART need to have their ART documented in the CM log.

For infants, do not record concomitant medications on the CM log; however, they should be documented in the source documentation.

It is helpful to ascertain the baseline medication information in the context of the baseline medical history. Participants should be asked open-ended questions to elicit participant report of current medications, and use the information obtained in the medical history to probe for additional medications that the participant may otherwise forget to report. For example, if the participant reports headaches as part of their medical history but does not spontaneously list any medications taken for headaches, ask what medications they take for headaches. Similarly, if a participant reports taking a medication for a condition that she inadvertently did not report when providing medical history information, add the condition to the baseline medical history source document.

At each follow-up clinic visit, retrieve the participant’s previously completed Concomitant Medications Log, record any new medications provided to the participant by study staff, and actively ask the participant whether she is still taking all previously-recorded medications, at the same dose and frequency. Also, actively ask whether the participant has taken any new medications since the last medical history was taken. To further probe for updates, if the participant reports any intercurrent illnesses, symptoms, etc. since her last medical history, ask whether she took any medications for those. Add all new information to the Concomitant Medications Log. If a participant reports taking a new medication for a condition that they inadvertently did not report when providing follow-up medical history information, add the condition to their follow-up medical history source document. To help ensure accurate reporting of concomitant medications information, participants should be encouraged to bring all medications to all study visits.

- Consult the CMC for instructions when a participant or provider decides it is in the participant’s best interest to initiate PEP.
- Consult the CMC for guidance in the case of a participant who has used TDF/FTC as PrEP during an extended absence from the study, such as extended lost to follow-up. If the participant returns to the site, she may be allowed to continue with study participation once use of clinically (outside of the study) obtained TDF/FTC for PrEP is stopped and study visits resume.
9.5.4.1 Precautionary and Prohibited Medications

In order to avoid AEs caused by drug interactions, whenever a concomitant medication is taken, site staff must review the concomitant medication's and study product’s most recent PI for Truvada® and IB for cabotegravir to obtain the most current information on drug interactions and contraindications. Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study.

For any precautionary or prohibited drug listed in the Truvada PI or cabotegravir IB, it is required that the HPTN 084 CMC be notified for recommendations for continuing or stopping (or holding) study product.

Experimental agents not otherwise specified in the SSP Manual may not be administered. Precautionary and prohibited medications may be found in the most recent versions of the protocol, Investigator’s Brochures, and template Informed Consent Forms.

9.5.4.2 Drugs to be used with caution in people using TDF/FTC

- Co-administration of the following drugs should be clinically monitored by site clinician, as per considerations below:
  - drugs that are eliminated by active tubular secretion (e.g. drug, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose (please refer to the table below) or multiple NSAIDS), as these may increase concentrations of emtricitabine, tenofovir, and/or the co-administered drug.
  - Drugs that decrease renal function (e.g., cause nephrotoxicity) as these may increase concentrations of emtricitabine and/or tenofovir.

- **NOTE:** Please report to the CMC if a participant takes a total daily dose of NSAIDS that meets or exceeds high dose, as designated in the table below, for MORE than 72 consecutive hours.

- **NOTE:** Acyclovir and valacyclovir may be used when indicated. If needed for treatment – sites do NOT need CMC permission for the use of these products, but sites should counsel the participant to increase hydration to avoid additive nephrotoxicity; no additional laboratory monitoring is required per protocol.
Table: Comparable NSAID Dose Levels*

<table>
<thead>
<tr>
<th>Nonselective NSAIDs</th>
<th>Low Dose</th>
<th>Medium Dose</th>
<th>High or Max Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac potassium</td>
<td>50mg bid</td>
<td>50mg tid</td>
<td>90mg qid (in OA/RA only)</td>
</tr>
<tr>
<td>Diclofenac sodium</td>
<td>50mg bid</td>
<td>75mg bid</td>
<td>50mg qid or 100mg SR bid (in RA only)</td>
</tr>
<tr>
<td>Fenoprofen</td>
<td>200-300mg qid</td>
<td>600mg tid-qid</td>
<td>800mg qid</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>50mg bid</td>
<td>50mg tid-qid</td>
<td>100mg tid</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>400mg tid</td>
<td>600mg tid-qid</td>
<td>800mg qid</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>25-50mg tid</td>
<td>75mg tid</td>
<td>IR =300mg/day (divided), SR =200mg/day</td>
</tr>
<tr>
<td>Naproxen</td>
<td>250mg tid</td>
<td>500mg bid</td>
<td>1250mg/day (divided)</td>
</tr>
<tr>
<td>Naproxen sodium</td>
<td>275mg tid</td>
<td>550mg bid</td>
<td>1375mg/day (divided)</td>
</tr>
<tr>
<td>Oxaprozin</td>
<td>600mg qd</td>
<td>1,200mg qd</td>
<td>1,200mg qd</td>
</tr>
<tr>
<td>Sulindac</td>
<td>150mg qd</td>
<td>200mg bid</td>
<td>200mg bid</td>
</tr>
<tr>
<td>Proxican</td>
<td>10mg qd</td>
<td>20mg qd</td>
<td>40mg per day (not indicated for OA or RA)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Partially-selective NSAIDs</th>
<th>Low Dose</th>
<th>Medium Dose</th>
<th>High or Max Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etodolac</td>
<td>200mg tid</td>
<td>400mg bid</td>
<td>1,200mg max (IR or SR divided doses)</td>
</tr>
<tr>
<td>Meloxicam/Mobic</td>
<td>7.5mg qd</td>
<td>7.5mg qd</td>
<td>15mg qd</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>1,000mg qd</td>
<td>1,000mg bid</td>
<td>2,000mg/day (qd or divided bid)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cox-2 inhibitors</th>
<th>Low Dose</th>
<th>Medium Dose</th>
<th>High or Max Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib/Glebelrex</td>
<td>200mg qd</td>
<td>200mg bid</td>
<td>200mg bid</td>
</tr>
</tbody>
</table>

COX = cyclo-oxygenase; IR = immediate release; NSAID = nonsteroidal antiinflammatory drug; OA = osteoarthritis; RA = rheumatoid arthritis; SR = sustained release
*This table does not represent exact or equivalent dosing conversions. It is based on U.S. Food and Drug Administration approved dosing ranges and comparative doses from clinical trials.
Source: www.ashp.org/emp/library/NSAIDsConversiontools.pdf

9.6 Injection Administration

As outlined in the SSP Section 8 – Study Product Considerations, injections must be administered within two hours of study product preparation by the site pharmacy. Therefore, coordination with the site pharmacy is important when scheduling and setting up the flow of these visits.

Instructional videos for administering IM injections in the gluteal muscle can be found on https://hptn.org/research/studies/hptn084 (password is “HPTN”). These videos are provided as examples only. Sites should use their clinical judgement and be guided by participant preference regarding which approach (ventrogluteal or dorsogluteal locations) to use for injections.

Specific instructions for the injections are as follows:
- Participants should be instructed not to take their oral study product on the day of their injection visit if they opted for an oral lead-in. However, if a participant takes study product on the day of the visit, DO NOT defer injection and document i in the participant’s file.
- Ensure appropriate supplies are on hand: alcohol wipes, gloves, and a filled syringe with the appropriate gauge and inch needle.
• An appropriate needle size (per BMI, as outlined above) should be used for each intramuscular (IM) injection. The needle should be long enough to reach the muscle mass and ensure an IM injection, but not so long as to involve underlying nerves, blood vessels, or bones. Longer needle lengths may be necessary for participants with higher body mass indexes (BMI > 30), to ensure that injections are administered intramuscularly as opposed to subcutaneously. The clinical staff should consult with the pharmacy staff regarding each participant and the appropriate needle length that should be used.

• Wash hands.

• Use alcohol to clean the area of the body to be injected.

• Use discretion as to where in the gluteus muscle each injection is given according to individual participant circumstance. If possible, injections should be spaced approximately 2 cm from one another, from the site of any previous injection or any injection site reaction.

• Hold the muscle of the injection site firmly between your thumb and fingers of one hand.

• With the other hand, hold the needle and syringe like a pencil. Using a quick dart-like motion, insert the needle at a 90-degree angle through the skin and into the muscle.

• Release your hold on the skin and muscle.

• Pull back slightly on the plunger to see if blood is present. If there is blood, remove the needle and syringe and start over with a new needle and syringe. If a new needle and syringe is needed, please discard the contaminated needle and syringe and request new participant’s study product from pharmacy. If there is no blood, inject the medicine.

**NOTE:** In the rare case the needle malfunctions, such that the full amount of the study product is not administered, remove the needle from the end of the syringe, place a new needle, and continue the injection with the same study product.

• Push the plunger slowly down to inject the study product into the muscle.

• Take the needle out.

• Apply pressure at the injection site and gently rub the site.

• Apply a bandage if needed.

• Discard the used needle and syringe properly.

• Check for any immediate injection site or other adverse reactions. There is no need to keep a participant in the clinic under observation after an injection.
• Instruct participants regarding how to manage any ISR at home, including:
  o If possible and if disclosure about participating in this study is not an issue, have someone look at the injection site if they cannot see/access it.
  o Note color, tenderness, any drainage. A picture should be taken if possible.
  o For pain, paracetamol, Ibuprofen/other NSAIDS, hot packs should be administered.
  o For swelling, Ibuprofen/other NSAIDS should be administered.
  o If any drainage, fever, chills, fatigue, weakness, the site should be contacted immediately.
  o Do not attempt to squeeze or drain any fluid from injection site.
  o Cover with a sterile bandage and contact clinic immediately if drainage occurs.

Questions regarding the injection instructions should be directed to the CMC.

9.6.1 Schedule of Injections

The injection schedule is included in Appendix VIII of the protocol.

Note that participants who elect to either begin or re-start CAB LA during the OLE must do so within the first 24 weeks of the OLE period. Participants initiating CAB LA will be permitted to choose between an oral run-in (4a) or a moving directly to injections (4b). Participants then move to Step 4c for 48 weeks of CAB LA injections.

9.6.2 Injection Visit Window Considerations

Timeliness of injections and adherence to visit windows must be carefully explained to participants. If participants present to the clinic outside of the visit windows (see Section 13 of this SSP for visit windows and refer to 9.7.3 below), contact the CMC for guidance. Injections may never be given with less than three weeks between them.

If participants who have delayed injections at study visits during Steps 4a, 4b and 4c, the sites must consult the CMC. Sites should also refer to all Data Communiques for visit coding.

9.6.3 Missed or Late Injections

First, CONTACT THE CMC.

Visit windows are contiguous. The following principles will be considered when advising sites on how to address missed injection visits.

- The interval between injections:
  i. Injections must not be given closer together than three weeks.
  ii. Delays between injections may require participants to be re-loaded.
- The visit schedule: The team should attempt to get the participant back onto her visit schedule; this may require the use of interim visits.
The availability of safety assessments: Prior to injection, a recent set of safety bloods should be available to confirm that it is safe to administer injections. At a minimum HIV testing and pregnancy testing should be performed prior to injection administration.

The site must consult the CMC regarding possible re-loading of the participant with delayed or missed visits. The CMC will use the guidance below to advise the sites:

<table>
<thead>
<tr>
<th>CAB LA Dose Delay For Any Injection (time from planned dose injection date)</th>
<th>Recommendation for All Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-7.5*+ weeks delayed</td>
<td>Give delayed dose and 600mg Q8W thereafter</td>
</tr>
<tr>
<td>≥7.5* weeks delayed</td>
<td>Give delayed dose, 600mg 4 weeks later, and 600mg Q8W thereafter (reloading required)</td>
</tr>
</tbody>
</table>

* An exception to the 7.5 week delayed interval re-load rule applies only to PPTs who were on a maintenance CAB LA dose prior to the OLE.

If the interval between the last target injection visit date and current visit is 7.5 weeks or less (52 days or less), then there is no requirement to re-load. The participant should be provided with her missed injection no matter the study week but not before confirming that all safety assessments are within normal limits. She should then return to her regular visit schedule, making sure that the subsequent injection is not less than 3 weeks after the last injection, and that safety parameters are within normal limits.

If the interval between the target visit date and the current visit is 7.5 or more weeks (53 days or more) then re-loading is required. The goal of this process is to ensure that participants are returned to steady state and target drug concentrations, which may have waned as a result of a long period without receiving injection. During re-loading participants will be required to receive the missed injection, and another 4 weeks later similar to the process observed with injections at the original study weeks 5 and 9. Thereafter there should be an attempt to ensure that participant visits return to the appropriate SOE. During the re-loading process, necessary safety assessments should be completed prior to injection.

The participant must be confirmed HIV and pregnancy negative prior to any injections being given. Once the first of the two loading dose injections is administered, the timing of subsequent injections will be adjusted to ensure that the participant is able to return to her visit schedule as soon as possible.

9.7 Specimen Collection

Blood and urine will be collected throughout the study. The protocol outlines the clinical procedures and corresponding testing to be performed according to Modified Section 5.0 of the HPTN 084 protocol. Sections 6 and 11 (checklists and lab) of the SSP also should
be consulted for further specifications. The following additional considerations should be noted:

- Since plasma samples for drug levels will be collected throughout the study, blood sample must be collected at injection visits PRIOR to the injections.
- Calculated creatinine clearance must be performed at every visit where chemistry testing is being performed. The formula is in Section 11.3.5 "Creatinine Clearance" of the SSP (Laboratory and Specimen Management Procedures Section). Note: Participants who initiated the trial on HPTN 084-01 using the Modified Bedside Schwartz equation will have creatinine clearance assessed per the Modified Schwartz equation at follow up visits.

9.8 Toxicity and Clinical Management

Sites should regularly consult the HPTN 084 Modified Protocol Appendix VIII – Toxicity Management as well as the Toxicity Management Diagrams at the end of this section, for guidance related to toxicities. It should be noted that Appendix VIII of the Protocol refers to several instances where the CMC must be contacted in the case of AE management and grading. For AEs that require CMC consultation, the CMC should be notified as soon as possible after site awareness, ideally within 72 hours.

All toxicity management must be fully documented in participant study records. When the CMC is consulted in relation to toxicity management, all communication should be filed in participant study records.

9.8.1 Suspected hepatotoxicity

In addition to the diagrams at the end of this SSP Section 9, sites should consider and investigate any potential causes leading to liver damage as proposed in the protocol.

In the event of permanent discontinuation for liver criteria, the site should consider the following tests to determine possible causes of hepatotoxicity in consultation with the CMC:

- Hep A IgM
- Hep B sAg; Hep B cAb
- Hep C RNA
- Hep E IgM
- CMV IgM
- EBV IgM
- RPR and syphilis screening
- Tox screen
- ANA; a-smooth muscle Ab; type - anti-liver kidney microsomal Ab, total IgG
- APAP (acetaminophen) level of reported use
- Review of any herbal meds and supplement use
9.9 HIV Considerations During Study Conduct

At all follow-up visits, HIV test results from previous visits and at least one HIV test result from the current visit must be available and reviewed by designated staff. All available HIV test results (results from previous visit and a current visit rapid test) must be confirmed to be negative/non-reactive prior to study product administration.

Positive/Reactive HIV Test

If a participant has a reactive or positive HIV test, product will be held. Sites should email the 084HIV@hptn.org and 084CMC@hptn.org alias lists in cases of reactive or “indeterminate” results regardless of the site interpretation (false positive, discordant, discrepant) or with questions about the HIV test algorithm. When emailing these groups, make sure to attach the template for documenting of all HIV results for the participant.

Further testing for confirmation of HIV infection will be done per Section 3.2 in Appendix VIII of the Protocol. Note: It may take several visits to confirm HIV infection. The SOE for seroconverters refers to the final steps once a participant has HIV infection confirmed and is linked to ART.

Participants who are determined not to be infected (i.e. false positive) may resume study products ONLY after CMC consultation.
**HIV testing log template for positive or indeterminate results**

**The subject line of the email:** 084 HIV: Participant 333-333-33333 – Reactive ELISA

**Body of email:**

Site name and number: 31033 Nowhere CRS
The person submitting a query: Zeb McGillicuty
PTID and Week on Study: 333-333-33333 Week 41
Query Type: Initial
Reason for query: rapid HIV positive

<table>
<thead>
<tr>
<th>Site name and number:</th>
<th>Nowhere CRS</th>
<th>31033</th>
</tr>
</thead>
<tbody>
<tr>
<td>The person submitting the query:</td>
<td>Zeb McGillicuty</td>
<td></td>
</tr>
<tr>
<td>PTID and Week on Study:</td>
<td></td>
<td>41</td>
</tr>
<tr>
<td>Query Type:</td>
<td>Initial Query</td>
<td></td>
</tr>
<tr>
<td>Treatment assignment during blinded trial:</td>
<td>TDF/FTC</td>
<td></td>
</tr>
<tr>
<td>Treatment assignment during OLE</td>
<td>CAB LA</td>
<td></td>
</tr>
<tr>
<td>Reason for query:</td>
<td>Positive Rapid HIV</td>
<td></td>
</tr>
</tbody>
</table>

A 32-year-old participant's rapid HIV test for week 40 was reactive. She had flu-like symptoms 3 weeks ago and has missed taking her pills on two occasions. She denies having unprotected sex in the past 6 months. We have called the participant to stop taking the study medication, and to come next week for confirmatory lab work.

Please advise if our plan is in order.

**Summary table of relevant HIV test results**

<table>
<thead>
<tr>
<th>Date/Visit Week</th>
<th>Date of last product</th>
<th>Rapid test 1</th>
<th>Rapid test 2</th>
<th>Laboratory based Instrumented Ag/Ab immunoassay</th>
<th>HIV RNA</th>
<th>Geenius if HIV Ag/Ab available and Instrumented test reactive</th>
<th>Other relevant test results</th>
</tr>
</thead>
</table>


Management of participants with discrepant HIV results.

Study staff should follow the guidance of the HIV alias regarding additional testing to confirm HIV status. Guidance on management of participants is provided in the Appendix I: Guidance for the Management of “Discordant/discrepant” HIV Testing Results – HPTN 083 and 084.

For some participants even with repeat testing their final HIV status may be uncertain. Investigators under guidance of CMC and HIV alias should engage participants on their options (see section 12 for counseling considerations).

For participants where treatment is recommended but in the context of atypical test results, investigators may want to explore with participants the option to start treatment to avoid the potential for emergence of INSTI resistance, with the potential for a subsequent treatment interruption 12-18 months later.

Some sites may be able to refer participants with atypical test results for enrolment and follow up in ACTG A5321. Sites should contact their CTU coordinator to determine whether this protocol is active at their CTU.

Some participants may be reluctant to start ART and may wish to wait for further test results. In this situation, participants should ideally be counselled about the potential risks for HIV infection if they are on PrEP hold and uninfected in addition to the risks for resistant infection if they are in fact HIV infected. All participant discussions should be adequately documented, and participants should be supported to make an informed choice that is appropriate to her personal circumstances.

9.10 Sexually Transmitted Infections (STIs)

As noted in the HPTN 084 protocol, treatment for STIs will be provided per local guidelines (and may include referral for treatment).

Symptomatic screening, or oropharyngeal screening for STIs beyond what is required by the protocol may be done at a site’s discretion and cost. Costs associated may come out of each site’s respective per participant study reimbursements.

9.11 Tuberculosis

As noted above in section on Concomitant Medications, rifampicin, rifapentine and rifabutin are contraindicated to concurrent use with cabotegravir. If TB treatment is required contact the CMC for guidance. For participants with suspected or confirmed tuberculosis, contact the CMC at 084cmc@hptn.org for further guidance.
9.12 Pregnancy

Prior to implementing version 3.0 or subsequent versions of the protocol, all sites should have a pregnancy management SOP in place that details how they will manage participants in terms of antenatal care, delivery and post-natal follow-up. The plan should include details about access to and recording of ultrasound information. See an example SOP attached in Appendix 9c. This SOP was loaned to 084 from a site; sites may modify/adapt it to best suit their needs as long as all 084 protocol requirements are met. Sites are not required to use the example SOP format.

- Pregnancy must be confirmed on two separate samples. Per protocol version 3.0 onwards, pregnancy can be confirmed on two separate samples on the same day.

- All participants interested in participating in Step 4d will be provided informed consent for this Step prior to any study activities. Participants cannot receive CAB LA during pregnancy without consenting to Step 4d.

- Participants with a positive pregnancy test may be ambivalent about their pregnancy. Participants can be given time within the visit window to decide about their pregnancy options and whether or not they wish to participate in the sub-study.

- Participants who are pregnant during Step 4 and Step 6 and who received at least one CAB LA injection during HPTN 084 (either blinded study, unblinded phase or during the OLE) are eligible to participate in Step 4d. In addition, participants in Step 5 who received a CAB LA injection within 8 weeks of pregnancy confirmation may join the Pregnancy and Infant Sub-Study.

- Participants who were in the TDF/FTC arm and are pregnant at the time of transition to the OLE and choose to take CAB during pregnancy are also eligible for Step 4d.
• Participants who received CAB LA and are pregnant at the transition are eligible for Step 4d.

• Sites should seek guidance from the CMC regarding study product administration procedures for participants who are pregnant at the time of the transition to the OLE.

**IN CONSULTATION WITH THE CMC, Women who are PREGNANT AT THE TIME OF TRANSITION TO THE OLE will be managed as follows:**

• Sites should consult with the CMC regarding pregnant participants transitioning to the OLE before implementing the guidance below.

• When transitioning to the 4d schedule, they will be allocated to the 4d visit week closest to gestational age. This guidance applies to participants who are pregnant at the time of transition ONLY.

• If an injection reload is required because they were on open-label Truvada, they will begin with a visit 4b prior to transitioning to the 4d schedule.

• If Estimated Gestational Age >12 weeks they should be referred for ultrasound at the time pregnancy is detected (or first pregnancy SOE visit).

• Syphilis testing should be conducted at the time pregnancy is detected (or first pregnancy SOE visit) if it has not been done as part of the step 2 pregnancy SOE. The rationale for this is that there is a 6 month gap in syphilis testing between week 0 and week 24 of the pregnancy SOE.

• GC/CT testing should be done at the time pregnancy is detected (or first pregnancy SOE visit) if there has been a > 3 month gap since last GC/CT testing and/or there is a long gap until the next scheduled GC/CT testing at the week 24 pregnancy visit. For women who present late in pregnancy (after week 24) and have not had GC/CT testing in the last three months, GC/CT testing should be done.

With respect to participants who become pregnant AFTER their transition to the open-label extension, the following considerations apply:

• Consult the CMC for guidance regarding product administration.

• Per above, if they require more time to consider their participation complete the visit 4c procedures for that visit up until product administration.

• Ask participant to return for a split visit within the window once she has had an opportunity to consider her pregnancy and study participation options.

• See section 12 on counseling support options.

• Participant will follow the schedule of evaluations for step 4d from week 0; participants should NOT be allocated to a visit on the SOE based on estimated gestational age.
For participants in Step 4d who experience pregnancy loss prior to 40 weeks gestational age

- Consult the CMC.
- Participants can return to either Step 4c or Step 6, whichever is appropriate, after entering 4d in these cases.
- Participants should return to the visit in the schedule of evaluations that reflects their last visit plus the period that they were on step 4d.
  - E.g. participant tested positive for pregnancy at Step 4 week 16 and had a miscarriage at step 4d week 16 would return to step 4c week 32.
- Report the pregnancy outcome on the appropriate CRF.

Ultrasound during pregnancy in all participants

All pregnant participants should have an ultrasound ideally before gestational age 12 weeks. Gestational age should ideally be calculated based on ultrasound. Ultrasound is preferred for the identification of fetal anomalies. With respect to fetal anomaly reporting, these should only be reported as an SAE/EAE at the time of delivery of the infant when surface examination can confirm the anomalies. Where there is pregnancy loss prior to delivery, the pregnancy outcome report should include comments on the fetal anomalies observed on ultrasound as part of the pregnancy outcome report. The CMC should be contacted regarding any pregnancy loss associated with fetal anomalies detected on ultrasound. ultrasound not available contact SDMC.

Management of Participants who are pregnant but decline participation OR are not otherwise eligible for Step 4d

As noted in Protocol Section 5.14, regardless of the step a pregnant participant is followed on, first semester ultrasound findings and pregnancy outcome data (infant growth assessment at delivery and approximately 48 weeks post partum) will be collected.

Note: ALL INFANT SAEs THAT OCCUR UP TO 48 WEEKS POST PARTUM WILL BE COLLECTED AND REPORTED.

Infant assessment

- Sites should aim to ensure that mother and infant visits are coordinated.
- Infant outcomes should be reported on the appropriate CRF.
- An Infant PTID should be created in Rave for all live births. In the event of a stillbirth if it is feasible to collect cord blood samples an Infant PTID number is also required.
- When preparing for an infant exam ensure that you
  - Plan assessments in advance
  - Supplies are laid out and within reach
  - Room is warm and well lit
  - Mother is informed and comfortable
  - Provider has washed hands
- Assess for any infant danger signs
  - stopped feeding well,
  - history of convulsions,
  - fast breathing,
  - severe chest in-drawing,
- no spontaneous movement,
- temperature >37.5°C,
- temperature <35.5°C
- any jaundice in first 24 hours of life, or yellow palms and soles at any age

- Complete infant examination in a systematic, step-wise manner and assess
  - Physical appearance
  - Length
  - Weight
  - Skin
  - Head (including fontanels and circumference)
  - Face (including mouth)
  - Neck
  - Chest
  - Abdomen and anus
  - Hips and genitalia
  - Arms, legs, fingers, and toes
  - Spine
  - Auscultation of chest
  - Neurologic assessment

- The following tools may assist with infant assessments
  - Video Guide to a Stepwise Surface Examination of Newborns
  - Global Birth Defects App for the assessment and classification of birth defects
  - Complete Examination of the Newborn. Effective Perinatal Care Geneva: World Health Organization
    [https://apps.who.int/iris/bitstream/handle/10665/43601/9789241595070_B_enq.pdf?sequence=2&isAllowed=y](https://apps.who.int/iris/bitstream/handle/10665/43601/9789241595070_B_enq.pdf?sequence=2&isAllowed=y)
    [https://www.who.int/publications/i/item/WHO-MCA-17.07](https://www.who.int/publications/i/item/WHO-MCA-17.07)

- To note only major structural congenital anomalies that per the WHO definition have significant medical, social or cosmetic consequences for the affected individual, and typically require medical intervention should be reported. E.g. cleft lip and spina bifida. Major structural anomalies are the conditions that account for most of the deaths, morbidity and disability related to congenital anomalies. In contrast, minor congenital anomalies, although more prevalent among the population, are structural changes that pose no significant health problem in the neonatal period and tend to have limited social or cosmetic consequences for the affected individual. E.g single palmar crease and
clinodactyly. See WHO Birth defects surveillance A manual for program managers 2nd edition [https://iris.who.int/bitstream/handle/10665/337425/9789240015395-eng.pdf?sequence=1] for more information

- In version 3.0, 4.0 and 5.0 all pregnant participants required follow-up of their infants until one year of age (for convenience this was linked to a week 48 visit), including those not in step 4d. In version 5, we have clarified what information we are seeking over the first 12 months of infant life. Specifically, we would like updates on any SAEs, growth parameters, and congenital anomalies. This information will be captured on the Ultrasound-OLE, Pregnancy Outcome-OLE, Infant Assessment form, for all live births in addition to the, Adverse Events- Infants form, where applicable.

- For participants in step 4d only, infant sample collection is required at visits specified in the protocol.
  - Ideally, a staff member with pediatric experience should collect infant samples to minimize discomfort and ensure adequate sample collection.

- For infants in step 4d, Infant adverse events should be discussed with CMC if these are considered related to potential product exposure. The CMC will provide guidance on product administration in these situations.

For missed injections during step 4d, consult the CMC.
Toxicity Management Diagrams (Only applies to direct recipients of study product)

General Guidance*

[Diagram]

*General Guidance applies only to toxicities not addressed under Guidance on Toxicity Management for Specified Toxicities
General Guidance*

* General Guidance applies only to toxicities not addressed under Guidance on Toxicity Management for Specified Toxicities

Any grade 3 or higher clinical or laboratory AE observed prior to their first injection of active CAB (i.e. in STEP 4b) will prompt consultation with the CMC prior to any injectable dosing.

¥ Investigator should re-evaluate the participant until resolution of the toxicity.

If study product is temporarily or permanently discontinued have participants return any pills as soon as possible.
General Guidance*

*General Guidance applies only to toxicities not addressed under Guidance on Toxicity Management for Specified Toxicities. Any grade 4 or higher clinical or laboratory AE observed prior to their first injection of active CAB (i.e., in STEP 4b) will prompt permanent study product discontinuation.
Guidance on Toxicity Management for Specified Toxicities
Nausea, Vomiting, and Diarrhea*

- Grade 1 and 2
  - Continue Study Product

- Grade ≥ 3
  - Temporarily discontinue study product

- Related to Study Product?
  - Yes
    - Is the AE Grade ≤ 2 within 7 days?
      - Yes
        - Resume Study Product
      - No
        - Consult the CMC for guidance
  - No

*For all grade levels, treat symptomatically
Guidance on Toxicity Management for Specified Toxicities
ALT Elevations
Oral CAB

Grade ≥ 3

- Report to the CMC
- Refest every two weeks until ALT ≤ Grade 1
- The CMC may direct an alternate interval for follow-up or return to clinical care

Cannot enter the injection phase of the study. Permanently discontinue from the study
Guidance on Toxicity Management for Specified Toxicities
ALT Elevations
Oral open label TDF/FTC

Grade ≥ 3 → Consult the CMC for guidance
Guidance on Toxicity Management for Specified Toxicities
ALT Elevations
Injectable CAB

- Repeat testing as soon as possible
- Retest every two weeks until ALT < Grade 1
- Report to the CMC, and the CMC may direct an alternate interval for follow-up or refer to clinical care with study termination

Grade ≥ 3

Permanently discontinue study product
Guidance on Toxicity Management for Specified Toxicities
Creatinine Clearance
Only applicable to Oral label TDF/FTC

Adverse events related to creatinine clearance should be based on examination of BOTH the absolute creatinine clearance AND the change in creatinine clearance from baseline (Enrollment/Visit 2.0).

- **Estimated CrCl < 60 mL/min**
  - Temporarily discontinue study product
  - Consult the CMC
  - Confirm calculated clearance within 1 week of receiving test results

- **Confirmed Calculated CrCl < 60 mL/min**
  - Permantly discontinue study product
  - Notify the CMC

- **Retesting CrCl ≥ 60 mL/min**
  - Consult the CMC for guidance
  - If it’s determined that case has stabilized, frequency of follow-up testing could decrease, and study product may resume
Guidance on Toxicity Management for Specified Toxicities
Injection Site Reactions (ISRs)

- Manage ISR discomfort symptomatically (e.g., cold/warm compress, acetaminophen, ibuprofen) Recommended interventions include:
  - Pre-treatment (prior to injection administration) warm compresses
  - Topical or oral pre-treatment with NSAID preparations, unless contraindicated
  - Immediate post-injection massage to injection location
  - Post-treatment warm or cold compresses
  - Post-treatment NSAID or other analgesic preparations, topically or orally
Guidance on Toxicity Management for Specified Toxicities: CPK

- **Grade 3**
  - Continue study product until repeat test results are available
  - Repeat assessment within 2-4 weeks.

- **Grade 4**
  - Continue study product until repeat test results are available if the elevation is thought to be possibly related to study product
  - Repeat assessment after abstaining from exercise for more than 24 hours. For persistent Grade 4 elevations possibly related to product follow on study/ off study product.
Guidance on Toxicity Management for Specified Toxicities
Allergic Reactions

- Grade 1 or 2
  - Continue Study Product

- Grade ≥ 3
  - Related to Study Product?
    - Yes
      - Permanently discontinue study product
    - No
      - Consult the CMC for guidance
Appendix 9a: HPTN 084 Cheat Sheet for Transitioning PPTs from V2.0 to V3.0

Note: Contact the CMC if there is any doubt whatsoever.

*Participants can choose CAB up until and including week 24, thereafter no changes to CAB allowed per protocol.

<table>
<thead>
<tr>
<th>Participant Status under v2.0 Protocol</th>
<th>Participant Options under v3.0</th>
<th>Where to Transition the Participant Under v3.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPT on TDF/FTC with no contraindications chooses between:</td>
<td>joining v3.0, staying on TDF/FTC</td>
<td>Start with Step 4c</td>
</tr>
<tr>
<td></td>
<td>joining v3.0, transitioning to CAB LA</td>
<td>Offer oral lead in (Step 4a) and straight to injection (Step 4b); Participant chooses; After completing Step 4b move to Step 4c</td>
</tr>
<tr>
<td></td>
<td>joining v3.0, does not want to take either product</td>
<td>Start with Step 4c, but without study product administration</td>
</tr>
<tr>
<td></td>
<td>not joining v3.0</td>
<td>Complete termination procedures</td>
</tr>
<tr>
<td>PPT on CAB LA with no contraindications chooses between:</td>
<td>joining v3.0, staying on CAB LA</td>
<td>Start with Step 4c</td>
</tr>
<tr>
<td></td>
<td>joining v3.0, transitioning to TDF/FTC</td>
<td>Start with Step 4c</td>
</tr>
<tr>
<td></td>
<td>joining v3.0 but does not want to take either product</td>
<td>Start with Step 4c, but without study product administration</td>
</tr>
<tr>
<td></td>
<td>not joining v3.0</td>
<td>Complete termination procedures</td>
</tr>
<tr>
<td>PPT who is confirmed HIV+ on v2.0 chooses between:</td>
<td>joining v3.0</td>
<td>Consent to v3.0. Contact the HIV alias AND the CMC. Follow their guidance for PPT management.</td>
</tr>
<tr>
<td></td>
<td>not joining v3.0</td>
<td>Complete termination procedures</td>
</tr>
<tr>
<td>PPT on the Contraceptive Sub-study chooses between:</td>
<td>joining v3.0 and continuing on contraceptive sub-study</td>
<td>Have PPT sign the ICF signature block for continuing the sub-study, Contact the CMC for PPT management</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NOTE: participants are permitted to change contraceptive method.</td>
</tr>
<tr>
<td>Participant Status under v2.0 Protocol</td>
<td>Participant Options under v3.0</td>
<td>Where to Transition the Participant Under v3.0</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>joining v3.0 and stopping the contraceptive sub-study</td>
<td>Have PPT sign the ICF signature block for declining the sub-study</td>
<td>Manage PPT as regular study PPT</td>
</tr>
<tr>
<td>not joining v3.0</td>
<td>Complete termination procedures</td>
<td></td>
</tr>
<tr>
<td>PPT on Annual Testing Schedule, with no safety contraindications, chooses between:</td>
<td>joining v3.0, taking TDF/FTC</td>
<td>Start with Step 4c</td>
</tr>
<tr>
<td></td>
<td>joining v3.0, wanting to take CAB LA</td>
<td>Offer oral lead in (Step 4a) and straight to injection (Step 4b); Participant chooses; After completing Step 4b move to Step 4c</td>
</tr>
<tr>
<td></td>
<td>not joining v3.0</td>
<td>Complete termination procedures</td>
</tr>
<tr>
<td>PPT on Annual Testing Schedule, WITH SAFETY contra-indications:</td>
<td>Participant may not join v3.0</td>
<td>Complete termination procedures</td>
</tr>
<tr>
<td>Participant who discontinued study product during v2.0 for safety reasons and was transitioned to open-label TDF/FTC for 48 weeks</td>
<td>joining v3.0</td>
<td>Consent to v3.0. Contact the CMC alias. Follow their guidance for PPT management.</td>
</tr>
<tr>
<td></td>
<td>not joining v3.0</td>
<td>Complete termination procedures</td>
</tr>
<tr>
<td>PPT who was on TDF/FTC (and never took CAB LA) and who is pregnant on v2.0 at the time of site transition to</td>
<td>joining v3.0, staying on TDF/FTC</td>
<td>Start with Step 4c</td>
</tr>
<tr>
<td>(note: This PPT is not eligible for the Pregnancy and Infant Sub-Study. She was never exposed to</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Note:**

- We will follow PPTs who on v2.0 are on OL TDF/FTC due to safety discontinuations according to the v3.0 protocol, Step 5. Each PPT will complete a total of 48 weeks of TDF/FTC. So, if the PPT was at Week 36 under v2.0 she still will be at Week 36 of Step 5 under v3.0.
<table>
<thead>
<tr>
<th>Participant Status under v2.0 Protocol</th>
<th>Participant Options under v3.0</th>
<th>Where to Transition the Participant Under v3.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>version 3.0, chooses between:</td>
<td>CAB LA and elects TDF/FTC for the pregnancy on v3.0.</td>
<td>Site staff to consult CMC for initiating CAB LA relative to due date</td>
</tr>
<tr>
<td>joining 3.0, transitioning to CAB LA, agrees to Pregnancy and Infant Sub-Study</td>
<td>(note: This PPT is eligible for the Pregnancy and Infant Sub-Study since she is electing to take CAB LA on v3.0. In fact, she must agree to join the Pregnancy and Infant Sub-Study for safety monitoring if she wants to take CAB LA.)</td>
<td>Offer oral lead in (Step 4a) and straight to injection (Step 4b); After completing Step 4b move to Step 4d</td>
</tr>
<tr>
<td>joining v3.0, declines study product</td>
<td>Follow up on 4c without study product administration; collect outcomes at delivery and 48 weeks if possible</td>
<td></td>
</tr>
<tr>
<td>not joining v3.0</td>
<td>Complete termination procedures</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participant Status under v2.0 Protocol</th>
<th>Participant Options under v3.0</th>
<th>Where to Transition the Participant Under v3.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPT who was on CAB LA (and had at least one CAB LA injection) and who is pregnant on v2.0 at the time of site transition to version 3.0, chooses between:</td>
<td>joining v3.0, staying on TDF/FTC for the pregnancy, declines Pregnancy and Infant Sub-Study</td>
<td>Start with Step 4c</td>
</tr>
<tr>
<td>(note: This PPT is eligible for Pregnancy and Infant Sub-Study because she had at least one CAB LA injection on the v2.0 protocol. However, she may choose not to join the Sub-Study if she takes TDF/FTC during pregnancy.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participant Status under v2.0 Protocol</td>
<td>Participant Options under v3.0</td>
<td>Where to Transition the Participant Under v3.0</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>--------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>joining v3.0, staying on TDF/FTC for the pregnancy, and agrees to join the Pregnancy and Infant Sub-Study (note: This PPT is eligible for Pregnancy and Infant Sub-Study because she had at least one CAB LA injection on the v2.0 protocol.)</td>
<td></td>
<td>Start with Step 4d</td>
</tr>
<tr>
<td>joining v3.0, transitioning to CAB LA and joining the Pregnancy and Infant Sub-Study (note: Any PPT who is eligible and elects to take CAB LA during pregnancy must join the Pregnancy and Infant Sub-Study for safety monitoring.)</td>
<td></td>
<td>Site staff to consult CMC for initiating CAB LA relative to due date. Offer oral lead in (Step 4a) and straight to injection (Step 4b); After completing Step 4b move to Step 4d</td>
</tr>
<tr>
<td>not joining v3.0</td>
<td></td>
<td>Complete termination procedures; if possible, try to at least get pregnancy outcome information</td>
</tr>
<tr>
<td>Participant who had a laboratory AE on either CAB or TDF/FTC and not discontinued but tests not required in new SOE</td>
<td>Transition to product choice</td>
<td>Follow up AE until grade 1; testing is acceptable under clinical care. Contact the CMC for guidance.</td>
</tr>
</tbody>
</table>
Appendix 9b: HPTN 084 Cheat Sheet for PPT transitions from V3.0 to V4.0

Not all participants who were followed under the first OLE (v3.0 of the protocol) are eligible for the v4.0 protocol (OLE2).

Below are the most common scenarios sites will encounter when transitioning PPTs from the v3.0 amendment to the v4.0 amendment. Please note that sites may have participants who do not fall neatly into the below categories; when that occurs the site must contact the CMC for transition guidance.

<table>
<thead>
<tr>
<th>Participant Status under v3.0 Protocol at the Consent Visit for v4.0</th>
<th>How to Manage PPT Under v4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Pregnant, PPT on Step 4c TDF/FTC</td>
<td>Has the PPT completed 48 weeks of TDF/FTC during the first OLE?</td>
</tr>
<tr>
<td>yes</td>
<td>Do not consent to v4.0 Release PPT from the study and transition to local HIV PrEP program</td>
</tr>
<tr>
<td>no</td>
<td>Consent to v4.0 Continue following PPT until step 4c completed full 48 weeks of TDF/FTC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not Pregnant, in Step 4c PPT on CAB LA</th>
<th>Does the PPT wish to continue CAB LA?</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>Consent to v4.0 Continue following PPT on the appropriate Week of Step 4c (so that the PPT receives the full 48 weeks of CAB LA) Once the Step 4c SOE is completed move the PPT to Step 6 for the full 48 weeks of CAB LA.</td>
</tr>
<tr>
<td>no</td>
<td>Consent to v4.0 Continue following PPT on the appropriate Week of Step 4c (so that the PPT receives the full 48 weeks of CAB LA) Once 48 weeks of step 4c completed, transition to TDF/FTC on Step 5 to cover the PK tail</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not Pregnant, on step 5</th>
<th>Completed step 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>Release participant from study</td>
</tr>
<tr>
<td>no</td>
<td>Consent to v4</td>
</tr>
<tr>
<td>Participant Status under v3.0 Protocol at the Consent Visit for v4.0</td>
<td>How to Manage PPT Under v4.0</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Not Pregnant, PPT seroconverted</td>
<td></td>
</tr>
<tr>
<td>Has participant had infection confirmed, been linked to care and evidence of viral suppression on ART confirmed</td>
<td>yes</td>
</tr>
</tbody>
</table>
| | no | Consent to v4.0  
| | | Continue to follow up with PPT until infection status confirmed, and/or participant referred to ART and viral suppression is confirmed, then release PPT from the study. |
| Pregnant, on Step 4c and taking TDF/FTC |                                |
| Step 4c visits completed? | yes | Consent to v4.0  
| | | Once the Step 4c SOE is completed move the PPT to Step 5 for the full 48 weeks of TDF/FTC. Collect pregnancy outcome information |
| | no | Continue following PPT on the appropriate week of Step 4c. Once the Step 4c SOE is completed move the PPT to Step 5 for the full 48 weeks of TDF/FTC. Collect pregnancy outcome information |
| Pregnant, on Step 4d taking CAB LA or TDF/FTC and being followed |                                |
| Visits in step 4d completed? | yes | Consent to v4.0  
| | | Consult CMC regarding continuation on step 6 |
| | no | Consent to v4.0  
| | | Continue following PPT on the appropriate week of Step 4d until 48 weeks post delivery, then consult CMC about step 6 |
Appendix 9c: Example SOP for the management of pregnancy

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<th>Supersedes Version:</th>
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<th>Prepared/Revised By</th>
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<table>
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<tr>
<th>Approved By</th>
<th>Signature</th>
<th>Date</th>
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<thead>
<tr>
<th>Annual Review By</th>
<th>Signature</th>
<th>Date</th>
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<tbody>
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</table>

**DOCUMENT HISTORY**

<table>
<thead>
<tr>
<th>Version</th>
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<th>Changes</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>
I. Purpose
To describe the procedures regarding management of participants who become pregnant.

II. Scope
This SOP applies to all [site] staff that manage the study participants who are pregnant such as study PI’s, Coordinator, Counselors, Nurses and Clinicians. This procedure applies to all studies. Specifics for the HPTN 084 study are included below in the Addendum.

III. Responsibilities
1. Clinicians
   a. To correctly identify clinical situations requiring obstetric care
   b. To deliver appropriate obstetric care to the participant and refer accordingly.
   c. To inform referral facility staff of the participant’s arrival.
2. Nurses
   a. To perform nursing duties to facilitate the appropriate obstetric care and monitoring to the participant
3. Community Educators
   a. Tracing participants and tracking medical records
4. HTS Counsellors
   a. Providing HIV testing and counselling
5. Clinic Aides
   a. Sample transportation and escorting participants to [XXXXX].

IV. Allowable Exceptions
This SOP is meant to be followed without deviation. However, it is an allowable exception to follow procedures specified in a protocol or Study Specific Procedure Manual (SSP) that may supersede this SOP.

1. BACKGROUND:
   [Site Name] CRS has extensive experience in research involving pregnant women and therefore already has existing collaborations and structures that will ensure the study participants have access to antenatal care including delivery and postnatal care. [XXX] has [XX] Obstetricians (Drs. XXXXX and XXXX) who are available to do obstetric scans for gestational age assessment as well as fetal anomaly scan [within the study site or referred to XXXX].

   The study site has a memorandum of understanding and strong working relationship with staff at the referral facilities in XXXX and therefore the study team will be able to access hospital records whenever required. The site team through its community educators will closely trace all participants referred for further care to obtain copies of medical records.

V. PROCEDURES
1. Referral of pregnant participants for antenatal care (ANC)
   1. To ensure access to antenatal care during pregnancy, a participant with a confirmed pregnancy on 2 different samples collected will be counselled about the need to
attend antenatal care services as required per XXXX Ministry of Health Guidelines. The pregnant participant will be referred for antenatal care to their health facility of choice. The study clinic will refer the participant for all applicable pregnancy-related services and will provide participant a referral letter to the antenatal care services detailing participation in the trial; certified copy of referral letter must be kept on participant file. However, the site will not be responsible for paying for pregnancy-related care.

2. We shall encourage participants to attend antenatal care at [XXX]. These facilities are affiliated with the site and we hope this will enable the site to collect the hospital records and the required samples at delivery as per the HPTN 084 study requirements.

3. Pregnant participants will be escorted by study community educator to register for antenatal care if necessary. The community educator will confirm that participant is enrolled in antenatal care as feasibly possible.

4. Pregnant participants will be asked to share their antenatal care records and certified copies of these will be made and kept in the participant chart. In the event that the participant is unable to bring the antenatal care records, the community educator will confirm from the health facility and obtain as much information as possible. This will only be done following verbal permission from the participant.

5. The study clinician will offer early monitoring to a participant who becomes pregnant and will refer participant for an ultrasound scan and evaluation, within 12 weeks of gestation.

6. Dating ultrasound scans for participants will be conducted by [XXXX]. All enrolled participants will be booked for a review by the obstetrician and will be scanned accordingly using a standard case report form. In cases where the site Obstetrician is not available, the participant may be referred for dating ultrasound scan at [XXXX]. Study clinicians (non-specialists) who are trained and certified to provide obstetric ultrasound scans may be allowed to offer the services as long as this is allowable by the study protocol and they are listed accordingly on the delegation of duty log. The Ultrasound scan reports will be given to the study participant and a copy of these will be kept on the participant chart.

- The Ultrasound will include the following reporting capabilities and parameters:
  1. Number of fetuses
  2. Ultrasound-estimated gestational age on the date of scan*
  3. Estimated date of delivery based on the scan
  4. Viability of fetus (heartbeat)
  5. Fetal abnormality
  6. Additional comments, if applicable

*Estimated gestational age should be measured via
  - First Trimester Crown-Rump length
  - Later Trimesters
    - Femur length
    - Abdominal circumference
    - Biparietal diameter OR Head circumference
- Trans cerebellar diameter (optional if the other biometry is present)

In the event that the participant comes to the study clinic with an ultrasound scan performed outside these providers; an ultrasound scan with all the above required parameters will be acceptable and a certified copy will be made and kept on the participant chart. A ultrasound scan will be repeated in case some parameters above are missing.

7. The study staff will discuss with the pregnant participant their delivery plan as they come for their scheduled visits. The participants will be encouraged to inform the study staff in case of any changes in their delivery plans. These delivery plans will enable the study staff to plan accordingly for the participant to ensure that the required samples at delivery are collected and the participant receives adequate care during their delivery as per the national guidelines.

8. For planning purposes, the study site will create schedules for expectant mothers with their expectant delivery dates (EDDs) and these will be shared with the community educators. The community educators will keep in contact with these participants and send reminders for required study visits and also regarding their delivery plans. Mothers will be asked to contact the study site at onset of labor or when admitted in hospital for delivery or any other complications.

9. Referral for obstetric complications will be made to [XXXX]. The site has already existing working relationship with [XXXX] team and two site Obstetricians who also provide clinical care at [XXX]. The site Obstetricians that are affiliated with [XXXX] will be contacted in case of any complications. Consultations will be done for non-study related complications of pregnancy and delivery, abnormalities on fetal ultrasound, birth outcomes and phenotyping of abnormalities etc.

10. Management of all obstetric emergencies will be done per site S.O.P XXXXX on Medical and Obstetric Emergencies. Pregnant participants with obstetric complications will be escorted by the clinic aide to [XXXX] to ensure they are worked on adequately. This will also enable easy follow up of participant in the hospital and access to their medical records as per permission from the hospital and the study participant.

11. The study site will consult Dr. [XXXXX] for birth outcomes and phenotyping of abnormalities noted during study follow up.

12. All efforts will be made to ensure that participants are followed up to ascertain outcome of pregnancy and appropriate study CRFs will be completed. Participants who are pregnant at the termination visit will continue to be followed until the pregnancy outcome is ascertained in consultation with the study clinical management teams.

2. Referral of pregnant participants and seroconverters for Prevention Mother To Child Transmission (PMTCT) of HIV programs
1. Refer to **SOP XXXX HIV Seroconversion** for guidance on participants who seroconverts during study follow up. A participant may be identified as being pregnant and a seroconverter (or possible seroconverter) in one of three ways.
   - A participant known to be pregnant (already off study drug) has a positive rapid HIV test.
   - A known seroconverter (already off study drug) has a positive pregnancy test.
   - A participant has a positive rapid HIV test and a positive pregnancy test at the same visit.
2. All pregnant HIV-1 positive participants will be referred by a study clinician to ANC health facilities with PMTCT services. Appropriate counseling concerning pregnancy and the importance of PMTCT will be provided at the study clinic by the study clinician and HTC counsellors.
3. The pregnancy and HIV test result information will be availed on the referral form to the health workers at the PMTCT Antenatal clinic. This will be documented on the participant’s chart and a certified copy of the referral form kept on the participants file.
4. Infant feeding counseling will be provided for HIV infected women by study clinician. As per WHO/[XXXX] Ministry of Health current guidelines, mothers known to be HIV-infected (and whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complementary foods thereafter, and continue breastfeeding for the first 12 months of life. Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast milk can be provided. The mother may still choose not to breastfeed and this is acceptable. The study counselors may also provide this counseling.

### 3.0 ADDENDUM FOR HPTN 084 STUDY

#### 3.1 Background

HPTN084/LIFE is a phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women.

During HPTN 084, women were required to be on a long-acting, reversible contraceptive (LARC). This was because we did not know how well CAB LA worked in women and a report from Botswana was released raising the possibility that a drug called dolutegravir (DTG) may have caused a very serious birth defect of the spinal cord and the brain in women who were taking DTG at the time they became pregnant for treatment of HIV. DTG is similar to CAB LA so we wanted to be careful during HPTN 084. Ever since the first Botswana report, doctors have continued to monitor babies born to mothers who have taken DTG during pregnancy. It now seems much less likely that DTG was the cause of the birth defects in babies. We now know that the difference in the rate of birth defects in mothers who took DTG and those that used other antiretrovirals for HIV treatment is essentially the same. Other studies that study large groups of pregnant women that use medications, including DTG during have not found this problem. CAB LA is not the same as DTG. CAB LA has not been shown to cause birth defects in animal studies. In blinded portion of HPTN 084 there were 50 confirmed pregnancies; none of the babies born to women in HPTN 084 had any birth defects.

Now that we know that CAB LA is safe and works to prevent HIV in women, we no longer will require study participants to use a LARC during this study.
Study staff will talk with participants about ways to avoid pregnancy if they wish to do so.

Addressing the use of CAB LA for HIV PrEP in pregnancy is important and timely. Women in high HIV prevalence settings may be at increased risk for HIV when planning to conceive, and need HIV prevention options, like PrEP that go beyond condoms. Pregnancy may also be a vulnerable period for HIV acquisition. Pregnancy and breastfeeding are periods marked by significant biological and behavioral changes that may have varying effects on the risk of HIV.

Preventing HIV in high-risk populations who are also at risk for pregnancy remains a priority for reducing both maternal and infant morbidity and mortality. As access to PrEP expands, data on the safety, acceptability and dosing requirements of PrEP agents during pregnancy are a priority.

Data on the safety and PK of CAB LA in pregnant women compared to non-pregnant women are critical. In particular, data on PK are important for informing the need for dose adjustments in pregnancy. Data on CAB LA concentrations in breastmilk are extremely limited. In pre-clinical pre- and post-natal development studies in female rats, no effect of CAB on lactation was seen at any dose. There was also no effect on rat pup growth and development, or AEs with exposure to CAB in maternal milk.

The HPTN 084 amendment provides an opportunity to offer participants the chance to reconsent to active CAB LA dosing during pregnancy and breastfeeding, while ensuring adequate monitoring of safety in both mother and infant. These data will provide important information on acceptability, tolerability, safety and PK of CAB LA during pregnancy and breastfeeding prior to wide scale implementation in demonstration projects and national programs where extensive monitoring may be limited.

3.2 Precautions taken to prevent pregnancy in HPTN084

3.2.1 Contraceptive requirements in the Open label extension (OLE) of the study;

Pregnancy prevention in the OLE is optional. Following counselling, a participant can decide to remain on family planning or stop family planning. Participants that opt to stop family planning will continue receiving study product depending on the choice of study product they will choose during the OLE. Participants that opt for a family planning method will receive it at the study clinic where possible and in case they receive it outside the clinic, we shall request for a copy of the family planning card or documents so that we can update the concomitant med Log and contraceptive Log in Medidata appropriately.

3. Procedures for HPTN 084 Pregnant Participants

1. All pregnancies that occur during the course of the study must be reported to the CMC within seven (7) days of site awareness (either upon confirmation by urine or blood pregnancy testing during a study visit or as reported by the participant between study visits). The CMC will now be contacted following the first positive pregnancy test.

2. At the first pregnancy test positive visit, participants will have their pregnancy confirmed on a second independent sample that could be taken off on the same day.

3. Participants should be counselled about the risks and benefits of continuing CAB through pregnancy and breastfeeding, and offered an opportunity to re-consent to receive CAB LA injections during pregnancy. Participants who need more time to consider their
decision can have their CAB LA injection temporarily deferred, within the remaining visit window.

4. Participants who decline to continue CAB LA during pregnancy and breastfeeding will be offered Open Label (OL) TDF/FTC.

5. All pregnant participants who have had at least one CAB LA injection will be followed up in accordance with the pregnancy schedule of evaluations in Step 4d. CAB LA injections will be administered every eight weeks in those that consent. Additional safety assessments and PK samples will be collected at study visits four weeks after every injection.

6. At delivery, a maternal blood sample and cord blood sample will be collected from the mother, and where feasible an infant blood sample will be collected (week 0).

7. During the post-partum period, blood and breastmilk samples will be collected from the mother, and blood samples from the infant per the Step 4d SOE. Infant outcomes will be assessed at delivery up to approximately 12 months later (Week 48 of Step 4d).

8. Participants who do not have a live birth outcome will be followed up in accordance with Step 4c visits. Pregnancy outcome data will still be collected in these participants at the time of the pregnancy outcome.

9. Participants who have never received a CAB LA injection will be followed up through Step 4c and through to pregnancy outcome. They will remain on the Step 4c SOE.

10. All participants who complete Steps 4c or d will have the option to link to a CAB LA access program or local HIV prevention program if preferred.

4.0 Tracking and documentation of pregnancy outcomes

4.1 All efforts will be made to ensure that participants are followed up to ascertain outcome of pregnancy. Participants who are pregnant at the termination visit will continue to be followed until the pregnancy outcome is ascertained or, in consultation with CMC, it is determined that the pregnancy outcome cannot be ascertained. In the event that a pregnant participant is lost to follow up, this will be documented on the CRF and source documents.

2. Data will be collected on outcomes of all participant pregnancies and recorded on appropriate study CRFs. Whenever possible, medical records documenting pregnancy outcomes will be obtained, photocopied and certified and filed in participant’s study records.

3. For all pregnancies which do not continue to term or end in stillbirth, data on the timing and nature of the loss will be recorded, including whether termination was spontaneous or elective.

4. Pregnancy outcomes meeting criteria for AE and/or EAE reporting per protocol will be reported accordingly (see HPTN084 Safety monitoring and reporting SOP).

5.0 Procedures for delivery, collection and processing of required samples at delivery

5.1 Study staff will encourage pregnant participants to deliver at XXX which is in the same facility as XXXX. XXX already has an existing MOU with XXXX allowing the conduct of several studies within the hospital. The study site will obtain clearance from the hospital to work with the HPTN084 study team on the pregnancy infant study. Each pregnant participant who consents to participate in the pregnancy infant sub study will also be asked to provide verbal permission to access her medical records at the point of consent to participate in the pregnancy infant sub study. This will be documented in the participant chart notes.

5.2 Since the management of pregnant participants will follow the standard of care, the site will on case by case support participants in need beyond the standard of care.
5.3 Part time midwives at XXX will be contracted by XXX to support pregnant participants as
contact persons when participants report in for ANC or labor and deliver to inform study staff
when needed. These midwives will be trained on the study prior to their addition to the Delegation
of duties Log. After adequate training and delegation, they will collect the study samples as
required at delivery.
5.6 Processing of samples collected at delivery; the protocol requires that the samples collected at
delivery for participants in the pregnancy infant sub study are processed within 6 hours of sample
collection. The samples that will be collected at XXX will be primarily processed by the XXX
Lab. The samples will be transported in cooler boxes as soon as possible within the allowable
protocol time by the XXX staff. These staff who transport the samples will be trained and
delegated to do so on the study delegation of duties Log.
5.7 We however anticipate that some of the deliveries will be occur outside the XXX lab
operational times. In such instances;
   • The study staff will keep in contact with the contracted midwives at XXXX and
     inform the XXXX Lab about any pregnant participants in labor that will not have
delivered by 5.30pm on a daily basis so that the XXXX study team can prepare
accordingly and have staff available to ensure samples collected at delivery are
transported to the Lab and processed within the allowable 6 hour period.
   • For any participant who reports to the hospital in labor outside the XXX Lab
     operational time, the contracted midwives at XXX will be requested to inform the
study staff as soon as possible with details on labor progress so that arrangements are
made accordingly.
   • Special support will be provided to the XXXX staff that will be required to deliver
     the samples to XXXX Lab processing staff who will ensure the samples collected are
     adequately processed within the required time as per SOE.
5.8 In case the site is unable to collect or process required samples at delivery for a participant as
required, CMC will be informed and protocol deviation will be reported accordingly. This also
applies to participants that will deliver in health facilities where we are unable to get the required
samples at delivery.

5.9 Sample collection in the postpartum period; Postpartum samples will be collected at XXXXXXX
clinic. Transport will be provided using the UNCPM vehicles. Mother and baby in the postpartum
period will be picked up and taken back home for their scheduled visits to ease their movements.

6.0 Procedures for Infant assessments in HPTN 084
6.1 Pregnancy outcome assessment including abbreviated infant examination will be conducted
at week 8 and week 48 postpartum. Whenever feasible, site will use delivery notes plus complete
assessment in clinic.
6.2 Infant feeding history will also be collected at weeks 8, 16 and 24 postpartum. These will be
documented in the chart notes.
6.3 Infant HIV testing will be performed if the mother is confirmed to have HIV infection. If
HIV testing indicates that an infant has HIV infection, a second confirmatory visit should be
conducted to confirm HIV infection in the infant. If infant infection is confirmed, resistance testing
should be performed locally using a separate (additional) infant sample collected for this purpose.
6.4 Cord blood and infant plasma collection and storage will be conducted at delivery and weeks
2,4,8,16,24 and 48. Assessments on stored samples will be performed retrospectively; results will
not be returned to study sites or participants, except as noted in the SSP. These samples will be
used for PK analysis and may be used for other assessments, including virology testing.
6.5 In the event that an infant is sick, the site will manage the infant accordingly, document in the required CRFs. Those that need referral will be referred for care as per national guidelines.

**Training Date and Method**

Unless otherwise specified:
1. All new or revised SOPs are presented at the next study team meeting. The IoR has ultimate responsibility for study conduct, including appropriate training of study staff. The CRS Coordinator or designee is responsible for assisting the IoR in training staff that are absent from study team meetings.
2. All staff are responsible for reviewing all SOPs yearly.
3. New employees are responsible for job specific SOPs within 30 days of hire and all SOPs within 90 days of hire.
Section 10. Adverse Event Reporting and Safety Monitoring

10.1 Overview of Section 10

This section contains information related to Adverse Event (AE) reporting and safety monitoring for HPTN 084. The following resources are relevant to AE reporting:

- DAIDS Table for Grading Adult and Pediatric Adverse Events, corrected version 2.1 dated July 2017
- Current Investigational Brochure (IB) for oral and injectable cabotegravir (CAB)
- Current Truvada® (emtricitabine/tenofovir disoproxil fumarate) Package Insert (PI)
- Sections 5.0 and 6.0 and Toxicity Management (in Appendix VIII of the HPTN 084 protocol as well as any accompanying Clarification Memos (CMs) or Letters of Amendment (LoAs)).

Safety Monitoring, Review, and Oversight

Primary safety monitoring of study participants is primarily the responsibility of study staff, under the direction of the Investigator of Record (IoR). The IoR and designated study staff are responsible for submitting required e-forms to the HPTN Statistics and Data Management Center (SDMC) and Expedited Adverse Event (EAE) reports to DAIDS, to ensure relevant safety data are available in a timely manner.

Safety monitoring bodies for this study include the Clinical Management Committee (CMC), SDMC Clinical Safety Associates, Independent Safety Reviewer (ISR), DAIDS Safety Office and Medical Officer, and the Study Monitoring Committee (SMC).
Descriptions of these groups and their responsibilities can be found in Section 14 and 15 of the HPTN MOP: https://www.hptn.org/resources/manual-of-operations.

10.2 Adverse Event

AEs are defined in Appendix VIII, Section 6 of the HPTN 084 protocol. This AE definition applies to all participants from the time a participant is enrolled/randomized to the point in time when the participant terminates from the study.

10.3 Documenting Adverse Events

Site staff are responsible for documenting all AEs reported or observed in study participants, regardless of presumed attribution, seriousness or severity, in the study source documentation. All AEs will be graded according to the DAIDS Table for Grading Adult and Pediatric Adverse Events, corrected version 2.1 dated July 2017 (referred to herein in this section as the “DAIDS Toxicity Table”). This table will be used throughout the entire study, and can be downloaded at: http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx.

Laboratory results that are outside of the normal range but are not abnormal enough to reach a Grade 1, can be identified as “NCS” (not clinically significant) in the source documentation, if determined by a study clinician.

All information obtained while conducting follow-up physical examinations, review of symptoms, and laboratory tests should be recorded in the source documentation according to site Standard Operating Procedures (SOPs). This information should be reviewed after each participant visit to determine if an AE has occurred. For events captured on the Adverse Experience Case Report Form (AE CRF), whenever possible, the final diagnosis, rather than the individual signs and symptoms, should be documented (in both the source documentation and on the AE CRF). If a diagnosis is not possible, each individual sign and symptom should be reported separately. Each site should develop a system for collecting signs, symptoms and diagnoses and ensuring that these events are captured appropriately in the source documents. All signs, symptoms and diagnoses reported as AEs must be assessed as to whether they are related or not related to study drug.

If an AE meets the criteria of a Serious Adverse Event (SAE) / EAE, see Section 10.5 below for guidance on documentation and reporting.

It should be noted that injection site reactions (ISRs) will be captured in the study database using the Injection Site Reaction e-CRF and not on the AE Log. It is important to distinguish between signs and symptoms from the actual injection procedure versus an ISR. See Section 9.4.7 of the SSP for further guidance. A participant may report an ISR at any time during the study. All ISRs are reported using the Injection Site Reaction eCRF, using the “Site Reactions to Injections and Infusions” category for grading as found in the DAIDS Toxicity Table.
10.3.1 Considerations for Pregnancy Outcome and Infant AE Reporting

Regardless of the Step a pregnant participant is followed on, first trimester ultrasound findings and pregnancy outcome data (infant growth assessment at delivery and approximately 48 weeks post birth) will be collected. Regardless of the Step, all infant SAEs that occur up to 48 weeks post-delivery will be collected and reported. Grade 2 and higher AEs will be reported into the database ONLY FOR PARTICIPANTS in STEP 4d.

What should be considered for when determining relationship to study product for infants?

Pregnancy Outcome Reporting for All Participants

All pregnancy outcomes that result in live infants are reported at delivery on the Pregnancy Outcome log. Additionally, fetal losses (i.e. spontaneous abortion, elective/therapeutic abortion, and stillbirth) are to be reported as pregnancy outcomes on a Pregnancy Outcome log. Generally, these outcomes are not reported separately as an AE. However, any complications of the pregnancy outcome (i.e. excessive bleeding, infection, etc.) that meet AE reporting criteria or pregnancy outcomes that meet SAE/EAE criteria are to be reported separately as AEs.

Infant Reporting
AE reporting for participants in Step 4d ONLY
We anticipate a fair number of infant AEs; however, it is expected that very few will be product-related. Once a baby is born the only exposure mechanism is through breast milk, and study product concentration in breast milk is small.

All AEs will be graded according to the DAIDS Table for Grading Adult and Pediatric Adverse Events, corrected version 2.1 dated July 2017.

Only Grade 2 and above infant AEs need to be reported in the database on the Infant Adverse Event form up to and including 24 weeks post-partum. Grade 1 AEs should be recorded in the chart notes but do not need to be captured in the database.

SAE Reporting for ALL participants with an infant, regardless of Step
All SAE/EAEs, including deaths and congenital anomalies, must be reported throughout Week 48 post-delivery.

If a mother has concerns about her infant, study sites will refer her to a local pediatrician.

10.4 Adverse Event Severity Grading

The severity of all AEs identified in HPTN 084 will be graded per the DAIDS Toxicity Table (link above). The term “severity” is used to describe the intensity of an AE. The severity of all AEs identified in HPTN 084 must be graded on a five-point scale:
Grade 1 = Mild
Grade 2 = Moderate
Grade 3 = Severe
Grade 4 = Potentially life-threatening
Grade 5 = Death

Severity is not the same as seriousness, which is based on the outcome or action associated with an event.

AEs not listed in the DAIDS Toxicity Table should be graded according to the “estimating severity grade” row of the table:

<table>
<thead>
<tr>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE-THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild symptoms causing no or minimal interference with usual social &amp; functional activities with intervention not indicated</td>
<td>Moderate symptoms causing greater than minimal interference with usual social &amp; functional activities with intervention indicated.</td>
<td>Severe symptoms causing inability to perform usual social &amp; functional activities with intervention indicated.</td>
<td>Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death</td>
</tr>
</tbody>
</table>
If the severity of an AE falls into more than one grading category on the Toxicity Table, assign the higher of the two grades to the AE.

If a single AE term is used as a unifying diagnosis to report a cluster of signs and symptoms, and the diagnosis is not specifically listed in the Toxicity Table, assign the AE the highest severity grade among each of the associated signs and symptoms. Record the diagnosis as the AE term and record each associated sign and symptom in the AE Log comments section.

Seasonal allergies should be graded according to the “Estimating Severity Grade for Parameters Not Identified in the Grading Table” row of the Toxicity Table (not the “acute systemic allergic reaction” row).

When grading using the “Estimating Severity Grade for Parameters Not Identified in the Grading Table” row of the Toxicity Table, note that if the condition requires treatment, it must automatically be graded at Grade 2 or higher.

10.5 AE Relationship to Study Product

When assessing an AE’s relationship to study product, the site clinician should consider the study product used.

OL1:
Step 4a- Procedures for Participants Initially Randomized to TDF/FTC Who Elect to Move to OL CAB LA with Optional Oral Lead-in first
Step 4b- Procedures for Participants Initiating or Re-starting CAB LA without the Optional Oral Lead-in; the Initial Dose Visit
Step 4c- Procedures for Participants on Maintenance Doses of CAB LA or TDF/FTC
Step 4d- Procedures for Pregnant/Breastfeeding Participants and Their Infants
Step 5- Procedures for Participants Taking OL TDF/FTC for 48 Weeks after Premature CAB LA discontinuation

If an AE onset date falls in between Steps (e.g. 4a vs. 4c or 5), the site clinician should assess the AE’s relationship to the study product used during the last completed Step in which the participant received study product.

OL2:
Step 4d- Procedures for Pregnant/Breastfeeding Participants and Their Infants
Step 5- Procedures for Participants Taking OL TDF/FTC for 48 Weeks after Premature CAB LA discontinuation
Step 6- Procedures for Participants on Maintenance Doses of CAB LA during weeks 49-96
One of the following relationship categories must be assigned to each reportable AE:

**Related:** There is a reasonable possibility that the AE may be related to the study product.

**Not related:** There is not a reasonable possibility that the AE is related to the study product.

**Note:** When an AE is assessed as “not related”, an alternative etiology, or explanation should be provided in the ‘Comments’ section of the CRF. If new information becomes available, the relationship assessment of any AE should be reviewed again and updated as required.

### 10.6 Reporting AEs to the HPTN SDMC

Using the AE Log CRFs, this study database will collect:

- Grade 1 and higher AEs for adult participants
- Grade 2 and higher AEs for infants in Step 4d up to and including 24 weeks after birth
- SAEs are reported for all infants, regardless of Step, up to and including 48 weeks post delivery
- any AE that leads to study product hold/discontinuation.

Infant AEs will be collected on the Adverse Event – Infant Log. Adult AEs will be collected on the Adverse Event Log.

Medical conditions, problems, signs, symptoms, abnormal laboratory value, and findings identified before enrollment/randomization (into the original study) but not meeting protocol exclusionary criteria were documented on the Medical History eCRF (Pre-Existing Conditions). If a condition was ongoing at the time of enrollment, it is a pre-existing condition. If this condition worsens (increases in severity or frequency) after enrollment/randomization (in the original study), the worsened condition is considered an AE. If a pre-existing condition resolves after enrollment/randomization (into the original study), but then recurs at a later date, the recurrence is considered a new AE.

For any AE at any severity grade that contributes to a temporary or permanent hold of study product, regardless of the presumed relationship, study staff should submit an AE e-Log to the HPTN SDMC and mark either “held” or “permanently discontinued” on the Action Taken with Study Product AE CRF e-Log.

If an AE increases in severity or frequency (worsens) after it has been reported on an AE Log e-CRF, the “old” AE should be marked “recovered/resoled” for the Outcome variable and the new AE should be submitted. When an AE improves to a lower severity or becomes less frequent, a new AE submission is not necessary.

Each AE identified in HPTN 084 must be followed clinically through study participation until the AE resolves (returns to baseline) or stabilizes. Please consult the CMC for
guidance on when to cease or reduce follow-up on an AE, or what constitutes “stability”. AE resolution date is the date that the condition is no longer present or stabilizes. If a participant is taking a medication to manage an AE that occurs during study participation, it is not considered resolved. If an event continues at end of study participation, the status/outcome of the AE should be updated to “not recovered/resolved.” Study sites should be prepared to have a plan to manage AEs with a severity grade of Grade 3 or higher, as well as an ALT≥3xULN PLUS total bilirubin≥2xULN, and any seizure event at end of study participation for each participant. The CMC (084cmc@hptn.org) is available for consultation of these events, if needed.

The following are tips and guidelines for assigning AE terms:

- Whenever possible, a diagnosis should be reported, rather than a cluster of signs and/or symptoms.

- Do not include information on relatedness to study product or timing of study product use in the AE term/description. Limit the AE text to the medical description and anatomical location, when needed.

- When it is not possible to identify a single diagnosis to describe a cluster of signs and/or symptoms, each individual sign and symptom must be reported as an individual AE. The term can be updated later when a diagnosis becomes available.

- When reporting a laboratory event, describe the direction of the abnormality, (e.g., decreased hemoglobin, elevated ALT).

- A specific medical term should be used whenever possible (e.g., “ulcers” instead of “sores”)

- Correct spelling for all terms should be used and site should avoid using abbreviations.

- When reporting an AE that is associated with an underlying condition, include the underlying condition in the AE term or description. For example, if a participant is experiencing pain related to an underlying cancer diagnosis, include the cancer diagnosis in the AE term or description.

- If possible, try to include the anatomical location of the event, such as, pain on the right arm.

- Procedures per se should not be reported as AEs; rather the underlying condition which leads to a procedure may be considered an AE. Any associated procedures may be considered treatments for the AE. For example, while “appendectomy” would not be considered an AE, “appendicitis” would, with “appendectomy” documented as a treatment provided for the AE. In addition, any event that occurs due to a study-related procedure should be recorded as an AE. Specify in the AE text description if the AE is related to a procedure (iatrogenic). For example, if a
participant experiences dizziness from a blood draw, then “dizziness due to blood draw” should be submitted as an AE.

- HIV seroconversion is not in of itself an AE. However, symptoms related to HIV could be categorized as an AE (e.g. fever sustained for 2 days of 39.2).

10.7 Additional Adverse Event Reporting Considerations

10.7.1 Reporting Injection Site Reactions (ISRs) and Post Injection Adverse Events (AEs)

- Injection Site Reactions should only be reported on the ISR log. If the site considers an event to be related to the injection but there is no code available on the ISR form, the event should be reported on the AE log.
- If an AE location is directly at the injection site, include the term “at injection site” in the reported Event diagnosis.
- “Local” is not a defined anatomic site.
- Recording that an AE occurred at the injection site is important, as complications at the site of study product administration are grouped separately in the coding and analysis of AEs.
- The term “post-injection” should only be used for AEs related to the injection procedure, generally occurring during or immediately after the injection procedure. “Post-injection” refers to the time after the act of delivering the study product with needle and syringe. This is distinct from an AE related to the study product. See below for examples.

<table>
<thead>
<tr>
<th>REPORT as the AE term</th>
<th>DO NOT report as the AE term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site rash</td>
<td>Rash</td>
</tr>
<tr>
<td>Post injection dizziness</td>
<td>Dizziness</td>
</tr>
</tbody>
</table>

10.7.2 Reporting procedure-related Adverse Events (AEs)

AEs that are complications of procedures belong to a separate classification (for example, complications/consequences of surgery, biopsy, or dental work). This applies to any procedure, whether or not the procedures are a part of the study. For example, infection, pain, bleeding, or lightheadedness that is a consequence of a procedure is different from these events happening spontaneously.

For an AE related to a procedure, indicate relationship to the procedure in the AE term so that the AE is classified as a procedural complication. Example:

- For a wound infection that happens directly as a result of surgery, this should be reported as “post-operative wound infection.”
### 10.7.3 Reporting laboratory abnormalities as AEs

If an abnormal laboratory test result is reported as an AE per protocol requirements, separate from any clinical diagnosis associated with the result, the type of test performed and the direction of the abnormality should be reported (e.g., elevated ALT). The specific value or the severity grade of the result should not be reported as part of the AE term. Laboratory values that fall outside of a site’s normal range but are below severity Grade 1 are not considered AEs. These out of range but below Grade 1 values are not documented as pre-existing conditions or AEs unless requested by the Investigator of Record (IoR) or designee. When assigning severity grades, note that some sites may have normal reference ranges that overlap with the severity grade ranges. Thus, it is possible for a participant to have a result that falls within the site’s normal range but is still gradable per the Toxicity Table. Assign the severity grade based on the Toxicity Table severity grade ranges, regardless of whether or not the lab result falls within the site’s normal reference range.

Lab abnormalities that meet the criteria for expedited reporting to DAIDS will be reported separately on the AE Log CRF and reported to DAIDS via the DAERS Reporting System.

Note: AEs must be followed to resolution even after a site transitions to a newer protocol version, and the newer version does not specify testing for the AE in the SOE. For example, if a participant has an AE ongoing under V3.0, but under V4.0 those same labs are not protocol specified, the site should still request those labs as part of clinical care purposes to ensure the AE returns to Grade 1 or resolves.

Sites should check the Toxicity Management section in the currently approved protocol version. If toxicities are specified in the toxicity tables, then sites must follow that guidance for AE resolution. Should sites have additional questions about AE resolution, they should contact the CMC (084cmc@hptn.org).

### 10.7.4 Reporting Recurrent Adverse Events

If an AE previously reported on an AE Log CRF resolves and then recurs at a later date, the second occurrence must be reported as a new AE on a new AE Log CRF (new log line in the study database).

Some participants may have chronic, episodic, pre-existing conditions. In these situations, if the participant experiences an episode of the condition during follow-up that has not increased in severity or frequency from the baseline condition, it is not considered an AE. For example, if a participant reports experiencing three (3) migraines a month before the study, and they continue at the same frequency and severity during the study, these migraines should not be reported as AEs.

### 10.7.5 Reporting Sexually Transmitted Infections (STIs) as Adverse Events (AEs)

When reporting sexually transmitted infections, sites need to report infections diagnosed as part of protocol-required testing for GC/CT and syphilis on the STI eCRF as well as...
the AE Log eCRF. All other STIs diagnosed as part of standard of care will be reported on the AE Log eCRF only. If sites only reported STIs in one place, is not required to report retroactively.

10.8 SAEs

ICH-E6 defines a serious adverse event (SAE) as any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,

**NOTE:** The term “life threatening” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. A grade 4 severity grading on the Toxicity Table does not necessarily mean that an event is life-threatening. When determining whether a grade 4 event meets the ICH definition of “life threatening”, consider the event in the context of any related symptoms the participant may have experienced.

- Requires in-patient hospitalization or prolongs an existing hospitalization. The following types of hospitalizations are not considered adverse events, serious or otherwise:
  - Any admission unrelated to an AE (e.g., for cosmetic procedures)
  - Admission for diagnosis or therapy of a condition that existed before randomization AND has not increased in severity or frequency since baseline.
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed above.

ICH guidance (E2A) also states that medical and scientific judgment should be exercised in deciding whether other adverse events not listed above should be considered serious.

SAEs are a subset of all reportable AEs. For each AE identified, an authorized study clinician must determine whether the AE meets the ICH definition of “serious”.

When assessing whether an AE meets the definition of serious, note that **seriousness is not the same as severity**, which is based on the intensity of the AE.

10.9 Expedited Reporting of AEs to DAIDS

Sites are responsible for reporting AEs per the Manual for Expedited Reporting of Adverse Events to DAIDS. The manual can be found at:

https://rsc.niaid.nih.gov/sites/default/files/manual-exped-aes-v2_0.pdf

All AEs that meet the definition of “serious” (SAEs), regardless of relationship to study
product, are expedited adverse events (EAE).

In addition to SAEs, sites will report in an expedited manner the following results:

- ALT $\geq 3x$ ULN AND total bilirubin $\geq 2x$ ULN (must be both at the same time in order to require expedited reporting)
- Any seizure event

This reporting is required for all participants from the time they are enrolled/randomized until their participation in the study ends. After this time, sites must report to DAIDS Serious, Unexpected, clinical Suspected Adverse Reactions (SUSAR), as defined in Version 2.0 of the DAIDS EAE Manual, if the study site becomes aware of the event on a passive basis, i.e., from publicly available information.

The study agents for the purposes of EAE reporting are: Oral CAB 30 mg tablet; CAB LA injectable suspension (600 mg/mL); TDF/FTC fixed dose combination tablet containing 200 mg of FTC and 300 mg of TDF.

Each site will use the DAIDS internet-based reporting system, DAERS (DAIDS Adverse Experience Reporting System), to report all AEs that require expedited reporting to DAIDS (see section 10.7 above for definition or refer to ). DAERS can be accessed at https://ncrms.niaid.nih.gov/.

The study Chairs and LOC staff should be notified of all EAEs and SAEs when the site reports them. To do this, sites should add the following to the report Notification Recipient list within DAERS:
Sinead Delany-Moretlwe at sdelany@whri.ac.za
Mina Hosseinipour at mina_hosseinipour@med.unc.edu
Scott Rose at srose@fhi360.org
Jennifer Farrior at jfarrior@fhi360.org

In the event of system outages or technical difficulties, expedited adverse events may be submitted via the DAIDS EAE form (paper format). This form is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting. For questions about DAERS, contact DAIDS-ES at DAIDSRCSafetyOffice@tech-res.com. Site queries may also be sent from within the DAERS application itself.

All EAEs must also be reported as AEs on the AE Log e-CRF and to be submitted to the HPTN SDMC within 72 hours of the site awareness date. When completing AE Log e-CRFs and EAE forms, study clinicians should carefully review all documentation of the event to ensure accuracy, completeness, and consistency. All AE descriptions and details (e.g., AE term, onset date, severity grade, relationship to study product) must be recorded consistently across all documents. All EAE forms received at the DAIDS Safety Office will be compared with the AE Log CRFs received at the HPTN SDMC to ensure that all key data elements are matched with consistent details.
### Table 10-1: Reference Guide for Reporting AEs and EAEs

The table below is an “at a glance” reference guide for reporting AEs to the study database at the HPTN SDMC, and AEs that also meet the definition for expedited reporting to DAIDS (EAEs). HPTN 084 will follow the SAE (Serious Adverse Event) Reporting Category for adverse events that require expedited reporting (EAEs), as defined in the Manual for Expedited Reporting of Adverse Events to DAIDS, January 2010. An SAE in this study is defined as: results in death, is life threatening, requires hospitalization, results in persistent or significant disabilities or incapacity, is a congenital anomaly/birth defect; is an important medical event – see below.

<table>
<thead>
<tr>
<th>AE</th>
<th>Report on AE Log</th>
<th>Report as EAE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SERIOUS ADVERSE EVENT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Results in death</td>
<td>Yes</td>
<td>Yes, regardless of relatedness to study drug</td>
</tr>
<tr>
<td>Is life-threatening</td>
<td>Yes</td>
<td>Yes, regardless of relatedness but does <strong>not</strong> include all Grade 4 events</td>
</tr>
<tr>
<td>Requires inpatient hospitalization or prolongation of existing hospitalization</td>
<td>Yes</td>
<td>Yes, regardless of relatedness to study drug (see Note 2 below)</td>
</tr>
<tr>
<td>Results in persistent or significant disabilities or incapacities</td>
<td>Yes</td>
<td>Yes, regardless of relatedness to study drug</td>
</tr>
<tr>
<td>Is a congenital anomaly/birth defect</td>
<td>Yes</td>
<td>Yes, regardless of relatedness to study drug</td>
</tr>
<tr>
<td>Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the above definition</td>
<td>Yes</td>
<td>Yes, regardless of relatedness to the study drug</td>
</tr>
<tr>
<td><strong>IS A REPORTABLE ADVERSE EVENT TO THE HPTN SDMC, BUT MAY OR MAY NOT ALSO BE A SERIOUS ADVERSE EVENT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 and higher AEs (adult participants)</td>
<td>Yes</td>
<td>Only if it meets the definition of an SAE as outlined above</td>
</tr>
<tr>
<td>Grade 1 AEs (infant participants)</td>
<td>No</td>
<td>Only if it meets the definition of an SAE as outlined above</td>
</tr>
<tr>
<td>Grade 2 and higher AEs (infant participants)</td>
<td>Yes</td>
<td>Only if it meets the definition of an SAE as outlined above</td>
</tr>
<tr>
<td><strong>OTHER ADVERSE EVENT IDENTIFIED FOR REPORTING</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT $\geq$ 3x ULN AND total bilirubin $\geq$ 2x ULN</td>
<td>Yes</td>
<td>Yes, regardless of relatedness to study drug</td>
</tr>
<tr>
<td>Any seizure event</td>
<td>Yes</td>
<td>Yes, regardless of relatedness to study drug</td>
</tr>
</tbody>
</table>

1: “Life-threatening” refers to an event in which the participant was at risk of death at the time of the event. It does **NOT** refer to an event that hypothetically might have caused death if it were more severe.

2: Per ICH SAE definition, hospitalization is **NOT** an adverse event (AE), but is an outcome of the event. **DO NOT REPORT: Any admission unrelated to an AE (e.g., cosmetic surgery, administrative or social admission for temporary placement for lack of a place to sleep); protocol-specified admission (e.g., for a procedure required by protocol); admission for diagnosis or therapy of a condition that existed before receipt of study agent(s) and has not increased in severity or frequency as judged by the clinical investigator.** *(NOTE: A new AIDS-defining event in a subject already known to be HIV-infected would be considered an increase in severity of a pre-existing condition [HIV infection] and would be reportable.)*

3: Clinically insignificant physical findings at births including those regarded as normal variants do **NOT** meet reporting criteria unless there is also a clinically significant anomaly being reported. Refer to the Manual for Expedited Reporting of Adverse Events to DAIDS for full details.
10.10 Social Impact Reporting

In addition to medical AEs, participants in HPTN 084 may experience social impacts — participant reported non-medical adverse consequences or benefits — as a result of their participation in the study. For example, participants could experience difficulties in their personal relationships with partners, family members, and friends, if they find out they are participating in the study. They also could experience stigma or discrimination from family members and members of their community. In the event that social impact occurs, study staff should fully document the issues or problems and make every effort to facilitate their resolution as described in this section. In addition, the social impact must be recorded on the Social Impact e-Log. As with medical AEs, follow all problems to resolution (until they no longer exist), or stabilization (they exist, but at a manageable level). Provide referrals as needed/appropriate to other organizations, agencies, and service providers that may be able to help address the problem.

If the reported social impact is associated with an AE, report the AE on the AE e-Log. If the social impact is associated with an AE that meets criteria for expedited reporting to DAIDS, report it on the AE e-Log and as an EAE. Also report the issue or problem to all IRBs/ECs responsible for oversight of HPTN 084, if required per IRB guidelines.

10.11 Product Safety Information

Once a site has completed protocol registration, it will begin to receive product safety information on the study product being used in the study. The information that the sites may receive is:

- Revised Investigator Brochures
- IND Safety Reports
- Safety Memos, reports or updates
- Other safety memoranda and updates

This information will be forwarded to the sites by the HPTN Leadership and Operations Center via an email alias set up for this purpose. Each site should maintain copies of each communication in their regulatory files. This information originates from the DAIDS Regulatory Support Center (RSC). Each email will indicate how the information is to be handled. **In many cases, this information must be submitted to the site’s IRB/EC.**

Product safety information does not require IRB/EC approval; however, sites should maintain a copy of the IRB/EC submission cover letters indicating the date of submission and identifying the content of the submission in their regulatory files. Any acknowledgements from the IRB/EC should also be filed in the regulatory file. The Investigator of Record and the Study Coordinator are responsible for reviewing this information, disseminating this information to their staff and ensuring that it is submitted to the IRB/EC.
Section 11. Laboratory and Specimen Management Procedures

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11.1 Overview of Section 11

This section contains information on the laboratory procedures performed in HPTN 084.

Laboratory procedures will be performed in a variety of settings, including:

1. Clinics
2. Local laboratories
3. The HPTN Laboratory Center (LC, Baltimore, MD, USA)
4. Other laboratories designated by the HPTN LC

Tables in this document list the time points, testing location(s), and specimen requirements for each test. In all settings, laboratory procedures will be performed according to the guidelines included in this section of the SSP and in addition study site Standard Operating Procedures (SOPs) that have been reviewed and approved by the LC. In addition, package insert instructions must be followed.

Ideally, one method, test kit, and/or combination of test kits will be used for each test throughout the duration of the study. **If for any reason a new or alternative method, kit, or test must be used after study initiation, site laboratory staff must inform the HPTN LC to determine if any test kit validation is required.**

Regardless of whether tests are performed in clinic or laboratory settings, study staff that perform the tests must be trained in proper testing and associated quality control (QC) procedures before performing the tests for study purposes; documentation of training should be available for inspection at any time.

As transmission of HIV and other infectious agents can occur through contact with contaminated needles, blood, blood products, and vaginal secretions, all study staff must take appropriate precautions when collecting and handling biological specimens. Guidance on universal precautions is available from the US Centers for Disease Control and Prevention at:

[https://www.cdc.gov/niosh/topics/healthcare/default.html](https://www.cdc.gov/niosh/topics/healthcare/default.html) and
[https://www.cdc.gov/niosh/topics/bbp/](https://www.cdc.gov/niosh/topics/bbp/)

Additional reference information can be requested from the HPTN LC. The information provided below is intended to standardize laboratory procedures for HPTN 084 across the study sites. Adherence to the specifications detailed in this section is essential to ensure that primary, secondary and exploratory endpoint data derived from laboratory testing will be considered acceptable to regulatory authorities.

11.2 Specimen Labeling

All containers into which specimens are initially collected (e.g., blood collection tubes) will be appropriately labeled according to local practices. Participant Identification (PTID) labels will be provided by the HPTN Statistical and Data Management Center (SDMC, SCHARP) if required.
for this function. Laboratory Data Management System (LDMS) Tracking Forms will also be provided for use if required although sites may use their own specimen transport documentation. The staff member who collects the samples will ensure the visit code, specimen collection date and time as well as their initials or code is documented.

More detailed information about the labeling procedures must be provided in the site’s Chain of Custody SOP.

When specimens are tested at the laboratories, any additional labeling required for in-country specimen management or chain of custody will be performed in accordance with site-specific SOPs. Stored specimens will be entered into the LDMS and labeled with LDMS-generated labels.

11.2.1 Local Specimen Processing and Storage

For samples that are processed and stored locally, each sample will be entered into the LDMS and labeled with the LDMS generated labels. If needed, any temporary labels (e.g. during plasma processing) for samples will include at least the full PTID, in addition to any other information required by lab SOPs.

11.2.2 Local Specimen Testing

Sites will follow local testing arrangements for the collection and testing of samples, this will be described in the site SOPs. All lab results must be recorded following local guidelines.

11.2.3 Remote Specimen Testing

Samples that will be sent to the HPTN LC will be entered into the LDMS and labeled with the LDMS generated labels.

11.2.4 Use of the LDMS

LDMS must be used at all sites to track specimens that will be tested, stored, or shipped off-site for testing. Detailed instructions for use of LDMS are available in the LDMS User Manual: https://www.ldms.org/resources/manuals/ Web (Cloud-Based) https://www.ldms.org/resources/ldms/web/

All sites are responsible for ensuring they are using the most recent version of LDMS. All sites must use the HPTN barcode label format in order to ensure that both the specimen ID and the global specimen ID assigned to each specimen are printed on LDMS-generated labels.

An example of a two-dimensional LDMS-generated barcode label is below:
<table>
<thead>
<tr>
<th>Windows</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Row 1</td>
<td>LDMS Specimen ID</td>
</tr>
<tr>
<td>Row 2</td>
<td>Global Specimen ID</td>
</tr>
<tr>
<td>Row 3</td>
<td>Patient Identifier (ID1) and Study/Protocol Identifier (ID2)</td>
</tr>
<tr>
<td>Row 4</td>
<td>Specimen Date or Harvest Date and Specimen Collection Time</td>
</tr>
<tr>
<td>Row 5</td>
<td>Primary Type, Additive Type, Derivative Type, and Sub Additive/Derivative Type</td>
</tr>
<tr>
<td>Row 6</td>
<td>Volume/Volume Unit and Visit/Visit Unit (VID)</td>
</tr>
<tr>
<td>Row 7</td>
<td>Other Specimen ID (if applicable)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Web</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Row 1</td>
<td>Global Specimen ID</td>
</tr>
<tr>
<td>Row 2</td>
<td>Patient Identifier (ID1) and Study/Protocol Identifier (ID2)</td>
</tr>
<tr>
<td>Row 3</td>
<td>Specimen Date or Harvest Date and Specimen Collection Time</td>
</tr>
<tr>
<td>Row 4</td>
<td>Primary Type, Additive Type, Derivative Type, and Sub Additive/Derivative Type</td>
</tr>
<tr>
<td>Row 5</td>
<td>Volume/Volume Unit and Visit/Visit Unit (VID)</td>
</tr>
</tbody>
</table>
Questions related to use of LDMS for HPTN 084 should be directed to Yaw Agyei (yagyei1@jhmi.edu).

Technical support for the general use of LDMS is available from Frontier Science. (www.LDMS.org)

**LDMS User Support at Frontier Science**
Regular Hours: 24-hour coverage 7 days a week with the exception of Select US Holidays – Thanksgiving Day, Christmas Day, New Year’s Day, Memorial Day, Independence Day. See below for contact details.

https://www.ldms.org/contact/

Phone: +1 (716) 834-0900, extension 7311

Email: ldmshelp@fstrf.org

Fax: +1 (716) 832-8448 (should be used to fax Installation Reports only)

When you contact LDMS user support, there are certain pieces of information that you can provide to help them better respond to your question. Please provide the following information in your email support:

1. **Your name**

2. **Your laboratory’s LDMS ID number**
   This is a 3-digit number assigned by Frontier Science to uniquely identify your laboratory. It appears when you start LDMS, and can also be found in the bottom-right corner of the screen.

3. **A full explanation of the issue**
   Your explanation should include any error messages or error numbers that appeared, what you were doing in LDMS at the time the issue occurred, and steps needed to reproduce the issue. The more details that you can provide, the faster LDMS User Support can help you.

4. **How you want to be contacted**
   If you want LDMS user support to call a specific telephone number, please provide that number and extension.

5. **(If applicable) The license code or challenge code being generated by LDMS**
   Note: If you are contacting user support about a license or challenge code, do not close the window with the code. Doing so will cause LDMS to generate a new code.
Below are a few other details that can also be helpful to include in your email:

1. Have there been any recent changes to the computer with LDMS, such as new hardware installed, a firewall upgrade, a network name change, or another change?

2. Are you or another user able to repeat the issue?

3. If you have LDMS installed on multiple computers, does the issue occur on all of them or does it only occur on a specific computer?

Each site using the Windows version of LDMS must export its LDMS data to Frontier Science (FSTRF) on a minimum weekly basis or whenever changes or additions are made to the LDMS database.

Exported data are used by the HPTN SDMC to generate daily Specimen Data Quality Check (SDQC) reports comparing the data from the LDMS with that entered onto the CRFs/Medidata Rave. Any discrepancies identified are included in the SDQC for each site. The HPTN SDMC reviews the discrepancy reports for critical samples (e.g., plasma needed for confirmatory HIV testing) that appear to be missing and works with the LC and site staff to undertake appropriate corrective action. All corrective action should be documented in paper-based clinic and/or laboratory records per site standards (CAPA or NTF) as appropriate and entered in the details section of LDMS. Any corrections to the LDMS need to be made following guidelines provided by FSTRF on behalf of the HPTN LC.

11.2.5 LDMS Reconciliation

All sites must follow the HPTN LC approved site-specific SOP for regular reconciliation and verification of specimens that are stored; these independent SOPs or detailed Chain of Custody procedures must be followed throughout the study. All sites must also create a monthly Primary Specimen report to submit to the HPTN LC for review. See section 11.12 for directions on how to make a primary specimen report. The report will provide the HPTN LC with the primary blood draw information for each participant logged into the LDMS. In addition, all sites must create a Specimen Log report to submit weekly to the HPTN LC for review. See section 11.12 for directions on how to make a specimen log report. The report will provide the HPTN LC with the participant, primary, and aliquot information for each of the specimens logged into the site LDMS during the week. The report also provides the condition codes, comments, and shipping information (if available) for the given specimens. In the event that the required volume or number of sample aliquots based on Sections 11.3 and 11.4 is not obtained at any time point, designated site clinic and lab staff must immediately inform the HPTN LC. The LC will liaise with the LOC, and HPTN SDMC and will provide guidance on how to respond to the problem. In addition to following this guidance, designated site and lab staff will work together to document the problem, take appropriate corrective and preventive action, and document all action taken. Reconciliation must be performed for all specimen types that are received by the laboratory and stored in the LDMS. It is the originating processing LDMS laboratory responsibility to notify subsequent laboratories with changes, corrections, and modification to LDMS entries of shipped samples e.g. DBS cards, Plasma aliquots.
11.3 Protocol related testing and sample collection

Samples will be collected and processed at the screening, enrollment, and follow up visits as indicated in tables 11-1, 11-2, 11-3.

Participants who have received at least one injection and refuse further injections or discontinue due to an AE will enter Step 3 and be followed on open-label TDF/FTC according to Step 3 as indicated in table 11-3.

Participants who are unable to receive the first injection for any reason will be terminated from the study. If the reason is due to HIV infection, those participants will be referred for care and will be terminated from the study.

Collect specimens and label tubes according to manufacturer recommendations and local regulations as well as the Blood Collection, Breast milk, Cord blood, and Urine Collection SOPs. Blood collection tubes must be filled to the appropriate fill level as indicated by the tube manufacturer. After collection:

- EDTA tubes should be gently inverted at least 8 times (or as specified by manufacturer) after specimen collection, to prevent clotting.
- EDTA collections must be performed after samples collected for serum chemistry testing.
- For plasma storage, 20 mL of whole blood should be collected into spray dried EDTA tubes, e.g. BD 366643 or other, to yield 5 x 1.8mL plasma aliquots.
- For Pharmacogenomic testing, a minimum of 1mL of whole blood should be collected in an EDTA tube.
- For Cord blood, collect in a 5mL K2EDTA tube, to yield 2 X 1.0ml plasma aliquots.
- For infant collections, collect 750uL to 1ml K2EDTA to yield 300uL of plasma.
- Breast milk will be collected in sufficient quantity to store a minimum of 3 mL of whole breast milk.
Table 11-1: Schedule of Study Visits and Specimen Collection – Step 1. Screening, Enrollment, Week 2 and 4.

<table>
<thead>
<tr>
<th>Test and Procedure</th>
<th>Screening</th>
<th>Day 0 Enrollment</th>
<th>Week 2</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing¹</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy testing²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>HBV and HCV testing³</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC with Differential</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry testing (BUN/urea, creatinine, CPK, calcium, phosphorous, glucose, amylase and lipase)</td>
<td>Creatinine only</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Liver Function Test (AST, ALT, total bilirubin, alkaline phosphatase)</td>
<td>ALT and Total Bilirubin only</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fasting Lipid Profile⁴</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis serological testing</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GC/CT and TV testing⁵</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinalysis (protein and glucose)⁶</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma Storage⁷</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage⁷</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole blood storage⁷</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional sample storage for participants enrolled in the Injectable Contraception Sub-Study⁷</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

---

¹ Following the HIV algorithms described in SSP figures 11.1 to 11.3, section 11.3. RNA testing for acute HIV must be negative and must be performed within 14 days of enrolling the participant. At least one HIV test must be available the same day as sample collection and before product is administered. HIV testing does not need to be performed after confirmation of HIV infection (based on results from samples collected on two separate dates).

² Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a negative result is obtained and the participant is still pregnant.

³ At Screening: HBsAg and HCV antibody testing. At Enrollment: HBsAb and HBcAb total testing. Note: These tests can all be done at Screening at the discretion of the IOR.

⁴ The fasting lipid profile includes total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.

⁵ GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab.

⁶ Urinalysis may be performed in the clinic or the laboratory. Results from urinalysis are not needed prior to enrollment.

⁷ See section 11.4 for plasma processing and storage instructions; section 11.6 for DBS processing and storage instructions; section 11.7 for whole blood storage instructions; section 11.5 for Injectable Contraception sub-study storage instructions. Blood must be collected prior to study product administration during the visit. Also, record the date that the participant’s LARC was last injected/inserted. Whole blood collection and storage is only required for participants who consent to genetic testing.
Table 11-2: Schedule of Study Visits and Specimen Collection – Step 2. Blinded Injections and Daily Oral Pills

<table>
<thead>
<tr>
<th></th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 9</th>
<th>Week 13</th>
<th>Week 17</th>
<th>Week 21</th>
<th>Week 25</th>
<th>Week 33</th>
<th>Week 41</th>
<th>Week 42</th>
<th>Week 49</th>
<th>Week 57</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing(^1)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy testing(^2)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HCV antibody testing</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CBC with Differential</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry testing (BUN/urea, creatinine, CPK, calcium, phosphorous, glucose, amylase and lipase)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>LFT (AST, ALT, total bilirubin, alkaline phosphatase)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fasting Lipid Profile(^3) (Total Cholesterol, HDL, LDL, Triglycerides)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Syphilis serological testing</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Urine GC/CT and TV testing(^4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td>X</td>
</tr>
<tr>
<td>Urinalysis (protein and glucose)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Plasma Storage(^5)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage(^5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Additional sample storage for participants enrolled in the injectable Contraception Sub-study(^5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

1 Following the HIV algorithms described in SSP figures 11.1 to 11.3, section 11.3.1. At least one HIV test must be available the same day as sample collection and before product is administered. HIV testing does not need to be performed after confirmation of HIV infection (based on results from samples collected on two separate dates). Additional HIV testing may be requested by the 084HIV alias.

2 Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant.

3 Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.

4 GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab.

5 See section 11.4 for plasma processing and storage instructions; section 11.6 for DBS processing and storage instructions; section 11.5 for Injectable Contraception sub-study storage instructions. Whole blood collection and storage is only required for participants who consent to genetic testing.
Table 11-2 (Cont’d): Schedule of Study Visits and Specimen Collection – Step 2. Blinded Injections and Daily Oral Pills

<table>
<thead>
<tr>
<th>Test</th>
<th>Week 65</th>
<th>Week 73</th>
<th>Week 81</th>
<th>Week 89</th>
<th>Week 97</th>
<th>Week 105</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy testing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HCV antibody testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC with Differential</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry testing (BUN/urea, creatinine, CPK, calcium, phosphorous, glucose, amylase and lipase)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>LFT (AST, ALT, total bilirubin, alkaline phosphatase)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fasting Lipid Profile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>(Total Cholesterol, HDL, LDL, Triglycerides)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis serological testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urine GC/CT testing and TV testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urinalysis (protein and glucose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Plasma Storage</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Additional sample storage for participants enrolled in the injectable Contraception Sub-study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Following the HIV algorithms described in SSP figures 11.1 to 11.3, section 11.3.1. At least one HIV test must be available the same day as sample collection and before product is administered. HIV testing does not need to be performed after confirmation of HIV infection (based on results from samples collected on two separate dates). Additional HIV testing may be requested by the 084HIV alias.

2 Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant.

3 Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.

4 GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab.

5 See section 11.4 for plasma processing and storage instructions; section 11.6 for DBS processing and storage instructions; section 11.5 for Injectable Contraception sub-study storage instructions. Whole blood collection and storage is only required for participants who consent to genetic testing.
Table 11-2 (Cont’d): Schedule of Study Visits and Specimen Collection – Step 2. Blinded Injections and Daily Oral Pills

<table>
<thead>
<tr>
<th></th>
<th>Week 113</th>
<th>Week 121</th>
<th>Week 129</th>
<th>Week 137</th>
<th>Week 145</th>
<th>Week 153</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing(^1)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy testing(^2)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HCV antibody testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CBC with Differential</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry testing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>(BUN/urea, creatinine, CPK, calcium, phosphorous, glucose, amylase and lipase)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LFT</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>(AST, ALT, total bilirubin, alkaline phosphatase)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting Lipid Profile(^3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>(Total Cholesterol, HDL, LDL, Triglycerides)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis serological testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urine GC/CT testing and TV testing(^4)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Urinalysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>(protein and glucose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma Storage(^5)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage(^5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

\(^1\) Following the HIV algorithms described in SSP figures 11.1 to 11.3, section 11.3.1. At least one HIV test must be available the same day as sample collection and before product is administered. HIV testing does not need to be performed after confirmation of HIV infection (based on results from samples collected on two separate dates). Additional HIV testing may be requested by the 084HIV alias.

\(^2\) Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant.

\(^3\) Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.

\(^4\) GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab.

\(^5\) See section 11.4 for plasma processing and storage instructions; section 11.6 for DBS processing and storage instructions.
### Table 11-2 (Cont’d): Schedule of Study Visits and Specimen Collection – Step 2. Blinded Injections and Daily Oral Pill

<table>
<thead>
<tr>
<th>Test</th>
<th>Week 161</th>
<th>Week 169</th>
<th>Week 177</th>
<th>Week 185</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing(^1)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy testing(^2)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HCV antibody testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC with Differential</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry testing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>(BUN/urea, creatinine, CPK, calcium, phosphorous, glucose, amylase and lipase)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LFT</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>(AST, ALT, total bilirubin, alkaline phosphatase)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting Lipid Profile(^3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Total Cholesterol, HDL, LDL, Triglycerides)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis serological testing</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine GC/CT testing and TV testing(^4)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinalysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(protein and glucose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma Storage(^5)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage(^5)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

---

\(^1\) Following the HIV algorithms described in SSP figures 11.1 to 11.3, section 11.3.1 HIV testing does not need to be performed after confirmation of HIV infection (based on results from samples collected on two separate dates). Additional HIV testing may be requested by the 084HIV alias.

\(^2\) Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant.

\(^3\) Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.

\(^4\) GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab.

\(^5\) See section 11.4 for plasma processing and storage instructions; section 11.6 for DBS processing and storage instructions.
Table 11-3: Schedule of Study Visits and Specimen Collection – Step 3. Open Label TDF/FTC Daily Oral (Post-Last Injection)

<table>
<thead>
<tr>
<th></th>
<th>Step 3 Day 0</th>
<th>Step 3 Week 12</th>
<th>Step 3 Week 24</th>
<th>Step 3 Week 36</th>
<th>Step 3 Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing¹</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy testing²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry testing³</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver function testing⁴</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis testing</td>
<td>X³</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GC/CT and TV testing⁶</td>
<td>X³</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma storage⁷</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage⁷</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

¹ Following the HIV algorithms described in SSP figures 11.1 to 11.3, section 11.3.1. At least one HIV test must be available the same day as sample collection and before product is administered. HIV testing does not need to be performed after confirmation of HIV infection (based on results from samples collected on two separate dates). Additional HIV testing may be requested by the 084HIV alias.

² Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant.

³ Chemistry testing includes: BUN/Urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.

⁴ Liver function testing includes: AST, ALT, TBili, and alkaline phosphatase.

⁵ Skip Day 0 if testing has occurred within the last 3 months of Day 0 and do only at Weeks 24 and 48.

⁶ GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab.

⁷ See section 11.4 for plasma processing and storage instructions; section 11.6 for DBS processing and storage instructions.
Table 11-4: Additional Procedures: Participants who have a Reactive or Positive HIV test at any time after Enrollment

<table>
<thead>
<tr>
<th>Procedure</th>
<th>HIV Confirmation visit</th>
<th>Post HIV + Week 12</th>
<th>Post HIV + Week 24</th>
<th>Post HIV + Week 36</th>
<th>Post HIV + Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 cell count.</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV viral load testing</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV resistance testing&lt;sup&gt;3&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry testing&lt;sup&gt;2&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(BUN/Urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, lipase)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>LFT&lt;sup&gt;3&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(AST, ALT, total bilirubin, alkaline phosphatase)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Plasma Storage&lt;sup&gt;4,5&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage&lt;sup&gt;5&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>The week 48 visit should be timed as closely as possible to 52 weeks after the participant received their last injection.

<sup>2</sup>The HIV confirmatory visit must be held on a different day from the visit where the participant had their initial reactive/positive HIV test. The testing algorithm for the HIV Confirmation Visit is provided in the SSP Manual. If HIV rapid testing is included in the HIV testing algorithm, this testing may be performed in the clinic or the laboratory. Additional HIV testing may be requested by the 084HIV alias.

<sup>3</sup>Sites may collect specimens for resistance testing at a local laboratory to assist with clinical management; results from resistance testing performed at local laboratories will not be reported to the SDMC. Stored plasma may not be used real-time/local resistance testing; additional samples must be collected for this testing.

<sup>4</sup>Stored plasma will be used for Quality Assurance testing and other assessments at the HPTN LC (see Section 9). Assessments will be performed retrospectively; results will not be returned to study sites or participants, except as noted in Section 9.0.

<sup>5</sup>See section 11.4 for plasma processing and storage instructions; section 11.6 for DBS processing and storage instructions.

The Seroconversion Committee (084HIV@hptn.org) must be notified immediately and study drug should be discontinued if one or more reactive HIV test results are obtained on the Laboratory based test at enrollment or at any follow up visit after enrollment. The procedures listed for Weeks 12, 24, 36, and 48 apply only to participants with confirmed HIV infection during Step 2 of the study. Participants with confirmed HIV infection in Step 3 of the study may undergo similar procedures and will be determined by the members of the 084HIV@hptn.org. Note that participants who acquire HIV infection during Step 1 will permanently discontinue study product, will be terminated from the study, and referred for HIV related care. The additional blood draw for HIV testing and plasma storage at the HIV confirmation visit should be performed on a different date than the blood draw that gave the initial reactive or positive HIV test.
Table 11-5: Schedule of Study Visits and Specimen Collection: For Pregnant Participants

<table>
<thead>
<tr>
<th>WEEKS in Study</th>
<th>4 weeks after first positive pregnancy test</th>
<th>Quarterly Visit 1 (12 weeks since first positive pregnancy test)</th>
<th>Quarterly Visit 2 (24 weeks since first positive pregnancy test)</th>
<th>Quarterly Visit 3 (36 weeks since first positive pregnancy test)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LOCAL LABORATORY EVALUATIONS &amp; PROCEDURES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV testing(^1)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy testing(^2)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry testing(^4)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver function testing(^5)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis testing</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal GC/CT and TV Testing(^3)</td>
<td>X(^7)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma storage(^6)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

\(^1\) The HIV testing algorithm is provided in the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory. At least one HIV test must be available the same day as sample collection and before product is administered.

\(^2\) Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant. If the confirmatory pregnancy test is positive, the participant is referred for an Ultrasound and evaluation by an obstetric specialist at about 12-14 weeks gestational age, for other testing, counseling, and management. Further biochemical blood testing may be done as indicated. All findings and outcomes will be collected and reported.

\(^3\) GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab.

\(^4\) BUN/urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.

\(^5\) AST, ALT, TBili, and alkaline phosphatase.

\(^6\) Stored plasma will be used for Quality Assurance testing and other assessments at the HPTN LC (see Section 9). Assessments will be performed retrospectively; results will not be returned to study sites or participants, except as noted in Section 9.0.

\(^7\) If not done within 4 weeks of initial positive pregnancy test.
Table 11-6: Schedule of Evaluations - Step 2, Injectable Contraceptive Substudy ONLY

<table>
<thead>
<tr>
<th>Weeks in study</th>
<th>5</th>
<th>6</th>
<th>9</th>
<th>13</th>
<th>21</th>
<th>25</th>
<th>33</th>
<th>41</th>
<th>42</th>
<th>49</th>
<th>57</th>
<th>65</th>
<th>73</th>
<th>81</th>
<th>89</th>
<th>97</th>
<th>105</th>
<th>113</th>
<th>121</th>
<th>129</th>
<th>137</th>
<th>145</th>
<th>153</th>
<th>161</th>
<th>169</th>
<th>177</th>
<th>185</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Plasma storage</td>
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<td>DBS</td>
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</tbody>
</table>

1. Additional stored plasma will be used for PK evaluations and DMPA, NET-EN, Etonogestrel
2. Blood must be collected prior to study product administration during the visit. Also, record the date that the participant’s LARC was last injected/inserted.
11.3.1 Open Label (OL) Cabotegravir samples.

Table 11-7: Schedule of Evaluations - Step 4a, Participants initially randomized to TDF/FTC who elect to move to OL CAB LA with optional Oral Lead-In First.

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>DAY 0/ of Step 4a</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing(^2)</td>
<td>X</td>
</tr>
<tr>
<td>HIV viral load testing(^3)</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy testing(^1)</td>
<td>X</td>
</tr>
<tr>
<td>CBC with differential,</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry testing(^4)</td>
<td>X</td>
</tr>
<tr>
<td>Liver function tests(^5)</td>
<td>X</td>
</tr>
<tr>
<td>Fasting lipid profile,</td>
<td>X</td>
</tr>
<tr>
<td>Plasma storage(^7,8)</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage(^8)</td>
<td>X</td>
</tr>
</tbody>
</table>

\(^1\) Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant.

\(^2\) HIV rapid testing may be performed in the clinic or the laboratory. At least one HIV test must be available the same day as sample collection and before product is administered.

\(^3\) This testing will be performed for all study participants, regardless of HIV status or the results of other HIV tests. This testing must be performed with an assay with a lower limit of quantification of 50 copies/mL or lower.

\(^4\) Albumin, BUN/urea, creatinine. Additional testing may be required if abnormalities of clinical significance are detected.

\(^5\) AST, ALT, total bilirubin.

\(^6\) Total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.

\(^7\) Stored plasma may be used for Quality Assurance testing, possible HSV-2 testing and other assessments at the HPTN LC.

\(^8\) Assessments on stored samples will be performed retrospectively; results will not be returned to study sites or participants, except as noted in the SSP.
### Table 11-8: Schedule of Evaluations - Step 4b, Participants initiating or re-starting CAB LA without the optional Oral Lead-In; the initial Dose Visit.

<table>
<thead>
<tr>
<th>Test Description</th>
<th>DAY 0/ of Step 4b</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing(^1)</td>
<td>X</td>
</tr>
<tr>
<td>HIV viral load testing(^2)</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy testing(^3)</td>
<td>X</td>
</tr>
<tr>
<td>CBC with differential, if not done in Step 4a</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry testing(^4)</td>
<td>X</td>
</tr>
<tr>
<td>Liver function tests(^5)</td>
<td>X</td>
</tr>
<tr>
<td>Fasting lipid profile, if not done in Step 4a(^6)</td>
<td>X</td>
</tr>
<tr>
<td>Plasma storage(^7,8)</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage(^8)</td>
<td>X</td>
</tr>
</tbody>
</table>

1 Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant.

2 HIV rapid testing may be performed in the clinic or the laboratory. At least one HIV test must be available the same day as sample collection and before product is administered.

3 This testing will be performed for all study participants, regardless of HIV status or the results of other HIV tests. This testing must be performed with an assay with a lower limit of quantification of 50 copies/mL or lower.

4 Albumin, BUN/urea, creatinine. Additional testing may be required if abnormalities of clinical significance are detected.

5 AST, ALT, total bilirubin.

6 Total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.

7 Stored plasma may be used for Quality Assurance testing, possible HSV-2 testing and other assessments at the HPTN LC.

8 Assessments on stored samples will be performed retrospectively; results will not be returned to study sites or participants, except as noted in the SSP.
Table 11-9: Schedule of Evaluations - Step 4c, Participants on maintenance Dose of CAB LA or TDF/FTC

<table>
<thead>
<tr>
<th>Time on OL Study Product</th>
<th>Week 0 of Step 4c</th>
<th>Week 8</th>
<th>Week 16</th>
<th>Week 24</th>
<th>Week 32</th>
<th>Week 40</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing(^2)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HIV viral load testing(^3)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy testing(^4)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CBC with differential, if not done in Step 4a or 4b</td>
<td>X(^5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Chemistry testing,</td>
<td>X(^4)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Liver function testing(^6)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fasting lipid profile(^7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Syphilis testing</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Vaginal GC/CT and TV testing(^8)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Urinalysis (protein, glucose)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Plasma storage(^8,9,10)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage(^9)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

\(^1\) Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant.

\(^2\) HIV rapid testing may be performed in the clinic or the laboratory. At least one HIV test must be available the same day as sample collection and before product is administered.

\(^3\) This testing will be performed for all study participants, regardless of HIV status or the results of other HIV tests. This testing must be performed with an assay with a lower limit of quantification of 50 copies/mL or lower.

\(^4\) Albumin, BUN/urea, creatinine. Additional testing may be required if abnormalities of clinical significance are detected.

\(^5\) Only for those who did not have this collected in steps 4a and 4b

\(^6\) AST, ALT, total bilirubin.

\(^7\) Total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.
GC/CT and TV testing to be done only if not performed in the past 3 months. GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab. If a woman is menstruating, the swab may be collected at a later visit and all testing using the swab may be performed at that later visit.

Stored plasma may be used for Quality Assurance testing, possible HSV-2 testing and other assessments at the HPTN LC.

Assessments on stored samples will be performed retrospectively; results will not be returned to study sites or participants, except as noted in the SSP.
### Table 11-10: Schedule of Evaluations - Step 4d, Participants who become pregnant during step 4 and who received at least one CAB LA injection.

<p>| Time on Pregnancy and Infant Sub-study | Week 0 | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24 | Week 28 | Week 32 | Week 36 | Week 40 | Delivery | Week 2, pp | Week 4, pp | Week 8, pp | Week 16, pp | Week 24, pp | Week 32, pp | Week 40, pp | Week 48, pp |
|---------------------------------------|--------|--------|--------|---------|---------|---------|---------|---------|---------|---------|---------|---------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| HIV testing(^1)                     | X      | X      | X      | X       | X       | X       | X       | X       | X       | X       | X       | X       | X        | X        | X        | X        | X        | X        | X        | X        |
| HIV viral load testing (^2)         | X      | X      | X      | X       | X       | X       | X       | X       | X       | X       | X       | X       | X        | X        | X        | X        | X        | X        | X        | X        |
| Pregnancy testing (^3)              |        |        |        |         |         |         |         |         |         |         |         |         | X        | X        | X        | X        | X        | X        | X        | X        | X        | X        |
| CBC with differential                 | X      |        |        |         |         |         |         |         |         |         |         |         | X        | X        | X        | X        | X        | X        | X        | X        | X        | X        |
| Chemistry testing (^4)              | X      | X      | X      |         |         |         |         |         |         |         |         |         | X        | X        | X        | X        | X        | X        | X        | X        | X        | X        |
| Liver function testing (^5)         | X      | X      | X      |         |         |         |         |         |         |         |         |         | X        | X        | X        | X        | X        | X        | X        | X        | X        | X        |
| Syphilis testing                      | X      | X      |        |         |         |         |         |         |         |         |         |         | X        | X        | X        | X        | X        | X        | X        | X        | X        | X        |
| Vaginal GC/CT and TV testing (^6)   | X      |        |        |         |         |         |         |         |         |         |         |         | X        | X        | X        | X        | X        | X        | X        | X        | X        | X        |
| Urinalysis (protein, glucose)         | X      |        |        |         |         |         |         |         |         |         |         |         | X        | X        | X        | X        | X        | X        | X        | X        | X        | X        |</p>
<table>
<thead>
<tr>
<th>Time on Pregnancy and Infant Substudy</th>
<th>Week 0</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 20</th>
<th>Week 24</th>
<th>Week 28</th>
<th>Week 32</th>
<th>Week 36</th>
<th>Week 40</th>
<th>Delivery</th>
<th>Week 2, pp</th>
<th>Week 4, pp</th>
<th>Week 8, pp</th>
<th>Week 16, pp</th>
<th>Week 24, pp</th>
<th>Week 32, pp</th>
<th>Week 40, pp</th>
<th>Week 48, pp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma storage&lt;sup&gt;7,8.&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Breastmilk storage&lt;sup&gt;8,9.&lt;/sup&gt;</td>
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<tr>
<td>DBS storage for women on TDF/FTC only&lt;sup&gt;8,10.&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Infant assessment</td>
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<tr>
<td>Infant HIV testing, if the mother has one or more reactive/positive HIV test result&lt;sup&gt;11&lt;/sup&gt;.</td>
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<tr>
<td>Cord blood storage&lt;sup&gt;8,12&lt;/sup&gt;</td>
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<tr>
<td>Dried Blood spot storage&lt;sup&gt;8,12&lt;/sup&gt;</td>
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</tbody>
</table>
NOTE: PK analysis will be performed on cord blood and infant plasma samples at an offsite laboratory.

1 HIV rapid testing may be performed in the clinic or the laboratory. At least one HIV test must be available the same day as sample collection and before product is administered.

2 This testing will be performed for all study participants, regardless of HIV status or the results of other HIV tests. This testing must be performed with an assay with a lower limit of quantification of 50 copies/mL or lower.

3 Pregnancy testing may be done if indicated. Pregnancy testing may be performed in the clinic or the laboratory. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant.

4 Albumin, BUN/urea, creatinine. Additional testing may be required if abnormalities of clinical significance are detected.

5 AST, ALT, total bilirubin.

6 GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab. If a woman is menstruating, the swab may be collected at a later visit and all testing using the swab may be performed at that later visit.

7 Stored plasma may be used for Quality Assurance testing, possible HSV-2 testing and other assessments at the HPTN LC.

8 Assessments on stored samples will be performed retrospectively; results will not be returned to study sites or participants, except as noted in the SSP.

9 Breastmilk collection does not need to be performed if the mother is not breastfeeding or producing milk.

10 DBS will be stored for participants who elect to receive TDF/FTC. Processing and storage procedures will be described in detail in the SSP. Assessments will be performed retrospectively; results will not be returned to study sites or participants.

11 Perform infant HIV testing at this visit and all subsequent study visits using local infant testing algorithms if the mother has one or more reactive/positive tests, even if HIV infection in the mother is not confirmed. If HIV testing indicates that an infant has HIV infection, a second confirmatory visit should be conducted to confirm HIV infection in the infant. If infant infection is confirmed, resistance testing should be performed locally using a separate (additional) infant sample collected for this purpose.

12 Stored cord blood, DBS, and plasma samples will be used for PK analysis and may be used for other assessments, including virology testing. Results from this testing will not be returned to the study sites or participants.
Table 11-11: Schedule of Evaluations - Step 5, Participants taking OL TDF/FTC for 48 weeks after premature CAB LA discontinuation.

<table>
<thead>
<tr>
<th>Time in Step 5</th>
<th>Step 5, Day 0*</th>
<th>Step 5, Week 12</th>
<th>Step 5, Week 24</th>
<th>Step 5, Week 36</th>
<th>Step 5, Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing¹</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HIV viral load testing²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy testing³</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry testing⁴</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Liver function testing⁵</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Syphilis testing</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>GC/CT and TV testing⁶</td>
<td>X⁷</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Plasma storage⁷,⁸</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage⁸</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

¹ HIV rapid testing may be performed in the clinic or the laboratory. At least one HIV test must be available the same day as sample collection and before product is administered.
² This testing will be performed for all study participants, regardless of HIV status or the results of other HIV tests. This testing must be performed with an assay with a lower limit of quantification of 50 copies/mL or lower.
³ Pregnancy testing may be done if indicated. Pregnancy testing may be performed in the clinic or the laboratory. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant.
⁴ Albumin, BUN/urea, creatinine. Additional testing may be required if abnormalities of clinical significance are detected.
⁵ AST, ALT, total bilirubin.
⁶ GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab. If a woman is menstruating, the swab may be collected at a later visit and all testing using the swab may be performed at that later visit.
⁷ Stored plasma may be used for Quality Assurance testing, possible HSV-2 testing and other assessments at the HPTN LC.
⁸ Assessments on stored samples will be performed retrospectively; results will not be returned to study sites or participants, except as noted in the SSP.
Table 11-12: Schedule of Evaluations – Participants with Reactive/Positive HIV tests during OL portion of the trial

<table>
<thead>
<tr>
<th>Participants who acquire HIV infection</th>
<th>HIV Confirmation Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing(^1)</td>
<td>X</td>
</tr>
<tr>
<td>CD4 cell count</td>
<td>X</td>
</tr>
<tr>
<td>HIV viral load testing(^2)</td>
<td>X</td>
</tr>
<tr>
<td>HIV resistance testing(^3)</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry testing(^4)</td>
<td>X</td>
</tr>
<tr>
<td>Liver function testing(^5)</td>
<td>X</td>
</tr>
<tr>
<td>Plasma storage(^6,7)</td>
<td>X</td>
</tr>
<tr>
<td>DBS Storage(^7)</td>
<td>X</td>
</tr>
</tbody>
</table>

\(^1\) The HIV confirmatory visit must be held on a different day from the visit where the participant had their initial reactive/positive HIV test. The testing algorithm for the HIV Confirmation Visit is provided in the SSP Manual. If HIV rapid testing is included in the HIV testing algorithm, this testing may be performed in the clinic or the laboratory. Additional HIV testing may be requested by the 084HIV alias committee.

\(^2\) This testing must be performed with an assay with a lower limit of quantification of 50 copies/mL or lower.

\(^3\) Sites may collect specimens for resistance testing at a local laboratory to assist with clinical management; results from resistance testing performed at local laboratories will not be reported to the SDMC. Stored plasma may not be used for real-time/local resistance testing; additional samples must be collected for this testing.

\(^4\) Required chemistry testing: Albumin, BUN/urea, creatinine

\(^5\) Required LFTs: AST, ALT, total bilirubin

\(^6\) Stored plasma will be used for Quality Assurance testing and other assessments at the HPTN LC.

\(^7\) Assessments on stored samples will be performed retrospectively; results will not be returned to study sites or participants, except as noted in the SSP. Additional HIV testing may be requested by the 084 HIV alias committee.
** Table 11-13: Schedule of Evaluations – Step 6, Participants on Maintenance Doses of CAB LA weeks 49-96 (or Weeks 49-112) **

<table>
<thead>
<tr>
<th>Time in Step 6 **</th>
<th>Week 56</th>
<th>Week 64</th>
<th>Week 72</th>
<th>Week 80</th>
<th>Week 88</th>
<th>Week 96</th>
<th>Week 104</th>
<th>Week 112</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV testing²</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HIV viral load testing³</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy testing, only if indicated¹</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry testing⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Liver function testing⁶</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Syphilis testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>GC/CT and TV testing⁶</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Plasma storage⁷,⁸</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DBS storage⁸</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

** Participants will flow from Step 4c into Step 6. **

1. Urine will only be collected when needed for pregnancy testing or for GC/CT testing. Pregnancy testing will only be conducted when clinically indicated and for participants who are either not on birth control or who have had a lapse in birth control coverage. Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant. If a participant has a positive pregnancy test, and is eligible, follow her according to the Step 4d SOE.

2. HIV rapid testing may be performed in the clinic or the laboratory. At least one HIV test must be available the same day as sample collection and before product is administered.

3. This testing will be performed for all study participants, regardless of HIV status or the results of other HIV tests. This testing must be performed with an assay with a lower limit of quantification of 50 copies/mL or lower.

4. Albumin, BUN/urea, creatinine. Additional testing may be required if abnormalities of clinical significance are detected.

5. GC/CT and TV testing to be done only if not performed in the past 3 months. GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab. If a woman is menstruating, the swab may be collected at a later visit and all testing using the swab may be performed at that later visit.

6. AST, ALT, total bilirubin.

7. Stored plasma may be used for Quality Assurance testing, possible HSV-2 testing and other assessments at the HPTN LC.

8. Assessments on stored samples will be performed retrospectively; results will not be returned to study sites or participants, except as noted in the SSP.

### 11.3.2 HIV Testing
All HIV test results from previous visits, and at least one HIV test result from the current visit, must be available and reviewed prior to administration of study products. If any of these tests is reactive/positive, study drug should not be administered. **HIV rapid testing must be performed the same day and prior to administration of study drug.**

HIV testing will be performed using blood collected by phlebotomy (no finger-stick or oral fluid testing) at participant visits in accordance with the testing algorithms described in Figures 11.1 through 11.3.

For further help on implementing the HIV testing algorithm prior to study start, seek guidance from the HPTN LC.

Whole blood will be collected according to site-specific procedures.

Participants with one or more reactive HIV test results at the screening visit (Figure 11.1) or enrollment visit (see notes associated with Figure 11.2 regarding result review) will not be eligible for enrollment, regardless of subsequent test results.

RNA testing for acute HIV infection must be collected and performed within the 14 days prior to the Enrollment visit.

RNA testing must be collected and performed at all visits after enrollment.

**Every time a blood specimen is drawn for HIV testing, additional blood must be drawn for plasma storage if it does not exceed the visit blood draw limits stated in your local consent forms. This includes split visits, interim visits, and all visits for repeat HIV testing and confirmatory testing. The amount of blood drawn if not limited by consent forms should be sufficient to yield 5 x 1.8mL (approximately) plasma aliquots. See additional testing information below for split and interim visits.**

**During the open-label part of this study, both the CMC (084cmc@hptn.org) and HIV alias (084HIV@hptn.org) lists should be contacted immediately about any HIV reactive or positive results or seroconversion events) at any follow-up visit after enrollment. In certain circumstances as outlined in Appendix I Discordant-Discrepant Testing Management, the Seroconversion committee may request further testing and additional sample collections on a case by case basis. Per Appendix I, participants may be placed on product hold and the additional testing results need to be communicated to the Seroconversion Committee promptly upon receipt. In addition, select samples will be requested for further testing at the HPTN LC in order to assist with the HIV diagnosis. These samples should be shipped as soon as possible per the instructions from the Seroconversion Committee.**

Additional HIV testing may be performed at any time at the discretion of the site investigator/clinician.

All tests and associated QC procedures must be documented on local laboratory log sheets or other laboratory source documents. Kit lot numbers and expiry dates must also be documented. Note that US FDA-cleared HIV rapid tests are required.
All staff involved in HIV testing and verification of HIV test results should be aware of the testing time frame for the HIV test, so that all tests are performed, read, and confirmed within the specified time frame of testing. Place appropriate timekeeping devices in all test settings to ensure that each test is read and verified at appropriate time points. Documentation is required for the testing start and stop times, as well as, result confirmation and verification times (second trained staff member confirms initial reading). These must be recorded on testing log sheets.

If a participant has a reactive or positive HIV test, the participant will not receive additional doses of study products pending further direction regarding testing and continued participation in the study from designated study team members.

If a participant has a reactive or positive HIV test at any time after enrollment, additional blood draw and testing is required as detailed in Table 11-4.

HIV infection must be confirmed using two independent samples collected on different days. Plasma storage is required at every visit at which HIV testing is performed.

For split visits, excluding confirmation visits (held specifically to perform further HIV testing), the laboratory-based HIV EIA (4th Gen/5th Gen) and viral load assay does not need to be repeated if the split visit (i.e. x.1) occurs less than seven days from the initial visit (i.e. x.0). If the split visit is seven or more days from the initial visit, all HIV lab assay must be repeated. This also applies to DBS samples if regularly scheduled for that visit (i.e. if repeating HIV testing at seven or more days, repeat DBS collection and storage with that day’s visit). Keep all samples from all visits unless specifically directed to handle stored samples differently by the HPTN LC.

Participants with confirmed HIV infection during Step 1, prior to receipt of their first injection will have oral study product permanently discontinued and will be transitioned to local HIV-related care and terminated from the study.

Participants with confirmed HIV infection during Step 2 will not receive additional injections or oral study product and will be followed per the Schedule of Evaluations and Procedures in Appendix II of the protocol for approximately 48 weeks.

Participants with confirmed HIV infection during Step 3 will be followed quarterly, at least for the duration of Step 3, with possible additional assessments and follow-up to be determined by the members of CMC and HIV alias.

Additional samples from participants with confirmed HIV infection may be sent to a local laboratory for resistance testing to assist with clinical management (results from resistance testing performed in local laboratories should not be reported to the HPTN SDMC or the HPTN LC).
Figure 11.1  HIV Testing Algorithm at the Screening Visit

HIV Testing Algorithm at Screening*

All Participants

US FDA-cleared HIV Rapid Test\(^a\)

Reactive

Non-reactive

Laboratory based HIV Immunoassay  
(Capable of detecting HIV antigen and antibody)\(^b\)

Reactive

Non-reactive

HIV RNA Test  
for acute HIV infection\(^c\)

Reactive

Non-reactive

This individual is not eligible for enrollment if any HIV test is reactive/positive. Follow local testing guidelines to determine HIV infection status.

NOTES

* Site-specific HIV testing plans must be approved by the HPTN LC before the study opens.

* Sites that are not able to obtain HIV rapid test kits that are cleared by the US FDA may seek approval from the HPTN LC to use an alternate kit.

\(^b\) This testing must be performed using a laboratory based, non-rapid HIV immunoassay that detects both HIV antigen and HIV antibody (either a 4\(^{th}\) generation or 5\(^{th}\) generation assay).

\(^c\) Screening for acute infection should be performed using an RNA test that, in the opinion of the site investigator, is able to detect early HIV infection. If possible, the site should use an assay that is FDA-cleared for this testing, such as the APTIMA HIV-1 RNA Qualitative Assay. RNA test results must be obtained from a specimen collected within 14 days prior to enrollment.
Figure 11.2  HIV Testing Algorithm at the Enrollment Visit

**HIV Testing Algorithm at Enrollment**

- **All Participants**
  - U.S. FDA-cleared HIV Rapid Test
    - Reactive: If result back before enrollment
    - Non-reactive

- **All prior HIV tests negative/non-reactive**
  - The individual is eligible for enrollment only if this result and all HIV test results from the Screening visit are available and are non-reactive/negative.

- **Possible HIV infection**
  - This individual is not eligible for enrollment. Follow local testing guidelines to determine HIV infection status.

- **Possible HIV infection**
  - Reactive: If result back after enrolled

- **Laboratory based HIV Immunoassay**
  - (Capable of detecting HIV antigen and antibody)
  - The participant may be enrolled and the oral drug may be given before this result is available.

- **Non-reactive**
  - All HIV tests negative/non-reactive
    - This individual may continue study visits as planned

**NOTES:**

* If acute HIV infection is suspected, do not enroll the participant or administer study product at this time. In addition to following the algorithm above, the site should send a sample for an RNA test that, in the opinion of the site investigator, is able to detect early HIV infection. If possible, the site should use an assay that is FDA-cleared for early HIV diagnosis, such as the APTIMA HIV-1 RNA Qualitative Assay. The site should contact the Seroconversion Committee (084HIV@hptn.org) for additional guidance once all of the test results from this visit (including the HIV RNA test) are available.

* Sites that are not able to obtain HIV rapid test kits that are cleared by the US FDA may seek approval from the HPTN LC to use an alternate kit.

* This testing must be performed using a laboratory based, non-rapid HIV immunoassay that detects both HIV antigen and HIV antibody (either a 4th generation or 5th generation assay).

* Before providing study drug, the site must ensure that the HIV rapid test from the Enrollment visit, and all HIV results from the Screening visit are available and are negative or non-reactive.
**Figure 11.3** HIV Testing Algorithm at the Follow up Visits

HIV Testing Algorithm for Follow up Visits

- **All Participants**
  - U.S. FDA-cleared HIV Rapid Test
    - Non-reactive or negative
      - All prior HIV tests documented as Not Detected, Negative, or Non-reactive
        - This individual may continue study visits as planned
    - Reactive or positive
      - Laboratory based HIV immunoassay
        - (Capable of detecting antigen and antibody)
        - AND
        - HIV viral load (LOD <50 copies/mL)
        - Study drug may be provided before these results are available.
      - Immunoassay reactive or positive, or HIV RNA detected
      - Immunoassay non-reactive or negative and HIV RNA not detected

- **Possible HIV infection**
  - Immediately consult the seroconversion committee. Follow local testing guidelines and simultaneously consult the CMC to determine HIV infection status. Do not administer any further study product without approval from the CMC.

- **All HIV tests documented as Not Detected, Negative, or Non-reactive**
  - This individual may continue study visits as planned

**NOTES:**

- If acute HIV infection is suspected, do not administer any further study product. Immediately consult the CMC. In addition to following the algorithm above, the site should send a sample for an RNA test that, in the opinion of the site investigator, is able to detect early HIV infection. If possible, the site should use an assay that is FDA-cleared for early HIV diagnosis, such as the APTIMA HIV-1 RNA Qualitative Assay. The site should contact the Seroconversion Committee (BNNHIV@hdpn.org) for additional guidance once all of the test results from this visit (including the HIV RNA test) are available.

- This testing must be performed using a laboratory based, non-rapid HIV immunoassay that detects both HIV antigen and HIV antibody (commonly referred to previously as either a 4th generation or 5th generation assay).

- At any visit where study product will be given, the site must ensure that the HIV rapid test from this visit, and all HIV results from prior study visits are negative or non-reactive or not detected.
11.3.3 Hepatitis Testing

Testing for HBV (HBsAb, HBsAg, HBcAb total) and HCV will be performed at screening, enrollment, and other time points as dictated by tables 11-1 and 11-2. Sites will follow local testing arrangements for the collection and testing of samples, this will be described in the site SOPs.

Test results are required for the enrollment visit.

Persons with a positive HBsAg and/or HCV antibody test will be excluded from the study.

11.3.4 Safety Testing

CBC, Chemistry, and LFTs will be performed at various time points throughout the study. Sites will follow local testing arrangements for the collection and testing of samples, this will be described in the site SOPs. Participants do not have to be fasting before having blood drawn for glucose.

Test results from the screening visit are required prior to enrollment.

Same day test results are not required prior to the issue of study product.

Note: Please inform the HPTN LC and SDMC before using your back-up laboratory. Use of your back up lab may result in different reference ranges used and reported via Medidata/Rave.

11.3.5 Creatinine Clearance

The calculated creatinine clearance will be performed at all visits where creatinine testing is performed, using the Cockcroft-Gault formula.

eCcr (female in mL/min = [(140 - age in years) x (actual body weight in kg)] / (72 x serum creatinine in mg/dL) x 0.85.

For participants who join from the HPTN 084-01 protocol, the calculated creatinine clearance (estimated Glomerular Filtration Rate eGFR) will be performed using the Modified Bedside Schwartz Equation (2009). HPTN 084 leadership requested that sites continue to use this equation. This equation is validated only for individuals <18yrs of age.

eGFR = (0.413 x height)/(serum creatinine)

eGFR units are mLs/minute per 1.73m², when height is by cm and serum creatinine as mg/dL

11.3.6 Fasting Lipid Profile

A fasting lipid profile (total cholesterol, HDL, triglycerides, LDL – calculated or measured) will be collected at the enrollment, week 57, and week 105 visits. Participants should be fasting for at
least 8 [preferably 12] hours prior to sample collection. If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.

Sites will follow local testing arrangements for the collection and testing of the lipid profile. This will be described in the site SOPs.

Results from the lipid profile at the enrollment visit are NOT required prior to the issue of study product.

11.3.7 Urinalysis Testing

Sites will follow local testing arrangements for the collection and testing of urine for urinalysis (only for protein and glucose). This will be described in the site SOPs. Urinalysis results from the enrollment visit are not required prior to enrollment.

11.3.8 Pregnancy Testing

Sites will follow local testing arrangements for the collection and testing of urine, plasma, or serum for beta human chorionic gonadotropin (βHCG) pregnancy test (sensitivity of ≤ 25 mIU/mL) performed and results known the same day and before initiating the protocol-specified study product(s) at Enrollment. Pregnancy test must be confirmed to be negative PRIOR to injection/dispensing of study products. This is a requirement at all visits at which study product is to be administered or continued. Pregnancy testing is not required at subsequent visits if a woman had a positive pregnancy test at a previous visit and this has been confirmed 4 weeks after the first test, and the participant is still pregnant.

This will be described in the site SOPs.

11.3.9 Syphilis Testing

Sites will follow local testing arrangements for the collection and testing of serum or plasma for syphilis testing. This will be described in the site SOPs.

11.3.10 Urine or Vaginal Sample for GC/CT Testing

Sites will follow local testing arrangements for the collection and testing of urine/vaginal swab sample for GC/CT nucleic acid testing. This will be described in the site SOPs. GC/CT results from the enrollment visit are not required prior to enrollment.

11.3.11 Vaginal Sample for Trichomonas vaginalis (TV) Testing

Sites will follow local testing arrangements for the collection and testing of Vaginal swabs for TV (Rapid test) or Wet mount. This will be described in the site specific SOPs.

11.4 Plasma Processing for Storage Main Study

Approximately 20 mL of EDTA whole blood should be drawn into spray dried EDTA tubes for plasma storage at each time point at which HIV testing is performed as indicated in Tables 11-1 to 11-3. Sites are requested to store 5 x 1.8 mL aliquots of plasma if possible. HPTN LC should be informed at any time that three or fewer aliquots of 1.8mL or less are stored via a NTF (see Section 11.2.4)
An additional 20 mL (approximately) of EDTA whole blood will be drawn for plasma storage for participants with a reactive or positive HIV test at any time after enrollment as indicated in Table 11-4. This additional plasma will be stored in the same way.

Sites will follow the instructions below or may follow site specific SOPs for plasma processing which will include the following:

- Collect blood into lavender top blood collection tubes (EDTA) labeled with a SCHARP-provided PTID label. The sizes of tubes will be reviewed by the HPTN LC to ensure blood draws will yield the required number of aliquots for storage. An alternate, site-specific labeling process may be used if an SOP is in place, and HPTN LC approved, but still must use the PTID with other identifiers. Size and number of collection tubes may vary depending on local lab requirements.

- Deliver the samples to the local LDMS laboratory along with the LDMS Specimen Tracking Sheet or site-specific requisition that contains the required information.

- Using the LDMS Specimen Tracking Sheet or site-specific requisition, log the sample into LDMS (specimen type = BLD) and generate the appropriate number of LDMS cryovial labels. The lab should store plasma in labeled cryovials. Cryovial size must be 2.0 mL. We require the use of Sarstedt tube (#72.694.006) 2 mL cryovials, or cryovials of the same dimension. Reminder: Do not add more than 1.8 mL due to expansion of plasma during freezing. Other cryovial types may only be used if specifically approved by the HPTN LC.

- Blood processing and plasma storage should be performed within 6 hours of sample collection.

- Centrifuge tube at 800 - 1000 x g for 10 minutes to separate cells and plasma.

- Carefully remove plasma and avoid disturbing the cell layer. Transfer the plasma to an appropriately labelled sterile centrifuge tube.

- Centrifuge plasma again at 800 - 1000 x g for 10 minutes to remove any contaminating debris, cells, or platelets.

- Log samples into LDMS and generate LDMS labels (PL2). Each aliquot will have its own individual identification number (Global Specimen ID).

- Store plasma in aliquot number order. For example, if there is only 3 mL of plasma for storage: store 1.8 mL in aliquot 1, then store the remaining 1.2 mL of plasma in aliquot 2 and adjust the aliquot volume in LDMS to indicate 1.2 mL. The remaining aliquots (3, 4, and 5) should be entered as QNS.

- Store the aliquots in the freezer locations assigned in LDMS in an ultra-low minus 70°C to minus 90°C freezer. Aliquots may be requested as needed.

Plasma for storage will be stored on site until all protocol-related testing is complete. Note that some testing will be performed after study visits have been completed. Study sites should plan to store specimens until all of the protocol specified testing (including assessments at the HPTN LC) has been completed and the primary research paper has been published.
LDMS Entry:

PL2 aliquots from the 20mL EDTA draw as follows:

- Several possible tube combinations equaling at least 20mL (per individual site chain of custody)
- A single primary container of EDTA whole blood is created
- 5 PL2 aliquots of 1.8mL are created (adjusted to approximate aliquot volume as needed during storage)
  - Primary container and aliquot entries should have the “SHV” (short volume) condition code used as needed when incomplete volumes are obtained. Change condition code to SAT or SHV only if you store < 5 aliquots for primary tubes, and SHV for any aliquots < 1.8 mL.
  - Please remember to contact the HPTN LC when using condition codes not listed in the SSP.
- No other aliquots are created from this primary container
- See figures 11.4 and 11.5

LDMS Specimen Code for Plasma Storage

<table>
<thead>
<tr>
<th>Test</th>
<th>Primary LDMS Code</th>
<th>Additive</th>
<th>Derivative</th>
<th>Sub Add/Deriv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Storage</td>
<td>BLD</td>
<td>DPE</td>
<td>PL2</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Codes used in table:

- BLD: Blood
- DPE: Spray Dried EDTA
- PL2: Plasma, Double Spun
- N/A: Not Applicable
- Other Spec ID: Not Applicable
All plasma vials are stored electronically in the LDMS and physically in an ultra-low minus 70°C to minus 90°C freezer. Selected aliquots will be shipped to HPTN Laboratory Center (LC) when requested.

All enrolled study participants must consent to collection and storage of their plasma for the duration of their study participation and until all protocol-specified testing has been completed. Participants are asked to consent separately to indefinite storage and possible future research testing of their plasma after the study is completed. Participants may refuse to consent to indefinite storage and possible future research testing and still enroll in the study. After all protocol-specified testing has been completed; the stored plasma of participants who do not consent to indefinite storage and possible future research testing must be destroyed. After all protocol-specified testing has been completed, the HPTN SDMC will provide each site with a list of participants who did not consent to indefinite storage and possible future research testing and the HPTN LC will provide detailed instructions for specimen destruction and documentation thereof.

Figure 11.4 Example LDMS Entry of Plasma (Windows LDMS)
Section 11: Laboratory and Specimen Management Procedures

Figure 2 - Example Visit 4.0 (follow-up) LDMS entry

<table>
<thead>
<tr>
<th>Group</th>
<th>TYPE1</th>
<th>TYPE2</th>
<th>TYPE3</th>
<th>ID3</th>
<th>Visit</th>
<th>Unit</th>
<th>DPD</th>
<th>CLINIC</th>
<th>Detail</th>
</tr>
</thead>
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</tbody>
</table>

2 primary containers for a 24mL EDTA collection

Figure 3 - Example Visit 5.0 (follow-up) LDMS entry

<table>
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<th>TYPE2</th>
<th>TYPE3</th>
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<th>Unit</th>
<th>DPD</th>
<th>CLINIC</th>
<th>Detail</th>
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</tr>
</tbody>
</table>

1 primary container for a 24mL EDTA collection
Figure 11.5 Example LDMS Entry of Plasma (Web LDMS)

Figure 4 - Web LDMS - Example Visit 2.0 (Enrollment)
24mL EDTA collection for 2 primary containers
11.5 Plasma Processing for IC Storage

Approximately 10 mL of EDTA whole blood should be drawn into spray dried EDTA tubes for plasma storage at each time point at which IC testing is performed as indicated in Tables 11-6. Sites are requested to store 3-4 x 1.0 mL aliquots of plasma if possible. HPTN LC should be informed at any time that three or fewer aliquots of 1.0 mL or less are stored via a NTF (see Section 11.2.4).

Sites will follow the instructions below or may follow site specific SOPs for plasma processing which will include the following:

- Collect blood into lavender top blood collection tubes (EDTA) labeled with a SCHARP-provided PTID label. The sizes of tubes will be reviewed by the HPTN LC to ensure blood draws will yield the required number of aliquots for storage. An alternate, site-specific labeling process may be used if an SOP is in place, and HPTN LC approved, but still must use the PTID with other identifiers. Size and number of collection tubes may vary depending on local lab requirements.

  - Deliver the samples to the local LDMS laboratory along with the LDMS Specimen Tracking Sheet or site-specific requisition that contains the required information.

  - Using the LDMS Specimen Tracking Sheet or site-specific requisition, log the sample into LDMS (specimen type = BLD) and generate the appropriate number of LDMS cryovial labels. The lab should store plasma in labeled cryovials. Cryovial size must be 2.0 mL. We require the use of Sarstedt tube (#72.694.006) 2 mL cryovials, or cryovials of the same dimension. Other cryovial types may only be used if specifically approved by the HPTN LC.

  - Blood processing and plasma storage should be performed within 6 hours of sample collection.

  - Centrifuge tube at 1300 x g for 10 minutes to separate cells and plasma.

  - Carefully remove plasma and avoid disturbing the cell layer.

  - Log samples into LDMS and generate LDMS labels (PL1). Each aliquot will have its own individual identification number (Global Specimen ID).

  - Store plasma in aliquot number order. For example, if there is only 2.5 mL of plasma for storage: store 2 x 1.0 mL in aliquot 1 and 2, then store the remaining 0.5 mL of plasma in aliquot 3 and adjust the aliquot volume in LDMS to indicate 0.5 mL.

  - Store the aliquots in the freezer locations assigned in LDMS in an ultra-low minus 70°C to minus 90°C freezer. Starting at visit 2 (enrollment visit), and until the end of the study, all plasma aliquots for IC sub study should be stored in a separate “to be shipped” box. The LC will notify sites when to ship these aliquots.

Plasma for storage will be stored on site until all protocol-related testing
is complete. Note that some testing will be performed after study visits have been completed. Study sites should plan to store specimens until all of the protocol specified testing (including assessments at the HPTN LC) has been completed and the primary research paper has been published.

**LDMS Entry:**

PL1 aliquots from the 10mL EDTA draw as follows:

- Several possible tube combinations equaling at least 10mL (per individual site chain of custody)
- A single primary container of EDTA whole blood is created
- 3 to 4 PL1 aliquots of 1.0 mL are created (adjusted to approximate aliquot volume as needed during storage)
  - Primary container and aliquot entries should have the “SHV” (short volume) condition code used as needed when incomplete volumes are obtained. Change condition code to SAT or SHV only if you store < 3 aliquots for primary tubes, and SHV for any aliquots < 1.0 mL.
  - Please remember to contact the HPTN LC when using condition codes not listed in the SSP.
- No other aliquots are created from this primary container
- See figures 11.4 and 11.5

**LDMS Specimen Code for Plasma Storage**

<table>
<thead>
<tr>
<th>Test</th>
<th>Primary LDMS Code</th>
<th>Additive</th>
<th>Derivative</th>
<th>Sub Add/Deriv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Storage</td>
<td>BLD</td>
<td>DPE</td>
<td>PL1</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Codes used in table:

- **BLD** Blood
- **DPE** Spray Dried EDTA
- **PL1** Plasma, Single Spun
- **N/A** Not Applicable

Other Spec ID: **IC**

All plasma vials are stored electronically in the LDMS and physically in an ultra-low minus 70°C to minus 90°C freezer. Selected aliquots will be shipped to HPTN Laboratory Center (LC) when requested.
11.6 Dried Blood Spots (DBS)

11.6.1 Supplies:

Possible vendors for DBS supplies: Thermo Fisher Scientific, VWR, Sigma Aldrich, and Market Lab. Some Whatman items may be listed as GE Healthcare Life Sciences. The following supplies may be used. Contact HPTN LC if alternate supplies are to be used.

- EDTA spray dried Blood Collection Tubes
- Whatman Protein Saver Card #903 (Whatman 10534612 or Fisher Scientific # 05-715-121). Please handle with gloves and do not touch spot areas.
- Whatman Plastic Sample Bags (Whatman 10548232 or Fisher Scientific # 09-800-16) or Whatman Foil-Barrier Sample Bags (Whatman 10534321 or Sigma Aldrich # WHA10534321).
- Desiccant pack (GE Healthcare Life Sciences (Whatman)10548234, or P/N WB100003 or Fisher Scientific # 09-800-17).
- Humidity indicator Cards (Manufacturer # MS200032 or MS200033; ADCOA # MS20003-2 or MS20003-3; Fisher Scientific # NC9511648, or NC0281067). Or similar products with similar indicator levels, suitable for storage bag size.
- Whatman card drying rack (VWR # 89015-592 or Sigma Aldrich # WHA10539521) or other suitable drying rack.
- Gloves, preferably powder free.
- Water proof marker (Fisher Scientific # 50853571 or VWR # 95042-566)
- LDMS labels.
- A fixed 25µL, variable 10-100µl, or 20-200µl micropipette with appropriate filtered pipette tips. Sites should check with local suppliers for appropriate tips for their micropipettes.

11.6.2 DBS Preparation and Storage

Sites will follow the instructions below or may follow site specific SOPs for DBS processing and storage which will include the following:

DBS will be prepared and stored at Week 4 (not week 5 injection), multiple injection follow-up visits, and HIV positive confirmation visits. See Tables 11-1 to 11-4 for complete schedules.

DBS should be prepared from an EDTA blood tube received in the laboratory. For HPTN 084 it is acceptable to use one of the tubes received for plasma storage before it is processed for plasma storage or a sample received for HIV rapid testing after testing has been performed.

The EDTA tube should be well mixed before preparing the DBS. Pipette 25 µl of whole blood directly onto the center of each spot on the filter paper so that it is contained within the circle (Figure 11.11).

- There will be a total of 5 blood spots created
- Whole blood for DBS should be stored at room temperature (approximately 15°C to 25°C) until spots have been created.
- Samples should be processed within 6 hours of the time of collection; the actual time of collection should be recorded on the Case Report Form, and DBS creation time in LDMS.
- Ensure that both hands are gloved before handling the Protein Saver (DBS) card; Do not
touch the areas where the blood spots will be placed (the filter paper portion).

- Label each Protein Saver Card with study protocol number, PID#, Study date and time of sample collection. Use a waterproof pen or a non-removable label.

- Create an LDMS label and enter specimen information into LDMS. See Figures 11.6 to 11.8.

- Assure the blood tube has been inverted 8 times and well mixed. Remove the cap from the EDTA tube and spot 25µl of blood, using a pipette, onto the center of the designated circles on the Protein Saver Cards (see Figures 11.11 to 11.13 below). Return the cap to the tube and process for other lab tests (i.e. plasma processing).
  - Pipette tip should be held approximately 3mm above the spot location and the blood dispensed onto the card with one single dispensing from the micropipette. Do not touch, press, or smear the spots.

- Air dry the cards in a card holder or other drying rack (Figure 11.14). Overnight drying (up to 16 hours) is acceptable, otherwise minimum drying time is 2 hours.

- Keep the DBS cards away from direct sunlight. Do not dry the DBS cards with a fan in an attempt to decrease drying time. Air dry only at temperature range of 15°C to 40°C.

- After DBS cards have dried, place DBS card in low gas-permeability plastic bags with humidity indicator and desiccant pack to reduce humidity. See figures 11.15 and 11.16.
  - The humidity indicator should be checked periodically as needed.
  - If the indicator indicates too much humidity (color change from blue to pink - 40% to 50% level), replace the old desiccant pack and indicator card with a new one.

- Store bag in an appropriately labeled box in an ultra-low minus 70 to minus 90°C freezer. Select DBS will be requested quarterly.

**LDMS Entry:**

**LDMS Specimen Code for DBS Storage**

<table>
<thead>
<tr>
<th>Test</th>
<th>Primary LDMS Code</th>
<th>Additive</th>
<th>Derivative</th>
<th>Sub Add/Deriv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dried Blood Spots Storage</td>
<td>BLD</td>
<td>DPE</td>
<td>DBS</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Codes used in table:**

- **BLD** Blood
- **DPE** Spray Dried EDTA
- **DBS** Dried Blood Spot
- **N/A** Not Applicable
- **Other Spec ID:** Not Applicable
Figure 11.6  Example LDMS Entry of DBS

In addition to the illustrations below, include the date and time of specimen receipt, date and time of DBS processing (spot time), and date and time of DBS completion and storage for each aliquot. Note the primary aliquot is BLD with 5 aliquots created from the primary specimen. Each aliquot will be 25μL having its own Global Specimen ID. DBS need to be entered into LDMS and stored in appropriate location so they can be easily retrieved when necessary. Each spot will have its own Global Specimen ID.
Figure 11.7 Example LDMS Entry of DBS (2)
Figure 11.8 Example LDMS Entry of DBS (3)

<table>
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<th>Project</th>
<th>HPTN</th>
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<td>CPID(s)</td>
<td>LO-TEST</td>
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<td>Protocol</td>
<td>083.0</td>
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### Visits for PROTOCOL 083.0

<table>
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<th>Clinic</th>
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<tr>
<td>Visit 1</td>
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</tbody>
</table>

### Primary Specimens for Visit 1, 09/Aug/2017

<table>
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<th>Status</th>
<th>Collection Time</th>
<th>Primary Type</th>
<th>Additive Type</th>
<th>Specimen Condition</th>
<th>Available Volume</th>
<th>Other Specimen ID</th>
<th>Specimen ID</th>
<th>Additional Time</th>
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<tbody>
<tr>
<td>9001-001/00G00-000</td>
<td></td>
<td>09:00</td>
<td>BLD</td>
<td>DPD</td>
<td>SAT</td>
<td>24 ML</td>
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</table>

### Aliquots for 9001-001/00G00-000

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<th>Sub Add/ Der Type</th>
<th>Specimen Condition</th>
<th>Available Volume</th>
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<th>Specimen ID</th>
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<td>DBS</td>
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<td>SAT</td>
<td>25 UL</td>
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</table>
Figure 11.9 Example DBS LDMS Labels for each aliquot

Figure 11.10 Suggested labeling of DBS cards
Note: 25µl spot volume may not completely fill target circle on DBS card.
Figure 11.12. Example of *incorrectly* spotted DBS card

![Incorrectly spotted DBS card]

Figure 11.13. Example of *incorrectly* spotted DBS card (continued)

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Invalid Specimens

1. Specimen quantity insufficient for testing.
2. Specimen appears scratched or abraded.
3. Specimen not dry before mailing.
4. Specimen appears supersaturated.
5. Specimen appears diluted, discolored or contaminated.
6. Specimen exhibits serum rings.
7. Specimen appears clotted or layered.
8. No blood.
Figure 11.14. Whatman card drying rack (VWR catalogue # 89015-592)

Figure 11.15 Properly labeled and packaged DBS card for storage
Figure 11.16 Properly labeled and packaged DBS card for storage (2)

DBS Shipping and Packing

When shipping DBS, ensure specimens are shipped on dry ice. Check the desiccant packs and humidity indicators before shipping and replace if needed. Boxes should be placed in a watertight secondary containers (Tyvek bags) to protect from humidity while in transit. Make sure to generate an LDMS shipping manifest with each shipment including all requested information.
11.7 Whole Blood Storage for Pharmacogenomic Testing

**Specimen Type:** Whole blood collected in dried EDTA anticoagulant ("purple top") tube.

**Specimen volume:** Minimum 1 mL whole blood

**Handling Instructions:** Whole blood is transferred to a suitable cryovial and frozen at minus 70°C to minus 90°C within 6 hours of collection.

Whole blood aliquot should be prepared from an EDTA blood tube received in the laboratory. For HPTN 084 it is acceptable to use one of the tubes received for plasma storage before it is processed for plasma storage or a sample received for HIV rapid testing after testing has been performed.

Sites will follow the instructions below or may follow site specific SOPs for whole blood storage which will include the following:

**Procedure – Stepwise**

- An appropriately labeled and filled EDTA whole blood tube will be received. Transfer a minimum of 1.0mL of the whole blood to a labeled cryovial using a transfer pipet.
- Do not fill cryovials to more than ¾ of capacity.
- Optional - Parafilm can be used to seal caps of the cryovials to prevent leakage during shipping.
- Ensure PTID, date, visit number and laboratory identifier are on the LDMS label.
- Store whole blood in an ultra-low freezer minus 70°C to 90°C until requested for shipment.
- Ship when requested on dry ice overnight for arrival on Monday through Friday only, site must follow appropriate shipping regulations.

**Batch shipment to:**

Estelle Piwowar-Manning/
Johns Hopkins University Hospital
Department of Pathology
Pathology Building, Room 313
600 North Wolfe Street
Baltimore, MD 21287
USA
LDMS Entry:

LDMS Specimen Code for Whole Blood Storage

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<tr>
<th>Test</th>
<th>Primary LDMS Code</th>
<th>Additive</th>
<th>Derivative</th>
<th>Sub Add/Deriv</th>
<th>Other Spec ID</th>
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</thead>
<tbody>
<tr>
<td>Whole Blood Storage</td>
<td>BLD</td>
<td>DPE</td>
<td>BLD</td>
<td>N/A</td>
<td>PGEN</td>
</tr>
</tbody>
</table>

Codes used in table:

- BLD: Blood
- DPE: Spray Dried EDTA
- N/A: Not Applicable
- Other Spec ID: PGEN

11.8 Breast Milk collection and processing for OL participants.

**Specimen Type:** Breast Milk.

**Specimen volume:** 5 mL unspun whole breast milk processed into 3-5 x 1 mL aliquots.

**Handling Instructions:** Whole breast milk is transferred to a suitable cryovial and frozen at minus 70°C to minus 90°C within 6 hours of collection.

**Procedure – Stepwise**

- Collect 3-5 mLs of Breast Milk in an appropriately labeled 50 mL conical tube.
- Store at 4°C (2 to 8°C acceptable) within 10 minutes of collection and send to the lab on wet ice.
- Process within 6 hours of collection.
- Transfer a minimum of 1.0mL of the whole breast milk in to a labeled cryovial using a transfer pipet.
- Log specimens into LDMS and generate LDMD labels (BMK), each aliquot should have each own individual identification number (Global Specimen).
- Store breast milk in aliquot number order
- Store the aliquots in the freezer location assigned in LDMS in the ultra-low -70°C to -90°C freezer.
- Aliquots will be requested as needed.
LDMS Entry:

LDMS Specimen Code for Breast Milk Storage

<table>
<thead>
<tr>
<th>Test</th>
<th>Primary LDMS Code</th>
<th>Additive</th>
<th>Derivative</th>
<th>Sub Add/Deriv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Breast Milk Storage</td>
<td>BMK</td>
<td>Non</td>
<td>BMK</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Codes used in table:

- BMK: Whole Breast Milk
- NON: No-Additive
- N/A: Not Applicable

11.9 Cord Blood collection and processing for OL participants.

Approximately 5 mL of whole cord blood (CRD) should be drawn into spray dried K2EDTA tube for plasma storage as indicated in Tables 11-10. Sites are requested to store 2 x 1.0 mL aliquots of plasma if possible.

Sites will follow the instructions below or may follow site specific SOPs for plasma processing which will include the following:

**Specimen volume:** 5 mL unspun whole cord blood processed into 2 x 1.0 mL plasma aliquots.

**Handling Instructions:** Whole cord blood is centrifuged and transferred to a suitable cryovial and frozen at minus 70°C to minus 90°C within 6 hours of collection.

**Procedure – Stepwise**

- Collect blood into lavender top blood collection tubes (K2EDTA) labeled with a SCHARP-provided PTID label. The sizes of tubes will be reviewed by the HPTN LC to ensure blood draws will yield the required number of aliquots for storage. An alternate, site-specific labeling process may be used if an SOP is in place, and HPTN LC approved, but still must use the PTID with other identifiers. Size and number of collection tubes may vary depending on local lab requirements.
- Deliver the samples to the local LDMS laboratory along with the LDMS Specimen Tracking Sheet or site-specific requisition that contains the required information.
- Using the LDMS Specimen Tracking Sheet or site-specific requisition, log the sample
into LDMS (specimen type = CRD) and generate the appropriate number of LDMS cryovial labels. The lab should store plasma in labeled cryovials. Cryovial size must be 2.0 mL. We require the use of Sarstedt tube (#72.694.006) 2 mL cryovials, or cryovials of the same dimension. Other cryovial types may only be used if specifically approved by the HPTN LC.

- Blood processing and plasma storage should be performed within 6 hours of sample collection.
- Centrifuge tube at 800 - 1000 x g for 10 minutes to separate cells and plasma.
- Carefully remove plasma and avoid disturbing the cell layer.
- Log samples into LDMS and generate LDMS labels (PL1). Each aliquot will have its own individual identification number (Global Specimen ID).
- Store plasma in aliquot number order. For example, if there is only 1.5 mL of plasma for storage: store 1.0 mL in aliquot 1, then store the remaining .5 mL of plasma in aliquot 2 and adjust the aliquot volume in LDMS to indicate .5 mL. The remaining aliquots (3,) should be entered as QNS.
- Store the aliquots in the freezer location assigned in LDMS in the ultra-low -70°C to -90°C freezer.
- Aliquots will be requested as needed.

**LDMS Entry:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Primary LDMS Code</th>
<th>Additive</th>
<th>Derivative</th>
<th>Sub Add/Deriv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Cord Blood Storage</td>
<td>CRD</td>
<td>DPE</td>
<td>PL1</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Codes used in table:**

- **CRD** Whole Cord Blood
- **DPE** No-Additive
- **N/A** Not Applicable

### 11.10 Infant Blood collection and processing for OL participants.

Approximately 500 µL to 2 mL of whole blood (if possible) should be drawn into spray dried K2EDTA tube for plasma storage as indicated in Tables 11-10. Sites are requested to store 2 x 250 µL aliquots of plasma if possible.

Sites will follow the instructions below or may follow site specific SOPs for plasma processing which will include the following:

**Procedure – Stepwise**

- Collect blood into lavender top blood collection tubes (K2EDTA) labeled with a
SCHARP-provided PTID label. The sizes of tubes will be reviewed by the HPTN LC to ensure blood draws will yield the required number of aliquots for storage. An alternate, site-specific labeling process may be used if an SOP is in place, and HPTN LC approved, but still must use the PTID with other identifiers. Size and number of collection tubes may vary depending on local lab requirements.

- Deliver the samples to the local LDMS laboratory along with the LDMS Specimen Tracking Sheet or site-specific requisition that contains the required information.
- Using the LDMS Specimen Tracking Sheet or site-specific requisition, log the sample into LDMS (specimen type = BLD) and generate the appropriate number of LDMS cryovial labels. The lab should store plasma in labeled cryovials. Cryovial size must be 2.0 mLs. We require the use of Sarstedt tube (#72.694.006) 2 mL cryovials, or cryovials of the same dimension. Other cryovial types may only be used if specifically approved by the HPTN LC.
- Blood processing and plasma storage should be performed within 6 hours of sample collection.
- Centrifuge tube at 800 - 1000 x g for 10 minutes to separate cells and plasma.
- Carefully remove plasma and avoid disturbing the cell layer.
- Log samples into LDMS and generate LDMS labels (PL1). Each aliquot will have its own individual identification number (Global Specimen ID).
- Store plasma in aliquot number order. For example, if there is only 250 µL of plasma for storage: store .250 µL in aliquot 1 in aliquot 1. The remaining aliquots (2,) should be entered as QNS.
- Store the aliquots in the freezer location assigned in LDMS in the ultra-low -70°C to -90°C freezer.
- Aliquots will be requested as needed.

**LDMS Entry:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Primary LDMS Code</th>
<th>Additive</th>
<th>Derivative</th>
<th>Sub Add/Deriv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant Blood Storage</td>
<td>BLD</td>
<td>DPE</td>
<td>PL1</td>
<td>N/A</td>
</tr>
</tbody>
</table>

### 11.11 Required LDMS data entry scheme

LDMS data entry is to be standardized across the sites participating in HPTN 084. This may not align with current practice or entry for other network studies.

### 11.11.1 PL2 aliquots from the 20mL EDTA draw (as per protocol and SSP)

a. Several possible tube combinations equaling at least 20mL (per individual site chain of custody)
b. A single primary container of EDTA whole blood is created
c. 5 PL2 aliquots of 1.8mL are created (adjusted to actual aliquot volume as needed during storage)
d. No other aliquots are created from this primary container
e. See Figures 11.4 and 11.5).
11.11.2 DBS from EDTA whole blood (example 4mL draw)

   a. A single primary container of 4mL EDTA whole blood is created
   b. 5 aliquots of 25uL each are created (1 for each spot on the DBS card)

11.11.3 Whole Blood for Pharmacogenomics (Example 4mL draw)

   a. Occurs only once at visit 2.0 (Enrollment)
   b. Single primary container
   c. Single 1mL whole blood aliquot
   d. “PGEN” entered into primary container Other Specimen ID field (Other Spec Id)

11.11.4 Blood for Injectable Contraceptive Sub-Study. (additional 10 mL draw)

   a. Plasma and DBS will be collected from selected sites at Steps 1 and 2.
   b. Follow plasma processing (see instructions above) and DBS instructions in sections 11.4 and 11.5.

11.11.5 Breast Milk

   a. 5 mLs collected in a single primary container of 50mL conical tube of whole breast milk is created.
   b. 3-5 aliquots of 1.0 mL each are created.
   c. Follow breast milk processing (see instructions above) instructions in section 11.8

11.11.6 Cord Blood

   a. A single primary container of 5mL K2EDTA whole cord blood is created.
   b. 2 aliquots of 1.0 mL each are created.
   c. Follow cord blood processing (see instructions above) instructions in section 11.9

11.11.7 Infant blood

   a. A single primary container of 500 µL to 2mL K2EDTA whole blood is created
   b. 2 aliquots of 250 µL each are created.
   c. Follow infant blood processing (see instructions above) instructions in section 11.10

11.12 Primary Specimen Report for HPTN 084 in PC-based LMDS

   a. Open the LDMS “Reports” module:
      i. Click on the “Reports” icon (under the main Menu bar) or click on the “Tasks” Menu and select “Reports” from the drop-down menu.
   b. In the Category box on the top-left of the Reports screen, highlight the “Specimen” line.
   c. In the Description box at the top of the Reports screen, highlight the “Primary Specimens Received” line.
   d. Under the “Selection Criteria” area at the bottom of the Reports screen:
      i. In the Field box, select “Group” from the drop-down menu.
      ii. In the Operator box, select “=” from the drop-down menu.
iii. In the Value box, select “HPTN” from the drop-down menu.

iv. Click on the “Add” button, to the right of the selection criteria, to save the information in the search options box to the right, for use with your search later.

e. Go back to the Selection Criteria area and repeat the process to enter protocol information:

i. In the Field box, select “Non-ACTG Prot/ID2” from the drop-down menu.

ii. In the Operator box, select “=” from the drop-down menu.

iii. In the Value box, select “084.0” from the drop-down menu.

iv. Click on the “Add” button, to the right of the selection criteria, to save the information in the search options box to the right, for use with your search later.

v. *If the drop-down “Value” options include both “084.0” and “084” as a choice, instruction “e” (this section) should be repeated so that both are included in the saved search options (as in the figure below). If only one is an option, instruction “e” only needs to be performed once.*

![Figure 1](image_url)

f. Go back to the Selection Criteria area and repeat the process to enter search date information. The following are ways to search for one day or one month within a single search:

i. To search only one day:

1. In the Field box, select “Received Date” from the drop-down menu.

2. In the Operator box, select “=” from the drop-down menu.

3. In the Value box, select the date for which you would like to check the status of the primary specimens.

4. Click on “Add” box – located on to the right of the Selection Criteria.

ii. To search within one month:

1. In the Field box, select “Received Date” from the drop-down menu.

2. In the Operator box, select “>=” from the drop-down menu.

3. In the Value box, select the first day of the month for which you would like to check the status of the primary specimens.

4. Click on “Add” box – located on to the right of the Selection Criteria.

5. In the Operator box, select “=” from the drop-down menu.

6. In the Value box, select the last day of the month for which you would like to check the status of the primary specimens.
7. Click on “Add” box – located on to the right of the Selection Criteria.

8. The figure below displays what you should see in the saved area to the right of selection criteria. Lines 4 and 5 together in the figure represent the two entries for the one-month search window.

**Figure 2**

<table>
<thead>
<tr>
<th>Field</th>
<th>Operator</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non ACTG Prot/ID2</td>
<td>=</td>
<td>084</td>
</tr>
<tr>
<td>Received Date</td>
<td>&gt;=</td>
<td>01/Nov/2017</td>
</tr>
<tr>
<td>Received Date</td>
<td>&lt;=</td>
<td>30/Nov/2017</td>
</tr>
</tbody>
</table>

g. There will now be multiple lines of information in the box to the right of the search criteria. The minimum lines that should be present is three, but there could be up to five lines if two protocol ID’s and two date criteria have been entered. One line will be present for each of the following:

i. The HPTN group

ii. The protocol number (ID2)

   1. Two lines are present if the additional protocol number (ID2) is included (e.g. 084.0 and 084 will have separate lines as in figure 1)

iii. The search date

   1. Two lines are present if a one-month window is to be searched (e.g. starting November 1st and ending November 31st will have separate lines as in figure 2)

h. In the “Valid sentence” field, write a search to use all the entered and saved criteria as needed.

i. A simple search with only 3 lines in the saved area will look like: “1 and 2 and 3” – referring to a search for HPTN samples, protocol 084.0, and the specified date.

ii. A search that uses two dates (for a one-month search) and two protocol ID’s (to search 084.0 and 084 entries) will look like figure 3: “1 and (2 or 3) and 4 and 5” – referring to a search for HPTN samples, any 084 or 084.0 protocol entries, and the month specified between the two dates.
Figure 3

<table>
<thead>
<tr>
<th>Add</th>
<th>Modify</th>
<th>Delete</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Non ACTG Prot/D2</td>
<td>4 Received Date</td>
<td>5 Received Date</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valid Sentence Items: and, or, (), or a number</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 and (2 or 3) and 4 and 5</td>
</tr>
</tbody>
</table>

i. Click on the “Execute” icon (the lightning bolt) at the top of the screen under the main menu bar.

j. The “Primary Specimens Received” report will automatically generate and pop-up once completed. This provides a detailed description of each primary specimen entry.

k. This report can then be exported into an Excel (CSV) format.
   i. Click the “Export Report” icon in the pop-up window (figure 4).

Figure 4

ii. In the “Save As” pop-up window, create a file name for the report and select to save as a “CSV” file type. See figure 5.
Figure 5

a. Email reports to the HPTN 084 LC staff (Estelle Piwowar-Manning epiwowa@jhmi.edu and Yaw Agyei yagyei1@jhmi.edu)

Windows: Specimen Log Report
1. Click on **Specimen** in the **Category** grid at the top left of the Reports screen
2. Click on **Specimen Log Report** in the Description window
3. Return to **Field** and select **Received Date**
   a. **Operator** is ‘=’
   b. In **Value**, set the Current Date
   c. Click **Add**
4. Click the **Execute** button on the LDMS toolbar
**Webs: Specimen Log Report**

This report provides the user with a specific set of information for each of their logged specimens. The report will provide the user with the participant, primary, and aliquot information for each of their specimens. The report also provides the user with the condition codes, comments, and shipping information (if available) for the given specimens. Using the search criteria below will provide the user with a list of all specimens received by the lab on a particular date.

1. On the LDMS menu bar, hover over **Reports** and click **Standard Reports**.
2. Select the following:
   a. Report Categories: **Specimen**
   b. Report: **Specimen Log Report**
3. In **Filter Criteria**:
   a. **Field**: Received Date
   b. **Operator**: ‘=’
   c. **Value**: Current Date
4. Set **File Type** to PDF; Click **Generate Report**
11.13 Shipping of Samples to the HPTN Laboratory Center

Each site will ship plasma, whole blood, Cord blood, infant plasma, or DBS samples to the LC or designated laboratory upon request, or following a shipping schedule as determined by the LC. The site will batch the shipment, export the LDMS data, and notify the LC.

a. The remaining plasma aliquots should be stored as per normal site standards.

b. Other samples, such as those from Seroconverters, will also be requested on an ad-hoc basis and may be included in quarterly shipments. Separate shipping instructions will be provided at that time by LC non-protocol team members.

c. Separate LDMS batches may be required depending on the shipping request.

Contact the HPTN LC at Johns Hopkins University (Estelle Piwowar-Manning: epiwowa@jhmi.edu and Paul Richardson: pricha18@jhmi.edu, +410-614-6737) to coordinate the timing and logistics of each shipment.

Sites will ship samples to the LC using the LDMS following the LC approved Shipping SOP indicating Lab 300 as the ship to lab ID number. The site should export the data to FSTRF after a batch has been made and notify the HPTN LC with the batch number.

Personnel involved in the shipping process must be IATA trained and certified for the shipping of Category B Biological specimens UN 3373 (Diagnostic) Packing Instructions 650.
Plasma, Cord Blood, Breast Milk and Whole blood for pharmacogenomics

Include a copy of the shipping manifest and box map with the shipment. For dry ice shipments, use diagnostics packing code 650, UN 3373, and address the shipment to:

Estelle Piwowar-Manning/Susan Eshleman MD  
Johns Hopkins University Hospital  
Department of Pathology  
Pathology Building, Room 313  
600 North Wolfe Street  
Baltimore, MD 21287  
USA

For some shipments, an alternate address may be provided at the time of request.

Notify the HPTN LC via email (epiwowa@jhmi.edu) when the shipment has been picked up from the site by the courier/shipping company. Attach an electronic copy of the shipping manifest and LDMS batch to the email notification and include the following information in the notification: name of courier/shipping company, shipment tracking number, number of boxes shipped, date of shipment, and expected date of arrival.

Dried Blood Spot cards

Storing Dried Blood Spots by individual participant will simplify the shipment process. Lists of DBS that are required to be shipped will be uploaded to the Atlas Portal. An email will be sent directly to the sites from the SDMC.

These Dried blood spot cards should also be shipped when requested. **Note: Sites can ship all samples to Johns Hopkins University, and the DBS will be forwarded to University of Colorado at Denver if indicated in the site MTA.**

Sites should ship the DBS cards directly to:

Lane Bushman  
C/O Pete Anderson  
University of Colorado at Denver  
Skaggs School of Pharmacy and Pharmaceutical Sciences  
C-238-V20, Rm V20-4410  
12850 East Montview Blvd  
Aurora, CO 80045  
USA  
Phone: 303-724-6132  
LDMS Number 533
11.14 HIV QA Testing

Selected plasma aliquots will be shipped to the HPTN LC for HIV QA testing according to the HPTN Manual of Operations; additional testing may be performed e.g. ABO typing.

When samples are received at the HPTN LC, the LC will perform additional QA and HIV testing. This will include:

- Quality assurance testing (to confirm results of in-country testing)
- Testing to confirm seroconversion events

Data from the HPTN LC will be submitted to the SDMC.

11.15 Pharmacology Testing

Plasma samples for drug levels will be collected throughout the study. These samples will be collected from all participants, although PK testing may be limited to a subset of the samples. At each injection visit a blood sample will be collected PRIOR to the injections. The actual date and time of each blood sample collection will be recorded, as well as the time of each injection. This information should be captured on the relevant CRF.

Specimens for pharmacology testing will be shipped following a shipping schedule as determined by the LC.

Pharmacology testing will be performed at the HPTN LC or at an outside laboratory designated by the HPTN LC. The primary pharmacologic assessments will be performed using assays that have been validated and approved by the Clinical Pharmacology Quality Assurance (CPQA) Committee. Results will not be returned to the sites or study participants.

Stored plasma may also be tested for the presence of other ARV drugs or other substances.

11.16 Pharmacogenomic Testing

Specimens for Pharmacogenomic analysis will be collected at the enrollment visit for participants who consent to Pharmacogenomic testing. Samples will be stored on site for shipment to the HPTN LC upon request. Assays will be performed at the HPTN LC. Results will not be returned to the sites or study participants.
11.17 Other Testing

The HPTN LC will perform QA testing, including testing to determine HIV infection status in selected cases. Additional assays may be performed at the HPTN LC or a laboratory designated by the HPTN LC. This testing may include the following tests for participants who acquire HIV infection: HIV viral load, HIV resistance testing, HIV subtyping, and other tests to characterize HIV viruses and/or the host response to HIV infection. Results will not be returned to the sites or study participants, with the exception of HIV testing (if results obtained at the HPTN LC do not agree with site results) and the exception for resistance test results, noted below.

Resistance testing will be performed at the HPTN LC or a laboratory designated by the HPTN LC. This testing will be performed retrospectively at the end of the study. If real-time resistance testing is needed for clinical management, that testing should be arranged by the site outside of the study; separate specimens should be collected for that testing. For sites that do not have the capacity for local resistance testing for clinical care, results from resistance testing may be provided at the end of the study at the request of the site IoR, with approval of the HPTN LC and Protocol Chair. Results from specialized resistance testing (e.g., minority variants analysis, if performed) will not be returned to study sites.

11.18 Laboratory Monitoring

LC staff will conduct periodic site visits to review in-clinic documentation, LDMS reports, specimen storage and other laboratory documentation relevant to this protocol.
Section 12. Counseling Considerations

12.1 Overview of Section 12

This section contains guidance on HIV Pre-/Post-Test counseling and adherence counseling provided in HPTN 084.

HIV Pre-/Post-Test counseling is required at all study visits. All counseling should be provided in a non-judgmental participant-centered manner that responds to current participant needs for information, education, support, skills building, and/or referrals. Participants’ needs are likely to change over time; counseling provided should also change over time accordingly.

All counseling process outcomes should be documented in participant study records. Proper documentation may be achieved by using counseling checklists, worksheets, and other tools, as well as counselors’ chart notes. To support ongoing participant-centered counseling over time, documentation of each counseling session should include sufficient information and detail to inform and guide the participant’s next counseling session.

During counseling, a site-specific tool may be used to guide any of the counseling sessions. During the session, counselors should engage in the discussion and be client oriented rather than focusing on taking notes. A summary of the counseling session should be written once the session is completed.

12.2 HIV Pre-/Post-Test Counseling

HIV testing is required at each scheduled HPTN 084 study visit for as long as participant is not found to be HIV infected.

Each site is encouraged to develop a Standard Operating Procedure (SOP) for this counseling. It is suggested that the SOP be site-specific and the following elements be incorporated:
• Each participant should be provided with information that allows her to decide whether to be tested (informed decision with informed consent). However, if a participant elects not to undergo HIV testing she may not receive study product and the Clinical Management Committee (CMC) must be contacted for participant management. CMC guidance will then be followed by the site.
• The HIV testing procedure should be organized to maximize confidentiality.
• HIV antibody testing should be linked with information and recommendations regarding HIV.
• Adequate pre- and post-testing counseling should be provided to all individuals being tested.
• Disclosing HIV status to others should be discussed with all participants.
• The need for additional and appropriate referrals should be addressed where possible.

All HIV counseling should be provided in accordance with local counseling standards. Study staff who provide HIV counseling should be trained to do so per local practice standards. Counseling staff should also be trained on study-specific HIV testing methods and interpretation of test results per the study testing algorithms in SSP manual Section 11. Information on interpretation of screening, enrollment, and follow-up test results is provided as part of the testing algorithms. These figures should be referenced as needed when providing pre-test and post-test counseling.

Given that HIV counseling will be provided at all HPTN 084 study visits, when providing pre-test and post-test counseling, it is especially important to avoid repetition of the same information at each counseling session. Participant-centered approaches should be used to assess participant knowledge of relevant information, dispel any misconceptions, ensure participant readiness for HIV testing, and ensure participant understanding of why HIV testing is being done on every visit and understanding test results.

HIV test results should be provided in the context of post-test counseling, which should begin when the first test results (rapid test results) are available the day of testing, and continued, as results become available. If it is convenient for the participant, or it is part of a site’s standard of care, interim visits may be scheduled to give HIV test results and conduct post-test counseling.

When results from the HIV tests are discordant, participants as well as staff members may feel anxious about the ambiguity of their HIV status. While following the HIV testing algorithm, participants should also be engaged in a discussion about the pros and cons of starting ART.
Additionally, mechanisms for linking individuals to appropriate HIV specialty care who acquire HIV infection during study participation is required to be detailed in an SOP for each site. “Appropriate care” should be locally defined and include consideration of language, geography, insurance status and type, provider cultural sensitivity, and resource availability. Ideally sites should build relationships with HIV care providers ahead of time so that discussions about participants with atypical results can be easily facilitated.

Risk reduction counseling should be incorporated into the HIV counseling approach noted above. Participant-centered approaches should be used when providing risk reduction counseling. For HPTN 084, risk reduction counseling will include condom use, data on the known effectiveness of both Truvada (TDF/FTC) and long-acting cabotegravir (CAB LA) as HIV pre-exposure prophylaxis. The counselor should ask open-ended questions, actively listen to participant responses, probe as needed for further information, and guide the participant in identifying his/her risk factors and barriers to risk reduction, as well as strategies and action plans to try to address these.

12.2.1 Counseling consideration for participants with discrepant results

Here are some counseling messages based on the tests results. It is advisable that clinicians provide counselling support in the context of discrepant blood results so that the can provide information in response to participant questions. Counsellors can provide additional counseling support but should seek guidance from clinicians on the interpretation of the test results and appropriate counseling messages.

<table>
<thead>
<tr>
<th>First test positive</th>
<th>“Your initial results indicate that you may be infected with HIV and we need to do additional testing in order to confirm this result. We will draw a new blood sample and results will be available in about XX days”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same day rapid test positive</td>
<td></td>
</tr>
</tbody>
</table>
| Non-rapid test positive | Your HIV status is not clear to us because while your first test was negative for HIV, your second test was reactive. We would like to conduct additional testing in order to feel sure about your HIV status.

*We will draw more blood today and results will be available in about XX days.* |

<table>
<thead>
<tr>
<th>Subsequent test results</th>
</tr>
</thead>
</table>
| HIV infection status uncertain; additional testing needed | Your HIV status is not clear to us
Thank you for your patience as we continue to work to determine your HIV status. We would like to draw more blood today. Those results should be available in about XX days.” |
| Likely false positive | “We do not believe that you have HIV. Even though your very first test was reactive, no subsequent tests have indicated HIV infection. The first test was likely a false-positive.” |
| Likely infected | Based on the results from additional tests, it is likely that you have HIV infection. It is important that we get you started on ART as soon as possible.

*It is also important that we draw additional bloods for study purposes, but we do not expect these tests to show a different result.”* |
In some instances, final determination of HIV status may be challenging particularly in participants with prior CAB exposure. In that situation, there may be uncertainty about whether to reinitiate PrEP or start ART. In this scenario, clinicians should engage participants in shared decision-making about the best possible treatment option based on her personal life circumstances. Clinicians should ideally address the following issues in their conversations with participants:

- False negative: In the context of long-acting CAB use, CAB may suppress virus replication and delay seroconversion making diagnosis with conventional diagnostics difficult.
  - Participants in this scenario may benefit from ART initiation to avoid potential emergence of INSTI resistance if they are infected and have a prolonged period of CAB monotherapy.

- False positive: False reactive test results are possible when testing is frequent. False reactive results can occur in the context of pregnancy, syphilis, malaria, other co-infections.
  - Participants in scenario may benefit from re-resting to exclude any lab errors.

- Risk balance:
  - In some scenarios it may not be possible to know for certain whether a participant has HIV infection e.g. an isolated HIV RNA result >200 copies where no other tests are positive
  - Consideration needs to be given to whether the participant needs to reinitiate PrEP to avoid ongoing HIV risk or start ART to avoid emergence of resistant infection. This decision will be influenced by available test results, and participants should be kept informed regarding the tests and timing of results so that they remain engaged in care.
  - It may be preferable to initiate ART when diagnosis is uncertain to avoid potential resistance and to plan for a treatment interruption in 12-18 months when CAB is considered cleared.
  - These decisions should be shared with participants so that the participant can make the most informed decision at that point in time. Study staff should communicate that those decisions may be revisited at a later timepoint if needs be as new information becomes available.
The decisional balance tool (Appendix 12A) can also be used as a tool to assist participants with indeterminate HIV test results to decide whether or not to start ART in the case of discrepant HIV test results where HIV diagnosis is uncertain and CAB monotherapy may be associated with the risk of emerging INSTI resistant infection.

12.3 Product Use Instructions and Adherence Counseling

Participants will be provided product use instructions and adherence counseling for the first time at their study enrollment visit, and per the schedule on the protocol and the adherence counseling protocol. The person providing product use instructions and adherence counseling will discuss with participants adherence to protocol requirements such as returning for study visits and not sharing product. Adequate time should be taken to explain the product use instructions thoroughly and to answer any questions the participant may have. Any questions or concerns raised by the participant should be documented in his/her study records so this information is easily available for reference at follow-up visits.

In general, adherence counseling will be provided in accordance with recommendations from PrEP clinical guidance documents and in-country implementation strategies (Centers for Disease Control [CDC], World Health Organization [WHO]). Using a participant-centered approach to frame discussions, adherence counseling for those on TDF/FTC will include education around the importance of daily pill adherence and supporting strategies that link pill taking to the participant’s daily routine (i.e., daily calendar, plans for travel, habits). For those choosing cabotegravir injections, counseling should be focused on attending study visits to receive the injections and what to expect before, during, and after injections, as well as daily adherence to oral tablets if the participant decides to take the oral lead-in.

12.4 Study Product Use Instructions

**Oral Product (either CAB or TDF/FTC)**

Participants will be instructed to take one tablet by mouth daily. The oral tablets should be taken as close to the same time each day as possible. If a participant misses a dose, the participant can take the missed dose within the same calendar day as soon they remember. The next dose will be taken by mouth as originally scheduled. Participants should be instructed not to take two doses of the same product on the same day. Participants should be reminded to store study tablets at room temperature, in a safe place and out of reach of children. Although tablets should be kept in original container with labels intact, participants may use pill boxes or other mechanisms they find helpful to assist with adherence or protect privacy. Such containers would need to accompany participants to their visits to perform pill counts as appropriate and medication reconciliation.
If a participant reports issues swallowing the tablets due to size, they may split the tablet in half and then swallow immediately. Although a pill cutter is preferred, it’s not required for pill-splitting. *NOTE: Antacid products containing divalent cations (e.g., aluminum, calcium and magnesium) must be taken at least 2 hours before or at least 4-6 hours after the oral formulation of CAB.*

**Injection Product**

See section 8 of this manual for information.

**12.5 Counseling Considerations**

Please refer to the decisional balance worksheet in Appendix 12A which can be used in your discussions with participants about the options in the OLE. Participants who opt into the oral CAB lead-in should be counseled on the purpose of the lead-in, with an emphasis placed on the fact that it is being conducted specifically to rule out any serious side effects of the study drug prior to the administration of injections, and that therefore it is important that the study drug be taken every day. Sites should refer to the HPTN 084 protocol for side effects of oral cabotegravir (CAB) (Section 1 and the Sample Informed Consent Form Template), as well as the Investigator’s Brochure (IB) and Section 9 of this manual.

For participants choosing CAB LA, counseling conducted prior to each injection should focus mainly on what to expect before, during, and after each injection is given, including any side effects that they may experience, and that it will last in their system for a long time (a year or more after a single injection) with clear explanation why participants get more than one injection at different intervals yet the long-acting formulation drug lasts for a year or more after a single dose. Participants should be informed of the schedule of injections and the expected timeframe they will receive them (based on their enrollment date, see Protocol Section 5 and SSP manual Section 6).

Additionally, it should be explained that the injection site (the buttocks) may have localized pain, be tender to palpitation, itch, swell, bruise, be temporarily discolored, feel warm or have a pulsing sensation. Participants must be encouraged to contact site staff after they have left the study clinic if any side effects occur, including suspected injection site reactions. Participants who report injection site reactions should be assessed by a clinician. Participants can be counselled on how best to minimize injection site pain using the guidance in section 9.

While the HPTN 084 protocol provides instructions regarding when to contact the CMC about adverse events, the CMC may be contacted at any time there is a question about any side effects of the oral or long-acting study product.
Participants choosing TDF/FTC will be counseled to identify reminder cues to assist with daily dosing, including reviewing calendars for daily habits, setting phone alarms, etc. The counseling should also include clear instructions about the product, any side effects anticipated, and strategies for maintaining daily adherence. Counseling may also incorporate conversations around disclosure of study participation to supportive others (see optional tools Appendix 12b).
Appendix 12A: Decisional Balance Worksheet for OLE

<table>
<thead>
<tr>
<th>STATE</th>
<th>Thank you for your ongoing participation in the HPTN 084 study. In this phase of the study, there are some choices for you to make. In order for you to weigh the pros and cons for yourself, you can use something called a decisional balance worksheet.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HANDOUT</td>
<td>Decisional Balance Worksheet</td>
</tr>
<tr>
<td>STATE</td>
<td>With a decisional balance sheet, you are listing pros and cons that are very specific to you, your life, your thoughts and your feelings. This allows you to weigh the drawbacks and benefits of all of your options in order to get a clearer understanding of what is right for you. Let’s review this worksheet together.</td>
</tr>
<tr>
<td>DISCUSS</td>
<td>Decisional Balance Worksheet with participant. Help with pros and cons if needed. Examples are just for discussion if needed.</td>
</tr>
</tbody>
</table>

**Choice to stay on TDF/FTC:**
Pros may include:
- Used to taking daily pill
- Don’t like injections

Cons may include:
- Not long-acting
- Product storage

**Choice of oral CAB lead-in or direct-to-inject:**
Pros may include:
- Getting used to the medication
- Avoiding allergic reaction

Cons may include:
- Taking a daily pill temporarily (if required)

**Choice to join the pregnancy substudy:**
Pros may include:
- Help gather valuable information for pregnant women in the future
- Monitoring of pregnancy by study staff; getting additional care

Cons may include:
- Additional study procedures
- Extra time at study visits

**Choice to start ART following discordant results:**
Pros may include:
- Benefits of early treatment
• Protecting sexual partners and potential pregnancies while waiting for determination of HIV status
• Not life long, might only for a period until a treatment interruption 12-18 months later could confirm uninfected

Cons may include:
• Preparation for daily pill intake/adherence
• Disclosure and stigma concerns
• Challenges with transfer to local ART clinics

<table>
<thead>
<tr>
<th>DISCUSS</th>
<th>Any questions or concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>STATE</td>
<td>When making big decisions, it is important to consider who can provide you with support. “Supportive others” are the people or groups of people who are most important in our lives. Supportive others may include parents, peers, family members, schools, health providers, faith communities, and dating partners. We all rely on supportive others to listen when we need to talk, give us advice, and shape our ideas about the decisions we make and the consequences of each decision. In this activity, let’s identify the people who are supportive to you.</td>
</tr>
<tr>
<td>ASK</td>
<td>If you could fill a room with the most important people in your life, who would be in the room?</td>
</tr>
<tr>
<td>DISCUSS</td>
<td>• Who are the people/groups in the room? • Why are they important to you? • Are there some that have more influence than others? • Are these people/groups you can count on when you are in trouble or in need? • Do they help you make good decisions? Always? Most of the time? Sometimes? Never? • Do you feel good about the decisions they help you make?</td>
</tr>
<tr>
<td>REVIEW</td>
<td>Who would help the participant make medical decisions – make sure that they have a qualified provider to support them if needed.</td>
</tr>
<tr>
<td>STATE</td>
<td>Thank you for completing this activity. I’m glad to understand who is important to you and how they may help with decision-making for this study.</td>
</tr>
<tr>
<td>DISCUSS</td>
<td>Any final questions or concerns</td>
</tr>
</tbody>
</table>
## Appendix 12B: PrEP Disclosure Activities

Disclosure tools should be approved by local IRB/EC prior to distributing to participants.

### ACTIVITY A: SAFE TALK- HOW DO I DISCLOSE THAT I AM ON PREP?

<table>
<thead>
<tr>
<th><strong>ASK PARTICIPANT</strong></th>
<th>How do you feel about telling people that you are taking PrEP?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DISCUSS</strong></td>
<td>Participants views on disclosing or not disclosing PrEP</td>
</tr>
<tr>
<td><strong>STATE</strong></td>
<td>If you are struggling with how to tell someone that you are taking PrEP, here is an acronym, T.A.L.K. that can help guide you through the process.</td>
</tr>
<tr>
<td><strong>HANDOUT</strong></td>
<td>“Safe TALK” handout.</td>
</tr>
<tr>
<td></td>
<td><strong>Timing</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Assertive Communication</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Location</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Know What to Say</strong></td>
</tr>
<tr>
<td><strong>STATE</strong></td>
<td>Timing, Assertive Communication, Location, Know What to Say.</td>
</tr>
<tr>
<td><strong>ASK</strong></td>
<td>Have the participant read text on the “SAFE Talk” handout.</td>
</tr>
<tr>
<td></td>
<td><strong>TIMING</strong></td>
</tr>
<tr>
<td></td>
<td>Choose an appropriate time to talk with your person. If the person that you need to talk with has a busy lifestyle, then it might be easier for you to set a meeting time. This way, each person’s attention can be focused on the issue.</td>
</tr>
<tr>
<td></td>
<td><strong>ASSERTIVE COMMUNICATION</strong></td>
</tr>
<tr>
<td></td>
<td>Clearly tell the person how you feel and what you want or need by being honest and direct. Think carefully about your relationship and pay attention to others’ responses. Depending on the specific person, you might have to address issues differently. Remember to use “I” statements, take deep breaths, keep a reasonable tone, and actively listen to the other person.</td>
</tr>
<tr>
<td></td>
<td><strong>LOCATION</strong></td>
</tr>
<tr>
<td></td>
<td>Choose a quiet place where you cannot be interrupted or overheard by others.</td>
</tr>
<tr>
<td></td>
<td><strong>KNOWING WHAT TO SAY</strong></td>
</tr>
<tr>
<td></td>
<td>Think about what you want to say in advance by sorting out your own feelings about the issue before talking with the other person. You might find that making a list or writing a letter of your thoughts and feelings will help you focus.</td>
</tr>
<tr>
<td>DISCUSS</td>
<td>Handout and answer any questions.</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>EMPHASIZE</td>
<td>You have control over whether you tell people, who you tell and how you tell them. Think about what is best for you and make sure YOU are ready.</td>
</tr>
<tr>
<td>STATE</td>
<td>Now we are going to practice telling someone you are on PrEP by doing some role-playing, even if you aren’t ready to tell someone yet. Choose someone who you may want to tell about PrEP in the future. Let me know who it is and provide me with some details about where the conversation is taking place. The more details you provide, the better. I will then pretend to be the person and react as I think the person might respond.</td>
</tr>
<tr>
<td>ALLOW</td>
<td>Time for participant to prepare then Conduct the role-play.</td>
</tr>
<tr>
<td>ASK</td>
<td>What was the most challenging thing about this role-play?</td>
</tr>
<tr>
<td></td>
<td>What part of this was easier than you thought it would be?</td>
</tr>
<tr>
<td></td>
<td>What surprised you going through this role-play?</td>
</tr>
<tr>
<td>ENCOURAGE</td>
<td>Participant to share one thing they liked, and one thing they wish they would do differently.</td>
</tr>
<tr>
<td>ALLOW</td>
<td>Time for discussion</td>
</tr>
</tbody>
</table>

**ACTIVITY B: ACTION PLAN: DISCLOSURE**

<table>
<thead>
<tr>
<th>NOTE</th>
<th>This activity is ONLY for participants who are interested in telling someone about being on PrEP.</th>
</tr>
</thead>
<tbody>
<tr>
<td>STATE</td>
<td>You have said that you are interested in telling someone that you are taking PrEP. Let’s develop an action plan to outline what steps you will take.</td>
</tr>
<tr>
<td>HANDOUT</td>
<td>“Action Plan: Disclosure” handout</td>
</tr>
<tr>
<td>STATE</td>
<td>Think about the specific person whom you would like to disclose your PrEP use to. Use this worksheet to think through the reasons why you want to disclose to that person. Then use this form to plan out the process.</td>
</tr>
<tr>
<td></td>
<td>Decide when you would like to tell them, where you will have the talk, what you will say, and how you will do it. Finally, think about what the potential costs and benefits of disclosing to this person would be.</td>
</tr>
<tr>
<td>ALLOW</td>
<td>Participants time to fill out their action plan. They may leave the worksheet with the counselor or take it home if they wish.</td>
</tr>
</tbody>
</table>
### ACTIVITY C: Negotiating PrEP Use in a Sexual Relationship

| STATE | You may decide that you want to talk to your husband, boyfriend or a sexual partner about using PrEP at some point. This might seem a bit difficult, but if you prepare yourself, it will be easier. Remember last time with discussed the “Safe TALK” strategy?  
Show “Safe TALK” handout and review if participant hasn’t seen it or doesn’t remember it |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMING</td>
<td>Choose an appropriate time to talk with your person. If the person that you need to talk with has a busy lifestyle, then it might be easier for you to set a meeting time. This way, each person’s attention can be focused on the issue.</td>
</tr>
<tr>
<td>ASSERTIVE COMMUNICATION</td>
<td>Clearly tell the person how you feel and what you want or need by being honest and direct. Think carefully about your relationship and pay attention to others’ responses. Depending on the specific person, you might have to address issues differently. Remember to use “I” statements, take deep breaths, keep a reasonable tone, and actively listen to the other person.</td>
</tr>
<tr>
<td>LOCATION</td>
<td>Choose a quiet place where you cannot be interrupted or overheard by others.</td>
</tr>
<tr>
<td>KNOWING WHAT TO SAY</td>
<td>Think about what you want to say in advance by sorting out your own feelings about the issue before talking with the other person. You might find that making a list or writing a letter of your thoughts and feelings will help you focus.</td>
</tr>
</tbody>
</table>
| STATE | Tell him some of the things you have learned about STIs and HIV. It’s also important to negotiate and listen to him. Keep in mind that it’s not only your right, but also your RESPONSIBILITY to make decisions that you will help you stay healthy.  
It’s very important to know what you will say in response to your partner’s questions, complaints, or efforts to change your mind. You can anticipate his reactions and responses and make the conversation a little easier for you. |
<p>| STATE | Let’s practice discussing PrEP with your husband/boyfriend. |</p>
<table>
<thead>
<tr>
<th>DISPLAY</th>
<th>How to talk PrEP with your partner handout...</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>What if your partner says...</td>
</tr>
<tr>
<td></td>
<td>• “I am faithful to you, you don’t need PrEP.”</td>
</tr>
<tr>
<td></td>
<td>• “PrEP doesn’t work.”</td>
</tr>
<tr>
<td></td>
<td>• “If you need PrEP, you must be sleeping around.”</td>
</tr>
<tr>
<td></td>
<td>• “You must have HIV and aren’t telling me.”</td>
</tr>
<tr>
<td>ASK</td>
<td>How would you respond to these statements by your partner? Let’s practice.</td>
</tr>
<tr>
<td>ROLE PLAY</td>
<td>Different ways to respond to the partner statements</td>
</tr>
<tr>
<td>DISCUSS</td>
<td>Alternative responses with the participant.</td>
</tr>
<tr>
<td>THANK</td>
<td>Participant for sharing her feelings and being open and honest about the process of disclosure.</td>
</tr>
</tbody>
</table>
SAFE T.A.L.K

TIMING

Choose an appropriate time to talk with your family or significant others. If the family member that you need to talk with has a busy lifestyle, then it might be easier for you to set a meeting time. This way, each person’s attention can be focused on the issue.

ASSERTIVE COMMUNICATION

Clearly tell your family member or significant others how you feel and what you want or need by being honest and direct. Think carefully about your relationship and pay attention to others’ responses. Depending on the specific person, you might have to address issues differently. Remember to use “I” statements, take deep breaths, keep a reasonable tone, and actively listen to your family member or significant others.

LOCATION

Choose a quiet place where you and your family member or significant others cannot be interrupted or overheard by others.

KNOWING WHAT TO SAY

Think about what you want to say in advance by sorting out your own feelings about the issue before talking with your family member or significant others. You might find that making a list or writing a letter of your thoughts and feelings will help you focus.
ACTION PLAN: DISCLOSURE

Think about one specific person to whom you would like to disclose your PrEP use. Let’s use this worksheet to think through the reasons why you might want to disclose to that person. Then use this form to plan out the process.

List all the reasons WHY you want to disclose to ________________.

**WHO am I disclosing to?**

**WHAT will I say?**

**WHERE will I say it?**

**WHEN will I have this conversation?**

**HOW will I do it?**

**Potential Costs:**

**Potential Benefits:**
How to talk PrEP with your partner…

Your partner says:

“So faithful to you, you don’t need PrEP.”

“PrEP doesn’t work.”

“If you need PrEP, you must be sleeping around.”

“You must have HIV and aren’t telling me.”
Section 13. Data Management

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The purpose of this document is to provide site staff with the information needed to complete electronic Case Report Forms (eCRFs) in MediData Rave.

The Statistics and Data Management Center (SDMC) for this study is the Statistical Center for HIV/AIDS Research and Prevention (SCHARP). SCHARP is located in Seattle, USA, and is in the US Pacific Time (PT) time zone.

**HPTN 084 SDMC Staff**

<table>
<thead>
<tr>
<th>Job Role</th>
<th>Name</th>
<th>Email Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sr. Clinical Data Manager**</td>
<td>Stephanie Beigel-Orme</td>
<td><a href="mailto:sbeigelo@scharp.org">sbeigelo@scharp.org</a></td>
</tr>
<tr>
<td>Clinical Safety Associate***</td>
<td>Sophie Hasan</td>
<td><a href="mailto:shasan@scharp.org">shasan@scharp.org</a></td>
</tr>
</tbody>
</table>

**For data management questions, contact the alias, sc.084cdm@scharp.org**

***For questions about clinical queries (queries that say “To Site from Safety” or “To Site from Coder”, please contact the SDMC Clinical Safety group: sc.clinsafety@scharp.org**
13.1 Medidata Rave Overview

Medidata Rave is the data management system used by SCHARP to receive and manage study data collected at study sites. Each site completes study eCRFs by entering data into the Medidata Rave study database. As specified in each site’s Source Documentation Standard Operating Procedure (SOP), data may be entered directly into the study database (i.e., electronic CRF is source), collected first on paper CRFs and then entered into the study database, and/or entered into the study database based on other non-CRF source documents (e.g., lab reports, testing logs, chart notes, etc.).

The HPTN 084 study database in Medidata Rave may be accessed at [www.imedidata.com](http://www.imedidata.com).

When using Medidata Rave, the internet browser chosen and internet connectivity quality will be the most critical factors affecting functionality, as Medidata is accessed via a URL using a web browser. Using an outdated browser will result in a warning banner on the log-in page of iMedidata. This warning will inform the user that their browser does not support security features that are being implemented in future iMedidata releases and to upgrade their browser. Users using any of the following browsers will see this banner:

- Internet Explorer – Versions older than 8.0
- Chrome – Versions older than 30.0
- Firefox – Versions older than 24.0
- Safari - Versions older than 7.0
- Opera - Versions older than 17.0

Each site’s Data Management SOP designates the site staff members responsible for entering data into the study database. SCHARP grants designated site staff access with specific user permissions to the study database. They are required to complete eLearning modules in Medidata, as assigned by SCHARP, before access is granted and data can be entered into the study database. For more detailed information, see the iMedidata Access Guide, posted on the HPTN 084 Atlas webpage.

Detailed guidance on data collection, entry, navigation and general use of Medidata Rave is provided in the Medidata Rave Electronic Data Capture (EDC) Training Manual, which is posted on the HPTN084 Atlas web page.

[https://atlas.scharp.org/cpas/project/HPTN/084/begin.view](https://atlas.scharp.org/cpas/project/HPTN/084/begin.view)

Site staff should contact the study Clinical Data Manager(s) with any questions related to study data collection and management. A representative from Medidata Solutions may be contacted (see contact information below) anytime a site has technical questions or problems related to access or use of the Medidata Rave software.
13.2 Data Entry/Quality Control

- Once data for an eCRF is completed and saved in the study database, the following may occur:
  - A system query may be automatically triggered in Medidata Rave (e.g., denoting incomplete or inconsistent data).
  - Manual data queries may be placed by the SCHARP Clinical Data Manager (CDM) and/or Clinical Safety Associate (CSA) after review of entered forms.
  - Data queries may be placed by the site monitor (i.e., PPD) after required review for certain forms and/or fields.
  - Coding queries may be placed by the SCHARP MedDRA coder to help clarify AE data.
  - Inconsistency queries may be manually placed during AE-EAE reconciliation.

- Queries, or QCs, appear in the Medidata Rave Task Summary on the study home page of designated site users (example below). Staff members designated by the site are responsible for routinely checking the Task Summary and correcting/updating study data to resolve any outstanding queries.

Task Summary Example:
• When site staff correct/update study data in response to a manual or coding query, SCHARP staff review the updated data and resolve the query or re-query as needed.

• When site staff correct/update study data in response to a monitoring query, the site monitor (i.e., PPD) reviews the updated data and resolves the query or re-queries as needed.

• If a site utilizes paper CRFs as source documents, any changes to the paper CRFs **must** be entered into the Medidata Rave study database.

**Electronic Signatures by Investigators**

Each site Investigator of Record or designee must sign off on each participant’s complete set of data, or ‘case book’ to attest that the data has been reviewed and is deemed to be accurate. Their iMedidata login credentials serve as their electronic signature. Please refer to the “Electronic Signature” section of the Medidata Rave EDC Training Manual and/or the Investigator e-Learning module for specific instructions on how to sign off on CRFs.

The SCHARP Clinical Data Manager(s) will provide directions for the timing of when the Investigator should perform the final review and sign the form pages. Please note that if an eCRF is signed off and a query is applied to the form or a change to the form occurs during the study, the electronic signature will be broken and the IoR will need to re-sign the form.

13.3 **eCRF Completion**

13.3.1 **Participant Identification number (PTID) Creation and Screening**

Each participant who provides written informed consent to be screened in HPTN084 will be assigned a Participant Identifier, or PTID. The PTID is created when site staff add a subject within their Medidata home study and site folder. Refer to the “Creating Subjects” section of the Medidata Rave EDC Training Manual and the CRF Completion Guidelines (CCGs) for specific instructions.
Each PTID is unique. It will be assigned to a single participant only at a given site and not assigned to any other participant at any site or in any study for which SCHARP is the SDMC.

PTIDs are nine digits, and formatted as “XXXYYYYYZ”. The PTID consists of three parts: the site number (XXX), the participant number (YYYYY), and a numerical check digit (Z). The check digit (Z) is a number generated by SCHARP with the participant number, and helps ensure that the correct PTID is recorded and entered.

If a participant does not enroll in the study, the following forms are required to document the Screening Visit: Screening Outcome, HIV Test Results, Plasma Storage, and VOICE Risk Score – Modified. Inclusion and exclusion criteria are documented on the Screening Outcome eCRF as well as reasons for not enrolling into the study.

If a participant returns at a later date to re-screen she must be assigned a new, unique PTID and treated as a new participant in the data management system.

13.3.2 Enrollment and Randomization

Prior to randomization eligibility must be confirmed, which includes a negative HIV test on a sample drawn at the Enrollment visit as well as a negative pregnancy test.

To randomize a participant, site staff mark ‘Yes’ to the question, “Is the participant ready to be randomized?” on the Randomization eCRF and click the “Save” button (see image below).

Once the Randomization eCRF is saved, a message will appear on the form that reads: “Subject successfully randomized” as shown in the image below. The Medidata Balance module will assign the participant to a treatment arm and the participant is considered successfully randomized. A participant is considered enrolled in the study once this step takes place.

Note that the participant’s randomly assigned treatment arm will not appear in the clinical study database, since the study is double-blinded. Rather, PAB-approved site pharmacists only (along with the study statisticians) will be provided restricted access to Medidata Balance to obtain the coded information needed to select and dispense the correct study medication.
Each time a participant is randomized an email confirmation will be sent to anyone with a Medidata account who is assigned the role of “CRC”, “IoR”, “Read only access” or “Pharmacist” to inform them of the new randomization. The randomization confirmation notice will include the following information:

Randomization Alert:
Study: HPTN084  
Environment: PROD  
Site Number: 12345  
Subject ID: 999999990

A Subject has been randomized at 2/9/2018 9:21:17 AM Calendar Date. Pharmacists can log into the [www.imedidata.com](http://www.imedidata.com) to view the participant’s assigned treatment.

All randomization notices should be kept in a secure location.

In the event the randomization confirmation email is not received, please follow the steps detailed below:

- Inform the site pharmacist that a randomization confirmation email for the randomized participant was not received (it does not mean that the participant was not randomized, just that the email did not get through to the site).
- Ask the site pharmacist to confirm the participant was successfully randomized by logging in to Balance.
- When final product preparations are to begin, provide the pharmacist with the PTID of the randomized participant and request that the pharmacist log into Medidata RTSM (Balance), locate the PTID, retrieve the treatment assignment, and prepare study product accordingly.
- Document all steps in the participant chart.
- Do not contact Medidata Support.

### 13.3.3 General Guidelines for eCRF Completion

- When completing an eCRF, refer to the CCG document, posted on ATLAS, for detailed instructions on data collection pertaining to the given form and fields on that form.
- Medidata Rave allows data to be entered directly into the study database (i.e., electronic CRF as source). Any data that is either collected first on paper CRFs or derived from non-CRF source documents (e.g., lab reports) should ideally be entered into Rave within 1-2 business days of the visit, though up to 5 days is acceptable.
- AEs should be entered within 3 days and EAEs within 24 hours.
- If some or all of the eCRFs will be completed first as paper CRFs, write the participant’s PTID and Visit Label (e.g., Week 6) or Visit code on the paper form. Any eCRF that does not collect study data does not need to be completed as a paper form, such as all “Y/N” forms that are used as triggers for log forms (e.g. Concomitant Medications Y/N or Adverse Event Y/N):
13.3.4 Visit Codes

Most eCRFs in the study database are set up within pre-defined study visit folders, so the visit name and code automatically appear (and do not need to be entered for required study visits). Interim Visit Codes do need to be assigned. For more information see section 13.6.

Please remember: For specimen collection, the visit code and date on the eCRF must match the visit code and date in the Laboratory and Data Management System (LDMS) database.

Visit codes for required visits are listed in table 13-1.

13.4 Visit Scheduling: Target Days and Visit Windows

Table 13-1 lists the HPTN 084 visit codes, target days and visit windows for each study visit. All windows are listed in days.

13.4.1 Target Days

A target date is the day in which a visit should ideally occur. Target dates for Step 1 visits are based on the date of Enrollment into the study; target dates for Step 2 visits are based on the date the Week 5 Visit is completed; and target dates for Step 3 visits on the day that the first Step 3 visit, Day 0, is conducted. Target dates do not change even if a visit in that step takes place before or after the target date. Whenever possible, visits should be completed on the target day for that visit.

13.4.2 Visit Windows

There are two types of visit windows in HPTN084. If a visit cannot be completed on the target date, it should be completed within the target visit window in order to be counted as “on time” in the Retention Report. If it is not possible to complete the visit on within the target window, the visit still needs to be completed within the allowable (larger) visit window in order to be considered “complete” in the Retention Report. Visits conducted before the target window opens but still within the allowable window are considered “complete” but “early” in the Retention Report. Visits conducted after the target window closes but still within the allowable visit window are considered “complete” but “late” in the Retention Report. If a visit doesn’t occur within the allowable window it will be considered “missed” in the Retention Report. Medidata Rave will not query for an overdue visit (i.e. the forms for that visit) until the allowable visit window has closed.
Table 13-1: HPTN 084 Visit Codes, Target Days, and Visit Windows

<table>
<thead>
<tr>
<th>Week</th>
<th>Visit Code</th>
<th>Day allowable window opens</th>
<th>Day target window opens</th>
<th>Target Day</th>
<th>Day target window closes</th>
<th>Day allowable window closes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>1.0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0/Enrollment</td>
<td>2.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Week 2</td>
<td>3.0</td>
<td>7</td>
<td>11</td>
<td>14</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>Week 4*</td>
<td>4.0</td>
<td>21</td>
<td>25</td>
<td>28</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0/Week 5*</td>
<td>5.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Week 6</td>
<td>6.0</td>
<td>4</td>
<td>4</td>
<td>7</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Week 9</td>
<td>7.0</td>
<td>18</td>
<td>25</td>
<td>28</td>
<td>31</td>
<td>41</td>
</tr>
<tr>
<td>Week 13</td>
<td>8.0</td>
<td>42</td>
<td>53</td>
<td>56</td>
<td>59</td>
<td>69</td>
</tr>
<tr>
<td>Week 17</td>
<td>9.0</td>
<td>70</td>
<td>81</td>
<td>84</td>
<td>87</td>
<td>97</td>
</tr>
<tr>
<td>Week 21</td>
<td>10.0</td>
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<td>126</td>
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<td>12.0</td>
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<td>Week 65</td>
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<td>Week 73</td>
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<td>Week 97</td>
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<td>617</td>
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<tr>
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<td>Week 185</td>
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<td>1253</td>
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### Step 3**

<table>
<thead>
<tr>
<th>Week</th>
<th>Visit Code</th>
<th>Day allowable window opens</th>
<th>Day target window opens</th>
<th>Target Day</th>
<th>Day target window closes</th>
<th>Day allowable window closes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0 (Step 3 only)</td>
<td>33.0</td>
<td>0</td>
<td>0</td>
<td>&lt;8 weeks from last injection</td>
<td>14</td>
<td>42</td>
</tr>
<tr>
<td>Week 12</td>
<td>34.0</td>
<td>43</td>
<td>70</td>
<td>84</td>
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<td>126</td>
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<td>Week 24</td>
<td>35.0</td>
<td>127</td>
<td>154</td>
<td>168</td>
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<td>210</td>
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<tr>
<td>Week 36</td>
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<td>211</td>
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<td>Week 48</td>
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<td>295</td>
<td>322</td>
<td>336</td>
<td>350</td>
<td>378</td>
</tr>
</tbody>
</table>

*Please note that the Week 4 and Week 5 Visits must be completed in order for a participant to move to Step 2. If a Week 4 or Week 5 Visit is delayed or missed, contact the CMC for further guidance.

**The target dates for all Step 2 visits are based off of the actual date of the Week 5 Visit. The target dates for all Step 3 visits are based off of the first Step 3 Visit, called “Step 3/Day 0”.

### Open Label Truvada Schedule

<table>
<thead>
<tr>
<th>Week</th>
<th>Visit Code</th>
<th>Day allowable window opens</th>
<th>Day target window opens</th>
<th>Target Day</th>
<th>Day target window closes</th>
<th>Day allowable window closes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0 (date injections permanently discontinue)</td>
<td>V201/or other*</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>202.0</td>
<td>43</td>
<td>70</td>
<td>84</td>
<td>98</td>
<td>126</td>
</tr>
<tr>
<td>Week 24</td>
<td>203.0</td>
<td>127</td>
<td>154</td>
<td>168</td>
<td>182</td>
<td>210</td>
</tr>
<tr>
<td>Week 36</td>
<td>204.0</td>
<td>211</td>
<td>238</td>
<td>252</td>
<td>266</td>
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<tr>
<td>Week 48</td>
<td>205.0</td>
<td>295</td>
<td>322</td>
<td>336</td>
<td>350</td>
<td>378</td>
</tr>
</tbody>
</table>

- Day 0 for Open Label Truvada Schedule may be a Step 2 visit code or 201. See Section 13.5 Alternate Visits.
### Pregnancy Schedule*

<table>
<thead>
<tr>
<th>Week</th>
<th>Visit Code</th>
<th>Day allowable window opens</th>
<th>Day target window opens</th>
<th>Target Day</th>
<th>Day target window closes</th>
<th>Day allowable window closes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0 (First positive Pregnancy Test)</td>
<td>XX.X</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>4 weeks after first positive pregnancy test</td>
<td>Interim visit XX.X</td>
<td>21</td>
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<td>28</td>
<td>--</td>
<td>35</td>
</tr>
<tr>
<td>Quarterly Visit 1 (12 weeks since first positive pregnancy test)</td>
<td>101</td>
<td>43</td>
<td>70</td>
<td>84</td>
<td>98</td>
<td>126</td>
</tr>
<tr>
<td>Quarterly Visit 2 (24 weeks since first positive pregnancy test)</td>
<td>102</td>
<td>127</td>
<td>154</td>
<td>168</td>
<td>182</td>
<td>210</td>
</tr>
<tr>
<td>Quarterly Visit 3 (36 weeks since first positive pregnancy test)</td>
<td>103</td>
<td>211</td>
<td>238</td>
<td>252</td>
<td>266</td>
<td>294</td>
</tr>
</tbody>
</table>

*Pregnancy schedule is to be followed throughout pregnancy and while participant is breastfeeding.

### Yearly/Annual Visits

<table>
<thead>
<tr>
<th>Week</th>
<th>Visit Code</th>
<th>Day allowable window opens</th>
<th>Day target window opens</th>
<th>Target Day</th>
<th>Day target window closes</th>
<th>Day allowable window closes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0 (Last visit participant at clinic HIV Test conducted)</td>
<td>XX.X</td>
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<td>0</td>
<td>0</td>
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<td>Yearly Visit 1</td>
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<td>358</td>
<td>365</td>
<td>372</td>
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<td>Yearly Visit 2</td>
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<td>730</td>
<td>737</td>
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<tr>
<td>Yearly Visit 3</td>
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<td>1088</td>
<td>1095</td>
<td>1102</td>
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<td>Yearly Visit 4</td>
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<td>1460</td>
<td>1467</td>
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<td>Yearly Visit 5</td>
<td>54.0</td>
<td>1642</td>
<td>1818</td>
<td>1825</td>
<td>1832</td>
<td>2008</td>
</tr>
<tr>
<td>Week</td>
<td>Visit Code*</td>
<td>Day allowable window opens</td>
<td>Day target window opens</td>
<td>Target Day</td>
<td>Day target window closes</td>
<td>Day allowable window closes</td>
</tr>
<tr>
<td>------------</td>
<td>-------------</td>
<td>----------------------------</td>
<td>-------------------------</td>
<td>------------</td>
<td>--------------------------</td>
<td>-----------------------------</td>
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<td>HIV Confirmatory Visit</td>
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<td>0</td>
<td>0</td>
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<td>43</td>
<td>70</td>
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<td>98</td>
<td>126</td>
</tr>
<tr>
<td>Week 24</td>
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<td>154</td>
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<td>182</td>
<td>210</td>
</tr>
<tr>
<td>Week 36</td>
<td>XX.X</td>
<td>211</td>
<td>238</td>
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<td>322</td>
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<td>350</td>
<td>378</td>
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</table>

*Due to unblinding considerations, there are no unique visit codes for seroconverters. The visit codes should reflect the next study visits for the participants.
Table 13-2: HPTN 084 Open Label Extension (OLE) Visit Codes, Target Days, and Visit Windows

<table>
<thead>
<tr>
<th>Week</th>
<th>Visit Code</th>
<th>Day allowable window opens</th>
<th>Day target window opens</th>
<th>Target Day</th>
<th>Day target window closes</th>
<th>Day allowable window closes</th>
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</thead>
<tbody>
<tr>
<td>4a Day 0 (Oral lead in)</td>
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<td>13</td>
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<tr>
<td>4c Day 0*</td>
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OLE Transition 1: Steps 4a → 4b → 4c

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<th>CAB / TDF/FTC</th>
<th>Day 0</th>
<th>Week 8</th>
<th>Week 16</th>
<th>Week 24</th>
<th>Week 32</th>
<th>Week 40</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>57.0 / 64.0</td>
<td>0</td>
<td>29</td>
<td>85</td>
<td>141</td>
<td>197</td>
<td>253</td>
<td>309</td>
</tr>
<tr>
<td>58.0 / 65.0</td>
<td>0</td>
<td>49</td>
<td>105</td>
<td>161</td>
<td>217</td>
<td>273</td>
<td>329</td>
</tr>
<tr>
<td>59.0 / 66.0</td>
<td>0</td>
<td>56</td>
<td>112</td>
<td>168</td>
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<td>280</td>
<td>336</td>
</tr>
<tr>
<td>60.0 / 67.0</td>
<td>0</td>
<td>63</td>
<td>119</td>
<td>175</td>
<td>231</td>
<td>287</td>
<td>343</td>
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<tr>
<td>61.0 / 68.0</td>
<td>0</td>
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<td>140</td>
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OLE Transition 2: Steps 4b → 4c

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<th>Week 16</th>
<th>Week 24</th>
<th>Week 32</th>
<th>Week 40</th>
<th>Week 48</th>
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<tbody>
<tr>
<td>57.0 / 64.0</td>
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<td>29</td>
<td>85</td>
<td>141</td>
<td>197</td>
<td>253</td>
<td>309</td>
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<tr>
<td>58.0 / 65.0</td>
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<td>105</td>
<td>161</td>
<td>217</td>
<td>273</td>
<td>329</td>
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<tr>
<td>59.0 / 66.0</td>
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<td>56</td>
<td>112</td>
<td>168</td>
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<td>280</td>
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<tr>
<td>60.0 / 67.0</td>
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<td>119</td>
<td>175</td>
<td>231</td>
<td>287</td>
<td>343</td>
</tr>
<tr>
<td>61.0 / 68.0</td>
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OLE Transition 3: Step 4c

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<th>CAB / TDF/FTC</th>
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<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 20</th>
<th>Week 24</th>
<th>Week 28</th>
<th>Week 32</th>
<th>Week 36</th>
<th>Week 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>57.0 / 64.0</td>
<td>3</td>
<td>25</td>
<td>53</td>
<td>81</td>
<td>109</td>
<td>126</td>
<td>154</td>
<td>182</td>
<td>210</td>
<td>238</td>
<td>266</td>
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<tr>
<td>58.0 / 65.0</td>
<td>3</td>
<td>28</td>
<td>56</td>
<td>84</td>
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<td>137</td>
<td>165</td>
<td>193</td>
<td>221</td>
<td>249</td>
<td>277</td>
</tr>
<tr>
<td>59.0 / 66.0</td>
<td>3</td>
<td>31</td>
<td>59</td>
<td>87</td>
<td>115</td>
<td>143</td>
<td>171</td>
<td>199</td>
<td>227</td>
<td>255</td>
<td>283</td>
</tr>
<tr>
<td>60.0 / 67.0</td>
<td>3</td>
<td>41</td>
<td>69</td>
<td>97</td>
<td>125</td>
<td>153</td>
<td>181</td>
<td>209</td>
<td>237</td>
<td>265</td>
<td>293</td>
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<tr>
<td>61.0 / 68.0</td>
<td>3</td>
<td>41</td>
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<td>181</td>
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<td>293</td>
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OLE Step 4d- Pregnant/Breastfeeding Participants**

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<th>Day 0</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 20</th>
<th>Week 24</th>
<th>Week 28</th>
<th>Week 32</th>
<th>Week 36</th>
<th>Week 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>57.0 / 64.0</td>
<td>3</td>
<td>28</td>
<td>56</td>
<td>84</td>
<td>112</td>
<td>140</td>
<td>168</td>
<td>196</td>
<td>224</td>
<td>252</td>
<td>280</td>
</tr>
<tr>
<td>58.0 / 65.0</td>
<td>3</td>
<td>31</td>
<td>59</td>
<td>87</td>
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<td>59.0 / 66.0</td>
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<td>41</td>
<td>69</td>
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<td>209</td>
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<td>265</td>
<td>293</td>
</tr>
<tr>
<td>60.0 / 67.0</td>
<td>3</td>
<td>41</td>
<td>69</td>
<td>97</td>
<td>125</td>
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<td>181</td>
<td>209</td>
<td>237</td>
<td>265</td>
<td>293</td>
</tr>
</tbody>
</table>

Delivery (Day 0) | 95.0**** | 0 | 0 | 0 | 3 | 6 |
Week 2, pp**** | 87.0 | 7 | 11 | 14 | 17 | 20 |
Week 4, pp | 88.0 | 21 | 25 | 28 | 31 | 31 |
Week 8, pp | 89.0 | 32 | 49 | 56 | 63 | 84 |
<table>
<thead>
<tr>
<th>Week</th>
<th>Visit Code</th>
<th>Day allowable window opens</th>
<th>Day target window opens</th>
<th>Target Day</th>
<th>Day target window closes</th>
<th>Day allowable window closes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 16, pp</td>
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<td>112</td>
<td>119</td>
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</tr>
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<td>Week 24, pp</td>
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<td>161</td>
<td>168</td>
<td>175</td>
<td>196</td>
</tr>
<tr>
<td>Week 32, pp</td>
<td>92.0</td>
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<td>224</td>
<td>231</td>
<td>252</td>
</tr>
<tr>
<td>Week 40, pp</td>
<td>93.0</td>
<td>253</td>
<td>273</td>
<td>280</td>
<td>287</td>
<td>308</td>
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<tr>
<td>Week 48, pp</td>
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<td>309</td>
<td>329</td>
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<td>364</td>
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</table>

**Step 5**

<table>
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<tr>
<th>Week</th>
<th>Visit Code</th>
<th>Day allowable window opens</th>
<th>Day target window opens</th>
<th>Target Day</th>
<th>Day target window closes</th>
<th>Day allowable window closes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0 (Day 0 no later than 8 weeks after the last injection)</td>
<td>71.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>70</td>
<td>84</td>
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**Step 6 (OLE2)**

<table>
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<tr>
<th>Week (continued from Step 4c CAB-LA Week 48 v 63)</th>
<th>Visit Code</th>
<th>Day allowable window opens</th>
<th>Day target window opens</th>
<th>Target Day</th>
<th>Day target window closes</th>
<th>Day allowable window closes</th>
</tr>
</thead>
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<tr>
<td>Week 56</td>
<td>116.0</td>
<td>365</td>
<td>385</td>
<td>392</td>
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<td>477</td>
<td>497</td>
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<td>Week 80</td>
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<td>Week 96</td>
<td>121.0</td>
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<td>122.0</td>
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<td>123.0</td>
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<td>777</td>
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<td>791</td>
<td>812</td>
</tr>
</tbody>
</table>

*Proceed with Step 4c*

**Additional pregnancies that also participate in 4d will be assigned visit codes in the following manner: pregnancy 2 176.0-196.0, pregnancy 3 276.0-296.0, etc. The visit windows will be as shown in the table for 4d.

***Delivery – OLE visit codes have been assigned 95.0-99.0 in the event of multiple deliveries for a single participant in the OLE.

****Post-partum visit
13.5 Types of Visits

Scheduled Visits

A scheduled visit is a required visit as dictated by the protocol.

Missed Visits

A scheduled visit is considered missed if it is not completed within its allowable visit window. Missed Visits are documented by completing a Missed Visit eCRF. Do not completed a Missed Visit CRF until you are sure that the visit has been missed (i.e. once the allowable window has closed and the participant has not returned to the clinic for that visit).

Split Visits

When a participant is not able to complete all required visit evaluations on the same day, the participant may return and complete the remaining evaluations on another day, as long as all evaluations for that visit are completed within the same allowable visit window for that visit. When such a split visit occurs, case report forms completed for the visit are all assigned the same visit code (even though some forms and evaluations will have different visit dates).

If a form contains a place to record a visit date, and a visit is split, record the date of the first visit associated with the split visit. The exception is the Week 5 Visit. If a Week 5 Visit is split, the date of visit will always be considered the date that the first injection was given.

Interim Visits

All interim visits/contacts with the participant should be documented in a chart note. Additionally, if the interim contact results in at least one newly-completed Medidata Rave CRF, the interim visit is assigned an interim visit code (visit number ending in something other than “.0”) and the Interim Visit eCRF is used to document the visit. All phone contacts that result in at least one newly-completed Rave CRF are also assigned interim visit codes.

To add an interim visit in Rave, click on ‘Add Event’ while in the participant’s folder and select ‘interim’:
An interim visit folder that contains the Interim Visit CRF is then added to the participant’s casebook, or set of folders.

13.6 Interim Visit Codes

Interim visit codes are assigned using the following guidelines:

- To the left of the decimal point, record the two-digit visit code for the most recently required follow-up visit even if the visit was missed and/or if the participant is within the next visit’s window.

- To the right of the decimal point:
  - #.1 = the first interim visit after the most recently-required visit,
  - #.2 = the second interim visit after the most recently-required visit,
  - #.3 = the third interim visit after the most recently-required visit, and so on.

**Example:** A participant completes all required study procedures at Week 6 (visit code =6.0). When the lab results are available later in the week, the site clinician notices the participant has an abnormal lab result that needs to be repeated. The participant returns a few days later to get her blood re-drawn. The second visit is considered an interim visit because the participant had already completed the required study procedures for visit 6.0. Since this is the first interim visit after visit 6.0, it is assigned visit code 6.1.

If participant is on alternate schedule, the interim visit code should reflect that. For example if she is on the Pregnancy Schedule and comes in after visit 102, the interim visit code should be 102.1.
13.7  **HPTN 084 Schedule of Forms**

The case report forms required for each study visit are summarized in Appendix 13A at the end of this SSP section.

13.8  **Completing Interviewer-administered Forms**

In order to standardize interviewer-administered data collection from site to site and to maximize quality, it is important that participant interviews be conducted with a non-biased, non-judgmental approach. Study staff should help a participant feel comfortable sharing personal information and opinions while asking the study questions in a consistent manner from participant to participant.

13.9  **Site Review (Quality Control) of CRFs**

As described in the site’s Data Management SOP, each site must perform Quality Control (QC) review steps, especially for paper CRFs prior to their data entry into the study database. While paper CRFs are being reviewed, it is important that they are stored and tracked systematically.

Below are specific review guidelines that should be followed for these QC review steps.

**QC Review Step #1**

- Review visit checklist to ensure all required procedures were completed
- Review completed paper CRFs and eCRFs based on participant responses to ensure completeness.

**QC Review Step #2 procedures for all visits:**

- Review visit checklist to ensure all required procedures were completed
- Ensure the PTID is correct, is recorded correctly on all paper source documents (including paper CRFs), and is the same on the paper source documents and the eCRFs for a given participant.
- Confirm that no participant identifiers other than the PTID are present on paper source documents, including paper CRFs.
- Ensure that the assigned visit code is correct, and is consistent between the paper source documents, including paper CRFs, the eCRFs, the LDMS Specimen Tracking Sheet, and LDMS for a given participant visit.
- If a log CRF is newly completed at a visit that is not an interim visit, make sure the corresponding “Y/N” CRF is marked “yes” for the visit. For example, if the Adverse Event CRF is completed, the Adverse Event Y/N CRF must be completed and marked “yes”.
• Concomitant Medications CRF: if a medication is taken for an AE, make sure the linked AE CRF is entered and saved first; then confirm on the Con Meds CRF that the appropriate, linked AE is selected. Also confirm that ‘Medication” is marked on the AE CRF.

**Additional QC Steps for Paper CRFs**

If some or all CRFs will first be completed on paper, the following review step should occur before forms are data-entered into the study database. Ideally, this review will happen once all lab results are available, so that all forms for a particular visit can be reviewed for consistency across documents. The goal is to correct data inconsistencies/errors prior to entering data into the study database, so that data is accurate, complete, and available at the time of data entry, thus minimizing the likelihood of data queries.

- Make sure a response has been recorded for each item, as required per instructions in the CCG document.
- If a response box with “other” or “specify” line is present, make sure there is text responding to that item.
- Make sure text responses are clearly recorded.
- For paper CRFs that are not source documents, make sure the data recorded on the paper CRFs matches or is consistent with the source documents.

**Additional QC Steps for Electronic CRFs (eCRF)**

When data is entered into the study database, and an eCRF is saved, system queries are automatically generated in response to inconsistent or incomplete data. Unlike the paper CRFs, which require manual review, eCRFs have the advantage of having the study database itself provide a real-time QC review to ensure data completeness.

No additional review steps are required for eCRFs that are source (i.e., the data is directly entered into the study database, rather than entered based on a separate paper CRF or other paper source document).

Electronic CRFs that are completed based on other paper source documents (e.g., data entry of paper CRFs or lab reports) should be reviewed to ensure that the data entered matches or is consistent with the source documents. The site’s Data Management SOP provides additional details, and specifies which staff members will perform the review.

**13.10 Form-Specific Completion Instructions**

Detailed form completion instructions for each form are provided in the Case Report Form Completion Guidelines (CCGs) document. The instructions document skip patterns, required items, formats of variables, and include guidance on completion of the eCRF in the study database. Some items on forms are straightforward and do not require specific instructions. Therefore, you may not see all forms or form items listed in the CCG, but rather only those items needing detailed explanation.
13.11 Case Report Forms

The current version of the eCRFs can be found on the HPTN084 Atlas web page.
### Appendix 13A: HPTN084 Schedule of Forms

<table>
<thead>
<tr>
<th>STEP</th>
<th>VISIT</th>
<th>FORM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Screening</td>
<td>Screening Outcome*</td>
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<td></td>
<td>Visit 1.0</td>
<td>Hematology</td>
</tr>
<tr>
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<td></td>
<td>Hepatitis B Test Results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatitis C Test Results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HIV Test Results*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medical History</td>
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<td>Pregnancy Test Results</td>
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<td>Screening Liver Function Test Results</td>
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<tr>
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<td>VOICE Risk Score - Modified*</td>
</tr>
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</table>

*All Screening forms are required if a participant enrolls in the study. In addition, the Conmeds and Contraception CRFs must be completed. If a participant does not enroll in the study, please complete only those forms identified with an *. 

<p>| 1    | Enrollment/Day 0 | Chemistry Testing                        |
|      | Visit 2.0        | Counseling                               |
|      |                 | Demographics                             |
|      |                 | Enrollment Visit                         |
|      |                 | Fasting Lipid Test Results               |
|      |                 | Hematology                               |
|      |                 | Hepatitis B Test Results                 |
|      |                 | HIV Test Results                         |
| 1    | Enrollment/Day 0 | Liver Function Test Results               |</p>
<table>
<thead>
<tr>
<th>STEP</th>
<th>VISIT</th>
<th>FORM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit 2.0</td>
<td>Pill Count – Enrollment</td>
</tr>
<tr>
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</tr>
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<td></td>
<td></td>
<td>Pregnancy Test Results</td>
</tr>
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<td>Urinalysis</td>
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<td>Whole Blood Storage</td>
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</table>

*Update the Concomitant Medications Log and Medical History Log at this visit as appropriate.*

1  

**Week 2**  
Visit 3.0  
Counseling  
Date of Visit – Step 1 Only  
Hematology  
HIV Test Results  
Pill Count – Step 1  
Plasma Storage  
Pregnancy Test Results

1  

**Week 4**  
Visit 4.0  
Counseling  
Date of Visit – Step 1 Only  
DBS Storage  
Hematology  
HIV Test Results  
Liver Function Test Results  
Pill Count – Step 1
<table>
<thead>
<tr>
<th>STEP</th>
<th>VISIT</th>
<th>FORM</th>
</tr>
</thead>
<tbody>
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</tr>
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<tr>
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<td>Pill Dispensation – Step 2 and 3</td>
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</tr>
</tbody>
</table>

*Complete the Injection Site Reaction Log if needed.*

<p>| 2    | Week 9 | Chemistry Testing                         |
|      | Visit 7.0 | Counseling                        |
|      |        | Date of Visit                           |</p>
<table>
<thead>
<tr>
<th>STEP</th>
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</thead>
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<td>Liver Function Test Results</td>
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<td>Pill Dispensation – Step 2 and 3</td>
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<td>Counseling</td>
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  - Date of Visit
  - Hematology
  - HIV Test Results
  - Liver Function Test Results
  - Plasma Storage
  - Pregnancy Test Results

*Complete the Injection Site Reaction Log if needed.*

<table>
<thead>
<tr>
<th>2</th>
<th>Week 17</th>
<th>Chemistry Testing</th>
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<tbody>
<tr>
<td></td>
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<td>Counseling</td>
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</table>

  - Date of Visit
  - Hematology
  - HIV Test Results
  - Injection Administration
  - Liver Function Test Results
  - Pill Dispensation – Step 2 and 3
<table>
<thead>
<tr>
<th>STEP</th>
<th>VISIT</th>
<th>FORM</th>
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<td><em>Complete the Injection Site Reaction Log if needed.</em></td>
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<td>Pill Dispensation – Step 2 and 3</td>
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<tr>
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<td></td>
<td><strong>Pregnancy Test Results</strong></td>
</tr>
</tbody>
</table>

*Complete the Injection Site Reaction Log if needed.*

2  
**Week 49**  
Visit 15.0  
Chemistry Testing  
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HIV Test Results  
Injection Administration  
Liver Function Test Results  
Pill Dispensation – Step 2 and 3  
Plasma Storage  
Pregnancy Test Results  

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**Week 57**  
Visit 16.0  
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Counseling  
Date of Visit  
Dried Blood Spot Storage  
Fasting Lipid Test Results  
Hematology  
Hepatitis C Test Results  
HIV Test Results  
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### Step 6

**V122.0 Week 104**
- Pregnancy Test Results - OLE

**V122.0 Week 104**
- Plasma Storage

**V122.0 Week 104**
- Dried Blood Spot Storage

**V122.0 Week 104**
- Injection Administration

**V122.0 Week 104**
- Missed Visit

**V122.0 Week 104**
- Additional Procedures - OLE

**V122.0 Week 104**
- Contraception - OLE

**V123.0 Week 112**
- Date of Visit - OLE

**V123.0 Week 112**
- Counseling

**V123.0 Week 112**
- HIV Test Results Y/N

**V123.0 Week 112**
- HIV Test Results

**V123.0 Week 112**
- Pregnancy Test Results - OLE

**V123.0 Week 112**
- Chemistry Testing

**V123.0 Week 112**
- Liver Function Tests

**V123.0 Week 112**
- STI Test Results

**V123.0 Week 112**
- Plasma Storage

### NOTE:

Some as-needed forms, such as the Adverse Event Log and the Product Hold/Discontinuation Log, can be found in the “Ongoing Logs” folder in the participant’s casebook. Other as needed forms, such as forms related to a participant’s pregnancy or early unblinding, can be added using the “Add Event” feature of Rave. Please see the CCGs for more information. The Product Choice CRF, which marks the start of the OL portion of the study is not listed along with Informed Consent V4 and V5 forms. In addition, all live births at 48 weeks, not in 4d require an Infant Assessment, this is not listed. Required CRFs for 4d apply for visit codes 176.0-194.0, 276.0-294.0, etc.
Appendix 13B: Participant Transfer and Receipt Process in Rave

Transferring Site:

1. When initiating a participant transfer to another site please contact the CDM alias ‘sc.084cdm@scharp.org’. Data managers included on the alias will facilitate the transfer process within Rave.
2. On the appropriate DOV CRF, indicate additional procedures were required to populate the Additional Procedures CRF. Then mark ‘Participant Transfer’ to populate that CRF.
3. Complete and save the Transfer form.
4. Ensure and all required eCRFs have been completed all data queries are resolved.
5. Investigator of Record (IOR) or designee must verify the data is complete and accurate by signing off on the participant’s eCRFs as follows:
   a. IoR (or designee) logs into Medidata and selects transferring PTID. On the Participant page, select “Grid View”:

   ![Grid View Image]

   b. Grid View lists all forms completed and expected for a participant.
   c. To sign off on all completed forms for the PTID, select “All” forms while in Grid View and then click “Sign and Save”.

   ![Sign and Save Image]
d. A signature prompt will display alongside a user ID and password text box. This serves as your electronic signature:

![Signature Prompt](image)

Note: The time that it takes for Medidata Rave to apply the IoR signature to all completed eCRFs will depend on the number of completed CRFs within the participant’s casebook. If there are a large number of completed eCRFs, the application of eSignatures may take up to several minutes.

IMPORTANT: When this step is complete please contact the SCHARP Clinical Data Manager so that the transfer can be completed within Rave. Please allow 1-2 days to complete this step.

**Receiving Site:**

1. Prior to the participant’s first scheduled visit at your site, confirm that the participant’s casebook is accessible within the Medidata Rave database from your site homepage. Note that the participant retains their original PTID.
2. When participant arrives for the first visit at your site, navigate to the participant’s Medidata casebook.
3. On the scheduled DOV CRF, indicate additional procedures were required to populate the Additional Procedures CRF. Then mark ‘Participant Receipt’ to populate that CRF.
4. Complete and save the Participant Receipt form.
5. Proceed with study visits in Rave.
Section 14. Computer Assisted Self-Interview (CASI)

14.1 Background

Computer Assisted Self-Interview (CASI) is a method for collecting information where a person reads questions on a computer screen and enters his or her answers directly into the computer. Many different types of electronic equipment (such as laptops, desktops, touch-screen computers or handheld devices) can be used to administer the CASI and various types of software can be used to design the data collection tool. For HPTN 084, the software used to design the survey is called REDCap Cloud (RCC). The HPTN084 Questionnaire is attached in Appendix 14A.

14.2 Technical Requirements

Device

The HPTN 084 CASI questionnaires are web-based (using RCC software) and can be taken from almost any device with a strong internet connection and a web browser. Please review RCC’s hardware and software requirements web page for more information:


In the room where the computer is located, there should be an electrical outlet and a jack for broadband connection unless a reliable wireless connection is used. If possible, the computer should be plugged into an AC power source. If a laptop is used, it is recommended that an external mouse be connected to the laptop. To minimize problems with computers, sites should avoid having food or drink nearby and keep the area where the computer is used clutter-free. An antivirus program should also be installed on the computer.

Each site is responsible for addressing issues of computer security and privacy as well as general issues such as lighting, ergonomics, and overall participant comfort. For questions about how to use a computer, sites should refer to the operations manual of the desktop or laptop. Issues such as where the computer(s) will be located and who is in charge of addressing computer-related issues should be addressed in each site’s study specific Data Management Standard Operating Procedure (SOP).
**Web Browser**

The following list of web browsers can be used to administer the CASI in RCC.

- Safari for macOS
- Microsoft Edge
- Google Chrome for Windows, macOS, and Linux desktops
- Mozilla Firefox for Windows, macOS, and Linux desktops

Make sure to always use the most current version of each browser to optimize the full capacity of the product’s features and functionality.

### 14.3 CASI Administration

The CASI will be administered to participants at many different visits. Participants are expected to complete each of the surveys. However, if the participant does not complete the survey (e.g., decides not to take it), this must be noted on the Behavioral Assessment CRF.

The questionnaire should **always be administered before any HIV/STD risk reduction counseling occurs** and the participant should complete the questionnaire in one sitting whenever possible.

#### 14.3.1 Survey URL

All surveys are accessed via a single URL provided by SCHARP. The link can be bookmarked in a web browser; however, **desktop shortcuts to the survey should not be created**: using a desktop link to connect to the survey will result in the site always connecting to the version of the survey that was running when they originally created the link rather than the most current version of the survey. It is likely that the survey will need to be updated over time; using a desktop link or shortcut will result in the old version of the survey being administered.

#### 14.3.2 CASI Practice for Site Staff

Staff members should be familiar with the content of the questionnaire in order to respond to participant questions. Staff members who will administer the survey should practice taking, and demonstrating how to use, the survey using test CASI Identification numbers (CASI IDs) provided by SCHARP. The staff member responsible for administering the CASI should be able to explain to the participant how to complete the survey, including how to use a computer and how to click through the questions using a mouse or touchpad.
14.3.3 Logging in to the CASI

When the participant is ready to begin the CASI, the staff member responsible for administering the survey will click on the appropriate URL. To find the surveys easily it is helpful to bookmark the URL you will be using in this study in your preferred web browser.

SCHARP will provide each site a list of CASI IDs in a link log to document the HPTN 084 PTIDs linked to each CASI ID.

Once the survey is opened, the staff member will enter a “CASI ID” from the list provided by SCHARP and the appropriate language (if applicable) and visit is selected. You will then be prompted to enter the PTID that is linked to the CASI ID.

Site staff will then answer one or more questions based on the visit; the answers to these questions will determine whether certain survey items will be included or excluded from the questionnaire.

Once these questions are answered, the participant is ready to take the survey on his or her own.

14.3.4 Navigating the Survey

Participants should navigate through the survey using the “< Prev” and “Next >” buttons that are part of the RCC software (Figure 1); they should not use the browser navigation buttons, which are the forward and back arrows usually located in the top left-hand corner of the browser (Figure 2). If the browser navigation buttons are mistakenly used, proper functioning of the survey can be disrupted, and data may be lost.

If a participant asks for help while taking the survey it is OK for a staff member to assist the participant. For example, if the Internet crashes, the survey freezes or the participant does not understand a question, it is OK for the site staff to help. For technical problems with RCC see Section 9.6.12.
14.3.5 Graphical Interface of the CASI

Most of the questions in the survey are answered by clicking on radio buttons (Figure 3), which consist of a group of circular white dots. When the participant selects one of the circles, a grey dot appears in the middle of the circle. Some of the questions in the survey are answered by clicking on check boxes (Figure 4). When the participant clicks on the check box, a blue check appears in the box. For some questions, instructions will indicate whether more than one check box may be selected.
Some questions require participants to type in a number (Figure 5). Sometimes an “other, specify” box is included as one of the response categories to capture participant responses that do not fit into one of the categories listed. When a participant’s response does not match or fit into one of the listed response categories, the participant may select “other” and type in their answer in the space provided (Figure 6).

When training the participant how to complete the survey on the computer, it can be helpful to point out the different ways they will be required to answer questions. There is also a brief (1-page) non-required section at the beginning of the survey for participants to practice entering responses, if desired.

14.3.6 Figure 3: Graphical Interface – Radio Buttons

Survey

3

Before we begin, would you like to answer some practice questions to make sure you understand how to complete the survey?

Yes

No

Figure 4: Graphical Interface – Check Boxes

Do you have any favorite colors? *Mark all that apply.*

- [ ] Not
- [x] Red
- [x] Yellow
- [x] Blue
- [ ] Green
- [x] Orange
- [ ] Purple
- [ ] Black
- [ ] White
- [ ] Other

*Prepared:
14.3.7 Submitting the Survey

Once the participant has answered the last question and clicked the “Submit” button, there will be a “thank you” message on the screen, which indicates the survey is complete.

It is important that the staff member responsible for administering the CASI survey double check that the participant has completed the survey before closing the browser.

14.3.8 What Happens to the Data?

It is important to understand, and to tell the participant, that the data the participant enters into the computer will never be stored on that computer. Each time the “next” button is clicked and the participant moves to the next question, the answer to the previous question will automatically be transmitted to the SCHARP-specific server. Site staff cannot access these data.
14.3.9 How to Resume a Partially Completed RCC Survey

If there is an intentional or accidental closure of the browser, if internet connection is lost, if the computer crashes, or if the participant needs to pause survey completion mid-visit for any reason, site staff will need to log the participant back in to the survey – once available - to allow completion.

Re-open the survey in a web browser and re-enter the participant ID. A page will appear with the following message: “We have located a survey in-progress. Would you like to continue where you last left off or start over?” (Figure 7).

Figure 7: Resuming a Partially Completed Survey

We have located a survey in-progress.

Would you like to continue where you last left off or start over?

Select the “Start-Over” button to open the survey to where the participant stopped.

14.3.10 Making Up a Missed CASI

If a participant misses taking the CASI at a required visit, or if there is a technical problem that cannot be resolved, the participant can take the CASI at a later time, but no later than the next required visit. If the survey was not done for Week 24 visit, it can be made up no later than Week 32 visit. *The original CASI ID/visit code combination for the missed survey is entered into the CASI.* For example, the Week 24 visit took place on 1 July 2023 but the survey was not done; the participant returned on 8 July and completed the survey. Week 24 would be entered into the survey.

14.3.11 Reminders

Before the participants take the survey, the site should remember to do the following:

- Explain the purpose of the survey and provide general instructions regarding how to use the computer, if necessary, such as how to use a mouse and how to “click” a button.
- Emphasize that the browser navigation buttons should never be used; only the buttons that say “Previous” and “Next” in the actual RCC survey should be used when navigating the survey.
- Remind the participants that their answers are completely confidential. The answers provided by the participants will never be permanently stored on the computer (they
are sent to a server that is only accessed by the Statistical and Data Management Center); therefore, none of the site staff will ever see their answers.

- Tell the participants that at the end of the survey they will see a “thank you” message on the screen. This indicates that the participants have completed the survey and they do not have to do anything else.
- Let the participants know that they can ask a site staff member for help, if needed.

14.4 Problems and Questions

If a problem with the CASI occurs, or for all other questions about the CASI including technical questions regarding RCC, contact the SCHARP Clinical Data Manager alias: sc.084cdm@scharp.org.

Stephanie Beigel-Orme
sbeigelo@scharp.org

Please remember that the SCHARP office is located in the Pacific Time Zone (GMT – 7:00). Therefore, “real time” responses to emails and phone calls may not always be possible. A response can be expected, however, within 24 hours.
HPTN 084 Open Label Extension Questionnaire
(CRF_43223_HPTN084OPENLABELEXTENSIONQUEST)

1

Please enter the participant's 9-digit PTID with no hyphens or spaces (for example: 999000111): *
(I_1685129829730_PTID)

Please enter the 5-7 digit CASI ID assigned to this participant (for example: EX001): *
(I_1685129829513_CASIID)

What visit is this?

Please select the visit from the dropdown menu.
* 
(I_1201319_VISIT)
<table>
<thead>
<tr>
<th>V77.0 - Step 4d - Week 4</th>
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<tbody>
<tr>
<td>V177.0 - Step 4d - Week 4</td>
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<td>V394.0 - Step 4d - Week 48 PP</td>
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<td>V494.0 - Step 4d - Week 48 PP</td>
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<td>V118.0 - Step 6-CAB LA - Week 72</td>
</tr>
<tr>
<td>V121.0 - Step 6-CAB LA - Week 96</td>
</tr>
</tbody>
</table>

Is participant currently pregnant?  
☐ Yes  ☐ No

[I_1201352_PREGNANT]
Language: *

[Language selection options: English, Shona, Setswana, Luganda, Zulu, Xhosa, Swahili, Luo, Chichewa, Afrikaans, Sotho, Siswati]

Is this questionnaire being completed by the participant directly or is an interviewer from the site staff reading the questionnaire to the participant and entering participant's responses? *

[Options: Participant is completing questionnaire, Interviewer is administering questionnaire]

Is this the first visit (transition) in Open label extension part of the study? *

[Options: Yes, No]

Did the participant switch study product at this visit? *

[Options: Yes, No]

Which study product is the participant is taking at this visit? *

[Options: CAB, TDF/FTC, None]

Is this study exit visit? *

[Options: Yes, No]
3

Thank you for joining this study. The following survey will ask you questions about your life, your beliefs, and your behavior.

Some of the questions ask about behavior that you may consider to be private or confidential. We are asking these questions because your answers could help us to understand whether the study product could help to slow the spread of HIV in your community. The information you provide is an important contribution to this study and will be kept confidential.

You can skip any question that makes you feel uncomfortable or stop taking the survey at any time.

(I_1685129829010_INTRO1_TXT)
Some questions will ask you about your behavior during a specific time period (for example, "in the past month"). Please pay close attention to the time period and only tell us about your behavior during that specific time.

Please do not use the browser back button to move through this survey as it may cause your answers to be lost. Only use the survey "Previous" and "Next" buttons at the bottom of each page to move through the survey.

If you have questions or need assistance, please let a member of the study staff know.

(I_1213839_ )
5

What did you like about an injectable method? 
*Mark all that apply.

- Nothing
- May protect against HIV
- Easier to use than other methods (i.e., don't have to remember to take pills; easier than condoms)
- May provide longer-term protection than other methods
- Can be used discreetly
- Is administered by a healthcare provider
- Does not interrupt sex
- Other
- Prefer not to answer

Other, specify:
(I_1685129826029_INJLIKESOTHERTEXT)

What concerns do you have about an injectable HIV prevention method? 
*Mark all that apply.

- None
- May not protect against HIV
- May be painful
- May cause harmful side effects
- Once injected
- Cannot be used discreetly
- Cost may be unaffordable
- Other
- Prefer not to answer

Other, specify:
(I_1685129825947_INJCONCERNOTHERTEXT)
If it were possible to change the way the injection was given, what kind of changes would you recommend? *  
Mark all that apply:
- None
- Reduce the volume of injectable
- Increase the duration of protection offered by the injectable (i.e., make it work for longer period of time)
- Receive the injection in the arm, instead of the buttock (bum)
- Receive the injection in the thigh, instead of buttock (bum)
- Other
- Prefer not to answer

Other, specify:

On a scale of 0 to 6, where 0 is none of the time and 6 is all of the time, please rate your responses to these questions.

How often do you find it inconvenient or difficult to receive your injection as recommended? *  

On a scale of 0 to 6, where 0 is no discomfort at all and 6 is a very great deal of discomfort, please rate your responses to these questions.
How much pain or discomfort have you experienced with your injection? *  
(I_1201262_DISCMFINJ)

- None at all
- 1
- 2
- Moderate discomfort
- 3
- 4
- 5
- A very great deal
- 6
- Prefer not to answer

What did/do you like about an oral pill method?  
Mark all that apply. *  
(I_1201188_ORALLIKES)

- Nothing
- May protect against HIV
- Easier to use than other methods (e.g., condoms)
- Can be used discreetly
- Does not interrupt sex
- Easily reversible
- Other
- Prefer not to answer

Other, specify:  
(I_1685129821351_ORALLIKESOTHERTEXT)

What concerns do you have about an oral HIV prevention method?  
Mark all that apply. *  
(I_1201244_ORALCONCRN)

- None
- May not protect against HIV
- May cause harmful side effects
- Requires taking a daily pill
- Cannot be used discreetly, without a partner's knowledge
- Cost may be unaffordable
- Other
- Prefer not to answer

Other, specify:  
(I_1685129824144_ORALCONCRNOTHERTEXT)
On a scale of 0 to 6, where 0 is none of the time and 6 is all of the time, please rate your responses to these questions.

How often do you find it inconvenient or difficult to take your oral study medication (i.e. the tablets) as recommended? *

None of the time 0
1
2
Half of the time 3
4
5
All of the time 6
Prefer not to answer

On a scale of 0 to 6, where 0 is no discomfort at all and 6 is a very great deal of discomfort, please rate your responses to these questions.

How much discomfort have you experienced with your oral study medication (i.e. the tablets)? *

None at all 0
1
2
Moderate discomfort 3
4
5
A very great deal 6
Prefer not to answer

What is your product choice today? *

Continue CAB LA
Continue TDF/FTC
Change to CAB LA with an oral lead in (4a)
Change to CAB LA with direct to injection (4b)
Stop CAB LA and start oral TDF/FTC
No prevention method
When making your choice about which PrEP method to use, who did you speak with to help you make the decision? *

(1_1201256_OLE_QORRES2)

○ No-one – it was my decision
○ The study staff
○ My mother
○ My sibling/s
○ My partner
○ My best friend
○ More than one of my friends
○ Others

What were the main reasons for making the choice you did today? *

(1_1201255_OLE_QORRES3)

○ This method suits my lifestyle best
○ This method feels safest for me
○ I want to get pregnant
○ I do not want my partner, family or friends to know that I am taking PrEP
○ Easier to use than other methods (e.g., condoms)
○ Does not interrupt sex
○ Easily reversible
○ Other
○ Prefer not to answer

Other, specify:

(1_1685129824888_OLE_QORRES3TEXT)

Which treatment option do you prefer? Please select one.

* (I_1201248_Q12)

○ CAB
○ TDF/FTC
○ Unsure

Considering the option you prefer, please answer the following questions:

(ad7cc850-cac8-4ed8-bfcc-88e337329118)
<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Neither Agree Nor Disagree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>I know which options are available to me. *</td>
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<td>(I_1685129821484_OLE_QORRES11)</td>
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<tr>
<td>I know the benefits of each option. *</td>
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<tr>
<td>I know the risks and side effects of each option. *</td>
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<td>(I_1685129821570_OLE_QORRES13)</td>
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<tr>
<td>I am clear about which benefits matter most to me. *</td>
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<tr>
<td>(I_1685129821612_OLE_QORRES14)</td>
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<tr>
<td>I am clear about which risks and side effects matter most to me. *</td>
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<td>(I_1685129821655_OLE_QORRES15)</td>
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</table>
I am clear about which is more important to me (the benefits or the risks and side effects). *
(I_1685129821698_OLE_QORRES16)

I have enough support from others to make a choice. *
(I_1685129821743_OLE_QORRES17)

I am choosing without pressure from others. *
(I_1685129821787_OLE_QORRES18)

I have enough advice to make a choice. *
(I_1685129821831_OLE_QORRES19)

I am clear about the best choice for me. *
(I_1685129821875_OLE_QORRES20)
I am satisfied with my decision. *
(I_1685129821920_OLE_QORRES21)

This decisions is easy for me to make. *
(I_1685129821963_OLE_QORRES22)

I felt I have made an informed choice. *
(I_1685129822008_OLE_QORRES23)

My decision shows what is important to me. *
(I_1685129822052_OLE_QORRES24)

I expect to stick to my decision. *
(I_1685129822096_OLE_QORRES25)
I am satisfied with my decision. *
5A

When you became pregnant this time, did you *

- [ ] want to become pregnant at this time
- [ ] want to wait a bit before becoming pregnant
- [ ] did not want to get pregnant at all.

Were you taking any of the study medicines when you became pregnant? *

- [ ] Yes
- [ ] No

If Yes, how often were you worried that the medicines would affect the baby? *

- [ ] Never worried
- [ ] Sometimes worried
- [ ] Often worried
- [ ] Prefer not to answer

Has being pregnant changed how much you feel at risk of getting infected with HIV? *

- [ ] Not at all
- [ ] A little
- [ ] A lot
- [ ] Prefer not to answer

If Yes, how often were you worried that the medicines would affect the pregnancy? *

- [ ] Never worried
- [ ] Sometimes worried
- [ ] Often worried
- [ ] Prefer not to answer

Aug 29, 2023 10:59:23 PM
6

We'd like to ask you some questions about yourself, your household, and your living circumstances.

How would you describe your current relationship status?
Note: Mark the response that best describes your situation.

- [ ] Married
- [ ] Not married, have a regular partner and live with him
- [ ] Not married, have a regular partner but do not live with him
- [ ] Sexually active, but no regular partner
- [ ] Not sexually active currently
- [ ] Prefer not to answer

Do you have a regular place or home where you stay and store your things?

- [ ] Yes
- [ ] No
- [ ] Prefer not to answer

On average, how many nights do you sleep in your regular place or home every week?

- [ ] Number of nights
- [ ] Prefer not to answer

Number of nights

- [ ] Yes
- [ ] No
- [ ] Prefer not to answer

Is the place you stayed last night your regular place or home?

- [ ] Yes
- [ ] No
- [ ] Prefer not to answer

With whom do you live?
Mark all that apply.

- [ ] Alone
- [ ] Partner
- [ ] Parent(s)
- [ ] Sibling(s)
- [ ] With own children
- [ ] Roommate(s)
- [ ] Other, specify:
- [ ] Prefer not to answer
Other, Specify
(I_1685129824019_LIVEWITHLWITHOTHTEXT)

In the past 6 months, how frequently did you worry that your household would not have enough food? *
(I_1201181_NOFOOD)

- Never worried
- Sometimes worried
- Often worried
- Prefer not to answer

In the last month, have you ever been paid for sex? *
(I_1201180_COMMSEX)

- Yes
- No
- Prefer not to answer

Do you identify yourself as a sex worker? *
(I_1201179_SEXWORKER)

- Yes
- No
- Prefer not to answer
We are now going to ask you questions about the people whom you might have talked to about this research.

Since your last visit, have you told anyone that you are taking part in this study? *

Did you specifically tell anyone that you are taking or using the study pills or injections? *

If you have told anyone you are participating in this study or taking or using the study pills or injections, answer "yes" or "no" for each person(s) you told in the list below.

Your regular or primary sex partner? *

Your mother or your father? *

Your sister or your brother? *
Other family members? *  
(I_1685129823770_TOLDOTHFAM)  
- Yes  
- No  
- Unsure  
- Not applicable  
- Prefer not to answer  

Friends? *  
(I_1685129823820_TOLDFRIEND)  
- Yes  
- No  
- Unsure  
- Not applicable  
- Prefer not to answer  

Neighbors? *  
(I_1685129823870_TOLDNEIGHBR)  
- Yes  
- No  
- Unsure  
- Not applicable  
- Prefer not to answer  

Nurse or doctor outside the study? *  
(I_1685129823920_TOLDRNMD)  
- Yes  
- No  
- Unsure  
- Not applicable  
- Prefer not to answer  

Other person(s)? Please specify: *  
(I_1685129823970_TOLDOTH)  
- Yes  
- No  
- Unsure  
- Not applicable  
- Prefer not to answer  

Other person(s)? Please specify:  
(I_1685129823549_TOLDOTH_TEXT)  

Was his/her/their reaction supportive?  
(2da42db2-975f-46df-b954-76a0f3070d2f)
Your regular or primary sex partner? * 
(I_1685129823161_SUPSP)

- Yes
- No
- Unsure
- Not applicable
- Prefer not to answer

Your mother or your father? * 
(I_1685129823209_SUPPARENT)

- Yes
- No
- Unsure
- Not applicable
- Prefer not to answer

Your sister or your brother? * 
(I_1685129823257_SUPSIBLING)

- Yes
- No
- Unsure
- Not applicable
- Prefer not to answer

Other family members? * 
(I_1685129823306_SUPOTHFAM)

- Yes
- No
- Unsure
- Not applicable
- Prefer not to answer

Friends? * 
(I_1685129823355_SUPFRIEND)

- Yes
- No
- Unsure
- Not applicable
- Prefer not to answer
Neighbors? *  
(I_1685129823404_SUPNEIGHBR)  

- Yes  
- No  
- Unsure  
- Not applicable  
- Prefer not to answer  

Nurse or doctor outside the study? *  
(I_1685129823452_SUPRNMD)  

- Yes  
- No  
- Unsure  
- Not applicable  
- Prefer not to answer  

Other person(s)? Please specify: *  
(I_1685129823500_SUPOTH)  

- Yes  
- No  
- Unsure  
- Not applicable  
- Prefer not to answer  

Other person(s)? Please specify:  
(I_1685129823089_SUPOTH_TEXT)
Here is a list of some things that other people do for us or give us that may be helpful or supportive.

**Please read each statement carefully and on a scale from 5 (meaning "As much as I would like") to 1 (meaning "Much less than I would like"), mark the response that is closest to your situation.**

1. I have people who care what happens to me. *
   - 5 As much as I would like
   - 4 Almost as much as I would like
   - 3 Some
   - 2 Less than I would like
   - 1 Much less than I would like
   - Prefer not to answer

2. I get love and affection. *
   - 5 As much as I would like
   - 4 Almost as much as I would like
   - 3 Some
   - 2 Less than I would like
   - 1 Much less than I would like
   - Prefer not to answer
I get chances to talk to someone about problems at work or school or with my housework. *

(I_1685129822802_WORKPROBS)

I get chances to talk to someone I trust about my personal or family problems. *

(I_1685129822850_FAMPROBS)

I get chances to talk about money matters. *

(I_1685129822897_MONEY)
I get invitations to go out and do things with other people. *
(I_1685129822945_INVITE)

- 5  As much as I would like
- 4  Almost as much as I would like
- 3  Some
- 2  Less than I would like
- 1  Much less than I would like
- Prefer not to answer

I get useful advice about important things in life. *
(I_1685129822992_ADVICE)

- 5  As much as I would like
- 4  Almost as much as I would like
- 3  Some
- 2  Less than I would like
- 1  Much less than I would like
- Prefer not to answer

I get help when I am sick. *
(I_1685129823041_HELPSICK)

- 5  As much as I would like
- 4  Almost as much as I would like
- 3  Some
- 2  Less than I would like
- 1  Much less than I would like
- Prefer not to answer
Now we'd like to ask some questions about your views on pregnancy.

**How important is it to you to NOT get pregnant now?**

<table>
<thead>
<tr>
<th>Option</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not important</td>
<td></td>
</tr>
<tr>
<td>Somewhat important</td>
<td></td>
</tr>
<tr>
<td>Very important</td>
<td></td>
</tr>
<tr>
<td>Prefer not to answer</td>
<td></td>
</tr>
</tbody>
</table>

**Compared to the other things in your life, how much do you worry about getting pregnant?**

<table>
<thead>
<tr>
<th>Option</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td></td>
</tr>
<tr>
<td>Somewhat</td>
<td></td>
</tr>
<tr>
<td>A lot</td>
<td></td>
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<tr>
<td>Prefer not to answer</td>
<td></td>
</tr>
</tbody>
</table>

**How would you describe your chances of getting pregnant in the next 6 months?**

<table>
<thead>
<tr>
<th>Option</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>No chance at all</td>
<td></td>
</tr>
<tr>
<td>Small chance</td>
<td></td>
</tr>
<tr>
<td>Moderate chance</td>
<td></td>
</tr>
<tr>
<td>Great chance</td>
<td></td>
</tr>
<tr>
<td>Prefer not to answer</td>
<td></td>
</tr>
</tbody>
</table>

**When do you think you might like to get pregnant?**

<table>
<thead>
<tr>
<th>Option</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td></td>
</tr>
<tr>
<td>As Soon as possible</td>
<td></td>
</tr>
<tr>
<td>Within next year</td>
<td></td>
</tr>
<tr>
<td>Within 2-5 years</td>
<td></td>
</tr>
<tr>
<td>Depends on circumstances</td>
<td></td>
</tr>
<tr>
<td>Unsure</td>
<td></td>
</tr>
</tbody>
</table>
Next, we will talk about how much you feel at risk of getting infected with HIV.

How much do you personally feel at risk of getting infected with HIV? *

- Not at all
- A little
- A lot
- Prefer not to answer

How much do you worry that your own behaviors put you at risk of getting infected with HIV? *

- Not at all
- A little
- A lot
- Prefer not to answer

How much do you worry that your partner or partners' behaviors put you at risk of getting infected with HIV? *

- Not at all
- A little
- A lot
- Prefer not to answer
The following questions are about times that you had different types of sex because you wanted to, not because you were forced or pressured to have sex.

Let's briefly go over the definitions of some terms so that you understand what is being asked. For vaginal sex, we mean when a man puts his penis into your vagina. For anal sex, we mean when a man puts his penis into your anus or buttocks (bum).

Please answer the following questions as honestly as you can. Remember that your answers are confidential.

At any time during the past month, have you had a primary partner?  
By primary partner, we mean a man you have sex with on a regular basis or who you consider to be your main or regular partner.

- Yes
- No
- Prefer not to answer
We'd like to know more about your relationship and the person that you have sex with regularly, i.e. your primary partner.

How old, in years, is your primary partner? If you are unsure of the exact age, please take your best guess. *

Age in years

Compared to you, is your primary partner much older, somewhat older, about the same age, somewhat younger, or much younger? *

Primary partner

How long have you been with your primary partner? Months

How long have you been with your primary partner? Years

Have you talked with your primary partner about his HIV status? *
Have you and your primary partner tested together for HIV? *
[I_1201348_MPTESTHIV]
- Yes
- No
- Prefer not to answer

What is the HIV status of your primary partner? *
[I_1201345_MPHIVSTAT]
- HIV negative
- HIV positive
- Don't know
- He doesn't know
- Prefer not to answer

Some people infected with the HIV virus are prescribed medication called antiretrovirals or ARVs by a doctor or a nurse to help them live longer. Is your primary partner taking ARVs? *
[I_1201185_MPART]
- Yes
- No
- Don't know
- Prefer not to answer

Do you think your primary partner had sex with anyone besides you in the past month? *
[I_1201183_MPOTHSEX]
- Yes
- No
- Unsure
- Prefer not to answer
In the past **month**, approximately how many male sex partners did you have – **including your primary partner, if you have one**? By sex partner, we mean someone who you had vaginal or anal sex with. *

**Number of partners**

Of these sex partners, approximately how many told you their HIV status?

**Number of partners**

Of these sex partners who told you their HIV status, how many were HIV positive?

**Number of partners**
Now we will shift to the number of times you had sex. If you can't recall exact numbers, please give your best estimate.

Number of times you had vaginal sex in the past month, approximately how many times did you have vaginal sex?

- Number of times
- Prefer not to answer

Number of times without a condom?

- Number of times
- Prefer not to answer

Of the times when you had vaginal sex in the past month, approximately how many times was it without a condom?

- Number of times
- Prefer not to answer

Of these times that you had vaginal sex without a condom in the past month, approximately how many were with partners whose HIV status you did not know?

- Number of times
- Prefer not to answer

That leaves times that you had vaginal sex without a condom with partners whose HIV status you did know in the past month. Of these times, approximately how many were with partners who were HIV positive?

- Number of times
- Don't know
- Prefer not to answer

Has the number of times you have sex changed since you became pregnant?

- Increased
- Decreased
- Stayed the same

Has the number of times you used a condom during sex changed since you became pregnant?

- Increased
- Decreased
- Stayed the same
In the past \textbf{month}, approximately how many times did you have anal sex? By "anal sex", we mean when your partner puts his penis into your anus or buttocks (bum). If you have not had anal sex in the past month, please enter '0'.

\begin{itemize}
  \item \texttt{I\_1201270\_NUMRA}
\end{itemize}

Number of times

\begin{itemize}
  \item \texttt{I\_1685129826110\_NUMRATEXT}
\end{itemize}

Of the times when you had anal sex in the past month, approximately how many times was it \textbf{without} a condom?

\begin{itemize}
  \item \texttt{I\_1201343\_RANOCOND}
\end{itemize}

Number of times

\begin{itemize}
  \item \texttt{I\_1685129830979\_RANOCONDTEXT}
\end{itemize}

Of these times that you had anal sex without a condom in the past month, approximately how many were with partners whose HIV status you \textbf{did not} know?

\begin{itemize}
  \item \texttt{I\_1201341\_RAHIVUNK}
\end{itemize}

Number of times

\begin{itemize}
  \item \texttt{I\_1685129830785\_RAHIVUNKTEXT}
\end{itemize}

That leaves times that you had anal sex without a condom with partners whose HIV status you \textbf{did} know in the past month. Of these times, approximately how many were with partners who were HIV positive?

\begin{itemize}
  \item \texttt{I\_1201337\_RAHIVPOS}
\end{itemize}

Number of times

\begin{itemize}
  \item \texttt{I\_1685129830373\_RAHIVPOSTEXT}
\end{itemize}

Has the number of times you have sex changed since you became pregnant?

\begin{itemize}
  \item \texttt{I\_1201335\_OLE\_QORRES31}
\end{itemize}

Has the number of times you used a condom during sex changed since you became pregnant?

\begin{itemize}
  \item \texttt{I\_1201334\_OLE\_QORRES32}
\end{itemize}
We as women often find ourselves in situations where we need someone to help us.

Sometimes people give or receive something in return for having sex. In the last month, have you had sex with a man because he provided you with or you expected that he would provide you with food, clothes, a place to sleep, a cell phone, money or other support?

* ☐ Yes ☐ No ☐ Prefer not to answer

What were you provided with in return for having sex? Mark all that apply.

☐ Food
☐ Clothes, shoes, accessories
☐ Cosmetics
☐ Cell phone
☐ Items for your child(ren) or family such as clothes, food, school fees
☐ Transport, tickets or money for transport
☐ Your own school fees or residence fees
☐ Somewhere to stay
☐ Cash
☐ Other
☐ Prefer not to answer

Other, specify:

(1685129822318_PROVIDEDOTHERTEXT)
Now we will ask you some questions about your relationships with any of your partners. We know that relationships can have good and bad moments. Some questions may be difficult to answer and we would like to remind you that your answers will be kept CONFIDENTIAL.

In the past 6 months, have any of your partners punched, slapped, kicked, bit you, or caused you any type of physical harm?

- Yes
- No
- Prefer not to answer

In the past 6 months, have any of your partners insulted, ignored or humiliated you, yelled at you, or made you feel ashamed or bad about yourself?

- Yes
- No
- Prefer not to answer

In the past 6 months, have any of your partners forced you to have sex or perform any sexual act, or touched you sexually in any way that you did not want?

- Yes
- No
- Prefer not to answer

In the past 6 months, have any of your partners made you feel afraid, unsafe or in danger?

- Yes
- No
- Prefer not to answer
18

We'd like to know more about the way you have felt or behaved in the past week. In the list below, please indicate how often you have felt this way during the past week by ticking the appropriate box for each question.

I felt depressed. *  
* I was bothered by things that usually don't bother me. *  
* I had trouble keeping my mind on what I was doing. *  
* I felt that everything I did was an effort. *

<table>
<thead>
<tr>
<th>Question</th>
<th>Rarely or none of the time (less than 1 day)</th>
<th>Some or a little of the time (1-2 days)</th>
<th>Occasionally or a moderate amount of time (3-4 days)</th>
<th>All of the time (5-7 days)</th>
<th>Prefer not to answer</th>
</tr>
</thead>
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<tr>
<td>I felt depressed.</td>
<td></td>
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<td>* I was bothered by things that usually don't bother me.</td>
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<tr>
<td>Question</td>
<td>Options</td>
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<tr>
<td>I felt hopeful about the future. *</td>
<td>- Rarely or none of the time (less than 1 day)</td>
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<td>- Some or a little of the time (1-2 days)</td>
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<td></td>
<td>- All of the time (5-7 days)</td>
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<td></td>
<td>- Prefer not to answer</td>
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<tr>
<td>I felt fearful or afraid. *</td>
<td>- Rarely or none of the time (less than 1 day)</td>
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<td></td>
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<td></td>
<td>- Prefer not to answer</td>
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<tr>
<td>My sleep was restless. *</td>
<td>- Rarely or none of the time (less than 1 day)</td>
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<td></td>
<td>- Prefer not to answer</td>
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<tr>
<td>I was happy. *</td>
<td>- Rarely or none of the time (less than 1 day)</td>
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<tr>
<td></td>
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<tr>
<td></td>
<td>- Prefer not to answer</td>
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<td></td>
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<tr>
<td>I felt lonely. *</td>
<td>- Rarely or none of the time (less than 1 day)</td>
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<td></td>
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<td></td>
<td>- Prefer not to answer</td>
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</tbody>
</table>
In your life, have you ever had any experience that was so frightening, horrible, or upsetting that, in the past month, you:

<table>
<thead>
<tr>
<th>(I_1685129826788_TRAUMA_TXT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have had nightmares about it or thought about it when you did not want to?</td>
</tr>
<tr>
<td>* (I_1201280_NIGHTMARE)</td>
</tr>
<tr>
<td>Tried hard not to think about it or went out of your way to avoid situations that reminded you of it?</td>
</tr>
<tr>
<td>* (I_1201279_AVOID)</td>
</tr>
<tr>
<td>Were constantly on guard, watchful, or easily frightened?</td>
</tr>
<tr>
<td>* (I_1201278_ONGUARD)</td>
</tr>
<tr>
<td>Felt empty, numb or detached from others, activities, or your surroundings?</td>
</tr>
<tr>
<td>* (I_1201277_NUMB)</td>
</tr>
</tbody>
</table>

I could not "get going", I did not feel motivated.  *

<table>
<thead>
<tr>
<th>(I_1685129827346_MHGETGOING)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rarely or none of the time (less than 1 day)</td>
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<td>Some or a little of the time (1-2 days)</td>
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<tr>
<td>Prefer not to answer</td>
</tr>
</tbody>
</table>

August 29, 2023 10:59:23 PM
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Now we would like to know more about your alcohol use. For alcohol, we mean beer, wine, home or local brews.

How often do you have a drink containing alcohol?

☐ Never
☐ Monthly or less
☐ 2 to 4 times a month
☐ 2 to 3 times a week
☐ 4 or more times a week
☐ Prefer not to answer

How many drinks containing alcohol do you have on a typical day when you are drinking?

☐ 1 or 2
☐ 3 or 4
☐ 5 or 6
☐ 7 to 9
☐ 10 or more
☐ Prefer not to answer

How often do you have six or more drinks on one occasion?

☐ Never
☐ Less than monthly
☐ Monthly
☐ Weekly
☐ Daily or almost daily
☐ Prefer not to answer

In the past month, did you have a drink containing alcohol just before or during sex?

☐ Yes
☐ No
☐ Prefer not to answer

In the past month, did you use drugs just before or during sex?

☐ Yes
☐ No
☐ Prefer not to answer
In the past month, has your partner been drunk from alcohol? * 

☐ Yes  
☐ No  
☐ Prefer not to answer

Now we'd like to ask you some questions about drug use. Don't include drugs that have been prescribed to you by a doctor or other health care provider.

In the past month, how often have you used each of the following substances? 

Cannabis (Also called marijuana, pot, grass, dakka, dagga or hash) * 

☐ Never  
☐ Less than monthly  
☐ Monthly  
☐ Weekly (At least once a week)  
☐ Daily or almost daily  
☐ Prefer not to answer

Cocaine (Also called coke, crack, or snow) * 

☐ Never  
☐ Less than monthly  
☐ Monthly  
☐ Weekly (At least once a week)  
☐ Daily or almost daily  
☐ Prefer not to answer

Amphetamine-type stimulants (For example Tik/Crystal Meth, ecstasy, speed, or diet pills) * 

☐ Never  
☐ Less than monthly  
☐ Monthly  
☐ Weekly (At least once a week)  
☐ Daily or almost daily  
☐ Prefer not to answer
Inhalants (For example glue, petrol, paint thinner, nitrous) *
(I_1685129828194_INHALANT)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Option</th>
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<tbody>
<tr>
<td></td>
<td>Never</td>
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<td></td>
<td>Less than monthly</td>
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<td></td>
<td>Weekly (At least once a week)</td>
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<td>Daily or almost daily</td>
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</table>

Sedatives or sleeping pills (For example serepax, rohypnol, quaaludes/mandrax) *
(I_1685129828255_SEDATIVE)

<table>
<thead>
<tr>
<th>Frequency</th>
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<tbody>
<tr>
<td></td>
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Hallucinogens (For example nyaope/whoonga, LSD, acid, mushrooms, PCP, Special K) *
(I_1685129828317_HALLUCIN)

<table>
<thead>
<tr>
<th>Frequency</th>
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<td>Daily or almost daily</td>
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<td>Prefer not to answer</td>
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</table>

Opioids (For example heroin, morphine, methadone, etc.) *
(I_1685129828377_OPIOID)

<table>
<thead>
<tr>
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<td>Daily or almost daily</td>
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<td>Prefer not to answer</td>
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</table>

Prescription drugs for non-prescription purposes (For example codeine (including cough syrup), efavirenz, valium) *
(I_1685129828437_RXDRUG)

<table>
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<tr>
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<tbody>
<tr>
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<td>Daily or almost daily</td>
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<td>Prefer not to answer</td>
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<tr>
<td>Question</td>
<td>Options</td>
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<td>-------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Have you ever used a needle to inject drugs?</td>
<td>Yes, No, Prefer not to answer</td>
</tr>
<tr>
<td>Have you used a needle to inject drugs in the past month?</td>
<td>Yes, No, Prefer not to answer</td>
</tr>
</tbody>
</table>

**Other**

(1_1685129828497_OTHDRUG)

(1_1201301_INJECTEVER)

(1_1201300_INJECTMO)
20

We will now ask you some questions about your experience participating in this trial.

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did you ever feel that people looked at you different because you were using TDF/FTC and injections?</td>
<td>Yes, No, Prefer not to answer</td>
</tr>
<tr>
<td>How difficult has it been for you to attend the study visits?</td>
<td>Not at all difficult, A little more difficult than I might have thought, Moderately difficult, Quite difficult, Prefer not to answer</td>
</tr>
</tbody>
</table>
21

We have asked you a number of questions today. Some of them may have caused you to feel worried or sad. Would you like to talk to someone about any of your answers? *

(I_1201333_NEED2TALK)

☐ Yes
☐ No
☐ Prefer not to answer

Thank you very much for taking the time to complete this survey. Please let a staff member know that you are done.

(I_1685129830046_ENDPAGETEXT)
Section 15. Reporting Plan

15.1 Purpose of Reporting Plan

The purpose of this reporting plan is to:

- identify the content of each HPTN084 report;
- identify those responsible for production and distribution of each report;
- identify who should receive and review the reports so corrective action (if necessary) is taken.

The reporting plan is prepared by the HPTN084 Clinical Data Manager at SCHARP in conjunction with SDMC HPTN084 statisticians and programmers.

15.2 Reports

The table below provides detailed information about each report that will be produced for HPTN 084, including the distribution frequency and distribution list. The exact day of the week these reports are distributed will be determined once data collection begins.
<table>
<thead>
<tr>
<th>Report Name</th>
<th>Purpose</th>
<th>Components</th>
<th>Distribution Frequency</th>
<th>Responsibility for Preparation</th>
<th>Distribution Platform</th>
<th>Distribution List</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Summarizes screening at each site as reflected by case report form data</td>
<td>The number of participants screened, number enrolled, and reasons not enrolled for all sites individually as well as all sites combined.</td>
<td>Daily</td>
<td>SDMC Protocol Programmer and/or Statistical Programmer</td>
<td>Atlas <a href="http://scharp.atlas.org">http://scharp.atlas.org</a></td>
<td>Anyone</td>
</tr>
<tr>
<td>Enrollment</td>
<td>To monitor participant accrual as reflected by case report form data</td>
<td>Enrollment data are presented for all sites individually as well as all sites combined. Includes site activation date, dates of first enrollments, duration of accrual, and the number of participants enrolled each week compared with weekly enrollment targets.</td>
<td>Daily</td>
<td>SDMC Protocol Programmer and/or Statistical Programmer</td>
<td>Atlas <a href="http://scharp.atlas.org">http://scharp.atlas.org</a></td>
<td>Anyone</td>
</tr>
<tr>
<td>Retention</td>
<td>To monitor participant retention as reflected by case report form data</td>
<td>Retention data are presented for all sites individually as well as all sites combined. Includes the total number participants randomized who 1) completed a visit</td>
<td>Daily</td>
<td>SDMC Statistical Programmer</td>
<td>Atlas <a href="http://scharp.atlas.org">http://scharp.atlas.org</a></td>
<td>Anyone</td>
</tr>
<tr>
<td>Report Name</td>
<td>Purpose</td>
<td>Components</td>
<td>Distribution Frequency</td>
<td>Responsibility for Preparation</td>
<td>Distribution Platform</td>
<td>Distribution List</td>
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</tr>
<tr>
<td>Data Management Quality</td>
<td>To provide information on site performance with regard to key data management and data quality metrics</td>
<td>Data are presented for all sites individually as well as all sites combined. Cumulative and previous-month statistics including: - Percentage of CRFs entered within 7 calendar days of study visits - Percentage of AEs entered within 3 days of date reported to site</td>
<td>Monthly</td>
<td>SDMC</td>
<td>Atlas</td>
<td><a href="http://atlas.scharp.org">http://atlas.scharp.org</a></td>
</tr>
</tbody>
</table>

Total retention is calculated as the number of enrolled participants who completed follow-up visits divided by the total number of participants expected for a visit.

(on time, early or late) and 2) did not complete a visit (visit was missed or ppt was terminated early).
<table>
<thead>
<tr>
<th>Report Name</th>
<th>Purpose</th>
<th>Components</th>
<th>Distribution Frequency</th>
<th>Responsibility for Preparation</th>
<th>Distribution Platform</th>
<th>Distribution List</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site-Specific Specimen Monitoring</td>
<td>To identify stored specimens whose information in LDMS does not match corresponding information collected on case report forms</td>
<td>Site-specific listings of all discrepancies between specimens listed as “stored” in case report forms and data entered into LDMS as well as LDMS data entry errors.</td>
<td>Bi-monthly</td>
<td>SDMC Lab Data Operations (LDO) Group</td>
<td>E-mail</td>
<td>Site Study Coordinator, Other site staff as requested, Laboratory Center Representative, SDMC Clinical Data Manager</td>
</tr>
<tr>
<td>Summary Specimen Monitoring</td>
<td>To provide the Laboratory Center (LC) with a summary for all sites of summary listing for all discrepancies between the case report form stored specimen data</td>
<td>Summary listing for all sites of all discrepancies between the case report form stored specimen data</td>
<td>Bi-monthly</td>
<td>SDMC Lab Data Management (LDM) Group</td>
<td>E-mail</td>
<td>Laboratory Center Representative,</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Report Name</th>
<th>Purpose</th>
<th>Components</th>
<th>Distribution Frequency</th>
<th>Responsibility for Preparation</th>
<th>Distribution Platform</th>
<th>Distribution List</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Monitoring Committee (SMC)</td>
<td>To monitor the overall progress of the study and study conduct at each site</td>
<td>Summary by site and overall. Report includes information on trial design and SMC history, accrual, baseline characteristics of participants, enrollment/randomization, and retention of participants, social harms/impacts, protocol deviations, completion of Computer-Assisted Self Interviewing (CASI) data, termination, and other study conduct information, as required by the SMC.</td>
<td>Will occur after ~ 4 months of enrollment and every 6 months thereafter</td>
<td>SDMC Statistical Research Associates (SRAs) and Protocol Statistician, with assistance from SCHARP study team</td>
<td>Atlas <a href="http://scharp.atlas.org">http://scharp.atlas.org</a></td>
<td>SMC (open and closed reports), Protocol Chairs (open report only), Selected members of HPTN LOC, SDMC, LC, DAIDS and Site IoRs, (open report only)</td>
</tr>
<tr>
<td>Report Name</td>
<td>Purpose</td>
<td>Components</td>
<td>Distribution Frequency</td>
<td>Responsibility for Preparation</td>
<td>Distribution Platform</td>
<td>Distribution List</td>
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</tbody>
</table>
| **Data Safety Monitoring Board (DSMB)** | To monitor efficacy and safety as well as to perform an administrative review and/or design review | Open report includes: all components listed for the SMC Open Report.  
Closed report includes: all components listed for the SMC report by treatment arm, with the addition of adverse event data and HIV-infection data. | Every 6 months or as determined by the DSMB | SDMS Statistical Research Associates and Protocol Statistician, with assistance from SCHARP study team | Mail or E-mail | DSMB members only |
Section 16. Data Communiqués

For HPTN084, SCHARP will use “Data Communiqués” to document and communicate data decisions and procedures that are made or revised during the study.

Data Communiqués are considered official study documentation. As such, each time a Data Communiqué is distributed, please circulate it among relevant staff for their review, print the Data Communiqué, and place it in this section of each HPTN084 SSP binder in your possession. Consider each Data Communiqué an official part of the SSP.

Each Data Communiqué sent will consist of three sections: a Reminders section, used to remind sites of specific data collection or forms completion procedures; a Clarification section, used to clarify data collection or form completion procedures; and an Updates section, used to communicate when an updated version of a form is being issued or to notify the sites that an updated version of the forms instructions is about to be distributed (for example).

Note that a “Data Communiqué” does not request specific actions or corrections to a particular participant’s data - it is just a listing of general items to keep in mind when performing data collection for the study.
Section 17. COVID-19 Measures

17.1 Overview of Section 17

This section provides a brief overview of recommendations for trial conduct during the COVID Pandemic.

17.2 Conducting visits

These recommendations are made with the goal of ensuring both participant and staff safety and respecting the public health recommendations to minimize disease transmission.

Sites may choose to provide ICFs to participants ahead of visits to minimize time on site and participant/site contact and to allow participants to read, make notes, discuss with family and friends if needed. Prior to implementing such a plan, sites should develop an SOP detailing the procedures and methods for the process which should also be approved by applicable ethics/regulatory authorities. The site may also contact the potential participant telephonically to discuss the forms and any questions she may have. When contacting the participant, the site must confirm the participant identity (name, date of birth, and potentially information known to the site and the participant but not a 3rd party) and document the conversation in chart notes. This does not mean that the consent process may be entirely remote. Sites that are able may deliver, mail, WhatsApp, or share by means of other communication platforms the Informed Consent(s) to participants prior to a study visit so that they may review the form. Given that the consent form is unsigned, it gives participants an opportunity to discuss with her partner or family prior to signing and to identify any potential barriers to consent prior to participation. When the participant presents to the clinic for a visit, staff will offer a general overview of the consent form and answer any questions and sites may then obtain the wet signature and assessment of understanding. In some cases, a complete review may be necessary.

Note: Make sure that any study materials (including blank informed consents and flyers) are shared without risk of harm.

- Sites can always counsel participants to think about who they want to talk to share information with ahead of time, and if the participant indicates that she is concerned about her partner then a secure channel for communication should be identified.
- The issues of security with sending blank informed consents via WhatsApp or other communication platforms apply to participants that are already enrolled and that are re-consenting.
Follow-up visits should continue to ensure safety of the participants in alignment with local guidance and protocol where possible.

1. In the event that CRS operations are diminished or suspended entirely, and where conduct of study visits is not possible either because of staffing or operational concerns, please note the following:

   For participants on maintenance doses of CAB LA: Injections may be lengthened to 12 weeks (ie the full visit window) in the event of prolonged lockdowns or ongoing COVID disruption. Every effort should be made to confirm participant identity prior to initiating data collection. For example, information like name, date of birth, and responses about clinic or study information might be considered reasonable ways to confirm participant identity. Participants may be reimbursed for telephonic data collection, given that there may be costs to them associated with phone calls, and this is acceptable to the local IRB/REC. If for some reason participants cannot receive study product, they are advised to take additional measures to prevent HIV infection and exposure by all means available until they can return to study site. If they use non-study provided open-label PrEP during this period they should be encouraged to keep a log of dates of use should they use this option.

   For participants on TDF/FTC: Participants should continue on daily unblinded oral product. Where participants cannot report for quarterly visits, participants should continue study product and where possible sites should explore delivery of product directly to participants from site investigational pharmacies. The DAIDS guidelines for shipping product should be followed. If not feasible, participants should be counselled to use other available means to protect themselves against HIV exposure and infection and pregnancy prevention until they are able to return to study participation. IoR can use their judgement about ongoing dispensation of oral product in these extraordinary circumstances without routine HIV and creatinine testing, based on known previous renal function, risk and adherence. Self-testing for HIV may also be useful in this setting if practical. The same guidance would apply to pregnant participants.

   For annual follow up if applicable: Annual visits should be delayed until study conduct can be resumed at the site.

2. PLEASE NOTE: Notify the protocol chairs, LOC, LC, SDMC and DAIDS as soon as possible of any updates to your site-specific plan. Please note that additional guidance was issued to CTU PIs and CRS leaders regarding considerations for visits during this extraordinary time by DAIDS.

   Sites should consider procedures for symptom screening and isolation of suspected cases and linkage to testing based on national guidelines.
17.3 **Incomplete or Missed Visits**

Any procedures that cannot be conducted per protocol should be recorded as protocol deviations per guidance in SSP Section 3, and per the Data Communique #8. Follow Data Communique #8 Dated 2 April 2020 for instructions on Missed Visits, Telephonic Visits, Partial Visits, Product Holds or Discontinuations, Open Label Truvada Administration and guidance on Pill Count/ Dissemination CRFs (https://www.hptn.org/sites/default/files/inline-files/HPTN084_Data_Communique_8_20200402.pdf).

In addition, teams should continue to send queries to the CMC. Where possible CMC queries should be sent ahead of anticipated participant visits to ensure sufficient response time from the CMC. Where queries are sent on the same day and where an immediate response is not possible, investigators may use their discretion regarding the dispensing of study product after assessment of safety parameters.

17.4 **Covid-19 vaccinations**

If a participant has been vaccinated please document this on the ConMeds CRF. If the vaccine is part of a clinical trial also contact the HPTN 084 CMC when you are made aware in order to manage participant/ trial burden.