Section 4: Study Procedures Overview

4.1 Overview of Section 4

This section provides an overview of requirements and study procedures during HPTN 091 Screening, Enrollment, and follow-up visits. Additional procedure-specific details can be found in the HPTN 091 protocol and relevant SSP manual sections (e.g., clinical, laboratory, data management procedures).

All study visits are expected to be completed at the study clinic; however, if in-person visits are not possible due to the COVID-19 pandemic, please contact the HPTN LOC CRM for guidance.

4.2 Study Visit Overview

The HPTN 091 study will begin with the Screening visit, followed by eight protocol-required visits:

- Enrollment Visit: within 40 days of signing the ICF
- GAHT Initiation Visit:
  - For participants randomized to Immediate Intervention Arm who accept GAHT to occur within approximately 10 days but no more than 14 days following the Enrollment Visit
  - For participants randomized to the Deferred Intervention Arm who accept GAHT to occur within approximately 10 days but no more than 14 days following the Week 26 (Month 6) study visit
- Quarterly Follow-up visits: Week 13 (Month 3), Week 26 (Month 6), Week 39 (Month 9), Week 52 (Month 12), Week 65 (Month 15), Week 78 (Month 18) after participant enrollment

In additional to the protocol-required visits, participants may have additional visits/contacts, please see further information about these visits in Section 4.3 below:

- Post GAHT Initiation Safety Visit for GAHT-Naïve Participants
- Peer Health Navigation Additional Contacts

4.3 Study Visits

Protocol-required visits: It includes all visits required by the protocol, as described in Sections 6.2-6.4 and Appendix Ia of the protocol: Screening, Enrollment, and quarterly follow-up visits. Please note, there are other protocol-required visits for a subset of participant taking part in the Drug-Hormone Interaction (DHI) and participants with Suspected or Confirmed HIV Infection, which are described in Sections 6.4.3, 6.7, and Appendices Ib-Ic of the protocol.

Visit windows for each required study visit are found in Section 6.5 of the Protocol and in Section 10.5 of the SSP. For each required study visit, there is an allowable visit window specifying on which study days (post-enrollment) 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 when study visits should ideally be conducted. Missed visits are only those that are not conducted within the allowable window. These windows are outlined in Table 4.1 below.

Table 4.1: Study Visit Windows

Visit	Target Visit Day	Target Visit Window	Allowable Visit Window
Screening			Up to 40 days before enrollment
Enrollment	Day 0		
GAHT Initiation Visit			Within 10 days but no more than 14 days post blood collection for estradiol and total testosterone testing
Week 13	Day 91	Day 77 - 105	Day 77 - 153
Week 26	Day 182	Day 168 - 196	Day 154 - 244
Week 39	Day 273	Day 259 - 287	Day 245 - 336
Week 52	Day 365	Day 351 - 379	Day 337 – 427
Week 65	Day 456	Day 442 - 470	Day 428 - 518
Week 78	Day 547	Day 533 - 561	Day 519 – study closure

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 investigator 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 based on the reason for it.

For study-documentation purposes, the following interim visit/contact will be documented as additional visits/contact; do not label these visits as “interim visit”:

- Peer Health Navigation Contacts: During the first six months of the intervention (starting at the Enrollment Visit for participants randomized to the Immediate Intervention Arm, and starting at Week 26 (Month 6) Visit for participants randomized to the Delayed Intervention Arm) participants could have two additional PHN contacts in between regularly scheduled study visits.

Peer Health Navigation Schedule During First Six Months of the Study Intervention

Immediate Intervention Arm PHN Visits	Deferred Intervention Arm PHN Visits
Enrollment	Week 26 (Month 6)
GAHT Initiation Visit	GAHT Initiation Visit
Optional PHN Contact (To occur between GAHT Initiation and Week 13 (Month 3) study visits)	Optional PHN Contact (To occur between GAHT Initiation and Week 39 (Month 9) study visits)
Week 13 (Month 3)	Week 39 (Month 9)
Optional PHN Contact (To occur between Week 13 (Month 3) and Week 26 (Month 6) study visits)	Optional PHN Contact (To occur between Week 39 (Month 9) and Week 52 (Month 12) study visits)
Week 26 (Month 6)	Week 52 (Month 12)

These additional contacts could be done by phone, videoconferencing, or in-person at the study site, based on participant's preference and availability. When the contact is done either by phone or videoconferencing, please ensure the participant is in a quiet and private area before initiating the conversation. Additionally, when videoconferencing, sites are asked to use a platform that features end-to-end encryption, like FaceTime, WhatsApp, and Google Duo.

Although these additional contacts are not required, they are highly encouraged to ensure participants have a clear understanding of the study intervention, and receive the necessary support. The number and nature of the contacts will be tracked by peer health navigators at the site. Detailed information about the PHN content and implementation is found on Appendix III of the SSP Manual.

Any other additional PHN contacts may be done at participant's request. PHN may also contact participants between required study visits for support and retention purposes.

- Post GAHT Initiation Safety Visit for GAHT-Naïve Participants: At the clinician's discretion, participants who are initiating GAHT for the first time AND their medications include either spironolactone or cyproterone should have an ad-hoc safety visit approximately one month following GAHT initiation. Please refer to Section 6.2.5.2 of the SSP manual for additional information.

Split visits: A split visit is defined as a visit conducted over multiple days within a visit window. 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), ideally within the 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).

Considerations for Split Visits:

- HIV testing is required on the second day of a split visit only if testing was not already performed on the first day of that split visit OR if PrEP will be dispensed on that day and the required HIV testing was performed seven or more days from the first day of the split visit. Please remember, all required HIV samples must be collected and at least one HIV test (e.g., HIV rapid test) must be resulted prior to the dispensation of PrEP. If the split visit is seven or more days from the first part of the split visit, all required HIV testing must be completed.

- Please contact the CMC for guidance if the second part of the visit is longer than 20 days from the first part of the study visit.

- Plasma storage collection is required whenever HIV testing is done, even when HIV testing is performed multiple times during a split visit.

Missed Visits: Even though study visits are "allowed" anytime during the study, for data management purposes, if a visit is not conducted within the allowable window, per Section 10 of the SSP, a Missed Visit e-CRF should be completed if a visit is missed and cannot be made up.

In general, when a visit is missed altogether and a participant reports to the site for the next scheduled visit, the procedures from the missed visit that are not also required for the current visit should be performed. Most of the follow-up procedures are done at all follow-up visits, except for CBC with differential and fasting lipid profiles. These procedures are only required at Week 26 (Month 6), Week 52 (Month 12), and Week 78 (Month 18). If a participant misses any of these visits, the collection of CBC with differential and fasting lipid profiles will be done at the next visit (e.g., Week 39 (Month 9), Week 65 (Month 15)). If a participant misses Week 78 (Month 18) study visit, every effort should be made to contact the participant and complete the visit, even if the allowable window has closed. In this case, contact the CMC for further guidance.

4.4 Screening Visit

The term "screening" refers to all procedures undertaken to determine whether a potential participant is eligible to take part in HPTN 091. The study eligibility criteria are listed in protocol Sections 4.1 and 4.2. Information on screening procedures is found in Section 6.2 and Appendix Ia of the Protocol. The HPTN 091 Informed Consent Form (ICF) must be administered before any study procedures are performed. As part of the informed consent process, staff should assess participant's understanding of the information. Once understanding is confirmed, participant can sign the ICF.

Assignment of Participant ID Numbers (PTID) for Screening and Enrollment

Each time a participant screens for the study, they will receive a new PTID; therefore, if the participant screens out and re-screens at a later time, a new PTID will be provided. Refer to Section 10 of the SSP for further details related to PTIDs.

Screening and Enrollment Logs

The DAIDS Policy for Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials (DWD-POL-RA-03.00) requires study sites to document screening and enrollment activity on screening and enrollment logs. Screening and enrollment logs may be maintained separately or combined into one document. Table 4.2 includes a sample screening and enrollment log that sites may choose to adapt for local use. This may also be used as a link log, if sites plan to separate participant identifying information files.
The DAIDS Policy for Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials (DWD-POL-RA-03.00) specifies that participant initials be recorded on screening and enrollment logs, in addition to PTID numbers. However, per HPTN policy and in agreement with DAIDS, participant initials need not be recorded on screening and enrollment logs if doing so presents a potential threat to participant confidentiality. In such cases, a separate document must be available to document the link between a participant's name and PTID.

Note: The Inclusion Exclusion Criteria CRF will be completed for all participants, including individuals who did NOT enroll in the study. This form is not a replacement for the screening and enrollment log as specified above.

Table 4.2: Sample HPTN 091 Screening and Enrollment Log

(May be adapted as needed for local use)

	Participant ID	Participant Name	Date Screened	Eligible	Date of enrollment (if not enrolled, note N/A)	If not enrolled, specify reason(s) (include all applicable codes).	Staff name/ Initials
1				Y N			
2				Y N			
3				Y N			
4				Y N			
5				Y N			
6				Y N			
7				Y N			
8				Y N			
9				Y N			
10				Y N			

Screening and Enrollment Tracking

Sites will use the electronic data capture system to document screening outcomes for all participants. For ineligible participants, this will include the exclusion criteria included in the protocol as reasons for the screening failure, including an "other" option. The HPTN SDMC will include a real-time, by-site randomization report on the Atlas website (atlas.scharp.org).

Screening Visit Procedures

A full list of screening procedures is included in the HPTN 091 protocol Sections 6.2 and Appendix Ia. Section 6 of the SSP includes details on clinical considerations for screening. Here are some other important considerations for screening:

- Potential participants may be screened for eligibility only after providing written informed consent. The informed consent comprehension assessment is part of the informed consent process and should be done prior to participant signing the ICF.

- The screening process starts as soon as the participant signs the informed consent form, even if no other screening procedures were done on that day.
- Screening may occur over one or more visits within 40 days of participant providing informed consent for the study, depending on availability of the participant and clinic staff. If the screening process is not completed within 40 days of participant providing informed consent, the participant needs to start a new screening attempt, starting with the administration of the ICF.
- Otherwise, eligible participants with an exclusionary test result (other than reactive HIV tests and Hepatitis testing (HBsAg)) can be re-tested once during the screening process. If a participant is re-tested and a non-exclusionary result is documented within 40 days of participant providing informed consent, the participant may continue with enrollment. If after re-testing the laboratory test results continue to be exclusionary, the participant is considered to have failed screening. At the discretion of the IoR or designee, an additional screening attempt may be done as per information on next bullet.
- Per Section 6.2 of the HPTN 091 protocol, participants who fail screening for any reason may rescreen one additional time, at the discretion of the IoR or their designee. However, potential participants with any reactive HIV test and/or positive HBV surface antigen (HBsAg) as outlined in the exclusion criteria in Section 4.2 of the protocol may not be re-screened. Participants with symptoms indicative of acute HIV infection (per IoR or designee) may be re-screened in consultation with the CMC once appropriate testing has ruled out acute HIV infection.
- Sites will follow the HIV testing algorithm for screening found in Appendix IE of the protocol and in Section 8 of the SSP manual.
- A participant will not be eligible for the study if they have any reactive or positive HIV test result at Screening or Enrollment, even if HIV infection is not confirmed. Additional testing to confirm HIV infection should be performed in accordance with local guidelines. If HIV infection is confirmed, participants will receive counseling and be referred for appropriate care.

Participants Found to be Ineligible (Screen Failures)

Screening procedures should be discontinued when the participant is determined to be ineligible. If the participant is found to be ineligible at the beginning of the screening visit, sites may choose to continue with clinical and laboratory evaluations as a service to the participant, per their site SOPs. If a participant fails screening due to a clinical condition requiring follow-up, appropriate referrals should be provided to ensure the well-being of the participant. Documentation of all referrals should be included in the participant chart. All lab results should be provided and explained to participants within a reasonable timeframe, regardless of eligibility determination. For all screened out participants, the following documentation should be in place:

- Completed ICF
- Reason(s) for ineligibility, with date of determination

- Necessary referrals on file (as appropriate) and documentation that any clinically significant abnormalities (labs, etc.) were communicated to the participant (even if referral is not necessary)
- All source documentation completed up until the time that ineligibility was determined
- Chart notes completed up until the time ineligibility was determined
- Indication of what visit procedures were conducted (on visit checklists)

4.5 Enrollment Visit Procedures

A full list of Enrollment Visit procedures can be found in Section 6.3 and Appendix Ia of the protocol. An eligibility checklist template has been provided to sites, which can be modified by sites for their use. Sites can also refer to the visit checklists distributed prior to site activation. Section 6 of this SSP includes clinical considerations for Enrollment.

Other important considerations for the Enrollment visit include:

- IoR or designee must confirm eligibility prior to randomization.
- The definition of enrollment is the point of randomization. That is, if a site successfully randomizes a participant in the randomization system, that participant is considered enrolled. In the event of a mistaken randomization, or if the participant changes their mind once randomization has occurred, that participant will still be considered enrolled. Mistaken randomizations (e.g., the site mistakenly enters the wrong PTID or randomizes prematurely) are considered reportable deviations. Contact Kaila Gomez-Feliciano (kgomez@fhi360.org) in the event that a mistaken randomization occurs or if a participant changes their mind directly or soon after randomization for further guidance.
- For participants initiating GAHT, testing for estradiol and total testosterone will need to be performed prior to hormonal therapy initiation. A GAHT initiation visit will be scheduled within approximately 10 days but no more than 14 days following the collection of samples for estradiol and total testosterone testing for initiation/re- initiation of GAHT. This timeframe will allow for sufficient time for sites to receive laboratory results and for participants taking part in the DHI sub-study to complete the DOT phase.
- HIV test results, including testing for acute HIV, from Screening and at least one HIV test result conducted at the Enrollment visit, must be available and confirmed to be negative/non-reactive prior to provision of study PrEP.
- A complete medical history and physical exam, including concomitant medications and a mental health assessment, must be performed as part of the Screening visit, and reviewed/confirmed at the Enrollment visit. The collection of height is a one-time collection at Screening only.

- Any abnormal laboratory value from samples collected at the enrollment visit, but prior to randomization (i.e., baseline sample) are considered pre-existing conditions and should be recorded as such.

4.6 Follow-up Visit Procedures

After participants enroll in the study, they are expected to complete six quarterly protocol-required follow-up visits. If participants choose to receive Gender Affirming Hormones, they also will have one GAHT initiation visit. Required follow-up visit procedures are listed in protocol Sections 6.4 and Appendix Ia.

- The Schedule of Events found in Appendix Ia of the protocol list all the administrative, behavioral, clinical, and laboratory procedures required in HPTN 091 at follow-up visits. Most of the procedures are required at all visits, except for:

GAHT Initiation Visit will be scheduled based on a participant's randomization assignment. For participants randomized to the Immediate Arm, this visit will be scheduled within approximately10 days but no more than 14 days of the enrollment visit (i.e., collection of samples for estradiol and total testosterone). For participants randomized to the Deferred Arm, this visit will be scheduled within approximately 10 days but no more than 14 days after Week 26 (Month 6) study visit, when the collection of samples for estradiol and total testosterone will take place. At the GAHT initiation visit, only the following procedures will be performed: GAHT counseling and support, provision of GAHT, and review of locator information.

Provision of study products will not be done at Week 78 (Month 18).

During follow-up, the following laboratory testing will be done only at:

Fasting lipid profile: Week 26 (Month 6) and Week 78 (Month 18)

CBC with differential: Week 26 (Month 6), Week 52 (Month 12), and Week 78 (Month 18)

HCV testing and HBV testing (HBsAg, HBsAb, HBcAb-Total): Week 78 (Month 18)

- Participants who voluntarily withdraw from the study or are lost to follow-up will be contacted for an interview to explore reasons for no longer participating. These interviews can be conducted either in person or by phone, based on the participant's availability and/or preference.

Considerations for the Termination Visit (Week 78 (Month 18)):

- The Termination Visit is the last scheduled study visit; however, there may be additional contact with the participant (either by phone or in-clinic visit) if needed, for example, to provide test results or referrals.

- Prior to the Termination Visit, sites should start the conversation with participants about transitioning services to locally available resources. By the time participant comes for the Termination Visit, participant should have identified the location they will continue services so there is not a lapse in product use, for both PrEP and GAHT.
- Although provision of study products will not be done at the termination visit, product use counseling should be done in the context of continuing services at institutions participants will be linked to after the Termination Visit.
- If needed, participants should also be referred to other services, such as mental health services, housing, or any other psychosocial services participants may need.

4.7 Procedures for Participants with Suspected or Confirmed HIV Infection

Information on procedures for participants with suspected or confirm HIV infection is found in Section 6.4.3 and Appendix Ib of the protocol and Section 8 of the SSP manual. A few important considerations:

- HIV testing will be performed at all scheduled study visits (with the exception of the GAHT Initiation Visit).
- If a participant has signs or symptoms consistent with acute HIV infection or expresses a concern about recent HIV acquisition, sites should perform HIV testing using an RNA test.
- If a participant has a reactive HIV test result at any follow-up visit, the status should be confirmed in all cases using two independent samples collected on different days, as per HIV testing algorithm found in Section 8 of the SSP.
- Samples from participants who are confirmed to be HIV-infected should 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 in an eCRF. The site IoR or designee should consult the HPTN LC if confirmatory testing does not confirm that the participant is HIV-infected.
- Participants who are confirmed to be HIV-infected will be linked to local HIV care services and will be offered linkage to GAHT services.

4.8 Follow Up Procedures for Participants Who Discontinue Study Products

A participant may discontinue use of PrEP and/or hormonal therapy and remain on study. Product may be held in response to a clinical event or participant-initiated decision. Discontinuation is defined as not using study product for 30 or more days, independently of the rational for study product discontinuation. If this occurs, study visits continue according to the Schedule of Events (SOE) found in Appendix Ia, with the exceptions noted in Tables 4.3 and 4.4.

NOTE: Injectable cabotegravir (CAB LA) will not be provided in this study. Participants that express a desire to switch from oral PrEP to injectable PrEP will be counseled about the study requirements. However, ultimately, it is the participant's

decision which PrEP agent is best for them. Participants who report switching to injectable cabotegravir (CAB LA) will continue to be followed as outlined in this section. CAB LA use will be documented on the Pre-exposure Prophylaxis Log eCRF.

Table 4.3: PrEP (held or discontinued)	
Procedure discontinued after product hold	Notes
Provision of PrEP	Participant should return remaining oral PrEP to the site if PrEP is held or discontinued.
PrEP counseling and support	Any participant who wishes to discontinue oral PrEP should be counseled on the implications of stopping PrEP, be offered additional risk reduction counseling and (if not during a regular visit where it is already provided) HIV testing.
Adherence and acceptability assessments	Adherence and acceptability assessments related to oral PrEP will be part of the ACASI. These specific questions will be included at the visit in which oral PrEP is held and discontinued at subsequent visits when product is not being provided (using a skip pattern).

Table 4.4: GAHT (held or discontinued)	
Procedure discontinued after product hold	Notes
Provision of GAHT	Participant should return remaining GAHT to the site if GAHT is held or discontinued.
GAHT counseling and support	Any participant who wishes to discontinue GAHT should be counseled on the clinical implications of stopping GAHT.
Estradiol and total testosterone testing	Hormonal monitoring and testing should be completed at the visit in which GAHT is held and discontinued at subsequent visits when GAHT is not being provided.

Table 4.4: GAHT (held or discontinued)	
Adherence and acceptability assessments	Adherence and acceptability assessments related to GAHT will be part of the ACASI. These specific questions will be included at the visit in which GAHT is held and discontinued at subsequent visits when product is not being provided (using a skip pattern).

4.9 Procedures for Participants who Initiate or Re-initiate Study Products

There are some situations when a participant may initiate or re-initiate product use during follow-up. This includes product that was held due to a clinical event or because a participant declined either PrEP or GAHT during follow-up. Re-initiation is defined as restarting study product use after 30 or more days off study product.

Participants who decline PrEP can begin (or reinitiate) PrEP at any time up to and including their Week 39 visit unless contraindicated. At the visit when PrEP is to be initiated or reinitiated, the following procedures should be conducted, and **results should be available prior to PrEP dispensation**:

- Creatinine clearance
- HIV testing
- Fasting lipid profile (for participant reinitiating PrEP, lipid profile is not required if done within six months of product re-initiation)

Participants may begin co-located GAHT any time after enrollment (Immediate Intervention Arm) or after the 6-month visit (Deferred Intervention Arm) up to and including the Week 39 visit unless contraindicated. At the visit when co-located GAHT is to be initiated or reinitiated, the following procedures should be conducted, and **results should be available prior to GAHT dispensation**:

- Estradiol and total testosterone testing

If either product was held due to a clinical event, sites need to assess the event and confirm resolution. This may be done by clinical assessment, medical history, and/or laboratory assessment.

The CMC may be consulted for additional guidance prior to initiation/re-initiation of study product(s).

4.10 Participant Transfers

At baseline, participants should not plan to move away from the site area within the next 18 months after Enrollment. However, if a participant moves during follow-up, they may be able to transfer to another HPTN 091 study site. Participants 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. If there is no way that the participant can return to the clinic where they enrolled and they are not close to another HPTN 091 clinic to transfer, the participant should remain in the study in case the situation changes, and the participant returns or moves to a location where there is an HPTN 091 site.

Upon identifying the need for a participant transfer to another site, the transferring site is responsible for notifying the HPTN 091 LOC CRM, HPTN 091 SDMC Protocol Manager, the HPTN 091 LC Representatives, and the DAIDS Protocol Pharmacist (see Section 1.3 of the SSP manual for contact information). Also, the alias list sc.hptn091@scharp.org should be included on the email. SCHARP staff included on the alias will facilitate the process within MediData Rave. Sites should allow 2-3 U.S. business days after the Transfer form has been completed and the IoR has signed off on all forms for the participant casebook to be transferred to the receiving site. Please refer to Receipt and Transfer forms in the CRF Completion Guidelines for further information. The transferring site is also responsible for contacting 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.
- For all other study records not found in Medidata Rave, the transferring site will ship **certified copies*** (see below) of all 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. Alternatively, the site could transfer documents electronically if the sites are able to send documents as encrypted files. 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 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 informed consent (and any others), along with their 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 they 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.

* See Appendix 1 of Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (https://www.niaid.nih.gov/sites/default/files/sourcedocappndx.pdf) listed under Copies: Certified for requirements for certification.

4.11 Drug-Hormone Interaction Sub-study

This section provides information for clinic staff on the procedures to be done at the clinic as part of the Drug-Hormone Interaction (DHI) sub-study. Information on laboratory-specific procedures, please refer to Section 8.8 of the SSP Manual.

The goal of the DHI sub-study is to characterize the relationship between GAHT and Descovy® for PrEP concentrations - parent TAF, TFV PBMC TFV-DP. To investigate this relationship, a directly observed therapy (DOT) of study product will be done to ensure that potential pharmacologic differences are not due to lapses in PrEP adherence.

Up to 50 participants enrolled at the San Francisco and Philadelphia sites will take part in the DHI sub-study. To qualify for the sub-study, participants must:

- Consent to participate in the DHI sub-study
- Choose Descovy® as the PrEP agent
- Choose to initiate co-localized PrEP and GAHT

Please note, participants enrolled to either study arm – Immediate Intervention Arm and Deferred Intervention Arm – are eligible to participate. Participants randomized to the Immediate Arm will start participation in the sub-study immediately after the Enrollment Visit and participants enrolled to the Deferred Intervention Arms will start participation immediately after their Week 26 (Month 6) study visit.

Since the purpose of the sub-study is to evaluate the impact of exogenous estradiol or other GAHT (such as spironolactone) on F/TAF concentrations, ideally, participants enrolled in the substudy should be GAHT naïve or not currently taking GAHT at baseline. If sites have questions regarding the enrollment of a participant who is using GAHT in the DHI substudy, please contact the CMC.

Once a site identifies a participant who meets the criteria for participation in the DHI sub-study, the study staff will discuss all the details of the sub-study, requirements, expectations from participants, and all additional procedures and visits. It is important to discuss how the DOT will be done and determine the participant's preference for completing this procedure.

DOT can take place either at the study site or by videoconferencing on a cell phone, computer, or tablet, using a platform like FaceTime, WhatsApp, and Google Duo. These platforms feature end-to-end encryption, meaning that only the communicating users can read/see the messages. These sessions will not be recorded via these apps. If done by videoconference, discuss with participant the location participant will be for these sessions. These locations need to be in a quiet and private place to ensure participant's confidentiality.

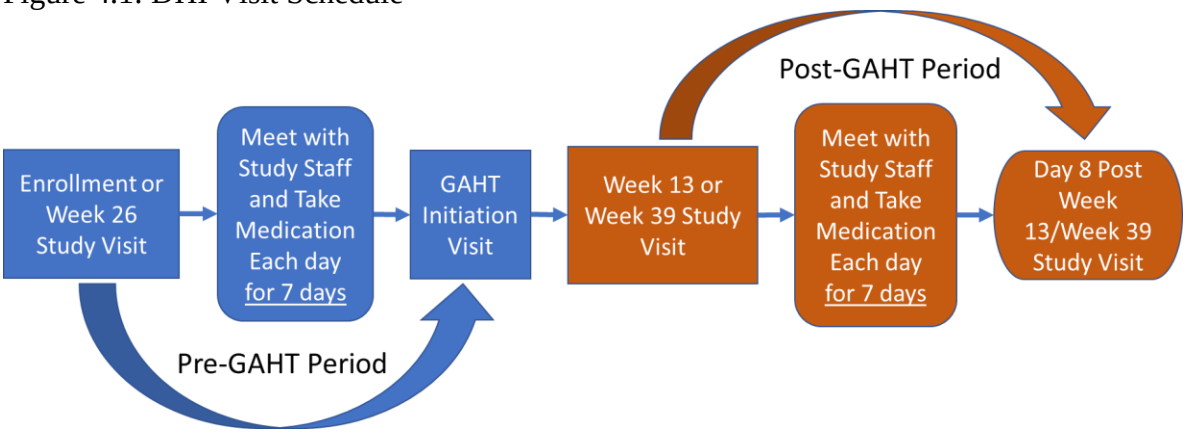
The DOT session, be done either in person or by videoconferencing, will be documented on an eCRF. The eCRF will collect date of the session, and time participant took PrEP. Sites should document any additional information on participant's file.

The DHI sub-study will include a one-week DOT:

- Immediate Arm: Pre-GAHT dosing phase will start immediately after enrollment; the Post-GAHT dosing phase will start after the Week 13 (Month 3)
- Deferred Arm: Pre-GAHT dosing phase will start immediately after Week 26 (Month 6) Visit; the Post GAHT dosing phase, which occurs after the Week 39 (Month 9) study visit

NOTE: For participants in the Deferred Arm, please confirm consent to participate in the DHI sub-study prior to initiation of any procedures. This is particularly important for these participants as the informed consent was obtained about six months prior to initiation of the sub-study. The participant's consent should be documented in their file.

Figure 4.1: DHI Visit Schedule



Scheduling Considerations:

- DOT should be scheduled based on when sites anticipate receiving the estradiol and total testosterone test results:
- Pre-GAHT Period: DOT should be scheduled so that the GAHT initiation visit happens right after the seven-day DOT. For example, if the site anticipates receiving the test results within 5 days of the Enrollment/Week 26 Visit, schedule the DOT to start immediately after Enrollment/Week 26 Visit:

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
					1	2
3	4 **Enrollment/Week 26 Visit**	5 **DOT**	6 **DOT**	7 **DOT**	8 **DOT**	9 **DOT**
10 **DOT**	11 **GAHT Initiation Visit**	12	13	14	15	16

However, if the test results are expected nine days after the Enrollment/Week 26 Visit, schedule the DOT to start three days after the Enrollment/Week 26 Visit so that GAHT Visit happens immediately following the seven-day DOT:

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
					1	2
3	4 **Enrollment/ Week 26 Visit**	5	6	7 **DOT**	8 **DOT**	9 **DOT**
10 **DOT**	11 **DOT**	12 **DOT**	13 **DOT**	14 **GAHT Initiation Visit**	15	16

- Post-GAHT Period: A visit will be scheduled eight days post-Week 13/Week 39. Therefore, the Week 13/Week 39 visit should be scheduled, in collaboration with the participant, based on when the 8-days post visit can occur, taking into consideration when test results are expected to be received and participant's schedule.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
					1	2
3	4	5	6 **Week 13/ Week 39 Visit**	7 **DOT**	8 **DOT**	9 **DOT**
10 **DOT**	11 **DOT**	12 **DOT**	13 **DOT**	14 **Day 8 After Week 13/ Week 39 Visit (In-Clinic)**	15	16

If a participant cannot attend the GAHT Initiation Visit or the Day 8 after Week 13/Week 39 Visit, the DOT should be continued until the visit can be conducted. If this occurs, please notify FHI 360 and LC.

4.12 Section Appendix: Informed Consent Process

Informed consent is a process by which an individual voluntarily expresses their willingness to participate in research, after having been informed of all aspects of the research that are relevant to their decision. Informed consent is rooted in the ethical principle of respect for persons. It is not merely a form or a signature, but a process, with four key considerations — information exchange, comprehension, voluntariness, and documentation — each of which is described below. See Section 4.8 of the ICH GCP guideline and the informed consent section of the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual for detailed guidance on the informed consent process and documentation requirements.

During the screening process, participants will be administered the IRB/EC locally-approved informed consent form prior to the administration of any study procedures. If a participant meets the eligibility criteria for the study and the study staff agree that the participant can fulfill the study requirements, they will be asked to enroll. For enrolled participants, informed consent should be considered as an ongoing process that continues throughout the duration of the study.

U.S. regulations specify the elements of informed consent that must be conveyed to research participants through the informed consent process (45 CFR 46 and 21 CFR 50). It is the responsibility of the IoR, and their delegated staff, to deliver all required information to potential research participants.

Based on the technical and regulatory reviews that are completed as part of the HPTN protocol development and study activation processes, there is adequate assurance that once the HPTN LOC has "activated" a site for study implementation, the site-specific informed consent form specifies all information required by the regulations. However, responsibility for informed consent does not end with preparation of an adequate informed consent form. It also is the responsibility of the IoR and designated study staff to perform the activities described in these sections.

Deliver All Required Information in a Manner that is Understandable to Potential Participants

If the participant is literate, give them a copy of the informed consent form to read during the screening/enrollment visits. Also provide the participant with other (IRB/EC-approved) informational materials developed to complement the informed consent form, if any. If the participant is not literate, the materials may be read to them verbatim. After the participant has read the written material (or had it read to them), verbally review the information provided. A checklist or the informed consent form itself may serve as a useful guide for this. For example, you 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 informed consent form 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.

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 study, 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 they need — and to talk about their potential participation with others, if they choose — before making a decision.

Confirm That the Participant Comprehends the Information

The participant must not be asked to agree to take part in the screening/study, or to sign the informed consent form, until they fully understand the screening process/study. Study staff are responsible for implementing procedures to ensure that each participant understands the screening process and the study prior to signing the screening and enrollment informed consent forms, respectively, and undertaking any screening or 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 4.5, found at the end of this section, 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 study, do not ask them to sign the informed consent form or screen/enroll in the study.

Similarly, if the participant has concerns about possible adverse impacts or indicates that they may have difficulty adhering to the study requirements, do not ask them to sign the informed consent form to screen/enroll in the study.

Document the Process

U.S. regulations require that informed consent be documented by "the use of a written informed consent form approved by the IRB/EC and signed and dated by the subject or the subject's legally authorized representative at the time of consent."

To fulfill this requirement, complete all signature and date blocks on the informed consent form per local IRB/EC requirements. Per the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual, participants must sign the informed consent form using their complete last name (not just initials); the policy also recommends, but does not require, that the participant's complete first name (not just an initial or nickname) be used as well. It is essential that the date documented on the form either precedes or coincides with the study screening date. In addition, enter a note in the participant chart documenting that informed consent was obtained prior to the initiation of any study procedures. Some sites find it helpful to use a cover sheet attached to the Informed Consent Forms to document all items in this process. See Table 4.4 for a sample coversheet that sites may wish to adapt and use. Finally, regulations require that participants be offered a signed copy of the informed consent forms. If a participant opts not to receive a copy, document this in the research record.

If a participant changes their legal name during study participation, the participant must sign a new informed consent form using the new name. Site must include in their files the rational for signing a new consent with a new name.

The DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual provides detailed requirements and suggestions for documenting the informed consent process. All requirements listed in the DAIDS SCORE Manual must be met. In order to also meet some of the suggestions listed in the DAIDS Policy, site staff may consider the use of an informed consent "coversheet" similar to the example included in this section.

Continue the Informed Consent Process throughout the Study

The previous sections describe aspects of obtaining informed consent from study participants prior to initiating their involvement in 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.

ICF Requirements for Protocol Amendments

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.

Informed Consent SOP

As a condition for study activation, each study site must establish an SOP for obtaining informed consent from potential study participants. This SOP should reflect all of the information provided in this section and minimally should contain the following elements:

- The minimum legal age to provide independent informed consent in the study site locale
- Procedures for ascertaining participant identity and age
- Procedures for ascertaining participant literacy (if applicable – some sites may choose to enroll only literate participants. The study allows illiterate participants.)
- Procedures for providing all information required for informed consent to the participant
- Procedures for ascertaining participant comprehension of the required information
- Procedures to ensure that informed consent is obtained in a setting free of coercion and undue influence
- Procedures for documenting the informed consent process
- Storage locations for blank informed consent forms
- Storage locations for completed informed consent forms
- Procedures for implementing a change in the version of the informed consent form used
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements
- QA/QC procedures related to the above (if not specified elsewhere)
- Attached copies and instructions for use of all forms, worksheets, or checklists to be used during the informed consent process

Table 4.5: HPTN 091 Sample Informed Consent Assessment Tool

Instructions: The comprehension assessment tool will be administered to each potential participant after participant has completed the informed consent discussion as per site's SOP and before participant is asked to sign the informed consent form. If the assessment results indicate misunderstanding of any aspect of the study, site staff should review those aspects again until the participant fully understands them.

Informed Consent Comprehension Assessment			
No.	Question	True	False
1	If you decide to join this research study, you will be in the study for about 18 months (1 ½ years)	☒	☐
2	Everyone who joins this study will receive hormonal therapy immediately after joining.	☐	☒
3	If the study staff determines that you have any medical problems, they will treat you or refer you to available sources of medical care for those problems	☒	☐
4	If you do not agree to future specimen storage, you cannot be in this research study	☐	☒
5	You may contact the study staff at any time if you have any questions or problems	☒	☐
6	It is important that I use the product just as the study staff ask me to.	☒	☐
7	If you decide not to join this research study, you can still come to the clinic for medical care	☒	☐
8	If you take part in the research study, you will have physical exams, testing for HIV and other tests to check on your health, and will be asked to answer questions about your experience using the study products. Some of these discussions will be recorded using a voice recorder.	☒	☐
9	The PrEP tablets or hormonal therapy could cause some bad effects like causing you to have an upset stomach or a headache	☒	☐
10	You will be randomized, meaning you will have an equal chance of being in either study arm	☒	☐
11	Pre-exposure prophylaxis (PrEP) are medications to prevent HIV	☒	☐
12	This study is being done to learn how to best provide HIV prevention among transgender women and assess the safety of this intervention	☒	☐
13	The intervention in this study include receiving PrEP, a peer to help them access services, and hormonal therapy	☒	☐
14	There is no chance you will feel embarrassed or uncomfortable with some of the questions you will be asked, some of the procedures that will be done, or some of the test results that you will receive	☐	☒
15	You will come to the site for at least 8 scheduled visits	☒	☐
16	If you decide to join this research study, you must stay in the study for as long as you are told to by the study staff	☐	☒