13 LABORATORY COMPONENT

The following section applies to any site laboratory performing a study under the guidance of the HPTN Laboratory Center (LC). These laboratories will be referred to as Clinical Trials Unit (CTU)/Clinical Research Site (CRS) laboratories in the remainder of this document.

All CTU/CRS laboratories are required to adhere to standards of the Division of AIDS (DAIDS) Good Clinical Laboratory Practice (GCLP) and local Standard Operating Procedures (SOPs) for proper handling and storage of laboratory specimens. For additional information on GCLP, (including recommended GCLP training), refer to the DAIDS Clinical Research Policies and Standard Procedures Documents website:

https://www.niaid.nih.gov/research/daids-clinical-research-laboratory-specimens-management

https://www.hanc.info/labs/TQM%20Document%20Library/Appendix%20A-PNL%20Communication%20Procedure%20for%20Safety%20Proficiency%20Testing%20v2.0%202010-01-07.pdf

The DAIDS GCLP guidelines outline specific requirements for laboratory Quality Management Plan (QMP) that includes Quality Assessment (QA) procedures and quality control QC activities. GCLP training is accessible on-line through the DLMS portal and through periodic regional offerings. References for applicable United States (US) federal and non-US regulations are also included. In addition, US laboratories should follow the Clinical Laboratory Improvement Amendments (CLIA) Act and CLIA – waiver policies:

https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/clia/

and

https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Certificate_of_-Waiver_Laboratory_Project.html

The CTU/CRS laboratories should also have in place a well-defined QMP that comprehensively covers specimen management issues including specimen collection/acquisition, tracking, processing, testing and storage, contingency plans, assay validations, training and competency, instrument and equipment maintenance and procedures for QA and QC.

In addition to these guidelines and policies, the Study Specific Procedures (SSP) Manual developed for each protocol contains a section on laboratory procedures that includes detailed instructions for the specific protocol.

13.1 HPTN CTU/CRS Laboratory Quality Management Plan (QMP)

DAIDS requires that CTU/CRS laboratories have a Quality Management Plan (or equivalent) that is the basis for a range of (QA) and (QC) activities:

https://www.niaid.nih.gov/research/daids-clinical-research-laboratory-specimens-management

Each site that participates in HPTN protocols is expected to develop its own Laboratory QMP. The site-specific QMP is designed to ensure accurate, timely, and reliable test results by providing routine monitoring of the overall laboratory operation. Site-specific QMP are a requirement for site activation for HPTN protocols; these procedures may be adapted from the GCLP guidelines or may be developed by the site. Documents related to the site's QMP

(non-US CRS governed labs) must be submitted upon request to the HPTN LC prior to protocol activation. Key areas covered in the QMP at study sites, are described below.

13.1.1 HPTN Laboratory Quality Assessment

The laboratory Quality Assessment section of the QMP is designed to monitor, evaluate, and improve the quality of laboratory data, ensure the reliability of test data, and evaluate the competency of the site laboratory and appropriate clinical staff; this includes personnel (laboratory and clinical) involved in phlebotomy, collection of other samples, and performing processing and testing in site clinics/laboratories. The Principal Investigator (PI) of each CTU/CRS is responsible for assuring the implementation of the quality assessment policy at the laboratories and clinics that support their CTU/CRS.

The objectives of the laboratory Quality Assessment Policy (and related programs) are to:

- Ensure that the quality assessment activities are comprehensive and coordinated and that appropriate information is reviewed and reported.
- Establish, maintain, support, and document an ongoing Quality Assessment program that includes effective and systematic mechanisms for monitoring, collecting, and evaluating information about important aspects of laboratory procedures. This may include quality indicators and process improvement indicators.
- Implement a corrective action/preventive action (CAPA) plan that will facilitate the ongoing remediation of laboratory-related issues, as well as the identification of solutions to prevent recurrent errors. Follow-up on identified problems is required to assure improvement and resolution.

Key components of laboratory performance are referred to as **Quality Assessment Monitors**. These monitors are tracked to ensure consistency and accuracy of laboratory data. These include:

- Proficiency testing (PT). Proficiency programs are used as an external evaluation on the quality of a test system. Results from the PT program in which the laboratory participates must be reviewed by the laboratory supervisor and/or director and/or designee. An appropriate investigative report (IR) must be completed and submitted to the DAIDS contractor upon request, and also to the Primary Network Laboratory (PNL) assigned to the CTU/CRS. It is possible that the HPTN LC may not be the PNL.
- Specimen management. Specimens sent to the laboratory are monitored to determine the effectiveness of the collection procedures outlined in the site-specific Specimen Management Plan and in the protocol-specific "chain of custody" SOP, in order to ensure the integrity, such as sufficient volume, unlabeled, mislabeled, and broken collection container of the specimens received.
- Monitoring of specimen storage locations. Specimens stored in the laboratory must have the storage temperature monitored as per GCLP guidelines. Specimen locations should be easily tracked through the Lab Data Management System (LDMS).

Reporting of results. Results that are released to clinic or study staff are monitored to determine the turnaround time, effectiveness of the laboratory review, reporting system, and chain of custody.

- Technical delays. Technical delays are monitored to help evaluate the overall effectiveness of the laboratory. Any time there is a delay in reporting participant test results due to a technical problem in the laboratory, the problem must be documented and reviewed by appropriate laboratory staff (ex. Quality assurance personnel, supervisor, designee); clinic and HPTN LC staff must be notified by the appropriate laboratory staff.
- Performance improvement monitoring. The laboratory will identify problems and potential areas for improvement within the laboratory. Problems and potential problems will be monitored for frequency, possible causes, corrective action, and improvement. This should also include a review of safety incidents for staff and study participants, as well as any laboratory related protocol, SSP or SOP deviations
- Staff development, training, and performance documents are kept in the employee file for systematic review. They are assessed and documented through:
    - Training documentation
    - Continuing education records
    - Initial, six-month and annual competency assessments of employees that may include: blinded specimen analysis, proficiency testing (PT) sample analysis, written exams, observation of a technique, and safety review
- Technical procedures and documents are monitored for:
    - Maintenance of equipment
    - Maintenance of sample storage equipment (e.g., freezers)
    - Procedure review
    - Storage of laboratory records
    - Result modification/amendment
    - Result reporting change
    - Reference intervals (age/gender appropriate)
    - Instrument validation
    - Assay verification or validation
    - Assay comparisons

13.1.2 Site Laboratory Quality Control

Site Laboratory QC contributes to the laboratory QMP. The implementation of appropriate QC practices will maximize the quality of reported results and will provide mechanisms for early identification of potential problems. As part of the laboratory QMP, each site is expected to develop its own internal QC procedures.

CTU/CRS QC programs are divided into the main areas of focus listed below:

- Monitoring of Internal QC (testing of known materials)
- Parallel testing — validation of new reagent lots against existing lots, as well as validation of new controls against manufacturer data.

- Proficiency (external) testing programs
- Quality assessment program feedback
- Result comparisons with back-up instruments/methods

13.2 CTU/CRS Laboratory Performance Assessment

CTU/CRS laboratories are evaluated by DAIDS contracted monitoring groups and HPTN LC to ensure that they meet an established standard for data quality and laboratory GCLP compliance. Key performance areas are monitored through collection, recording, and investigation of data pertaining to the laboratory area; findings are evaluated to detect trends and overall compliance with the laboratory QMP. When indicated, corrective action will be implemented and documented. Monitoring is on-going to assure appropriate action is taken and that those actions result in successful remediation.

13.2.1 Non-US CTU/CRS Laboratories

For each HPTN protocol, the HPTN LC will send the CTU/CRS labs a study specific Protocol Analyte List (PAL) to be completed by the laboratory. This document is reviewed by DAIDS Clinical Laboratory Oversite Team (DCLOT) and forwarded to the DAIDS contractor. DAIDS has arranged for many of the existing laboratories outside of the US that participate in DAIDS- funded research to receive proficiency panels from vendors such as the College of American Pathologists (CAP), OneWorld (Digital PT), the United Kingdom National External Quality Assessment Service (UK NEQAS) and other approved proficiency providers - through DAIDS-funded contractors/partners for protocol-related analytes. When a new CTU/CRS is included in a new or existing HPTN protocol, the HPTN LC will work with the site to produce a study specific PAL to allow DAIDS contractors to ensure coverage of protocol analytes; costs related to participation in these PT programs may need to be paid for by the site or by the study, unless another arrangement can be made. Each year, the appropriate DAIDS contractor will re-enroll sites based on the assays that are or will be done at that specific site for DAIDS-sponsored protocols; the PAL lists will be prepared with input from the individual networks whose studies are being performed.

To facilitate communication between the LCs of different networks and CTUs/CRSs outside of the US, the leadership of the various DAIDS clinical trials networks has assigned a Primary Network Laboratory (PNL) to each non- US site. A list of the PNL assignments can be found on the HIV/AIDS Network Coordination HANC website (see Section 13.15 for URL). The appropriate DAIDS contractor and the LC personnel monitor the results of PT and communicate directly with the sites and the HPTN LC, as well as the PNL (if HPTN is not the PNL), regarding any issues or problems with the results, and work with the sites and the PNL to identify appropriate investigational responses and/or corrective actions.

DAIDS staff and/or DAIDS contractors may conduct laboratory-specific audit visits to determine laboratory readiness to participate in clinical trials. Audits of sites enrolled in DAIDS trials may also be performed. These audits are conducted annually at sites outside of the US, unless the laboratory has been certified by CAP and/or has been deemed in good standing by the DCLOT. Sites will be audited for GCLP compliance. DAIDS reserves the rights to conduct for cause or ad- hoc audits at any laboratory in the US or outside of the US that is participating in DAIDS-sponsored clinical trials. After an audit, an audit report will be distributed to the laboratory. The laboratory is responsible for working with DAIDS, their contractors, the HPTN LC and any other affiliated network LC to resolve the audit report findings. Audit report findings must be adequately addressed by the CTU/CRS laboratory to maintain a satisfactory performance standard. The types of audits performed and process

for resolution of audit findings are described GCLP Lab Audit Information document. Information regarding this process can be found on the HANC website https://www.hanc.info/labs/labresources/qualityManagement/Documents/DAIDSPresentation-Lab%20Audit%20Process-June-2012.pdf

In addition to the annual assessments described above, the CTU/CRS may undergo an annual visit (protocol training or protocol-related assessment visit) by HPTN LC staff. At these visits, the HPTN LC staff will provide the CTU/CRS with any recommendations or corrective actions deemed necessary and will send this information to the appropriate site representatives, LOC, SDMC and the DAIDS HPTN LC program officer. In some circumstances additional visits by the HPTN LC may be warranted. The HPTN LC routinely reports on site performance related to protocol testing to the protocol Study Monitoring Committees and if necessary to the HPTN Executive Committee (EC).

13.2.2 Non-affiliated External Laboratories Outside the U.S.

In certain circumstances (e.g., analyzer repair or breakdown, lack of available consumables, lack of required reagents or control material, continued failure in an External Quality Assurance (EQA) program), a laboratory may need to use back-up equipment or a back-up laboratory for testing and reporting study specimen results. To ensure the safety of study participants and the quality of data produced using back-up equipment and/or laboratories, the primary testing laboratory must be able to demonstrate acceptable equivalency between the primary and back-up instruments and methods. Tools such as laboratory audit reports, EQA history, instrument validations, regular specimen comparisons, and reference intervals may also be used. Assays such as qualitative tests may just require the back-up lab to perform EQA and to be in good standing.

The development and approval of a back-up plan that demonstrates equivalency between back-up instruments and/or laboratories is the responsibility of the director of the primary testing laboratory. The HPTN LC must be notified whenever the back-up lab is used. Specific details of back up labs is included in the PAL.

The guidelines for the use of back-up equipment and/or laboratories for DAIDS-sponsored clinical trials is available on the HANC website.
https://www.hanc.info/labs/labresources/qualityManagement/Pages/guidelinesPlanBackupLabs.aspx

13.2.3 Proficiency Testing

Each site will be enrolled in PT programs as appropriate for each HPTN protocol. Prior to protocol activation, the laboratory must be in good standing for the required EQA as determined by the HPTN Network Laboratory staff. After a protocol is activated at the site, the recommendations for PT are as follows:

- Any proficiency deficiency (<100%), regardless of the scoring, will require an investigational response by the CTU/CRS laboratory. The HPTN LC considers scores between 80% and 100% to be passing scores. Any non-protocol analyte that has been evaluated and scores <100% requires an internal investigation.
- If a CTU/CRS laboratory fails to report to the appropriate DAIDS contractor that a panel has not been received, this will be considered unsatisfactory.
- If the results are not graded by the proficiency provider because the results were submitted late, the appropriate DAIDS contractor will make an effort to grade the results and will document that the panel is considered late.

- If the results of an analyte are not graded by the proficiency provider for any reason, the DAIDS contractor may decide that they will determine if grading is applicable.
- When a site receives a score <80% for any analyte, the DAIDS contractor will trigger a report to the site.
- For CTU/CRS laboratories that receive unsatisfactory results (failures) on two out of three consecutive panels or three panels in a row for the same analyte, the HPTN LC will provide instructions to the laboratory on what additional measures must be taken in addition to the corrective action reporting.
- For CTU/CRS laboratories that receive unsatisfactory results on three consecutive panels, the HPTN LC may stop all testing for that analyte and implement a back-up plan at the CTU/CRS. Other LCs may communicate their decisions about testing (e.g., stop/continue) directly with the site staff or through the PNL. Determinations will be on a case by case basis, depending on the reason for the PT failure and the standing of the back-up option at that time.
- DAIDS contractors periodically provide reports regarding EQA. For example, pSMILE maintains an on-going database regarding EQA that networks and DCLOT staff use to inform other participatory groups on decision made based on EQA performance at a site.
- Additional information can be found: https://www.hanc.info/labs/TQM%20Document%20Library/SafetyQA_Guidelines_v2.0_2010-01-07.pdf

DAIDS contractors that provide PT support to CTU/CRS laboratories currently include:

- pSMILE (safety laboratory tests; each CTU/CRS will have a main contact)
- Virology Quality Assurance (VQA; HIV viral load, HIV DNA PCR, HIV genotyping)
- Immunology Quality Assurance (IQA; CD4/CD8, Viable PBMC)
- Pharmacology Quality Assurance (PQA)
- Microbicides Quality Assurance (MQA)

13.2.4 US CTU Laboratory Certification

CTU/CRS laboratories within the US that participate in HPTN protocols are required to have Clinical Laboratory Improvement Amendments (CLIA) certification and or waiver and to provide documentation of this certification to the HPTN LC. At US labs, due to the many different local and State requirements, attainment of appropriate certification is the responsibility of the site leadership, not the HPTN LC.

13.3 HPTN LC Oversight of CTU/CRS Laboratories

HPTN LC staff conduct periodic site visits to assess the implementation of laboratory QA procedures, including proper maintenance of laboratory testing equipment and appropriate use of reagents as they relate to HPTN protocol testing. Each site will be visited approximately annually by one or more of the QA/QC coordinators and/or Deputy Director, or more often if necessary. Annual visits for each HPTN protocol are not required. The purpose and scope of the visit are discussed with site personnel prior to the visit. Details of the visit will be recorded in a report. In addition, the HPTN LC may place an HPTN LC staff member onsite or regionally in certain areas. HPTN LC staff work directly with the on-site

QA/QC coordinator to address and resolve any QC or quality assessment problems identified either through PT or site visits, or by the site during study preparation or implementation.

13.4 Laboratory Monitoring by the Clinical Site Monitor

DAIDS Clinical Site Monitors will periodically conduct a complete site audit prior to or during the conduct of an HPTN protocol. This audit may include aspects of the laboratory. Peripheral blood mononuclear cell (PBMC) specimens should NOT be disturbed during any laboratory audits.

13.5 Specimen Handling and Processing

Each CTU/CRS laboratory should have documented procedures for handling and processing of specimens to be used in DAIDS-sponsored clinical trials. Such information will often be detailed in the SSP. In addition, each laboratory is required to utilize the Laboratory Data Management System (LDMS) for collection, testing (specific to HIV RNA if protocol required), storage, and labeling of certain biological samples identified by the HPTN LC for each HPTN protocol, as described below. Each CTU/CRS should ensure that the laboratory has enough freezer space for storage of protocol related aliquots. Samples will be stored on site unless requested for shipment or destruction.

13.5.1 Laboratory Data Management System

Each CTU/CRS is required to utilize the LDMS. LDMS training may be provided at annual meetings, regional meetings, at the Frontier Science and Technology Research Foundation (FSTRF), onsite or remotely e.g. webinar. Each CTU/CRS is required to maintain the training records of their staff members and is fiscally responsible for the training. The CTU/CRS is responsible for maintaining their LDMS system, including hardware and software upgrades. HPTN LC staff will provide protocol related data entry information for the LDMS in the laboratory section of the protocol SSP. This ensures that specimens are entered correctly into the system. Additional details on the FSTRF website.

All sites must establish SOPs for weekly reconciliation and verification of all archived specimens including (but not limited to): plasma, serum, whole blood, PBMCs, dried blood spots (DBS), tissue, breast milk, amniotic fluid, and genital secretions. These SOPs must be followed throughout the study.

On a periodic basis (at a minimum, monthly), the SDMC will send each CTU/CRS laboratory that is storing samples for an HPTN protocol a CRF-LDMS discrepancy report, an LDMS error report and missing storage report. This report is an Excel file that lists samples that were indicated as collected on the Case Report Form (CRF) and are missing from the LDMS. This could include samples that are logged in incorrectly, not stored, or not received by the laboratory. The CTU/CRS is responsible for informing the HPTN LC of their plans to resolve the issues within 1 week.

13.5.2 Specimen Shipping

HPTN specimens must be transported in accordance with International Air Transport Association (IATA) regulations and with US federal, international, and local laws and regulations. This applies to transportation of specimens on-site, to and from clinics and laboratories, from CTU/CRS to the HPTN LC, or from sites or external laboratories to other laboratories or sites, including the HPTN LC.

IATA shipping certification renewal is required every two years with a review of the IATA Dangerous Guidelines annually to check for any new or changed requirements. Each staff

member who handles shipments must be trained and certified. Each CTU/CRS is responsible for obtaining the appropriate training and annual IATA dangerous goods guidelines.

Each site should follow local regulations regarding transportation of samples by dedicated couriers. The US Department of Transportation (DOT) regulates the transportation of infectious substances within the US. Sites within the US must follow the DOT requirements (see 49 CFR Part 171). Sites outside the US are subject to their own country's government regulations for transportation of infectious substances.

Importation of human pathogens to the US from abroad requires an importation permit from the US Centers for Disease Control and Prevention (CDC). The HPTN LC maintains a worldwide importation license that covers all materials sent from CTU/CRS sites to the HPTN LC at Johns Hopkins University and its affiliated laboratories. Specimens sent from the sites to other locations within the US not part of the HPTN LC are not covered under this importation permit.

Sites may also require a separate Material or Specimen Transfer Agreement (MTA) between the site and the HPTN LC. This is determined by the site and the site is responsible for communicating with the HPTN LC about the specific details they require. The HPTN LC will liaise with the JHU Office of Research Administration (ORA) to ensure that legal concerns are addressed. The ORA official will sign on behalf of the HPTN LC.

Useful websites with information concerning specimen handling and shipment are provided in Section 13.15.

13.6 Laboratory-related Site-specific Protocol Activation Requirements

A specific set of protocol activation requirements will be created for each HPTN protocol. Requirements may vary between studies and sites. Examples of these requirements are:

- Laboratory Quality Management Plan
- SOP for study-specific specimen management plan and "chain of custody" related to clinical/safety testing and management of samples for the study endpoints
- Confirmation of current CVs of key laboratory personnel
- Sites in the United States (US) must identify local back up laboratory arrangements. Non-US sites must identify back up for laboratory testing in their Protocol Analyte List (PAL)
- Verification of Laboratory Data Management System (LDMS) set-up and training
- Verify current International Air Transport Association (IATA) specimen shipping certification for all staff members involved in the specimen management plan
- Good Clinical Laboratory Practice (GCLP) training for the appropriate laboratory staff
- The following for non-CLIA accredited laboratories
    - proficiency in performing protocol-required tests
    - appropriate validation and documentation of validation for protocol analytes
    - any other applicable certification

Prior to protocol activation, each site is required to establish a Specimen Management Plan for local specimen handling and maintenance of "chain of custody" related to testing for

primary endpoints. This plan must be approved by the HPTN LC. The plan should specify or refer to other documents that include:

- How a sample is obtained
- How a sample is transported from the clinic to the laboratory
- What documentation accompanies each sample
- How a sample's departure from one place and arrival at another is documented
- The temperature at which a sample is transported
- Any time requirements for the delivery of the sample
- How a sample is handled and processed once it reaches the laboratory
- How discrepancies and rejected samples are handled

Specific information that must accompany each specimen includes the participant identification, collection date, and visit code. Specimen labels provided by the SDMC include this key information. Accountability for the samples should be maintained with recommendation for signatures of each individual who is involved in the overall chain of custody of the samples. The site SOP should also detail:

- How the results are returned from the laboratory to the clinic
- How problem samples are reported back to the clinic
- How critical values are handled
- How to dispose of samples that arrive in unsuitable or unusable condition

The HPTN LC notifies the LOC Clinical Research Manager (CRM) for the study when the site's laboratory-related procedures, facilities, and staff are deemed acceptable and the site is appropriately prepared for study activation. This HPTN LC approval constitutes local laboratory readiness for CTU/CRS laboratories outside of the US. This approval may be rescinded at any time the HPTN LC deems there is a failure in maintaining key systems or requirements, such as failure to appropriately use the LDMS, follow GCLP standards or other items of concern.

13.7 Validation of HIV Antibody Testing Algorithms

The HPTN LC may require validation of HIV testing algorithms at a CTU/CRS site. For a given protocol, the HPTN LC will determine if a validation study is needed, and if so, what type of validation study is needed for each site/algorithm. The Cross-Network Guidelines for Diagnosing HIV-1 Infection in DAIDS-sponsored Clinical Trials Protocols is available on the HANC website but sites should follow instructions given in SSP manual regarding determination of infection status.

13.8 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all study personnel in the drawing of blood and shipping and handling of all specimens for HPTN studies.

13.9 HPTN Laboratory Center

HPTN LCs performing diagnostic assays for the HPTN protocols that will be reported back to participants are required to be CLIA- certified. Some quality assurance testing performed at the HPTN LC may fall under GCLP guidelines. Other laboratories may not fall under CLIA or GCLP guidelines because they fall under research or developmental testing. Each of these labs will have their own QMP as deemed appropriate for the type of testing performed.

13.10 Centralized Testing

The HPTN LC will oversee any non-standardized or specialized testing (e.g., testing that must be standardized across the sites or across HPTN protocols) and any QA/endpoint confirmation testing, unless prior approval has been granted by the HPTN LC for another arrangement. Endpoint QA testing and specialized assays will be performed at the HPTN LC, or at a laboratory designated by the HPTN LC. Each of the HPTN LC cores will oversee their own specific testing and associated compliance with GCLP and Quality Management Plan.

13.11 QA Testing

The HPTN LC will develop a plan for each protocol to verify the HIV infection status of clinical trial participants. This will include QA testing at the HPTN LC and may include specialized testing. The plan may change during the conduct of a protocol and may vary among study sites (e.g., if testing problems at one or more sites are identified, if sites are using different testing algorithms). These assessments are typically performed at the end of enrollment (e.g., for each study site), but may occur earlier or be ongoing in larger studies or studies in which problems in site testing or sample/data management are suspected or identified. QA testing continues during the course of the study, in batched assessments and/or evaluation of specific participants, sites, or sample subsets. In certain trials, primary endpoint QA testing will occur at the end of the trial.

In most HPTN protocols, baseline plasma/serum samples from 50 participants, or ten percent (whichever is greater) of randomly-selected enrolled adult subjects at each site are evaluated at the HPTN LC to determine/confirm HIV status. Samples from all subjects enrolled at a site will be evaluated if there are fewer than 50 trial subjects at that site. If testing problems are identified (e.g., in the event of a false positive or false negative result that changes the infection status of the subject), samples from additional participants will be evaluated at the HPTN LC. In some HPTN studies, 100% of study samples will be retested at the LC (e.g., if significant testing problems are suspected or identified, if different testing assays or algorithms are used at different sites that may differ in sensitivity or specificity). Additional QA testing will be performed to confirm HIV seroconversion events. This may include testing samples prior to seroconversion for evidence of acute HIV infection. In some cases, QA testing may include assays such as ABO blood group back-typing (to detect sample mix-ups) or antiretroviral drug screening (to explain viral loads that are low or undetectable). Results of testing performed for QA purposes will not be returned to the sites but will be submitted to the SDMC in an agreed upon format utilizing a Data Transfer Plan (DTP). The LC will determine which QA data will be transferred to the SDMC; this will be determined for each study protocol.

The SDMC is responsible for:

- Reviewing the Specimen Data Request form submitted by the HPTN LC
- Providing specimen testing/data/shipping lists for QA analysis by the LC, which will include PTIDs, specimen IDs, global specimen IDs, specimen collection dates, visit types, and visit numbers

- Receiving the QA test results from the HPTN LC
- Comparing the retest results with the results collected on CRFs
- Notifying the HPTN LC of any discrepancies, omissions or other issues in timely manner
- Creating and distributing a report of discrepancies for an Endpoint Adjudication Committee (EAC) review, if necessary

The HPTN LC QA Core is responsible for:

- Developing a Specimen Data request that is submitted to the SDMC in regards to the QA testing plan for the particular protocol
- Working with sites to ship samples to LC for testing
- Conducting the QA testing
- Providing the SDMC with QA test results in accordance with manufacturer product claims
- Working with CTU/CRS laboratories to determine causes of any discrepancies
- Working with the SDMC to collate necessary material for an EAC, if necessary

13.12 HIV Endpoint Determination

The HPTN LC is responsible for specifying HIV testing algorithms in HPTN protocols that are scientifically appropriate for the study population and study objectives. The site HIV testing algorithm will be described in the SSP Manual. HPTN Investigators of Record (IoRs) will make every effort to ensure that protocol-specified HIV testing algorithms are followed throughout the period of study implementation.

Supplemental protocol specific testing algorithms may be required for certain studies, these may not have been specified by the HPTN LC. Sites will be informed by protocol leadership whenever the use of such algorithms is required.

The HPTN LC performs QA and confirmatory HIV testing for HPTN studies as specified in HPTN protocol documents and/or the SSP Manual. In some cases, some of this testing may be performed at a regional laboratory designated by the HPTN LC. The QA testing plan and the extent of QA testing (e.g., the proportion of study samples evaluated at the HPTN LC) are determined by the HPTN LC PI and HPTN LC QA/QC Core Director. QA test results are reviewed by the HPTN LC QA/QC Core Director and the HPTN LC QA/QC Coordinator for the protocol.

Complex cases or cases where there are incomplete and/or discrepant results are also reviewed by the HPTN LC PI.

Protocol teams will refer all issues and questions related to HIV endpoint determination to the HPTN LC. The SDMC statistician for each study (or designee) will provide data reports to the HPTN LC as needed to support review and decision-making by the HPTN LC. For blinded studies, data provided to the HPTN LC will not include participants' treatment assignments or information regarding treatment failures, with limited exceptions (e.g., to identify samples for pharmacology testing). In some cases, an Endpoint Advisory Committee will be convened by the HPTN LC at the start of a protocol or during a protocol to evaluate primary endpoint events (see Section 13.14).

13.13 Endpoint Adjudication Committee (EAC)

In some cases, the HPTN LC may choose to convene a protocol-specific External Adjudication Committee (EAC) to review cases where there are incomplete HIV test data (e.g., due to missed testing or loss-to-follow up at study sites) or where results from site and/or HPTN LC testing do not clearly define the infection status of one or more study participants. An EAC may also be convened to address issues such as:

- Failure of one or more study sites to follow a protocol-specified HIV testing algorithm
- Indeterminate test results persist at study exit
- An unusual pattern of test results is observed

Depending on the number of endpoints and the complexity of the endpoint data, one of three types of EACs will be convened: an Internal EAC (IEAC), and external Virology EAC, or a Specialty EAC (Tier 1, Tier 2, and Tier 3 review, as described below). The type of EAC convened for each study will be determined by the HPTN LC, in consultation with the Protocol Chair(s) and Study Statistician. In addition to those named above, DAIDS Prevention Sciences Program (PSP) representatives may take part in EAC meetings as non-voting discussants or observers.

Tier 1 Review: Internal EAC (IEAC)

An IEAC will be convened for protocols that have a limited number of primary endpoints (typically <20) with no or few complicated cases. In these cases, the LC will first review HIV testing data and identify the primary endpoint events. The LC will present those data to the IEAC for comment. The following individuals will be invited to participate in the IEAC review:

- LC PI‡
- LC QAQC Core Director‡
- LC QAQC Representative
- Protocol Statistician
- Protocol SRA
- Protocol Chair(s)
- LOC Representative
- Others as required

‡Voting members (independent of the study team; these with special expertise in interpretation of HIV diagnostic tests).

For these studies, final endpoint decisions will be made by the LC, after discussion with the IEAC.

Tier 2 Review: external Virology EAC (VEAC)

A VEAC will be convened for protocols that have a larger number of primary endpoints (typically >20) or have complicated cases. The composition of VEACs will include:

- LC PI‡
- LC QAQC Core Director‡
- LC QAQC Representative

- 2-3 External Virologists, selected by the HPTN LC‡
- Protocol Statistician
- Protocol SRA
- Protocol Chair(s)
- LOC Representative
- Others as required

‡Voting members (independent of the study team; these with special expertise in interpretation of HIV diagnostic tests).

For these studies, final endpoint decisions will be made by the HPTN LC, HPTN LC QAQC Core Director, and Protocol Statistician, after reviewing the responses from the voting members.

Tier 3 Review: Specialty EAC (SEAC)

An SEAC will be convened for protocols that have complex primary endpoints requiring special expertise for review (e.g., phylogenetically-linked HIV infections, infections in the setting of long-acting PrEP, where viral replication and antibody responses may be delayed or reduced). In these cases, an alternate committee that includes non-laboratory clinicians may be convened during a protocol to review test data and advise study sites in cases where an HIV diagnosis may be in question. Those activities will be separate from the final endpoint review by the SEAC. The composition of SEACs will include:

- LC PI‡
- LC QAQC Core Director‡
- LC QAQC Representative
- 3-4 External Virologists with special expertise‡
- Protocol Statistician
- Protocol SRA
- Protocol Chair(s)
- LOC Representative
- Others as required

‡Voting members (independent of the study team; these with special expertise in interpretation of HIV diagnostic tests).

For these studies, final endpoint decisions will be made by the HPTN LC, HPTN LC QAQC Core Director, and Protocol Statistician, after reviewing the responses from the voting members.

Additional considerations

For each protocol, the LC will prepare written "Terms of Reference" to guide the committee's review and decision-making. This will include guidelines for interpreting test results where there are deviations from protocol-specified testing algorithms, or where there is discordance between results obtained at the HPTN LC and the local laboratories. The Terms of Reference will specify the membership of the EAC for the protocol, procedures for communication with the protocol team, and the format and frequency of EAC meetings. The

Terms of Reference document must be finalized for before undertaking any EAC data reviews.

Designated staff from the SDMC will provide administrative support to the EACs. Ideally, the SDMC staff will arrange and convene EAC meetings. The LC will document EAC decisions. It may be necessary to convene the meetings through email. SDMC statisticians will incorporate EAC decisions into HPTN study databases for purposes of HIV endpoint analyses and documentation. The SDMC statistician for each study (or designee) will assist the LC in the preparation of reports used by the EACs for data review and decision making. For blinded studies, data provided to the EAC will not include participants' treatment assignments. Endpoint data for EAC reviews will be distributed to the committee by secure email or by posting the data on a secure website. Depending on the number of endpoints and complexity of the endpoint data, multiple reviews may be needed for a protocol. Decisions of the EACs (IEAC, VEAC, or SEAC) are considered final for purposes of primary analyses of HIV endpoints.

13.14 HPTN Sample Destruction

CTU/CRS laboratories are required to store samples for HPTN studies. Some of these samples may be sent to other laboratories for other required testing as mandated by the respective protocols. Each study should address short- and long-term storage of specimens before study initiation.

It is the responsibility of the CTU leadership to estimate the total number of samples for storage, the storage requirements and to provide appropriate facilities and equipment for storage that will meet GCLP guidelines. The HPTN LC does not have a repository.

At the completion of a study, when there are specimens still being stored on-site, a determination will be made by the sponsor(s) of the study or the PI(s), in consultation with the HPTN LC when to destroy specimens from participants who did not consent to long term storage and/or to continue to store the long-term specimens. The laboratory will be notified by the study team(s) via the HPTN LC if specimens must be destroyed. This process will also specify exactly which samples are to be destroyed.

Each site will draft a Sample Destruction SOP that will be reviewed by the HPTN LC. This SOP should include a form that will be used to maintain the chain of custody of the samples throughout the destruction process. All hospital and/or university policies, as well as local regulations, must be followed when handling or discarding specimens. For older studies, the executive group of the Network may make a determination to destroy or continue to store the specimens in question.

Copies of the storage reports will be kept along with the Destruction of Samples documentation logs. Storage will be as per DAIDS policies.

13.15 Referenced or Useful Web Links

Websites for general information related to topics covered in this section, as well as those specifically cited, are listed:

Resources:

pSMILE	https://psmile.org/index.cfm
HIV/AIDS Network Coordination	https://www.hanc.info/Pages/default.aspx https://www.hanc.info/labs/labresources/qualityManagement/Pages/guidelinesPlanBackupLabs.aspx https://www.hanc.info/labs/TQM%20Document%20Library/SafetyQA_Guidelines_v2.0_2010-01-07.pdf
DAIDS	https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures
CLIA	https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/clia/ and https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Certificate_of_-Waiver_Laboratory_Project.html

Specimen Shipping, Shipping Materials and Information:

CDC Shipping Regulations	http://www.cdc.gov/od/ohs/biosfty/shipregs.htm
Code of Federal Regulations	http://www.gpoaccess.gov/cfr/index.html
US Postal Service	http://www.usps.com
Saf-T-Pak	http://www.saftpak.com
CDC Office of Health and Safety - Biosafety	http://www.cdc.gov/biosafety/
International Air Transport Association	http://iata.org/index.htm
FedEx Dangerous Goods Shipping Seminars	http://fedex.com/us/services/options/express/dangerousgoods/seminars.html?link=4
Dangerous Goods	http://www.danrgerousgoods.com
DHL	http://www.dhl-usa.com/solutions/express.asp?nav=dhlExp
US Department of Transportation	http://www.dot.gov/

US DOT/Transporting Infectious Substances Safely	http://www.phmsa.dot.gov/staticfiles/PHMSA/Hazmat/digipak/pd fs/presentation/Infectious_Substances(04_07).pdf

Risk Group Assessments:

Risk Group Classification for Infectious Agents	https://my.absa.org/Riskgroups
American Biological Safety Association	http://www.absa.org/
CDC Regulation	http://www.cdc.gov/biosafety/
CDC Select Agent Listings and Regulations	http://www.selectagents.gov/
USDA Plant and Animal Pathogen Select Agents	https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/animal-and-animal-product-import-information/sa_ag_select_agent