IMPAACT Guidance Document:
Template Protocol Language for Determination of HIV Status

This document is provided as a tool for protocol teams to use when developing study-specific eligibility criteria.

- Determination of HIV status is typically required for inclusion in IMPAACT studies, with eligibility requirements specified in protocol Section 4.1, Inclusion Criteria. For studies that include both participants living with HIV and participants not living with HIV, further specifications for determining HIV status are typically described in an additional sub-section of protocol Section 4 (often Section 4.3).

- When specifying HIV testing and eligibility requirements for a given study, careful attention must be paid to participant age and feeding methods. For potential participants less than two years of age, or who have recently breastfed, maternal HIV status must be considered as well, with the expectation that nucleic acid testing methods will be specified as required when maternal antibodies may affect test results.

- The template wording provided below may be adapted by protocol teams as applicable for the study population. Options provided in this document are not intended for use at individual study sites.

- Study sites must specify HIV testing algorithms for each IMPAACT study consistent with protocol specifications. These algorithms include the testing methods and assays to be used. The algorithms must be reviewed and approved by the IMPAACT Laboratory Center or Westat Laboratory Specialists prior to site-specific study activation. Approved algorithms must be consistently followed at each site. For studies that include determination of HIV status as part of the protocol eligibility criteria, test results meeting protocol requirements must be available for final eligibility determination prior to enrollment of each study participant, unless otherwise specified by the protocol.

1. HIV Testing Requirements

For purposes of eligibility determination, IMPAACT protocols typically specify HIV testing requirements for two samples (Sample #1 and Sample #2). For studies involving participants not living with HIV, documented testing of only one sample may be sufficient. For studies involving participants living with HIV, documented testing of two samples is typically required. Standard requirements for testing of Sample #1 and Sample #2 are provided below:

Sample #1 may be tested using any of the following:

For participants two years of age and older with no exposure to breast milk in the past 28 days:

- Two rapid antibody-based tests from different manufacturers or based on different principles and epitopes (combination antigen-antibody-based rapid tests may be used)
- One enzyme immunoassay (EIA) or Western blot (WB) or immunofluorescence assay or chemiluminescence assay
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One HIV total nucleic acid test

For studies involving participants not living with HIV, consideration can be given to requiring only one rapid test (rather than two as shown above). However, use of two rapid tests is preferred for diagnostic purposes and is required as standard of care at many sites.

For participants less than two years of age or participants two years of age and older with any exposure to breast milk in the past 28 days:

- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One HIV total nucleic acid test

Sample #2 may be tested using any of the following:

For participants two years of age and older with no exposure to breast milk in the past 28 days:

- Rapid antibody-based test. If this option is used in combination with two rapid tests for Sample #1, at least one of the three rapid tests must be FDA-approved and the third rapid test must be from a third manufacturer or based on a third principle or epitope. Combination antigen-antibody based rapid tests may be used.
- One EIA or WB or immunofluorescence assay or chemiluminescence assay
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One HIV total nucleic acid test

For participants less than two years of age or with any exposure to breast milk in the past 28 days:

- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One HIV total nucleic acid test

Note: If the participant or the participant's mother is receiving antiretroviral drugs, an HIV DNA assay may be more sensitive.

For studies that require testing of two samples, the protocol should provide instructions if applicable for management of discordant results. Example is as follows:

In the event that the second test does not confirm an initial positive result, the CMC should be consulted for guidance on next steps to clarify the participant's HIV status. Pending confirmatory testing, prophylaxis and treatment should be managed consistent with local standards of care.

2. Template Wording for Studies Involving Only Participants Living with HIV

For studies only involving participants living with HIV, the text shown below should be included (with adaptions as needed) in protocol Section 4.1, Inclusion Criteria.

4.1.X Confirmed HIV-1 infection based on documented testing of two samples collected from two separate blood collection tubes per Sample #1 and Sample #2 requirements. Test results may be obtained from medical records or from testing performed during the study screening period:

- For results obtained from medical records, adequate source documentation, including the date of specimen collection, date of testing or date of test result, name of test/assay performed, and test result, must be available in study records prior to study entry. Requirements related to laboratory operations (e.g., GCLP, CLIA, VQA) and related to regulatory authority approvals (e.g., FDA) do not apply to results obtained from medical records.
- If adequate source documentation is not available, Sample #1 and/or Sample #2 should be collected during the study screening period and tested in the site's designated testing laboratory. If both samples are tested using antibody tests, at least one of the samples must be tested in a laboratory that operates according to CLIA or equivalent (for US sites) or GCLP (for non-US sites) guidelines and participates in an appropriate external quality assurance program. If nucleic acid testing is used, at least one test must be performed in the site's CLIA-certified or equivalent (for US sites) or VQA-certified (for non-US sites) laboratory.

Sample #1 may be tested using any of the following:

- [insert applicable options and notes per Section 1 of this document]

Sample #2 may be tested using any of the following:

- [insert applicable options and notes per Section 1 of this document]

All study-specific samples tested to determine HIV status must be whole blood, serum, or plasma. HIV testing methods and algorithms must be approved for each site by the IMPAACT Laboratory Center (for NIAID-funded sites) or Westat (for NICHD-funded sites). Testing methods should be FDA-approved, if available.

3. Template Wording for Studies Involving Only Participants Not Living with HIV

For studies only involving participants not living with HIV, the text shown below should be included (with adaptions as needed) in protocol Section 4.1, Inclusion Criteria.

4.1.X Has no evidence of HIV-1 infection based on testing at screening (i.e., from a specimen collected within XX days prior to entry) using one of the following methods:

- [insert applicable options and notes per Section 1 of this document]

Samples tested to determine HIV status must be whole blood, serum, or plasma. HIV testing methods and algorithms must be approved for each site by the IMPAACT Laboratory Center (for NIAID-funded sites) or Westat (for NICHD-funded sites). Testing methods should be FDA-approved, if available.

Alternatively, protocol teams may choose to require use of a single testing method for all participants. In this case, the wording shown above would typically be modified to specify a negative result from the required test. See IMPAACT 2009 for an example of this approach.

4. Template Wording for Studies Involving Participants Living with HIV and Participants Not Living with HIV

For studies involving both participants living with HIV and participants not living with HIV, the text shown below should be included (with adaptions as needed) in protocol Section 4.1, Inclusion Criteria.

4.1.X HIV status determined based on testing meeting the requirements specified in Section 4.3.

In addition, Section 4.3 would be included in the protocol as shown below (with adaptions as needed).

4.3 Determination of HIV Status

HIV status must be determined prior to study entry as specified below. Initial steps will be based on whether a potential participant is presumed to be living with or without HIV based on available medical history information. HIV testing will then be performed as needed to determine each participant's status as specified in the remainder of this section.

4.3.1 Presumed Living Without HIV

For potential participants initially presumed by study staff to be living without HIV based on available medical history information and/or participant/guardian report, HIV testing must be performed in the study site's designated testing laboratory during the study screening period per the Sample #1 requirements in Section 4.3.3.

- Potential participants with negative results will be considered living without HIV at entry.
- Potential participants with positive results should be referred to non-study sources of HIV care and treatment as soon as possible. These potential participants may be considered for entry into the study as participants living with HIV if HIV infection is confirmed per the requirements in Sections 4.3.2 and 4.3.3.

4.3.2 Presumed Living With HIV

For potential participants initially presumed by study staff to be living with HIV based on available medical history, HIV status must be confirmed based on test results from two samples collected from two separate blood collection tubes per the Sample #1 and Sample #2 as described in Section 4.3.3. Test results may be obtained from medical records or from testing performed during the study screening period:

- For results obtained from medical records, adequate source documentation, including the date of specimen collection, date of testing or date of test result, name of test/assay performed, and test result, must be available in study records prior to study entry. Requirements related to laboratory operations (e.g., GCLP, CLIA, VQA) and related to regulatory authority approvals (e.g., FDA) do not apply to results obtained from medical records.
- If adequate source documentation is not available, Sample #1 and/or Sample #2 should be collected during the study screening period and tested in the site's designated testing laboratory. If both samples are tested using antibody tests, at least one of the samples must be tested in a laboratory that operates according to CLIA or equivalent (for US sites) or GCLP guidelines (for non-US sites) and participates in an appropriate external quality assurance program. If nucleic acid testing is used, at least one test must be performed in the site's CLIA-certified or equivalent (for US sites) or VQA-certified (for non-US sites) laboratory.

4.3.3 HIV Testing Requirements

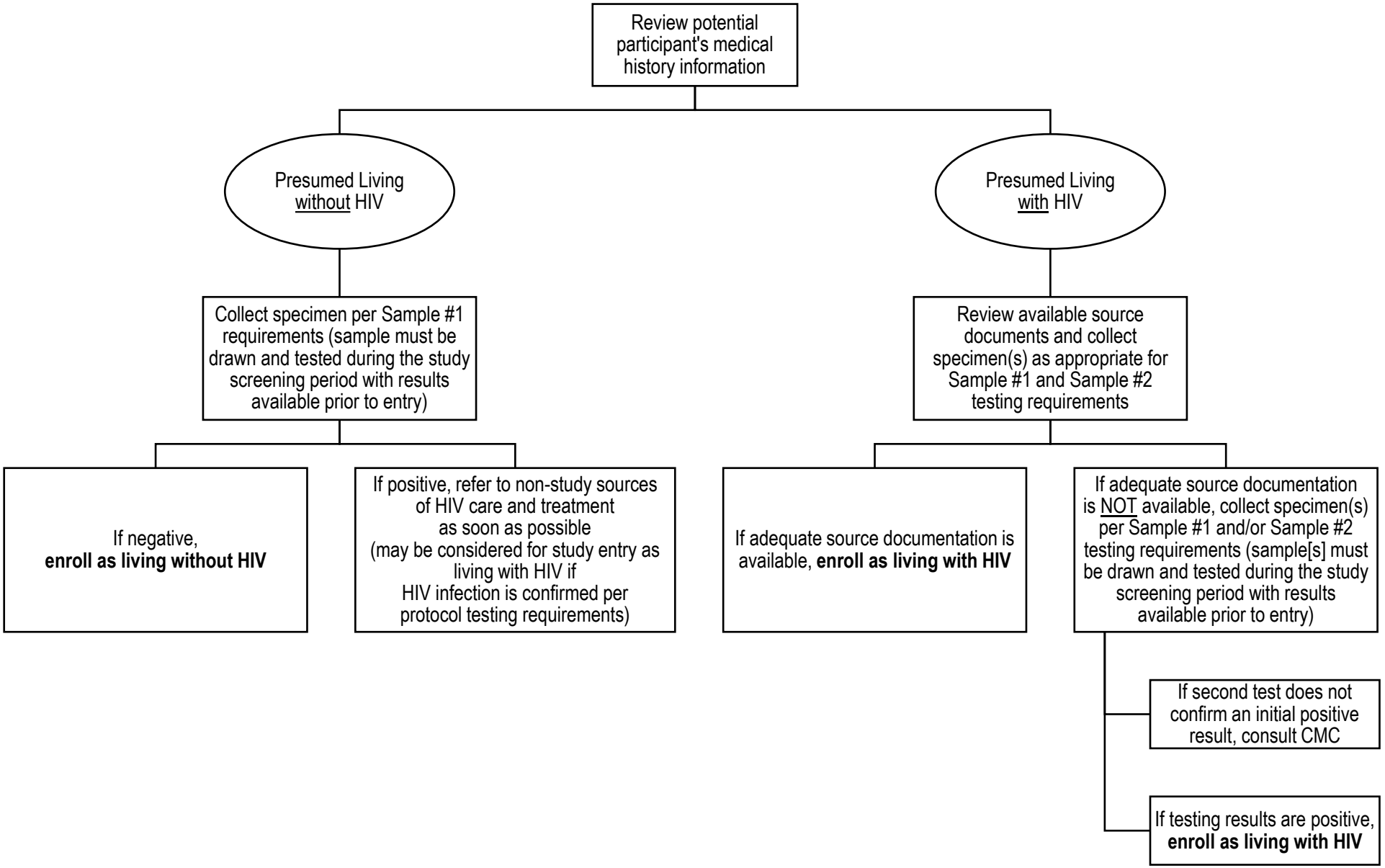
Sample #1 may be tested using any of the following:

- [insert applicable options and notes per Section 1 of this document]

Sample #2 may be tested using any of the following:

- [insert applicable options and notes per Section 1 of this document]

All study-specific samples tested to determine HIV status must be whole blood, serum, or plasma. HIV testing methods and algorithms must be approved for each site by the IMPAACT Laboratory Center (for NIAID-funded sites) or Westat (for NICHD-funded sites). Testing methods should be FDA-approved, if available.


Review potential participant's medical history information
Presumed Living without HIV
Presumed Living with HIV
Collect specimen per Sample #1 requirements (sample must be drawn and tested during the study screening period with results available prior to entry)
Review available source documents and collect specimen(s) as appropriate for Sample #1 and Sample #2 testing requirements
If negative, enroll as living without HIV
If positive, refer to non-study sources of HIV care and treatment as soon as possible (may be considered for study entry as living with HIV if HIV infection is confirmed per protocol testing requirements)
If adequate source documentation is available, enroll as living with HIV
If adequate source documentation is NOT available, collect specimen(s) per Sample #1 and/or Sample #2 testing requirements (sample[s] must be drawn and tested during the study screening period with results available prior to entry)
If second test does not confirm an initial positive result, consult CMC
If testing results are positive, enroll as living with HIV