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

[Note: The only revisions made to this version, relative to the prior Version 1.0, dated 2 November 2018, include clarification that rapid antibody tests are antibody-based testing, which may include use of a combination antigen-antibody based test, for Samples #1 and #2.]

[Note: This document is provided as a tool for protocol teams to use when developing study-specific eligibility criteria. Sections should be modified or, if not applicable to the study or population, removed to align with protocol requirements. In particular:

- If HIV infection or HIV un-infection are required inclusion or exclusion criterion, these sections would generally be modified for inclusion in the main Inclusion Criteria, protocol Section 4.1, or Exclusion Criteria, protocol Section 4.2. If HIV infection status must be known but inclusion or exclusion by status is not required, these sections would generally be modified to be a separate sub-section of Section 4, directly following the eligibility criteria, i.e., Section 4.3. For example, if only participants with HIV infection are to be enrolled in the study, the text included in Sections 4.1, 4.1.2, and 4.3, below, would generally be included as one Inclusion Criterion in protocol Section 4.1. Similarly, if only participants without HIV infection are to be enrolled in the study, the text included in Sections 4.1, 4.1.1, and 4.3, below, would generally be included as one Inclusion Criterion in protocol Section 4.1.
- If subsets of age or breastfeeding status as described below are not included in the protocol, these sections should not be included in the protocol. For example, if a study is enrolling only participants 18 years of age and older, requirements related to participants less than two years of age should be removed and the qualifying statement "For participants two years of age and older with no exposure to breast milk in the past 28 days" may also be removed.

Protocol teams may modify or clarify this guidance text to meet protocol-specific requirements. Sites should NOT use this guidance text to inform protocol-specific criteria as the protocol will continue to remain the source for these requirements.]

4.1 Documentation of HIV Status

[This sentence to be included only if applicable.] HIV status must be determined prior to study entry based on the age- and exposure-based criteria as described below.

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

[Note for protocol teams' consideration: The use of whole blood-derived, dried blood spots (DBS) may be used for HIV diagnosis and monitoring provided that the assay's limit of detection for this sample type meets the protocol requirements.]

4.1.1 Presumed HIV-uninfected

[Leading italicized text to be included only if studies are enrolling both HIV-uninfected and HIV-infected participants] For participants initially presumed by study site staff to be ***HIV-uninfected*** *based on medical records, prior to study participation, or participant/guardian report:*

A study-specific sample must be collected during the study screening period and tested per Sample #1 requirements as described in Section 4.1.3.

- Participants with negative results from this testing will be considered HIV-uninfected at entry.
- Participants with positive test results should be referred to non-study sources of HIV care and treatment as soon as possible and may be considered for entry into the study as HIV-infected participants, following confirmation of HIV infection per Sample #1 and Sample #2 requirements as described in Section 4.1.3.

4.1.2 Presumed HIV-infected

*[Leading italicized text to be included only if studies are enrolling both HIV-uninfected and HIV-infected participants] For participants initially presumed by study site staff to be **HIV-infected** based on medical records, prior to study participation, or participant/guardian report:*

HIV infection must be confirmed based on test results from two samples collected from two separate blood collection tubes per Sample #1 and Sample #2 as described in Section 4.1.3. 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, 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., CLIA, GCLP, or 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 study 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-certified (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 study site's CLIA-certified (for US sites) or VQA-certified (for non-US sites) laboratory.

Participants with positive results from Sample #1 and Sample #2 meeting the requirements listed above will be considered HIV-infected at entry.

4.1.3 HIV Testing Requirements

4.1.3.1 Sample #1

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, which may include use of a combination antigen-antibody based test.
  - *For potential participants presumed HIV uninfected:* HIV-infection may be ruled out for purposes of eligibility determination based on a negative result from at least one FDA-approved HIV rapid test (in this context, it is not necessary to perform two rapid tests). [Note for protocol teams' consideration: For studies in which confirmation of HIV-uninfection is important for participant management or the study intervention, protocol teams may consider requiring two rapid tests.]

- *For potential participants presumed HIV-infected*: Two rapid tests should be performed.

- One EIA or Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One HIV culture (prior to August 2009)
- One total HIV nucleic acid test

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 total HIV nucleic acid test

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

NOTE: Use of 'on demand' testing for nucleic acid based testing may be acceptable for use in the testing algorithm as either Sample 1 or Sample 2.

4.1.3.2 Sample #2

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. The use of combination antigen-antibody based rapid tests is allowed.
- One EIA or Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One HIV culture (prior to August 2009)
- One total HIV nucleic acid test

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 total HIV nucleic acid test

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

NOTE: Use of 'on demand' testing for nucleic acid based testing may be acceptable for use in the testing algorithm as either Sample 1 or Sample 2.

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.

To add in relevant Section 6 subsection: HIV Testing for Participants Enrolled as HIV-uninfected

All participants determined HIV-uninfected at Entry will have routine HIV testing throughout the study, as shown in Appendix X-X or as clinically indicated.

Any participant with a positive HIV test result should be recalled to the clinic for confirmatory testing as soon as possible and within 28 days of specimen collection for the initial test. As is the case at other visits when HIV testing is performed, XX mL of blood should be collected for the confirmatory testing. In the event that the second test does not confirm the initial result, the CMC should be consulted for guidance on next steps to clarify the participant's HIV status. Pending confirmatory testing, ARVs should be managed consistent with local standards of care.

All participants identified with HIV infection during the study will remain in study follow-up and will be referred to non-study sources for HIV care and treatment as soon as possible. Study visits will be conducted as originally scheduled with the exception that no further HIV diagnostic tests will be performed. Study sites may perform additional laboratory testing as needed to facilitate rapid initiation of ART for infected children.

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