Guidance for the management of "discordant/discrepant" HIV testing results – HPTN 083 and 084

Raphael J. Landovitz MD MSc, on behalf of the HIV Prevention Trials Network Team
January 9, 2018 – Version 1.01

Expert Consultants to the Guidance

Grace Aldrovandi MD PhD – University of California, Los Angeles
Jared Baeten MD PhD – University of Washington
Bernard Branson MD – Scientific Affairs Inc.
David Burns MD – NIH Division of AIDS
Connie Celum MD MPH – University of Washington
Wafaa El-Sadr MD MPH – Columbia University, HPTN Co-Principal Investigator
Sue Eshleman MD PhD – HPTN Laboratory Center
Jennifer Farrior – FHI360
Myron S. Cohen MD - University of North Carolina, Chapel Hill, HPTN Co-Principal Investigator
Deborah Donnell, PhD - SCHARP
Joseph J. Eron MD – University of North Carolina, Chapel Hill
Kailazarid Gomez-Feliciano – FHI360
Robert Grant MD PhD – UCSF Gladstone Institute
Beatriz Grinsztejn MD PhD – IPEC/Fiocruz Institute, Rio de Janeiro, Brazil
Mina Hosseinipour MD MPH – UNC Malawi Project, Lilongwe, Malawi
James P. Hughes PhD - SCHARP
Sinead Delaney-Moretlwe - University of Witwatersrand, HPTN 084 Protocol Chair
Daniel R. Kuritzkes - Brigham and Women's Hospital, Harvard Medical School
David A. Margolis, MD MPH – ViiV Healthcare
Marybeth McCauley – FHI360
Jean-Michel Molina MD PhD – Univeristy of Paris Diderot
Deborah Persaud MD PhD – Johns Hopkins University
Estelle Piwowar-Manning – HPTN Laboratory Center
James Rooney MD – Gilead Sciences
Paul E. Sax MD – Brigham and Women's Hospital, Harvard Medical School
Scott Rose – FHI360
Nirupama Deshamane Sista PhD – FHI360
Sheryl Zwerski RN PhD – NIH Division of AIDS

Clinical experience of the effectiveness of TDF/FTC PrEP for HIV prevention has matched or exceeded clinical-trial based efficacy estimates. When providing PrEP, serial monitoring for HIV infection status is important to ensure patient/participant safety, and to reduce the chance of exposure to non-suppressive levels antiretroviral (ARV) drugs that could select for drug-resistant HIV in individuals who become infected while using PrEP.

Clinical trial data suggest that TDF/FTC PrEP use may delay or reduce the antibody response to HIV infection, making it difficult to detect and/or confirm HIV infection.[1-4] Viral replication may also be significantly suppressed[5], and in some cases, HIV RNA is undetectable[6], further complicating HIV diagnosis. Case reports have documented HIV seroconversion despite TDF/FTC PrEP use; some of these infections occurred after exposure to highly-resistant virus,[5] or after high-inoculum exposure.[6,7] In several cases, atypical HIV test results were obtained, including delayed or intermittent patterns of antibody reactivity[6] and suppression of viral replication with HIV RNA levels that are below the level of detection/quantification.[5,6] In at least one case, nascent infection was only unmasked after discontinuation of TDF/FTC PrEP. However, discontinuation of PrEP in high-risk populations is not without risk, since HIV infection may occur once drug levels decline below protective levels.

Discordant or discrepant HIV test results are very likely to be observed in HPTN 083 and 084, since the injectable drug persists for a prolonged interval after injections are stopped. If long-acting cabotegravir (CAB-LA) behaves similarly to TDF/FTC, it may suppress antibody formation and HIV replication for a considerable time. A nuanced and pragmatic approach for HIV diagnosis is needed in these trials to minimize risk to individual participants who have evidence of possible HIV infection (e.g., an isolated reactive HIV screening test result). Standardized approaches to HIV testing and counseling are needed for consistent clinical management and messaging of results, and to maintain the integrity of the study design. Laboratory procedures must be used that maximize the ability to discriminate between false positive test results and true (atypical) infections. Distinguishing between these scenarios is not always straightforward. The problem with false positive test results has been extensively discussed.[8-14] Individuals who are considered to have false positive test results should be allowed to continue blinded study products (oral cabotegravir, CAB-LA or TDF/FTC) or open-label TDF/FTC PrEP, depending on operational feasibility. Individuals who are confirmed to be infected or are likely to be infected based on available laboratory results should be offered fully suppressive, standard-of-care ARV treatment (ART).

Considerations

All HIV tests/assays will have some false positive test results. The positive predictive value of a reactive result is dependent on the pre-test probability of true infection. In most settings, this would be most impacted by the HIV prevalence/incidence in the population. However, in the presence of a highly effective biomedical prevention intervention, positive predictive value may be significantly lower than anticipated.

In settings where PrEP is used and HIV test results may be atypical early in infection, temporary discontinuation of PrEP should allow viral replication and antibody levels to increase, allowing confirmation of HIV infection. However, the risks of discontinuing PrEP to establish or rule-out HIV infection must be balanced against the increased risk of incident infection off PrEP in populations that are at high risk for HIV acquisition.

In one case where diagnosis was complicated by viral suppression by TDF/FTC PrEP, HIV RNA was detected 3 weeks after TDF/FTC withdrawal.[6] There are no data available on the time to HIV RNA detection in the setting of occult HIV infection masked by cabotegravir (oral or injectable). It is reasonable to assume that the timeline for viral detection after discontinuation of oral cabotegravir would similarly to that observed for oral TDF/FTC, based on the pharmacokinetic properties of these drugs.

The amount of time between the last CAB-LA injection and detection of HIV RNA can be estimated to be similar to the amount the time that it takes for cabotegravir levels to decay below 4x PA-IC90.

1. The time to 4x PA-IC90 varies among individuals, with greater variability between men and women (approximately 8 weeks and 12 weeks post-injection for males and females, respectively).
2. The frequency and patterns of discordant/discrepant HIV test results (such as those seen with TDF/FTC PrEP) has not been evaluated in individuals exposed to CAB-LA.

In HPTN 083 and 084, HIV testing includes use of HIV rapid tests, instrumented HIV antigen/antibody (Ag/Ab) combination tests, HIV discriminatory tests (e.g., the Geenius HIV ½ Confirmatory Assay), and HIV RNA tests. The available HIV diagnostic assays and the algorithms used for HIV diagnosis at follow-up visits vary among study sites, based on local HIV testing guidelines. For example, some African sites confirm HIV infection using two HIV rapid tests, while other sites use a discriminatory test to confirm HIV infection.

Proviral HIV DNA can be detected and quantified in cell pellets; HIV DNA tests have been used for HIV diagnosis in infants.[15] The ability of HIV DNA tests to confirm or exclude HIV infection in the setting of PrEP has not been evaluated. Detection of proviral DNA in the setting of PrEP may require use of highly-sensitive assays, since the viral reservoir in these settings may be much smaller than the viral reservoir in newly-infected infants.

Objective

There are currently no guidelines for managing unconfirmed HIV infection in clinical or research settings where PrEP is used for HIV prevention. The purpose of this report is to establish guidelines for HIV diagnosis in HPTN 083 and 084, based on available data and expert opinion. This document focuses on HIV diagnosis in participants receiving TDF/FTC and cabotegravir PrEP (the two drugs used for PrEP in HPTN 083 and 084).

The management of potential infections in people receiving broadly-neutralizing anti-HIV antibodies with or without PrEP will be discussed in a separate report.

Possible etiologies of discordant/discrepant HIV test results

Possible causes of discordant/discrepant HIV test results in the setting of PrEP include:

1. False positive test results due to non-biologic causes (e.g., sample contamination, technical error, data errors)
2. HIV infection acquired prior to PrEP initiation, suppressed/immunologically altered by PrEP agents
3. HIV infection acquired while on PrEP, suppressed/immunologically altered by PrEP agents, including:
    a. Generalized infection
    b. Compartmentalized infection (e.g., HIV infection localized to GALT)
4. Antibody responses to repeated HIV exposures (immunological priming), without true infection
5. Aborted (cured) HIV infection with an immunological footprint without viremia or a latent HIV proviral pool.

Assumptions Guiding the Approach

A number of assumptions were considered in preparation of this guidance document.

1. In HPTN 083 and 084, all participants were required to have a non-reactive HIV rapid test using a phlebotomized blood sample, a negative instrumented HIV Ag/Ab test (e.g., 4th or 5th gen test), and a negative HIV RNA test, prior to enrollment. Therefore, it very unlikely that participants will be enrolled with established or acute HIV infection. HIV acquisition between screening and enrollment is possible; these cases will be identified retrospectively by stored enrollment samples for HIV RNA.
2. <u>In the absence of detectable HIV RNA</u>, the risk of selection of drug-resistant viral quasispecies is minimal, even in the presence of one or two ARV drugs.

Protocol-Specified HIV Testing Algorithms

At the screening visit, testing includes an FDA-cleared HIV rapid test on phlebotomized blood, an instrumented Ag/Ab test (e.g., 4th or 5th generation test), and an HIV RNA test.

At all follow-up visits, testing includes an FDA-cleared HIV rapid test on phlebotomized blood (some sites perform two HIV rapid tests) and an instrumented Ag/Ab test. Some sites include an HIV discriminatory test (e.g., the Geenius HIV ½ Confirmatory Assay) and/or an HIV RNA test in their HIV testing algorithms, consistent with recommendations from the US Centers for Disease Control (CDC).

Plasma is stored at all study visits.

Overarching Diagnostic Principles

This document includes guidelines and HIV testing algorithms for cases in which HIV testing yields discordant/discrepant results. The following principles were used for drafting this document:

(1) Any reactive/positive HIV test will trigger an immediate return visit for confirmatory testing and sample collection (the confirmatory visit must be conducted on a different day than the visit where the first reactive/positive test result was obtained). In this document, the first sample with a reactive or positive HIV test is referred to as the index sample; the sample from the subsequent visit is referred to as the confirmatory sample.
(2) In all cases where a reactive/positive HIV test result is obtained, an HIV RNA assay will be performed on both the index and confirmatory samples.
(3) Cell pellet samples will also be collected/prepared at the confirmatory visit for proviral HIV DNA testing. HIV DNA testing will be performed at the HPTN Laboratory Center (LC) using a highly-sensitive HIV DNA assay developed for the HIV CURE agenda.
(4) In some cases, additional HIV tests will be collected at a third visit (after a 4-week product hold) to help determine HIV status.

Overarching Therapeutic Principles

An indeterminate or positive discriminatory test, a positive HIV RNA test, or a positive proviral HIV DNA test on any sample will be considered sufficient evidence of HIV infection to permanently discontinue study products and recommend immediate initiation of a fully-suppressive, standard-of-care (SOC) HIV treatment.

Management Plan

Clinical Scenario #1

Index Sample: Reactive HIV rapid test, Negative instrumented HIV Ag/Ab test

Clinical Management: Hold study products after the first reactive rapid test result is received. PrEP may be resumed if all of the following tests are negative for both the index and confirmatory samples: (1) instrumented Ag/Ab tests, (2) HIV RNA tests, and (3) discriminatory tests (if performed). Cell pellets will be prepared at the confirmatory visit and will be sent to the HPTN LC for HIV DNA testing. PrEP may be resumed before the HIV DNA test result is available. If any test other than the HIV rapid test is reactive, indeterminate or positive, the participant will permanently discontinue study product and will be referred for SOC ART.

Rationale: This scenario is consistent with false-positive HIV rapid testing. In the absence of a positive instrumented Ag/Ab test, an indeterminate or positive discriminatory test, or a positive HIV RNA test, it is very unlikely that a reactive point-of-care HIV rapid test represents true infection. The goal of this management strategy is to

minimize time off study-product in a high-risk population. The risk of selecting for drug-resistant HIV by continuing PrEP with a single ARV (cabotegravir) or a dual-agent regimen (TDF/FTC) is very low. If a positive HIV DNA test result is obtained from the confirmatory visit after study product is resumed, study products will be permanently discontinued and SOC ART will be initiated. If HIV rapid tests are reactive at subsequent study visits for participants who resume study product, please refer to additional considerations below ("Persistently Positive/Reactive HIV Screening Tests").

Clinical Scenario #2

Index Sample: Reactive HIV rapid test, Reactive instrumented HIV Ag/Ab test (as defined by the manufacturer)

Clinical Management: Hold study products after the first reactive HIV rapid test result is received. When the reactive result is obtained for the instrumented Ag/Ab test, study product will be permanently discontinued and SOC ART will be initiated. Additional HIV testing will be performed at the index and confirmatory visits. However, results of that testing will not change clinical management, unless there is clear evidence that the reactive/positive HIV screening test results were the result of a sample/data error.

Rationale: Participants are presumed to be HIV infected when reactive/positive results are obtained for two different HIV screening assays, even if discriminatory tests, HIV RNA tests, and the HIV DNA test are negative. In these cases, viral replication and anti-HIV antibody production may be suppressed by PrEP. The guiding principle for this management strategy is to minimize the time from presumptive incident infection to initiation of fully suppressive ART, to minimize establishment of an HIV and maximize the potential for future elimination/cure of HIV infection.

Guidance for Scenarios #3 and #4:

Scenarios #3 and #4 use the signal-to-cutoff ratio (S/CO) generated in the Abbott Architect HIV Ag/Ab Combo test to guide clinical management. The S/CO ratio for this assay is not validated for clinical use and is not intended to be reported to physicians or other health practitioners. Some laboratories will not include this value on their reports, and will not release this information. A written report from the laboratory that includes the S/CO ratio is required to use the algorithm for Scenario #3 (verbal reports from the laboratory are not acceptable).

Clinical Scenarios #3 and #4

Index Sample: Negative HIV rapid test, Reactive instrumented HIV Ag/Ab test (as defined by the manufacturer)

Clinical Management: Hold study products when the instrumented HIV Ag/Ab test result is received. Sites that do not use the Abbott Architect HIV Ag/Ab Combo test will ship

samples from index and confirmatory visits to a regional center that performs this test. Additional HIV testing will be performed at the index and confirmatory visits.

Scenario #3:
Index sample: Negative rapid HIV test, Reactive Architect HIV Ag/Ab test with a signal-to-cutoff ratio (S/CO) >10.

Clinical Management: Permanently discontinue study product and initiate SOC ART, regardless of the results of other tests from the index and confirmatory visits. Additional HIV testing will be performed at the index and confirmatory visits. However, results of that testing will not change clinical management, unless there is clear evidence that the reactive/positive Ag/Ab test result was the result of a sample/data error.

Rationale: Participants are presumed to be HIV infected if the Architect HIV Ag/Ab Combo test is reactive with a S/CO ratio >10. In these cases, viral replication and anti-HIV antibody production may be suppressed by PrEP. The guiding principle for this management strategy is to minimize the time from presumptive incident infection to initiation of fully suppressive ART, to minimize establishment of an HIV and maximize the potential for future elimination/cure of HIV infection.

Scenario #4:
Index sample: Negative rapid HIV test, Reactive Architect HIV Ag/Ab test with a signal-to-cutoff ratio (S/CO) ≤10 or S/CO ratio not reported by the laboratory.

Clinical Management: Hold study products when the instrumented HIV Ag/Ab test result is received. Samples will be sent for testing using a discriminatory test (if available, index and confirmatory visits), an HIV RNA test (index and confirmatory visits) and an HIV DNA test (confirmatory visit only). Additional HIV testing will also be performed after a 4-week product hold; this will include an HIV rapid test, a discriminatory test (if available), an HIV RNA test, and an HIV DNA test. Blinded study product may be restarted after the 4-week product hold if the Architect Ag/Ab test from the confirmatory visit is ≤10 (or if this value is not reported by the laboratory), and if the HIV rapid tests, the discriminatory tests, HIV RNA tests, and HIV DNA tests from the index visit, the confirmatory visit, and the post-product hold visit are all non-reactive/negative.

Rationale: There is some evidence that HIV RNA should be detected 4 weeks after TDF/FTC discontinuation. Negative test results for a discriminatory test (if performed), an HIV RNA test, and an HIV DNA test, all performed 4 weeks after TDF/FTC discontinuation, provide reasonable assurance that a participant is not infected. There are no data on the amount of time required after injections stop before HIV antibody, HIV RNA or HIV DNA will be detected in individuals who become infected while receiving CAB-LA PrEP. One could argue that 4 weeks after discontinuation of CAB-LA injections would not be long enough for HIV

infection to be unmasked. However, withholding of PrEP from participants at high-risk for HIV acquisition for 8 or 12 weeks (the time anticipated for CAB-LA to "decay" to 4 x PA-IC90) is not prudent. In addition, in the absence of detectable HIV RNA and HIV DNA, the risk of selecting for drug-resistant HIV in those with true infection should be very low. Further, continued use of single- or dual-drug PrEP, even in cases with low-level reservoir seeding, could theoretically lead to reservoir eradication (cure of infection). Therefore, a 4-week interval after the last CAB-LA injection seems to provide a reasonable balance of risks and benefits in this setting. If instrumented HIV Ag/Ab tests are reactive at subsequent study visits for participants who resume study product, please refer to additional considerations below ("Persistently Positive/Reactive HIV Screening Tests").

Persistently Positive/Reactive HIV Screening Tests

In scenarios above that allow resumption of study products (blinded in Step 1 or 2, open-label in Step 3), management of participants who have repeatedly reactive HIV rapid tests or repeated reactive/positive instrumented HIV Ag/Ab tests is challenging. For these cases, the protocol-specified HIV testing algorithm used for follow-up visits will be modified to include HIV RNA testing and cell pellet storage at all subsequent visits. Test results that are consistent with patterns of reactivity/positivity observed for an individual participant at his/her previous visits will not warrant immediate study product holds. If the participant has new or different patterns of reactive/positive test results at subsequent study visits, clinical management should follow the algorithms presented above.

Long-term Clinical Management

For cases where study drug is permanently discontinued and participants are referred for ART, the decision whether participants should be continued on life-long ART or undergo a carefully-monitored treatment interruption at some future time point is a complex and nuanced clinical decision beyond the scope of clinical trial management. The HPTN 083 or 084 leadership teams will be happy to help local investigators with these decisions.

Discussion

Clinical management decisions in PrEP trials are complicated for participants who have discordant/discrepant HIV test results. Management in this setting requires clinical judgment, knowledge of the performance characteristics of each HIV test, and a pragmatism that allows clinical management decisions to be standardized and generalized to the clinical settings in which the study products are likely to be used if licensed. In other words, a secondary aim of PrEP trials is to collect information that will guide implementation of PrEP after the trial has been completed.[1]

Clinical management of participants with discordant/discrepant HIV test results has an immediate effect on the conduct of a clinical trial and on the well-being of study

participants. Decisions to observe participants off study PrEP agents are particularly nuanced. Immediate unblinding of participants who have discordant/discrepant HIV test results would allow individual management of participants (e.g., for time off study-product), but would compromise the integrity of the study by precluding reinitiation of blinded study products. Furthermore, it may be very difficult to discriminate between true HIV infection from false reactive/false positive test results if HIV RNA and HIV DNA are not detected. Permanent discontinuation of PrEP in these cases could place study participants at increased risk for HIV acquisition. In Phase 3 studies, unblinding should be reserved for situations in which the safety of an individual participant depends on knowledge of the treatment assignment; this is not the case in the HPTN 083/084 studies. An argument that continuing cabotegravir monotherapy in these cases would put participants at risk is theoretical and deserves careful evaluation of the guidelines provided here, taking into consideration the rigor of the trials needed to best inform clinical management and implementation of this product for PrEP.

The possibility that participants could have compartmentalized infection or low-reservoir infection that could be cured with ongoing administration of PrEP agents provides further justification for shortening the proposed observation period off study products. One could argue that it would be best to immediately resume study products without a 4-week pause for participants who have negative HIV RNA tests (simulating the most likely clinical practice scenario). However, the absence of data for the safety of such a strategy, and the absence of experience with long-acting injectable products, strongly argue for a more measured and conservative approach.

The opposite extreme was also considered: permanent discontinuation of study products for all participants who have a reactive HIV rapid test or positive instrumented HIV Ag/Ab test. However, this strategy would imperil the power of the study (compromising the value of all participants' involvement) and would put uninfected study participants (those with false positive test results) at risk for HIV acquisition. This approach might also cause untold emotional distress, stigma, and other potential harms by implying that a participant is infected, in the absence of confirmation of infection.

The proposed management plan (subject to change as new information is obtained) provides the best pathway for evaluating discordant/discrepant HIV test results, minimizing risk to participants, and addressing critically-important questions about the efficacy and safety of CAB-LA as a potential PrEP agent.

A separate document will address the clinical messaging with each scenario.

REFERENCES

1. Donnell D, Ramos E, Celum C, et al. The effect of oral preexposure prophylaxis on the progression of HIV-1 seroconversion. *Aids.* 2017;31(14):2007-2016.
2. Curtis KA, Kennedy MS, Luckay A, et al. Delayed maturation of antibody avidity but not seroconversion in rhesus macaques infected with simian HIV during oral pre-exposure prophylaxis. *Journal of acquired immune deficiency syndromes (1999).* 2011;57(5):355-362.
3. Cranage M, Sharpe S, Herrera C, et al. Prevention of SIV rectal transmission and priming of T cell responses in macaques after local pre-exposure application of tenofovir gel. *PLoS Med.* 2008;5(8):e157; discussion e157.
4. Kersh EN, Adams DR, Youngpairoj AS, et al. T Cell Chemo-Vaccination Effects after Repeated Mucosal SHIV Exposures and Oral Pre-Exposure Prophylaxis. *PLoS ONE.* 2011;6(4):e19295.
5. Markowitz MMD, Grossman HMD, Anderson PLMD, et al. Newly Acquired Infection With Multidrug-Resistant HIV-1 in a Patient Adherent to Preexposure Prophylaxis. *JAIDS Journal of Acquired Immune Deficiency Syndromes.* 2017;76(4):e104-e106.
6. Hoornenborg E, Prins M, Achterbergh RCA, et al. Acquisition of wild-type HIV-1 infection in a patient on pre-exposure prophylaxis with high intracellular concentrations of tenofovir diphosphate: a case report. *The Lancet HIV.*4(11):e522-e528.
7. Knox DC, Anderson PL, Harrigan PR, Tan DHS. Multidrug-Resistant HIV-1 Infection despite Preexposure Prophylaxis. *New England Journal of Medicine.* 2017;376(5):501-502.
8. Ndase P, Celum C, Kidoguchi L, et al. Frequency of false positive rapid HIV serologic tests in African men and women receiving PrEP for HIV prevention: implications for programmatic roll-out of biomedical interventions. *PLoS One.* 2015;10(4):e0123005.
9. Delaugerre C, Antoni G, Mahjoub N, et al. Assessment of HIV Screening Tests for Use in Preexposure Prophylaxis Programs. *J Infect Dis.* 2017;216(3):382-386.
10. Hurt CB, Nelson JAE, Hightow-Weidman LB, Miller WC. Selecting an HIV Test: A Narrative Review for Clinicians and Researchers. *Sex Transm Dis.* 2017;44(12):739-746.
11. Curlin ME, Gvetadze R, Leelawiwat W, et al. Analysis of False-Negative Human Immunodeficiency Virus Rapid Tests Performed on Oral Fluid in 3 International Clinical Research Studies. *Clin Infect Dis.* 2017;64(12):1663-1669.
12. Keating SM, Pilcher CD, Busch MP. Editorial Commentary : Timing Is Everything: Shortcomings of Current HIV Diagnostics in the Early Treatment Era. *Clinical Infectious Diseases.* 2016;63(4):562-564.
13. de Souza MS, Pinyakorn S, Akapirat S, et al. Initiation of Antiretroviral Therapy During Acute HIV-1 Infection Leads to a High Rate of Nonreactive HIV Serology. *Clin Infect Dis.* 2016;63(4):555-561.
14. Sivay MVP, Li MM, Piwowar-Manning EBSMT, et al. Characterization of HIV Seroconverters in a TDF/FTC PrEP Study: HPTN 067/ADAPT. *JAIDS Journal of Acquired Immune Deficiency Syndromes.* 2017;75(3):271-279.

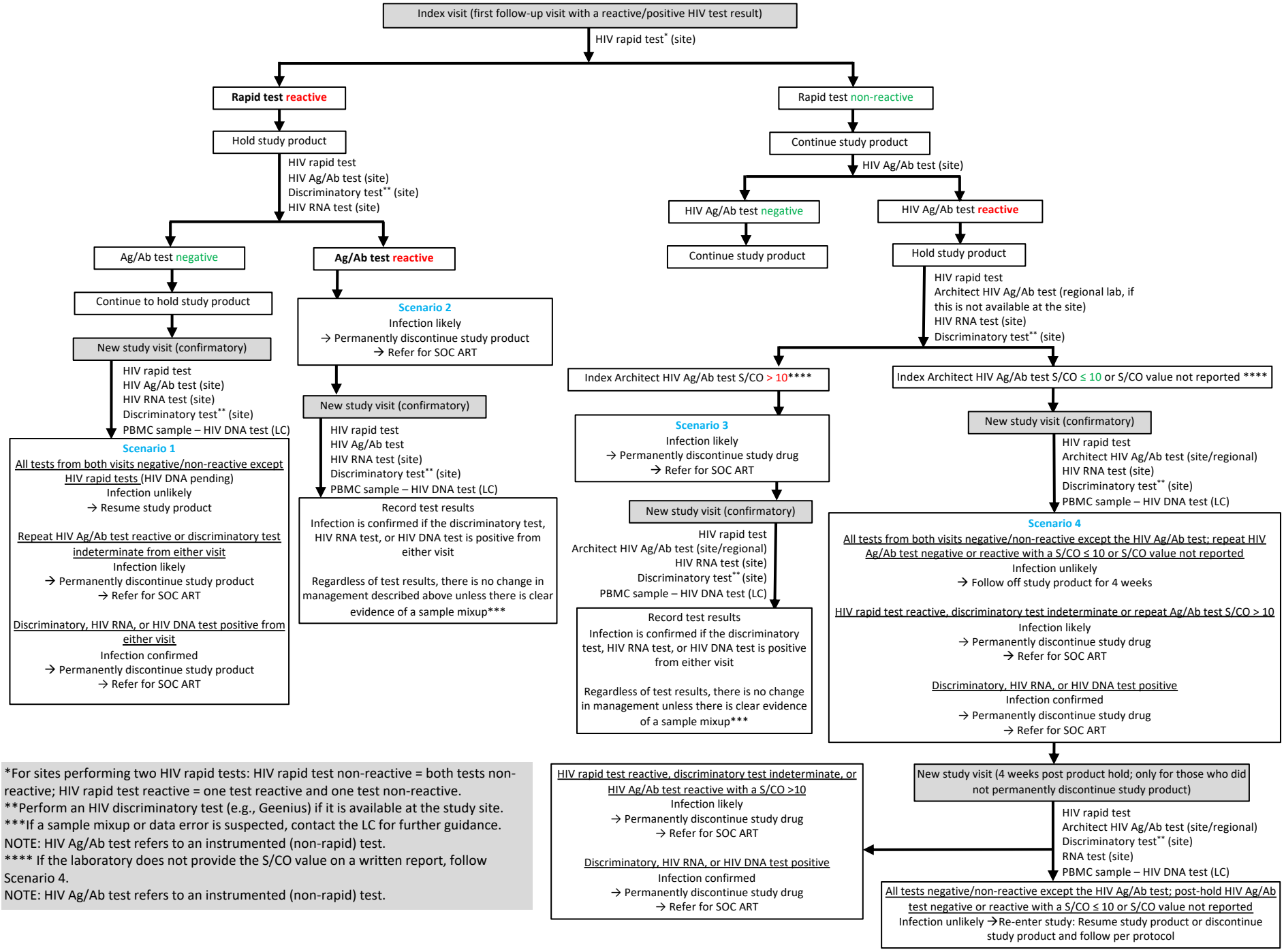
15. World Health Organization. Diagnosis of HIV Infection in Infants and Children: WHO Recommendations. Geneva, Switzerland: World Health Organization; 2010.

Supplemental HIV Testing Algorithm for Participants with Discordant/Discrepant HIV Tests

HPTN 083 and HPTN084

Sites should follow the routine HIV testing algorithm for enrollment and follow-up visits. The HIV testing algorithm presented here is to be used only for participants who have discordant/discrepant HIV test results after enrollment.

Sites should refer to the document, “Management of discordant/discrepant HIV testing results – HPTN 083 and HPTN 084” for further guidance.


Index visit (first follow-up visit with a reactive/positive HIV test result)
HIV rapid test* (site)
Rapid test reactive
Hold study product
HIV rapid test
HIV Ag/Ab test (site)
Discriminatory test** (site)
HIV RNA test (site)
Ag/Ab test negative
Continue to hold study product
New study visit (confirmatory)
HIV rapid test
HIV Ag/Ab test (site)
HIV RNA test (site)
Discriminatory test** (site)
PBMC sample – HIV DNA test (LC)
Scenario 1
All tests from both visits negative/non-reactive except HIV rapid tests (HIV DNA pending)
Infection unlikely
→ Resume study product
Repeat HIV Ag/Ab test reactive or discriminatory test indeterminate from either visit
Infection likely
→ Permanently discontinue study product
→ Refer for SOC ART
Discriminatory, HIV RNA, or HIV DNA test positive from either visit
Infection confirmed
→ Permanently discontinue study product
→ Refer for SOC ART
Ag/Ab test reactive
Scenario 2
Infection likely
→ Permanently discontinue study product
→ Refer for SOC ART
New study visit (confirmatory)
HIV rapid test
HIV Ag/Ab test
HIV RNA test (site)
Discriminatory test** (site)
PBMC sample – HIV DNA test (LC)
Record test results
Infection is confirmed if the discriminatory test, HIV RNA test, or HIV DNA test is positive from either visit
Regardless of test results, there is no change in management described above unless there is clear evidence of a sample mixup***
Rapid test non-reactive
Continue study product
HIV Ag/Ab test (site)
HIV Ag/Ab test negative
Continue study product
HIV Ag/Ab test reactive
Hold study product
HIV rapid test
Architect HIV Ag/Ab test (regional lab, if this is not available at the site)
HIV RNA test (site)
Discriminatory test** (site)
Index Architect HIV Ag/Ab test S/CO > 10****
Scenario 3
Infection likely
→ Permanently discontinue study drug
→ Refer for SOC ART
New study visit (confirmatory)
HIV rapid test
Architect HIV Ag/Ab test (site/regional)
HIV RNA test (site)
Discriminatory test** (site)
PBMC sample – HIV DNA test (LC)
Record test results
Infection is confirmed if the discriminatory test, HIV RNA test, or HIV DNA test is positive from either visit
Regardless of test results, there is no change in management unless there is clear evidence of a sample mixup***
Index Architect HIV Ag/Ab test S/CO ≤ 10 or S/CO value not reported ****
New study visit (confirmatory)
HIV rapid test
Architect HIV Ag/Ab test (site/regional)
HIV RNA test (site)
Discriminatory test** (site)
PBMC sample – HIV DNA test (LC)
Scenario 4
All tests from both visits negative/non-reactive except the HIV Ag/Ab test; repeat HIV Ag/Ab test negative or reactive with a S/CO ≤ 10 or S/CO value not reported
Infection unlikely
→ Follow off study product for 4 weeks
HIV rapid test reactive, discriminatory test indeterminate or repeat Ag/Ab test S/CO > 10
Infection likely
→ Permanently discontinue study drug
→ Refer for SOC ART
Discriminatory, HIV RNA, or HIV DNA test positive
Infection confirmed
→ Permanently discontinue study drug
→ Refer for SOC ART
New study visit (4 weeks post product hold; only for those who did not permanently discontinue study product)
HIV rapid test
Architect HIV Ag/Ab test (site/regional)
Discriminatory test** (site)
RNA test (site)
PBMC sample – HIV DNA test (LC)
All tests negative/non-reactive except the HIV Ag/Ab test; post-hold HIV Ag/Ab test negative or reactive with a S/CO ≤ 10 or S/CO value not reported
Infection unlikely →Re-enter study: Resume study product or discontinue study product and follow per protocol
HIV rapid test reactive, discriminatory test indeterminate, or HIV Ag/Ab test reactive with a S/CO >10
Infection likely
→ Permanently discontinue study drug
→ Refer for SOC ART
Discriminatory, HIV RNA, or HIV DNA test positive
Infection confirmed
→ Permanently discontinue study drug
→ Refer for SOC ART
*For sites performing two HIV rapid tests: HIV rapid test non-reactive = both tests non-reactive; HIV rapid test reactive = one test reactive and one test non-reactive.
**Perform an HIV discriminatory test (e.g., Geenius) if it is available at the study site.
***If a sample mixup or data error is suspected, contact the LC for further guidance.
NOTE: HIV Ag/Ab test refers to an instrumented (non-rapid) test.
**** If the laboratory does not provide the S/CO value on a written report, follow Scenario 4.
NOTE: HIV Ag/Ab test refers to an instrumented (non-rapid) test.