

# A Strategy for PrEP Clinicians to Manage Ambiguous HIV Test Results During Follow-up Visits

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Prompt determination of HIV infection status is critical during follow-up visits for patients taking pre-exposure prophylaxis (PrEP) medication. Those who are uninfected can then continue safely taking PrEP, and those few who have acquired HIV infection can initiate an effective treatment regimen. However, a few recent cases have been reported of ambiguous HIV test results using common testing algorithms in PrEP patients. We review published reports of such cases and testing options that can be used to clarify true HIV status in these situations. In addition, we review the benefits and risks of 3 antiretroviral management options in these patients: (1) continue PrEP while conducting additional HIV tests, (2) initiate antiretroviral therapy for presumptive HIV infection while conducting confirmatory tests, or (3) discontinue PrEP to reassess HIV status after a brief antiretroviral-free interval. A clinical consultation resource is also provided.

**Keywords.** PrEP; pre-exposure prophylaxis; HIV testing; seroconversion.

Utilization of daily oral antiretroviral pre-exposure prophylaxis (PrEP) in the United States to reduce HIV transmission has increased markedly over the past 5 years, with more than 120 000 persons estimated to have initiated PrEP from 2012 into early 2017 [1, 2]. With quarterly HIV screening of more than 100 000 patients, there will be some number of false-positive and false-negative test results occurring among them. Existing HIV testing recommendations and algorithms for PrEP patients [3] are intended to resolve inconclusive test results. However, the presence of antiretrovirals used as PrEP at the time of infection may alter the dynamics of viremia and a patient's immune response in ways that can affect how these algorithms perform. Recent cases of indeterminate or otherwise unclear (ambiguous) HIV test results, despite use of common testing algorithms, have been reported in persons who acquired HIV infection while adherent to daily doses of tenofovir disoproxil fumarate (TDF) coformulated with emtricitabine (FTC) taken as PrEP [4–7]. An additional 2 cases of unambiguous HIV test results in men who have sex with men who acquired HIV infection while adherent to daily PrEP [8] or TDF for treatment of hepatitis B infection [9] have been reported (Table 1). Accurate and quick resolution of ambiguous test results enables timely and proper clinical management to minimize potential harm, such as antiretroviral drug (ARV) resistance and psychological stress. We

suggest strategies to clarify ambiguous test results among persons taking PrEP, as well as options for antiretroviral management, until the patient's HIV status is confirmed.

## POTENTIAL SCOPE OF THE PROBLEM

### Frequency of HIV Infection Among Persons Taking PrEP

Acquiring HIV infection by persons taking PrEP is uncommon. In 32 international open-label demonstration projects, Mera et al. reported 67 infections during  $\geq 7061$  cumulative person-years of FTC/TDF exposure for a seroconversion rate of 0.95/100 person-years of use (95% CI, 0.74, 1.21) [10]. Marcus et al. reported no seroconversions during 5104 person-years of PrEP in an observational cohort in northern California [11]. Thus, the expected frequency of new infections when patients are taking PrEP as prescribed is expected to be low, but the absolute number of new infections may increase as PrEP is more widely used.

### Frequency of False-Positive HIV Test Results Among Persons Taking PrEP

In the context of PrEP, the probability of someone who is not infected testing falsely positive is low; however, with more testing, the number of false-positive tests observed will increase. Rigorous licensing and manufacturing requirements help ensure that false-positive HIV test results are rare. For example, in the iPrEx PrEP trial, there were 8 reactive test results resolved as false-positive among 50 260 tests of 2499 study participants [12]. In the US PrEP Demonstration Project, there were 6 reactive rapid point of care (POC) HIV test results and 3 reactive antigen/antibody (Ag/Ab) laboratory tests resolved as false-positive among 2680 and 2673 tests, respectively [13]. In both studies, a negative HIV RNA test was used to resolve HIV status as uninfected.

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**Table 1. Case Reports of HIV Test Results of Men Who Have Sex With Men Who Acquired HIV Infection While Taking Tenofovir for Hepatitis Treatment or TDF/FTC for PrEP, US, Germany, Canada, and the Netherlands, 2017–2018**

First Author of Case Report	HIV Tests Before PrEP Initiation	Time After Last Negative HIV Test	Antigen/Ab	Supplemental or Confirmatory Tests	Qualitative NAT	Quantitative NAT, Copies/mL	Antiretroviral Management	Resistance Mutations
Seroconversions on PrEP with ambiguous HIV test results								
Knox [4]	Ag/Ab-nonreactive	3 mo	Reactive	Negative WB	28 000 copies (3 mo + 7 d)	28 000 copies (3 mo + 7 d)	TDF/FTC for PrEP; darunavir, ritonavir, raltegravir added for treatment regimen at 3 mo + 4 d	41I, 67G, 69D, 70R, 184V, 215E, 181C, 10L, 51Y, 92Q
Markowitz [5]	Ag/Ab-nonreactive, qualitative NAT–nonreactive	19 wk	Reactive	Nonreactive multispot	Reactive	Not detected	TDF/FTC for PrEP until week 22	K65R, M184V, K103S, E138Q, Y199L (25 wk)
		21 wk	Reactive	Nonreactive multispot	Reactive	<20 copies		
		22 wk					Dolutegravir added to TDF/FTC for treatment regimen	
Zucker [6]	POC antibody–nonreactive, Ag/Ab-nonreactive, pooled NAT–negative	25 wk 28 d	Reactive Reactive	Nonreactive multispot Negative WB	Nonreactive Reactive	Not detected	TDF/FTC for PrEP until 32 d	Not assessed
		32 d	Nonreactive		Nonreactive	<20 copies	Dolutegravir added to TDF/FTC for treatment regimen	
Hoornborg [7]	Ag/Ab-nonreactive, pooled NAT–negative	46 d 10 wk	Reactive Reactive Ab, nonreactive p24 Ag	Indeterminate WB	Reactive	Not detected	TDF/FTC for PrEP until 11 wk	None
		11 wk	Reactive	Negative WB	Nonreactive	Not detected		
		12 wk				Not detected		
		14 wk				12 882 copies		
		15 wk		Weak positive WB		101 156 copies	Started TDF/FTC, ritonavir, darunavir, dolutegravir for treatment regimen	
		19 wk		Positive WB				
Seroconversions on PrEP with unambiguous HIV test results								
Thaden [8]	Ag/Ab-nonreactive	16 mo	Reactive		27 316 copies	27 316 copies	TDF/FTC for PrEP until month 16, started on dolutegravir, rilpivirine, darunavir/cobicistat for treatment	M164V, K65R, K70T, K103N, V109, V1971
Streek [9]	Ag/Ab-nonreactive	103 d	Reactive		59 copies	59 copies	TDF for hepatitis B treatment until day 103, FTC and ritonavir-boosted darunavir added for treatment regimen	K65R

Abbreviations: Ab, antibody; Ag, antigen; FTC, emtricitabine; NAT, nucleic test; POC, point of care; PrEP, pre-exposure prophylaxis; TDF, tenofovir disoproxil fumarate; WB, Western blot.

## HIV TESTING IN THE CONTEXT OF PREP PROVISION

Before prescribing PrEP, the absence of acute or chronic HIV infection should be confirmed [3]. During the earliest weeks of HIV infection (ie, acute phase of infection), antibody to HIV may not yet be measurable but viral antigens can be. While the patient is taking PrEP, HIV testing should be repeated at least every 3 months before PrEP prescriptions are refilled or reissued. Testing is also recommended when there has been low medication adherence and when signs or symptoms consistent with acute HIV infection occur [14], recognizing that during the earliest stages of infection there is increased probability for false-negative testing. This frequent testing schedule is intended to ensure that HIV infection is diagnosed and treated early to limit immune system injury, minimize the risk of inducing HIV drug resistance from exposure to incompletely suppressive PrEP regimens, and prevent onward HIV transmissions.

## CURRENT RECOMMENDATIONS FOR HIV TESTING

For HIV testing, the Centers for Disease Control and Prevention (CDC) and the Association of Public Health Laboratories (APHL) recommend that infection be diagnosed using an instrumented, laboratory-based Ag/Ab screening immunoassay, followed, when reactive, by an HIV-1/HIV-2 Ab differentiation immunoassay [15]. When the differentiation assay interpretation is negative or indeterminate for HIV-1, an HIV-1 nucleic acid test (NAT) for HIV RNA should be performed. Instrumented Ag/Ab tests are preferred over rapid POC tests (which can be either Ab only or Ag/Ab tests) because the former are more sensitive to HIV during acute infection. All positive POC test results should be confirmed by drawing blood for testing in the laboratory [15].

Characteristics of currently available Food and Drug Administration–approved HIV tests are available on the CDC website [16]. These tests can be grouped into 3 major categories: NATs, Ag/Ab tests, and Ab-only tests [17]. HIV tests are very accurate, but no test can detect the virus during the first few days after infection, when replication is limited to tissues near the site of infection. Once HIV enters the circulatory system, infection is detectable in blood. The earliest that HIV infection can be detected is with a NAT, typically between 10–33 days after an exposure. However, NATs are expensive compared with other tests and are usually used when either recent exposure or acute HIV infection is suspected. Ag/Ab blood tests performed by a laboratory can usually detect HIV infection 18–45 days after an exposure. Ab-only tests can also typically detect HIV within the first weeks after infection but in some cases may take up to 90 days before detectable levels of antibody are present. Most POC HIV tests are rapid Ab-only tests that use either whole blood or oral fluid; using blood can detect infection earlier than oral fluid [18], so oral fluid testing is not recommended for

persons taking PrEP. HIV infection is considered established when both HIV RNA and antibody are present.

The performance characteristics of the HIV tests described above were derived using specimens from individuals not exposed to ARVs during infection [19]. The presence of ARVs in PrEP patients during infection may alter these trajectories [20], suppressing or slowing viral replication and the development of antibodies, which may also occur out of synchrony, such as detectable antibody in the absence of detectable antigen. In persons who become HIV-infected while taking PrEP, HIV testing may produce results that could be interpreted as ambiguous or falsely negative (ie, erroneously interpreted as uninfected) [21], thus delaying accurate diagnosis. Technical issues related to false-positive testing (ie, erroneously interpreted as infected), specifically repeated false-positive Ag/Ab test results in an HIV-uninfected person taking PrEP, can also pose a challenge, taking time to reconcile and creating psychological stress.

## AMBIGUOUS TEST RESULTS IN PERSONS TAKING PREP WHO ACQUIRED HIV INFECTION

At least 4 breakthrough PrEP infections with ambiguous HIV test results that could not be resolved with the HIV testing algorithms used have been reported among persons using oral daily FTC-TDF or TDF (Table 1) [4, 5, 9, 22]. In all 4 cases, the screening test was an Ag/Ab assay, which was reactive. Supplemental testing, when done, was not always consistently reactive and included Western blot (WB), HIV-1/2 differentiation assays, and/or HIV RNA tests. The presence of infection was confirmed in 1 of 2 ways: either by (1) continuing PrEP in 3 cases and adding a protease and/or integrase inhibitor for treatment of presumptive HIV infection while performing additional testing, including HIV RNA and/or DNA tests, or (2) stopping PrEP in 1 case and subsequently documenting the presence of both a stable antibody response and presence of HIV RNA. Resolving ambiguous test results created delays in the diagnosis of HIV infection and may have contributed to an opportunity for ARV resistance to develop, such as the K65R mutation, which can confer resistance to tenofovir and cross-resistance to FTC; this mutation was observed in 2 persons. One patient also had the M184V mutation, which confers resistance to FTC. Two persons also did not have high concentrations of HIV RNA, possibly as a result of suppression of viral replication by PrEP or combined with the addition of an integrase inhibitor to the treatment regimen of 1 patient while testing continued [4]. In the second patient, PrEP was stopped, and the infection was allowed to progress, producing diagnostic levels of HIV RNA but obviating the potential benefit of blunting early viral dissemination.

Two PrEP studies, the HPTN 067/ADAPT and iPreX studies, that retrospectively studied stored blood specimens also demonstrated the increased sensitivity of plasma NAT for detecting breakthrough HIV-1 infection

in persons for whom parallel rapid tests are falsely nonreactive or discordant [12, 21]. Interestingly, Ag/Ab combo tests were also nonreactive for 7 persons in the HPTN 067/ADAPT study at the first HIV testing visit, and development of drug resistance mutations (M184I, K65R) was seen in 3 seroconvertors.

### **FALSE-POSITIVE TEST RESULTS IN PERSONS TAKING PREP WHO DO NOT HAVE HIV INFECTION**

Repeated false-positive Ag/Ab tests are rare but are problematic when they occur in the context of PrEP. This phenomenon was observed in 1 participant in Project DETECT, an ongoing study funded by the CDC and being conducted at the Public Health Seattle King County STD clinic (J Steckler MD, et al. accepted, OFID, August 2018). Similar cases have also been reported to the CDC by providers who administer PrEP outside of this study. Documenting patterns of HIV test results in these patients will be informative. Promptly establishing the absence of infection in these cases is critical, not only to relieve psychological stress but to be able to continue the protection that PrEP use confers.

### **PATIENT MANAGEMENT DECISIONS WHILE HIV STATUS IS BEING CONFIRMED**

Two issues arise from these situations with unusual HIV testing results. First, how to confirm the presence or absence of infection. Second how to manage antiretroviral medications while infection status is being confirmed, specifically whether to continue PrEP, transition to an ART regimen, or discontinue PrEP. There are pros and cons to each of these antiretroviral management strategies.

#### **Options for Confirming HIV Status in the Presence of PrEP**

In the unusual circumstance that testing according to recommended algorithms [15] produces ambiguous results, repeat testing a few days to weeks later with a fresh blood sample may provide resolution, based on the assumption that the ambiguous results were due to very early infection or technical issues (eg, mislabeled sample, specimen-to-specimen contamination, device performance). Testing for (1) HIV RNA in plasma, (2) total HIV-1 nucleic acids (RNA and DNA) in plasma, peripheral blood mononuclear cells (PBMCs), or whole blood [23], and/or (3) proviral DNA enriched from CD4+ T cells [5, 12, 20, 21] may help confirm infection. This additional testing may be an option if a decision is made to continue PrEP or start ART that could suppress viral replication and the presence of HIV nucleic acids in the bloodstream (see below). At present, total HIV-1 nucleic acid and proviral DNA testing are research use-only assays available at select research laboratories. Repeatedly positive Ag/Ab testing in the context of a negative confirmatory test merits discussion with the testing laboratory to see if repeat testing with an Ag/Ab test from another manufacturer can be done.

#### **Antiretroviral Management Option 1: Continue PrEP**

For persons with ambiguous HIV test results who are not infected with HIV or who have repeatedly reactive Ag/Ab tests that may be falsely positive, continuing PrEP maintains protection against infection if exposed. Because of the high effectiveness of PrEP in adherent patients, the pretest probability that adherent patients are uninfected is high. If infected with HIV, continuing PrEP offers some level of viral suppression and potential preservation of immune function but is inadequate for treatment and creates drug pressure that may select drug resistance mutations if not already present. Thus, if continuing PrEP, access to testing that can rapidly resolve ambiguous results, as described above, is imperative to facilitate timely transition to ART and minimize risk of antiretroviral resistance if HIV infection is present. The longer the use of PrEP continues during undiagnosed HIV infection, the greater the chance of the virus developing resistance. However, a well-tolerated HIV treatment regimen can be constructed for PrEP patients who become HIV-infected with transmitted or acquired mutations associated with resistance to TDF or FTC [24].

#### **Antiretroviral Management Option 2: Initiate ART**

For persons with ambiguous HIV test results who are not infected with HIV or who have repeatedly reactive Ag/Ab tests that may be falsely positive, initiating ART maintains protection against infection but briefly exposes the person unnecessarily to at least 1 additional drug and its side effects and drug-drug interactions (ie, by adding a third ARV drug to their 2-drug PrEP regimen). If determined to be infected with HIV, continuing ART treats the infection as soon as possible and may limit seeding of reservoirs to minimize early immune damage [25–29] while reducing the risk of onward HIV transmission.

An important practical consideration is insurance coverage for ART, which, without an HIV diagnosis, may force persons awaiting a resolution of their HIV infection status to pay out of pocket. One option is to use a postexposure prophylaxis (PEP) diagnosis code (eg, ICD-10-CM Z20.6, contact with and [suspected] exposure to HIV) and add a third drug for up to 28 days, consistent with the PEP guidelines [30], while additional testing resolves the true HIV status of the patient. This is especially applicable when patients report nonadherence to daily PrEP. A presumptive diagnosis of HIV infection could be entered in the patient record to obtain insurance coverage for ART. However, if testing confirms the absence of infection, then reversing or extirpating this diagnosis in their medical record may be difficult. In addition, it will be psychologically distressing to such patients to receive changing information about whether they need treatment or PrEP.

#### **Antiretroviral Management Option 3: Discontinue PrEP**

For persons with ambiguous HIV test results who are not infected with HIV or who have repeatedly reactive Ag/Ab tests that may be falsely positive, discontinuing PrEP in the absence of other HIV prevention interventions (eg, consistent and correct condom use) may place them at risk for infection

if exposed to HIV. If infected with HIV, discontinuing PrEP for 1–2 weeks may facilitate diagnosis by allowing viral replication resulting in detectable blood levels of HIV RNA in blood. Such patients should develop viremia within days and could rapidly be placed on ART with a definitive diagnosis, whereas persons who have not acquired HIV infection will not develop detectable HIV RNA and can confidently be restarted on PrEP. This option provides a definitive HIV status quickly and is operationally simple. However, for uninfected persons, it provides no antiretroviral protection against infection, and for HIV-infected persons, it may obviate the individual virologic or immune benefits of ART initiation during acute infection, as well as the early prevention benefit against onward transmission.

## CONCLUSION

Persons prescribed PrEP merit a high index of suspicion for possible HIV infection. Ambiguous HIV test results appear to be rare using the recommended CDC/APHL laboratory HIV testing algorithm. Rapid and accurate resolution of ambiguous test results can minimize harm. Persons with ambiguous test results require counseling about options to manage antiretroviral medications while ambiguous results are resolved. By ensuring that such persons understand the potential benefits and harms of each option to their own health and to their risk of transmitting HIV to others, they can, together with their health care provider, make informed choices most appropriate to their individual circumstances.

More experience is needed in the management of PrEP, as is a broader understanding of how HIV tests perform in the context of the rare breakthrough HIV infection while taking PrEP. In addition, more data are needed to provide a clearer understanding of how to quickly resolve false positive test results for PrEP patients eventually determined not to have acquired HIV infection. In the meanwhile, providers in the United States with questions about management of specific testing results for PrEP patients, or who wish to report ambiguous HIV test results in PrEP patients, can call the PrePline toll-free at 855-448-7737 (11 AM–6 PM EST). Providers may also want to consult with local infectious disease specialists or colleagues with more expertise in HIV diagnosis options.

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