Navigating Human Immunodeficiency Virus Screening Recommendations for People on Pre-Exposure Prophylaxis and the Need to Update Testing Algorithms

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Incident HIV infections occurring in people on PrEP may have delayed seroconversion. New CDC guidelines recommend the addition of HIV-1 viral load for screening for all on PrEP. We believe antigen/antibody screening should continue for tenofovir-based PrEP at this time.

Keywords. cabotegravir; HIV drug resistance; HIV testing; PrEP; tenofovir.

Recently updated guidelines from the Centers for Disease Control and Prevention (CDC) for the management of pre-exposure prophylaxis (PrEP) for human immunodeficiency virus (HIV) recommend dual use of HIV antigen/antibody (Ag/Ab) and ribonucleic acid (RNA) testing (rather than sole Ag/Ab testing) for regular screening for individuals on PrEP [1, 2]. The rationale for this change comes from an analysis of incident HIV infections in HPTN 083 showing Ag/Ab assays are unpredictable for individuals on PrEP, because they can remain negative or indeterminate for several additional weeks after acute infection [3, 4].

HPTN 083 was a randomized, double-blinded clinical trial that showed superiority of injectable cabotegravir (CAB) compared with oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) as PrEP for HIV prevention for cisgender men and transgender women who have sex with men, with 13 incident HIV infections in the CAB arm and 39 in the TDF/FTC arm (hazard ratio, 0.34; 95% confidence interval, 0.18–0.62; P < .001) [5]. Data from HPTN 083 shed key insights into the phenomenon of delayed seroconversion [6]. Retrospective analysis of 51 of the study’s 52 incident HIV infections found delayed detection of infection in several cases (see Table 1).

In the CAB arm, 7 of the 12 (58.3%) incident cases were not detected on routine Ag/Ab testing at a study visit, leading to a median delay of diagnosis of 98 days (range, 35–185) [6]. In the TDF/FTC arm, delayed detection was found in 7 of the 39 (17.9%) incident cases, with a median delay of 31 days (range, 7–68). However, viral load testing detected infection earlier in 5 of the 7 cases in the CAB arm and 6 of the 7 cases in the TDF/FTC arm. Reversion of the Ag/Ab assay from reactive to nonreactive was also reported among some who developed HIV infection in the CAB arm, further demonstrating the limitations of Ag/Ab tests for individuals on CAB.

The implications of delayed HIV diagnosis include development and possible transmission of resistant HIV. In HPTN 083, 4 of the 12 (33%) incident HIV infections in the CAB arm had integrase strand transfer inhibitor (INSTI) class resistance that would impact second-generation INSTIs, including dolutegravir (DTG) and bictegravir (BIC), that are the backbone of all first-line antiretroviral (ARV) regimens currently recommended by the National Institutes of Health [7]. This resistance occurred in 2 individuals with good adherence in the oral lead-in phase and in 2 individuals receiving appropriately scheduled CAB injections with expected plasma CAB levels. In the TDF/FTC arm, 4 of the 39 (10.3%) incident HIV infections had nucleoside reverse-transcriptase inhibitor (NRTI) resistance including M184V (3 cases) and K65R (1 case) mutations, with exposure to drug-resistant HIV, rather than emergent resistance, which is believed to be the explanation in all 4 cases [6]. In fact, of the 39 incident infections in the TDF/FTC arm, just 2 occurred in individuals with serum drug levels consistent with good adherence [5]. Therefore, of the approximately 0.2% of all participants in HPTN 083 who had key class resistance mutations...
after an incident HIV infection, emergent INSTI resistance was seen more often in infections on CAB and transmitted NRTI resistance in the TDF/FTC arm.

A comprehensive review of drug resistance in PrEP trials preceding HPTN 083 found a similar, low rate of NRTI resistance (most commonly M184V or K65R, and occasionally both) for incident infections in tenofovir (TFV) study arms (17 of the 319 incident infections, 5.3%) [8]. Of note, at the time of that review, there were just 6 reported breakthrough HIV infections in individuals with confirmed good PrEP adherence, with M184V in 5 cases, K65R in 2 of those cases, and 1 case with neither mutation.

The longer half-life of CAB (approximately 40 days) versus TFV (17 hours serum/60 hours intracellular) may explain the higher relative risk of emergent class drug resistance per incident HIV infection for CAB than for TDF/FTC, for instance with 33% vs. 10.3% emergent class resistance for CAB vs. TDF/FTC incident infections in HPTN 083 (see Table 1) [9, 10]. The relative clinical importance of CAB-associated resistance is also greater. The mutations reported among incident HIV cases in the CAB arm included Q148R/K and R263K, which are associated with virologic failure with DTG and BIC [11, 12]. Therefore, in such patients, providers would need to select non-INSTI-based regimens that have some important limitations. In the nonnucleoside reverse-transcriptase inhibitor (NNRTI) class, efavirenz has lower rates of viral suppression than DTG [13]. Rilpivirine has a relatively low barrier to resistance and needs to be administered with food and without acid blocking medications [14]. The newer NNRTI doravirine has a relatively high barrier to resistance and, when coadministered with lamivudine (3TC) and TDF, has been shown to be effective for both treatment-naive and experienced patients, although it has not yet been studied head-to-head against current first-line INSTI-based regimens [15, 16]. Protease inhibitors such as atazanavir and darunavir (DRV) have numerous drug-drug interactions potentially limiting other therapeutic options for patients with multiple comorbidities [17]. In addition, mixed reports suggest that DRV may be associated with increased cardiovascular risk [18, 19].

On the other hand, numerous recent studies suggest that NRTI resistance (including very high-level resistance) may have limited clinical importance in the modern antiretroviral era. For instance, the Nucleosides and Darunavir/Dolutegravir in Africa (NADIA) trial found very high levels of viral suppression for individuals on DTG and 2 NRTIs, even if resistance to included NRTIs was predicted [20]. Other studies have shown similar good outcomes for individuals on BIC/TAF/FTC with high level NRTI resistance, including for those with signature FTC and TFV mutations, M184V and K65R, respectively [21]. In patients with an archived M184V mutation, it may even be possible to eventually use certain, increasingly popular 2-drug antiretroviral regimens, including DTG/3TC, because accumulating evidence shows this mutation may not be associated with virologic failure for durably virally suppressed individuals who switch to DTG/3TC [22–25]. Therefore, contrary to incident HIV infections that occur on TFV-based PrEP, which typically do not require the use of second-line ARVs, many incident HIV infections on CAB PrEP are unlikely to be treatable with most currently recommended first-line HIV regimens.

ARGUMENT IN FAVOR OF HUMAN IMMUNODEFICIENCY VIRUS-1 RIBONUCLEIC ACID SCREENING FOR PEOPLE ON PRE-EXPOSURE PROPHYLAXIS

Current CDC HIV testing guidelines continue to recommend using an Ag/Ab assay for general HIV screening outside the context of people on PrEP [26]. The addition of an RNA assay, recommended in the updated PrEP screening guidelines, makes good sense for individuals on CAB, given that we can expect to see a low rate of PrEP failures with potential for high impact emergent INSTI resistance (likely to occur somewhat more frequently in real-world setting than the approximately 2 in 1000 cases seen in HPTN 083). Moreover, prompt identification of these cases will be essential to initiate effective treatment rapidly and to prevent potential development and transmission of INSTI-resistant HIV. Among the 4 patients in the CAB arm of HPTN 083 with important INSTI resistance, 3 had the mutations when their infections were first detected by viral load assays. This suggests that among CAB PrEP failures, INSTI resistance may be present at first detected viremia approximately one quarter of the time (3 of 12 cases in HPTN 083); continuing CAB after new

Table 1. Summary of Relevant Findings from HPTN 083

| Finding from HPTN 083 | CAB Arm | TDF/FTC Arm |
|-----------------------|---------|-------------|
| Number of incident HIV infections | 12 | 39 |
| Number with delayed detection | 7 (58.2%) | 7 (17.9%) |
| Median delay in diagnosis in days (range) | 98 (35–185) | 31 (7–68) |
| Earlier detection with viral load testing | 5/7 (71.4%) | 6/7 (85.7%) |
| Emergence of important class resistance | 4/12 (33%) | 4/39 (10.3%) |

Abbreviations: CAB, cabotegravir; HIV, human immunodeficiency virus; HPTN 083, The HIV Prevention Trials Network 083 study; TDF/FTC, tenofovir disoproxil fumarate and emtricitabine.
infection could lead to development of resistance in additional individuals. Potential benefits of extending routine RNA testing to those on oral PrEP include somewhat earlier identification of all new HIV infections and harmonization of testing for all people on PrEP, regardless of formulation, which might lead to less confusion among PrEP providers.

ARGUMENT AGAINST ROUTINE HUMAN IMMUNODEFICIENCY VIRUS-1 RIBONUCLEIC ACID TESTING FOR PEOPLE ON ORAL PRE-EXPOSURE PROPHYLAXIS IN CURRENT CONTEXT

Although evident for CAB PrEP, the added benefit of an RNA assay is less clear for individuals on TFV-based PrEP. Data from HPTN 083 show that delayed diagnosis is less frequent per incident case for TFV versus CAB PrEP failures and that delays are shorter in duration. As discussed earlier, the relative importance of delayed diagnosis is also less because the associated resistance is not as problematic. Moreover, the logistics and costs of adding a second molecular test for all PrEP patients are not trivial. Expanded laboratory capacity including equipment and personnel would be needed at a time when testing for many other viral infections (most notably SARS-CoV-2 and other respiratory viral infections) is at extremely high levels. Viral load tests currently have higher costs and longer turnaround times than Ag/Ab tests, which may limit scale up of PrEP programs. In underresourced settings, access to viral load testing may be limited, and this monitoring may not be feasible. The individual- and population-level benefits of additional RNA testing for individuals on TFV-based PrEP should be studied but may be marginal at the time. In addition, although there is great interest in injectable PrEP, it is likely that TFV will remain the predominant form used for at least the next several years [27, 28].

REASONABLE APPROACH AND FUTURE DIRECTIONS

Although dual screening for individuals on CAB-PrEP is appropriate, with currently available testing, implementing quarterly RNA testing for all individuals on TFV-based PrEP may be neither practical nor worthwhile. Therefore, we believe it is reasonable to continue Ag/Ab screening combined with acute HIV symptom assessment at this time for individuals on TFV-based PrEP, and we suggest that it should be reflected as acceptable in guidelines. For those with a positive acute HIV symptom screen, viral load testing should be ordered or, if not available, these individuals should return sooner than 3 months for repeat HIV Ag/Ab testing.

CONCLUSIONS

We appreciate the importance of the earliest possible diagnosis of all new HIV infections, and we advocate for moving beyond current HIV screening algorithms to eventually use HIV-1 viral load testing as part of regular screening for HIV. An HIV-1 viral load test has been validated for the diagnosis of HIV and was found to detect incident HIV infection approximately 6 days earlier than current Ag/Ab assays [29]. Although it has not been yet been studied for monitoring for individuals on PrEP, it should detect rare incident infections earlier than Ag/Ab tests. Combining antibody and viral load testing in a single assay, although ideal, would require merging 2 different molecular platforms: an enzyme-linked immunoassay and a nucleic acid amplification test (NAAT). Rapid NAATs have become widely available for SARS-CoV-2 diagnosis and should be developed for HIV screening and rolled out for use in PrEP clinics [30]. A rapid HIV NAAT could allow for reversing the current screening algorithm by starting with a rapid RNA test in clinic and simultaneously checking
an antibody test (see Figure 1). Combining viral load and antibody testing would capture those who might initially have an undetectable viral load in the presence of ARV pressure from PrEP agents or early immunologic control, as was reported in HPTN 083 (case D2) [6]. Therefore, although we agree in principle with the goal of moving towards universal RNA testing, we suggest in principle with the goal of moving to
to have an undetectable viral load in individuals on oral PrEP.

Combining viral load and antibody tests.

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