Open Forum Infectious Diseases

PERSPECTIVES

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, .18–.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

Received 15 February 2022; editorial decision 4 April 2022; accepted 7 April 2022; published online 15 April 2022

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Open Forum Infectious Diseases®2022

https://doi.org/10.1093/ofid/ofac191

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.

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 of 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

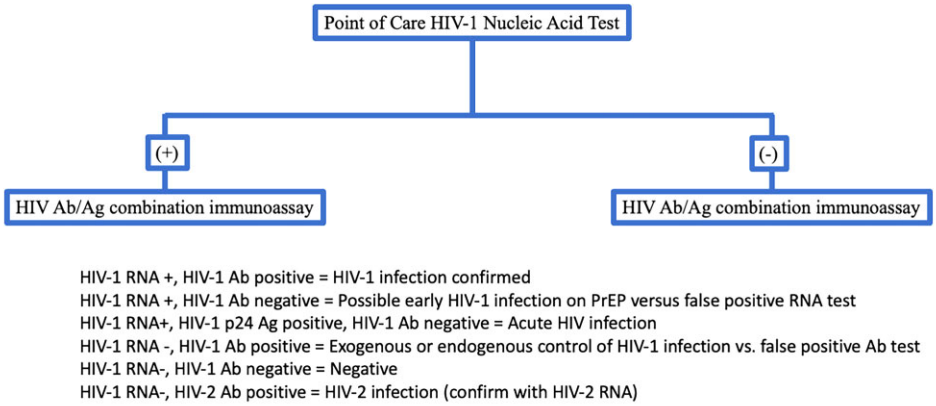

Figure 1. Proposal for reverse human immunodeficiency virus (HIV) screening algorithm. Ab/Ag, antibody/antigen; HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; RNA, ribonucleic acid.

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 that in the current context it is reasonable to continue sole Ag/Ab testing with acute HIV symptom assessment for most individuals on oral PrEP.

Acknowledgments

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Centers for Disease Control and Prevention, US Public Health Service. Preexposure prophylaxis for the prevention of HIV infection in the United States—2021 update: a clinical practice guideline. Available at: https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf Accessed 10 February 2022.
2. Centers for Disease Control and Prevention, US Public Health Service. Preexposure prophylaxis for the prevention of HIV infection in the United States—2017 update: a clinical practice guideline. Available at: https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf Accessed 10 February 2022.
3. Johnson KA, Chen MJ, Kohn R, et al. Acute HIV at the time of initiation of pre-exposure or post-exposure prophylaxis: impact on drug resistance and clinical outcomes. J Acquir Immune Defic Syndr **2021**; 87:818–25.
4. Lee SS, Anderson PL, Kwan TH, et al. Failure of pre-exposure prophylaxis with daily tenofovir/emtricitabine and the scenario of delayed HIV seroconversion. Int J Infect Dis **2020**; 94:41–3.
5. Landovitz RJ, Donnell D, Clement ME, et al. Cabotegravir for HIV prevention in cisgender men and transgender women. N Engl J Med **2021**; 385:595–608.
6. Marzinke MA, Grinsztejn B, Fogel JM, et al. Characterization of human immunodeficiency virus (HIV) infection in cisgender men and transgender women who have sex with men receiving injectable cabotegravir for HIV prevention: HPTN 083. J Infect Dis **2021**; 224:1581–92.
7. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv. Accessed 3 February 2022.
8. Gibas KM, van den Berg P, Powell VE, Krakower DS. Drug resistance during HIV pre-exposure prophylaxis. Drugs **2019**; 79:609–19.
9. Cattaneo D, Gervasoni C. Pharmacokinetics and pharmacodynamics of cabotegravir, a long-acting HIV integrase strand transfer inhibitor. Eur J Drug Metab Pharmacokinet **2019**; 44:319–27.
10. Kearney BP, Flaherty JF, Shah J. Tenofovir disoproxil fumarate: clinical pharmacology and pharmacokinetics. Clin Pharmacokinet **2004**; 43:595–612.
11. Rhee SY, Grant PM, Tzou PL, et al. A systematic review of the genetic mechanisms of dolutegravir resistance. J Antimicrob Chemother **2019**; 74:3135–49.
12. Acosta RK, Willkom M, Martin R, et al. Resistance analysis of bictegravir-emtricitabine-tenofovir alafenamide in HIV-1 treatment-naive patients through 48 weeks. Antimicrob Agents Chemother **2019**; 63:e02533-18.
13. Kanters S, Vitoria M, Zoratti M, et al. Comparative efficacy, tolerability and safety of dolutegravir and efavirenz 400 mg among antiretroviral therapies for first-line HIV treatment: a systematic literature review and network meta-analysis. EClinicalMedicine **2020**; 28:100573.
14. Crauwels H, van Heeswijk RP, Stevens M, et al. Clinical perspective on drug-drug interactions with the non-nucleoside reverse transcriptase inhibitor rilpivirine. AIDS Rev **2013**; 15:87–101.
15. Kumar P, Johnson M, Molina JM, et al. Brief report: switching to DOR/3TC/TDF maintains HIV-1 virologic suppression through week 144 in the DRIVE-SHIFT trial. J Acquir Immune Defic Syndr **2021**; 87:801–5.
16. Martin EA, Lai MT, Ngo W, et al. Review of doravirine resistance patterns identified in participants during clinical development. J Acquir Immune Defic Syndr **2020**; 85:635–42.
17. Rathbun RC, Liedtke MD. Antiretroviral drug interactions: overview of interactions involving new and investigational agents and the role of therapeutic drug monitoring for management. Pharmaceutics **2011**; 3:745–81.
18. Costagliola D, Potard V, Lang S, et al. Is the risk of myocardial infarction in people with human immunodeficiency virus (HIV) associated with atazanavir or darunavir? A nested case-control study within the French hospital database on HIV. J Infect Dis **2020**; 221:516–22.
19. Ryom L, Lundgren JD, El-Sadr W, et al. Cardiovascular disease and use of contemporary protease inhibitors: the D:A:D international prospective multicohort study. Lancet HIV **2018**; 5:e291–300.
20. Paton NI, Musaazi J, Kityo C, et al. Dolutegravir or darunavir in combination with zidovudine or tenofovir to treat HIV. N Engl J Med **2021**; 385:330–41.
21. Sax PE, Rockstroh JK, Luetkemeyer AF, et al. Switching to bictegravir, emtricitabine, and tenofovir alafenamide in virologically suppressed adults with human immunodeficiency virus. Clin Infect Dis **2021**; 73:e485–93.
22. Gagliardini R, Ciccullo A, Borghetti A, et al. Impact of the M184V resistance mutation on virological efficacy and durability of lamivudine-based dual antiretroviral regimens as maintenance therapy in individuals with suppressed HIV-1 RNA: a cohort study. Open Forum Infect Dis **2018**; 5:ofy113.
23. Rial-Crestelo D, de Miguel R, Montejano R, et al. Long-term efficacy of dolutegravir plus lamivudine for maintenance of HIV viral suppression in adults with and without historical resistance to lamivudine: week 96 results of ART-PRO pilot study. J Antimicrob Chemother **2021**; 76:738–42.
24. Charpentier C, Montes B, Perrier M, et al. HIV-1 DNA ultra-deep sequencing analysis at initiation of the dual therapy dolutegravir + lamivudine in the maintenance DOLULAM pilot study. J Antimicrob Chemother **2017**; 72:2831–6.
25. Baldin G, Ciccullo A, Rusconi S, et al. Long-term data on the efficacy and tolerability of lamivudine plus dolutegravir as a switch strategy in a multicentre cohort of HIV-1-infected, virologically suppressed patients. Int J Antimicrob Agents **2019**; 54:728–34.
26. National Center for HIV/AIDS, Viral Hepatitis, and TB Prevention (U.S.), Division of HIV/AIDS Prevention, Association of Public Health Laboratories. 2018 Quick reference guide: Recommended laboratory HIV testing algorithm for serum or plasma specimens. Published: January 2018. Available at: https://stacks.cdc.gov/view/cdc/50872 Accessed 10 February 2022.
27. Meyers K, Wu Y, Qian H, et al. Interest in long-acting injectable PrEP in a cohort of men who have sex with men in China. AIDS Behav **2018**; 22:1217–27.
28. Meyers K, Wu Y, Brill A, et al. To switch or not to switch: intentions to switch to injectable PrEP among gay and bisexual men with at least twelve months oral PrEP experience. PLoS One **2018**; 13:e0200296.
29. Nair SV, Kim HC, Fortunko J, et al. Aptima HIV-1 Quant Dx—A fully automated assay for both diagnosis and quantification of HIV-1. J Clin Virol **2016**; 77:46–54.
30. Basu A, Zinger T, Inglima K, et al. Performance of Abbott ID Now COVID-19 rapid nucleic acid amplification test using nasopharyngeal swabs transported in viral transport media and dry nasal swabs in a New York City academic institution. J Clin Microbiol **2020**; 58:e01136–20.