Published in final edited form as:

Drugs. 2019 April ; 79(6): 609–619. doi:10.1007/s40265-019-01108-x.

Drug Resistance during HIV Preexposure Prophylaxis

Kevin M. Gibas^{#1}, Polly van den Berg^{#1}, Victoria E. Powell¹, and Douglas S. Krakower^{1,2,3}

¹Beth Israel Deaconess Medical Center, Boston, MA

²The Fenway Institute, Fenway Health, Boston, MA

³Department of Population Medicine, Harvard Medical School, Boston, MA

[#] These authors contributed equally to this work.

Abstract

Clinical studies have demonstrated that use of tenofovir disoproxil fumarate with or without emtricitabine as antiretroviral preexposure prophylaxis (PrEP) can decrease the risk of HIV acquisition when medication adherence is high. However, the potential for PrEP to promote antiretroviral resistance remains an important public health consideration. We performed a search of the medical literature to identify studies that address HIV drug resistance during PrEP use. In this review, we summarize findings about emergent drug resistance during clinical trials of PrEP, case reports of seroconversions in adherent PrEP patients, and animal studies of PrEP effectiveness against drug resistant viral strains. We also discuss the potential utility of novel PrEP formulations for protection against drug resistant HIV, the impact of drug resistance on HIV treatment options, and mathematical models that estimate the potential contribution of PrEP to population-level drug resistance. Evidence suggests that selection for HIV drug resistance with PrEP use is infrequent and most likely to occur when PrEP is used during undiagnosed acute HIV infection. Breakthrough infections during PrEP use with high adherence are possible, but appear to be rare. The prevalence of drug resistant HIV strains needs to be monitored as PrEP is scaled-up. However, the benefit of decreased HIV incidence with wider PrEP use is likely to outweigh the risk of harms from possible increases in the prevalence of HIV drug resistance.

1. Introduction

As there are over 1.8 million new HIV infections globally each year [1], including 38,500 in the United States [2], effective HIV prevention strategies are needed. Clinical studies have demonstrated that use of tenofovir disoproxil fumarate (TDF) with or without emtricitabine (FTC) as preexposure prophylaxis (PrEP) can decrease the risk of HIV acquisition in men who have sex with men (MSM) and transgender women [3], heterosexual persons [4], people who inject drugs [5], and HIV-serodiscordant partners [6] when used with high adherence. In 2012, The United States Food and Drug Administration approved the use of TDF co-formulated with FTC (TDF/FTC) to prevent HIV transmission, and efforts to scale-up PrEP are underway globally. However, increased use of antiretroviral medications for

PrEP has the potential to select for and promote HIV drug resistance, which could compromise the effectiveness of antiretroviral medications for both treatment and prophylaxis.

Given the potential for antiretroviral drug resistance with PrEP, previous studies have addressed clinical scenarios in which resistance to TDF/FTC may develop. These include the initiation of TDF/FTC as PrEP among individuals with undiagnosed acute HIV; continued PrEP use by people who acquire HIV while using PrEP; and HIV infection of adherent PrEP users with viral strains that are resistant to TDF/FTC (“breakthrough infections”) [7]. It is also important to consider how drug resistance that emerges after HIV infection in PrEP users might affect HIV treatment options and effectiveness. In this narrative review, we summarize studies that address the extent to which PrEP use might select for and disseminate antiretroviral drug resistance, the potential for breakthrough infections by drug-resistant strains of HIV, and the impact of drug resistance after PrEP failures on HIV treatment.

2. Methods

We performed a search of the medical literature using medical subject headings (MeSH) to find original research articles that addressed HIV drug resistance and PrEP. Our literature search included the terms “Pre-exposure prophylaxis”, “Preexposure prophylaxis”, “PrEP”, “Drug Resistant” and “Drug Resistance” in *PubMed*, *Embase*, *Web of Knowledge*, ClinicalTrials.gov, and the *Cochrane Database of Systematic Reviews*. A total of 440 papers were identified after duplicate articles were removed, including 152 articles in *PubMed*, 207 in *Embase*, 77 in *Web of Knowledge*, 4 in ClinicalTrials.gov, and 0 in the *Cochrane Database*. The abstracts of these papers were read by two independent reviewers, and papers were included or excluded for further review based on predetermined exclusion criteria. Exclusion criteria included studies: 1) not related to PrEP drug resistance; 2) addressing societal, psychological, healthcare provider, insurer, or patient resistance to PrEP use; 3) focusing on HIV drug resistance exclusively in the context of antiretroviral treatment (ART) and not PrEP; 4) addressing antibacterial drug resistance or non-HIV viral infections; and 5) forms of preexposure prophylaxis unrelated to HIV. After applying exclusion criteria, 107 papers remained. We summarize the findings of those studies that shed light on how drug resistance during PrEP use impacts clinical management or population health for HIV treatment or prevention.

3. Emergence of HIV Drug Resistance with PrEP Use

3.1 HIV Drug Resistance in Randomized Clinical Trials of PrEP

Thirteen randomized studies have investigated the efficacy and/or optimal dosing schedule of oral TDF with or without FTC as PrEP and have reported rates of antiretroviral drug resistance observed during study follow-up [3–6, 8–26]. These studies demonstrated that PrEP is safe, well tolerated and able to decrease HIV transmission in multiple priority populations. The efficacy of TDF/FTC as PrEP was as high as 75% in the intention to treat analysis in the Partners PrEP Study, an efficacy study of TDF with or without FTC as PrEP for HIV-serodiscordant couples in Africa [6]. These studies demonstrated that efficacy was

highly correlated with medication adherence. Subgroup analyses in the iPrEx Study, an efficacy study of TDF/FTC as PrEP for MSM and transgender women, found that among subjects adherent to PrEP, as measured by detectable drug levels, there was a 92% risk reduction of HIV [3]. The thirteen randomized PrEP studies represent thousands of participants who were followed prospectively for HIV seroconversion with or without exposure to PrEP, and thus provide an opportunity to understand how HIV acquisition in the context of exposure to TDF/FTC impacts selection for drug resistance.

In these studies, there were 699 participants with HIV seroconversion after being provided with PrEP or placebo (Table 1). Of these, 77 (11%) individuals had acute HIV infection (i.e. they were HIV antibody negative and HIV RNA positive) at time of trial enrollment or randomization. Among 77 participants with acute HIV, 18 (23%) individuals were subsequently found to have mutations that conferred resistance to FTC (i.e. substitution of valine or isoleucine for methionine at the 184th amino acid positions [M184V/I]) or TDF (i.e. substitution of lysine for arginine at the 65th amino acid position [K65R]). Fifteen of 18 (83%) acutely infected participants had mutations that conferred resistance to FTC, 14 of which were assigned to take TDF/FTC and one was assigned to placebo. Two of 18 (11%) individuals were found to have mutations that engender resistance to TDF: one was assigned to TDF/FTC and one was assigned to take TDF monotherapy. One participant had mutations that conferred resistance to TDF and FTC and was assigned to use TDF/FTC (Table 2).

Most (622/699; 89%) participants with seroconversions acquired HIV during study follow-up (i.e. after study entrance or randomization), and 19 of 622 (3%) individuals who did so had viral genetic mutations that conferred resistance to TDF or FTC. Of those 19 participants with resistance, 15 (79%) had viral mutations associated with FTC resistance: 10 were assigned to use TDF/FTC, four were assigned to use placebo, and one was assigned to use TDF only. Two participants had viral mutations associated with TDF resistance and both were assigned to placebo. Two participants had both TDF and FTC mutations and both were assigned to use TDF/FTC (Table 3).

Resistance mutations for FTC were more common than those for TDF irrespective of the timing of seroconversion (i.e. prior to or after study entry), which is consistent with the higher genetic barrier to resistance for TDF as compared to FTC [27]. As many participants in these randomized studies were non-adherent to PrEP, there might not have been sufficient drug exposure to select for drug resistant mutations in some cases of seroconversion. Thus, additional data on rates of drug resistance among individuals who acquire HIV while using PrEP consistently are needed to understand the potential for PrEP to promote dissemination of drug resistant HIV.

3.2 Drug Resistance with PrEP Use during Undiagnosed Acute HIV Infection

A closer examination of drug resistance among individuals who enrolled in PrEP studies with undiagnosed acute HIV can shed light on factors that might promote resistance. In iPrEx, there were 10 individuals who were retrospectively found to have been HIV infected at the time of enrollment. Of these individuals with undiagnosed HIV infection, three individuals had FTC mutations; two were in the TDF/FTC arm of the study and one was in the placebo arm. Of the two participants assigned to use TDF/FTC, one individual had an

M184V mutation and the other had an M184I mutation. These mutations were detected using ultrasensitive testing methods, and because the frequencies of these mutations were less than 1%, these may reflect normal variation rather than selected resistance. One of these participants had insufficient plasma HIV viral RNA levels at enrollment to perform resistance testing; the other participant had no evidence of HIV resistance mutations on testing of enrollment samples, indicating that their resistance mutations were acquired during the first 4 weeks of TDF/FTC use. No TDF-resistant HIV infections were observed [3, 8].

In the Partners PrEP efficacy trial and a subsequent open-label extension study, three individuals who were discovered retrospectively to have had undiagnosed acute HIV at treatment assignment had HIV resistance mutations detected using ultrasensitive sequencing methods [6, 9]. Two individuals assigned to use TDF/FTC had FTC resistance mutations and one individual assigned to use TDF had a TDF resistance mutation. All three individuals had detectable levels of tenofovir in plasma samples. These data support the notion that PrEP use during undiagnosed acute HIV is a high risk period for selection of drug resistance.

In the ADAPT study (HPTN 067), an open-label study comparing adherence to daily versus non-daily PrEP dosing schedules, three individuals out of 622 enrolled had undiagnosed acute HIV prior to a lead-in phase of the study [16]. In this lead-in phase, participants received once-weekly, directly observed treatment with TDF/FTC. One individual with undiagnosed HIV was found to have a K65R mutation, one had an M184I mutation, and one had no resistance mutations. The development of resistance mutations in 2 of these 3 participants suggests that even limited PrEP drug exposure (i.e. weekly dosing) may be associated with drug resistance. However, it is important to note that these cases may reflect transmitted as opposed to acquired drug resistance.

Drug resistance mutations were not detected after acute HIV infection in a study of TDF/FTC for young African women (FEM-PrEP) in which adherence was generally very low [11], which might reflect minimal drug exposure and thus limited selection pressure. In a study of event-driven TDF/FTC as PrEP for MSM in France, Germany, and Canada (IPERGAY), no resistance was found despite detectable concentrations of PrEP at the time of resistance testing in three of four participants with acute HIV [14, 15]. Collectively, the data from these studies suggest that the inadvertent use of PrEP during acute HIV increases the likelihood of drug resistance, but that resistance is not a universal outcome.

A meta-analysis of six PrEP efficacy studies by Fonner et al. examined the relationship between drug exposure and resistance during acute HIV more rigorously. This study found that individuals with acute HIV infection who were assigned to use PrEP were more likely to have drug resistance mutations than those assigned to placebo (risk ratio=3.34, 95% CI: 1.11–10.06, $P=0.03$), with resistance to FTC more common than mutations for TDF [28]. Consistent with this meta-analysis, selection for drug resistant viral strains in the randomized studies summarized in our narrative review appears to be most frequent among those who used FTC-containing PrEP during undiagnosed acute HIV, which might be a consequence of drug exposure that is sufficient to select for drug resistance but insufficient to achieve viral suppression. As recommended by clinical guidelines, this suggests that

clinicians will need to be rigorous in excluding HIV infection before prescribing PrEP, including conducting detailed assessments for acute HIV, to prevent drug resistance.

3.3 Drug Resistance after HIV Acquisition during PrEP Use or Non-Adherence

In randomized PrEP studies, relatively few participants who acquired HIV after study initiation had evidence of drug resistance. In iPrEx, only 2/48 (4%) individuals in the TDF/FTC study arm who acquired HIV during the study had FTC resistance mutations, and these were only detected with ultrasensitive assays (i.e. frequency of <1%). Only 8/48 (17%) participants in the TDF/FTC study arm who acquired HIV had detectable drug levels within 90 days of seroconversion and only four participants had detectable drug levels prior to, but not at, the seroconversion visit, suggesting that HIV infection tended to occur during limited drug exposure [8]. Similarly, only one-quarter of the 68 women who acquired HIV during FEM-PrEP, an efficacy study of daily oral TDF/FTC PrEP for African women, had detectable levels of tenofovir [29], though two of four women with FTC resistance that were assigned to TDF/FTC did have detectable drug levels. It could not be determined in some cases of HIV acquisition in these trials whether drug resistance emerged in response to drug selection pressure or whether preexisting resistance mutations were transmitted.

In the ADAPT study, two individuals acquired during the lead-in phase of the study and did not have any resistance mutations. Following the lead-in period, six individuals who were randomized to one of three PrEP dosing schedules (daily, time-driven [i.e. twice-weekly plus a post-coital dose], or event-driven [i.e. pre and post-coital doses]) were found to have incident HIV infection. Five of these individuals had low adherence to their dosing schedules and had no detectable resistance mutations, while one individual who was generally adherent to PrEP developed K65R and M184I mutations after infection following a 7-day period of non-adherence, which could be consistent with selection of resistance in the presence of low residual drug levels [16]. In this study, adherence was measured by drug levels in blood samples and by calculating the proportion of doses taken as recommended for each specific dosing schedule.

Overall, these data suggest that drug resistance is uncommon when HIV is acquired during periods of low medication adherence, likely because drug selection pressure is minimal. A high-risk scenario for developing drug resistance to PrEP, therefore, likely includes HIV acquisition with partial adherence to PrEP but not complete nonadherence, in addition to PrEP initiation during acute HIV infection.

For clinicians, in addition to understanding their patients' risk of developing drug resistance with HIV infection, it is important to understand the extent to which PrEP can protect their patients against circulating HIV viral strains that are already resistant to TDF, FTC, or both.

4. Breakthrough Infections with Drug-Resistant HIV during PrEP Use

Animal models have tested whether PrEP with TDF/FTC can avert infection with TDF-resistant and FTC-resistant retroviral strains. In a study with macaques, TDF/FTC maintained high protective efficacy during challenge with FTC-resistant retroviral isolates [30], which might be due to increased susceptibility of HIV to tenofovir in the presence of

M184I/V mutations. In another macaque study, though, oral TDF/FTC delayed but did not reliably prevent infection with K65R-mutant retroviral strains [31], suggesting that those using TDF/FTC as PrEP might be vulnerable to infection with these strains. The effectiveness of TDF/FTC as PrEP against circulating HIV strains containing M1 84V mutations may also depend on the presence of other reverse transcriptase mutations. For example, the hypersusceptibility of HIV to tenofovir may be lost for M1 84 V mutants containing other thymidine analogue mutations, which could ultimately result in a PrEP regimen with only a single effective agent (i.e. TDF).

In humans, there have been six reported cases of HIV acquisition in patients who were prescribed PrEP during routine care and confirmed to be taking PrEP consistently (Table 4). Genetic and phenotypic analyses in five patients detected resistance mutations for TDF and/or FTC [32–36], while the sixth patient acquired wild-type HIV-1 [37]. Genotype testing in the five patients with drug resistance also detected in some cases mutations associated with non-nucleoside reverse transcriptase inhibitors (NNRTIs). As TDF/FTC would not select for NNRTI resistance, these mutations suggest acquisition of circulating multidrug-resistant HIV strains and failure of TDF/FTC to avert infection. Further supporting the possibility of transmitted drug resistance, one patient was able to identify their HIV-transmission partner, who was not virally suppressed and was infected with a viral strain with matching resistance mutations [36]. In these cases, high adherence was confirmed using tenofovir-diphosphate levels in dried blood spots or segmental hair analyses, which are objective measurements of recent prior tenofovir use.

Notably, the patient who was infected with wild-type HIV despite high adherence reported engaging in condomless receptive anal intercourse with up to seventy-five partners per month and had previously been infected with multiple bacterial sexually transmitted infections (STIs). One possible explanation for his HIV infection despite PrEP, therefore, is that intensive exposure, potential rectal mucosal injury, and STIs (which can potentiate HIV transmission) might have overcome the protective effect of PrEP. In light of animal studies and case-reports in humans, clinicians will need to counsel their patients that PrEP does not offer complete protection against HIV infection despite high adherence, particularly with intensive HIV exposures and other factors that facilitate HIV acquisition, and that using other risk-reduction strategies with PrEP (e.g. condoms) might be beneficial in some cases.

5. Drug Resistance and Novel Formulations of PrEP

Studies demonstrating infection with HIV viral strains that are resistant to TDF and/or FTC suggest a need for PrEP medications that maintain protective activity despite resistance mutations for TDF and FTC. Cabotegravir, an integrase strand transfer inhibitor (INSTI) that can be delivered as a long-acting injectable formulation (i.e. every 2 months), has shown promise in early phase human studies and is being tested for its efficacy as PrEP in a multinational randomized controlled trial (NCT 02720094). This agent would be expected to be protective against strains of HIV that are resistant to TDF and FTC because it does not target the same HIV enzyme (reverse transcriptase) as these agents. Additional animal and human studies may be helpful in elucidating whether or not long-acting cabotegravir confers protection against integrase-resistant strains of HIV. The bi-monthly dosing schedule being

tested for cabotegravir might also improve medication adherence for some individuals, which could decrease HIV infections and thus prevent opportunities for drug resistance to emerge. However, because injectable cabotegravir has a long half-life, people who discontinue cabotegravir for PrEP could have a prolonged period with low (and possibly non-protective) drug levels, which might potentially increase selection for INSTI-resistance mutations. Additional data on the effectiveness of cabotegravir as PrEP, its propensity to select for INSTI resistance, and any impact it may have on INSTI-based treatment options for those who acquire HIV, given that INSTI-based regimens represent first-line antiretroviral treatments for HIV infection, will be important in evaluating the usefulness of this promising strategy.

In addition to injectable agents, studies have also demonstrated modest protective efficacy of PrEP with drug-eluting intravaginal rings containing dapivirine, an NNRTI. In these studies, there was no detection of dapivirine-specific resistance mutations among women who acquired HIV [38–40]. It is possible that low plasma concentrations of dapivirine, which achieves high local tissue concentrations, might reduce selection pressure for drug resistance after HIV acquisition. Like cabotegravir, dapivirine is expected to be active against strains with TDF or FTC resistance given its different mechanism of action. Dapivirine is currently being considered for licensure and might thus be available for prescribing in the near future.

6. Impact of PrEP-Related Drug Resistance on Antiretroviral Treatment Options for HIV Infection

Drug resistance that results from use of PrEP with TDF/FTC could potentially affect HIV treatment options, as tenofovir and FTC are also components of first-line HIV treatment regimens. Given generally limited cross-resistance among different antiretroviral drug classes and safe, efficacious antiretroviral agents from multiple classes, there are fortunately multiple options for HIV treatment even with TDF and/or FTC resistance. Individuals who acquired HIV while using PrEP during routine care in the US have been successfully treated with various regimens from multiple classes [33–35, 37]. In TDF2, a study of TDF/FTC as PrEP for heterosexual men and women in Botswana, a participant who acquired HIV with M184V and K65R mutations achieved virologic suppression using zidovudine, lamivudine, and lopinavir/ritonavir, a boosted protease inhibitor [4]. This suggests that acceptable options for HIV treatment in the setting of PrEP-related drug resistance can be accessed in settings with more limited formularies and resources than the US.

In clinical studies, PrEP-related resistance mutations have tended to decay shortly after discontinuation of PrEP which might limit their impact on HIV treatment. In iPrEx, viral strains with M184V mutations that emerged after PrEP use during acute HIV infection decreased to frequencies of less than 0.5% within 14–29 weeks and remained at background levels after cessation of PrEP [8]. In Partners PrEP, M184V and K65R resistance mutations detected using highly sensitive assays were no longer detected after six months [41]. Additional data are needed to determine whether and to what degree low-frequency resistance mutations after PrEP use affect HIV treatment efficacy, as archived resistance mutations may subsequently re-emerge under drug selection pressure.

7. Forecasting the Future: Modeling the Impact of PrEP on Transmitted Drug Resistance

Mathematical models have been developed to predict how PrEP might affect population-level HIV resistance. A model of the HIV epidemic among MSM in San Francisco predicted that widespread PrEP use would be likely to increase the proportion of HIV infections with drug resistance, but that the total number of resistant infections could either increase or decrease depending on changes in risk behaviors and PrEP effectiveness [42, 43]. A model of PrEP dissemination in Botswana predicted that PrEP would increase numbers of drug resistant HIV infections but would decrease HIV incidence. This model also concluded that TDF/FTC would drive less resistance than TDF monotherapy, and that TDF/FTC was therefore preferable [44].

A model of heterosexual HIV epidemics in sub-Saharan Africa was developed to identify the strongest determinants of drug resistance in these populations. With optimistic assumptions of high PrEP efficacy and population coverage and low inadvertent PrEP use among those with undiagnosed HIV infection, prevalence of drug-resistant HIV would be 2.5% after 10 years; more pessimistic assumptions would result in a prevalence of 40%. This model suggested that the main driver of drug resistance for PrEP overall would be inadvertent use during undiagnosed HIV [45]. An additional model examined the effects of implementing ART alone, PrEP alone, or PrEP plus ART on HIV incidence and drug resistance in South Africa, where a generalized HIV epidemic exists [46]. The model predicted that ART implementation alone would prevent 20% of HIV infections and increase drug resistance prevalence to 6.6% over a 10-year period, whereas PrEP use alone would prevent 21% of HIV infections with only 5% resistance prevalence. ART plus PrEP would decrease HIV infections by one-third but increase resistance prevalence to 8.2%.

A limitation to these models is that they were developed prior to many of the PrEP efficacy studies that have since generated data on patterns of drug resistance with PrEP exposure as described in this review. As PrEP use has remained limited in most jurisdictions thus far, there are limited real-world data to confirm or refute these models' predictions. Because modeling studies suggest that scaling-up both PrEP and ART is likely to have the greatest impact on HIV incidence, and public health goals include expanded use of both of these interventions, strategies to track and mitigate drug resistance with this expansion will be important.

8. Conclusions

This review builds upon previous reviews of drug resistance with PrEP use [28, 47] by summarizing more recent evidence about resistance to TDF and FTC when used as PrEP. We also extend prior reviews by integrating information about the potential for resistance with new PrEP formulations, discussing the forecasts of mathematical models of drug resistance with PrEP, and summarizing evidence about breakthrough HIV infections despite high adherence to PrEP.

The potential for PrEP to promote antiretroviral drug resistance and thus affect HIV treatment options, as well as to impact the effectiveness of PrEP itself, is an important public health consideration. Fortunately, evidence suggests that selection for HIV drug resistance with PrEP provision is infrequent and most likely to occur when PrEP is used during undiagnosed HIV infection. There is evidence that breakthrough infections with drug-resistant HIV strains can occur despite high adherence to PrEP, but that these events are likely to be rare. As most of the evidence about drug resistance with PrEP comes from clinical trials in which adherence was variable, it will be critical to assess rates of drug resistance with PrEP provision in care settings, and how resistance impacts HIV treatment options and effectiveness. In addition, as evidence about drug resistance with PrEP use comes primarily from studies of oral TDF with or without FTC, studies of drug resistance with use of additional antiretroviral agents and formulations will be needed [39, 40, 47, 48].

Despite the need for vigilance about increased drug resistance with PrEP, it is important to note that between 8 and 50 new HIV infections can be prevented for every one case of FTC resistance from inadvertent PrEP use during acute HIV infection [28]. Moreover, recent studies have demonstrated that jurisdictions with increased PrEP use in the United States and Australia have been shown to have significant decreases in HIV incidence [49]. Thus, resources should be invested to increase PrEP provision in domestic and international settings, as the expected benefits of PrEP in decreasing HIV incidence are likely to outweigh the risk of harms from possible increases in the prevalence of drug resistant HIV.

Acknowledgments

Compliance with Ethical Standards

Dr. Krakower has conducted studies funded by research grants to his institution from Gilead Sciences and has been compensated to author or present continuing medical education materials for Medscape, MED-IQ, DKBmed, and UptoDate, Inc. The authors have no other conflicts of interest to declare. This manuscript was made possible with help from the Harvard University Center for AIDS Research (CFAR), a National Institutes of Health funded program (P30 AI060354).

REFERENCES

1. UNAIDS. Global HIV & AIDS statistics-2018 fact sheet, <http://www.unaids.org/en/resources/fact-sheet>. Accessed November 15, 2018.
2. Centers for Disease Control and Prevention. HIV in the United States: At A Glance. 2018 <https://www.cdc.gov/hiv/statistics/overview/ata glance.html>. Accessed November 15, 2018.
3. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *New England Journal of Medicine*. 2010;363(27):2587–99. [PubMed: 21091279]
4. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *New England Journal of Medicine*. 2012;367(5):423–34. [PubMed: 22784038]
5. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *The Lancet*. 2013;381(9883):2083–90.
6. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *New England Journal of Medicine*. 2012;367(5):399–410. [PubMed: 22784037]

7. Dimitrov DT, Body M-C, Hallett TB, Albert J, Boucher C, Mellors JW et al. How much do we know about drug resistance due to PrEP use? Analysis of experts' opinion and its influence on the projected public health impact. *PloS one*. 2016;11(7):e0158620.
8. Liegler T, Abdel-Mohsen M, Bentley LG, Atchison R, Schmidt T, Javier J et al. HIV-1 drug resistance in the iPrEx preexposure prophylaxis trial. *The Journal of infectious diseases*. 2014;210(8): 1217–27. [PubMed: 24740633]
9. Lehman DA, Baeten JM, McCoy CO, Weis JF, Peterson D, Mbari G et al. Risk of drug resistance among persons acquiring HIV within a randomized clinical trial of single-or dual-agent preexposure prophylaxis. *The Journal of infectious diseases*. 2015;211(8): 1211–8. [PubMed: 25587020]
10. Baeten JM, Donnell D, Mugo NR, Ndase P, Thomas KK, Campbell JD et al. Single-agent tenofovir versus combination emtricitabine plus tenofovir for pre-exposure prophylaxis for HIV-1 acquisition: an update of data from a randomised, double-blind, phase 3 trial. *The Lancet infectious diseases*. 2014; 14(11): 1055–64. [PubMed: 25300863]
11. Van Damme L, Cornell A, Ahmed K, Agot K, Lombaard J, Kapiga S et al. Preexposure prophylaxis for HIV infection among African women. *New England Journal of Medicine*. 2012;367(5):411–22. [PubMed: 22784040]
12. Chirwa LI, Johnson JA, Niska RW, Segolodi TM, Henderson FL, Rose CE et al. CD4+ cell count, viral load, and drug resistance patterns among heterosexual breakthrough HIV infections in a study of oral preexposure prophylaxis. *Aids*. 2014;28(2):223–6. [PubMed: 24361682]
13. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodini N, Nair G et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *New England Journal of Medicine*. 2015;372(6):509–18. [PubMed: 25651245]
14. Molina J-M, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *New England Journal of Medicine*. 2015;373(23):2237–46. [PubMed: 26624850]
15. Delaunay C, Rodriguez C, Capitant C, Nere M-L, Mercier-Darty M, Carette D et al. Drug resistance among patients who acquired HIV infection in a preexposure prophylaxis trial. *AIDS*. 2018;32(16):2353–61. [PubMed: 30096070]
16. Sivay MV, Li M, Piwowar-Manning E, Zhang Y, Hudelson SE, Marzinke MA 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):271–9. [PubMed: 28328548]
17. Baeten JM, Heffron R, Kidoguchi L, Mugo NR, Katabira E, Bukusi EA et al. Integrated delivery of antiretroviral treatment and pre-exposure prophylaxis to HIV-1-serodiscordant couples: a prospective implementation study in Kenya and Uganda. *PLoS medicine*. 2016;13(8):e1002099.
18. Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *The Lancet infectious diseases*. 2014; 14(9):820–9. [PubMed: 25065857]
19. Hosek S, Rudy B, Landovitz R, Kapogiannis B, Siberry G, Rutledge B et al. An HIV pre-exposure prophylaxis (PrEP) demonstration project and safety study for young MSM. *Journal of acquired immune deficiency syndromes (1999)*. 2017;74(1):21. [PubMed: 27632233]
20. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *The Lancet*. 2016;387(10013):53–60.
21. Grohskopf LA, Chillag KL, Gvetadze R, Liu AY, Thompson M, Mayer KH et al. Randomized trial of clinical safety of daily oral tenofovir disoproxil fumarate among HIV-uninfected men who have sex with men in the United States. *JAIDS Journal of Acquired Immune Deficiency Syndromes*. 2013;64(1):79–86. [PubMed: 23466649]
22. Peterson L, Taylor D, Roddy R, Belai G, Phillips P, Nanda K et al. Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial. *PLoS clinical trials*. 2007;2(5):e27. [PubMed: 17525796]
23. Mutua G, Sanders E, Mugo P, Anzala O, Haberer JE, Bangsberg D et al. Safety and adherence to intermittent pre-exposure prophylaxis (PrEP) for HIV-1 in African men who have sex with men and female sex workers. *PloS one*. 2012;7(4):e33103. [PubMed: 22511916]

24. Kibengo FM, Ruzagira E, Katende D, Bwanika AN, Bahemuka U, Haberer JE et al. Safety, adherence and acceptability of intermittent tenofovir/emtricitabine as HIV pre-exposure prophylaxis (PrEP) among HIV-uninfected Ugandan volunteers living in HIV-serodiscordant relationships: a randomized, clinical trial. *PLoS One*. 2013;8(9):e74314. [PubMed: 24086333]
25. Heffron R, Ngunjiri K, Odoyo J, Bulya N, Tindimwebwa E, Hong T et al. Pre-exposure prophylaxis for HIV-negative persons with partners living with HIV: uptake, use, and effectiveness in an open-label demonstration project in East Africa. *Gates Open Research*. 2017; 1.
26. Grant RM, Liegler T, Defechereux P, Kashuba AD, Taylor D, Abdel-Mohsen M et al. Drug resistance and plasma viral RNA level after ineffective use of oral pre-exposure prophylaxis in women. *Aids*. 2015;29(3):331–7. [PubMed: 25503265]
27. Clutter DS, Jordan MR, Bertagnolio S, Shafer RW. HIV-1 drug resistance and resistance testing. *Infection, Genetics and Evolution*. 2016;46:292–307.
28. Fonner VA, Dalglish SL, Kennedy CE, Baggaley R, O'reilly KR, Koechlin FM et al. Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. *AIDS (London, England)*. 2016;30(12):1973.
29. Comeli AL, Deese J, Wang M, Taylor D, Ahmed K, Agot K et al. FEM-PrEP: adherence patterns and factors associated with adherence to a daily oral study product for pre-exposure prophylaxis. *Journal of acquired immune deficiency syndromes (1999)*. 2014;66(3):324. [PubMed: 25157647]
30. Cong M-e Youngpairoj AS, Zheng Q, Aung W, Mitchell J, Sweeney E et al. Protection against rectal transmission of an emtricitabine-resistant simian/human immunodeficiency virus SHIV162p3M184V mutant by intermittent prophylaxis with Truvada. *Journal of virology*. 2011;85(15):7933–6. [PubMed: 21632769]
31. Cong M-e Mitchell J, Sweeney E, Bachman S, Hanson DL, Heneine W et al. Prophylactic efficacy of oral emtricitabine and tenofovir disoproxil fumarate combination therapy against a tenofovir-resistant simian/human immunodeficiency virus containing the K65R mutation in macaques. *The Journal of infectious diseases*. 2013;208(3):463–7. [PubMed: 23633402]
32. Knox DC, Anderson PL, Harrigan PR, Tan DH. Multidrug-resistant HIV-1 infection despite preexposure prophylaxis. *New England Journal of Medicine*. 2017;376(5):501–2.
33. Colby DJ, Kroon E, Sacdalan C, Gandhi M, Grant RM, Phanuphak P et al. Acquisition of Multidrug-Resistant Human Immunodeficiency Virus Type 1 Infection in a Patient Taking Preexposure Prophylaxis. *Clinical Infectious Diseases*. 2018;67(6):962–4. [PubMed: 29961859]
34. Thaden JT, Gandhi M, Okochi H, Hurt CB, McKellar MS. Seroconversion on preexposure prophylaxis: a case report with segmental hair analysis for timed adherence determination. *Aids*. 2018;32(9):F1–F4. [PubMed: 29683856]
35. Markowitz M, Grossman H, Anderson PL, Grant R, Gandhi M, Horng H 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–e6. [PubMed: 29076941]
36. Cohen SE, Sachdev D, Lee SA, Scheer S, Bacon O, Chen M-J et al. Acquisition of tenofovir-susceptible, emtricitabine-resistant HIV despite high adherence to daily pre-exposure prophylaxis: a case report. *The Lancet HIV*. 2019;6(1):e43–e50.
37. Hooenenborg E, Prins M, Achterbergh RC, Woittiez LR, Cornelissen M, Jurriaans S 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*. 2017;4(11):e522–e8. [PubMed: 28919303]
38. Parikh U Sensitive Next-generation Sequencing of HIV-1 From Seroconverters in the MTN-020/ASPIRE Dapivirine Vaginal Ring Study. *HIVR4P; Madrid, Spain*2018.
39. Nel A, van Niekerk N, Kapiga S, Bekker L-G, Gama C, Gill K et al. Safety and efficacy of a dapivirine vaginal ring for HIV prevention in women. *New England Journal of Medicine*. 2016;375(22):2133–43. [PubMed: 27959766]
40. Baeten JM, Palanee-Phillips T, Brown ER, Schwartz K, Soto-Torres LE, Govender V et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. *New England Journal of Medicine*. 2016;375(22):2121–32. [PubMed: 26900902]
41. Weis JF, Baeten JM, McCoy CO, Warth C, Donnell D, Thomas KK et al. PrEP-selected Drug Resistance Decays Rapidly After Drug Cessation. *AIDS (London, England)*. 2016;30(1):31.

42. Supervie V, García-Lerma JG, Heneine W, Blower S. HIV, transmitted drug resistance, and the paradox of preexposure prophylaxis. *Proceedings of the National Academy of Sciences*. 2010;107(27):12381–6.
43. Baggaley RF, Powers KA, Boily M-C. What do mathematical models tell us about the emergence and spread of drug-resistant HIV? *Current Opinion in HIV and AIDS*. 2011;6(2): 131. [PubMed: 21505388]
44. Supervie V, Barrett M, Kahn JS, Musuka G, Moeti TL, Busang L et al. Modeling dynamic interactions between pre-exposure prophylaxis interventions & treatment programs: predicting HIV transmission & resistance. *Scientific reports*. 2011;1:185. [PubMed: 22355700]
45. Abbas UL, Hood G, Wetzel AW, Mellors JW. Factors influencing the emergence and spread of HIV drug resistance arising from rollout of antiretroviral pre-exposure prophylaxis (PrEP). *PloS one*. 2011;6(4):e18165. [PubMed: 21525976]
46. Abbas UL, Glaubius R, Mubayi A, Hood G, Mellors JW. Antiretroviral therapy and pre-exposure prophylaxis: combined impact on HIV transmission and drug resistance in South Africa. *The Journal of infectious diseases*. 2013;208(2):224–34. [PubMed: 23570850]
47. Parikh UM, Mellors JW. Should We Fear Resistance from Tenofovir/Emtricitabine PrEP? *Current opinion in HIV and AIDS*. 2016;11(1):49. [PubMed: 26633640]
48. [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/NCT02720094) HPTN 083: a phase 2b/3 double blind safety and efficacy study of injectable cabotegravir compared to daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), for pre-exposure prophylaxis in HIV-uninfected cisgender men and transgender women who have sex with men. <https://clinicaltrials.gov/ct2/show/NCT02720094>. Accessed March 1, 2019.
49. Grulich AE, Guy R, Amin J, Jin F, Selvey C, Holden J et al. Population-level effectiveness of rapid, targeted, high-coverage roll-out of HIV pre-exposure prophylaxis in men who have sex with men: the EPIC-NSW prospective cohort study. *The Lancet HIV*. 2018.

Key Points

- HIV Preexposure prophylaxis (PrEP) using tenofovir disoproxil fumarate (TDF) with or without emtricitabine (FTC) can decrease the risk of acquiring HIV when used with high adherence, but there is potential for PrEP to promote antiretroviral drug resistance.
- Evidence from clinical trials, case reports, animal studies, and mathematical models suggests that selection for HIV drug resistance with PrEP use is likely to be infrequent and most likely to occur when PrEP is used inadvertently during undiagnosed HIV infection.
- The benefit of decreased HIV incidence with wider PrEP use is likely to outweigh the risk of harms from possible increases in the prevalence of HIV drug resistance.

Table 1.

Seroconversions in randomized studies of oral tenofovir disoproxil fumarate with or without emtricitabine as HIV preexposure prophylaxis.

Study	Reference	Acute HIV prior to randomization			Incident HIV after randomization		
		TDF/FTC	TDF	Placebo	Total	TDF/FTC	Placebo
Bangkok Tenofovir Study	Choopanya et al. (2013)	-	0	2	2	-	17
HPTN 082/Partners Demonstration Project	Baeten et al. (2016), Hefron et al. (2017)	14	-	-	14	4	-
FEM-PrEP	Van Damme et al. (2012)	1	-	1	2	33	35
HPTN 067/ADAPT ^a	Sivay et al. (2017)	3	-	-	3	8	-
IPERGAY	Delaugerre et al. (2018)	4 ^b	-	0	4	2	13
iPrEx	Liegler et al. (2014)	2	-	8	10	48	83
iPrEx OLE	Grant et al. (2014)	0	-	-	0	28	-
Partners PrEP + Open Label Extension/Continuation Study ^c	Baeten et al. (2012), Lehman et al. (2015)	4	8	6	18	21	52
Project PrEPare 2	Hosek et. (2017)	2	-	-	2	4	-
PROUD	McCormack et. (2016)	3 ^d	-	-	3	2	-
TDF2	Thigpen et al. (2012), Chirwa et al. (2014)	1	-	2	3	9	24
US MSM Safety Trial	Grohskopf et al. (2013)	-	0	1	1	-	3 ^e
VOICE ^f	Marrazzo et al. (2015)	9	5	1	15	55	60
Total		43	13	21	77	214	303

TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; PrEP, preexposure prophylaxis

^a 3 individuals had undiagnosed acute HIV at the start of a lead-in phase of the study with directly observed treatment (DOT). 2 participants acquired HIV during the DOT phase. 6 participants acquired HIV after the DOT phase. One individual was not randomized to receive PrEP due to pregnancy and seroconverted after the DOT phase, and thus was excluded from our table.

^b 4 participants had undiagnosed acute HIV at time of entrance and receipt of PrEP in the open-label phase of the study.

^c Baeten et al. (2012) conducted a three-group efficacy study of daily oral TDF and FTC-TDF as PrEP in heterosexual HIV-1 serodiscordant couples in Kenya and Uganda. In July 2011, the placebo arm of the efficacy study was discontinued, and subjects were randomized to receive FTC/TDF or TDF as part of an open-label extension (Lehman et al. (2015)). Of 122 total seroconverters included in Partners PrEP plus the open-label study, 121 participants had plasma available for highly sensitive resistance testing and were included in this table.

^d Only includes participants randomized to receive PrEP at study initiation (i.e. immediate study arm) given lack of resistance data for the delayed study arm. Two participants had undiagnosed acute HIV infection at enrollment, and 1 participant had seroconverted by week 4 and was thought to have been infected with HIV prior to initiating PrEP. The delayed study arm included an additional individual with undiagnosed acute HIV at enrollment and 20 incident HIV infections (not reflected in the table).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

3 incident HIV infections occurred among participants randomized to receive PrEP or placebo at study initiation (immediate study arm), and 3 additional incident infections occurred among participants in the delayed study arm prior to receiving any study medications (not reflected in the table).

f Participants were randomized to receive oral TDF, oral TDF-FTC, TFV vaginal gel, or placebo vaginal gel. Participants randomized to receive vaginal gel are not included in this table. Of total 334 seroconversions, 322 participants had plasma available for resistance testing (21 of 22 individuals with acute HIV infection and 301 of 312 individuals with incident HIV infection). 55 of 61 participants with incident HIV infection in the TDF/FTC arm had samples available for resistance testing.

Table 2.

Drug resistance mutations in study participants with undiagnosed acute HIV prior to randomization procedures.

Study	Reference	TDF/FTC Arm			TDF Arm			Placebo			All Arms			Total
		FTC Mutation ^a	TDF Mutation ^b	TDF and FTC Mutation ^c	FTC Mutation	TDF Mutation	TDF and FTC Mutation	FTC Mutation	TDF Mutation	TDF and FTC Mutation	FTC Mutation	TDF Mutation	TDF and FTC Mutation	
Bangkok Tenofovir Study	Choopanya et al. (2013)	-	-	-	-	-	-	-	0	-	-	0	-	0
HPIN 082/Partners Demonstration Project	Baeten et al. (2016), Heffron et al. (2017)	5	0	0	-	-	-	-	-	-	5	0	0	5
FEM-PrEP	Van Damme et al. (2012)	0	0	0	-	-	0	0	0	0	0	0	0	0
HPIN 067/ADAPT	Sivay et al. (2017)	1	1	0	-	-	-	-	-	-	1	1	0	2
IPERGAY	Delaugerre et al. (2018)	0	0	0	-	-	0	0	0	0	0	0	0	0
iPrEx ^d	Liegler et al. (2014)	2	0	0	-	-	1	0	0	0	3	0	0	3
iPrEx OLE	Grant et al. (2014)	-	-	-	-	-	-	-	-	-	-	-	-	-
Partners PrEP + Open Label Extension/ Continuation Study ^{d,e}	Baeten et al. (2012), Lehman et al. (2015)	2	0	0	0	1	0	0	0	0	2	1	0	3
Project PrEPare 2	Hosek et. (2017)	0	0	0	-	-	-	-	-	-	0	0	0	0
PROUD	McCormack et. (2016)	2	0	0	-	-	-	-	-	-	2	0	0	2
TDF2	Thigpen et al. (2012), Chirwa et al. (2014)	0	0	1	-	-	0	0	0	0	0	0	1	1
US MSM Safety Trial	Grohskopf et al. (2013)	-	-	-	-	-	-	-	0	0	0	0	0	0
VOICE	Marrazzo et al. (2015)	2	0	0	0	0	0	0	0	0	2	0	0	2
Total		14	1	1	0	1	0	1	0	0	15	2	1	18

TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; PrEP, preexposure prophylaxis

^aDefined as M184 V/I mutation.

^bDefined as K65R or K70E mutations.

^cDefined as having FTC and TDF-associated mutations.

^dHighly sensitive assays were used. All other studies used standard assays.

^eAlthough high sensitivity resistance testing was used, analyses focused on frequencies >1%, and thus only participants with resistance frequencies >1% were included in this table.

Table 3.

Drug resistance mutations in study participants with incident HIV infection.

Study	Reference	TDF/FTC Arm			TDF Arm			Placebo			All Arms			Total
		FTC Mutation ^a	TDF Mutation ^b	TDF and FTC Mutation ^c	FTC Mutation	TDF Mutation	TDF and FTC Mutation	FTC Mutation	TDF Mutation	TDF and FTC Mutation	FTC Mutation	TDF Mutation	TDF and FTC Mutation	
Bangkok Tenofvir Study	Choopanya et al. (2013)	-	-	-	-	0	-	-	0	-	-	0	-	0
HPIN 082/Partners Demonstration Project	Baeten et al. (2016), Heffron et al. (2017)	0	0	0	-	-	-	-	-	-	0	0	0	0
FEM-PrEP	Van Damme et al. (2012), Grant et al. (2015)	4 ^d	0	0	-	-	-	1	0	0	5	0	0	5
HPIN 067/ADAPT	Sivay et al. (2017)	0	0	1	-	-	-	-	-	-	0	0	1	1
IPERGAY	Delaugerre et al. (2018)	0	0	0	-	-	-	0	0	0	0	0	0	0
iPrEx ^e	Liegler et al. (2014)	2 ^f	0	0	-	-	-	1	1	0	3	1	0	4
iPrEx OLE	Grant et al. (2014)	1	0	0	-	-	-	-	-	-	1	0	0	2
Partners PrEP + Open Label Extension/ Continuation Study ^{e, g}	Baeten et al. (2012), Lehman et al. (2015)	2	0	1	1	0	2	0	0	0	5	0	1	6
Project PrEPare 2	Hosek et. (2017)	0	0	0	-	-	-	-	-	-	0	0	0	0
PROUD	McCormack et. (2016)	0	0	0	-	-	-	-	-	-	0	0	0	0
TDF2	Thigpen et al. (2012), Chirwa et al. (2014)	0	0	0	-	-	-	0	1 ^h	0	0	1	0	1
US MSM Safety Trial	Grohskopf et al. (2013)	-	-	-	-	-	-	-	0	-	0	0	0	0
VOICE ⁱ	Marrazzo et al. (2015)	1	0	0	0	0	0	0	0	0	1	0	0	1
Total		10	0	2	1	0	0	4	2	0	15	2	2	19

^aDefined as M184 V/I mutation.

^bDefined as K65R or K70E mutations.

^cDefined as having FTC and TDF-associated mutations.

^dFor 3 of the 4 patients who seroconverted, the hypothesized window of infection was broad and may have included enrollment, suggesting they might have had an undiagnosed acute HIV infection at study entry rather than incident HIV infection.

^eHighly sensitive assays were used. All other studies used standard assays.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

f_i Detected via ultrasensitive testing; given frequency $<1\%$, this may reflect normal variation rather than selected resistance.

g_i Although high sensitivity resistance testing was used, analyses focused on frequencies $>1\%$, and thus only participants with resistance frequencies $>1\%$ were included in this table.

h_i One participant assigned to received placebo had a K65R mutation intermittently and at very low levels ($<1\%$) after seroconversion, although the mutation was not detected in the blood sample that had been obtained closest to the estimated date of seroconversion.

i_i Only 55 of 61 participants with incident HIV in the TDF/FTC arm had samples available for resistance testing.

Table 4.

Cases of incident HIV during PrEP use with confirmed high adherence.

Case	Reported	Method of Confirming PrEP Adherence	Clinically Significant NRTI Resistance Mutations			NNRTI Resistance Mutations	Other Mutations
			M184V (FTC Resistance)	K65R (TDF Resistance)	Other Resistance Mutations		
1	Knox et al. (2017)	Dried Blood Spot	Present	Not present	M41L, D67G, T69D, K70R, Y215E	Y181C	H51Y, E92Q, L10I
2	Markowitz et al.(2017)	Dried Blood Spot	Present	Present	None reported	K103S, E138Q, Y188L	K46M, S68G, G93E, A98S, I142T, S163Y, Q174K, V179I, T200A, Q207E, R211K, F214L, V245M
3	Thaden et al.(2018)	Segmental Hair Analysis	Present	Present	K70T	K103N, V179I, V90I	None reported
4	Colby et al.(2018)	Dried Blood Spot	Present	Not present	None reported	A98G, K103N	None Reported
5	Hoomenborg et al.(2017)	Hair Analysis & Dried Blood Spot	Not present	Not present	None reported	None Reported	None Reported
6	Cohen et al. (2019)	Segmental Hair Analysis & Dried Blood	Present	Not present	L74V	K103N, L100I	D30N, G73S, G48E

NRTI, nucleos(t)ide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor. Resistance mutation abbreviations reflect standard amino acid nomenclature.