




Antiretroviral Drug Treatment of Individuals that Used Preexposure Prophylaxis (PrEP) Before Diagnosis

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Recommendations

- First-line antiretroviral drug treatment of individuals that used PrEP before diagnosis should be optimized based on a genotypic resistance test.
- Although there are no systematic studies on the optimal treatment of individuals in whom drug resistance due to PrEP is found, there is anecdotal evidence that the emtricitabine-associated mutation M184I/V and/or the tenofovir-associated mutation (K65R) can be treated with currently recommended first-line regimens including dolutegravir-based, bictegravir-based, or darunavir-based regimens boosted with tenofovir plus emtricitabine or lamivudine.
- Due to a lack of data, induction treatment using dual therapy including dolutegravir and lamivudine is not recommended. Maintenance treatment with dual therapy can be considered after achieving viral suppression.

Keywords HIV · PrEP · Drug resistance · Antiretroviral drug treatment · M184I/V · K65R

Abstract

Purpose of review The antiretroviral drugs, tenofovir and emtricitabine used as preexposure prophylaxis (PrEP), are also used in treatment of HIV. Drug resistance due to PrEP can therefore jeopardize future treatment options. This review discusses treatment of individuals that used PrEP in whom viral mutations against tenofovir (K65R) or emtricitabine (M184I/V) are found.

Recent findings Although no studies systematically investigated the optimal treatment of individuals who used PrEP before diagnosis, there is anecdotal evidence that HIV including the K65R and/or M184I/V can be successfully treated using recommended first-line regimens.

Summary Drug resistance can be ascribed to use of PrEP while having an unrecognized acute HIV infection, partial adherence to PrEP, and transmission of HIV resistant to PrEP drugs. First-line antiretroviral drug treatment in individuals who used PrEP before diagnosis must be optimized based on genotypic resistance test results. Individuals in whom M184I/V and/or K65R is detected can be treated with dolutegravir-based, bictegravir-

based, or darunavir-based regimens plus tenofovir plus lamivudine or emtricitabine. Dual therapy using dolutegravir plus lamivudine is not recommended for induction therapy in individuals with viral mutations against the drugs used as PrEP. There is an urgent need to confirm the anecdotal evidence for successful treatment using first-line regimens.

Introduction

The continuous development of novel antiretroviral drugs has resulted in significant improvements in the treatment and prevention of HIV. Due to these improvements, individuals living with HIV can have a near-normal life span when they adhere to antiretroviral drug treatment [1]. Antiretroviral drugs can be used for prevention of HIV transmission as individuals living with HIV that are virally suppressed due to antiretroviral drug treatment cannot transmit the virus to others [2, 3]. Another important antiretroviral drug-based strategy for prevention of HIV transmission is the use of preexposure prophylaxis (PrEP) with the antiretroviral drugs tenofovir alone or in combination with emtricitabine (FTC) in individuals at high risk of infection [4]. (Tenofovir is given as the prodrug tenofovir disoproxil fumarate-TDF, or tenofovir alafenamide fumarate-TAF.) Based on these breakthroughs, the World Health Organization (WHO) has declared ending the AIDS pandemic as one of its sustainable development goals in 2030 which aim to achieve a better and sustainable future for all people across the World [5].

To reach the ambitious goal of ending the AIDS pandemic, the WHO recommends a comprehensive

package of prevention strategies including condoms, counselling, male circumcision [6, 7], and HIV testing followed by immediate antiretroviral drug treatment in those testing positive [2, 3]. The WHO also recommends that people with a substantial risk of HIV infection are offered PrEP [8]. Importantly, the PrEP drugs tenofovir and emtricitabine are frequently prescribed for treatment of HIV, and drug resistance arising due to the use of PrEP can therefore jeopardize future treatment options [9].

The aim of this review is to discuss antiretroviral drug treatment in individuals that used PrEP before diagnosis. To address this aim, we will first describe the mutations that are involved in drug resistance to the PrEP drugs tenofovir and FTC. We will then discuss the processes by which drug resistance can emerge and the drug resistance-associated mutations that have been reported in randomized controlled trials on the efficacy of PrEP for prevention of HIV transmission and in real-world settings. We will then discuss diagnosis and treatment of drug resistance in individuals who had used PrEP before diagnosis.

Resistance-Associated Mutations to Tenofovir and Emtricitabine

Drug resistance to the PrEP drugs tenofovir and FTC is well-characterized. Only a single point mutation in the reverse transcriptase gene of the viral genome is required for resistance to tenofovir (K65R). Additionally, drug resistance to tenofovir can occur in HIV that has accumulated multiple thymidine associated mutations (TAMs), a complex set of mutations associated with resistance to thymidine analogues, such as zidovudine. In particular, the response to tenofovir is reduced if at least three different TAMs are present including M41L or L210W (the other TAMs are D67N, K70R, T215F/Y, and K219Q/E/R/N) [10].

Resistance to FTC is encoded by a single point mutation in reverse transcriptase (M184V) [11, 12]. In patients developing resistance to emtricitabine, the M184I mutation usually emerges before M184V [13–20, 21••].

Cross-resistance between the drugs used as PrEP is limited as HIV including the hallmark FTC mutation M184I/V remains susceptible to tenofovir. Similarly, HIV containing multiple TAMs remains susceptible to FTC. K65R has been reported to result in intermediate resistance to emtricitabine. Irrespective of cross-resistance, it is important to note that viruses harboring both the K65R and M184V/I mutations are rarely detected. Instead, K65R and M184V/I are frequently found as single mutations on different genomes [22].

Processes by Which Drug Resistance Jeopardizes PrEP

Epidemiological studies from randomized controlled trials that studied the efficacy of PrEP (Table 1) [13–20, 21••] and from real-world settings (Table 2) [24, 25•, 26] have identified several processes by which drug resistance jeopardizes PrEP. These processes include the rapid emergence of resistance while using PrEP during an unrecognized acute infection [13–20, 21••], the emergence of drug resistance in individuals that are partially adherent to PrEP [18], and transmission of drug-resistant HIV to individuals using PrEP [24, 25•, 26]. The three processes will be discussed in further detail in the following paragraphs.

Start of PrEP During an Unrecognized Acute Infection

PrEP should only be started after a negative HIV test as the genetic barrier for resistance, defined as the number of mutations required to overcome drug selected pressure [11, 27], is too low for tenofovir and FTC. Consequently, resistance can emerge in individuals using tenofovir and FTC as their only antiretroviral drugs. Unfortunately, HIV tests cannot identify very acute infections in the time period between infection and when the HIV test can reliably detect the infection (window period) [28]. Individuals who test negative for HIV during this window period, which depending on the HIV test is at least 10–12 days after exposure [28], can have an unrecognized acute HIV infection at the time that they start using PrEP [13–20, 21••].

The randomized controlled trials showed that the few individuals that started PrEP while having an unrecognized HIV infection [13–20, 21••] have a substantially high risk for drug resistance. Among 35 individuals randomized to receive TDF/FTC or TDF as PrEP during an unrecognized HIV infection, drug resistance was later found in nine individuals (26%). The high risk of drug resistance in individuals with an unrecognized acute infection can be explained by the high viral replication rate during the acute stage and high viral mutation rate of HIV [29] which can result in the rapid selection of drug resistance associated mutations.

The most commonly found drug resistance-associated mutation was M184I/V which was detected in seven out of nine individuals who had started PrEP at the time when they had an unrecognized acute infection (78%) [13–20, 21••]. K65R was reported in two individuals, of whom one person used TDF as the single PrEP drug [14]. The second person in whom K65R was found used TDF/

Table 1. Drug resistance to drugs used as preexposure prophylaxis (PrEP) in randomized controlled trials

Study	Efficacy PrEP (95% confidence interval)*	Country	Risk group**	Arm***	number	Seroconversions (including resistance)	
						After randomization	Between enrollment and randomization
iPrex	44% (15–63%)	South Africa, USA, Peru, Brazil, Thailand	MSM	TDF/FTC placebo	1251 1248	36 (0) 64 (0)	8 (2 M184I/V) 2 (1 M184I/V, T215Y, K103N) [13]
PartnersPrEP	67% (44–81%) 75% (55–87%)	Kenya, Uganda	SDC	TDF TDF/FTC placebo	1584 1579 1584	17 (0) 13 (0) 52 (0)	5 (1 K65R) 3 (1 M184V) 6 (-) [14]
TDF2	62% (22–83%)	Botswana	SDC	TDF/FTC placebo	611 608	9 (0) 24 (0)	1 (1 K65R, M184V, A62V) [15] 2 (1 K65R, low level 1%) ****
FEM-PrEP	IRR vs placebo* 0.94 (0.59–1.52)	South Africa, Kenya, Tanzania	Women	TDF/FTC placebo	1062 1058	33 (4 M184I/V) 35 (1 M184V)	1 (-) [16, 23] 1 (-)
VOICE	IRR vs placebo* 1.49(0.97–2.29) 1.04(0.73–1.49) 49% (10–72%)	South Africa, Uganda, Zimbabwe, Thailand	Women IDU	TDF TDF/FTC placebo TDF placebo	1007 1003 1009 1204 1209	52 (-) 61 (1 M184V) 60 (-) 17 (0) 33 (0)	5 (-) [18] 9 (2 M184I/V) 1 (-) 0 (-) [17] 2 (-)
IPERGAY	86% (40–98%)	France, Canada	MSM	TDF/FTC placebo	199 201	2 (0) 14 (0)	1 (-) [19] 1 (-)
PROUD	86% (64–96%)*	United Kingdom	MSM	Immediate Deferred	275 269	3 (0) 20 (0)	2 (2 M184I/V) 1 (-) [20]
Discover	IRR TAF/FTC vs TDF/FTC*: 0.47 (0.19–1.15)	USA, UK, France, Germany, Spain	MSM, TGW	TAF/FTC TDF/FTC	2694 2693	7 (-) 15 (4 M184I/V)	Not reported Not reported [21••]

*Efficacy is the reduction in the risk of acquiring HIV in individuals randomized to receive PrEP versus those randomized to receive placebo. The FEM-PrEP and VOICE studies reported the incidence rate ratio (IRR) in women receiving PrEP as compared to placebo [16, 18]. Similarly, the PROUD study [20] and Discover study [21••] reported the IRR of immediate versus deferred PrEP [20] and TAF/FTC vs TDF/FTC [21••], respectively.

**Risk groups are MSM men who sex with men, SDC sero-disorderant couples, IDU injecting drug users, TGW transgender women

***Antiretroviral drugs used as PrEP are TDF tenofovir disoproxil fumarate, TAF tenofovir alafenamide fumarate, FTC emtricitabine

****Present in 1% of all HIV as detected by a sensitive

Table 2. Summary of patients who became infected with HIV despite being adherent to PrEP and in whom the infections were ascribed to transmission of a virus that is resistance to the drugs used as PrEP

Country	Risk	Patients	Period using PrEP	Resistance	Treatment
Canada 2 years,			(Toronto) adherent at time of infection*	MSM Genotypic: M184V, thymidine analogue mutations (M41L, D67G, T69D, K70R, T215E), Y181C, H51Y, E92Q Phenotypic resistance to lamivudine, emtricitabine, efavirenz, etravirine, nevirapine, rilpivirine, raltegravir, elvitegravir, and dolutegravir	1 After confirmation of infection treatment with dolutegravir, cobicistat boosted darunavir, rilpivirine
USA	MSM	1	> 1 year, adherent at time of infection**	M184V, K65R, K70T, K103N	dolutegravir, rilpivirine, and darunavir/cobicistat. Later simplified to DTG/RPV
USA (New York)	MSM	1	5 months, adherent at time of infection**	K65R, M184V; K103S, E138Q, Y188L	Tenofovir disoproxil fumarate, emtricitabine and dolutegravir. Later cobicistat boosted darunavir was added.

*Based on detection of tenofovir in plasma

**Based on the detection of tenofovir in plasma and in hair

FTC and came from Botswana [15], where HIV is predominantly of subtype C. K65R emerges more rapidly in subtype C viruses [30], which has been ascribed to the unique subtype C sequence context in the region of K65R. Specifically, subtype C includes a span of five consecutive adenines preceding the adenine at the second position in the K65 codon rendering it more likely to be mutated during reverse transcription [31].

Emergence of Drug Resistance in Individuals that Are Partially Adherent to PrEP

The emergence of drug resistance after randomization is reported by three randomized controlled trials [16, 18, 21••], of which two studies did not find a HIV preventative benefit of PrEP [16, 18] (Table 1). Two randomized controlled trials, FEM-PrEP and Discover [16, 21••], reported that patients were found to be infected early during the study. Because FEM-PrEP and Discover did not systematically investigate if individuals had seroconverted between the time of HIV testing and the start of PrEP and consequently could not rule out that people had started using PrEP while having an unrecognized acute infection [16, 21••]. The third study reported poor adherence to PrEP based on the detection of tenofovir-plasma levels above a particular threshold which indicated the recent use of PrEP. The emergence of resistance in this third study may therefore be explained by (partial) non-adherence allowing HIV to select for drug resistance-associated mutations after infection [16, 18].

Transmission of Drug Resistance

Drug resistance can jeopardize the preventative benefits of PrEP when an individual becomes infected with a virus that is resistant to the drugs used as PrEP. Three patients have been reported who became infected with a drug-resistant strain of HIV despite being consistently adherent to PrEP [24, 25•, 26], as confirmed by detection of tenofovir in plasma [24, 25•, 26] or in hair of the individuals [24, 26] (Table 2). All three patients were infected with a multi-drug-resistant virus which not only included resistance associated mutations to emtricitabine, M184I/V [24, 25•, 26], and tenofovir (K65R in two individuals [25•, 26], and a combination of TAMs in one patient [24]) but also to non-nucleoside reverse transcriptase inhibitors [24, 25•, 26] and in one individual also to integrase inhibitors [24].

Risk of Resistance in Real-World Settings

During recent years, two studies reported M184I/V in 23% (out of 91 individuals) [32•] and 26% (22 individuals) [33••] who had used TDF/FTC as PrEP before diagnosis [32•, 33••]. The studies did not find K65R in any of the individuals who had used PrEP. The high risk of resistance could be ascribed to the use of PrEP after being infected with HIV, as indicated by the observation that one-third of patients in one study were in the acute stage of infection [32•]. Similarly, the second study reported a strongly reduced HIV-1 RNA load at the time of diagnosis among PrEP users compared to non-users of PrEP [33••]. Such low level of HIV-1 RNA among one group could indicate the continued use of PrEP at the time of infection or a blunted viremia during breakthrough infections with PrEP [34].

Treatment of HIV-Infected Individuals that Used PrEP Before Diagnosis

Although the emergence of resistance has been recognized as a limitation of the use of PrEP, there are no reports that systematically studied the optimal antiretroviral drug treatment regimen for individuals who have been exposed to PrEP before HIV diagnosis. Considering the relatively high rate of drug resistance mutations detected in patients who fail PrEP, first-line antiretroviral drug treatment must be optimized based on the genotypic resistance test results [35•]. Treatment optimization based on a genotypic resistance test resulted in virological suppression in the three patients presented in Table 2 that became infected due to transmission of HIV that had drug resistance-associated mutations to tenofovir and emtricitabine [24, 25•, 26]. In particular, all three patients were treated successfully with dolutegravir plus cobicistat-boosted darunavir [24, 25•, 26], in combination with rilpivirine [24, 26] or TDF/FTC [25•].

In the following paragraphs, we will discuss the treatment options for the most frequently reported mutations associated with resistance to PrEP. We will follow the preferred initial antiretroviral drug regimens of the International Antiviral Society-USA which recommends to start treatment with any of the following combinations: bictegravir plus TAF plus FTC, dolutegravir plus TAF or TDF plus FTC/lamivudine, or dolutegravir plus lamivudine [35•].

M184I/V

A key challenge in the detection of M184I/V is that these mutations rapidly revert to a drug susceptible wild-type virus if PrEP is discontinued [36]. Importantly, after reversion, drug resistance-associated mutations can still be detected in latently infected long-lived reservoir cells. Consequently, a genotypic resistance test may not identify M184I/V in plasma, but this drug-resistant strain can re-emerge by stochastic reactivation of drug-resistant proviruses from the reservoir [37].

The M184I/V mutation does not only result in resistance to emtricitabine but also to lamivudine [38, 39] and to abacavir [40]. Importantly, the presence of M184I/V is not a contraindication to combination treatment including FTC or lamivudine. M184I/V is associated with lower viral replication resulting in reduced HIV-1 RNA load [38, 39], and which in turn reduces the risk of emergence of AIDS-related morbidity and mortality [41]. In addition, M184I/V also increases the susceptibility of HIV to tenofovir [42]. There exists some evidence that patients with the M184I/V viral mutation, ascribed to the use of PrEP before diagnosis, can indeed be successfully treated with combination treatment containing FTC [33••]. This limited evidence comes from four patients who had undetectable HIV viral load 3 months into treatment despite the presence of the M184I/V mutation ascribed to the use of PrEP before diagnosis, after treatment with a regimen including emtricitabine (in addition to FTC, two patients were also treated with the recommended initial regimen TDF and dolutegravir [35•]; and two were also treated with TDF and cobicistat-boosted darunavir) [33••]. Given its cross-resistance with emtricitabine, it is likely that M184I/V can also be successfully treated with lamivudine, which is recommended in initial regimens [35•]. The limited impact of M184I/V is also reported in clinical studies that report that patients with an archived M184V/I

mutation detected by proviral DNA genotyping can successfully be treated with bictegravir or dolutegravir plus TAF/FTC or dolutegravir plus abacavir plus lamivudine [35•, 43–45]. In addition, the DAWNING study showed that patients who fail first-line antiretroviral drug treatment with emergence of the M184I/V mutation in plasma can be successfully treated with dolutegravir combined with 2 nucleoside reverse transcriptase inhibitors [46].

Simplifying initial three drug antiretroviral drug regimens to two drug regimens has been documented to maintain viral suppression in individuals without prior virological failure or evidence of drug resistance [35•, 47]. Recent studies have reported that patients who had the M184I/V viral mutation before viral suppression can be successfully switched to a two drug regimen including lamivudine [48, 49]. It should be noted that all these studies are on maintenance therapy; i.e., patients who were already virologically suppressed with combination antiretroviral drug therapy consisting of at least three different antiretroviral drugs were switched to dual therapy. There is currently no data published on the virological suppression rates in patients who start dual therapy (induction therapy to achieve virological suppression immediately after diagnosis) while being infected with a HIV strain harboring M184I/V mutation or who failed PrEP. Thus, the recommended first-line dual therapy with dolutegravir and emtricitabine cannot be recommended yet in patients who failed PrEP [35•].

K65R

The K65R viral mutation reduces the susceptibility to all nucleoside reverse transcriptase inhibitors except zidovudine. Treatment with zidovudine is, however, not recommended because of high rates of serious toxicities, including peripheral neuropathy and mitochondrial toxicity that may lead to myopathy, hepatic steatosis, lactic acidosis, lipodystrophy, and bone marrow suppression [50]. Contrary to the frequently reported M184I/V mutation [51], K65R is rarely reported [52]. Consequently, there are few studies that systematically investigated the risk of K65R on future virological failure. One study including a small number of patients suggested that bictegravir plus TAF/FTC may be effective when the K65R mutation is present [35•, 44]. There are no studies on the impact of K65R on regimens that include TDF.

Despite of the limited information on the impact of K65R that is available, the International Antiviral Society-USA for antiretroviral drug treatment of HIV recommends that dolutegravir-based, bictegravir-based, or darunavir-based regimens boosted with TDF or TAF plus FTC or lamivudine would still be expected to achieve high rates of viral suppression even in the presence of K65R and/or M184I/V [35•] and can be subsequently tailored according to clinical resistance test results.

There have been no systematic studies on maintenance therapy or on induction therapy with dual therapy in the presence of the K65R mutation. Thus, evidence is currently lacking to recommend dual therapy in PrEP failures. Anecdotal evidence from a single patient that became infected with PrEP-resistant virus including K65R and M184V found that treatment could be successfully simplified to dolutegravir and rilpivirine after achieving viral suppression [25•]. Induction treatment with dual therapy in individuals with the K65R viral mutation cannot be recommended.

Discussion

In this review, we have shown that drug resistance due to PrEP can emerge due to three different processes including the start of PrEP, while having an unrecognized acute infection, partial adherence after infection with HIV, and transmission of a virus that is resistant to the drugs used as PrEP. If drug resistance arises, then it usually involves the M184I/V viral mutation and to a lesser extent the K65R viral mutation. It should, however, be noted that K65R could emerge more frequently in subtype C as this clade more rapidly for K65R as compared to other subtypes [30, 31].

The treatment regimen in individuals that used PrEP before diagnosis should be adjusted based on the genotypic resistance results before start of antiretroviral drug treatment [35]. Adjustment of treatment is especially important in PrEP using individuals that became infected with a virus that is resistant to the drugs used as PrEP [24, 25, 26]. Although no studies have investigated the optimal treatment regimen of individuals that used PrEP before HIV diagnosis, there is limited evidence that patients infected with a M184I/V and/or K65R viral mutation can be treated with a preferred initial regimen of a second-generation integrase inhibitor (bictegravir or dolutegravir) and two nucleoside reverse transcriptase inhibitors as recommended by the International Antiviral Society-USA. Importantly, before any strong recommendations can be made, it is important that this limited impact on future treatment options is confirmed in a clinical study including individuals that used PrEP before diagnosis. Simplification of treatment to a two-drug regimen seems possible in those virologically suppressed individuals that had the M184V viral mutation before start of treatment, but not for induction therapy.

This review was limited to the currently available PrEP agents including TAF/FTC, TDF and TDF/FTC. In future years, novel antiretroviral agents that can be used as PrEP are expected to become available. These novel PrEP drugs include long-acting agents including the integrase inhibitor cabotegravir [53] and a novel reverse transcriptase translocation inhibitor islatravir [54]. Cabotegravir has cross-resistance to all licensed integrase inhibitors [55]. Resistance to islatravir involves the M184V viral mutation [54].

Conclusion

In conclusion, drug resistance can emerge in individuals who use PrEP. Although the evidence that is available suggests that drug resistance due to PrEP usually does not have a profound impact on future treatment options, the antiretroviral drug regimen should be adjusted using a genotypic resistance test in patients that used PrEP before diagnosis. There is an urgent need for clinical studies that investigate the optimal treatment of individuals who were PrEP users before diagnosis of HIV. These studies should also be performed in areas in where subtype C is common, given the rapid selection of K65R in this clade [30, 31].

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Declarations

Conflicts of interest

Drs Mukherjee and van Kampen do not report any conflict of interest.

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