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BRIEF REPORT

Acquisition of Multidrug-Resistant Human Immunodeficiency Virus Type 1 Infection in a Patient Taking Preexposure Prophylaxis

Donn J. Colby,[1] Eugene Kroon,[1] Carlo Sacdalan,[1] Monica Gandhi,[2] Robert M. Grant,[2] Praphan Phanuphak,[1] Jintanat Ananworanich,[3,4] Merlin L. Robb,[3,4] and Nittaya Phanuphak[1]

[1]Thai Red Cross AIDS Research Centre, Bangkok, Thailand; [2]University of California, San Francisco; and [3]US Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, and [4]Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, Maryland

We report a case indicating that acquisition of multidrug-resistant human immunodeficiency (HIV) virus type 1 during preexposure prophylaxis with combination tenofovir disoproxil fumarate and emtricitabine or evolution of resistance after HIV seroconversion remains a risk.

Keywords. HIV; transmission; preexposure prophylaxis; resistance.

Preexposure prophylaxis (PrEP) with combination tenofovir (TFV) disoproxil fumarate and emtricitabine (TDF/FTC) has proved very effective at preventing human immunodeficiency virus type 1 (HIV-1) infection when taken with good adherence. However, acquisition of multidrug-resistant HIV-1 during PrEP or evolution of resistance after HIV seroconversion remains a risk, as illustrated in this case report.

CASE REPORT

A 28-year-old Thai man started PrEP with combination TDF/FTC in March 2016. HIV testing with a third-generation (3rdG) antibody test (Alere Determine HIV 1/2) was nonreactive at PrEP initiation and after 5 weeks of PrEP use. After 8 weeks of PrEP use, the patient had another nonreactive 3rdG antibody test result with a different test kit (Genscreen HIV 1/2, version 2.0) at a different location but a positive qualitative HIV-1 RNA test result (Aptima) from the same sample, prompting referral for evaluation and treatment of acute HIV infection.

The patient was from a rural area in Northeastern Thailand but had lived for 2 years working as a sex worker in Pattaya, Thailand, where the PrEP had been prescribed through a local nongovernmental organization. He reported substance use 2–4 times per month, including crystal methamphetamine by inhalation, poppers (inhaled amyl nitrate), and 5–6 alcoholic drinks. He did not use tobacco products. He had no significant medical history and took no medication other than TDF/FTC. Adherence to PrEP was reported as good, missing only about 3 doses per month.

The patient had several events of condomless insertive and receptive anal intercourse with a foreign male client during the first 1–2 weeks that he was taking PrEP, but he could not recall the exact dates. All other acts of anal intercourse with male clients and casual male partners before taking PrEP and during the preceding 2 months of PrEP use were reportedly with condoms.

Results of clinical and laboratory testing are presented in Table 1. Four days after the initial positive qualitative HIV-1 RNA test result, the quantitative HIV-1 RNA value was 116 187 copies/mL. Serologic results had converted to reactive on both 3rdG and fourth-generation (4thG) testing (Architect HIV Ag/Ab Combo), but results of less-sensitive second-generation (2ndG) testing (Avioq HIV-1 Microelisa) remained nonreactive. P24 antigen was detectable, but Western blot test results were negative.

Antiretroviral therapy (ART) was started, with a combination of zidovudine (AZT), lamivudine, and lopinavir/ritonavir with discontinuation of TDF/FTC. After 8 weeks of ART, the quantitative viral load was <20 copies/mL. At 12 weeks, results of repeated HIV-1 serology were positive by 2ndG, 3rdG, and 4thG antibody testing and Western blot.

Hair samples taken 4 days after cessation of TDF/FTC showed levels of TFV and FTC indicative of daily dosing of medication in the preceding 6 weeks (Table 1) [1]. A plasma sample taken 40 hours after the last PrEP dose had a TFV level of 25 ng/mL, consistent with the patient report of good drug adherence until cessation the previous day [2].

Genotypic resistance testing performed before initiation of ART revealed the M184V mutation conferring resistance to the nucleoside reverse-transcriptase inhibitor (NRTI) FTC and 2 mutations (A98G and K103N) conferring resistance to first-generation nonnucleoside reverse-transcriptase inhibitors (NNRTI) (Table 1). No major or minor mutations were detected in the protease gene.

DISCUSSION

This is one of only a very few reported cases of multidrug-resistant (MDR) HIV-1 infection acquired in an individual adherent to PrEP with TDF/FTC, and to our knowledge the first report from a developing country. Two previously published reports both concerned cases in men who have sex with men (MSM) in North America [3, 4]. In all cases, patient self-report of good

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Correspondence: D. Colby, SEARCH, Thai Red Cross AIDS Research Centre, 104 Ratchadamri Rd, Pathumwan, Bangkok 10330, Thailand (donn.c@searchthailand.org).

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Table 1. Clinical Laboratory Results for Dates in 2016

	TDF/FTC Treatment				AZT/3TC/LPV/r	
Test	16 March	22 April	13 May	17 May	19–23 May	3 August
3rdG HIV Ab	NR	NR	NR	R	…	R
4thGHIV Ag/Ab	…	…	…	R	…	R
2ndG HIV Ab	…	…	…	NR	…	R
P24 Ag, pg/mL	…	…	…	3.18	BD	BD
Western blot	…	…	…	Negative	Negative	Positive
Qualitative HIV-1 RNA	…	…	Positive	…	Positive	…
Quantitative HIV-1 RNA, copies/mL	…	…	…	116 187	80 624	<20
CD4 cell count, cells/μL (%)	…	…	…	…	712 (25)	673 (41)
CD4/CD8 ratio	…	…	…	…	0.64	1.28
TFV in hair, ng/mg	…	…	…	…	0.126[a]	…
TFV in plasma, ng/mL	…	…	…	…	25[b]	…
FTC in hair, ng/mg	…	…	…	…	1.55[a]	…
RT genotype (NRTI mutations)	…	…	…	…	M184V	…
RT genotype (NNRTI mutations)	…	…	…	…	A98G, K103N	

Abbreviations: 2ndG, second-generation; 3rdG, third-generation; 3TC, lamivudine; 4thG, fourth-generation; Ab, antibody; Ag, antigen; AZT, zidovudine; BD, below detection; FTC, emtricitabine; HIV, human immunodeficiency virus; LPV/r, lopinavir/ritonavir; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NR, nonreactive; NRTI, nucleoside reverse-transcriptase inhibitor; R, reactive; RT, reverse-transcriptase; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

[a]Consistent with daily drug dosing.

[b]Consistent with dosing within the previous 2–3 days.

adherence was confirmed by objective biomarkers of adherence through measurement of TFV and FTC concentrations in hair and blood. All cases had mutations in the RT gene, resulting in resistance to both NRTI and NNRTI drugs.

The genotype in this our patient showed only 1 mutation causing resistance to the NRTI drug class, M184V, which gives high-level resistance to FTC. In a case of MDR HIV-1 transmission in a man who has sex with men and was taking PrEP in Toronto, Canada, the M184V mutation was present with a number of other NRTI mutations that resulted in low-level resistance to TDF, whereas phenotypic testing showed viral susceptibility to TDF [3]. Although phenotypic testing was not performed in our patient, the relatively high viral load at diagnosis despite good PrEP adherence indicated that TDF alone was not sufficient to fully suppress viral replication. The only studies of daily PrEP for MSM that have shown efficacy have used a combination of TDF and FTC [5, 6]. Further evidence comes from 2 cases of HIV-1 acquisition in MSM taking TDF monotherapy for treatment of hepatitis B infection, despite lack of TDF resistance mutations in the 1 patient in whom genotype testing was available [7]. These cases together suggest that in vitro measurements of TDF sensitivity alone may not be predictive of PrEP efficacy, and that both TDF and FTC in combination may be required for full protection against HIV infection in MSM.

The exact timing of HIV-1 acquisition in our patient is not clear. Nucleic acid testing (NAT) can definitively rule out HIV infection if performed with HIV antibody testing before PrEP initiation, but it was not available in this case. Although HIV-1 transmission before PrEP use cannot be ruled out, the history of high-risk behavior only after PrEP use started, the fact that 3rdG HIV-1 antibody test results remained nonreactive after 5 weeks of PrEP, and the high viral load at first measurement after 8 weeks of PrEP all argue against the presence of HIV-1 infection at PREP initiation.

It is possible that our patient acquired HIV in the first week of PrEP use, before the drugs were fully efficacious. Pharmacokinetic studies have shown that 4 doses of TDF/FTC per week provide adequate blood levels for efficacy [8], and just 2 TDF/FTC tablets taken 2–24 hours before sexual exposure, followed by 2 additional doses after exposure (an intermittent on-demand PrEP regimen) have shown equivalent efficacy to daily PrEP [9]. However, this would not preclude HIV transmission in the first few days of PrEP use. One limitation in this case is that genotype testing is not available from the time of HIV acquisition, or from the transmitting partner. Another limitation is that the standard sequencing performed can only detect resistance mutations present in at least 20% of circulating virions; next-generation sequencing was not available in our case but could potentially detect minor variants with greater antiretroviral resistance.

Our patient may have acquired an MDR virus with both NRTI and NNRTI resistance. However, acquisition of an NNRTI-resistant virus and subsequent evolution of NRTI resistance after transmission and during the period of good adherence to the 2-drug TDF/FTC regimen cannot be ruled out. We have previously reported transmitted drug resistance prevalences of 2.6% and 2.2% for NRTI and NNRTI drugs, respectively, among MSM with acute HIV infection in Thailand [10].

The diagnosis of HIV-1 infection in our case was based on reactive qualitative NAT results concurrent with a nonreactive

3rdG HIV antibody test result. Earlier diagnosis of HIV-1 infection during PrEP use through the use of NAT or 4thG HIV antibody testing has been demonstrated in PrEP clinical trials [11], but these testing modalities are less practical for routine use owing to their higher costs and technical requirements compared with rapid 3rdG HIV antibody testing. The development of point-of-care quantitative or qualitative HIV-1 RNA test kits would allow earlier diagnosis of HIV-1 infection in many settings where PrEP implementation is expanding, such as in community-based organizations or office-based practices.

HIV-1 transmission in the context of PrEP use should raise a high suspicion for transmitted or acquired antiretroviral drug resistance. In the case we report, the treating physicians prescribed ART using a protease inhibitor-based regimen that did not include TDF. AZT, although less well tolerated than TDF, maintains antiviral activity in the presence of TFV resistance [12]. Therefore, AZT/lamivudine may be the best or only alternative NRTI available for use in many low- and middle-income countries in the context of HIV transmission during PrEP use, when the potential for TFV resistance is high. Subsequent resistance testing validated the choice of this regimen, and the HIV-1 viral load was suppressed to undetectable within 8 weeks. The patient's CD4 cell count remained within the normal range, and no clinical symptoms of HIV infection ever developed. Despite infection with MDR HIV-1, the prompt initiation of an appropriate ART regimen resulted in a favorable clinical outcome without morbid effects.

Our case, in addition to previously reported cases in North America, illustrates that acquisition of MDR HIV-1 during PrEP use is possible, either through transmission of MDR virus or through the evolution of additional mutations after acquisition, providing a challenge to HIV diagnosis and treatment. Providers prescribing PrEP and individuals taking TDF/FTC should be aware of this risk.

Notes

Disclaimer. The views expressed are those of the authors and should not be construed to represent the positions of the participating institutions, the US Army, or the Department of Defense.

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