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Case Report

Failure of pre-exposure prophylaxis with daily tenofovir/emtricitabine and the scenario of delayed HIV seroconversion

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ABSTRACT

Failure of pre-exposure prophylaxis (PrEP) with tenofovir disoproxil fumarate and emtricitabine may occur despite perfect adherence, although this is uncommon. Failure results in breakthrough HIV infection. Delayed seroconversion associated with antiretroviral use may complicate the picture, causing uncertainties in interpreting adherence patterns for establishing the true cause of PrEP failure.

Introduction

Pre-exposure prophylaxis (PrEP) with co-formulated tenofovir disoproxil fumarate (TDF, 300 mg) and emtricitabine (FTC, 200 mg) (Truvada) has been proven to be effective for preventing HIV transmission (Fonner et al., 2016). Standard guidelines are in place to ensure effective implementation of PrEP (Centers for Disease Control and Prevention: US Public Health Service, 2020), and failure is uncommon if adherence is upheld and maintained (Marcus et al., 2017). Only a handful of cases have failed to be protected from HIV infection despite confirmed adherence to the daily regimen (Knox et al., 2017; Hoornenborg et al., 2017; Cohen et al., 2019). We report a failure case and discuss the challenges of differentiating between true failure and defective protection due to suboptimal adherence.

A case of PrEP failure

A 24-year-old man who has sex with men (MSM) of Chinese ethnicity joined a clinical trial of PrEP for HIV prevention in Hong Kong. The trial involved sequential prescription of daily TDF/FTC (Truvada) crossing over to on-demand PrEP, each for a 4-month period. On initial assessment (week 0), he had a history of good health and no past diagnoses of any sexually transmitted infection (STI). He admitted engagement in the sexualized use of recreational drugs (chemsex) occasionally with gamma-hydroxybutyric acid (GHB) and Viagra in conjunction with unprotected anal sex. His baseline test on September 15, 2018 with a fourth-generation HIV Ag/Ab rapid test was negative, creatinine was 59 μmol/l, and he was hepatitis B virus surface antibody (anti-HBs)-positive. On screening for STIs, he tested positive for syphilis serology and was positive for pharyngeal *Neisseria gonorrhoeae* and rectal *Chlamydia trachomatis* by nucleic acid amplification tests (NAATs).

Daily Truvada was started on September 19, 2018 (day 0), after which he tested negative with the same HIV rapid test on day 10, week 4, and week 10. After 18 weeks of the daily regimen, he was switched to on-demand Truvada on January 19, 2019 (week 18) in accordance with the IPERGAY regimen (Molina et al., 2017). He again tested HIV-negative 2 weeks afterwards (week 20), but 6 weeks later on March 16, 2019 (week 26), the rapid test showed a positive result (for antibody but not antigen). HIV infection was confirmed with both ELISA and Western blot on his serum specimen collected on the same day (Figure 1). He attended an HIV specialist clinic when his baseline viral load was 9600 copies/ml. He was started on an antiretroviral regimen comprising dolutegravir, TDF, and zidovudine on April 15, 2019, and his viral load became undetectable 6 weeks later.

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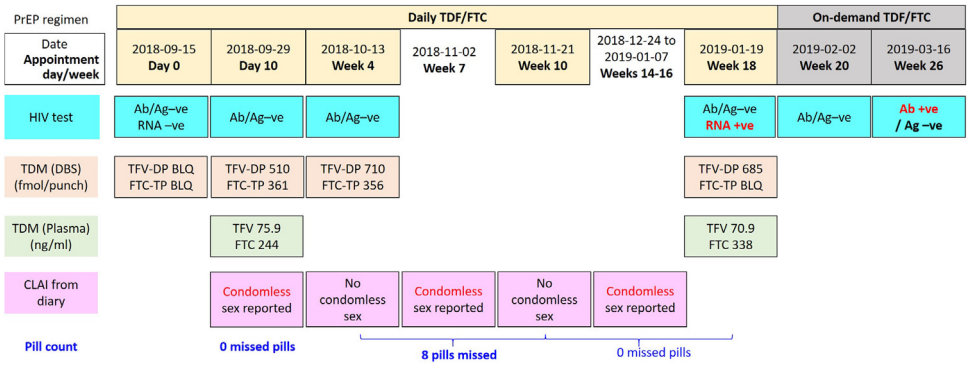

Figure 1. Summary of laboratory and point-of-care test results at baseline and following pre-exposure prophylaxis.

Genotype resistance testing revealed that the HIV-1 carried the M184 V mutation suggestive of FTC resistance. Archived plasma samples collected at multiple time-points were retrieved for supplemental investigations. HIV RNA testing was negative at baseline but turned positive on the blood sample collected at week 18 while the patient was on daily Truvada, 8 weeks before the positive HIV antibody test result of week 26. It was therefore considered that antibody seroconversion might have occurred any time after week 20, but the date could not be pinpointed as no archived samples between then and week 26 were available for testing. The patient claimed good adherence with Truvada throughout the 18 weeks of daily PrEP. Tablet-counting showed that he had taken all of the Truvada doses except for occasional omissions between October 13 (week 4) and November 21 (week 9). Self-completion of an online diary was done on most of the days while he was on PrEP, except between October 13 and 20 (week 4–5), during which he claimed to have had no condomless anal sex. The diary showed omission of Truvada on November 1 and 2 (week 7) and an episode of unprotected anal sex with an unknown partner on November 2.

To validate the adherence pattern, dried blood spots (DBS) were tested for tenofovir diphosphate (TFV-DP) and emtricitabine triphosphate (FTC-TP) on day 0, day 10, week 4, and week 18. A threshold of 700 fmol/punch commensurate with ≥4 doses per week was used as a cumulative dosing marker for evaluating adherence (Brooks and Anderson, 2018). The week 18 level of 685 fmol/punch suggested imperfect adherence in the preceding 2–6 weeks before the blood draw. The reading was just above the threshold on Oct 13 (710 fmol/punch), but there were no concurrent sexual activities in the week before and afterwards. If HIV exposure did occur on November 2, TFV-DP testing on January 19 would hardly be appropriate for assessing his adherence 11 weeks before the test. Plasma TFV levels were determined with an in-house assay on two samples: one collected 16 h after the last dose on day 10 and the other collected 1.5 h after the last dose at week 18. The undetectable FTC-TP (a recent dosing marker) in DBS paralleling a good level of plasma FTC but marginally low level of plasma TFV at week 18 could be explained by the recent intake of Truvada 1.5 h before sampling. Combining all results, it is likely that failure of Truvada had occurred after the initiation of PrEP, resulting in the emergence of FTC resistance. HIV exposure had probably taken place during a short period of suboptimal adherence associated with high-risk sexual activities and consequently delayed HIV antibody seroconversion 13–19 weeks afterwards. However, HIV exposure in the presence of full adherence to daily Truvada 4–12 weeks before seroconversion cannot be entirely excluded.

Discussion

PrEP failure can be broadly defined as the occurrence of breakthrough HIV infection at any time along the PrEP continuum of care (Marcus et al., 2017; Nunn et al., 2017). Such failure could be a result of HIV exposure either before or after the initiation of PrEP, the latter often consequent to suboptimal adherence. Delayed seroconversion poses a challenge in the investigation of suspected PrEP failure, making it difficult to temporally correlate a person's adherence with the corresponding history of potential HIV exposure (Zucker et al., 2018). Conventionally, 95% of acute HIV infections should be detected by a fourth-generation Ab/Ag test within 4 weeks of exposure (Fiebig et al., 2003). However, the interval for HIV antibody seroconversion (Fiebig phase V) has been shown to be prolonged to over 100 days in 17% of individuals on PrEP (Donnell et al., 2017), a phenomenon partly complicated by the limited number of tests performed for site detection. If the HIV infection in our case did occur on November 2, the antibody test showed a positive result between 90 and 130 days after exposure. The interval appeared to be longer than 11 weeks (Markowitz et al., 2017), 35 days (Colby et al., 2018), and 8 weeks (Zucker et al., 2018) in three other failure cases reported in the literature. The non-detectability or missed detection of HIV antigen was an observation reported in two other failure cases with perfect adherence (Hoornenborg et al., 2017; Zucker et al., 2018). Another case reported the transient presence of HIV antigen for 7 days (Knox et al., 2017).

The current case of isolated M184 V mutation was probably a result of the transmission of resistant virus, although the emergence of resistance following infection cannot be excluded. Analyses based on the results of the iPrEX study suggested that the use of Truvada for 4 days per week was associated with a 96% reduction in virus transmission (Anderson et al., 2012), underlining the rationale for the time-driven approach to PrEP. As imperfect daily adherence might not necessarily lead to failure, other pharmacological or non-pharmacological factors associated with PrEP failure are yet to be uncovered.

Currently, 3-monthly monitoring is recommended in the implementation of a PrEP program (Centers for Disease Control and Prevention: US Public Health Service, 2020). Coupled with delayed seroconversion while on Truvada, the detection of breakthrough infection could be deferred by over 6 months. So far, the concurrent occurrence of delayed seroconversion does not appear to be associated with additional risks of resistance (Donnell et al., 2017). The phenomenon nevertheless argues for the avoidance of infrequent follow-ups of PrEP users so that the diagnosis of failure and prompt combination antiretroviral therapy will not be inadvertently delayed.

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Ethical approval

The study was approved by Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (CRE2016.719). The clinical trial referred to in this report was approved by the Department of Health, Hong Kong (Certificate number 101143) and has been registered at the Centre for Clinical Research and Biostatistics, The Chinese University of Hong Kong (Trial number CUHK_CCRB00606).

Conflict of interest

PLA has received research grants and contracts paid to his institution and fees from Gilead Sciences. All other authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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References

Anderson PL, Glidden DV, Liu A, Buchbinder S, Lama JR, Guanira JV, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Sci Transl Med 2012;4(151)151ra125.

Brooks KM, Anderson PL. Pharmacologic-based methods of adherence assessment in HIV prevention. Clin Pharmacol Ther 2018;104(6):1056–9.

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. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf. Published March 2018.

Cohen SE, Sachdev D, Lee SA, Scheer S, Bacon O, Chen MJ, et al. Acquisition of tenofovir-susceptible, emtricitabine-resistant HIV despite high adherence to daily pre-exposure prophylaxis: a case report. Lancet HIV 2019;6(1):e43–50.

Colby DJ, Kroon E, Sacdalan C, Gandhi M, Grant RM, Phanuphak P, et al. Acquisition of multidrug-resistant HIV Type 1 infection in a patient taking preexposure prophylaxis. Clin Infect Dis 2018;67(6):962–4.

Donnell D, Ramos E, Celum C, Baeten J, Dragavon J, Tappero J, et al. The effect of oral preexposure prophylaxis on the progression of HIV-1 seroconversion. AIDS 2017;31(14):2007–16.

Fiebig EW, Wright DJ, Rawal BD, Garrett PE, Schumacher RT, Peddada L, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. AIDS 2003;17(13):1871–9.

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 2016;30:1973–83.

Hoornenborg E, Prins M, Achterbergh RCA, 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. Lancet HIV 2017;4(11):e522–8.

Knox DC, Anderson PL, Harrigan PR, Tan DH. Multidrug-resistant HIV-1 infection despite preexposure prophylaxis. N Engl J Med 2017;376(5):501–2.

Marcus JL, Hurley LB, Nguyen DP, Silverberg MJ, Volk JE. Redefining human immunodeficiency virus (HIV) preexposure prophylaxis failures. Clin Infect Dis 2017;65(10):1768–9.

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. J Acquir Immune Defic Syndr 2017;76(4):e104–6.

Molina JM, Charreau I, Spire B, Cotte L, Chas J, Capitant C, et al. Efficacy, safety, and effect on sexual behaviour of on-demand pre-exposure prophylaxis for HIV in men who have sex with men: an observational cohort study. Lancet HIV 2017;4(9):e402–10.

Nunn AS, Brinkley-Rubinstein L, Oldenburg CE, Mayer KH, Mimiaga M, Patel R, et al. Defining the HIV pre-exposure prophylaxis care continuum. AIDS 2017;31(5):731–4.

Zucker J, Carnevale C, Rai AJ, Gordon P, Sobieszczyk ME. Positive or not, that is the question: HIV testing for individuals on pre-exposure prophylaxis. J Acquir Immune Defic Syndr 2018;78(2):e11–3.