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Case report

A case study of chewed Truvada® for PrEP maintaining protective drug levels as measured by a novel urine tenofovir assay

Linden Lalley-Chareczko[1], Devon Clark[1], Athena F Zuppa[2], Ganesh Moorthy[3], Caitlin Conyngham[1], Karam Mounzer[1], Helen Koenig[1,4]*

[1]Philadelphia FIGHT Community Health Centers, Philadelphia, PA, USA
[2]Division of Pediatric Critical Care Medicine, The Children's Hospital of Philadelphia, Philadelphia, PA, USA
[3]Division of Clinical Pharmacology & Therapeutics, The Children's Hospital of Philadelphia, Philadelphia, PA, USA
[4]Division of Infectious Diseases, MacGregor Infectious Diseases Clinic, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

*Corresponding author e-mail: lchareczko@fight.org

Emtricitabine/tenofovir disoproxil fumarate (FTC/TDF; Truvada®) given as pre-exposure prophylaxis (PrEP) successfully blocks HIV when taken once daily prior to potential HIV exposure. A 22-year-old male reported difficulty swallowing FTC/TDF for PrEP and subsequently began chewing the FTC/TDF tablets. Monthly urine samples assessed using liquid chromatography-tandem mass spectrometry (LC-MS/MS) indicated tenofovir levels >1,000 ng/ml, indicative of protection from HIV acquisition, over a 48-week period. Data from observational studies of HIV-positive patients details the successful treatment of HIV using crushed FTC/TDF delivered via feeding and gastronomy tubes while small, randomized trials of healthy volunteers demonstrate bioequivalence between whole and crushed FTC/TDF.

Introduction

Emtricitabine and tenofovir disoproxil fumarate (FTC/TDF; Truvada®) given as pre-exposure prophylaxis (PrEP) is hypothesized to reduce HIV transmission by limiting the number of free virions transmitted from an HIV-positive individual, allowing the host immune response to successfully block infection [1]. Standard dosing of FTC/TDF for PrEP, as endorsed by the CDC [2,3], consists of one tablet daily, taken orally, for HIV-uninfected individuals [4]. While few reports and/or case studies have examined the efficacy of crushed FTC/TDF as part of a treatment regimen for HIV-positive adults, no data exist on daily administration of FTC/TDF for PrEP in forms other than the whole tablet (that is, crushed, crushed and mixed with water or juice, or chewed). The following describes the case of a 22-year-old male who reported chewing his once daily FTC/TDF for PrEP in the context of a clinical trial assessing PrEP adherence and programme retention.

Case presentation

The patient was a 22-year-old, Caucasian, biological male who originally presented for PrEP services and was subsequently enrolled in the IN-US-276-1295 clinical trial that measured programme retention and PrEP adherence over a 48-week period at an urban federally qualified health centre (FQHC) tailoring services towards youth and young adults at risk for HIV infection. The subject identifies as a man who has sex with men, has a past medical history of irritable bowel syndrome and was diagnosed with depression during his first visit. Screening serum creatinine and creatinine clearance measurements were within normal range. The patient initiated PrEP in April 2015 and was taking no other daily medications at that time.

1 week after initiation of FTC/TDF for PrEP, the patient contacted clinic staff complaining of an inability to swallow the tablet due to its size. The patient reported severe gagging and retching when attempting to swallow FTC/TDF, which was not improved by drinking a larger volume of water or juice. The patient was also markedly upset by his inability to swallow FTC/TDF, stating he was concerned for his safety and reporting multiple sexual partners. The patient stated he had problems in the past swallowing 'large' tablets

though he has no medical history of oesophageal disease or malformation. The patient also reported having no family history of swallowing or neurological disorders. Physical examination on the day of PrEP initiation and throughout the study yielded no significant findings.

Management and outcome

At the recommendation of pharmacy staff at our centre, the patient was instructed to crush the FTC/TDF tablet, mix it with 100 ml [5] of water or juice and drink it immediately. The patient was warned there might be a bitter taste and to ensure the entire mixture was consumed [6]. The patient agreed to try crushing the tablets in order to maintain his adherence. In August 2015, the patient presented to the clinic for a scheduled PrEP follow-up visit and told clinic staff he had started to chew the FTC/TDF tablets whole rather than crush the pills and mix them in water or juice. The patient stated he found it easier to chew the tablets because he was often not at home when dosing (travelling to and from school and work).

The IN-US-276-1295 protocol collects bi-weekly or monthly urine samples from each patient for the purpose of monitoring urine tenofovir concentrations as an objective measure of PrEP adherence; flexible dispensation schedules are a unique feature of this particular youth clinic, and under study for that reason. In this case, the patient presented to the clinic monthly, and urine samples were collected at each visit. Comparator plasma tenofovir samples were also measured at 24 and 48 weeks after the initiation of FTC/TDF.

Within the IN-US-276-1295 protocol, urine tenofovir levels are assessed using liquid chromatography-tandem mass spectrometry (LC-MS/MS) and analysed to show whether tenofovir is present or absent in the urine samples [7]. In this case, the patient's urine samples consistently displayed tenofovir concentrations of >1,000 ng/ml over the 48-week period. This concentration is indicative of protective levels of tenofovir (dosing within the last 1–2 days of measurement) despite the patient having chewed the FTC/TDF tablet. Plasma tenofovir samples were also collected at weeks 24 and 48 of the IN-US-276-1295 trial. Both plasma samples yielded tenofovir concentrations >10 ng/ml, which, due to a 2 log differential in sensitivity [7], are consistent with the corresponding urine samples and indicate protective levels of medication. Furthermore, all IN-US-276-1295 participants underwent safety lab draws every 12 weeks. This patient's serum creatinine and creatinine clearance (estimated glomerular filtration rate [eGFR]) remained within normal limits throughout 48 weeks of participation (serum creatinine range 0.80–0.99 mg/dl over 48 weeks; eGFR range 109–127 ml/min/1.73 m^2 over 48 weeks). Adverse events reported include dizziness, fatigue, nausea, migraines, yeast infection of the skin, strep throat and concussion. Dizziness, fatigue and nausea resolved after 3 days and without treatment. Migraines, yeast infection of the skin, strep throat and concussion were deemed not related to FTC/TDF.

Discussion

The prescribing information (10/2013) for FTC/TDF addresses administration for the purposes of PrEP and recommends one tablet once daily with or without food [8]. The prescribing information does not detail the impact of crushing or chewing FTC/TDF administered for PrEP. Despite this, research has demonstrated the efficacy of crushed FTC/TDF in HIV-positive patients. A single-centre case series presented at the *British HIV Association Annual Conference* (2015) described the overall positive outcomes of 11 (5 paediatric and 6 adolescent/adult) patients given crushed FTC/TDF through feeding tubes for a median period of 33 months [9]. Sandovsky *et al.* [10] and Lindholm *et al.* [11] report similar success after the administration of FTC/TDF as part of an antiretroviral regimen via a jejunostomy/gastronomy tube to 52-year-old and 20-year-old males, respectively. In the former patient, Sandovsky *et al.* [10] observed a plasma tenofovir concentration of 320 ng/ml at 2 h post dose (patient's last tube feeding 7 h prior to measurement) and 94 ng/ml at 12 h post dose (patient's last tube feeding 3 h prior to measurement). Measurements were obtained using high-pressure liquid chromatography-mass spectroscopy [10]. Lindholm *et al.* [11] note the successful use of crushed FTC/TDF may be due to the lack of enteric coating.

Several small, randomized trials have been conducted to assess the stability/bioequivalence of crushed single-tablet antiretroviral regimens containing FTC/TDF. Data presented at *CROI* (2016) from a randomized trial of 24 healthy adults indicated bioequivalence between Stribild (elvitegravir, cobicistat, emtricitabine/TDF) taken as a whole tablet, crushed/suspended and administrated orally with food, and crushed/suspended with drip administration [12]. A small, randomized trial of 14 healthy subjects (mean ± standard deviation 33.3 ±10.9) given Atripla (efavirenz, emtricitabine, TDF) dissolved in 5 ml of water or 20 ml of Ora-Sweet solution found tenofovir concentrations above the range indicative of bioequivalence when compared to historical, steady-state data from HIV-positive patients [13].

Summary

This case illustrates the unique case of a healthy 22-year-old male who chewed FTC/TDF tablets due to an inability to swallow them. Urine and plasma tenofovir levels assessed using LC-MS/MS consistently

displayed concentrations indicative of protection from HIV acquisition over a 48-week period. This is the first case report to indicate chewed FTC/TDF remains efficacious when taken for HIV prevention, just as similar administrations have been shown to be effective for treatment of HIV.

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Disclosure statement

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