Original research article

INTERNATIONAL JOURNAL OF STD & AIDS

International Journal of STD & AIDS
0(0) 1–4

DOI: 10.1177/0956462419841144
journals.sagepub.com/home/std
SAGE

Quantification of tenofovir disoproxil fumarate and emtricitabine in generic pre-exposure prophylaxis tablets obtained from the internet

Xinzhu Wang[1], Will Nutland[2], Michael Brady[3], Ian Green[3], Marta Boffito[1,4] and Myra McClure[1]

Abstract

In this study, we addressed the recent concerns over the authenticity of generic pre-exposure prophylaxis (PrEP) purchased online by sampling 14 generic PrEPs from different manufacturers and suppliers and measuring tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) content using high-performance liquid chromatography. We confirmed that all the PrEP tablets contained 94.3% to 104.9% of the 300 mg of TDF claimed on the label and 97.3% to 104.4% of the 200 mg FTC claimed on the label.

Keywords

Generic PrEP, HIV prevention, liquid chromatography, quantification, tablet form

Date received: 14 January 2019; accepted: 20 February 2019

Background

Despite advances in antiretroviral therapy (ART) and implementation of HIV prevention campaigns in various countries, HIV incidence remains high in developed countries, particularly in defined risk groups.[1,2] Pre-exposure prophylaxis (PrEP) with tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) dramatically reduces the risk of HIV acquisition among HIV-negative individuals when taken daily or in an event-driven fashion.[3–5] The World Health Organization (WHO) updated its guideline in 2014 to recommend oral PrEP as a prevention choice for people at high risk of HIV infection.[6]

Since 2014, several countries have adopted to include PrEP in their national HIV prevention guidelines. These include the United States, France, Norway, Belgium and Scotland. However, the adoption process of PrEP has been slow in other developed countries, in part because of the cost involved. The NHS in England has declined to commission PrEP, leading high-risk individuals to purchase generic versions online (e.g. via websites such as www.iwantprepnow.co.uk). To address initial concerns over the authenticity of the PrEP purchased online, we provided therapeutic drug monitoring for tenofovir (TFV) and FTC in 2016–2017 for 293 individuals taking generic PrEP and reported that plasma concentrations were all above target values.[7]

From October 2017, NHS England started the three-year Impact Trial on PrEP, to which 13,000 people are being recruited to assess the need, uptake and duration of use of the drug, which is required to determine the commissioning of future access to PrEP.[8] The Impact study is very likely to be over-subscribed before the trial finishes due to the restricted number of places, leaving some high-risk individuals unable to access PrEP by this means. Recently, new concerns

[1]Department of Medicine, Imperial College London, London, UK
[2]PrEPster, London, UK
[3]Terrence Higgins Trust, London, UK
[4]HIV/GUM department, Chelsea and Westminster Hospital, London, UK

Corresponding author:
Xinzhu Wang, Jefferiss Research Trust Laboratories, Department of Medicine, Imperial College London, London W2 1PG, UK.
Email: xinzhu.wang@imperial.ac.uk

have arisen over the amount of TDF/FTC contained in the generic PrEP tablets. In the present study, we sampled generic PrEP from mainstream brands and suppliers and measured TDF and FTC in the purchased tablet form.

Methods

Generic PrEP tablets in sealed bottles of different brands and from different suppliers were obtained from the internet through test purchases. The suppliers selected were those featured on UK-based PrEP education websites as the most commonly used suppliers of generic PrEP. One sample bottle (30 pills) from each brand of PrEP available from each website was obtained. Purchases were obtained from six online suppliers. None of the online PrEP suppliers was informed that the test purchase was taking place. The purchase was made by a number of volunteers (not known to suppliers as PrEP activists) who were instructed to order specific brands of PrEP from specific suppliers. Volunteer purchasers were required to navigate the particular purchasing requirements for the site that they purchased PrEP from. For example, some sites required a copy of the purchaser's passport; some required payment by bank transfer, rather than credit or debit card. None of the sites required a prescription for purchasing PrEP. Truvada from Gilead was purchased from Imperial College Healthcare NHS Trust. PrEP tablets were also obtained from the IMPACT trial. The brand and supplier of the generic PrEP samples were blinded from the researcher carrying out the analysis.

Ten tablets were weighed and the weight recorded, and ground to a fine powder using a pestle and mortar. The average weight of each tablet was calculated and the quantity equivalent to 300 mg TDF and 200 mg FTC was transferred to a 100 mL volumetric flask. The powder was dissolved to 100 mL with methanol: water (50/50; v/v) and sonicated for 1 h. The solution was filtered through 0.2 μm filter membrane and diluted in water to prepare the test solutions containing 60 μg/mL TDF and 40 μg/mL FTC. Stock TDF and FTC standard (1 mg/mL) was prepared by dissolving TDF and FTC (Carbosynth, UK) in methanol: water (50/50; v/v) and diluted further in water to give final concentration of 10, 20, 30, 40, 60 and 80 μg/mL. TDF and FTC were separated on an ACQUITY UPLC BEH C8 column (1.7 μm, 2.1 × 100 mm) (Waters, Elstree, UK) using ultra-performance liquid chromatography (ACQUITY; Waters). The mobile phase consists of solvent A, 0.1% formic acid in water and 5 mM ammonium acetate and solvent B, 0.1% formic acid in methanol. The flow rate was set to 0.3 mL/min and 5 μL of the samples were injected for each analysis. TDF and FTC were eluted through a gradient and quantified at wavelengths of 260 nm and 280 nm, respectively. The method was validated for linearity, accuracy, precision and limit of detection.

Results

The calibration curve, consisting of six concentration points, was used to calculate the TDF and FTC concentrations of QC samples and test samples. Both calibration curves were linear in the concentration range of 10–80 μg/mL, with correlations of 0.99999. The limit of detection was 1.5 μg/mL and 0.4 μg/mL for TDF and FTC, respectively. The overall accuracy ranged from 92.6% to 98.3% and from 105% to 106% for the three different concentrations of quality control samples (25 μg/mL, 50 μg/mL, 70 μg/mL) for TDF and FTC, respectively. Intra-assay variability was 1.9% and inter-assay variability ranged from 1.1% to 5.6% for TDF. Intra-assay variability was 0.2% and inter-assay variability ranged from 0.1% to 0.4% for FTC. A total of 16 samples were obtained for analysis, including Truvada™ from Gilead, PrEP used in the IMPACT trial and 14 generic PrEP tablets obtained from Mylan, Cipla, Hetero Healthcare and Emcure, Adcock Ingram and GPO. The suppliers were All Day Chemist, Dynamix International, Green Cross Pharmacy, In House Pharmacy, Silom Pulse and United Pharmacy (in alphabetic order). As summarised in the Table 1, all the PrEP tablets contained 94.3% to 104.9% of the 300 mg of TDF claimed on the label and 97.3% to 104.4% of the 200 mg FTC claimed on the label.

Discussions

Internet improves access to generic drugs, but it circumvents established safeguards against aspects of quality control, from manufacturing to distribution. Quantification of active pharmaceutical ingredients in other generic drugs were reported previously.[9–12] As for all generic drugs, without specialised analytical equipment, it is impossible to inform individuals who purchase generic PrEP online of the quality or authenticity of the drugs. Confirming drug content in generic PrEP drugs, as one of the ways to assess quality of the drugs, is valuable as governments, charities and activist groups advocate for PrEP use in high-risk groups. To our knowledge, the present report represents the first study measuring drug content in generic PrEP obtained via the internet.

All PrEP tablets sampled in this study contained the claimed amount of TDF and FTC. However, no generalised conclusion should be drawn based on the current study that this applies to all generic PrEP drugs, as

Table 1. Characteristics and measured quantity of tenofovir disoproxil fumarate and emtricitabine of PrEP samples.

					Tenofovir disoproxil fumarate		Emtricitabine	
Drug name	Manufacture	Lot no.	Expiration date	Supplier source	Measured amount in mg	% of label claim (300 mg)	Measured amount in mg	% of label claim (200 mg)
Truvada	Gilead	5595307D	19 Nov	Imperial Healthcare NHS Trust	300.1	100.0	201.2	100.6
TENVIR-EM	Cipla	GG80516	20 Feb	All Day Chemist	300.2	100.1	205.9	103.0
RICOVIR-EM	Mylan	3067417	20 Apr	Dynamix International	307.4	102.5	201.6	100.8
TENOF-EM	Hetero Healthcare	31171625	20 Apr	Dynamix International	306.4	102.1	205.2	102.6
TENVIR-EM	Cipla	GG80516	20 Feb	Dynamix International	312.0	104.0	208.7	104.4
RICOVIR-EM	Mylan	8074289	20 Feb	Dynamix International	288.7	96.2	198.4	99.2
TENOF-EM	Hetero Healthcare	31171625	20 Apr	Green Cross Pharmacy	313.2	104.4	207.2	103.6
Adco-Emtevir	Adcock Ingram	W042494	19 Aug	Green Cross Pharmacy	301.6	100.5	207.0	103.5
TENVIR-EM	Cipla	GK80203	20 Mar	Green Cross Pharmacy	296.1	98.7	202.1	101.1
RICOVIR-EM	Mylan	8074289	20 Feb	Green Cross Pharmacy	286.8	95.6	9197.8	98.9
Emtricitabine/ Tenofovirdisoproxil	Mylan	1091973	Not available	IMPACT trial	299.2	99.7	198.3	99.2
TENVIR-EM	Cipla	GG80516	20 Feb	In House Pharmacy	314.8	104.9	208.4	104.2
TENO-EM	GPO	W615110	20 Feb	Silom Pulse	305.0	101.7	205.4	102.7
RICOVIR-EM	Mylan	3077012	20 Nov	Silom Pulse	296.9	99.0	200.6	100.3
TAVIN-EM	Emcure	E16HX18001	20 Dec	United Pharmacy	283.0	94.3	194.7	97.3
TENVIR-EM	Cipla	GG80114	19 Dec	United Pharmacy	307.5	102.5	203.5	101.8

Suppliers of the generic PrEP samples are listed in alphabetic order.

we only sampled a relative small number. Moreover, it is important to note that this is not a bioavailability study, so we could not draw any conclusion on the efficacy or safety of the generic PrEP drugs. We did not include all pharmaceutical assurance methods, namely uniformity of mass, dissolution, analysing impurities and related substances. Therefore, we could not totally exclude, for example, the possible contamination/potential for toxicity. Furthermore, as this was not a post-marketing surveillance activity, the guidelines on the Conduct of Surveys of the Quality of Medicines by WHO[13] were not fully followed. However, this study provides reassurance to the community purchasing generic PrEP online via safe sources and is a good example of a close collaboration between academics, clinicians, HIV charities and PrEP advocates: as soon as the latter expressed concerns about the authenticity of PrEP agents, clinical academics and scientists addressed them in a time-sensitive manner by swiftly designing, executing and presenting the study results to reassure the community who takes HIV PrEP.

Acknowledgement

We are grateful to NIHR Imperial BRC for its support of this study.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Marta Boffito has received travel and research grants from and has been advisor for Janssen, Roche, ViiV, Bristol-Myers Squibb, Merk Sharp & Dohme, Gilead, Mylan, Cipla, Teva. Xinzhu Wang, Will Nutland, Michael Brady, Ian Green and Myra McClure report no conflicts of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The work was supported by funding from Terrence Higgins Trust.

ORCID iD

Xinzhu Wang http://orcid.org/0000-0003-2825-2763

References

1. Beyrer C. Strategies to manage the HIV epidemic in gay, bisexual, and other men who have sex with men. *Curr Opin Infect Dis* 2014; 27: 1–8.
2. van Griensven F, de Lind van Wijngaarden JW, Baral S, et al. The global epidemic of HIV infection among men who have sex with men. *Curr Opin HIV AIDS* 2009; 4: 300–307.
3. McCormack S, Dunn DT, Desai M, 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. *Lancet* 2016; 387: 53–60.
4. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010; 363: 2587–2599.
5. Molina J-M, Capitant C, Spire B, et al. On-demand pre-exposure prophylaxis in men at high risk for HIV-1 infection. *N Engl J Med* 2015; 373: 2237–2246.
6. World Health Organization. Department of HIV/AIDS. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV 2015. Available from https://apps.who.int/iris/handle/10665/186275.
7. Wang X, Nwokolo N, Korologou-Linden R, et al. InterPrEP: internet-based pre-exposure prophylaxis with generic tenofovir disoproxil fumarate/emtrictabine in London – analysis of pharmacokinetics, safety and outcomes. *HIV Med* 2018; 19: 1–6.
8. NHS commissioning: PrEP trial updates, www.england.nhs.uk/commissioning/spec-services/npc-crg/blood-and-infection-group-f/f03/prep-trial-updates/ (accessed 20 March 2019).
9. Veronin MA and Nguyen NT. Comparison of simvastatin tablets from the US and international markets obtained via the internet. *Ann Pharmacother* 2008; 42: 613–620.
10. Veronin MA, Nutan MT and Dodla U. Quantification of active pharmaceutical ingredient and impurities in sildenafil citrate obtained from the internet. *Ther Adv Drug Saf* 2014; 5: 180–189.
11. Onwujekwe O, Kaur H, Dike N, et al. Quality of antimalarial drugs provided by public and private healthcare providers in south-east Nigeria. *Malar J* 2009; 8: 22.
12. Baert B, Annavarapu S, Burvenich C, et al. Analytical, biopharmaceutical and regulatory evaluation of topical testosterone preparations. *Eur J Pharm Biopharm* 2009; 72: 275–281.
13. WHO. Guidelines on the conduct of surveys of the quality of medicines. WHO technical report series, no. 996, 2006, Annex 7.