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Gender-Affirming Hormone Pharmacokinetics Among Adolescent and Young Adult Transgender Persons Receiving Daily Emtricitabine/Tenofovir Disoproxil Fumarate

Jenna Yager,[1] Kristina M. Brooks,[1] Jennifer Brothers,[2] Kathleen Mulligan,[3] Raphael J. Landovitz,[4] Daniel Reirden,[5] Meenakshi Malhotra,[2] Carrie Glenny,[5] Paul Harding,[6] Tina Powell,[6] Peter L. Anderson,[1] and Sybil Hosek[2]

Abstract

Transgender persons have an increased vulnerability to HIV infection yet have not been well-represented in past clinical trials for pre-exposure prophylaxis (PrEP). Because of this, there are few data available to understand whether gender-affirming hormone concentrations are influenced by PrEP agents in transgender men (TM) and transgender women (TW). The objective of this study was to compare gender-affirming hormone concentrations with versus without emtricitabine (F, FTC)–tenofovir disoproxil fumarate (TDF). TM and TW without HIV, aged 15–24 years, were enrolled for 1 month of directly observed daily F/TDF. Participants were required to be receiving a stable hormone dose (estradiol or testosterone) for at least 1 month or three consecutive doses, whichever was longer, before enrollment and willing to continue the same dose. Intensive pharmacokinetic (PK) sampling for gender-affirming hormones was collected before and 2–3 weeks after daily F/TDF. Serum estradiol and total testosterone were determined by liquid chromatography–tandem mass spectrometry; free testosterone by equilibrium dialysis. Maximum concentrations (C_{max}) and area under the curve (AUC_{last}) were log-transformed and compared between baseline and on F/TDF using geometric mean ratios (GMRs) with 95% confidence intervals (CIs). Twenty-five TW and 24 TM were enrolled (median age: 20 and 21 years, respectively). In TW, estradiol C_{max} (GMR [95% CI]: 0.85 [0.65–1.11]) and AUC_{last} (GMR [95% CI]: 0.87 [0.73–1.03]) were comparable on F/TDF versus baseline. In TM, similar comparability was observed for PrEP versus baseline including total testosterone C_{max} (GMR [95% CI]: 0.91 [0.80–1.03]) and AUC_{last} (GMR [95% CI]: 0.91 [0.81–1.04]) and free testosterone C_{max} (GMR [95% CI]: 0.89 [0.74–1.07]) and AUC_{last} (GMR [95% CI]: 0.88 [0.74–1.03]). Estradiol and testosterone exposures in young TW and TM did not significantly differ on F/TDF versus baseline. These findings should reassure patients and providers that F/TDF can be used as PrEP without concern for altering gender-affirming hormone PK. ClinicalTrials.gov (NCT03652623).

Keywords: PrEP, transgender women, transgender men, estradiol, testosterone, GAHT

[1]Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Aurora, Colorado, USA.
[2]Department of Psychiatry, Stroger Hospital of Cook County, Chicago, Illinois, USA.
[3]Department of Medicine, Division of Endocrinology and Metabolism, University of California San Francisco, San Francisco, California, USA.
[4]Department of Medicine, University of California Los Angeles, Los Angeles, California, USA.
[5]Department of Adolescent Medicine, Children's Hospital of Colorado, Aurora, Colorado, USA.
[6]Department of Pediatric Infectious Diseases, University of Colorado–Anschutz Medical Campus, Aurora, Colorado, USA.

Introduction

Transgender women (TW) and transgender men (TM) are at an increased risk of HIV infection relative to the general population.[1] Despite this, they are often underrepresented in clinical trials for HIV pre-exposure prophylaxis (PrEP), with TM often being excluded or unrecognized, and TW being grouped along with cisgender men who have sex with men (MSM). For example, the iPrEx trial was a seminal clinical trial conducted to assess the prevention efficacy of emtricitabine (F, FTC)–tenofovir disoproxil fumarate (TDF) in MSM and TW without HIV.[2] The trial enrolled 2,499 participants in total, but only 339 (14%) were TW, and TM were excluded.[2,3]

One important component of gender-affirming care among transgender individuals is the use of exogenous hormone therapy, with the goal of developing secondary sex characteristics that are better aligned with their gender identity.[4,5] For TW, this typically includes exogenous estradiol [e.g., oral/sublingual (PO/SL), transdermal, or intramuscular (IM) estradiol] with or without an anti-androgen, such as spironolactone. In TM, gender-affirming hormone therapy typically consists of exogenous testosterone including IM, subcutaneous (SC), topical gel/cream, or testosterone patch. The lack of inclusion of transgender populations in clinical trials and corresponding lack of specific PrEP guidance for transgender populations has raised concerns that oral F/TDF as PrEP could affect gender-affirming hormone concentrations.[6] Although the pharmacology of these agents does not suggest a clear mechanism for such an interaction, it is important to adequately address these concerns to improve overall PrEP uptake.

Very few studies have assessed the potential for interaction between PrEP and gender-affirming hormones,[7–10] and data remain particularly limited among adolescents and TM. Some studies have focused on whether hormone use affects PrEP pharmacokinetics (PK), but not necessarily whether PrEP use affects hormone PK.[7,10–12] To our knowledge, two other studies have evaluated the effects of PrEP use on hormone PK.[8,9] Both of these studies focused specifically on adult TW, and neither found significant differences in estradiol concentrations with versus without concomitant PrEP use, which is reassuring for adult TW.

However, no similar studies to our knowledge have assessed for a potential interaction between testosterone and PrEP among TM, or specifically among adolescent and young adult transgender persons. This study used directly observed (DOT) daily F/TDF to determine the effects of estradiol and testosterone PK in adolescent and young adult TW and TM without HIV.

Patients and Methods

Study design

This was a prospective, observational, PK study conducted at the Children's Hospital Colorado, University of Colorado Anschutz Medical Campus (Aurora, CO) and the Stroger Hospital of Cook County (Chicago, IL). The study was approved by the Colorado Multiple Institution Review Board (COMIRB) and the Cook County Health Institutional Review Board. All participants provided written informed consent.

Study participants

Participants were eligible if they were between the ages of 15 and 24 years and self-identified as TW or TM. They were required to receive a stable hormone dose (estradiol with or without spironolactone in TW or testosterone in TM) for at least 1 month before enrollment, or three doses, whichever was longer, and willing to maintain that same dose throughout the study period. Based on the most commonly prescribed regimens, and to ensure consistency within groups, only PO/SL or IM estradiol routes of administration were permitted, and only SC or IM testosterone were permitted. Participants were excluded if they were recently hospitalized, exhibited a condition that interfered with their ability to comply with study procedures, had previously participated in a HIV vaccine trial, or had a contraindication to F/TDF.

Study procedures

Participants received 1 month of DOT F/TDF. Direct observation was conducted either in person or through time-stamped video using a secure smart phone application. Dose dates and times were then recorded by study personnel. Hormone dosing was not DOT, but dose dates and times at intensive sampling time points (below) were recorded, as well as all available additional dosing times during the study period.

At baseline, before beginning F/TDF, and again after 2–3 weeks of daily F/TDF dosing, serum estradiol (TW) or serum total and free testosterone (TM) were measured at prespecified time points based on hormone dosing schedule.

Table 1. Baseline Demographic and Clinical Characteristics of Study Population

	TW (N = *25*)	*TM* (N = *24*)
Age (years)	20.0 ± 2.5	20.3 ± 2.3
Weight (kg)	69.3 ± 12.1	68.5 ± 21.4
CrCl (mL/min)	136.3 ± 35.1	116.9 ± 48.4
Race/ethnicity, *n* (%)[a]		
White	18 (72)	20 (83.3)
Black	4 (16)	2 (8.3)
Asian	0 (0)	2 (8.3)
Hispanic	9 (39.1)	2 (8.3)
Other	4 (16)	3 (12.5)
Route of hormone administration, *n* (%)		
Oral/sublingual	13 (52)	—
Intramuscular	12 (48)	12 (50)
Subcutaneous	—	12 (50)
Hormone dosing frequency, *n* (%)		
Daily	13 (52)	—
Weekly	11 (44)	23 (95.8)
Biweekly	1 (4)	1 (4.2)
Spironolactone use, *n* (%)[b]	18 (72)	—

All values are given as mean ± SD or *n* (%). CrCl calculated using Schwartz equation for participants <18 years of age and Cockcroft–Gault for participants ≥18 years; actual bodyweight and sex at birth were used in this calculation.

[a]Participants may have identified as more than one race/ethnicity.

[b]There were eight TW receiving progesterone, one receiving finasteride, and one receiving leuprolide as part of their gender-affirming hormone therapy.

CrCl, creatinine clearance; SD, standard deviation; TM, transgender men; TW, transgender women.

Table 2. Estradiol Pharmacokinetics by Route of Administration in Transgender Women

	Route of estradiol	N	*Baseline GM [95% CI]*	*On F/TDF GM [95% CI]*	*On F/TDF versus baseline GMR [95% CI]*	p
AUC_{last} (h × pg/mL)	Oral/sublingual	13	1,531 [1,110–2,112]	1,434 [980–2,099]	0.94 [0.70–1.25]	.630
	Intramuscular	12	67,386 [46,530–97,588]	53,666 [36,979–77,883]	0.79 [0.63–1.01]	.056
C_{max} (pg/mL)	Oral/sublingual	13	191 [357–102]	161 [307–85]	0.85 [0.53–1.34]	.443
	Intramuscular	12	614 [443–852]	524 [346–793]	0.85 [0.61–1.18]	.308

AUC, area under the curve; CI, confidence interval; GM, geometric mean; GMR, geometric mean ratio; F/TDF, emtricitabine/tenofovir disoproxil fumarate.

Although sampling times varied by hormone dosing schedule, the same time points were used at baseline and on F/TDF for each individual participant. For daily PO hormone dosing, serum was collected at 0 (predose), 1, 2, 4, 6, 8, and 24-h postdose. For weekly IM or SC hormone dosing, serum was collected at 0 (predose), 1, 2, 4, and 7 days postdose. For biweekly IM or SC dosing, serum was collected at 0 (predose), 1, 2, 4, 7, and 14 days postdose. These are nominal times; actual times were recorded by study staff at the time of collection.

Blood was collected in serum separator tubes, which were allowed to clot in the upright position for 30 min, followed by centrifugation at 1,200 × *g* for 10 min at 4°C. Samples were then aliquoted and stored at −70°C until shipment to Brigham Research Assay Core Laboratory (BRAC; Mass General Brigham; Boston, MA) for analysis. Serum estradiol and testosterone were quantified using liquid chromatography–tandem mass spectrometry (LC-MS/MS), and free testosterone was measured by equilibrium dialysis followed by LC-MS/MS.

Analysis

Serum hormone exposures, measured as area under the curve (AUC_{last}), and maximum concentrations (C_{max}) were calculated at baseline and on PrEP for each participant using noncompartmental methods in Phoenix WinNonlin version 8.2.[13] If a trough concentration was missing (i.e., not collected or participant dosed before collection), the predose level was used in its place. AUC_{last} and C_{max} were then log-transformed and compared within participants on F/TDF versus baseline using geometric mean ratios (GMRs) and paired *t*-test.

Results

Twenty-six TW and 24 TM were enrolled and completed the study. One TW did not have serum samples collected during the intensive PK sampling time points, and was excluded from the analysis, leaving a total of 25 TW. Baseline clinical and demographic characteristics for these 49 participants are given in Table 1.

Serum estradiol in TW

Of the 25 TW, 13 received daily PO/SL estradiol, and 12 received IM estradiol, 11 weekly and 1 biweekly. At baseline, the geometric mean (GM; 95% confidence interval [CI]) estradiol AUC_{last} and C_{max} were 9,416 [4,115–21,546] h × pg/mL and 334 [221–507] pg/mL, respectively. After 2–3 weeks of daily F/TDF use, GM [95% CI] estradiol AUC_{last} and C_{max} were 8,160 [3,662–18,182] h × pg/mL and 284 [183–440] pg/mL, respectively. The corresponding GMRs [95% CI] were as follows: 0.87 [0.73–1.03]; $p = .106$ for AUC_{last} and 0.85 [0.65–1.11]; $p = .215$ for C_{max}. In subgroup analyses by route of estradiol administration, these differences remained nonsignificant ($p > .05$ for all comparisons; Table 2). However, there was a trend toward lower estradiol exposures on F/TDF versus baseline in those receiving IM estradiol (GMR [95% CI]: 0.79 [0.63–1.01]; $p = .056$).

Serum testosterone in TM

Of the 24 TM included, 12 each received IM and SC testosterone. There was only one participant receiving biweekly testosterone; all others dosed weekly.

Total testosterone GM [95% CI] AUC_{last} and C_{max} at baseline were 111,783 [96,490–129,501] h × ng/dL and 813 [708–933] ng/dL, respectively. With 2–3 weeks of daily PrEP use, total testosterone GM [95% CI] AUC_{last} and C_{max} were 102,038 [84,258–123,569] h × ng/dL and 739 [616–886] ng/dL, respectively. Corresponding GMRs [95% CI] were 0.91 [0.80–1.04]; $p = .148$) for AUC_{last} and 0.91 [0.80–1.03]; $p = .119$ for C_{max}. In subgroup analyses by route of testosterone administration, these differences remained nonsignificant ($p > .05$ for all comparisons; Table 3). The results for free testosterone followed total testosterone and are summarized in Table 4.

Table 3. Total Testosterone Pharmacokinetics by Route of Administration in Transgender Men

	Route of testosterone	N	*Baseline GM [95% CI]*	*On F/TDF GM [95% CI]*	*On F/TDF versus baseline GMR [95% CI]*	p
AUC_{last} (h × ng/dL)	Subcutaneous	12	108,892 [91,163–130,069]	105,887 [79,960–140,221]	0.97 [0.83–1.14]	.700
	Intramuscular	12	114,752 [88,028–149,589]	98,328 [72,430–133,487]	0.86 [0.69–1.07]	.147
C_{max} (ng/dL)	Subcutaneous	12	776 [650–927]	737 [573–948]	0.95 [0.81–1.11]	.493
	Intramuscular	12	851 [670–1,080]	740 [546–1,004]	0.87 [0.71–1.07]	.168

Table 4. Free Testosterone Pharmacokinetics by Route of Administration in Transgender Men

	Route of testosterone	N	*Baseline GM [95% CI]*	*On F/TDF GM [95% CI]*	*On F/TDF versus baseline GMR [95% CI]*	p
AUC_{last} (h × ng/dL)	Subcutaneous	12	3,596 [2,682–4,823]	3,416 [2,280–5,120]	0.95 [0.74–1.23]	.667
	Intramuscular	12	4,456 [3,640–5,454]	3,617 [2,668–4,904]	0.81 [0.64–1.04]	.086
C_{max} (ng/dL)	Subcutaneous	12	28 [21–37]	26 [18–37]	0.92 [0.69–1.23]	.558
	Intramuscular	12	35 [30–41]	30 [21–42]	0.85 [0.65–1.13]	.231

Discussion

In this prospective, observational, before–after PK study among adolescent and young adult transgender individuals, there were no significant differences in estradiol or testosterone PK with concomitant F/TDF. These observations are consistent with those reported in earlier studies among adult TW receiving oral F/TDF, and collectively should provide reassurance that F/TDF does not significantly impact gender-affirming hormone concentrations.[8,9]

Although nonsignificant, there were slightly lower estradiol and testosterone concentrations/exposures observed on F/TDF versus baseline, particularly for the parenteral routes of administration. It is unclear if these insignificant findings were by chance, or underlie a biological effect. Additional work is needed to elucidate the latter. Of importance, the hormone concentrations remained well within therapeutic ranges. According to the Endocrine Society Guidelines for the Treatment of Gender-Dysphoric/Gender-Incongruent Persons,[5] estradiol levels should be maintained between 100 and 200 pg/mL among TW, and testosterone levels should be maintained between 320 and 1,000 ng/dL among TM. The overall estradiol and testosterone maximum concentrations across all TW and TM while on F/TDF were 284 pg/mL and 739 ng/dL, respectively, well within or above these target ranges, suggesting that the small nonsignificant decreases were not clinically significant.

There are many strengths in this study, including its prospective design with DOT F/TDF dosing, and the ability to compare PK within subjects who were on the same hormone dose at both time points. However, there are also some limitations in that we only included PO/SL or IM estradiol with and without spironolactone and SC or IM testosterone. This was based on the preferred formulations at study sites, and to allow for stratification of results by route of administration. Because of this limitation, we are unable to assess whether serum hormone PK is affected among those on other formulations of estradiol (e.g., transdermal patches), testosterone (e.g., topical gels/creams), or anti-androgens. In addition, the majority of participants were white, which limits our ability to extrapolate these results to other populations including persons with HIV. Finally, the outcomes assessed in this study were limited to PK findings, and we did not evaluate pharmacodynamics of the gender-affirming hormones.

In conclusion, this study among adolescent and young adult transgender persons extended the findings of Shieh et al and Hiransuthikul et al among adult TW, showing no significant difference in serum estradiol with versus without concomitant F/TDF.[8,9] This study provides additional data in TM to support that, similar to estradiol in TW, testosterone PK was not significantly changed by F/TDF. Transgender persons and their providers should find reassurance in these findings, which support using daily oral F/TDF for PrEP in these populations without concern for significant alteration in PK of gender-affirming hormones.

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Author Disclosure Statement

J.Y. is an employee of Gilead Sciences and holds stock interest in the company. P.L.A. has received consulting fees from Gilead, ViiV, and Merck, and grants from Gilead Sciences, paid to his institution.

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Address correspondence to:
Peter L. Anderson
Department of Pharmaceutical Sciences
Skaggs School of Pharmacy
and Pharmaceutical Sciences
University of Colorado Anschutz
Medical Campus
12850 E Montview Blvd, Aurora
CO 80045 | Mail Stop C238
USA

E-mail: peter.anderson@cuanschutz.edu