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Authors

Grant, Robert M
Pellegrini, Marion
Defechereux, Patricia A
et al.

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Sex Hormone Therapy and Tenofovir Diphosphate Concentration in Dried Blood Spots: Primary Results of the Interactions Between Antiretrovirals And Transgender Hormones Study

Robert M. Grant,[1] Marion Pellegrini,[2] Patricia A. Defechereux,[1] Peter L. Anderson,[3] Michelle Yu,[1] David V. Glidden,[4] Joshua O'Neal,[2] Jenna Yager,[3] Shalender Bhasin,[5] Jae Sevelius,[1] and Madeline B. Deutsch[1]

[1]Department of Medicine, University of California–San Francisco, San Francisco, California, USA, [2]San Francisco AIDS Foundation, San Francisco, California, USA, [3]Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado-Anschutz Medical Campus, Aurora, Colorado, USA, [4]Department of Epidemiology and Biostatistics, University of California - San Francisco, San Francisco, California, USA, and [5]Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA

(See the Editorial Commentary by Krakower on pages e2124–6.)

Background. Sex hormone and preexposure prophylaxis (PrEP) drug interactions among transgender women (TGW), transgender men (TGM), and cisgender men (CGM) are not fully understood.

Methods. TGM and TGW on at least 6 months of stable sex hormone therapy containing testosterone or estradiol (respectively) were enrolled in a 4-week study of directly observed dosing of daily oral coformulated emtricitabine and tenofovir disoproxil fumarate (FTC/TDF). TFV-DP in dried blood spots and sex hormones in serum were measured at weekly intervals. TFV-DP was compared with 2- and 4-week samples from Directly Observed Therapy Dried Blood Spots (DOT-DBS) Study (NCT02022657).

Results. From May 2017 to June 2018, 24 TGM and 24 TGW were enrolled. Testosterone (total and free) and estradiol concentrations were comparable before and after 4 weeks of PrEP use in TGM and TGW, respectively. Historical controls included 17 cisgender women (CGW) and 15 CGM. TFV-DP concentrations at week 4 were comparable between TGW and TGM (mean difference, −6%; 95% confidence interval [CI], −21% to 12%; $P = .47$), comparable between TGW and CGM (mean difference, −12%; 95% CI, −27% to 7%; $P = .21$) and were lower among TGM compared with CGW (mean difference, −23%; 95% CI, −36% to −7%; $P = .007$). All persons in all groups were projected to reach the TFV-DP threshold that has been associated with high protection from human immunodeficiency virus.

Conclusions. CGM, TGM, and TGW had comparable TFV-DP concentrations in dried blood spots after 4 weeks of directly observed daily FTC/TDF PrEP use. Serum hormone concentrations were not affected by FTC/TDF PrEP use.

Clinical Trials Registration. NCT04050371.

Keywords. HIV; preexposure prophylaxis; transgender; sex hormones; pharmacokinetics.

Pre-exposure prophylaxis (PrEP) with oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) reduces the risk of human immunodeficiency virus (HIV) transmission by 91% in cisgender men who have sex with men when dosed appropriately [reviewed in [1, 2]]. Only 1 randomized trial, the Iniciativa *Profilaxis Preexposición* (iPrEx) trial (Preexposure prophylaxis initiative), included substantial numbers of transgender women (TGW), and no trial included transgender men (TGM) [3, 4]. The subgroup analysis of iPrEx revealed that TGW were less likely than men who have sex with men to have protective concentrations of PrEP medications in an intention-to-treat analysis, especially if they also reported using feminizing hormone therapy [5]. In a subsequent, more sophisticated transportability analysis, PrEP efficacy among TGW was comparable to efficacy among cisgender men (CGM) who have sex with men when adjusted for the following baseline factors: depression score (using Center for Epidemiologic Studies in Depression Scale [CESD]), number of partners in the previous 3 months, any condomless receptive anal intercourse in the previous 3 months, living situation, any history of transactional sex in the previous 6 months, and any sexually transmitted infection diagnoses in the previous 6 months [6].

Three small pharmacokinetic studies have raised concerns for FTC/TDF interactions with feminizing hormones. These studies suggest that the concurrent use of feminizing hormones may be

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Correspondence: R. M. Grant, 2330 Post Street, Ste 420, San Francisco, CA 94143 (robert.grant@ucsf.edu).

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associated with slightly lower tenofovir concentrations in blood plasma (by approximately 12%) and lower active tenofovir concentrations or tenofovir/natural substrate ratios in rectal cells [7–9]. The number of participants and effect sizes were small in these studies, and PrEP dosing was self-reported in 2 of 3 studies, calling for larger and better controlled pharmacokinetic studies in transgender populations. Studies are also needed that focus on TFV-DP in dried blood spots (DBSs) as this moiety consistently and strongly correlates with TFV exposure, adherence, and PrEP outcomes [4, 10–12]. PrEP research has not been conducted in TGM who use masculinizing hormones.

Tenofovir, emtricitabine, and sex hormones have different metabolic pathways, such that drug–drug interactions are not expected. Tenofovir disoproxil fumarate (TDF) did not affect ethinyl estradiol and 17-deacetyl norgestimate concentrations among 20 women receiving oral contraception over 7 days [13]. TDF-containing PrEP does not affect hormone contraceptive efficacy [14, 15], and progesterone contraception does not affect PrEP efficacy in cisgender women (CGW) [16].

This study was conducted using directly observed dosing of oral FTC/TDF among TGW and TGM not living with HIV on a stable feminizing regimen of estradiol or masculinizing regimen of testosterone to evaluate how such hormone therapy might affect concentrations of TFV-DP in DBSs.

METHODS

Population

TGW and TGM were eligible if they had been on a stable sex hormone therapy regimen that included estradiol or testosterone, respectively, for at least 6 months. Inclusion criteria included age >18 years, willing and able to receive video or in-person directly observed therapy for a 4-week period, no antiretroviral use for the previous 90 days, HIV antibody negative, and willing and able to provide written informed consent. Four weeks accounts for 75% of the accumulation of TFV-DP deemed sufficient to estimate PrEP drug pharmacokinetics. Risk factors for HIV were not required. Enrollment was capped at 24 for both TGW and TGM, sufficient to evaluate drug–drug interactions in each group. The University of California–San Francisco Institutional Review Board approved the protocol. The control populations were from the DOT-DBS Study, which included CGM and CGW receiving directly observed FTC/TDF dosing with specimens collected, processed, and stored as previously reported (NCT02022657) [17, 18].

Intervention

After a screening visit, participants started daily oral FTC/TDF PrEP with a directly observed therapy (DOT) at the enrollment visit. Blood was collected before the dose at enrollment and at weeks 1, 2, 3, and 4. Dosing was directly observed in person or by video on all days, including observation of placing the tablet in the mouth, the swallowing movement, and a check of the mouth for the tablet afterward. On days when a live video connection was not possible, a recorded video could be sent on the same day using a password for encryption that was provided earlier that day.

Measurements

DBSs were prepared, processed, frozen, and shipped to the Colorado Antiviral Pharmacology Laboratory as previously described [17, 19]. Intracellular TFV-DP and emtricitabine-triphosphate (FTC-TP) were quantified with a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay as previously described, with the exception of using a 50:50 methanol:water DBS extraction solution. This 50:50 methanol DBS extraction solution was developed and validated for optimized extraction recovery and improved precision. Because the initial analysis for DOT-DBS samples was done in 2014–2016, this optimized extraction was used to reanalyze DOT-DBS samples at the same time as the current Interactions Between Antiretrovirals And Transgender Hormones (iBrEATHe) samples. The new extraction led to a threshold of 800 fmol/punch for ≥4 doses/week from the DOT-DBS Study (rather than 700 fmol/punch from the previous assay, which is associated with high PrEP efficacy). The serum was frozen and shipped for batch analyses by LC-MS/MS for estradiol, estrone, and testosterone at Brigham Research Assay Core Laboratory at the Brigham and Women's Hospital (Boston, MA) [20, 21]; these assays have been certified by the Hormone Standardization Program of the Centers for Disease Control and Prevention. Sex hormone binding globulin was measured using an immuno-chemiluminescence assay [20, 21].

Symptoms relating to hormone level fluctuations were measured using the Menopausal Rating Scale (MRS), which has been previously used to describe symptoms associated with perimenopausal hormone level fluctuations and hormone treatment in cisgender women [22, 23]. Adverse events were recorded at every visit.

Statistical Analyses

We compared TFV-DP drug concentrations in trans- vs cisgender individuals after 4 weeks of PrEP use; the dataset of TFV-DP levels in cisgender controls was provided to us from the DOT-DBS Study [17, 18]. While 4 weeks is sufficient to estimate PrEP drug accumulation rates, information emerged after this study was designed that indicates that steady-state concentrations are achieved after 8 weeks. TFV-DP concentrations at steady state (CSS) at 8 weeks were projected using the following formula: $CSS = Cday/[1 - \exp(-0.04 \times day)]$ where day is the day at which the concentration is obtained. Comparisons of percent differences by groups used regression models of log-transformed TFV-DP controlling for creatinine clearance, weight, age, site of enrollment (San Francisco vs

Denver), and study arm (current intervention vs historical control). Comparisons of demographics between groups used the Fisher exact or Kruskal-Wallis test as appropriate. Correlations between hormone and TFV-DP concentrations were based on the Spearman rank correlation. Figures, including box plots, were created and regression models for this analysis were generated using STATA software.

RESULTS

Between June 2017 and June 2018, 51 people were screened and 48 were enrolled (Figure 1). Of these, 1 withdrew consent at week 2 (not due to an adverse event) and 47 completed all study visits. Among the enrolled cohort, 24 were TGM and 24 were TGW, and the median age was 31 years (interquartile range [IQR], 28 to 40; Table 1). Race/ethnicity (nonexclusive) was 27 (57%) white, 10 (21%) black, and 15 (32%) Latinx. In the week before enrollment, 24 (50%) reported using alcohol, 39 (81%) reported using caffeine, 17 (35%) reported using nicotine (including tobacco), and 27 (56%) reported using marijuana. There were no differences in these characteristics between TGM and TGW.

Among 24 TGW, all used estradiol including oral (20) or injected (4) routes. Oral progesterone was used by 3, oral medroxyprogesterone acetate by 1, and spironolactone (used as an antiandrogen) by 9. Among 24 TGM, testosterone included injected testosterone cypionate (18), injected testosterone enanthate (2), topical testosterone gel (2), and implanted testosterone pellets (1). Finasteride, an antiandrogen, was used by 3.

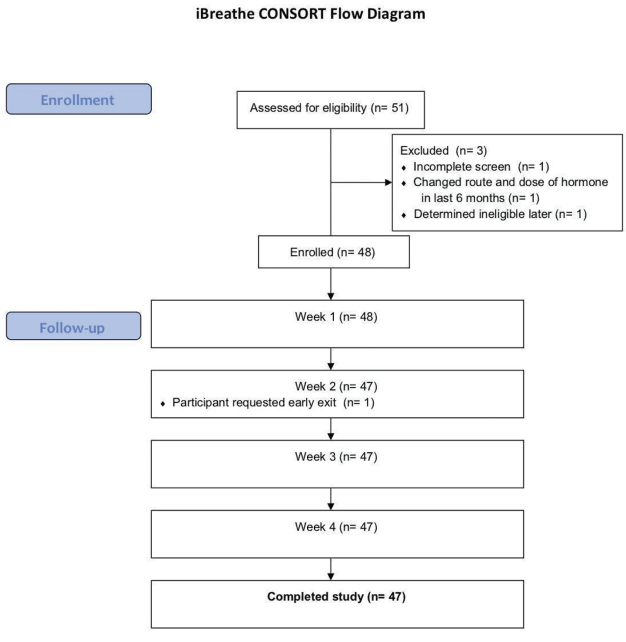

Figure 1. Interactions Between Antiretrovirals And Transgender Hormones Study (iBrEATHe) consort diagram. There were 24 transgender women and 24 transgender men enrolled in a stratified enrollment design.

TGM and TGW had similar weight (median, 74 kg; IQR, 67 to 91; $P = .45$), body mass index (BMI; median, 26; IQR, 23 to 30; $P = .28$). Serum creatinine was higher among TGM (median, 1.0 mg/dL vs 0.8 mg/dL; $P = .0001$), such that the estimated creatinine clearance (eCrCl) was lower among TGM compared with TGW ($P < .0001$) regardless of the estimating equation (Modification of Diet in Renal Disease vs Cockcroft-Gault) or whether sex at birth or current gender was used.

Among the 47 participants followed through 28 days of dosing, 1309 of 1316 (99.5%) PrEP doses were reported to have been taken. Of these, dosing was directly observed by video for 1271 (96.9%) and in person for 20 (1.5%). Nonobserved doses included 12 (0.9%) by text message, 2 (0.15%) by telephone, and 6 (0.5%) by patient report.

Serum estradiol concentrations were higher among TGW (Figure 2A), and serum testosterone concentrations were higher among TGM (Figure 2B; $P < .0001$, both comparisons) as expected based on self-reported exogenous use. Comparing visits on the day PrEP was started and on the day of completing 4 weeks of daily oral FTC/TDF, there were no differences in estradiol, estrone, total or free testosterone, dihydrotestosterone, or sex hormone binding globulin.

For the analysis of TFV-DP, comparison groups were 17 CGW and 15 CGM who had completed 4 weeks of directly observed daily FTC/TDF PrEP dosing. There were no differences in TFV-DP concentrations during the first 2 weeks of PrEP comparing TGW, TGM, and CGM ($P = .87$). The median fold increase in TFV-DP from week 2 to week 4 overall was 1.54 (IQR, 1.34–1.74) and was slightly higher among CGM at 1.63 (IQR, 1.55 vs 1.84; $P = .05$). TFV-DP concentrations at week 4 were comparable between TGW and CGM (Figure 3; mean difference, −12%; 95% CI, −27% to 7%; $P = .21$) and were lower among TGM compared with CGW (mean difference, −23%; 95% CI, −36% to −7%; $P = .007$). These comparisons were not substantially altered after adjusting for eCrCl, age, weight, spironolactone use, height, and BMI (comparing TGW with CGM: mean difference, −17%; 95% CI, −36% to 8; $P = .17$; comparing TGM with CGW: mean difference, −24%; 95% CI, −41% to −2%; $P = .04$). All persons in all groups were projected to reach steady-state TFV-DP >800 fmol/punch by 8 weeks, comparable to the 700 fmol/punch level using prior extraction methods reported to be highly protective in prior studies [4].

There was no association between serum estradiol concentration and TFV-DP among TGW ($P = .35$) or TGM ($P = .15$). Similarly, there was no association between total or free testosterone concentrations and TFV-DP among TGW ($P = .60$ and $P = .08$, respectively) and TGM ($P = .21$ and $P = .73$, respectively).

There were 23 treatment emergent adverse events reported among 18 participants, including 11 (46%) TGM and 7 (29%) TGW ($P = .4$). The most common complaints were nausea (10 events), diarrhea or soft stools (5 events), fatigue (4 events), and

Table 1. Demographic and Selected Characteristics, Overall and by Birth Sex and Gender

		Interactions Between Antiretrovirals And Transgender Hormones (iBrEATHEe) Study		Directly Observed Therapy Dried Blood Spots (DOT-DBS) Study		
	Overall	Transgender Men	Transgender Women	Cisgender Women	Cisgender Men	
	(n = 74)	(n = 23)	(n = 24)	(n = 17)	(n = 15)	
Characteristic	N	N	N	N	N	*P* Value[a]
Race/ethnicity						
White	46 (58%)	11 (48%)	16 (67%)	9 (53%)	10 (67%)	.5115
Black/African American	15 (19%)	6 (26%)	4 (17%)	4 (24%)	1 (7%)	.5067
Hispanic/Latino	23 (29%)	9 (39%)	6 (25%)	4 (24%)	4 (27%)	.6757
Age (y)[b]	30 (27–38)	34 (29–40)	29 (26–40)	30 (27–32)	28 (26–39)	.1738
Weight (kg)[b]	75 (66–94)	75 (65–85)	74 (68–100)	63 (59–94)	82 (76–102)	.0524
Height (cm)[b]	172 (163–177)	169 (164–172)	175 (175–181)	162 (158–164)	177 (170–183)	<.0001
Body mass index (kg/m^2)[b]	27 (23–30)	27 (24–30)	25 (22–30)	24 (22–33)	27 (24–30)	.6314
Serum creatinine (mg/dL)[b]	0.8 (0.8–1.0)	1.0 (0.9–1.0)	0.8 (0.7–0.9)	0.8 (0.7–0.8)	1.0 (0.8–1.0)	<.0001
Creatinine clearance (MDRD)[b]	89 (76–110)	71 (63–79)	116 (101–142)	96 (84–102)	88 (81–108)	<.0001
Creatinine clearance (CG) sex at birth[b]	119 (98–165)	95 (87–110)	165 (119–197)	116 (100–140)	135 (104–152)	<.0001
Creatinine clearance (CG) gender identity[b]	121 (103–155)	112 (103–129)	141 (101–168)	116 (100–140)	135 (104–152)	.3687

Abbreviations: CG, Cockcroft-Gault Equation; MDRD, Modified Diet in Renal Disease Study equation.

[a]Fisher exact *P* values for frequency data; Kruskal-Wallis *P* values for continuous variables.

[b]Median with interquartile range.

abdominal pain (3 events). The numbers of adverse events reported decreased over time (12 at week 1, 3 at week 2, 5 at week 3, and 3 at week 4). No one discontinued PrEP due to adverse events. No HIV acquisitions were detected.

There were no changes before and after PrEP use in hormone-related symptoms on the MRS. Question 10, which was related to vaginal dryness, was excluded from the analysis for TGW. The mean MRS score among 24 TGW was 5.5 (standard deviation [SD], 5.4) before PrEP and 5.9 (SD, 5.3) after PrEP ($P = .5$); among 22 TGM, the mean MRS score was 4.9 (SD, 3.4) before PrEP and 4.9 (SD, 4.1) after PrEP ($P = .7$). Vaginal dryness did not change before and after PrEP among TGM (score 0.3 before PrEP, 0.2 after PrEP; $P = .7$).

DISCUSSION

This drug–drug interaction study demonstrated that 4 weeks of directly observed daily oral use of FTC/TDF does not affect concentrations of estradiol or estrone in TGW or concentrations of free or total testosterone in TGM. No changes in hormone dosing were reported during the study. There were no clinical or self-reported signs of hormone withdrawal during the first 4 weeks of PrEP use.

TGW, TGM, and CGM had similar TFV-DP concentrations in DBSs at 2 and 4 weeks. As reported previously in the DOT-DBS Study, CGW had higher TFV-DP concentrations compared with CGM. This difference has not been explained and could reflect differences in drug transport and metabolism in red blood cells or differences in blood cell clearance. A limitation of this analysis was that the DOT-DBS samples were collected and stored 3–4 years before reanalysis concurrent with iBrEATHe analysis. However, the laboratory has demonstrated stability of TFV-DP measurement in samples stored at −80°C for >5 years (1835 days), so TFV-DP degradation is not expected in this 3- to 4-year time frame. Initially, the iBrEATHe samples were analyzed with the original extraction procedure in an attempt to match the initial analysis of DOT-DBS conducted 3–4 years prior. This approach could be biased by assay drift. To control for assay drift, we contemporaneously reanalyzed both the DOT-DBS and the iBrEATHe specimens with the new extraction procedure to allow the most rigorous comparison with minimal confounding.

These results support current recommendations for PrEP dosing using regimens that contain TDF [24]. Although men who have sex with men and TGW are different in multiple important respects, dosing recommendations are similar based on findings that trends in differences in efficacy in the intention-to-treat subgroup analyses did not reach statistical significance ($P = .09$), that the relationships between blood concentrations and protective benefits are similar, and that baseline characteristics explain trends in observed efficacy [5, 6]. These findings of comparable accumulation kinetics in these 2 groups support application of similar dosing recommendations across these groups. Our findings also suggest that previously observed lower concentrations of TFV-DP in DBSs among TGW in the iPrEx trial were due to less use of the medication, rather than differences in metabolism [4].

All participants in all populations were projected to achieve concentrations of >800 fmol/punch by week 8 (analogous to >700 fmol/punch for the original extraction procedure); this concentration was associated with high levels of protection

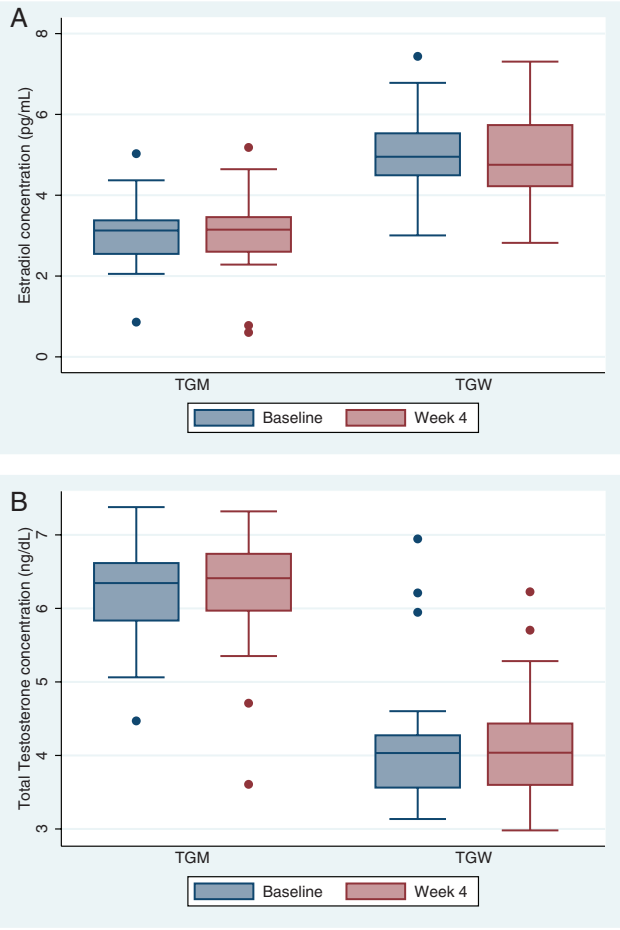

Figure 2. Box plots of hormone concentrations before and after emtricitabine and tenofovir disoproxil fumarate (FTC/TDF) preexposure prophylaxis dosing. Serum estradiol concentrations (*A*) and total testosterone concentrations (*B*) are depicted on a natural logarithmic scale before FTC/TDF dosing and after 4 weeks of directly observed daily dosing among TGM and TGW. The boxes represent median values and the interquartile range, and the whiskers represent the 95% confidence intervals; dots beyond the whiskers are outliers. There are no statistically significant differences. Abbreviations: TGM, transgender men; TGW, transgender women.

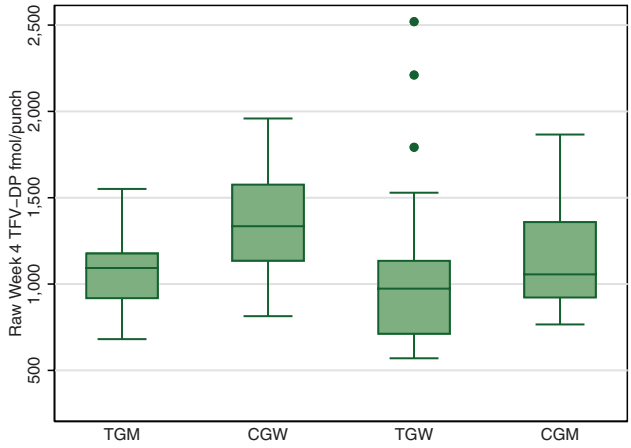

Figure 3. TFV-DP concentrations in dried blood spots after 4 weeks of directly observed daily dosing. The boxes represent median values and the interquartile range, and the whiskers represent the 95% confidence intervals; dots beyond the whiskers are outliers. Abbreviations: CGM, cisgender men; CGW, cisgender women; TFV-DP, tenofovir diphosphate; TGM, transgender men; TGW, transgender women.

from HIV acquisition [4]. Our findings comparing TFV-DP between TGW and CGM was −11% with a 95% CI of −27% to 10% ($P = .27$), indicating similar pharmacokinetics in TGW. A strength of our study was the use of DOT to control for bias in self-reported adherence and evaluation of TFV-DP in DBSs, a parameter that has been robustly associated with adherence and clinical outcomes. The results confirm that the effects of hormones are small and not expected to erode clinical protection from PrEP. A prior study could be confounded by biased reports of adherence [8]. Another study used DOT but did not adjust plasma drug concentrations for substantial differences in body weight (mean weight was 98 kg for TGW and 83 kg for CGM) [9]. The observed plasma concentrations in both of these studies among TGW were 2200–2500 hr × ng/mL (area under the curve), which is well within plasma tenofovir concentrations observed in regulatory pharmacokinetic studies (approximately 2000–3000 hr × ng/mL), further supporting the conclusion that pharmacokinetics are similar in TGW [13].

Messaging about PrEP efficacy has used correct and compelling qualitative terms, emphasizing that protection can be expected if PrEP is used as directed, and this message applies to all populations studied so far, including transgender people [25]. There are remarkably few cases of HIV infection that have occurred when PrEP is used as directed, and all have occurred among CGM who have sex with men [26–28]. Large cohorts of TGM and TGW taking PrEP have been and are being studied; HIV infections in these cohorts would be expected if PrEP were not highly effective [5, 29].

There are multiple limitations of this study. As described above, there was a difference of several years in the enrollment of historical control groups comprising cisgender men and women to compare with TGM and TGW. Additionally, cisgender participants were recruited from both Denver and San Francisco, while transgender participants were studied only in San Francisco. The control study had broader visit windows, although the actual date of the visit was used in the analysis. The 17-day half-life minimizes the effect of small differences in collection days. Recruitment patterns would necessarily differ between these populations. Specimen-handling protocols were identical, although different study sites and staff were used. Importantly, a DBS is not a target tissue for HIV replication or transmission. A DBS is a convenient specimen for monitoring long-term exposure and adherence, and this study confirms similar relationships between FTC/TDF PrEP use and DBS drug concentrations over the first 4 weeks among TGW, TGM, and CGM. However, the relationships between TFV-DP concentrations in DBSs and HIV acquisition risk are most confidently known for CGM. The tissues that are most relevant for HIV transmission are CD4-bearing cells in the rectal and

genital mucosa and lymphatics, and concentrations of FTC-TP and TFV-DP in these tissues were not studied [30]. Two small studies found no statistical difference in rectal tissue TFV-DP among TGW vs CGM ($P = .53$), although 1 study reported a lower TFV-DP:dATP (natural substrate) in TGW [7, 9]. Finally, drug accumulation did not reach steady state in this 4-week study, so steady-state projections were estimated. The MRS has not been validated for use among transgender populations. The results of this study may not apply to tenofovir alafenamide, a different formulation of tenofovir that has different pharmacokinetics in tissues [31].

FTC/TDF PrEP was demonstrated to be safe and effective in an ambitious and diverse phase 3 program [1, 2]. The trials involved nearly 20 000 men and women in Asia, Africa, South America, Europe, and the United States. Subgroup analysis and meta-analysis found that the only significant mitigator of efficacy was adherence; age, sex at birth, current gender, hormone use, condom use, concomitant sexually transmitted infections, and other factors did not significantly interact with PrEP efficacy once adherence was controlled [1, 5]. Pharmacokinetic studies should use directly observed therapy given that self-reported adherence is highly affected by social desirability bias, and such biases differ by setting and population. Given that HIV acquisition during PrEP use is rare, assurance of nearly complete clinical protection among transgender populations calls for active surveillance in large samples.

Notes

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Potential conflicts of interest. P. L. A. has received grants and consulting fees from Gilead Sciences. R. M. G. and P. L. A. have led studies in which Gilead Sciences donated the study drug. D. V. G. has received consulting fees from Gilead Sciences and Merck and Company. S. B. reports grants from AbbVie, FPT LCC, Transition Therapeutics, Alivegen, and MIB LLC; travel expenses and speaker fees from AbbVie; consulting fees from OPKO; has equity interest in FTP LLC; and is co-holder of a patent on calculating free testosterone outside the submitted work. R. M. G. reports grants to the institution from Gilead Sciences outside the submitted work. P. L. A. reports grants and personal fees from Gilead Sciences outside the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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