Title
HIV pre-exposure prophylaxis in transgender women: a subgroup analysis of the iPrEx trial

Journal
The Lancet HIV, 2(12)

ISSN
2405-4704

Authors
Deutsch, Madeline B
Glidden, David V
Sevelius, Jae
et al.

Publication Date
2015-12-01

DOI
10.1016/s2352-3018(15)00206-4

Peer reviewed

HHS Public Access

Author manuscript

Lancet HIV. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

Lancet HIV. 2015 December ; 2(12): e512–e519. doi:10.1016/S2352-3018(15)00206-4.

HIV pre-exposure prophylaxis in transgender women: A subgroup analysis of the iPrEx trial

Madeline B. Deutsch, MD[1], **Prof. David V. Glidden, PhD**[1], **Jae Sevelius, PhD**[1], **Joanne Keatley, MSW**[1], **Vanessa McMahan, MS**[2], **Juan Guanira, MD**[3], **Esper G. Kallas, MD**[4], **Prof. Suwat Chariyalertsak, MD**[5], and **Prof. Robert M. Grant, MD**[1,2,6] **For the iPrEx Study Team**

[1]University of California, San Francisco, USA [2]Gladstone Institutes, San Francisco, USA [3]INMENSA, Lima, Peru [4]University of Sao Paulo, Sao Paulo, Brazil [5]RIHES, University of Chiang Mai, Chiang Mai, Thailand [6]San Francisco AIDS Foundation, San Francisco, USA

Summary

Background—Oral emtricitabine-tenofovir disoproxil fumarate (FTC/TDF) pre-exposure prophylaxis (PrEP) is used to prevent the sexual acquisition of HIV. Transgender women (TGW) have unique characteristics that may relate to PrEP use, effectiveness, and safety.

Methods—The iPrEx trial was a randomized controlled trial (RCT) of oral FTC/TDF PrEP *versus* placebo among men who have sex with men (MSM) and TGW, followed by an open label extension (OLE). Drug concentrations were measured in blood by liquid chromatography and tandem mass spectroscopy.

Findings—Of the 2499 participants enrolled in the RCT, 29 (1%) identified as women, 296 (12%) identified as “trans”, 14 (1%) identified as men but reported use of feminizing hormones, such that 339 (14%) reported one or more of these characteristics (TGW). Compared with MSM, TGW more frequently reported transactional sex, receptive anal intercourse without a condom, or more than 5 partners in the past 3 months. Among TGW, there were 11 HIV infections in the active arm and 10 in the placebo arm, representing a hazard ratio of 1.1 (95% CI: 0.5 to 2.7). Among active arm participants, drug was detected in none of the TGW at the seroconversion visit, 18% (6/37) of seronegative TGW (P=0.31), and 52% (58/111) of seronegative MSM (P < 0.0001).

Corresponding Author: Robert M Grant, MD, Gladstone / UCSF, 1650 Owens Street, San Francisco, CA 94158, Robert.Grant@ucsf.edu, Tel: 415-350-8909. Alternate Corresponding Author: Madeline B. Deutsch, University of California, San Francisco, 2356 Sutter Street, 4th Floor, San Francisco, CA 94115, Madeline.Deutsch@ucsf.edu, Tel: 415-797-7136.

Contributors. MBD created the first draft of the manuscript, revised by RMG and JS. DG performed the statistical analysis. JG, SC, EGK led study sites that collected the data. VM coordinated both phases of iPrEx. All authors critically reviewed and contributed to the final manuscript.

Declaration of Interests: The iPrEx study was sponsored by the US National Institutes of Health with cofunding from the Bill and Melinda Gates Foundation; study medication was donated by Gilead Sciences, which also supported travel expenses for non-US investigators to attend study meetings. RMG has received a consulting fee and a research grant from ViiV, a manufacturer of an investigational compound being investigated for use as PrEP.

PrEP use was not linked to behavioral indicators of HIV risk among TGW, while MSM at highest risk were more adherent.

Interpretation—There were no HIV infections among TGW having drug concentrations commensurate with use of 4 or more FTC/TDF tablets per week. TGW receiving PrEP had low drug concentrations, especially at times of potential HIV exposure, leading to no PrEP effectiveness among this subgroup.

Funding—U.S. National Institutes of Health and the Bill and Melinda Gates Foundation; study medication was donated by Gilead Sciences.

Introduction

Transgender refers to a person whose gender identity differs from their assigned birth sex (1). While regional and national data on transgender populations are not available, a recent statewide Massachusetts telephone survey found that 0.5% of respondents identified as transgender (2). Due to incomplete or inconsistent collection of gender identity data (such as birth sex and current gender identity), transgender people's participation in research is frequently obscured (3, 4).

The prevalence of human immunodeficiency (HIV) infection is high in transgender communities (5); A 2008 meta-analysis of 22 U.S. regional studies (that did report HIV infection rates for TGW) found an HIV infection prevalence of 27.7% based on laboratory confirmation, and 11.8% based on self-report (6). In 2011, the US Centers for Disease Control (CDC) reported that TGW have the highest HIV-1 incidence (incidence of 2.1%, compared to 1.2% among non-transgender men and 0.4% among non-transgender women) (7). A 2013 meta-analysis of data from 15 countries found an estimated HIV prevalence of 19.1% among transgender women, with an odds ratio of 49 in comparison to the general adult population (5).

Transgender women frequently face structural barriers, including inadequate legal protections against discrimination, and resulting insecurities in income, food, and housing, that contribute to the disproportionate burden of HIV among TGW (8, 9). TGW have had limited engagement in PrEP research that has been primarily focused on MSM (10). Research and services adapted for transgender populations includes staff training and procedures for ensuring gender affirmation and provision of gender affirming hormone therapy.

There are no evidence-based HIV prevention interventions designed specifically for TGW. PrEP acceptability studies among MSM and TGW have typically included few TGW, with no consideration for the sociocultural (and perhaps anatomical) differences between these two dissimilar communities (11, 12). Guidelines may assume similar practices and efficacies in MSM and transgender populations. For example, World Health Organization (WHO) guidelines provide no specific considerations for the provision of PrEP to TGW (13). United States Centers for Disease Control (CDC) guidelines for PrEP implementation make no mention of TGW (14). PrEP demonstration projects to date have reported low or unclear levels of enrollment of TGW (15).

This report describes the subgroup of TGW in iPrEx with respect to PrEP efficacy, effectiveness, PrEP drug concentrations, and patterns of adherence in the TGW subgroup.

Methods

Study Design

The iPrEx trial was a randomized, double-blind, placebo-controlled Phase III clinical trial of oral emtricitabine/tenofovir disoproxil fumarate for HIV prevention of once daily oral FTC/TDF PrEP conducted between 2007 and 2011 in Brazil, Ecuador, Peru, South Africa, Thailand, and the United States (16). The randomized clinical trial (RCT) was followed by an open label extension (OLE) between 2011 and 2013 (17).

Participants

Inclusion and exclusion criteria for the iPrEx trial have been reported in detail previously (16). People assigned male sex at birth were eligible for the iPrEx study, regardless of their current gender identity. Current gender identity was self-reported using a computer assisted self-interview (CASI), which asked whether the participant currently identified as a man or a woman (trans was not given as an option). A second CASI question asked “How do you identify yourself?” and included “trans” and “woman” among other options in a “check all that apply” format. The word “travesti” was used in Ecuador as the word “trans” was not in common use. Use of feminizing hormones, including the use of hormones obtained without a prescription, was assessed and recorded as concomitant medications at every visit by medical history, and was coded using the Uppsala Monitoring Centre WHO Drug Dictionary Enhanced (Sweden). Information about gender affirming surgeries was extracted from the medical record. Feminizing hormones were defined as any estrogen, progestagen, or anti-androgen. Finasteride was not included as a TGW-defining characteristic, as this medication was primarily used for androgenic alopecia rather than feminization. Except as noted, the “TGW” subgroup is defined as participants who were assigned male sex at birth and who currently identify as women (regardless of trans identification), or who identified as trans (regardless of self-reported gender), or who used feminizing hormones (regardless of reported gender or trans status). In analyses stratified by feminizing hormone use, and in the analysis of PrEP drug detection by sexual HIV risk, we refer to trans/women (vs MSM) based only on reported gender identity regardless of hormone use.

Outcomes

Testing for emtricitabine and tenofovir and their active metabolites was performed by liquid chromatography and tandem mass spectroscopy as previously described.(17, 18) All available plasma and peripheral blood mononuclear cells (PBMC) in iPrEx RCT and OLE were tested in the active arm seroconverters as well as controls who remained seronegative. Testing of drug in iPrEx OLE additionally measured active drug metabolites in dried blood spots (DBS).(17, 19)

Procedures

Enrolled participants were followed for HIV seroconversion and adverse events at weeks 4, 8, 12, and every 12 weeks thereafter in the RCT and OLE. There was an additional

scheduled visit at week 16 in the RCT. DBS was collected only in OLE. Hormone therapy was not provided to study participants by any of the study sites.

Randomisation and Masking—During the iPrEx RCT, enrolled participants were randomly assigned 1:1 to daily oral FTC/TDF vs a matching placebo in randomized blocks of 20. During iPrEx OLE, all eligible participants were offered oral FTC/TDF PrEP and were followed for HIV seroconversion regardless of PrEP uptake.

Statistical Analysis

A separate analysis of MSM and TGW was not planned. Testing of pharmacology specimens in the RCT was conducted among participants randomized to FTC/TDF who became HIV+ during the study (cases) who were each matched (by site and week in the study) to HIV− participant (controls). Testing of specimens in OLE used a case-cohort design (20) which tested all available specimens longitudinal in patients electing to take PrEP who became HIV+ (cases) and a randomly selected (stratified by site) HIV− cohort. Using the case-cohort, the probability of selection for testing was known by the design of our case cohort study. The reciprocal of the probability of selection was incorporated as a probability weight in the OLE analyses of the risk HIV acquisition by drug level using Poisson regression which permits estimation of average rates, estimated person years and rate ratios. Analyses comparing the relative rate of HIV by levels of TFV-DP (Figure 2 and Table 3) in MSM and TG participants adjusted for potential confounders of the association of TFV-DP with HIV acquisition: report of non-condom receptive anal intercourse, age, number of partners and diagnosis of syphilis.

Comparison of HIV acquisition between FTC/TDF and placebo for HIV infection in the RCT used a stratified (by site) Cox proportional hazards model. The proportional hazards assumption was verified by Schoenfeld test. The p-value for the Schoenfeld test of proportional hazard was P=0.45, suggesting the proportional hazard assumptions was approximately satisfied. Comparisons in bone mineral density and creatinine values used the t-test with unequal variances. Normal quantile plots suggested the normal assumptions were approximately satisfied. Very similar results were obtained using the Mann-Whitney U-test. Comparison of proportions between groups were adjusted for study site by logistic regression with the relevant group and study site as the factors in the logistic regression otherwise specified. Logistic regression model fits were verified by the methods of Hosmer and Lemeshow. All p-values were two sided.

Role of the Funding Source

As sponsor the iPrEx RCT and OLE, the NIH reviewed and approved the study protocol and study manuals. The Bill and Melinda Gates Foundation and Gilead Sciences had no role in protocol development or the interpretation of results. The sponsor and funders of the study had no role in data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In the RCT, among 2,499 enrolled participants across all 11 sites, 296 (12%) participants identified as transgender and 29 (1%) participants identified as a woman. An additional 14 (1%) male-identified participants reported exogenous female hormone use of some kind. The total number of participants from each of these three categories aggregated into the TGW group was 339 (14%). The distribution of TGW participants as well as sub-identities within this group did not differ between the intervention and placebo arms. Study sites in the Andes and Thailand recruited a larger proportion of TGW, and the majority of TGW overall in the study (Table 1).

In the iPrEx RCT, use of feminizing hormones was reported by 67/339 (20%) of TGW; 48 of 296 (16%) trans-identified participants, 5 of 29 (17%) women participants, and 14/2160 (0.6%) of participants who did not identify as either trans or women. Among 163 feminizing regimens reported by 67 participants, 60 (37%) contained synthetic estrogens, 58 (35%) contained natural estrogens, 121 (74%) contained progestogens, and 38 (23%) contained antiandrogens, either alone or in combination with other hormones.

There were multiple demographic and behavioral differences between TGW and MSM (Table 2). TGW were younger (p=0.010) on average, although there was no difference in age after controlling for study site (P=0.43). TGW had less schooling (p<0.0001), more sexual partners (p<0.0001), less condom use for receptive anal sex (p<0.0001), more reported STIs (p<0.0001), more cocaine or methamphetamines use (p<0.0001), and were more likely to live alone (p<0.0001) and have a history of transactional sex (p<0.0001).

In iPrEx OLE, 192 TGW enrolled and were eligible for PrEP, of whom 151 (79%) chose to take PrEP for at least part of the study period; PrEP uptake was 76% (1074/1409) among MSM and was comparable to TGW (p=0.96).

Among seronegative participants in iPrEx OLE receiving PrEP, TGW had lower PrEP drug concentrations compared with MSM overall, regardless of hormone use as reported previously (17). TGW had less time with protective drug concentrations compared with MSM (33/200 person years or 17% vs 464/1332 person years or 35%, P < 0.0001, Table 3), while having comparable time with any drug detected (142/200 person years or 71% vs 1006/1332 person years or 76%, P=0.17, Table 3), especially at week 4 after starting PrEP (93% [33/35] vs 93% [251/274], P=0.99, Fig 1a).

Among participants not reporting feminizing hormone use, a similar proportion of trans/women and MSM had drug detected at any concentration over time (OR = 1.27, 95% CI = 0.83 to 1.93, p = 0.29) while also in this group of non-hormone users there was a trend toward lower proportions of trans/women having protective drug concentrations indicating use of 4+ tablets per week (OR = 0.71, 95% CI = 0.49 to 1.03, p=0.07). Trans/women who reported use of feminizing hormones were less likely to have any drug detected (Fig. 1a) or protective drug concentrations (Fig. 1b) compared with trans/women not using hormones (OR = 0.32, 95% CI = 0.16 to 0.66, p = 0.002 for any drug detection; OR = 0.14, 95% CI 0.05 to 0.41, p < 0.0001 for protective concentrations) and compared with MSM who were not using hormones (OR = 0.41, 95% CI = 0.23 to 0.74, p =0.003, for any drug detection;

OR = 0.10, 95% CI 0.04 to 0.28, p < 0.0001, for protective concentrations). There were no differences in drug concentrations comparing trans/women using synthetic estrogens versus trans/women using natural estrogens (P=0.74). None of the trans/women using progestogens were included in the cohort selected for drug concentration analysis.

In the RCT, compared with MSM of any hormone status, PrEP drug testing among trans/women (regardless of hormone use) revealed less consistent PrEP use (always vs less than always, OR=0.39, 95% CI 0.16 to 0.96, P=0.04, Fig. 3). Among all MSM regardless of hormone use, those who reported non-condom receptive anal intercourse were more likely to use PrEP compared with those who reported consistent condom use or no anal intercourse (never vs any, OR=2.5, 95% CI 1.4 to 4.2, P < 0.0005), while trans and women of any hormone status reporting this risk factor tended to be less likely to use PrEP (never vs any, OR = 0.38, 95% CI 0.04 to 3.6, P= 0.40). There was a trend toward an interaction between gender in the relationship between risk and PrEP use (P=0.12).

In the modified intention-to-treat analysis of the RCT (excluding only participants who were already HIV infected when they started PrEP), 11 TGW participants in the intervention group seroconverted as compared to 10 in the placebo group (HR 1.1, 95% CI 0.5 to 2.7; p=0.77 for effectiveness in TGW). This hazard ratio among TGW tended to be higher, reflecting lower effectiveness, than was observed among MSM (HR 0.50, 95% 0.34 to 0.75; P=0.001 for effectiveness in MSM; p=0.09 for the difference in PrEP effectiveness between TGW and MSM. Two TGW seroconverted after receiving PrEP in iPrEx OLE, and one in the group that elected not to use PrEP.

Among TGW seroconverterters in iPrEx RCT, none (0 of 11) had drug detected in blood plasma or PBMC at the time of infection, compared with 6 of 33 (18%) of seronegative TGW (p=0.31). Among TGW, the HIV incidence was 0 (95% CI not calculable) if drug was detected, and 4.9/100py (95% CI 3.0 to 7.7) if drug was not detected. Among MSM, the HIV incidence was 0.4/100PY (95% CI 0 to 0.8) if drug was detected, and 2.8/100py (95% CI 1.8 to 3.7) if drug was not detected.

Among TGW seroconverters in iPrEx OLE, one had DBS levels below the limits of quantitation and 1 had drug concentrations that indicated average use of fewer than 2 PrEP tablets per week. The relationship between drug concentration in DBS and HIV incidence was comparable among MSM and TGW (Table 3, Figure 2). As with MSM, there were no HIV infections among TGW having drug concentrations commensurate with use of 4 or more tablets per week (HR 0, 95% CI 0 to 10.1). Drug concentrations commensurate with use of 2 to 3 tablets per week were present in 12% (24/200 py) of follow-up of TGW, and there were no infections that group as well (HR 0, 95% CI 0 to 13.0).

Among TGW, moderate and severe adverse events (AEs) were rare, and there was no difference comparing the active and placebo arms (31 *vs.* 28 events, P=0.73). There were 2 deaths among TGW: one in the placebo arm was due to homicide and another in the active arm was due to acute liver failure probably due to lymphoma that occurred after at least 336 days of no detectable PrEP drugs in blood plasma or PBMC. There was a non-significant mean difference from baseline in estimated creatinine clearance at week 24 of −1.0 ml/min

(95% CI: −3.8 to +1.8, P=0.48) in the active arm, which was similar to differences in MSM. (21) Bone mineral density (BMD) at the hip changed +0.5% (95% CI: −0.5 to +1.5 from baseline in TGW at week 24, compared with −0.4% (95% CI: −0.7 to −0.2) among MSM (P=0.08 for the difference between MSM and TGW), and at the spine, BMD changed +0.3 (95% CI: −0.8 to +1.3) from baseline in TGW and −0.7% (95% CI: −0.3 to −1.2) among MSM (P=0.08 for the difference between MSM and TGW). Liver function abnormalities occurred at comparable rates in the active *versus* the placebo arms among TGW (4 [6/170] vs. 3% [5/169], P=0.90).

Discussion

PrEP use in transgender populations is protective in the setting of drug adherence; none of the TGW who became infected in the RCT had detectable drug at the time of seroconversion in the randomized phase. Furthermore, quantitative analysis of long-term drug exposure, afforded by use of DBS in iPrEx OLE, revealed that seroconversion occurred only among TGW having drug concentrations commensurate with using less than 2 tablets of FTC/TDF per week on average. The lack of protection appears to be due primarily to low adherence leading to low drug exposure, as measured by drug concentrations.

To be effective, medications used for PrEP must be at a protective concentration at the time of exposure to HIV infection. TGW in iPrEx who reported sexual practices conferring the highest risk of HIV infection tended to be less likely to have PrEP drug detected in blood (Fig. 3). This is of particular concern given that TGW reported greater overall exposure to HIV (more partners, less condom use, more sexually transmitted infections) and had lower overall adherence. In contrast, the positive associations observed between PrEP adherence and indicators of sexual risk among MSM likely account for why PrEP effectiveness was commensurate with drug exposure in that group.

Considerations unique to TGW could undermine PrEP use (22). The lack of PrEP effectiveness on an intention-to-treat basis among TGW, and low levels of PrEP drug exposure, are similar to findings from two PrEP trials in non-transgender women that showed no effectiveness and very low levels of PrEP drug exposure (23, 24). These trials also found a negative association between behavioral factors associated with HIV incidence and detection of drug levels (24, 25), as we have found for TGW. Linkage between HIV exposure and PrEP use is important for PrEP impact, and could have contributed to the effectiveness of PrEP among MSM despite moderate PrEP use observed here.

There were lower TDF-DP concentrations in DBS among TGW using feminizing hormones compared with other TGW. This may reflect less PrEP adherence among TGW whose concerns about drug-drug interactions that were not fully addressed during the trial. FTC and TDF are cleared in the kidney while estrogens and progestogens are metabolized in the liver, so no systemic drug-drug interactions are expected. TDF has been found to have no interactions with a coformulated oral contraceptive (OCP) consisting of ethinyl estradiol and norgestimate (27), and PrEP use does not appear to diminish contraceptive efficacy of hormonal medications (28). Furthermore, oral TDF or FTC/TDF PrEP efficacy has been shown to not be diminished by depot medroxyprogesterone acetate (29). Analysis by

progestogen use was not performed in the current study as none of the subjects who reported only progestogen use (without estrogens) had DBS levels obtained.

No pharmacological interaction studies have been done in TGW using both PrEP and gender affirming feminizing hormones, which differ from contraceptives in several respects. For example, in order to achieve consistent ovulation suppression oral contraceptives contain the synthetic estrogen ethinyl estradiol, while most recommended regimens for feminization utilize 17-beta estradiol (30). Potent anti-androgens, such as spironolactone, may be included in feminizing hormone therapy but is not used in contraceptives. Future study of potential interactions between PrEP and feminizing hormone regimensshould include drug transporters that are affected by both nucleoside analogues and female sex hormones and could affect PrEP drug concentrations in cells infected by HIV (31, 32).

Interactions between exogenous female sex hormones and HIV susceptibility are also important for PrEP protection, which can be overcome if viral exposure efficiently leads to transmission during gaps in PrEP use. While estrogens preserve pelvic tissues, including anal epithelium, and reduce viral susceptibility in an animal model (reviewed in(33)), medroxyprogesterone acetate may decrease vaginal thickness and increase HIV susceptibility in non-transgender women (34). How this effect translates to the anal epithelium is unknown. To the extent that feminizing hormone regimens typically utilize estrogens in place of or in addition to progestogens, these hormonal effects might decrease HIV susceptibility overall.

TGW often prioritize hormone use over other health concerns, and some HIV-positive TGW report hesitance to use antiretroviral medications out of a fear of negative interactions between PrEP and hormones (35, 36). Information about drug-drug interactions was not provided routinely to TGW in this study, as little information was available and no such interactions were predicted. PrEP programs aimed at TGW should include education strategies on what is known about the coadministration of these two treatments. Monitoring the clinical outcomes of feminizing hormone therapy within PrEP services would provide additional assurance and information to TGW using PrEP. As has been seen in the arena of HIV treatment, negative experiences with clinics and providers unsupportive of transgender identities or not fluent in transgender culture (either in the past or in a current PrEP program) may make transgender women less likely to engage in PrEP programs or use PrEP when provided.(22, 37)

The primary limitation of this subgroup analysis is that the study was not designed to detect differences in effectiveness among TGW and MSM, or to confirm efficacy in either subgroup. The other primary limitation arises from difficulties encountered in identifying TGW. This challenge was compounded by reliance on hormone use data collected by self-report, and by the inclusion of participants defined by a range of terminology, languages and cultures spanning four continents. While best practices for collection of gender identity have been described for populations in the United States (4), future study of global populations should engage local communities to inform gender identity collection methods to be used in each cultural and linguistic setting. This study identified multiple differences between MSM and TGW and sexual practices and PrEP use; there may be unmeasured or unknown factors

that explain these differences. Retention in iPrEx was comparably high among TGW and MSM (84% and 85% respectively), and the main risk factor for HIV acquisition in both groups was receptive anal intercourse without a condom.

PrEP is a proven method of HIV prevention that is controlled by the receptive partner, whether a non-transgender woman, a receptive MSM, or a receptive TGW. Best practices for PrEP services among TGW could arise from gender-affirming clinical settings that integrate PrEP with hormone therapy and other sexual health services. Studies of PrEP use in TGW populations should be designed and tailored specifically for this population, rather than adapted from or subsumed into studies of MSM.

Acknowledgments

We thank study participants for trusting that the research could improve the lives of their communities. The iPrEx study team includes Robert M. Grant, Juan Guanira, Javier Lama, Mauro Schechter, Esper G. Kallas, Valdilea Veloso, Suwat Chariyalertsak, Linda-Gail Bekker, Kenneth Mayer, Susan Buchbinder, Albert Liu, Orlando Montoya, Rivet Amico, Kim Koester, Kathy Mulligan, Martin Casapia and David Glidden. We thank John Carroll for preparation of graphics.

References Cited

1. Kuba, S. Sexually and gender-variant individuals: International and multicultural perspectives. In: Lowman, RL., editor. Internationalizing multiculturalism : expanding professional competencies in a globalized world. 1. Washington, D.C: American Psychological Association; 2013. p. 109-42.
2. Conron KJ, Scott G, Stowell GS, Landers SJ. Transgender health in Massachusetts: results from a household probability sample of adults. Am J Public Health. 2012 Jan; 102(1):118–22. [PubMed: 22095354]
3. Deutsch MB, Keatley J, Sevelius J, Shade SB. Collection of gender identity data using electronic medical records: survey of current end-user practices. J Assoc Nurses AIDS Care. 2014 Nov-Dec; 25(6):657–63. [PubMed: 24880490]
4. Cahill S, Makadon H. Sexual Orientation and Gender Identity Data Collection Update: U.S. Government Takes Steps to Promote Sexual Orientation and Gender Identity Data Collection Through Meaningful Use Guidelines. LGBT Health. 2014; 1(3):157–60. [PubMed: 26789707]
5. Baral SD, Poteat T, Stromdahl S, Wirtz AL, Guadamuz TE, Beyrer C. Worldwide burden of HIV in transgender women: a systematic review and meta-analysis. Lancet Infect Dis. 2013 Mar; 13(3): 214–22. [PubMed: 23260128]
6. Herbst JH, Jacobs ED, Finlayson TJ, McKleroy VS, Neumann MS, Crepaz N, et al. Estimating HIV prevalence and risk behaviors of transgender persons in the United States: a systematic review. AIDS Behav. 2008 Jan; 12(1):1–17. [PubMed: 17694429]
7. Centers for Disease Control and Prevention. HIV Surveillance Report. 2011; 23 [Accessed March 29, 2015] http://www.cdc.gov/hiv/topics/surveillance/resources/reports/. Published February 2013.
8. Operario D, Nemoto T. HIV in transgender communities: syndemic dynamics and a need for multicomponent interventions. J Acquir Immune Defic Syndr. 2010 Dec; 55(Suppl 2):S91–3. [PubMed: 21406995]
9. Poteat T, Wirtz AL, Radix A, Borquez A, Silva-Santisteban A, Deutsch MB, et al. HIV risk and preventive interventions in transgender women sex workers. Lancet. 2015 Jan 17; 385(9964):274–86. [PubMed: 25059941]
10. Escudero DJ, Kerr T, Operario D, Socias ME, Sued O, Marshall BD. Inclusion of trans women in pre-exposure prophylaxis trials: a review. AIDS Care. 2015 May; 27(5):637–41. [PubMed: 25430940]
11. Golub SA, Gamarel KE, Rendina HJ, Surace A, Lelutiu-Weinberger CL. From efficacy to effectiveness: facilitators and barriers to PrEP acceptability and motivations for adherence among

MSM and transgender women in New York City. AIDS Patient Care STDS. 2013 Apr; 27(4):248–54. [PubMed: 23565928]

12. Golub SA. Tensions between the epidemiology and psychology of HIV risk: implications for pre-exposure prophylaxis. AIDS Behav. 2014 Sep; 18(9):1686–93. [PubMed: 24719201]
13. World Health Organization. Geneva: World Health Organization; 2012. Guidance on Pre-Exposure Oral Prophylaxis (PrEP) for Serodiscordant Couples, Men and Transgender Women Who Have Sex with Men at High Risk of HIV: Recommendations for Use in the Context of Demonstration Projects [Internet]. [cited 2015 Mar 7]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK132003/
14. USPHS-CDC. Preexposure prophylaxis for the prevention of HIV infection in the United States - 2014: A clinical practice guideline. http://www.cdc.gov/hiv/pdf/PrEPguidelines2014.pdf2014
15. Liu A, Cohen S, Follansbee S, Cohan D, Weber S, Sachdev D, et al. Early experiences implementing pre-exposure prophylaxis (PrEP) for HIV prevention in San Francisco. PLoS Med. 2014 Mar.11(3):e1001613. [PubMed: 24595035]
16. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. The New England journal of medicine. 2010 Dec 30; 363(27):2587–99. Epub 2010/11/26. eng. [PubMed: 21091279]
17. Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. Lancet Infect Dis. 2014 Sep; 14(9):820–9. [PubMed: 25065857]
18. 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 Sep 12.4(151):151ra25. Epub 2012/09/14. Eng.
19. Castillo-Mancilla JR, Zheng JH, Rower JE, Meditz A, Gardner EM, Predhomme J, et al. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. AIDS Res Hum Retroviruses. 2013 Feb; 29(2):384–90. [PubMed: 22935078]
20. Prentice RL. A case-cohort design for epidemiologic cohort studies and disease prevention trials. Biometrika. 1986; 73(1):1–11.
21. Solomon MM, Lama JR, Glidden DV, Mulligan K, McMahan V, Liu AY, et al. Changes in renal function associated with oral emtricitabine/tenofovir disoproxil fumarate use for HIV pre-exposure prophylaxis. AIDS. 2014 Mar 27; 28(6):851–9. [PubMed: 24499951]
22. Sevelius J, Keatley J, Calma N, Arnold E. “I am not a man”: Trans-specific barriers and facilitators to PrEP acceptability among transgender women. submitted.
23. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, et al. Preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2012 Aug 2; 367(5):411–22. Epub 2012/07/13. eng. [PubMed: 22784040]
24. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodi N, Nair G, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2015 Feb 5; 372(6):509–18. [PubMed: 25651245]
25. Corneli AL, Deese J, Wang M, Taylor D, Ahmed K, Agot K, et al. FEM-PrEP: adherence patterns and factors associated with adherence to a daily oral study product for pre-exposure prophylaxis. J Acquir Immune Defic Syndr. 2014 Jul 1; 66(3):324–31. [PubMed: 25157647]
26. Molina, J.; Capitant, C.; Spire, B.; Pialoux, G.; Chidiac, C.; Charreau, I., et al., editors. On demand PrEP with oral TDF/FTC in MSM: results of the ANRS Ipergay trial; Conference on Retroviruses and Opportunistic Infections; Seattle. 2015.
27. Kearney BP, Mathias A. Lack of effect of tenofovir disoproxil fumarate on pharmacokinetics of hormonal contraceptives. Pharmacotherapy. 2009 Aug; 29(8):924–9. [PubMed: 19637945]
28. Murnane PM, Heffron R, Ronald A, Bukusi EA, Donnell D, Mugo NR, et al. Pre-exposure prophylaxis for HIV-1 prevention does not diminish the pregnancy prevention effectiveness of hormonal contraception. AIDS. 2014 Jul 31; 28(12):1825–30. [PubMed: 24785951]

29. Heffron R, Mugo N, Were E, Kiarie J, Bukusi EA, Mujugira A, et al. Preexposure prophylaxis is efficacious for HIV-1 prevention among women using depot medroxyprogesterone acetate for contraception. AIDS. 2014 Nov 28; 28(18):2771–6. [PubMed: 25493602]

30. Stanczyk FZ, Archer DF, Bhavnani BR. Ethinyl estradiol and 17beta-estradiol in combined oral contraceptives: pharmacokinetics, pharmacodynamics and risk assessment. Contraception. 2013 Jun; 87(6):706–27. [PubMed: 23375353]

31. Minuesa G, Volk C, Molina-Arcas M, Gorboulev V, Erkizia I, Arndt P, et al. Transport of lamivudine [(−)-beta-L-2′,3′-dideoxy-3′-thiacytidine] and high-affinity interaction of nucleoside reverse transcriptase inhibitors with human organic cation transporters 1, 2, and 3. J Pharmacol Exp Ther. 2009 Apr; 329(1):252–61. [PubMed: 19141712]

32. Hayer-Zillgen M, Bruss M, Bonisch H. Expression and pharmacological profile of the human organic cation transporters hOCT1, hOCT2 and hOCT3. Br J Pharmacol. 2002 Jul; 136(6):829–36. [PubMed: 12110607]

33. Hel Z, Stringer E, Mestecky J. Sex steroid hormones, hormonal contraception, and the immunobiology of human immunodeficiency virus-1 infection. Endocr Rev. 2010 Feb; 31(1):79–97. [PubMed: 19903932]

34. Heffron R, Donnell D, Rees H, Celum C, Mugo N, Were E, et al. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. Lancet Infect Dis. 2012 Jan; 12(1):19–26. [PubMed: 21975269]

35. Sevelius JM. Gender Affirmation: A Framework for Conceptualizing Risk Behavior among Transgender Women of Color. Sex Roles. 2013 Jun 1; 68(11–12):675–89. [PubMed: 23729971]

36. Sevelius JM, Patouhas E, Keatley JG, Johnson MO. Barriers and facilitators to engagement and retention in care among transgender women living with human immunodeficiency virus. Ann Behav Med. 2014 Feb; 47(1):5–16. [PubMed: 24317955]

37. Melendez RM, Pinto RM. HIV prevention and primary care for transgender women in a community-based clinic. J Assoc Nurses AIDS Care. 2009 Sep-Oct;20(5):387–97. [PubMed: 19732697]

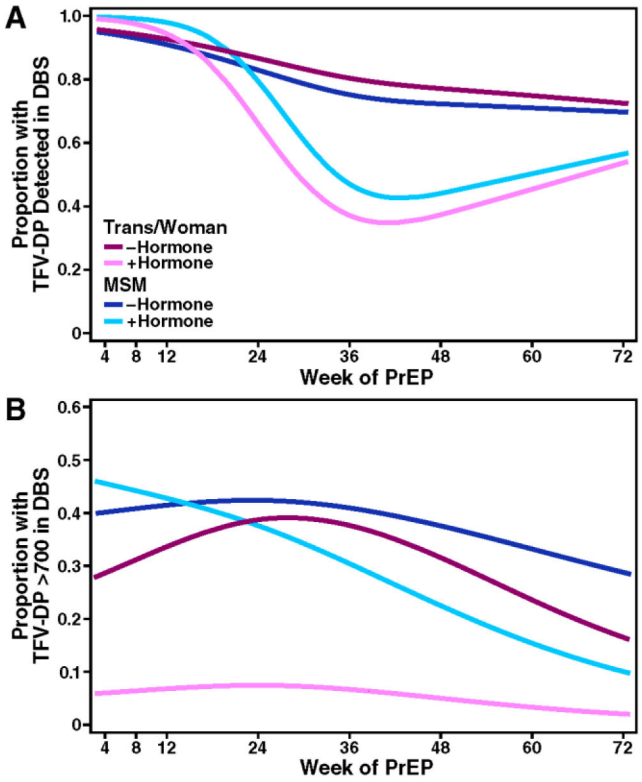

Figure 1.

Tenofovir Diphosphate (TFV-DP) in dried blood spots (DBS) in iPrEx OLE over duration of PrEP use by gender and use of feminizing hormones. Gender and hormone use were assessed at enrollment. A) depicts the proportion of participants with any TFV-DP detection vs below limit of quantitation (BLQ), representing approximately 1 or more tablets taken in the past 4 weeks. B) depicts the proportion of participants with TFV-DP greater than 700 fmol/punch, which was associated with 100% protection regardless of identity or hormone use.

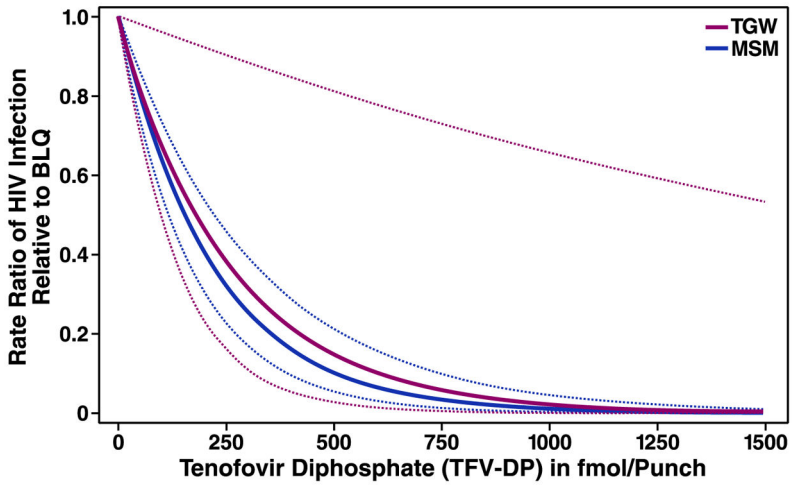

Figure 2.

HIV rate ratios for HIV infection by TFV-DP levels detected in blood in iPrEx OLE by gender. Drug concentrations from MSM (blue) and TGW (purple) were testing used PBMCs collected on the visit at seroconversion. HR is relative to visits among a randomly selected participants on PrEP, matched by gender, who remained seronegative and had TFV-DP levels below the limits of quantation (BLQ). The exponential regression curve is solid and the 95% CI is dotted. There was no difference between the groups (P=0.85).

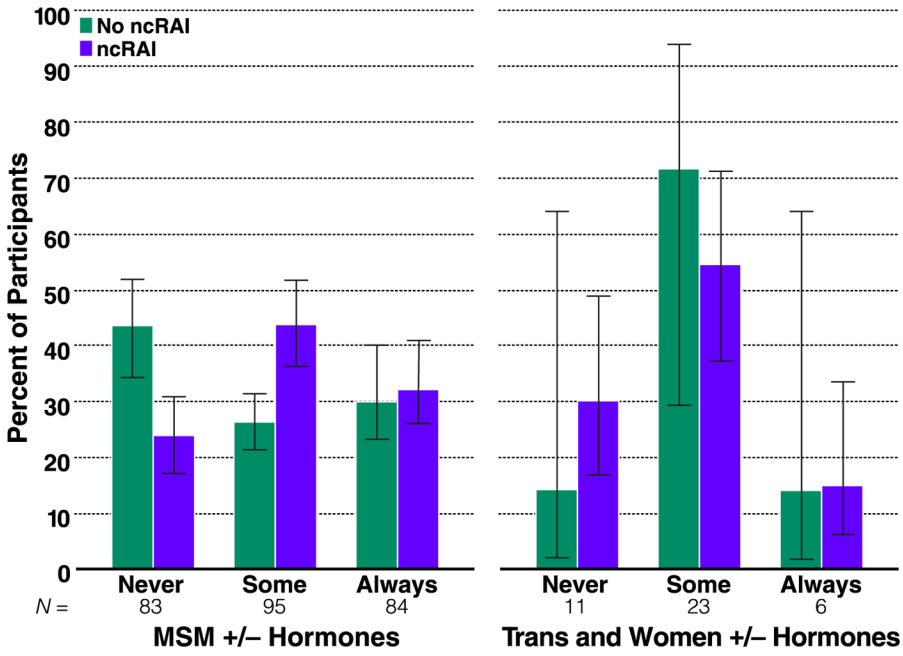

Figure 3.

Proportion of participants by consistency of drug detection, gender, and non-condom receptive anal intercourse (ncRAI). Only participants with 3 or more measurements of TFV-DP over time are included. “Never” represents no detection of TFV-DP at any visit, “Some” is detection at more than one but less than all visits, and “Always” is detection at all visits.

Table 1

Breakdown of TGW participants among HIV negative participants in iPrEx RCT by study region.

Region	All TWG (%)	Trans-identified (%)	Women (%)	Male identified but using feminizing hormones (%)
Andes (N=1700)	247 (15%)	221 (13%)	18 (1%)	8 (0%)
Brazil (N=370)	38 (10%)	30 (8%)	4 (1%)	4 (1%)
USA (N=227)	6 (3%)	5 (2%)	0 (0%)	1 (0%)
South Africa (N=88)	5 (6%)	4 (5%)	1 (1%)	0 (0%)
Thailand (N=114)	43 (38%)	36 (32%)	6 (5%)	1 (1%)
Total (N=2499)	339 (14%)	296 (12%)	29 (1%)	14 (1%)

Table 2

Demographics of MSM v. TGW in the iPrEx Randomized Trial.

Variable	Value	TGW N=339	MSM N=2160	P-value*
Age (mean)		26.2	27.3	P = 0.43
Education	Less than HS	126 (37%)	397 (19%)	P < 0.0001
	High School	169 (50%)	1209 (57%)	
	College	42 (13%)	527 (25%)	
Partners (baseline)	<=1	14 (4%)	198 (9%)	P < 0.0001
	>1–5	82 (24%)	803 (37%)	
	>5–10	50 (15%)	476 (22%)	
	>10	193 (57%)	683 (32%)	
Condomless receptive anal intercourse (ncRAI)	No	49 (14%)	965 (45%)	P < 0.0001
	Yes	290 (86%)	1195 (55%)	
Cocaine or methamphetamine use	No	302 (89%)	2020 (94%)	P < 0.0001
	Yes	37 (11%)	140 (7%)	
STI (past 6 mos)	No	212 (63%)	1635 (76%)	P < 0.0001
	Yes	127 (38%)	525 (24%)	
Circumcised	No	323 (96%)	1835 (85%)	P = 0.003
	Yes	13 (4%)	320 (15%)	
Living Situation	With Partner	27 (8%)	154 (7%)	P < 0.0001
	Alone	77 (23%)	306 (14%)	
	With family/friends	230 (68%)	1663 (77%)	
	Other	5 (2%)	37 (2%)	
Transactional Sex	No	122 (36%)	1350 (63%)	P < 0.0001
	Yes	217 (64%)	810 (38%)	

*P-values were adjusted for study site.

Table 3

Drug Concentrations and HIV incidence in iPrEx OLE by subgroup.

Drug Level by Dried Blood Spot	Gender	Person Years	Percent of FU	Number HIV+	Rate HIV/100 PY	Rate Ratio Off-PrEP Ref	*P* Value	Rate Ratio BLQ Ref	*P* Value
Off PrEP	**MSM**	**447**		**12**	**2.68** (1.56–5.03)	Reference			
	TGW	**53**		**1**	**1.90** (0.11–8.35)	Reference			
BLQ	**MSM**	**326**	**24**	**17**	**5.21** (3.28–8.77)	**1.94** (0.94–4.17)	**0.08**	Reference	
	TGW	**58**	**29**	**1**	**1.72** (0.10–7.56)	**0.91** (0.04–22.86)	**0.94**	Reference	
<2 Pills/Week	**MSM**	**324**	**24**	**8**	**2.47** (1.26–5.55)	**0.92** (0.36–2.23)	**0.86**	**0.49** (0.20–1.04)	0.06
	TGW	**76**	**38**	**1**	**1.31** (0.07–5.79)	**0.69** (0.03–17.50)	**0.80**	**0.39** (0.02–19.08)	0.84
2–3 Pills/Week	**MSM**	**156**	**12**	**1**	**0.64** (0.04–2.83)	**0.24** (0.01–1.22)	**0.09**	**0.12** (0.01–0.56)	0.0037
	TGW	**24**	**12**	**0**	**0.00** (0.00–7.80)	**0.00** (0.00–13.03)	**0.39**	**0.00** (0.00–14.16)	0.41
4–6 Pills/Week	**MSM**	**288**	**22**	**0**	**0.00** (0.00–0.67)	**0.00** (0.00–0.27)	**<0.001**	**0.00** (0.00–0.13)	<0.0001
	TGW	**28**	**14**	**0**	**0.00** (0.00–6.84)	**0.00** (0.00–10.93)	**0.36**	**0.00** (0.00–12.08)	0.38
Daily	**MSM**	**176**	**13**	**0**	**0.00** (0.00–1.09)	**0.00** (0.00–0.44)	**0.00**	**0.00** (0.00–0.22)	<0.0001
	TGW	**5**	**3**	**0**	**0.00** (0.00–35.18)	**0.00** (0.00–56.25)	**0.66**	**0.00** (0.00–62.16)	0.67
Missing	**MSM**	**62**	**5**	**0**	**0.00** (0.00–3.08)	**0.00** (0.00–1.25)	**0.08**	**0.00** (0.00–0.63)	0.01
	TGW	**9**	**4**	**0**	**0.00** (0.00–21.47)	**0.00** (0.00–34.33)	**0.58**	**0.00** (0.00–37.93)	0.59
If 4–6 and Daily were combined									
≥4 Pills/Week	**MSM**	**463**	**35**	**0**	**0.00** (0.00–0.41)	**0.00** (0.00–0.17)	**<0.001**	**0.00** (0.00–0.08)	<0.0001
	TGW	**34**	**17**	**0**	**0.00** (0.00–5.73)	**0.00** (0.00–9.16)	**0.32**	**0.00** (0.00–10.12)	0.34

Abbreviations: FU is Followup. BLQ is below limit of quantitation. MSM is men who have sex with men. TGW is trans/women identified participants, or MSM who report use of feminizing hormones.