would also decrease wait times associated with testing, another dominant barrier to HIV services.\textsuperscript{17,18}

Clients in our study highlighted the importance of HIVST demonstration and one-on-one support as a component of a testing experience, and this finding has been shown in other HIVST studies, specifically for accurate use and interpretation of test results.\textsuperscript{17,18}

Facility HIVST in outpatient waiting spaces was perceived to be highly acceptable. This strategy may provide a high-impact, sustainable, and scalable approach for improving HIV testing throughout sub-Saharan Africa. Further research is needed to understand real-world acceptability and use of the strategy.

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**Baseline Characteristics Explain Differences in Effectiveness of Randomization to Daily Oral TDF/FTC PrEP Between Transgender Women and Cisgender Men Who Have Sex With Men in the iPrEx Trial**

**INTRODUCTION**

Daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for HIV pre-exposure prophylaxis (PrEP) nearly eliminates the risk of HIV infection when taken consistently.\textsuperscript{1–3} PrEP could be particularly impactful for transgender women—a key population carrying one of the highest HIV burdens globally.\textsuperscript{4} However, PrEP uptake in this...
## Table 1. Baseline Characteristics by Gender

| Characteristic                                      | TGW (N = 333) | MSM (N = 2112) | P     |
|----------------------------------------------------|---------------|----------------|-------|
| Age at baseline, mean (SD)                         | 26 (7)        | 27 (9)         | 0.030 |
| CES-D score, mean (SD)                             | 17 (8)        | 17 (8)         | 0.63  |
| Number of partners in previous 3 months, median (IQR) | 15 (5–55)     | 5 (3–13)       | <0.001|
| Any condomless receptive anal intercourse in the previous 3 months | 286 (86%)*    | 1172 (55%)     | <0.001|
| Country                                            |               |                |       |
| The United States                                  | 6 (2%)        | 217 (10%)      |       |
| Peru                                               | 184 (55%)     | 1192 (56%)     |       |
| Ecuador                                            | 60 (18%)      | 228 (11%)      |       |
| Brazil                                             | 37 (11%)      | 327 (15%)      |       |
| South Africa                                       | 4 (1%)        | 77 (4%)        |       |
| Thailand                                           | 42 (13%)      | 71 (3%)        |       |
| Treatment assignment                               |               |                | 0.88  |
| Placebo                                            | 165 (50%)     | 1056 (50%)     |       |
| Active arm                                         | 168 (50%)     | 1056 (50%)     |       |
| Ethnicity                                          |               |                | 0.25  |
| Non-Hispanic/Latino                                | 84 (25%)      | 597 (28%)      |       |
| Hispanic/Latino                                    | 249 (75%)     | 1515 (72%)     |       |
| Race                                               |               |                | <0.001|
| Black/African American                             | 19 (6%)       | 186 (9%)       |       |
| White                                              | 38 (11%)      | 386 (18%)      |       |
| Mixed/other                                        | 234 (70%)     | 1452 (69%)     |       |
| Asian                                              | 42 (13%)      | 88 (4%)        |       |
| Marital status                                     |               |                | 0.005 |
| Single                                             | 237 (71%)     | 1594 (75%)     |       |
| W/partner                                          | 95 (29%)      | 455 (22%)      |       |
| Married                                            | 0 (0%)        | 33 (2%)        |       |
| Divorced                                           | 1 (<1%)       | 28 (1%)        |       |
| Widowed                                            | 0 (0%)        | 2 (<1%)        |       |
| Living situation                                   |               |                | <0.001|
| With family/friends                                | 226 (68%)     | 1628 (77%)     |       |
| W/male partner                                     | 26 (8%)       | 120 (6%)       |       |
| Alone                                              | 75 (23%)      | 299 (14%)      |       |
| W/female partner                                   | 1 (<1%)       | 30 (1%)        |       |
| Other                                              | 5 (2%)        | 35 (2%)        |       |
| Education level                                    |               |                | <0.001|
| Less than secondary                                | 125 (38%)     | 385 (18%)      |       |
| Completed secondary                                | 122 (37%)     | 744 (35%)      |       |
| Postsecondary                                      | 84 (25%)      | 960 (45%)      |       |
| No answer/missing                                   | 2 (1%)        | 23 (1%)        |       |
| Sexual role                                        |               |                | <0.001|
| Top                                                | 14 (4%)       | 609 (29%)      |       |
| Bottom                                             | 238 (71%)     | 587 (28%)      |       |
| Versatile                                          | 75 (23%)      | 858 (41%)      |       |
| Do not know                                        | 6 (2%)        | 58 (3%)        |       |
| Any transactional sex in previous 6 months         | 214 (64%)     | 790 (37%)      | <0.001|
| Any sexually transmitted infection diagnosis in previous 6 months | 126 (38%)     | 515 (24%)      | <0.001|
| Alcoholic drinks per day in the past month          |               |                | 0.008 |
| None/conce a month                                 | 63 (19%)      | 427 (20%)      |       |
| 1–4 per day                                        | 67 (20%)      | 557 (26%)      |       |
| ≥5 per day                                         | 150 (45%)     | 756 (36%)      |       |
| Refused/missing/do not know                         | 53 (16%)      | 372 (18%)      |       |
| Any cocaine use in the past month                  | 25 (8%)       | 105 (5%)       | 0.055 |

*All variables are N (%) except where noted.
IQR, interquartile range.
population has been low, and this may be in part due to a lack of high-quality evidence about PrEP in transgender women.\textsuperscript{5}

iPrEx was the only placebo-controlled randomized study of daily oral PrEP that included any transgender women who have sex with men (TGW), and consequently, the trial’s results play an outsized role in our understanding of PrEP’s efficacy in TGW.\textsuperscript{6} Although randomization to the active arm reduced HIV incidence by 44\% in the sample overall, stratified analyses found no benefit for TGW [hazard ratio 1.1, 95\% confidence interval (CI): (0.5 to 2.7)].\textsuperscript{7}

A closer look at drug levels found that tenofovir concentrations were generally lower in TGW compared with cisgender men who have sex with men (MSM), and drug was not detected at the seroconversion visit in any TGW on the active arm who became HIV-positive.\textsuperscript{7}

There are at least 2 possible explanations for the iPrEx results. First, there were numerous measured baseline differences between TGW and MSM. If these differences occurred across characteristics that were important modifiers of PrEP’s effectiveness—either by affecting adherence to PrEP or by modifying HIV risk—then even in the absence of any biological differences in TDF/FTC’s efficacy, the intention-to-treat (ITT) estimates of PrEP’s effectiveness might differ between the 2 groups.\textsuperscript{8}

Second, there may be other unknown or unmeasured differences between TGW and MSM that might impact TDF/FTC’s effectiveness. For example, recent small pharmacological studies suggest that feminizing hormones might interfere with the ability of tenofovir to block HIV infection by lowering the available blood concentration of tenofovir diphosphate.\textsuperscript{9,10} Understanding how randomization to PrEP was not effective in TGW in iPrEx may have useful implications for PrEP implementation.

Here, we assess to what extent differences in measured baseline characteristics between MSM and TGW could explain the observed effect heterogeneity in iPrEx. We frame this issue as a transportability\textsuperscript{11} question and estimate what the ITT effect of randomization to PrEP would have been in MSM if they had the same distribution of baseline characteristics as TGW in the study.\textsuperscript{12,13} If this transported estimate is similar to the observed ITT estimate in TGW, then the effect heterogeneity observed in iPrEx might be due to measured population composition differences alone. If, on the other hand, the transported estimate is not similar to what was observed in iPrEx, then unique contextual or biological factors (or unmeasured differences in population composition) contributed to the effect heterogeneity in the study.

\section*{METHODS}

\subsection*{Study Population and Procedures}

iPrEx was a placebo-controlled randomized trial of daily oral TDF/FTC PrEP conducted between 2007 and 2011 in Brazil, Peru, Ecuador, the United States, South Africa, and Thailand. iPrEx enrolled 2499 cisgender men and TGW.\textsuperscript{6} All participants were HIV-negative at enrollment, reported risk behavior for HIV, and were assigned male sex at birth. Gender identity was recorded through a computer-assisted structured interview. We additionally included any participant who reported taking feminizing hormones (irrespective of gender identity) as a TGW.\textsuperscript{7}

The same baseline computer-assisted structured interview also asked participants about their demographics, living situation, relationship status, recent and lifetime sexual history, and substance use. Depressive symptoms were measured through an interviewer-administered Center for Epidemiologic Studies Depression Scale (CES-D). Detailed study procedures can be found in Grant et al.\textsuperscript{8}

\subsection*{Variable Selection and Statistical Methods}

We first estimated the observed ITT incidence rate ratio in MSM (IRR\textsubscript{msm}) and TGW (IRR\textsubscript{tgw}) using a Poisson regression including an offset for follow-up time. We excluded individuals who were HIV-positive at enrollment or who contributed no follow-up time.

We estimated what the IRR would have been in MSM if they had the same distribution of baseline characteristics as the TGW study participants (−IRR\textsubscript{msm}). We identified 15 candidate baseline characteristics that we hypothesized were both associated with HIV incidence and differed between MSM and TGW in iPrEx: age; total number of partners in the previous 3 months; any condomless receptive anal sex in the previous 3 months; sexual role (top, bottom, or versatile); race; ethnicity (Hispanic/Latino or non-Hispanic/Latino); country of residence; highest level of education; marital status; living situation (“With whom do you live primarily?”); past month alcohol consumption; history of transactional sex in the past 6 months; any sexually transmitted infections in the past 6 months; past month cocaine use; and past week depressive symptoms. Using a data-driven variable selection algorithm, we narrowed this list of 15 candidate covariates to include only those that both modified the ITT IRR among MSM and differed in distribution between MSM and TGW.\textsuperscript{14}

Using this reduced set of variables (\textsuperscript{W})∗, we applied a generalization of the g-formula\textsuperscript{15} to estimate −IRR\textsubscript{msm}.\textsuperscript{15,16} This approach is analogous to model-based direct standardization in which the MSM population is standardized to resemble the distribution of covariates observed in TGW.\textsuperscript{17} Assuming correct model specification, −IRR\textsubscript{msm} estimates what the ITT IRR would have been in MSM had they shared the same distribution of baseline covariates as TGW in iPrEx. We estimated the percent of the observed effect heterogeneity between MSM and TGW that can be accounted for by differences in these baseline characteristics as \(\frac{\log(\text{IRR}\textsubscript{tgw}) - \log(\text{IRR}\textsubscript{msm})}{\log(\text{IRR}\textsubscript{tgw}) - \log(\text{IRR}\textsubscript{msm})} \times 100\). Analyses were performed using R v3.4.1 and STATA 15.1.\textsuperscript{18,19}

\section*{RESULTS}

Of the 2499 participants enrolled in iPrEx, 10 were HIV-positive at enrollment and 44 did not return for follow-up visits. Of the remaining 2445 participants, 290 identified as trans, 29 identified as women, and 14 identified as men but reported using feminizing hormones. Together, these participants comprised the TGW group [N = 333/
DISCUSSION

Differences in baseline characteristics between MSM and TGW explained the observed effect heterogeneity in iPrEx. This finding suggests that biological differences in TDF/FTC’s efficacy in TGW or other unmeasured factors were unlikely to have been major drivers of the effect heterogeneity observed in the iPrEx trial.

Whether feminizing hormones reduce the absorption of tenofovir diphosphate enough to produce clinical differences in PrEP’s efficacy remains an important open question. Only 20% of TGW in iPrEx reported taking feminizing hormones, and there were no HIV infections among the participants taking feminizing hormones who were assigned to the placebo arm. Consequently, we cannot evaluate whether feminizing hormones reduced PrEP’s effectiveness using the iPrEx study data. Ongoing studies designed to explicitly address this question will soon provide more insight into the interaction between hormones and PrEP.

The small number of TGW included in iPrEx is a major obstacle for understanding PrEP in this key population. By using transportability, we were able to better describe the effect heterogeneity in iPrEx after accounting for numerous differences between TGW and MSM, which would have been impossible with traditional regression adjustment. Given that iPrEx is the only placebo-controlled randomized trial of PrEP that included any TGW, any insights about the effects of PrEP in this population are helpful even if substantial uncertainty remains.

Moving forward, there remains an urgent need for high-quality, trans-specific research on HIV prevention strategies. The effect heterogeneity in iPrEx exemplifies why transgender women should not be aggregated with cisgender men when conducting research, and future studies should ensure that enough transgender women are included to provide adequate power to analyze these groups separately. Further research is also needed on PrEP for transgender men or nonbinary individuals to ensure that implementation programs meet the needs of everyone who could benefit from PrEP.

Overall, our study—along with others from iPrEx and iPrEx OLE—suggests TDF/FTC PrEP works similarly for MSM and TGW when accounting for other characteristics. PrEP should be offered to anyone at risk of HIV infection regardless of gender identity.

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