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Transgender Women in Clinical Trials of Pre-Exposure Prophylaxis

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Abstract: Lessons were learned with trans women who participated (as volunteers and investigators) in trials of HIV pre-exposure prophylaxis (PrEP). Trans women are not men. Compared with men who have sex with men, trans women trial participants were more likely to be involved with transactional sex, had more sexual partners, and were less likely to have PrEP medications detected in blood. Trans women define themselves differently in different cultures. One best practice is to ask at least 2 gender questions: sex assigned at birth and current gender. More information is needed to fully situate PrEP efficacy for trans women, including analysis of drug–drug interactions between PrEP medications and feminizing hormones and PrEP drug penetration into neovaginal tissues. Including trans women in studies is helpful only if their participation is specifically reported, as could occur in a table of baseline characteristics of the enrolled cohort. Gender-affirming care is important to foster appropriate uptake and use of PrEP. Such care includes use of preferred pronouns and names, safety to use the bathroom of choice, and access to gender-affirming hormone therapy and surgery. The consistent finding that PrEP works when taken across diverse populations having diverse practices related to gender, sexual intercourse, and hormone use provides a basis for offering PrEP to people at substantial risk of acquiring HIV although some subgroups may not have been fully represented in trials. Nonetheless, specific PrEP implementation science for trans women (and men) is essential to develop best practices for PrEP delivery and use.

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In November 2010, results of the iPrEx trial were published showing that oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) was safe and effective for preventing acquisition of HIV infection among “men and trans women who have sex with men.” At that time, we described 29 participants (1%) of 2499 who were assigned male sex at birth and who currently described their gender as women.¹ Nearly 5 years later, and with the encouragement and insistence from transgender community leaders, we published a subgroup analysis that focused on the experience of 339 (14%) of participants who self-identified as “trans,” identified as female, or who used feminizing hormones.² These are some lessons learned about the inclusion of trans women in HIV prevention trials.

Trans Women Are Not Men

Prevention trials that include men who have sex with men (MSM) have conventionally made trans women eligible for participation. Trans women often carry a disproportionate burden of HIV infection.³ In some settings, nontransgender MSM and trans women are on a multidimensional gender continuum defined by feminine behavior, use of women’s clothing, use of feminizing hormones, gender reassignment surgeries, and adopting gender-specific identities either part-time or full-time. The desire to include a broader range of this continuum has been laudable.

Yet, trans women are not men. Trans women may or may not have sex with men. In the iPrEx studies, trans women were more likely to be involved in transactional sex, had more male sexual partners on average, and were less likely to use PrEP effectively as indicated by consistent detection of PrEP drugs in the body.² Like nontrans women in 2 PrEP trials,^{4,5} trans women were less likely to have PrEP drugs detected when they were at higher HIV risk.² This is in marked contrast with MSM, among whom PrEP uptake and use was strongly and positively associated with sexual behavior that would otherwise increase HIV infection rates.^{6,7} Finding ways to foster such strategic use of oral PrEP among women, including trans women, is an important challenge facing HIV prevention today. Long-acting PrEP agents, such as long-acting injectable cabotegravir,⁸ offer other possibilities for

increasing the effective use of PrEP. As effectiveness trials of these agents are planned, recruitment strategies and goals for inclusion of trans women (and trans men) will be important.

How Trans Women Define Themselves

Trans women may define themselves in different ways in different cultures. A best practice for identifying trans people in surveys has emerged for use in the United States.⁹ The practice assesses trans status using 2 questions related to sex assigned at birth and current gender identity. Ideally, diverse options would be offered for each time reference (birth and current). At birth, some cultures will assign either male or female sex although intersex assignments at birth may be allowed in some health jurisdictions. Current gender identity should be defined in the protocols and embrace local categories, which may include “male,” “female,” “trans woman,” “trans man,” “gender non-conforming/non-binary/genderqueer,” or “gender not listed here.” Additional terminology can be adapted based on local communities or languages, for example, “travesti.” or “transsexuais” in some parts of South America or “kathoe” in Thailand. How best to adapt these practices for global use, while respecting local gender practices, and promote systematic tracking and reporting of trans women’s experiences is an important area for further research within prevention science.

Situating PrEP Efficacy

HIV-prevention research has been highly gendered. One rationale has been possible or known differences between mucosal surfaces for the penis, vagina, and rectum. Higher tenofovir concentrations after oral dosing of tenofovir disoproxil fumarate (TDF) have been found in the rectum compared with the vagina,^{10,11} likely reflecting the poor bioavailability of TDF leaving more unabsorbed compound available in the lower intestinal tract. Such high concentrations of tenofovir in the rectum may explain the near complete protection observed with PrEP dosing of 4–6 tablets per week among men and trans women who have sex with men, whose HIV exposure is primarily by anal intercourse,^{2,6} whereas seroconversion was observed among several vaginally exposed nontrans women at this level of PrEP use.¹² Recent modeling of concentrations of active drug (tenofovir diphosphate and emtricitabine triphosphate), relative to the native nucleotides, supported the suggestion that although 4 doses per week may be sufficient to high-level protection from rectal HIV exposure, 6–7 doses per week may be needed to achieve high-level protection from vaginal HIV exposure.¹³

Pharmacological studies in neovaginal tissues among postsurgical trans women are not yet available. Neovaginal tissues are typically derived from penile and/or scrotal tissue or can be created by a transposition of part of the sigmoid colon. After surgical transposition of these tissues to form the neovagina, it is not known whether such tissues sustain all of their original patterns of microtrauma and inflammation, including interactions with sexually transmitted infections or alloantigens, or adapt to their new anatomical context.

Reporting Trans Women’s Experience

Although trans women were eligible for PrEP trials designed for MSM, their experience and their numbers were not reported separately. For example, the Ipergay study protocol indicates that trans women were eligible for the study, yet the primary study report indicated that all participants were men.¹⁴ In the situation of iPrEx, the original study report described that only 1% of the enrolled cohort described their current gender as “woman” although only binary options were offered in the structured interview.¹ Initial scientific reports from iPrEx included the entire randomized cohort, including both MSM and trans women, although the inclusion of trans women was not always clear or consistently described and subgroup analysis was not attempted.⁶ When computer-assisted self-interview information became available, the investigators found that 12% of the cohort had identified as “trans” when given the opportunity to do so, and another 1% identified as men yet reported use of feminizing hormones. Combined with the 1% who identified as women, a total of 14% of the cohort was on the trans spectrum.² Such systematic assessment of different aspects of gender transitions and identities can easily fit into the table of baseline characteristics of randomized cohorts that is required for reporting clinical trial results and implementation science.

Inclusion of researchers with expertise in gender identity was helpful in all aspects of this research, including identification of subgroups, interpretation of findings relevant to the group, and reporting the results.

Gender-Affirming Care

The lower adherence to PrEP observed among trans women is not fully understood. Qualitative research suggests that trans women often prioritize gender-affirming care over HIV prevention.^{15,16} Such gender-affirming care aims to create a clinical environment where trans women and men feel safe and affirmed in their gender identity. Such environments are based on transcultural competence and include use of preferred pronouns, safety in using the bathroom of choice (which can be gender neutral bathrooms), and if available, access to gender-affirming hormone therapy and surgery.

The value of integrating hormone therapy into clinical services for trans women is highlighted by recent findings of treatment outcomes among 400 HIV-positive trans women of color in the United States.¹⁷ When the source of the hormone prescription was the HIV primary care provider, there was a substantially increased likelihood of current ARV use, undetectable viral load, and receipt of HIV primary care services within the past 6 months. Nonetheless, effective PrEP use was achieved among the majority of trans women in PrEP Brazil, a demonstration project that provided important aspects of gender-affirming care, although hormone therapy was not provided at the project site.¹⁸ Although creation of gender-affirming clinical care services is important, achieving full access to health care services by trans women (and trans men) will involve changes in the social, cultural, and political context.

We Are All People

The prevention science community has become interested in understanding the diverse social, cultural, and biological contexts in which HIV transmission occurs. To help assure generalizability, PrEP trials included participants in Asia, Africa, South America, North America, and Europe. The trials included an ethnically and racially diverse population of men and women, including trans women. The results were remarkably consistent; when PrEP was used, as indicated by having any PrEP medication detected in the blood, there was a substantial reduction in HIV incidence.^{19,20}

The commonalities among people should be highlighted. Although the tissue distribution of PrEP medications by mucosal site may differ, both FTC and tenofovir penetrate into all relevant tissues. Furthermore, the predominate risk factor for HIV acquisition among trans women is receptive anal sex without a condom^{21,22}; in this, trans women are similar to MSM. Anal intercourse is reported among many nontrans women as well and is a risk factor for HIV acquisition.²³ Oral PrEP containing FTC/TDF is effective for preventing HIV acquisition among men and women.^{24–26} Trans women were protected when drug concentrations were detected.² Nontrans women use female hormones for contraception, albeit there may be differences in formulation or dose, and such hormone use did not alter PrEP efficacy.²⁷ Trans men have not been studied although such men are receiving PrEP in clinical practice based on information about PrEP efficacy from men and women.

Randomized evaluation of differences in PrEP effectiveness by current gender, by historical gender identity, by feminizing hormone use, by sexual practices, by type of gender-affirming surgery, and other factors would require very large studies that are beyond the scope of existing research funding. Such separate randomized evaluation of PrEP effectiveness in every circumstance and subgroup becomes further out of reach once all participants are provided access to proven prevention methods.

Trans-Specific PrEP Implementation Projects

A new generation of PrEP demonstration projects tailored for the needs of trans women is planned in California²⁸ and Brazil.²⁹ The California projects will also formally include trans men for the first time in PrEP research.

Trans-specific PrEP implementation will have to consider the contexts and practices of trans women. These contexts include gender-based violence, gender inequality, transphobia, male privilege, and a lack of legal protections for human rights, including the rights of transgender people. In many countries, many trans women participate in sex work, which involves special challenges and benefits related to PrEP use. Genital hygiene practices, like rectal douching, that are used by some trans women could impact rectal drug concentrations and HIV susceptibility. Gender-affirming hormones are available in some countries without a prescription; informal use leads to variations in hormone regimens (often including oral contraception or depo-provera), dosing route (oral or injection), and dose. Some trans women use high doses of hormones, hoping to achieve

more rapid results. Integrating PrEP to an existing hormone regimen could facilitate PrEP use or disrupt adherence if the hormone regimen changes frequently. Trans women are more likely to be the receptive partner, which affords less control and greater risk of acquiring HIV infection. Other trans-specific social and contextual factors related to PrEP uptake and adherence may include the need for trans-specific social marketing of PrEP, educational materials tailored to trans people's unique questions and concerns about PrEP, and addressing issues such as medical mistrust because of past negative health care experiences.

Much will be learned from implementation science, pharmacology, and tissue studies that are specifically designed for trans women (and men) and by careful observation of PrEP performance as it scales up in diverse settings. Finding ways to share detailed information and insights from such clinical and public health practice is a key challenge for the next generation of prevention research.

CONCLUSIONS

Inclusion of trans women and men in HIV research is helpful only if their experience is shared in clear and specific ways. Although there will rarely be sufficient power to prove efficacy in any particular subgroup, a specific analysis can be shared with statistical testing to evaluate whether any apparent differences could have occurred by chance alone. Research to fully characterize drug–drug interactions between candidate PrEP agents and feminizing (and masculinizing) hormones is needed to directly address the concerns of trans people. Studies of drug penetration in tissues should include neovaginal tissues and rectal tissues after douching. Improving clinical practice for trans people requires efforts to implement gender-affirming care and the capacity to share insights and lessons learned from these efforts. PrEP scale-up should include specific funding for services that are tailored for trans women and men in resource rich and resource limited settings. Given the diversity of trans populations, an implementation research format is particularly important to fully characterize the spectrum of participants along the gender spectrum and the clinical practice models that are associated with the broadest inclusion, the most appropriate uptake of PrEP, and the most effective PrEP use.

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