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Inclusion of transgender and gender diverse people in Phase 3 trials: Examples from HIV pharmacologic prevention studies

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Abstract

Although at least 25 million adults are transgender worldwide, few Phase 3 clinical trials have enrolled transgender and gender diverse (TGD) people. HIV is the only therapeutic area to include TGD people intentionally in Phase 3 randomized clinical trials during the development of certain newer HIV pharmacologic prevention interventions. Pharmacologic assessments for HIV prevention efficacy in TGD populations are important, as there may be specific considerations for product use and potential interactions with hormone therapies. Herein, we summarize ongoing and completed Phase 3 HIV trials that included TGD people as part of the study population, we examine investigators' strategies for recruiting and engaging TGD priority populations in these Phase 3 trials, and we comment on the implications of these studies for prioritizing TGD populations in clinical pharmacology research within the Phase 3 clinical trial landscape.

Keywords

HIV; sex; gender; Phase 3; clinical trials; transgender

INTRODUCTION

"Transgender and gender diverse" (TGD) is an umbrella term to describe people whose gender identity or gender expression differs from the cultural expectation associated with the sex assigned at birth.[1] This term includes nonbinary people (gender identity outside the binary of woman or man), and it is used irrespective of an individual's desire to receive gender-affirming medical treatments for their gender expression goals. From 2006

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to 2017, US HIV prevalence estimates (laboratory confirmed and self-reported) were 18.8% among transgender women and 2.0% among transgender men.[2] Several factors contribute to the HIV burden among transgender people, including poverty, homelessness, substance abuse, survival sex work, and prevalence of polyamorous culture/multiple sexual partners.[3–5] Although beyond the scope of this review, we refer readers to Scheim *et al.*[1] and Baral *et al.*[6] for comprehensive discussions on structural stigma, social determinants of health, and implications for TGD people in the US and globally.

Language in this review

We use "TGD" throughout this manuscript to recognize diverse gender identities, but we also use language consistent with specific Phase 3 randomized controlled trials (RCTs) as appropriate. We include the terms transgender women (or transfeminine adult) to describe people identifying as women or along the feminine spectrum and assigned male at birth. Transgender men (or transmasculine adult) describe people identifying as men or along the masculine spectrum and assigned female at birth. We used "estrogen treatment" and "testosterone treatment" to characterize specific hormone regimens that TGD people may take. These approaches are not intended to overlook or minimize the diversity of gender identities; rather, they reflect prior literature and clinical trials inclusive of these populations.

TGD people are underrepresented in all aspects of healthcare and the research enterprise

TGD people represent an increasingly visible population globally, with an estimated 25 million individuals self-identifying in this manner.[7] Many TGD people are active participants in their health and remain resilient while navigating healthcare settings.[8,9] However, TGD people face stigma and discrimination, leading to barriers to accessing healthcare and health disparities.[1,10] Systemic discrimination within the healthcare system impedes access, adherence, and compliance with social and biomedical interventions to prevent HIV infection, including HIV pre-exposure prophylaxis (PrEP).[11] As one example, from 2014–2015, 35.6% of US transgender women and 31.6% of transgender men reported having ever had an HIV test in their lifetime, which was numerically similar to the prevalence of HIV testing for cisgender, heterosexual adults (35.2%).[12] In addition to confounders that prevent access to care, there are additional barriers to recruiting and enrolling TGD people in HIV-focused research, including research and medical mistrust, fear of mistreatment, and concerns about safety, exploitation, and confidentiality.[13]

Based on global prevalence estimates, transgender women have a 66-times higher odds, and transgender men have a 6.8-times higher odds of HIV acquisition than the general population.[14] HIV prevalence data are unavailable for nonbinary people. Although HIV prevalence estimates are available for transgender women and transgender men, knowledge about HIV care for these populations are limited by several factors including non-standardized terminology for describing gender identity and history, limited data collection strategies that do not collect gender identity data accurately, and exclusion of TGD people from national public health surveillance systems.[1,15,16] Investigators have made efforts to address these gaps in knowledge. One example is the American Cohort to Study HIV Acquisition among Transgender Women in High-Risk Area (LITE), the first multi-site US cohort study that will characterize HIV acquisition, risk factors for HIV, and access to HIV

prevention and linkage to HIV care for a diverse cohort of more than 1000 transgender women exclusively.[17]

Importance of HIV pharmacology research in transgender medicine

Hormone therapy (testosterone treatment or estrogen treatment) is one part of the standard of medical care for TGD people.[18] Although not all TGD people choose to access hormone therapies, based on the 2015 US Transgender Health Survey, which was a non-probability survey of approximately 30,000 TGD adults, nearly 80% of respondents wanted to take hormone therapy at some point in their lives.[19] Because TGD people accessing hormone therapy may prioritize gender affirming hormone treatment over PrEP,[9,11,20] integrated HIV care and clinical medical gender affirmation management (including hormone therapy) can serve as the "bedrock of gender-affirmative healthcare."[5] Researchers observed that active hormone therapy use was associated with 1.5-higher odds of linkage to HIV primary care (P=0.04), 2.04-higher odds of retention in HIV care (P<0.001), and 1.89-higher odds of viral suppression (P<0.001) for transgender women living with HIV relative to transgender women not using hormones.[21]

Despite the prominent role of hormone therapy in transgender medicine, pharmacologic knowledge gaps remain for gender affirming hormone therapies, which hamper investigators' ability to predict the effects of hormone therapy on drug safety and efficacy for TGD people.[22] Hormone therapy may markedly alter body composition (e.g., increased total fat during estrogen treatment), which may increase the volume of distribution of lipid-soluble medications.[22] Hormone therapy may also alter drug-metabolizing enzyme or drug transporter activities (e.g., cytochrome P450 3A or P-glycoprotein efflux transporter),[23] potentially increasing or decreasing systemic concentrations of antiretrovirals handled by these pathways. The effects of hormone therapy on kidney function for TGD people remain to be determined.[24] Some investigators have observed higher estimated creatinine clearance for transgender women taking estrogen treatment compared with cisgender men (60%, P=0.04).[25] Clinical trial simulations observed that estimated creatinine clearance significantly influenced tenofovir and emtricitabine clearance for transgender women on estrogen treatment.[26] HIV prevention is the only therapeutic area to integrate drug-hormone interaction studies specific for TGD participants in post-marketing pharmacokinetic studies.

PRIORITIZING TGD POPULATIONS IN HIV CLINICAL TRIALS

Although the US FDA continues to prioritize diverse clinical trial representation based on published guidance to promote clinical trial diversity,[27,28] this guidance falls short of acknowledging the inclusion of TGD people in clinical trials.[29] TGD people are underrepresented in all clinical trials (Phases 1, 2, and 3), and most published transgender health-focused research is limited to cross-sectional or retrospective study designs using convenience sampling strategies.[15] Over several decades, despite concerns regarding their participation in research, transgender women have advocated for increased representation in HIV research.[30] Several Phase 1 or open-label studies have responded to concerns voiced by TGD community members and characterized antiretroviral drug pharmacology

for transgender persons, predominantly among transgender women undergoing estrogen treatment.[31,32]

The National Institutes of Health (NIH) has issued requests for applications (RFAs) calling for research with transgender populations. Several NIH-funded HIV clinical trials networks have recruited transgender women in their study populations, including the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) and the HIV Prevention Trials Network (HPTN). For example, HPTN 091, an ongoing open-label study, is evaluating the feasibility, acceptability, and impact of integrated HIV prevention services, gender-affirming medical care (hormone therapy), and peer health navigation to increase pre-exposure prophylaxis (PrEP) uptake and persistence (i.e., duration of prescribed PrEP use).[33] HPTN 091 focuses on transgender health and HIV prevention, and it is the first HIV network trial to exclusively enroll transgender women. These activities highlight efforts to expand research initiatives among transgender women across clinical phases of drug development.

Although investigators have focused primarily on transgender women due to the HIV epidemic, representation is still needed for all TGD people in Phase 3 HIV prevention efficacy trials. Further, TGD people should not be analyzed as an extension of cisgender populations, as behavioral, social, and biomedical needs differ between these groups.[34–36] The Phase 3 RCTs summarized below highlight advancements and limitations in Phase 3 HIV pharmacologic prevention studies inclusive of TGD populations.

PHASE 3 CLINICAL TRIALS: DAILY ORAL PRE-EXPOSURE PROPHYLAXIS (PrEP)

Emtricitabine/tenofovir disoproxil fumarate (F/TDF)

The HIV Pre-Exposure Prophylaxis Initiative (iPrEx) was one of two Phase 3 RCTs that supported 2012 FDA approval of daily oral emtricitabine/tenofovir disoproxil fumarate (F/TDF) for HIV prevention. iPrEx enrolled transgender women and cisgender men at risk of HIV and reported a 44% relative HIV risk reduction among participants randomized to F/TDF (Table 1).[37] During study screening procedures, investigators collected participant-reported gender identity information via a computer-assisted self-interview (participant reads each question and provides their responses directly into a computer). Questions included whether participants “identified as a man or a woman,” and separately, “How do you identify yourself?” with a “check all that apply” response list that included both “trans” and “woman.”[37] Although the iPrEx RCT and the iPrEx open-label extension mentioned inclusion of transgender women in the primary publication, investigators did not stratify HIV incidence between transgender women and cisgender men. Baseline participant characteristics were not disaggregated between groups.[37]

Following advocacy within the transgender community,[36,37] Deutsch *et al.*[37] re-analyzed gender identity data and identified 339 transgender people within the iPrEx RCT (14% total participants) and iPrEx open-label extension study populations: 296 participants identified as “transgender,” (48 reported taking hormone therapy), 29 identified as “woman,” (5 reported taking hormone therapy), and 14 “male-identified participants [who] reported exogenous

female hormone use of some kind."[37] Hormone therapies reported by participants included synthetic or bioidentical estrogens, progestogens, and/or antiandrogens. Among 192 transgender women enrolled in the iPrEx open-label extension, 17% participants had tenofovir-diphosphate concentrations associated with "protective" concentrations (i.e., intraerythrocytic concentrations of tenofovir-diphosphate, the active tenofovir anabolite, in dried blood spots consistent with at least four F/TDF doses/week) compared with 35% cisgender men (33/200 person years vs. 464/1332 person years, respectively, $P<0.0001$).[37] Investigators attributed this finding to low F/TDF uptake among transgender women participants.[36,37]

Motivated by findings from iPrEx and by the unknown effects between hormone therapy and PrEP,[9,11,20] several investigators evaluated oral F/TDF concentrations among transgender women undergoing estrogen treatment[25,32,38–43] and transgender men and nonbinary people on testosterone treatment.[32,40,42] Most studies observed modest decreases in tenofovir and emtricitabine plasma area under the concentration-time curves among transgender women undergoing estrogen treatment (12%-27%),[25,32,38–40] although clinical implications for PrEP efficacy remain to be determined. Investigators observed no significant difference in tenofovir or emtricitabine exposures during testosterone treatment.[32,40,42] These data provide reassurance for transgender women and transgender men undergoing hormone therapy and taking daily oral F/TDF as PrEP. However, investigators have not performed extensive bi-directional drug-hormone interaction analyses within the Phase 3 F/TDF efficacy trials.

Emtricitabine/tenofovir alafenamide (F/TAF)

In 2019, the US FDA approved oral, fixed-dose F/TAF for daily HIV prevention. DISCOVER, a Phase 3 non-inferiority trial, compared fixed-dose regimens of once-daily F/TAF 200 mg/25 mg to F/TDF 200 mg/300 mg among adults at high risk of HIV, recruiting both transgender women and cisgender men who have sex with men (Table 1).[44] TAF, a tenofovir prodrug, was developed as an alternative to the TDF prodrug and resulted in 90% lower plasma tenofovir concentrations compared with TDF, reducing tenofovir-related adverse effects.[44] In DISCOVER, investigators collected information about "transgender status" during study screening via a computer-assisted self-interview.[45] However, investigators neither enriched recruitment for transgender women nor stratified analyses of the primary study endpoint (HIV incidence) between transgender women and cisgender men. Thus, although nearly 5400 participants enrolled in DISCOVER, only 1% were transgender women (74 participants). Investigators did not comment whether they collected information about nonbinary identities within the study population.

In a subset of 27 transgender women randomized in DISCOVER who reported hormone use, investigators observed no differences in emtricitabine-triphosphate or tenofovir-diphosphate concentrations in peripheral blood mononuclear cells during daily oral F/TAF or F/TDF, as compared with concentrations from cisgender men.[31] Although investigators did not directly observe the administration of medications in this exploratory analysis (including hormone therapies, F/TDF, or F/TAF), these data align with earlier pharmacokinetic data and suggest neither F/TDF nor F/TAF concentrations are significantly altered for transgender women

undergoing estrogen treatment. Studies have not characterized the effect of testosterone treatment for transgender men or nonbinary people on F/TAF disposition.

An exploratory analysis examined the effects of estrogen treatment on daily oral F/TAF in a subset of 17 transgender women randomized in DISCOVER.[39] Relative to cisgender men, investigators observed no differences in tenofovir-diphosphate and emtricitabine-triphosphate concentrations in peripheral blood mononuclear cells during daily oral F/TAF for transgender women undergoing estrogen treatment.[39] Although investigators did not directly observe the administration of hormone therapies or F/TAF, these findings align with earlier F/TDF outcomes and suggest neither F/TDF nor F/TAF concentrations are significantly altered for transgender women undergoing estrogen treatment. No studies have characterized the effect of testosterone treatment on F/TAF disposition for transgender men or nonbinary people.

PHASE 3 CLINICAL TRIALS: LONG-ACTING PREP

Cabotegravir (HPTN 083)

In December 2021, the US FDA approved long-acting injectable cabotegravir (CAB-LA) as the first long-acting pharmacologic intervention to reduce the risk of sexually acquired HIV-1 transmission. Cabotegravir (CAB) is an integrase strand transfer inhibitor with favorable physicochemical characteristics for a long-acting antiretroviral agent, including low aqueous solubility and a high melting point, as well as favorable pharmacologic characteristics including high antiviral potency and a long half-life (5.6 to 11.5 weeks).[46,47] The drug was formulated as an extended-release injectable nanosuspension for intramuscular delivery.[46]

HPTN 083, an ongoing Phase 2b/3 non-inferiority trial, compared cabotegravir-based regimens to daily oral F/TDF (Table 1). Overall, HPTN 083 demonstrated superiority of CAB-LA in preventing HIV via sexual transmission.[48,49] During recruitment, investigators enriched enrollment for transgender women globally through education and outreach at participating study sites and by collaborating with local community advisory boards at each site.[50] Among 4566 participants in the HPTN 083 intent-to-treat analysis, 570 (12.5%) were transgender women, exceeding the protocol-specified enrollment goal of 10%.[48,50] Although not included as part of the primary, secondary, or tertiary study objectives, investigators disaggregated and reported incident HIV infections between transgender women and cisgender men who have sex with men, leading to product labeling that disaggregated efficacy data between transgender women and cisgender men.[47]

Among transgender women, 330 participants reported taking estrogen treatment during the study. In an exploratory drug-hormone interaction analysis of a subset of transgender women in HPTN 083, investigators observed no difference in plasma cabotegravir concentrations over 83 weeks post-randomization among 30 transgender women undergoing hormone therapy compared with 23 transgender women not reporting hormone use.[51] These findings were a positive signal that transgender women can take estrogen treatment and cabotegravir without an impact on PrEP efficacy. CAB-LA pharmacology in the background of exogenous testosterone therapy has not been assessed.

Lenacapavir (PURPOSE-2)

Lenacapavir is an investigational, long-acting HIV capsid inhibitor administered as a twice-yearly injection for HIV prevention. A novel first-in-class agent, lenacapavir inhibits HIV capsid assembly and prevents viral transport and maturation.[46] Results of Phase 3 trials of lenacapavir for HIV treatment are described elsewhere.[46] For HIV prevention, PURPOSE-1 and 2 trials are ongoing Phase 3 RCTs that will compare a lenacapavir-based regimen (600 mg oral lenacapavir lead-in for 2 days plus subcutaneous 927 mg lenacapavir injections every 26 weeks) to either daily oral F/TAF or F/TDF (PURPOSE-1) or daily oral F/TDF only (PURPOSE-2) (Table 1). While PURPOSE-1 is recruiting cisgender women only, PURPOSE-2's priority populations are transgender women and cisgender men (all ages ≥16 years and at risk of HIV). PURPOSE-2's design includes a blinded phase over at least 52 weeks, an open-label extension, and a pharmacokinetic analysis during the lenacapavir "tail" phase.

The PURPOSE-2 enrollment goal is 3000 adults, with investigators establishing a 20% study-wide enrollment goal for transgender women based on country-specific HIV prevalence estimates specifically for transgender women.[52] PURPOSE-2 enrollment is open to transgender men and nonbinary individuals. However, investigators could not set data-driven enrollment goals for these populations due to a lack of local-level HIV incidence data for these populations.[52] The PURPOSE-2 study team utilized several evidence-based approaches to engage historically underrepresented individuals during protocol development.[52] These efforts included engaging US and global stakeholders through a Global Community Advisory and Accountability Group and including members of the priority population within the study team. Although the investigators did not specify a plan to stratify the primary endpoint (HIV incidence) between transgender women and cisgender men,[53] the study design indicates a positive movement toward inclusion of TGD people throughout study design and completion. Primary findings are anticipated in 2024.

Islatravir (IMPOWER 24)

Islatravir, an investigational, once-monthly oral nucleoside reverse transcriptase translocation inhibitor, was in Phase 3 development for both HIV treatment and prevention.[46] Investigators planned to include transgender women in the Phase 3 non-inferiority trial between islatravir and F/TDF or F/TAF among 1500 adults at high risk for HIV (IMPOWER 24). However, as of July 2022, FDA paused islatravir-based clinical trials because of decreased lymphocyte and CD4+ T-cell counts. Further information about the inclusion of transgender women in IMPOWER 24, and islatravir's future role in HIV prevention for TGD people, remains unclear.

CURRENT GAPS AND OPPORTUNITIES FOR INCREASING INVOLVEMENT OF TGD PEOPLE IN PHASE 3 TRIALS

Various studies and meta-analyses have highlighted the inclusion, in small numbers in some cases, of transgender women in HIV prevention research.[4] Many Phase 3 trials have conflated transgender women with cisgender men who have sex with men.[35,54] Beyond the inherent invalidation of referring to transgender women as "men who have sex with men,"

this approach fails to convey differences in social determinants that may drive HIV exposure between cisgender men and transgender women who have sex with men.[36]

Transgender men and nonbinary people remain underrepresented in clinical research.[4,11] US CDC population-based HIV/AIDs surveillance surveys have not included transgender men as a priority population, and knowledge about HIV prevalence and risk-related behaviors for transmasculine and nonbinary people is limited.[55] Further, transmasculine persons were thought to have sex primarily with cisgender women at low risk for HIV.[3] Nearly 600 transmasculine adults in a large cross-sectional clinic-based study reported having diverse sexual partnerships, and 32% reported having at least one cisgender male sex partner.[56] Additional survey data suggest that up to 55% of transmasculine respondents met the eligibility criteria for HIV PrEP.[3,57]

Although nonbinary and gender-diverse people are historically underrepresented in HIV surveillance and prevention efforts, investigators have begun to include these populations in HIV research and identify HIV-associated risk factors specific to gender-diverse people.[58] PURPOSE-2 expanded its priority populations to include transgender men and nonbinary people based on community advisory board feedback.[52] Still, more work is needed to include these populations in Phase 3 HIV trials. Phase 3 trials should consider opportunities to enrich for all populations at risk of acquiring HIV, including transmasculine and nonbinary persons. Several opportunities exist for addressing and increasing the inclusion of TGD people across randomized clinical trials broadly, exclusive of cisgender persons, as described below.

Hormone Knowledge Gaps in Phase 3 RCTs

Although the aforementioned Phase 3 RCTs made efforts to recruit and enroll TGD in clinical trials, an ongoing gap lies with the need for robust data to evaluate the bi-directional relationship between hormone therapy and approved or investigational PrEP agents. In efficacy studies, investigators typically capture gender via self-report. Some trials captured data regarding specific gender affirming hormone therapeutic agents accessed by study participants. Measurement of hormone concentrations is uncommon in RCTs. Consequently, investigators have relied on small phase 1, open-label trials to understand the relationship between PrEP agents and hormone therapies. Several small exploratory pharmacokinetic analyses observed no clinically significant effect of F/TDF on hormone concentrations for TGD adults undergoing either estrogen or testosterone treatment.[43,59,60] However, given diversity of hormone therapy regimens provided globally,[22] it is unclear whether these small studies can be extrapolated to broader TGD communities. Thoughtful inclusion of sub-studies focused on drug-hormone interactions would enhance the richness of data collected from RCTs and mitigate potential concerns within the TGD community and among clinical providers regarding the impact of PrEP agents on hormone therapy efficacy.

Opportunities for recruitment and enrollment

HPTN 083 and PURPOSE-2 used enrichment to increase the number of transgender women enrolled in both trials (Table 1). Specifically, investigators recruited and enrolled transgender people at risk of HIV acquisition (prognostic enrichment).[48,52,61] Given this population's

disproportionate HIV burden, investigators have prioritized the enrichment of transgender women in Phase 3 HIV prevention trials. To adequately enrich future trials on antiretrovirals, studies on HIV prevalence estimates inclusive of all TGD persons must be prioritized.

Although not described extensively in Phase 3 clinical trials above, investigators have recommended using a "2-step" method for collecting gender expression data for study populations (Figure 1).[62] The 2-step method includes collecting information on a participant's gender identity or expression and their sex assigned at birth as two variables.[62] Investigators have implemented this approach in survey-based research.[36] However, some TGD community members have pushed back on the 2-step method,[63] as asking a TGD person to identify their sex assigned at birth draws focus to a potentially harmful and triggering aspect of their lived experience, while reinforcing biological essentialism on social constructs.

Investigators have recommended using surgical history ("anatomical inventory") paired with open gender identification as part of baseline demographic data collection.[1,52] Briefly, an anatomical inventory may include an electronic health record-based checklist of organs and surgeries intended to guide patient-centered health screenings and post-surgical care plans.[64] Anatomical inventories provide information about a participant's anatomy directly, rather than holding to the cultural assumptions corresponding with sex assigned at birth, while highlighting rates of genital affirmation surgeries among the population. This statistic would go unexamined if sex assigned at birth were collected only. Because studies on HIV transmission via neovagina or neophallus are lacking,[2] this information could prove invaluable in determining the efficacy of antiretroviral therapies in a post-surgical population. Finally, incomplete gender identity data collection can underestimate the number of TGD people in clinical research.[37] Consistent data collection, including an open question for participant-articulated gender and an anatomical inventory when appropriate, is important for these reasons.

Opportunities for participant retention and engagement

Reisner *et al.*[15] suggested researchers focus on "patient-centeredness" when engaging with TGD participants in clinical studies, conducting research "with," and not "on," community members. Study-specific community advisory and accountability groups are evidence-based approaches to increase study retention for underrepresented clinical trial participants and to support patient-centeredness throughout the trial design (Figure 1).[52] PURPOSE-2 and HPTN 083 worked with either local or global community advisory boards during protocol development and study recruitment.[50,52] While PURPOSE-2 participant data are forthcoming, HPTN 083 exceeded its recruitment goal and illustrated the positive impact of enhanced recruitment efforts for transgender women. Additionally, TGD community members have advocated for their inclusion within study teams.[30,34,65–67] Using Global Community Advisory and Accountability Group feedback, PURPOSE-2 included study investigators and staff who were members of the study's priority population.[52] Diverse study teams can support participant retention efforts while minimizing potential harm to the communities participating in the research.[34] Finally, although not addressed directly in the RCTs covered here, experts have advocated for applying a trauma informed research

approach, in which investigators acknowledge TGD participants' experiences of trauma and minimize trauma-related stress throughout the HIV research process.[68]

CONCLUSION AND DIRECTIONS FOR RESEARCH

TGD people have been underrepresented in Phase 3 clinical trials. Although HIV pharmacologic prevention is one area in which investigators have increased TGD representation in randomized clinical trials, additional work remains. Recent randomized clinical trials for HIV pharmacologic prevention interventions have increased study team engagement with TGD communities and team members. These approaches have included (1) establishing or leveraging existing community and global advisory boards comprised of TGD community members, (2) enriching enrollment for transgender women, and (3) modifying protocol language and recruitment efforts to include transgender men and nonbinary people in the study priority population. These approaches should be considered widely for Phase 3 trials across any therapeutic area that relates to disparities prominent in the TGD population.

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CONFLICT OF INTEREST

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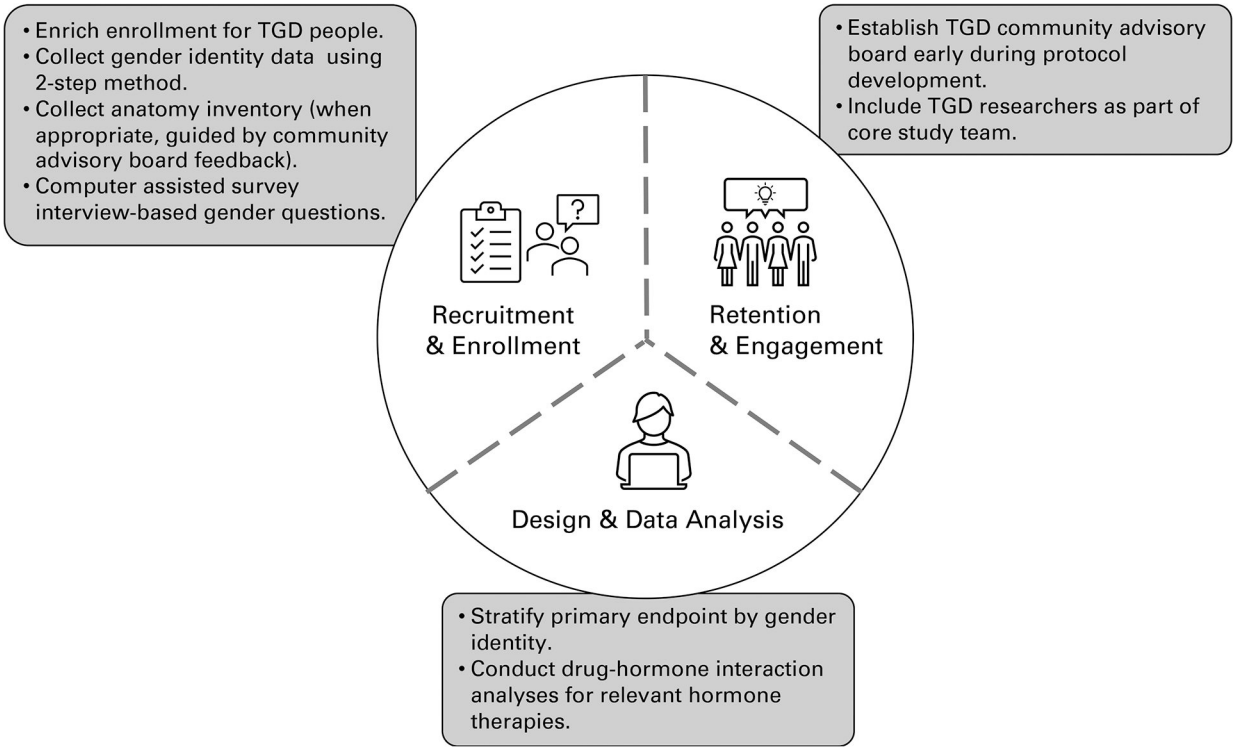

Figure 1.

Strategies for including transgender and gender diverse (TGD) participants in randomized clinical trials throughout recruitment and enrollment, retention and engagement, and design and data analysis.

Table 1.

Summary of Phase 3 clinical trials in HIV pharmacologic prevention interventions inclusive of transgender women, transgender men, or nonbinary people

	iPrEx (36, 37)	**DISCOVER (44)**	**HPTN 083 (48)**	**PURPOSE-2 (52)**
Countries	Peru, Ecuador, Thailand, Brazil, South Africa, US	Austria, Denmark, France, Germany, Ireland, Italy, Netherlands, Spain, the UK, Canada, and US	Argentina, Brazil, Peru, South Africa, Thailand, Vietnam, US	Brazil, Peru, South Africa, US
Intervention(s)	Daily oral FDC F/TDF vs. placebo	Daily oral FDC F/TAF vs. F/TDF	Oral/injectable CAB (oral lead-in) vs. F/TDF	Oral/injectable LEN (oral lead-in) vs. F/TDF
% TGD people in study population (total enrolled population)	14% (2599) – transgender women only	1% (5387) – transgender women only	12.5% (4566) – transgender women only	20% (3000) – transgender women (transgender men and nonbinary people eligible)
Enriched for TGD people?	No	No	Yes	Yes

Abbreviations: CAB, cabotegravir; FDC, fixed-dose combination; F/TAF, emtricitabine/tenofovir alafenamide fumarate; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; TGD, transgender and gender diverse; UK, United Kingdom; US, United States