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REVIEW ARTICLE

The Importance of Human Immunodeficiency Virus Research for Transgender and Gender-Nonbinary Individuals

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Transgender and gender-nonbinary (trans/GNB) individuals are disproportionally affected by human immunodeficiency virus (HIV), yet they are not adequately represented in HIV research and often underserved in clinical care. By building on community strengths and addressing structural, psychological and biological challenges, we can improve the engagement of trans/GNB people in research and ultimately improve prevention, testing, and care for this population. Here, we review the current state of the science related to HIV for trans/GNB people and discuss next steps to expand research that aims to improve the lives and well-being of trans/GNB persons.

Keywords. HIV research; transgender; gender non binary, inclusion.

Transgender and gender-nonbinary (trans/GNB) individuals are disproportionally affected by human immunodeficiency virus (HIV) and experience unique health challenges and disparities [1], yet they are not sufficiently represented in HIV research [2–4]. For example, since the beginning of the HIV epidemics, HIV risk and care data from transgender women have been routinely merged with data from men who have sex with men (MSM) [1], and gender identity information has been inadequately documented. These decisions have long masked the real burden of HIV among trans/GNB persons.

While the World Professional Association for Transgender Health (WPATH) has published separate medical care guidelines for trans/GNB people since 1979 [5], disparities in caring for these patients continue to exist. In the 2010 National HIV/AIDS strategy, trans/GNB individuals were mentioned as a target high-risk population for HIV prevention [6]. In 2013 the US President's Emergency Plan for AIDS Relief (PEPFAR) designated trans/GNB people as a "key population" for HIV risk, independent from MSM [7]. The World Health Organization (WHO) issued for the first time separate recommendations for trans/GNB populations within its HIV guidelines in 2014 (which were updated in 2016 [8], based on the transgender implementation tool [9]). Furthermore, the National Institutes of Health (NIH) and its clinical research networks have recently developed a number of strategies to engage trans/GNB individuals in NIH-funded HIV/AIDS clinical trials [10].

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Despite these important steps forward, there is more work to be done. While trans/GNB individuals share many of the same needs as the general population, they also have unique medical needs to increase gender alignment, such as gender-affirming hormone therapy and surgeries [11]. Many psychosocial factors contribute to their marginalization including exposure to enacted and felt stigma [12], violence, and discrimination [13–16]. All of these factors should be considered when conducting research in these populations, as they impact recruitment, retention, and outcomes.

LANGUAGE FOR TRANSGENDER AND GENDER-NONBINARY PEOPLE

While the language used to describe trans/GNB people is being continually refined and improved, it is crucial to use terminology that is respectful, nonpathologizing, and consistent with the complex social and cultural framework of the trans/GNB community [17]. Terms such as "sex" and "gender" are linked, but they are not synonyms. The word "sex" is used to refer to the physical/biological differences between male and female, while the word "gender" is used in connection to the behavior and cultural practices of men and women. Importantly, "gender" is a spectrum and is not limited to 2 possibilities (male or female) but includes "nonbinary" and "fluid" identities, among others. It is important to understand and appropriately distinguish concepts such as gender identity, expression, sex, and sexual orientation (Figure 1). To best address and engage the trans/GNB population in research, a knowledge of the appropriate terminology and the gender spectrum is required. WPATH provides specific guidelines to facilitate clear and respectful communication with trans/GNB individuals [5, 18]. Researchers are encouraged to follow WPATH's guidelines when interacting with the trans/GNB community and use detailed, precise,

Terminology and Definitions.

- **Sex**: Sex assigned at birth, based on assessment of external genitalia, chromosomes, and gonads.
- **Gender Identity**: A person's internal sense of self and how they fit into the world, in regard to gender.
- **Gender expression**: The manner in which an individual expresses their gender (eg, clothing and hairstyle). Gender identity and gender expression can differ (eg, a cisgender women can have an androgynous appearance).
- **Transgender**: A person whose gender identity differs from the sex that was assigned at birth.
- **Cisgender**: A person whose gender identity matches the sex that they were assigned at birth (cis = 'same side' in Latin).
- **Gender incongruent**: A person whose gender identity differs from that which was assigned at birth, but may be more complex, fluid, multifaceted, or otherwise less clearly defined than a transgender person.
- **Nonbinary**: A transgender or gender–nonconforming person who identifies as neither male nor female.
- **They/Them/Their**: Neutral pronouns used by some individuals with a nonbinary or nonconforming gender identity.
- **Sexual orientation**: Describes sexual attraction only and is not related to gender identity. The sexual orientation of transgender people is described based on their gender identity (eg, a transgender woman attracted to other women would be a lesbian).

Figure 1. Summary of terminology and definitions.

and scientifically based language when presenting their work in papers and scientific conferences.

STUDY DESIGN AND METHODOLOGY

Trans/GNB individuals constitute an important focus for HIV research, but studies in this population present unique methodologic and implementation challenges [19]. Various methods have been used, each with its advantages and limitations (reviewed in [3]). For example, population-based studies are powerful but require data sources (eg, Department of Motor Vehicles, voter registration lists) to collect information on gender beyond binary "sex" categories. Electronic medical records offer easy access to comprehensive data (eg, Veterans Health Administration, health maintenance organizations) but will miss key subgroups (eg, uninsured or not engaged in healthcare). Clinic-based approaches offer excellent opportunities for in-depth data collection, specimen acquisition, and access to various trans/GNB subgroups; however, putting together a sufficient cohort requires including multiple sites, which is resource intensive and may introduce potential confounding biases [19]. Other methods, such as venue-based approaches, respondent-driven sampling, or internet-based recruitment cannot offer generalizable results and often have poor retention rates [20]. Implementing appropriate study designs and sampling strategies is crucial to address key research questions unique to trans/GNB people [3]. Additionally, it is important to define the target research population within the gender spectrum, select appropriate controls, and define endpoints while taking into account the mentioned limitations.

OUTREACH AND RECRUITMENT

The trans/GNB population is particularly hard to reach and engage in research activities [21]. A lack of legal recognition, active criminalization, and lack of protection against employment and housing discrimination in most countries contribute to their marginalization [16, 22]. Developing strategies to engage and link this population to appropriate research activities is an urgent priority and will require case management or client-centered care above and beyond the usual retention efforts.

To successfully recruit and retain trans/GNB individuals, all research personnel should be educated and trained about trans/GNB unique issues. Providers and research staff who routinely engage in research with MSM may not be adequately equipped to interact with the trans/GNB community [23]. Similarly, research studies designed for MSM do not always fit the priorities of the trans/GNB population. In fact, many psychosocial drivers of HIV risk among transwomen are similar to those of cisgender (cis-) women, such as intimate partner violence, sex work, misogyny, less power to negotiate safe sex, and body shaming [23, 24]. If resources are not available to develop a trans/GNB-specific program, then research opportunities should be offered to transwomen as they are for cis-women rather than MSM, and similarly for transmen [25]. Because trans/GNB individuals often prioritize hormonal therapy [16], engaging trans/GNB individuals in HIV research opportunities at the time and location of gender-affirming medical care will provide synergistic results [26]. Ultimately, the passage and enforcement of legislation that protects trans/GNB people against discrimination in public accommodations, including healthcare settings, represents a critical structural intervention to reduce health inequities and will facilitate outreach, enrollment, and retention in research studies.

TRANSGENDER AND GENDER-NONBINARY PREVALENCE

Assessing the impact of HIV research on trans/GNB individuals will require better knowledge of their representation within

the population. Recent meta-analyses reported an estimated population size of 390–560 trans/GNB adults per 100 000 in the United States (0.4%–0.6%), or 1–1.4 million adults nationally [27, 28] but this is likely an underestimate, as most official records do not report consistent data on gender identity. To obtain precise data, the use of the "2-step method" for the collection of gender identity is recommended, which includes both gender identity and birth-assigned sex [29–31]. Trans/GNB people can be identified as those whose gender identity differs from their birth-assigned sex. This method is superior to a single question querying gender/sex with choices of "male," "female," and "transgender," as some trans/GNB individuals may choose "male" or "female" based on how they identify, resulting in effective invisibility of their transgender status [31, 32].

HUMAN IMMUNODEFICIENCY VIRUS PREVALENCE AMONG TRANSGENDER AND GENDER-NONBINARY INDIVIDUALS

Data on prevalence and incidence of HIV in the trans/GNB population are not well documented. Compared with all adults of reproductive age, transwomen have almost 50 times the odds of HIV infection [1], with yearly incidence rates between 3.5% and 8%, which are even higher for those engaged in sex work [16]. The Centers for Disease Control and Prevention (CDC) currently estimates that one-quarter of all transwomen in the United States are HIV infected, and half of all transwomen diagnosed with HIV are black/African American [33]. Since black/African Americans represent a small fraction of all trans/GNB individuals in the United States, the disparity is evident [34].

The prevalence of HIV among transmen is significantly lower (0–3%), but transmen who have sex with cis-MSM are also at substantial risk for acquiring HIV [35, 36]. Figure 2 summarizes the most recent epidemiological data for the trans/GNB population in the United States.

Unfortunately, many trans/GNB people living with HIV are not aware of their HIV status or are not included in the statistics, so these numbers are likely underestimated. There is also variability of HIV risk and scientific knowledge across the various gender subgroups. Thus, future research studies should collect data specific for transmen vs transwomen vs nonbinary genders, with consideration of those who do not identify as feminine or masculine or who integrate both.

HUMAN IMMUNODEFICIENCY VIRUS PREVENTION IN TRANSGENDER AND GENDER-NONBINARY INDIVIDUALS

There is growing commitment in public health to understand and improve the health of trans/GNB individuals. As mentioned above, many trans/GNB people live in contexts of social discrimination, lack of legal recognition, and exclusion from employment and educational opportunities [22]. These social determinants can undermine their sexual relationships and limit their ability to pursue safe and effective HIV prevention. Trans/GNB individuals often report having multiple sexual partners, engaging in sex work for survival, and using recreational drugs, all of which are associated with increased risk of HIV acquisition and transmission [37]. A recent study showed that about 70% of transmen attributed new sexual behaviors and increased frequency of sexual activity to testosterone use [38]. While social and behavioral factors are crucial, the biology associated with HIV transmission in the trans/GNB population is understudied. For example, little is known about how hormonal therapy might affect HIV transmission and preexposure prophylaxis (PrEP) or how HIV and various drugs penetrate neovaginal tissue.

The effectiveness of PrEP in trans/GNB individuals is a particularly important question, which requires attention [19]. Even though Truvada (emtricitabine and tenofovir disoproxil) is currently indicated for use broadly in the trans/GNB population, more studies are needed to determine current efficacy, barriers to use, and effectiveness. Pharmacokinetic studies have shown no evidence of drug–drug interaction between Truvada and oral contraception in cis-women; similarly, clinical trials have shown no decrease in efficacy of hormone-based contraception (oral pills, injections, or implants) in cis-women taking PrEP [39, 40]. While these data are reassuring, no formal pharmacological interaction study has been performed in trans/GNB individuals on PrEP and hormonal therapy [25].

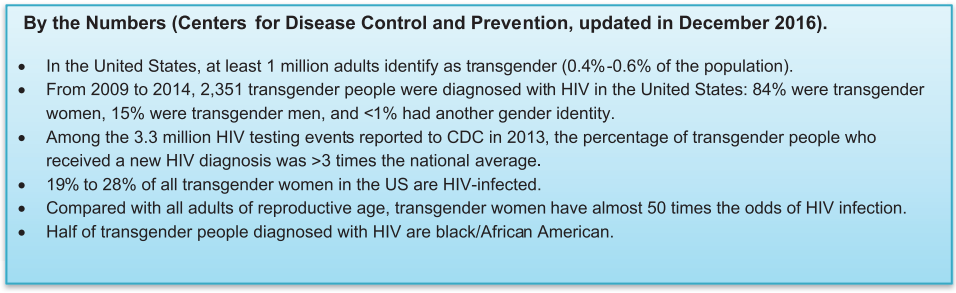

Figure 2. Summary of recent epidemiological data for the transgender/gender-nonbinary population in the United States. Abbreviations: CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus.

The original pre-exposure prophylaxis initiative clinical trial [41] described only 1% of their participants as transgender; on a subsequent reanalysis after reclassifying participants (according to self-reported gender identity, different gender than at birth or men taking feminizing hormones), the authors reported up to 14% of their participants as transgender, mostly within non-US sites [42]. In this secondary analysis, there was no difference in efficacy between the PrEP and placebo arms for trans/GNB people. However, among the active PrEP arm, the drug was detected in only about 18% of the trans/GNB participants, a lower proportion than the overall group, suggesting lower adherence among trans/GNB individuals.

Prospective studies are needed to evaluate PrEP efficacy and drug levels in combination with various hormonal therapy. To address some of these issues, in 2016 the California HIV Research Program funded the first large-scale PrEP demonstration projects specifically for trans/GNB populations, which are currently ongoing [43].

HUMAN IMMUNODEFICIENCY VIRUS CARE

Trans/GNB people living with HIV/AIDS face unique psychosocial challenges that complicate access and adherence to HIV care. Trans/GNB people living with HIV/AIDS are less likely to be on antiretroviral therapy (ART) [44] and demonstrate lower medication adherence than cisgender individuals [45]. They often report less confidence in their abilities to integrate treatment regimens into their daily lives [46]. A study evaluating the care continuum among newly diagnosed transwomen in San Francisco found that, compared to the general population, 77% were linked to primary care within 3 months of their HIV diagnosis (vs 85%), 65% were taking ART (vs 83%–89%), and only 44% achieved virological suppression (vs 50%) [47, 48]. While differences exist between studies, the low rate of virological suppression among trans/GNB people has important public health implications and amplify HIV transmission between HIV-positive trans/GNB people and their partners.

Concerning comorbidities associated with HIV, current research suggests an increased mortality in trans/GNB individuals as compared to cisgender persons, and a modest increase in cardiovascular risk and osteoporosis related to hormonal therapy in transwomen [4, 49]. Future longitudinal studies should be performed to consider the impact of HIV on mortality and morbidity in combination with the effects of mental health, as well as gender-affirming medical and surgical interventions.

HORMONE THERAPY AND ANTIRETROVIRAL THERAPY

Hormonal therapy is an important aspect of gender-affirming care used as part of medical transition [50]. Concerns about adverse interactions between ART and hormonal therapy are frequent among the trans/GNB population. Studies have shown reduced ART compliance in transwomen with HIV due to concerns that ART will decrease the effects of hormonal therapy [51]. There are no studies on the pharmacokinetics or pharmacodynamics of ART use in trans/GNB individuals using feminizing or masculinizing hormones, and all data on drug–drug interactions are extrapolated from oral contraceptives in cis-women or testosterone therapy for cis-men with hypogonadism [52–56]. Furthermore, use of progesterone and anti-androgens, such as spironolactone, cyproterone acetate, and gonadotropin-releasing hormone agonists, is frequent among trans/GNB individuals, and few to no pharmacokinetic data are available on the impact of ART and these medications [57].

Generally, HIV and its treatment are not contraindications to hormonal therapy and based on available data in cis-women, most ART regimens can be combined safely with estrogens (with the exception of amprenavir, unboosted fosamprenavir, and stavudine, which are not part of modern ART regimens) [58]. Similarly, testosterone replacement in cis-men with hypogonadism on ART has shown to be safe and to improve quality of life [59]. Overall, providing hormonal therapy in the context of HIV care improves engagement, retention in care, and adherence [23, 46]. Clinicians should remain vigilant about possible interactions and have an open dialogue with their trans/GNB patients. More research is needed to understand how to best deliver hormonal therapy with ART.

HORMONE THERAPY, THE VIRUS, AND THE IMMUNE SYSTEM

Hormonal therapy for gender affirmation may impact HIV transmission and disease progression. Most research has focused on estrogen and progesterone used by cis-women and is conflicting [60]. Studies have shown both increased and decreased HIV transcription due to effects of 17-β estradiol, while others showed reduced susceptibility of $CD4^+$ T cells mediated by estradiol [61–63]. Both endogenous and exogenous estrogen (in oral contraception) are mainly protective against HIV transmission by reducing the frequency of HIV target cells, inflammatory T cells, and macrophages in the vaginal epithelial and stromal tissues, whereas progesterone seems to increase risk of HIV transmission by enhancing the expression of HIV target cells and recruitment of inflammatory cells in the vaginal epithelium [64]. In vitro studies demonstrated direct associations between estrogen-dominant states and decreased HIV transcription and replication, mediated by estrogen receptor α- and β-catenin-dependent mechanisms [61, 65].

Little is known about the effects of testosterone on HIV replication or disease progression in transmen as most available data derive from HIV-infected cis-men who are on testosterone replacement for hypogonadism [56, 66]. One study investigated the effects on body composition and strength of physiologic testosterone replacement in cis-women living with HIV/AIDS, and showed no adverse effects on HIV replication or $CD4^+$

counts, albeit the target testosterone levels were much lower than traditionally used in trans/GNB patients [67].

To date, there are no specific studies on the effects of exogenous testosterone, estradiol, or antiandrogens at the doses typically used in trans/GNB patients on HIV transmission or disease progression. The guidelines to provide hormonal therapy for trans/GNB individuals are not well standardized. For example, transwomen can use estradiol patches, tablets, and injections in various doses as well as different androgen blockers. This void in scientific knowledge creates a challenge in preventing and treating HIV infection in the trans/GNB population. Future research should focus on the effects of the various doses, formulations, and combinations of hormonal therapy on viral transmission and suppression specifically in trans/GNB individuals.

HUMAN IMMUNODEFICIENCY VIRUS RESERVOIR AND BARRIERS FOR ERADICATION

It is likely that hormonal therapy has implications regarding HIV persistence and eradication. Estrogens at physiologic levels are strong inhibitors of HIV transcription [61, 68]. A recent study provided evidence that estradiol may inhibit HIV transcriptional reactivation in a sex-specific manner, but it is unclear how this mechanism might affect HIV persistence in trans/GNB individuals taking estrogen-based hormonal therapy. In particular, agents that are designed for "kick and kill" strategies may be impacted by estradiol-mediated mechanisms. Regarding HIV cure efforts, it is possible that estrogens may make HIV eradication both more difficult (diminishing the "kick" effect by inhibiting transcription) and less difficult (smaller reservoir due to decreased ongoing replication). The effect of other hormones (eg, progesterone, anti-androgens) on HIV persistence has not been systemically investigated, and future studies should consider these factors when designing HIV eradication strategies that are applicable across the spectrum of gender.

CALL TO ACTION TO INCLUDE MORE TRANSGENDER AND GENDER-NONBINARY INDIVIDUALS IN HUMAN IMMUNODEFICIENCY VIRUS RESEARCH

Trans/GNB individuals have disproportionately experienced discrimination in most aspects of their lives, including within the medical community. Trans/GNB people experience multiple obstacles when attempting to access adequate primary healthcare [11]. Many trans/GNB people who report bad experiences in the medical setting and do not get treated appropriately might also express apprehension in becoming part of research studies.

To explore barriers and facilitators to enrollment of transwomen in clinical trials, the HIV Vaccine Trials Network conducted focus groups of transwomen in 4 urban areas [69]. Recognized barriers included (1) stigma, (2) misinformation, (3) feeling excluded from research, (4) mistrust in the scientific community, and (5) possible side effects. Facilitators included (1) increased information and awareness, (2) culturally competent research staff, (3) recommendation from a trusted trans-friendly healthcare provider, and (4) assistance with basic needs. While these data are limited to transwomen in US metropolitan areas, they do suggest that reducing discrimination and ensuring access to culturally competent and high-quality research opportunities is a priority (Figure 3).

Including all key populations, such as trans/GNB people, in research studies and offering culturally appropriate research opportunities is not only important for scientific advancement, but it also empowers the populations being studied. There is a growing demand within the scientific and trans/GNB community to increase resources to engage people across

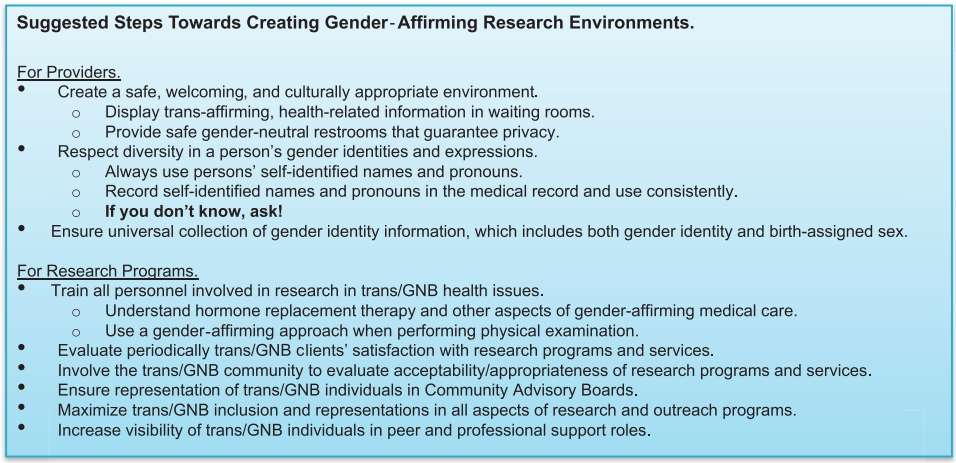

Figure 3. Summary of suggested steps necessary to create a gender-affirming healthcare and research environment. See also "Stepping up: a Consensus Statement by Trans Leaders" (https://www.aidsunited.org/resources/stepping-up-a-consensus-statement-by-trans-leaders?docid=79). Abbreviations: GNB, gender nonbinary.

the gender spectrum in research. It is essential that the trans/GNB community be involved in the planning and implementation of research efforts and clinical studies that affect them. A coordinated, collaborative approach that integrates health and human rights is integral to addressing the needs and cultural barriers of trans/GNB research and ensuring that all populations will be effectively represented in future research efforts. By appropriately engaging trans/GNB individuals in research designed to address their needs, we can inform evidence-based care and advance the healthcare of trans/GNB people worldwide.

Notes

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