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A descriptive analysis of transgender participants in phase 1-2a trials of the HIV Vaccine Trials Network (HVTN) in the United States and Peru

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ABSTRACT

Background: HIV disproportionately impacts transgender populations globally, creating challenges to inclusion in trials requiring low HIV risk profiles (LHRP) for acquisition. Our knowledge of transgender individuals with LHRP is limited. We conducted an analysis of transgender and cisgender individuals in HVTN trials enrolling individuals with LHRP.

Methods: We analyzed data from 694 participants enrolled in the phase 1-2a HVTN trials in the US and Peru from 2009 to 2014 that included individuals who reported gender identity (GI) differing from assigned birth sex (transgender [TG]), and compared them with those who reported a congruent GI (cisgender [CG]).

Results: 681 participants (98%) were CG and 13 (2%) were TG. Mean age was 25 years. 16% were Hispanic and most (69%) were White. Reasons for enrolling included to help find an effective vaccine (TG 100%; CG 98%) and help their community (TG 100%; CG 96%). Significant differences by GI were observed in reported pre-existing conditions ($p = 0.004$); however, approximately 10% of pre-existing conditions reported by TG were GI-related (e.g., gender dysphoria). Significant differences were observed in hormone therapy use ($p < 0.001$) and mental health medications ($p = 0.007$). Retention was excellent with 2.1% missed visits and no discontinuations of vaccination for TG and 3% missed visits and 7.1% discontinuations among CG. There was no statistically significant difference in HIV incidence.

Conclusions: Primary reasons for participation were altruistic for all participants. Comparable to CG counterparts, TG participants maintained LHRP, followed trial procedures, and had high retention, facilitating meaningful early phase HIV preventive vaccine trial contributions.

1. Introduction

It is estimated that transgender women (reporting male sex assigned at birth and female gender identity), transgender men (reporting female sex assigned at birth and male gender identity) and gender nonconforming people (individuals who have a gender identity or expression that differs from their sex assigned at birth) [1], comprise between 0.5% and 0.9% of the global population [2–5]. The disproportionate burden of HIV on the global transgender community, particularly the transfeminine population (individuals who were assigned male sex at birth and express their gender along a feminine spectrum) [6], is well documented [6–8]. HIV risk among transgender populations is driven by multilevel social and structural factors including poverty, discrimination, mental illness, homelessness, abuse, distrust of the health care community, illicit drug use, and concerns about disclosing transgender status [8,9]. Although some transgender persons may be at particularly high risk for HIV because of condomless anal intercourse and/or sex work [8,10,11], the transgender population is incredibly heterogeneous, with wide variations of risk profiles.

The factors that increase HIV risk for transgender individuals also create barriers that hinder participation in HIV research [12,13]. Clinical settings are often perceived as unwelcoming for transgender individuals. For example, transgender individuals in Peru face pervasive social stigma and discrimination in public and private spaces. Many of the structural factors limiting access

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to healthcare for transgender individuals in Peru are directly tied to legislation that restricts changes to gender markers and legal names on official documents [14,15]. In 2015, the US Transgender Survey (USTS) [9] reported that one-third (33%) of transgender participants who saw a health care provider in the year prior to completing the survey reported at least one negative health care experience related to being transgender. These experiences included verbal harassment and refusal of treatment because of their gender identity. Almost one quarter (23%) of respondents reported that fear of mistreatment as a transgender person led to active avoidance of health care [9]. Additionally, 33% did not seek health care when needed due to a lack of financial resources [9]. These and other exclusion mechanisms may undermine authentic access to healthcare for transgender and other gender minorities in health settings and compromise the health and wellbeing of transgender populations, as well as their participation in research that is conducted in healthcare settings [16,17].

Globally, transgender individuals and communities are socially marginalized. Many transgender individuals have multiple intersecting stigmatized identities (e.g., race, ethnicity, resource limited, economically disenfranchised, sex work, etc.) in addition to a gender identity that is not validated by their sex assigned at birth. These factors result in unique HIV-related vulnerabilities and highlight the need for innovative and effective HIV prevention strategies. Development and dissemination of these strategies require increased participation of transgender individuals in research.

At the HIV Vaccine Trials Network (HVTN), a Transgender Working Group was established in 2007 to identify and provide input regarding operational and clinical needs related to the inclusion of transgender volunteers in HVTN trials. The objectives and activities of this working group to date have led to the implementation of several important initiatives. First, the HVTN's demographics Case Report Forms (CRFs) were redesigned to adopt the recommendation of the U.S. Centers for Disease Control (CDC) to collect data on sex assigned at birth and self-identified gender utilizing a two-step approach (Fig. 1) [18]. For the second initiative, we recognized that the USTS reports gender transition peaks at 18–44 years of age [9], the typical age range for HVTN trial participants. During this time, factors that may negatively impact retention include gender transition procedures, health status, hormone use and identity documents specifying gender, all of which may require more of the participants' time and attention, potentially creating barriers to adhering to scheduled visits. We facilitate training for Clinical Research Site (CRS) staff in the identification and implementation of processes and procedures to support retention of transgender volunteers who may need assistance and support during these changes. Third, we have worked to inform and improve HIV risk assessment and risk-related eligibility criteria for trial participation, including reaching out to several researchers and experts in the field to obtain correlates of HIV incidence. Few data sets exist with HIV outcome data, and among those the transgender sample is low [19–22]. As such, identifying correlates of HIV risk is challenging, but there are several large cohort studies underway and a few will have HIV outcome data. Finally, we have noted that our knowledge of transgender individuals who present with low HIV risk profiles is also lacking. In preventive HIV vaccine clinical trials, knowledge gaps among medical providers and other CRS staff may pose challenges to recruitment, eligibility assessment, on-study HIV testing, and adverse event interpretation.

To address existing knowledge gaps and better understand our Phase 1 and Phase 2a participants who identify as transgender and present with a lower HIV risk profile, we compared phase 1-2a transgender participants to phase 1-2a cisgender participants on relevant health and HIV outcome variables.

2. Methods

2.1. Study design

Our analysis included data from six HVTN phase 1 (HVTN 076, 083, 085, 090, 094) and 2a (HVTN 205) preventive HIV vaccine clinical trials conducted between February 2009 and August 2014 in the United States and Peru, enrolling 694 individuals. These trials assessed safety, tolerability, and immunogenicity of various experimental preventive HIV vaccine products in healthy, HIV seronegative individuals with behavioral profiles indicating low risk for HIV acquisition. Review of demographic, pre-existing conditions and concomitant medication data in these six trials indicated enrollment of at least one participant who reported discordance between their sex assigned at birth and current gender identity. This analysis excludes an equivalent number of participants enrolled in other phase 1 trials conducted during this period that were not identified as having enrolled transgender individuals. This cross-protocol study is covered by an approval from the Fred Hutchinson Cancer Research Center Institutional Review Board (IR 8023).

2.2. Study participants

Participants who enrolled had to meet inclusion criteria including being healthy, HIV seronegative, aged 18–50 years, at low risk for becoming HIV infected, willing to maintain a low risk profile throughout the trial, and able to comprehend the purpose of the study and provide written informed consent. Three of the protocols tested an adenovirus-5 (Ad5) vectored vaccine; since a similar Ad5 vaccine was associated with increased risk of HIV acquisition, especially in individuals with an uncircumcised penis, any participants born with a penis had to be fully circumcised to be enrolled in these 3 studies.

Volunteers were recruited and screened; those determined to be eligible and who provided informed consent were enrolled and followed for a protocol-specified period following final vaccination. Several clinical parameters were used to screen potential participants and determine final eligibility based on the results of laboratory tests, medical and psychiatric history, and physical examinations. Transgender individuals with organs that make pregnancy possible were required to agree to use effective contraception for sexual activity that could lead to pregnancy from at least 21 days prior to enrollment and throughout the study-specified period (e.g., until 3 months after the final study vaccination).

In addition, all individuals with organs that make pregnancy possible underwent pregnancy testing prior to each study vaccination unless medical records verified total hysterectomy, bilateral oophorectomy, or tubal ligation.

2.3. Variables and measures

At the time of analysis, participants had completed all of their scheduled clinic visits. Data from Case Report Forms (CRFs) with relevant variables (i.e., pre-existing conditions, reasons for enrolling, social impacts, adverse events and concomitant meds) were analyzed at baseline and final visits, and responses of transgender and cisgender participants were compared. Sociodemographic items included age, race, ethnicity, current gender identity, and sex assigned at birth.

Pre-existing conditions were measured at baseline. Any reported pre-existing condition was accompanied by the date of diagnosis and/or surgery, indication of whether it was an ongoing condition (Yes, No), and whether the participant was currently under care for the condition (Yes, No).

STEP 1: SEX
What sex were you assigned at birth, on your original birth certificate? (check one)
Female
Male
STEP 2: GENDER IDENTITY
How do you describe yourself? (check one)
Female
Male
Transgender
Do not identify as female, male, or transgender

Source: Reisner SL, Conron KJ, Tardiff LA, Jarvi S, Gordon AR, Austin SB. 2014

Fig. 1. The Two Step Method.

Reasons for enrolling in the clinical trial were measured at baseline using a list of 10 statements (e.g, "I receive free counseling", "I am helping my community", "I know someone with HIV infection") indicating reasons why a participant might have joined the vaccine trial. Participants were asked to indicate how strongly they agreed or disagreed with each statement, utilizing a 5 point Likert scale from agree strongly to disagree strongly.

Social impacts were measured using a two part scale. In Part 1 participants indicated if they had any negative experiences or problems because of their participation in the study (Yes, No). They were surveyed on a list of 10 negative experiences or problems that might result from participation in the study (e.g., had any negative experiences with your family, friends, significant others, or sex partners; been turned down for a new job, lost a job, or experienced other problems at work) and an additional open-ended "other" option. Any problems were further assessed for impact on quality of life and status (e.g., resolved, unable to resolve, continuing), and interventions were provided if indicated (e.g., support, counseling, communicating with outside organizations on the participants behalf). In Part 2, participants indicated if participation in the study had a beneficial impact on their life (Yes, No), and then indicated the benefit(s) experienced. These included a series of closed-ended options (e.g., personal relationships; feel good helping others; medical care; risk reduction counseling) and an additional open-ended "other" option.

Data on adverse events and concomitant medications were collected at every clinic visit. Concomitant medications reviewed for all participants included mental health medications and hormone therapy. For each medication reported, information was collected on indication, start and stop date, frequency, dose and route of administration was obtained. Each adverse event report included the date of onset, severity, relationship to study product, status/outcome, status/outcome date, and any treatment that was received. Sex-specific laboratory reference ranges (e.g., hemoglobin and creatinine) sometimes posed an issue if reported values were automatically based on sex assigned at birth, without consideration of duration of medical gender affirming hormone therapy. Retention was measured by assessing the frequency of missed clinic visits and discontinuation of vaccination during trial participation.

Analyses were performed using SPSS Statistics 25. Chi Square tests were used to assess statistical differences between cisgender and transgender participants in interim HIV testing (between scheduled study visits), use of hormone therapy or medications

for mental health indications, and adverse events. Independent sample t-tests were used to compare cisgender and transgender participants' retention (missed visits and discontinuation of vaccination), reasons for enrolling, negative social impacts, and social benefits. Statistical significance for all tests was defined as a p value < 0.05.

HIV incidence data were derived from results of HIV-testing assays conducted during the main study period. Total follow-up time in the main study for each group was obtained by summing follow-up times for all group members. In this analysis, follow-up time for individuals is the time from study enrollment to the date of the last HIV-test performed in the main study period for participants that remain HIV-1 uninfected, and from enrollment to date of diagnosis during the main study period for those participants who became HIV-1 infected. HIV-incidence rates were compared using an exact test of homogeneity of Poisson rates. The test was performed in R (3.2.3) using function poisson.test of package 'stats'. An exact test was employed due to the small number of infections in each group.

3. Results

Participants [N = 694, mean age = 27 years (SD = 7.8)] were 388 (55.9%) cisgender men, 292 (42.1%) cisgender women, 12 (1.7%) transgender women, and 1 (0.001%) transgender man (Table 1). All transgender individuals were enrolled at US sites. The majority of participants were White (69.2%). Over thirteen percent (13.5%, n = 94) were Black/African American, 9.1% (n = 63) identified as some other race, 3.9% (n = 27) identified as multiracial, 3.5% (n = 24) identified as Asian and 0.70% (n = 5) identified as Native American/Alaskan Native/Native Hawaiian/Pacific Islander. Sixteen percent (n = 109) identified as Latinx. Forty-eight (44%) of the Latinx-identifying participants were from Peru.

Reasons for enrolling in an HIV vaccine trial were similar for transgender and cisgender participants. The most common reasons for enrolling were: to help find an effective vaccine (transgender 100% and 98% cisgender); to help their community (transgender 100% and cisgender 96%); and to be informed about HIV research (transgender 85% and 77% cisgender). Transgender individuals were more likely than cisgender participants to report knowing someone with an HIV infection as a reason for enrolling (62% vs 43%) and less likely to report financial incentives as a motivator (43% vs. 62%) (Fig. 2).

In total, 3963 pre-existing conditions were reported in the sample. Transgender individuals reported 198 pre-existing conditions (M 15.2, SD = 10.0) and cisgender individuals reported 3765 pre-existing conditions (M 5.5, SD = 4.2). Significant differences by gender identity were observed in reported pre-existing conditions (p = 0.004); however, approximately 10% of all pre-existing conditions reported by transgender individuals were for gender-identity-related conditions such as gender dysphoria. Removing the 10% of gender identity related conditions did not change the statistical significance (p = 0.011).

Significant differences were observed in reports of use of hormone therapy (p < 0.001) and medications for a mental health indication (p = 0.007). Nearly all transgender individuals (n = 12 (92%), p < 0.001) reported hormone therapy for a gender identity indication, while only 22% (n = 149) of cisgender participants reported any hormone therapy use. Among cisgender individuals, hormone therapy indications included contraception and irregular menses. Six (46%) transgender participants reported use of medication for a mental health indication, while 98 (14%) cisgender individuals reported use of medication for a mental health indication (p = 0.007).

As reported in Table 2, transgender participants reported a total of 62 adverse events (mean 4.8, SD = 3.9). Two adverse events were deemed related to the vaccine product and one of these was considered severe by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. Among cisgender participants, a total of 1886 adverse events were reported (mean 2.8, SD = 2.7). One hundred sixty-four were deemed related to vaccine product and 54 were considered severe by DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Although transgender participants experienced a greater number of adverse events on average than cisgender participants, no significant differences were observed in category or severity of adverse events.

Across all six of the trials included in the analysis, retention of transgender participants was excellent with only three (2.1%) missed visits and no discontinuation of vaccination. Retention was also very good among cisgender participants with only 203 (3.0%) missed visits and 49 (7.1%) discontinuations of vaccination. Transgender participants were significantly less likely to discontinue vaccinations than cisgender participants (p < 0.001).

Transgender participants reported no negative social impacts due to trial participation and 93% of transgender participants iden-

Table 1
Demographics of transgender and cisgender participants in phase 1-2a HIV Vaccine Trial Network Trials, 2009–2014.

Participant Characteristic		Transgender N = 13 n (%)	Cisgender N = 681 N (%)	All Participants N = 694 N (%)
Age	Median (SD)	25yo (2.4)	25yo (7.8)	25yo (7.8)
Race	White	10 (76.9)	470 (69)	480 (69.2)
	Black/African American	1 (7.7)	93 (13.7)	94 (13.5)
	Multiracial	1 (7.7)	26 (3.8)	27 (3.9)
	Asian	0	24 (3.5)	24 (3.5)
	Native American/Alaskan Native/Native Hawaiian/Pacific Islander	0	5 (0.7)	5 (0.7)
	Other	1 (7.7)	62 (9.1)	63 (9.1)
Country of Origin	Peru	0	48	48
	United States	13	633	646
Ethnicity	Latinx	3 (23.1)	106 (15.6)	109 (15.7)
Sex assigned at birth	Male	1 (7.7)	388 (57)	389 (56.1)
	Female	12 (92.3)	293 (43)	305 (43.9)
Gender	Male	6 (46)	388 (57)	394 (56.8
	Female	1 (8)	293 (43)	294 (42.4)
	Transgender Male	5 (38)	0	5 (0.7)
	Non-Binary	1 (8)	0	1 (0.1)

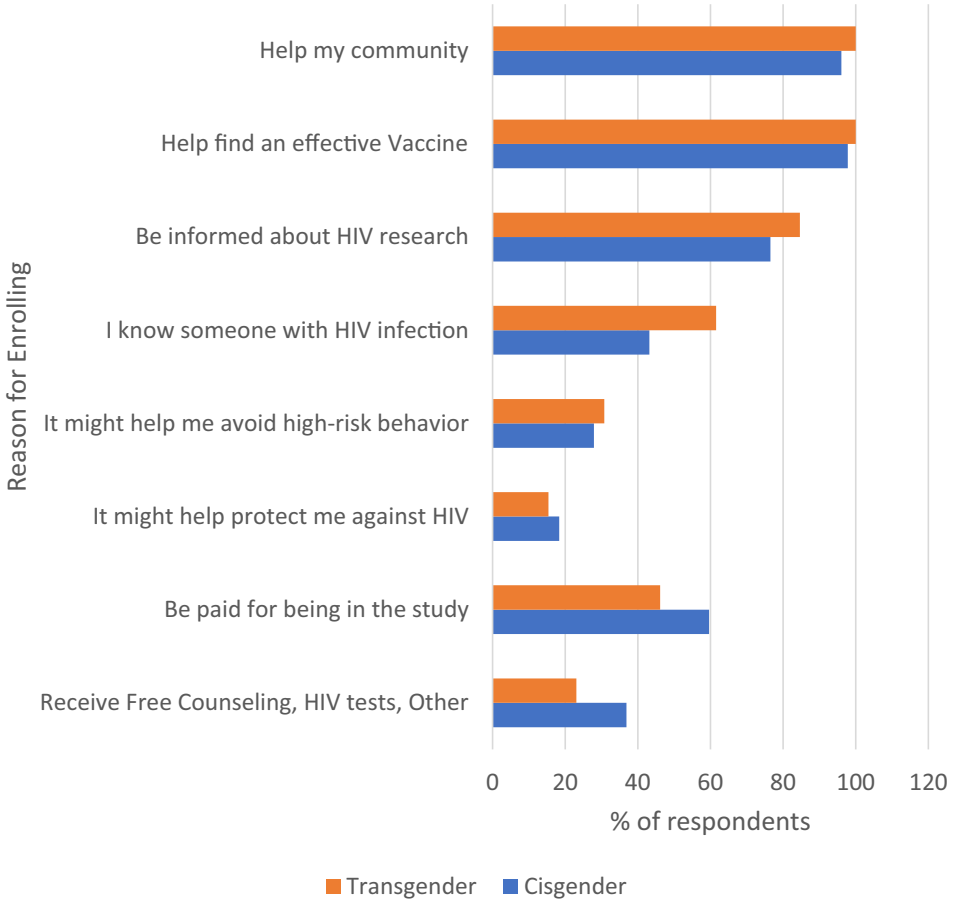

Fig. 2. Reasons for enrolling in Phase 1-2a HIV Vaccine Trial Network Trials 2009–2014.

Table 2
Comparison of missed visits, vaccine discontinuations, pre-existing conditions, adverse events, medications among transgender and cisgender participants in phase 1-2a HIV Vaccine Trial Network Trials, 2009–2014.

Variable		Transgender n = 13		Cisgender n = 681		p-value*
		Frequency	Mean (SD)	Frequency	Mean (SD)	
Missed Visits		3 (2.1%)	0.23 (0.60)	203 (3.0%)	0.29 (0.81)	0.716
Discontinuation of Vaccinations†		0	N/A	49 (7.1%)	0.07 (0.26)	0.000
Ppts Reporting Outside HIV Testing		0	0 (0)	22 3.2%)	0.03 (0.20)	0.561
Pre-existing Conditions		198♦	15.23 (10.0)	3765	5.53 (4.24)	0.004*
Adverse Events	Any AE	62	4.80 (3.94)	1886	2.77 (2.68)	0.093
	AE deemed related only	2	0.15 (0.38)	164	0.24 (0.68)	0.647
	Severe AE only	1	0.08 (0.28)	54	0.08 (0.37)	0.982
Ppts Reporting Medication for Mental Health†		6 (46%)	N/A	98 (14.3%)	N/A	0.007*
Ppts Reporting Hormone Therapy†		12 (92%)	N/A	148 (21.8%)	N/A	<0.001*

* Statistically significant.
† Fisher's exact test.
♦ Approximately 10% of these are directly referable to the participants' transgender identity (e.g., "gender identity disorder" or "post-mastectomy").

tified having experienced at least one social benefit of participation. Seven percent of cisgender participants reported a negative social impact. The large majority of these (84%) were negative attitudes about study participation expressed by family, friends and/or intimate partners, and less than 2 percent were reported as a moderate or major disturbance. Eighty three percent of cisgender participants reported having experienced at least one social benefit of participation. The most common benefit across all participants was feeling good helping others (96% transgender, 77% cisgender). Other common social benefits included receiving medical care (82% transgender and 61% cisgender), receiving risk reduction counseling (31% transgender, 14% cisgender), and positive impacts on personal relationships (31% transgender, 18% cisgender) (Table 3).

There was a large observed difference in HIV incidence estimates between transgender (0.1024 [95% CI: 0.0025, 0.5708]) and cisgender participants (0.0038 [95% CI: 0.0005, 0.0136]) however it fell just short of statistical significance (p = 0.053). In our analysis of the 3 individuals who became HIV infected, 2 identified as MSM and 1 as transgender; 1 identified as Latinx; 1 identified as White, 1 Black and another as "Other" race; 1 was from Peru and 2 were from the US.

Table 3
HIV Incidence of transgender and cisgender participants in phase 1-2a HIV Vaccine Trial Network Trials, 2009–2014. There is no statistically significant difference in HIV incidence between transgender & cisgender participants in Phase 1-2a HVTN trials.

Group	Number Infected	Total person-years follow-up	Rate (infections/person-years)	95% CI for the rate
Transgender (n = 13)	1	9.76	0.1024 (9.58/100p-y)	(0.0025, 0.5708)
Cisgender (n = 666[†])	2	532.39	0.0038 (0.38/100p-y)	(0.0005, 0.0136)

[†] Data missing for 15 cisgender participants (p = 0.05).

4. Conclusions

Transgender people enrolled in Phase 1-2a preventive HIV vaccine trials across the HVTN are motivated participants with excellent retention and adherence to clinic visits, comparable to or exceeding that of cisgender participants. Although 1 transgender individual in this analysis became HIV infected, the remaining 12 transgender individuals with lower HIV risk profiles who enrolled in these preventive HIV vaccine trials were able to maintain low risk profiles for the duration of their trial participation. It is critical to note that transgender individuals' participation in and eligibility for these "low risk" trials is often met with concern due the incidence and prevalence of HIV in their communities. Our data provide evidence that transgender individuals can not only be eligible for low risk trials, but are also able to remain HIV uninfected over the course of trial participation, though with the small number of transgender individuals enrolled in these trials our statistical power to evaluate this is limited. The ongoing receipt of risk reduction counseling, a benefit endorsed by over 30% of transgender participants across these trials, may be an important influence on risk.

Transgender vaccine trial participants at low risk of HIV infection—and, thus, eligible to participate in Phase 1-2a trials—are more likely to be in communities of high HIV incidence, which may explain one key difference in trial participation motivators among transgender and cisgender participants: more transgender participants than cisgender participants cite knowing someone with HIV as a motivator to contribute to a preventive HIV vaccine trial. For the majority of transgender individuals in this analysis, altruism and concern for their community were the primary motivators reported for enrolling in a preventive HIV vaccine clinical trial. Given the well-established economic challenges faced by transgender people, it is important to note that we found that altruism outweighs financial incentives in decisions to participate in preventive HIV vaccine research. The initial motivation of altruism may be strengthened by the positive feelings associated with helping others they experienced as a trial participant.

Our findings underscore the heightened vulnerability of transgender participants who were more likely to report use of medication for mental health and hormone therapy, and were more likely to have a greater number of pre-existing conditions. Mental illness incidence approximated that reported from other surveys [6,9,17] of transgender individuals and, importantly, was not accompanied by social impacts or poor trial retention (eg, missed visits), indicating that these factors did not detract from participation. Indeed, the rates of adverse events and retention are similar among transgender and cisgender participants. An earlier systematic review found that among patients receiving trans-affirmative healthcare, 80% reported improved quality of life and decreased mental health concerns [23]. Importantly, the HVTN has implemented several data-driven strategies [24–26] to create gender-affirming environments across the Network. Although not measured in this study, receipt of ongoing care and risk reduction counseling in gender affirming environments may also motivate continued participation and retention. In our sample, 92% of the transgender participants indicated that medical care was a benefit of participation, and this may be a powerful contributor to retention rates.

Our work, of course, is not without limitations. The generalizability of the current study is limited by the cross-sectional analyses of self-report data. Due to the small dataset of transgender participations, only limited conclusions can be drawn. This is particularly true of the HIV incidence data. The vast majority of phase 1 trials conducted by the Network did not collect data that would allow for the identification of discordant sex assigned at birth and current gender identity. As such, there may be several transgender individuals who have not been identified in these trials, and are either not included in these analyses or are included as cisgender participants.

The unequal health burden borne by transgender individuals, particularly transgender women, has long been evident. Few studies of any kind have been conducted with transgender men. The inclusion of transgender individuals in HIV research is paramount in any efforts to effectively address HIV in their community. Although our findings do not draw a complete map for inclusion of transgender participants in phase 1-2a clinical trials, we believe our results illustrating the importance, benefits, and contribution of transgender participation, provide some direction and evidence-based support for the inclusion of transgender individuals in early phase preventive HIV clinical trial research.

Declaration of Competing Interest

Mary Allen is employed by NIAID, the study sponsor. The coauthors are current recipients of NIAID funding, and the publication is a result of activities funded by NIAID. Ms. Allen was not involved in the process of funding these awards, nor in their administration or scientific aspects, and, in accordance with NIAID policies, is deferred from decisions regarding funding of coauthors for a requisite period. None of the other authors have competing interests.

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