The Journal of Infectious Diseases

SUPPLEMENT ARTICLE

Characteristics of REPRIEVE Trial Participants Identifying Across the Transgender Spectrum

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Because persons who identify across the transgender spectrum (PATS) are a key population in human immunodeficiency virus (HIV) yet are underreported in HIV and cardiovascular research, we aimed to characterize this population within the REPRIEVE global clinical trial (n = 7770). Acceptance of gathering gender identity was high (96%). Participation by PATS was 1.7% overall, 2.4% among natal males, 0.3% among natal females, and varied across geographic regions (from 0% in sub-Saharan Africa to 2.3% in High Income Region). Thirty percent of natal male PATS identified other than transgender. Some characteristics differed by gender. Most notably, 38% of natal male PATS receiving gender-affirming treatment had waist circumference >102 cm (compared with ≤25% in other groups). Given that PATS is a key population, HIV research should routinely report trial participation and outcomes by gender in addition to natal sex, to provide the results needed to optimize medical care to PATS.

Keywords. cardiovascular; gender-affirming hormone treatment; gender identity; HIV; transgender spectrum.

Individuals whose gender identity differs from their sex assigned at birth—transgender persons and persons identifying across the transgender spectrum, hereafter referred to collectively as PATS—are at increased risk for acquiring human immunodeficiency virus (HIV) and are overrepresented among persons with HIV (PWH) in the United States and around the world. Recent prevalence estimates of HIV in the United States are 14.1% (95% confidence interval [CI], 8.7%–22.2%) among trans women and 3.2% (95% CI, 1.4%–7.1%) among trans men [1]. Across 15 countries, pooled HIV prevalence estimates among PATS are 19.1% (95% CI, 17.4%–20.7%), with odds 49 times that of all reproductive age adults across 16 countries [2]. PATS also experience high rates of gender-based discrimination stigma and violence [3, 4], which have deleterious effects on many health outcomes [5, 6]. Despite being a key population of PWH [7], this group is underrepresented in many areas of health research [8], including HIV clinical trials [9].

In age-adjusted comparisons with cisgender persons, PATS have significantly higher rates of myocardial infarction and death by cardiovascular disease (CVD), with excess risk suspected to be attributable to hormone use as part of gender-affirming treatment (GAT) [10]. In particular, estrogen use in GAT has been linked to more than 5-fold higher risk of venous thromboembolism [10]. Gender-affirming treatment using testosterone has been associated with increases in blood pressure, insulin resistance, and changes in lipid profiles such as higher low-density lipoprotein and lower high-density lipoprotein levels [10, 11]. Although associations between GAT and these and other CVD risk factors have been reported, causal linkage of GAT to excess CVD morbidity and mortality is complicated by (1) studies generally being conducted in young people (with low rates of other CVD risk factors) and (2) the absence of evidence from randomized clinical trials and prospective studies [11]. Among natal male PWH in the United States, PATS have a higher prevalence of anemia compared with age- and race-matched controls, but information on inflammation and immune activation is needed [12]. There is potential for drug-drug interactions (DDIs) between antiretroviral treatment (ART) and GAT, and adherence to ART may be compromised because of concern over these potential interactions [13]. Suboptimal control of HIV, either due to problems with medication adherence or DDIs, may contribute to the increased risk of CVD in this population. Given that characterization of the PATS community in the context of HIV is scarce, we aimed to better understand gender identity within an ongoing, global randomized clinical trial for CVD prevention among midlife PWH.

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The Journal of Infectious Diseases® 2020;222(S1):S31–40

DOI: 10.1093/infdis/jiaa213

OBJECTIVES

We evaluated participant and research personnel acceptability of self-identified gender assessment in the context of a global HIV clinical trial. We also evaluated whether the observed percentage of PATS is representative of the larger population from which the study sample is drawn. We summarized and compared a subset of baseline characteristics by gender within natal sex. Finally, we described use of gender-affirming hormones/hormone blockers as part of GAT.

METHODS

REPRIEVE (ClinicalTrials.gov Identifier: NCT02344290; date of initial registration: January 22, 2015) enrolled PWH between 40 and 75 years of age, on stable combination ART with $CD4^+$ lymphocyte count >100 cells/mm^3 and low to moderate traditional CVD risk by the American College of Cardiology/American Heart Association risk calculator [14]. Enrollment occurred between March 2015 and July 2019 at sites in United States, Canada, and Spain (High Income Global Burden of Disease [GBD] region); Brazil, Peru, Puerto Rico, and Haiti (Latin America and Caribbean GBD region, hereafter called Latin America); Thailand and India (Southeast/East Asia and South Asia GBD regions, hereafter called Asia); and South Africa, Uganda, Zimbabwe, and Botswana (sub-Saharan Africa GBD region, hereafter called Africa). Each research site obtained institutional review board/ethics committee approval and any other applicable regulatory entity approvals. Participants received study information, including discussion of risks and benefits, and were asked to sign the approved declaration of informed consent. Further details about trial design and objectives have been published [14], and a summary of baseline characteristics among all participants and Supplemental Methods for REPRIEVE can be found elsewhere in this issue.

Collection of Sex Assigned at Birth, Current Gender Identity, and Exogenous Sex Hormone Use

Participants' sex assigned at birth (ie, natal sex) was collected during the screening process and was used to stratify treatment randomization. Collection of current gender identity in REPRIEVE was introduced in early 2017, after the trial had been enrolling participants for almost 2 years. For those participants enrolled subsequently, gender identity was to be collected during the entry visit. For participants enrolled before 2017, current gender identity was to be collected at the next observed clinic visit (scheduled every 4 months).

Gender identity (but not natal sex or sexual orientation) was recorded after an interview with the participant, rather than the self-directed questionnaire. Researchers recorded all identities endorsed by the participant (male, female, transgender male, transgender female, gender queer, gender variant, gender nonconforming, and self-identify), with self-identification captured in open-text. There were 2 additional reporting categories: "Prefer not to answer" (to record cases of participant opt-out) and "Information not Collected" (to record when the interview was not performed). Research staff did not receive any study-specific training regarding collecting gender identity. Clinical research sites affiliated with the AIDS Clinical Trials Group ([ACTG] which recruited 62% of REPRIEVE participants) received additional information regarding gender identity collection when the network data collection began in 2016. Starting in August 2018, sites not affiliated with ACTG had access to transgender-focused training materials and online courses via the Division of AIDS (DAIDS) Learning Portal.

To preserve confidentiality of participant responses, open-text responses were aligned to the following from the National Institute of Allergy and Infectious Diseases DAIDS language reference guide [15] for reporting: nonbinary, genderqueer, gender nonconforming, gender fluid, agender, bigender, pangender, trans(gender), and cisgender.

Because natal sex is an important variable with respect to HIV and clinical research [16], we report groups by both sex and gender identity. Persons identifying across the transgender spectrum includes trans men and trans women, as well as other identities across the transgender spectrum listed above. Persons whose natal sex aligned with gender identity were labeled cisgender. The resulting mutually exclusive groups are natal female PATS (PATS-F), natal male PATS (PATS-M), cisgender women (CIS-F), and cisgender men (CIS-M). We limit named reporting by location to GBD region.

Participants' sexual orientation was not collected. Endorsed mode(s) of HIV acquisition may have included answers such as "homosexual contact" or "heterosexual contact". We reported modes of HIV acquisition as endorsed, without adjustment for gender identity.

Trial materials noted that spironolactone for gender affirmation did not require reporting. However, this as well as other antiandrogens (eg, cyproterone, finasteride) were reported, and so they are summarized here. Gender-affirming treatment utilization informed the quality control processes on classification by natal sex and gender, and absence of GAT was confirmed.

Statistical Analysis

To assess whether the observed percentage of PATS in REPRIEVE is representative of the percentage of PATS among PWH in the absence of a directly estimated percentage, we performed a simulation using external inputs [1, 17, 18] to Bayes' theorem [19] to estimate a CI or plausible range of percentages. Details of this simulation appear in the Supplemental Materials.

Within natal males, selected baseline characteristics were compared between PATS-M and CIS-M using either χ^2 tests (for discrete outcomes) or Wilcoxon's rank-sum tests (for continuous outcomes). Because gender identity may change over time, we repeated comparisons within the subset of participants

where gender identity was available within the first year after enrollment. We also repeated comparisons excluding geographic regions where no PATS were reported. Inference was based on a nominal significance level (0.05) for all comparisons, with no formal adjustment for multiple comparisons. Therefore, interpretation of statistical significance (*P* values) should be made in light of the number of comparisons performed. Due to small sample sizes, formal statistical comparisons were not performed between PATS-F and CIS-F groups. All analyses used SAS for the UNIX platform version 9.4.

RESULTS

Gender Identity Collection

Of the 7770 participants enrolled in REPRIEVE, gender identity is available from 7492 (96%) (Table 1). The majority of participants without gender identity discontinued trial follow-up before an interview (190 participants, 2% of the trial sample; 2–3 of those missing gender). Only 7 participants (0.1% of the trial sample) opted out of providing gender identity. Research site personnel did not collect gender identity for 81 participants (1%); most of these cases are located at various research sites in North America or Europe (data not shown).

Gender Identity Reporting

The percentage of PATS participating in REPRIEVE is 1.7% (129 of 7492), up to 4.7% by country (data not shown), and ranging from 0% in Africa to 2.3% in High Income Region (Table 2). Among 2367 natal females, 8 (0.3%) identify across the transgender spectrum, reflecting up to 1.7% by country (data not shown). The percentages of PATS-F range from 0% in Africa to 0.7% in High Income Region (Table 2). Seven of these 8 participants identify as male or transgender male, and 1 identifies as genderqueer.

Among 5125 natal males, 121 (2.4%) identify across the transgender spectrum, reflecting up to 6.7% by country. Across geographic regions, the percentages of PATS-M range from 0% in Africa, 2.1% in Latin America, 2.7% in High Income Region, to 2.9% in Asia (Table 2). A total of 85 (70%) of these participants' identities is either female or transgender female. There is diversity among the gender identities of the remaining 36 participants: genderqueer persons (22), gender nonconforming persons (8), bigender persons (2), and 1 of each the following identities: agender, gender fluid, nonbinary, and pangender.

From the simulation using population inputs published in meta-analyses [1], population-based surveys [17], and Centers for Disease Control and Prevention HIV prevalence estimates [18], the estimated lower bound of the 95% CI for the percentage of PATS-M living with HIV from the United States was 7%. This lower bound implies that the true, but unknown percentage of adult, natal males living with HIV in the United States who identify across the transgender spectrum is higher than 7%, and as such it represents a potential benchmark for representation. The observed percentage of PATS-M within the subset of US sites participating in REPRIEVE was 2.9% (data not shown).

Gender-Affirming Treatment With Sex Hormones or Sex Hormone Blockers

Among the 8 PATS-F, 1 (11%) reported current testosterone use at trial entry. Among the 121 PATS-M, a total of 46 (38%) reported current or recent use of GAT, and among the 85 PATS-M who identify as female or trans female, 45 (53%) reported GAT. Among the 46, 25 reported estrogen-only, 12 reported estrogen plus antiandrogen (spironolactone, cyproterone, or finasteride), 4 reported estrogen plus progesterone, 3 each reported antiandrogen only, and 2 reported medications from all groups. Gender-affirming treatment use was associated with region: 49% among PATS-M from High Income Region: 29% from Latin America; and none from Asia.

Clinical Characteristics by Sex and Gender

A subset of baseline characteristics among participants is provided by gender group within natal sex (Tables 3 and 4). Among natal males, age was similar but race differed by gender, which follows from differing representation across regions. Although smoking and alcohol rates were similar, half (50%) of PATS-M reported current or former substance use (including use of cocaine, methamphetamine, or intravenous drug [IV]), compared with 35% of CIS-M. Difference by gender was not observed when comparing only IV drug use (data not shown) (Table 3).

Many CVD and metabolic risk factors are observed to be similar between groups (Table 3). However, differences

Table 1. Derivation of Analysis Sample

Participant Milestone	Total	Natal Females	Natal Males
Enrolled	7770	2418	5352
Gender identity not available/unknown	278 (4%)	51 (2%)	227 (4%)
• Discontinued trial participation before interview for gender identity	(190)	(39)	(151)
• Participant opted out of providing gender identity	(7)	(1)	(6)
• Research site did not perform gender identity interview	(81)	(11)	(70)
Gender identity available	7492 (96%)	2367 (98%)	5125 (96%)
Gender assessed within 1 year of entry	6002	1955	4047
Gender assessed >1 year postentry	1490	412	1078

Table 2. Distribution of Gender Identity Groups by Natal Sex and GBD Region

	Total	High Income	Latin America and Caribbean	Southeast/East Asia/South Asia	Sub-Saharan Africa
Sample Subgroup	(N = 7492)	(N = 3823)	(N = 1419)	(N = 1090)	(N = 1155)
Among All Participants, n (%)					
PATS	129 (1.7%)	88 (2.3%)	22 (1.6%)	19 (1.7%)	0 (0%)
CIS	7363	3740	1397	1071	1115
Among Natal Females, n (%)					
PATS-F	8 (0.3%)	6 (0.7%)	1 (0.3%)	1 (0.2%)	0 (0%)
CIS-F	2359	823	401	461	674
Among Natal Males, n (%)					
PATS-M	121 (2.4%)	82 (2.7%)	21 (2.1%)	18 (2.9%)	0 (0%)
CIS-M	5004	2917	996	610	481

Abbreviations: CIS, cisgender persons; GBD, global burden of disease; PATS-F(M), persons identifying across transgender spectrum among natal females (males); PATS, persons identifying across the transgender spectrum.

are observed for high waist circumference, defined as >102 centimeters. Approximately one quarter of PATS-M (26%) have a high waist circumference compared with approximately one fifth of CIS-M (19%). As shown in Table 5, this difference may be attributed to the subset of PATS-M taking GAT, among whom the rate is 38%. By contrast, PATS-M not taking GAT have similar rates compared with CIS-M (19% in both groups across all regions, and 22%–25% in both groups within the High Income and Latin American regions where GAT was reported). In Table 3, fewer PATS-M (31%) have renal function abnormality (estimated glomerular filtration rate <90 mL/min per 1.73 mm^2; see Supplemental Methods for REPRIEVE for details), compared with 41% of CIS-M. As noted in Overton et al [20] elsewhere in this issue, urine albumin results, available in the future, may provide further insight into this difference. Male PATS have slightly lower hemoglobin levels compared with CIS-M (Table 3). This difference is stronger when PATS-M are divided by GAT use (Table 5). However, hemoglobin between the lower eligibility limit of 9 and 11 g/dL (threshold for abnormal hemoglobin [21]) was rare in all groups (≤2.5%) (Table 5).

Although groups are similar in age (median 50 years) (Table 3), PATS-M have more years since HIV diagnosis than CIS-M (medians of 16 and 12 years, respectively), and similarly more years of ART use (medians of 12 and 10 years, respectively) (Table 4). Self-reported mode of HIV acquisition differs by gender; although homosexual contact is the most common route reported in both groups, it was endorsed by 82% PATS-M compared with 50% of CIS-M; whereas heterosexual contact was endorsed by 6% and 35%, respectively. Differences by gender in HIV disease stage or treatment, or other comorbidities, were not observed. Exposure to thymidine analogs was similar (48%, median 7 years among PATS-M; 47%, median 6.7 years among CIS-M) (data not shown).

Comparisons among those natal males whose gender was known near baseline (n = 4047, ie, excluding natal males first enrolled, who were mostly from the United States) were similar (data not shown). After excluding all 1115 CIS-M from Africa, observed differences for substance use and waist circumference were slightly attenuated (eg, 26% high waist circumference among PATS-M versus 20% among CIS-M).

Parallel characteristics are summarized by gender subgroup within natal females (PATS-F and CIS-F) in Tables 3 and 4. As previously noted, small sample size precluded formal comparisons. The median ages were 48 among PATS-F and 49 years among CIS-F. Even though no PATS-F were reported in Africa, a majority, irrespective of gender, self-identify as black (or African American), in contrast to natal males (approximately one third identify as black). Among PATS-F, most (6 of 8) were current or former smokers, whereas two thirds of CIS-F were never smokers. Similar to natal males, the number people reporting current or former substance use (3 of 8) among PATS-F is numerically higher than CIS-F. The body habitus and lipid profiles among PATS-F do not appear to be different from CIS-F. Persons identifying across the transgender spectrum among natal females have a median of 19 years since HIV diagnosis, which is numerically higher than CIS-F and appears parallel to gender comparison within natal males. Similar to natal males, exposure to thymidine analogs was 5 of 8, 63% (median 6 years) among PATS-F and 55% (median 6 years) among CIS-F (data not shown).

DISCUSSION

In this analysis of gender identity within a global randomized clinical trial for CVD prevention among midlife PWH, we observed that collecting gender identity was feasible, and that representation of PATS varied across GBD regions and by natal sex. Based on estimated targets within the United States, we observed that PATS-M are likely underrepresented in the current trial, likely due to known selection biases such as, but not limited to, barriers accessing healthcare. Among natal males, where there were enough PATS to perform comparisons, we observed that PATS have significantly higher

Table 3. Demographics, Behavioral, Cardiovascular, and Metabolic Characteristics by Gender Group Within Natal Sex

	Natal Males			Natal Females[b]	
Characteristic[a]	PATS-M (N = 121)	CIS-M (N = 5004)	*P* Value	PATS-F (N = 8)	CIS-F (N = 2359)
Demographics and Behavioral					
Age (years)					
Median (Q1, Q3)	50 (45, 53)	50 (46, 55)	.10*	48 (45, 57)	49 (44, 55)
Race					
Black or African American	35 (29%)	1810 (36%)	<.01**	5 (63%)	1412 (60%)
White	46 (38%)	2159 (43%)		1 (13%)	358 (15%)
Asian	19 (16%)	648 (13%)		1 (13%)	464 (20%)
Other	21 (17%)	387 (8%)		1 (13%)	125 (5%)
Smoking status					
Current	33 (27%)	1385 (28%)	.42**	4 (50%)	401 (17%)
Former	41 (34%)	1434 (29%)		2 (25%)	363 (15%)
Never	47 (39%)	2182 (44%)		2 (25%)	1591 (68%)
Substance use					
Current	3 (3%)	117 (2%)	<.01**	0 (0%)	25 (1%)
Former	56 (47%)	1650 (33%)		3 (38%)	417 (18%)
Never	61 (51%)	3235 (65%)		5 (63%)	1913 (81%)
Alcohol use					
Usually/Often	9 (8%)	330 (7%)	.81**	1 (13%)	58 (2%)
Sometimes	24 (20%)	1108 (22%)		2 (25%)	347 (15%)
Rarely/Never	87 (73%)	3555 (71%)		5 (63%)	1948 (83%)
Cardiovascular and Metabolic					
History of hypertension	29 (24%)	1021 (20%)	.34**	3 (38%)	672 (28%)
History of diabetes	2 (2%)	45 (1%)	.39**	1 (13%)	17 (1%)
BMI (kg/m^2)					
Median (Q1, Q3)	25.8 (23.2, 29.4)	25.3 (22.5, 28.3)	.16*	25.3 (22.4, 28.8)	27.2 (23.3, 32.0)
<18.5	1 (1%)	200 (4%)	.31**	1 (13%)	82 (3%)
18.5–24.9	53 (44%)	2178 (44%)		3 (38%)	774 (33%)
25–29.9	43 (36%)	1809 (36%)		3 (38%)	710 (30%)
30–34.9	16 (13%)	623 (12%)		0 (0%)	395 (17%)
35–39.9	5 (4%)	132 (3%)		0 (0%)	256 (11%)
40+	3 (2%)	56 (1%)		1 (13%)	141 (6%)
Waist Circumference[c]					
Normal	88 (74%)	4004 (81%)	.05**	5 (63%)	876 (38%)
High	31 (26%)	938 (19%)		3 (38%)	1448 (62%)
Triglycerides (mg/dL)					
Median (Q1, Q3)	129 (84, 175)	122 (84, 182)	.62*	85 (61, 266)	102 (75, 144)
LDL-C (mg/dL)					
Median (Q1, Q3)	101 (80, 121)	107 (86, 127)	.21*	81 (65, 97)	111 (90, 131)
HDL-C (mg/dL)					
Median (Q1, Q3)	47 (38, 56)	45 (37, 56)	.41*	60 (55, 66)	54 (45, 65)
eGFR (mL/min per 1.73 mm^2)[d]					
<60	1 (1%)	139 (3%)	.04**	1 (13%)	49 (2%)
60 to <90	36 (30%)	1922 (38%)		2 (25%)	643 (27%)
≥90	84 (69%)	2942 (59%)		5 (63%)	1665 (71%)
HGB (g/dL)					
Median (Q1, Q3)	14 (13, 15)	15 (14, 16)	<.01*	13 (13, 14)	13 (12, 14)

Abbreviations: BMI, body mass index; CIS-F, cisgender women; CIS-M, cisgender men; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HGB, hemoglobulin; LDL-C, low-density lipoprotein cholesterol; PATS-F, persons identifying across the transgender spectrum among natal females; PATS-M, persons identifying across the transgender spectrum among natal males.

[a]All statistics are calculated out of participants with data collected. Missing data include the following: smoking status (n = 7); substance use (n = 7); alcohol use (n = 18); BMI (n = 7); waist circumference[c] (n = 99); medical history (n = 4).

[b]Statistical comparisons among natal females are not made because the cohort size is too small to detect meaningful differences.

[c]High waist circumference classified as >102 cm in natal males and >88 cm in natal females. Waist circumference and BMI are the only 2 anthropometric measurements evaluated.

[d]Calculated by CKD-EPI formula.

*Wilcoxon *P* value.

**χ^2 *P* value.

Table 4. HIV-Related Health Status and Comorbidity Characteristics by Gender Group Within Natal Sex

	Natal Males			Natal Females[b]	
Characteristic[a]	PATS-M (N = 121)	CIS-M (N = 5004)	*P* Value	PATS-F (N = 8)	CIS-F (N = 2359)
HIV-Related Health Status					
Time since HIV diagnosis (years)					
Median (Q1, Q3)	16 (9, 21)	12 (7, 19)	<.01*	19 (9, 26)	13 (8, 19)
Mode of HIV Acquisition					
Heterosexual contact	7 (6%)	1741 (35%)	<.01**	4 (50%)	2112 (90%)
Homosexual contact	99 (82%)	2495 (50%)		1 (13%)	17 (1%)
Multiple modes	4 (3%)	237 (5%)		1 (13%)	26 (1%)
Injection drug use	3 (2%)	146 (3%)		2 (25%)	39 (2%)
Does not want to report	0 (0%)	54 (1%)		0 (0%)	4 (<0.5%)
Transfusion	1 (1%)	25 (<0.5%)		0 (0%)	31 (1%)
Occupational exposure	1 (1%)	18 (<0.5%)		0 (0%)	14 (1%)
Hemophilia-association injections	1 (1%)	6 (<0.5%)		0 (0%)	0 (0%)
Unknown	5 (4%)	279 (6%)		0 (0%)	115 (5%)
Nadir CD4 count (cells/mm^3)					
<50	26 (21%)	943 (19%)	.21**	2 (25%)	378 (16%)
50–199	32 (26%)	1507 (30%)		1 (13%)	788 (33%)
200–349	35 (29%)	1320 (26%)		2 (25%)	610 (26%)
≥350	28 (23%)	1052 (21%)		3 (38%)	522 (22%)
Unknown	0 (0%)	182 (4%)		0 (0%)	61 (3%)
History of AIDS-defining event	30 (25%)	1220 (24%)	.92**	1 (13%)	565 (24%)
CD4 count (cells/mm^3)					
<350	17 (14%)	784 (16%)	.21**	1 (13%)	224 (10%)
350–499	17 (14%)	988 (20%)		1 (13%)	377 (16%)
≥500	87 (72%)	3227 (65%)		6 (75%)	1755 (74%)
HIV-1 RNA below LLQ (copies/mL)					
<20	54 (53%)	1929 (48%)	.37**	6 (86%)	663 (40%)
<40	37 (36%)	1465 (37%)		1 (14%)	703 (42%)
<400	0 (0%)	99 (2%)		0 (0%)	88 (5%)
≥LLQ	11 (11%)	489 (12%)		0 (0%)	202 (12%)
Total ART use (years)					
Median (Q1, Q3)	12 (7, 16)	10 (5, 15)	.02*	12 (8, 18)	10 (5, 14)
ART regimen class					
NRTI + NNRTI	46 (38%)	2188 (44%)	.65**	3 (38%)	1372 (58%)
NRTI + INSTI	38 (31%)	1438 (29%)		2 (25%)	388 (16%)
NRTI + PI	22 (18%)	902 (18%)		2 (25%)	455 (19%)
NRTI-sparing	5 (4%)	135 (3%)		1 (13%)	48 (2%)
Other NRTI-containing	10 (8%)	339 (7%)		0 (0%)	96 (4%)
Other Comorbidities					
History of cancer	6 (5%)	209 (4%)	.67**	0 (0%)	64 (3%)
History of non-AIDS cancer	3 (2%)	104 (2%)	.76**	0 (0%)	40 (2%)
History of kidney disease	0 (0%)	24 (<0.5%)	.44**	0 (0%)	4 (<0.5%)
Chronic active HBV	4 (3%)	151 (3%)	.86**	0 (0%)	39 (2%)
Chronic active HCV	5 (4%)	99 (2%)	.10**	0 (0%)	36 (2%)

Abbreviations: AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; CIS-F, cisgender women; CIS-M, cisgender men; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INSTI, integase strand tranfer inhibitors; LLQ, below the limit of quantification; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PATS-F, persons identifying across the transgender spectrum among natal females; PATS-M, persons identifying across the transgender spectrum among natal males; PI, protease inhibitors; RNA, ribonucleic acid.

[a]All statistics are calculated out of participants with data collected. Missing data include the following: time since HIV diagnosis (n = 3); HIV-1 RNA below LLQ (n = 1745); total ART use (n = 2); ART regimen class (n = 2); medical history (n = 4).

[b]Statistical comparisons among natal females are not made because the cohort size is too small to detect meaningful differences.

*Wilcoxon *P* value.

**χ^2 *P* value.

rates of waist circumference >102 cm, and of substance use, but not smoking. It is notable that gender differences in high waist circumference appeared strongest among the subset of PATS-M using GAT where this rate was 38%, whereas PATS-M not using GAT had similarly lower rates (≤25%) to CIS-M. Moreover, these differences persisted when repeated

Table 5. Waist Circumference and Hemoglobin by Gender, Receipt of Gender-Affirming Treatment (GAT) at Study Entry and Region, Among Natal Males[a]

Characteristic	PATS-M Taking GAT	PATS-M not Taking GAT	CIS-M	*P* Value*
High waist circumference [>102 cm]				
Overall	17/46 38%	14/75 19%	937/5001 19%	.006
Within High Income and Latin American regions	17/46 38%	14/57 25%	863/3910 22%	.05
Hemoglobin g/dL: Median (Q1, Q3)				
Overall	13.7 (12.9, 14.4)	14.4 (13.7, 15.1)	14.8 (13.9, 15.6)	<.001
Within High Income and Latin American regions	13.7 (12.9, 14.4)	14.3 (13.5, 15.0)	14.8 (14.0, 15.6)	<.001
% with hemoglobin 9 to <11 g/dL				
Overall	2.2%	1.3%	0.7%	.2
Within High Income and Latin American regions	2.5%	2.4%	0.4%	.05

Abbreviations: CIS-M, cisgender men; GAT, gender affirming treatmeant; PATS-M, persons identifying across the transgender spectrum among natal males.

[a]GAT may include 1 or more of estrogen, progesterone, or antiandrogen (eg, spironolactone).

*P values from χ^2 tests among all 3 groups, except % with low hemoglobin, which reflects Fisher's exact test.

NOTE: All PATS-M taking GAT (n = 46) reside in the High Income and Latin American regions. All PATS-M with high waist circumference (n = 31) also happen to reside in these 2 regions.

within the High Income and Latin American regions, and so they are not confounded by representation from regions with lower distributions of body mass index or no representation among PATS. In interpreting this and other differences, it is important to note that this sample is drawn from a randomized clinical trial, and so it has selected for PWH engaged in care, receiving antiretroviral therapy, and meeting the other trial eligibility criteria. Therefore, this sample may not be representative of the larger population of midlife, PATS, or cisgender PWH. Nonetheless, this is an important signal observed from the subpopulation of PWH identifying across the transgender spectrum concerned with CVD prevention, for whom identification of such unique risk factors may be important.

Overall, 1.7% of REPRIEVE trial participants are PATS; this rate varied across geographic regions. No participants from Africa identifying as PATS raises the question of whether this reflects a truly lower percentage in this region, or whether differences in gender terminology [22], or social and cultural influences (eg, discrimination, stigma, or legal statutes) related to gender, influenced self-reporting among participants residing in Africa. In contrast to country-level data of PATS in the context of HIV in some regions, less is known about PATS in Africa [23, 24]. Given that there were fewer than 10 cases of participant opt-out and 1% of omission of gender identity interview for participants still in follow-up, we conclude that eliciting gender identity among midlife PWH who are participating in a clinical research trial is, in general, feasible and acceptable. These conclusions may not apply in Africa, where social stigma or discriminatory laws may prevent persons from revealing their gender, even in a confidential clinical research setting. Some sites in this region noted that due to transgender-oriented health services being provided elsewhere (eg, private sector), their research site does not typically serve the local PATS population. In addition, some sites in Africa were unaware of the ways to report cases of participant or site opt-out.

We observed that half of PATS-M who identify as female are using sex hormones or sex hormone blockers as part of GAT, and that approximately 10% of PATS-F are using testosterone-based GAT. Such treatment among PATS-M has been reported to be associated with increased cardiovascular event risk and various known CVD risk factors [10, 12, 25], but these reports have emphasized the knowledge gaps regarding these associations and their long-term implications [11]. Because only half of PATS-M who identify as female reported GAT, for efficacy and safety outcome analyses of REPRIEVE it may be important to (1) consider multiple subgroups informed by gender and (2) separately explore those with exposure to GAT.

In REPRIEVE, the percentage of PATS among natal females (PATS-F) is 0.3%, and among natal males (PATS-M) is 2.4%. Given that the simulation suggests a target percentage >7% among PATS-M in the United States, observation of 2.9% PATS-M from the United States suggests underrepresentation in REPRIEVE. A recent trial, whose results supported approval of tenofovir alafenamide for pre-exposure prophylaxis for men, enrolled cisgender MSM and transgender women. However, of >5000 participants enrolled, only 1.3% were transgender women [26]. The reported percentage of PATS participating in any of 6, phase III ACTG network trials (pooled sample size >5294), enrolling between 2003 and 2013, was only 0.25% [9]. Because access and retention to care are prerequisites to participation in trials, underrepresentation of PATS in clinical trials continues to occur. Given that this population experiences barriers along many steps in the HIV care continuum, such as lower retention in HIV-related medical care [27], reduced access to care, and lower adherence to antiretroviral therapy and viral suppression [28], more efforts are needed to engage this key population to fill knowledge gaps to optimize health outcomes. This issue is

compounded among natal female PATS, who by virtue of their sex are also historically underrepresented in HIV research [29].

One approach to reduce information gaps for underrepresented populations is to combine data across studies, using pooled or meta-analytic techniques [9, 30–32]. Challenges to this approach are (1) the requirement for complete and uniformly defined gender identity data and (2) distinguishing research results where natal sex is commonly mislabeled as gender [33]. Absence of a consensus on terminology is another hurdle to combining information across sources. With terminology such as trans-feminine, transgender women, trans male, and transgender, it is sometimes unclear whether those persons whose gender identity is not trans—eg, genderqueer, nonbinary, and other gender-nonconforming identities—are included (or not). In this report, we have presented yet another alternative, persons identifying across the transgender spectrum, or PATS. Because 30% of PATS-M in REPRIEVE did not identify as female or transgender female (and so are "not" captured by terms such as trans woman), we propose that more inclusive and clear terminology is warranted. There are recent efforts towards comprehensive collection and reporting by gender that will allow future pooling of data. National Institutes of Health-funded HIV collaborative networks have been collecting gender identities and revising procedures with the guidance of a cross-network working group focused on gender issues [34, 35]; in 2019, the ACTG mandated that all presentations of network studies include descriptions of participants by gender, in addition to sex. In July 2019, the US Department of Health and Human Services updated their Adult and Adolescent Antiretroviral Treatment guidelines with a new section—*transgender people with HIV*—under the special patient populations section [36]. The 2020 Conference for Retroviruses and Opportunistic Infections also mandated posters for accepted abstracts (1) present information on both sex and gender and (2) cite as a limitation the absence of either [37].

Other than pooling data across studies, alternative approaches to maximizing knowledge gain include quotas for overrepresentation of PATS within larger sized studies (while avoiding adding PATS to studies designed for men who have sex with men, which often results in little information gleaned about PATS due to an absence of disaggregated analyses [38]) and conducting studies designed for and exclusively enrolling PATS. Increasing the enrollment of PWH who are PATS into clinical trials, regardless of the research design, requires making the research enterprise more gender-inclusive by using strategies such as involving PATS more in the development of the research agenda and operations, as researchers and staff, and training of all clinical staff in gender-affirming practices.

Limitations

REPRIEVE did not strictly use the 2-step method, in which sex assigned at birth and gender identity are discussed and recorded at the same time. It is possible that this methodology, which has been endorsed and recommended by many as best practice [39], may have prevented the small number of cases in which participants provided sexual orientation rather than gender or endorsed a transgender identity that matched their natal sex.

Target percentages of PATS were estimated for 1 natal sex and region using a simulation and Bayes' theorem. Target percentages could not be estimated for many locations represented in this trial due to unknown inputs. The baseline characteristics analysis was biased by selecting out those participants discontinuing early, because they could not have provided gender identity due to the mid-trial introduction of the gender interview. Actual hormone use may be higher than reported here due to participants not revealing hormones obtained without a prescription.

Finally, the absence of any PATS in Africa is concerning; however, these data cannot provide a definitive reason. It is possible that underreporting, linked to social stigma, may have led participants to endorse cisgender identity or that the prevalence of PATS is lower in this region.

CONCLUSIONS

REPRIEVE instituted a collection of gender identity that appeared to be accepted by both participants and research staff. We noted that a large proportion of PATS did not define themselves as transgender but with other identities across the transgender spectrum. We also note that the percentage of PATS in the trial is probably less than the overall proportion of PATS with HIV in the United States and worldwide. This underrepresentation is likely due to factors such as less access to HIV care and research and the need to improve gender inclusiveness in recruitment and involvement in the clinical trial development process. Finally, we observed that although 26% of all PATS-M had waist circumference >102 cm (compared with only 19% of CIS-M), this rate was 38% within the subgroup of PATS-M receiving GAT, compared with 19% of PATS-M not on GAT. This lends additional evidence that GAT may contribute to CVD-related health risks. By consistently reporting gender identity and GAT use in studies, we will be able to fill the knowledge gaps needed to treat and prevent illness in PWH who identify across the transgender spectrum.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Simulation Methods

A total of 10 000 simulations sampled from 3 independent lognormal distributions, with the following properties: (1) from [1], the probability of a transgender women in the United States with HIV is 0.14 (95% CI, .087–.22); (2) from [17], the

probability of US adults ages 25–64 who identify as transgender is 0.0058 (95% credible interval, 0.0034–0.01); (3) from [18], the probability of a US male >13 years old having diagnosed HIV infection is 0.00565 (95% CI, .00554–.00577). From each simulation, Bayes' theorem calculated a target percentage of PWH who identify as PATS (within natal males from United States) from the 3 lognormal distributions as specified above. The 95% CI on the estimated target percentage was calculated from the observed 2.5th and 97.5th percentiles from the distribution of simulation-generated percentages.

Notes

Acknowledgments. We thank the study participants, site staff, and study-associated personnel for their ongoing participation in the trial. In addition, we thank the following: the AIDS Clinical Trial Group (ACTG) for clinical site support; ACTG Clinical Trials Specialists for regulatory support; the data management center, Frontier Science Foundation, for data support; and the Statistical and Data Management Center for statistical support.

Disclaimer. The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute or the National Institute of Allergy and Infectious Diseases, the National Institutes of Health, or the US Department of Health and Human Services.

Financial support. This work was funded by the National Heart, Lung, and Blood Institute (Grant Numbers U01 HL123336 and U01 HL123339) with additional support from the National Institute of Allergy and Infectious Diseases (NIAID) (UM1 AI068636, UM1 AI106701).

Supplement sponsorship. This supplement is sponsored by Massachusetts General Hospital, through NIH funding including U01HL123336.

Potential conflicts of interest. S. K. G. reports grant support through his institution from Kowa Pharmaceuticals America, Inc., and Gilead Sciences, Inc., for the conduct of the study and from Theratechnologies, Navidea, and Viiv Healthcare outside the submitted work. L. M. S. reports grants from the National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI) during the conduct of the study as well as grants from NIH/NIAID outside the submitted work. P. S. D. reports grant support from Kowa Pharmaceuticals America, Inc., and Gilead Sciences, Inc., for the conduct of the study. K V. F. reports an educational grant from Gilead Sciences, Inc., outside the submitted work. M. V. Z. reports an investigator-initiated research grant from Gilead Sciences, Inc., to her institution, outside the submitted work. H J. R. reports grants from NIH/NHLBI and Kowa Pharmaceuticals America, Inc., during the conduct of the study. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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