HIV incidence and mortality in transgender women in the eastern and southern USA: a multisite cohort study

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Lancet HIV 2023; 10: e308–19

Published Online February 28, 2023 https://doi.org/10.1016/S2352-3018(23)00008-5

See Comment page e276

For the Spanish translaton of the abstract see Online for appendix 1

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Summary

Background Epidemiological monitoring of HIV among transgender women is minimal despite prioritisation of this group in the US National HIV/AIDS Strategy (2022–2025). We aimed to estimate HIV incidence in a multisite cohort of transgender women in the eastern and southern USA. Participant deaths were identified during follow-up; thus, we felt it was an ethical imperative to report mortality alongside HIV incidence.

Methods In this study, we established a multisite cohort across two modes: a site-based, technology-enhanced mode in six cities (Atlanta, Baltimore, Boston, Miami, New York City, and Washington, DC) and an exclusively digital mode that spanned 72 eastern and southern US cities that matched the six site-based cities based on population size and demographics. Trans feminine adults (≥18 years) who were not living with HIV were eligible and followed up for at least 24 months. Participants completed surveys and oral fluid HIV testing with clinical confirmation. We ascertained deaths through community and clinical sources. We estimated HIV incidence and mortality using the number of HIV seroconversions and deaths, respectively, divided by person-years accumulated from enrolment. Logistic regression models were used to identify predictors of HIV seroconversion (primary outcome) or death.

Findings Between March 22, 2018, and Aug 31, 2020, we enrolled 1312 participants with 734 (56%) in site-based and 578 (44%) in digital modes. At the 24-month assessment, 633 (59%) of 1076 eligible participants consented to extending participation. 1084 (83%) of 1312 participants were retained at this analysis based on the study definition of loss to follow-up. As of May 25, 2022, the cohort participants had contributed 2730 accumulated person-years to the analytical dataset. Overall HIV incidence was 5·5 (95% CI 2·7–8·3) per 1000 person-years and incidence was higher among Black participants and those living in the south. Nine participants died during the study. The overall mortality rate was 3·3 (95% CI 1·5–6·3) per 1000 person-years, and the rate was higher among Latinx participants. Identical predictors of HIV seroconversion and death included residence in southern cities, sexual partnerships with cisgender men, and use of stimulants. Participation in the digital cohort and seeking care for gender transition were inversely associated with both outcomes.

Interpretation As HIV research and interventions are increasingly delivered online, differences by mode highlight the need for continued community and location-based efforts to reach the most marginalised transgender women. Our findings underscore community calls for interventions that address social and structural contexts that affect survival and other health concerns alongside HIV prevention.

Funding National Institutes of Health.

Introduction

Transgender women have a disproportionately high burden of HIV and low access to health care. Multiple biological, behavioural, and interpersonal risks for HIV among transgender women are driven and reinforced by structural barriers that limit access to HIV prevention, testing, care, and other health services.[1,2] Because of such vulnerabilities, studies among transgender women in the USA have estimated HIV prevalence to be 14–42%, with significant disparities across race and ethnicity.[3,4] Gender-based discrimination and health-care stigma are barriers to HIV testing, prevention, care, and treatment.[5–7] As a result, transgender women are recognised as a priority population in the Ending the HIV Epidemic in the US (EHE) and National HIV/AIDS strategies.[8,9]

Multisite cohorts that focus on transgender women are needed to monitor epidemic trends, to identify drivers of HIV acquisition, and to assess if and how national health policies and HIV prevention efforts, including new pre-exposure prophylaxis (PrEP) modalities, affect HIV epidemic trends. To our knowledge, only one cohort in the USA, the San Francisco site of the TransNational Study, has exclusively focused on transgender women to understand their unique risks for HIV acquisition.[10] HIV cohort models are moving towards exclusively online (digital) methods to reduce infrastructure costs and might facilitate inclusion of people who are otherwise

Research in context

Evidence before this study

Transgender women are a priority population in the US National HIV/AIDS Strategy (2022–2025). We searched PubMed and Google Scholar using Medical Subject Headings and keyword terms ("transgender" AND "HIV" or "incidence" or "mortality") for English-language publications that reported HIV incidence and mortality in transgender women in the USA in the past ten years (Jan 1, 2012 to July 1, 2022). Peer-reviewed articles predominantly report HIV prevalence among transgender women in the USA. Becasen and colleagues' 2019 systematic review identified 13 articles that reported laboratory-confirmed HIV prevalence among transgender women in the USA, published between 2006 and 2017. Becasen and colleagues estimated laboratory-confirmed HIV prevalence among transgender women in the USA to be 14·1% (95% CI 8·7–22·2; I^2=96%). Prevalence differed by race and ethnicity, but there was high heterogeneity across studies. The authors estimated that 55% of included studies were representative of the general transgender population, whereas the remaining studies showed evidence that study samples over-represented people with increased vulnerability to HIV. No cohort studies were described in this systematic review. To our knowledge, only one cohort study has reported HIV incidence exclusively for transgender women in the USA. McFarland and colleagues published a brief report describing HIV incidence among transgender women recruited via long-chain peer referral in the San Francisco site of the TransNational Study. Among 415 participants, HIV incidence was 1·3 cases per 100 person-years (95% CI 0·7–2·7), with increased rates among transgender women of colour, aged 18–24 years, with a history of incarceration, and without health insurance. Transgender women have participated in many domestic and international facility-based and online HIV cohort studies and trials. Aggregation with other populations has resulted in enrolment numbers that are frequently insufficient for transgender women-specific estimations of HIV incidence, risks, and mortality. Community advocacy focuses attention on the burden of violence, trauma, and premature death for transgender women. Prospective research cohorts provide an opportunity to measure health trends and mortality. However, few cohorts have reported mortality rates for populations not living with HIV and, to our knowledge, none have reported mortality rates for transgender women in the USA. A cohort from Amsterdam has provided some insight. Among 2927 transgender women enrolled in a gender clinic between 1972 and 2018, contributing 40 232 person-years, cumulative mortality was 10·8%, significantly higher than among cisgender women (standardised mortality ratio [SMR] 2·8, 95% CI 2·5–3·1), with no change in rates across decades. Cause-specific rates were higher among transgender women than among cisgender women for cardiovascular disease (SMR 2·6, 95% CI 1·9–3·4), cancer (1·6, 1·3–2·0), infection (8·7, 4·7–14·1), and non-natural causes (6·1, 4·2–8·4).

Added value of this study

We report epidemiological data from a multisite cohort study exclusively of transgender women in the eastern and southern USA. Using a mixed-mode approach, we enrolled 1312 participants between March 22, 2018, and Aug 31, 2020, in a technology-enhanced, site-based or fully digital mode. We followed up the participants for at least 24 months, accruing 2730 person-years. The overall HIV incidence was 5·5 cases per 1000 person-years (95% CI 2·7–8·3) and higher among Black participants and those living in the south. Overall mortality was 3·3 deaths per 1000 person-years (95% CI 1·5–6·3) and higher among Latinx participants. Shared predictors of HIV seroconversion and death included residence in the south, sexual partnerships with cisgender men, and use of stimulants. Participation in the online cohort and seeking gender transition-related care were inversely associated with both outcomes. To our knowledge, this study provides the first multisite estimates of HIV incidence and mortality among transgender women in the USA, a population that is prioritised in the national strategy but for whom little prospective, population-specific data are available. Our study findings also provide an opportunity to evaluate the trade-offs of transitioning from site-based to fully digital cohort modalities.

Implications of all the available evidence

HIV incidence and mortality are high among transgender women in the USA, particularly among Black and Latinx transgender women. Differences across cohort modes suggest that mixed-mode approaches might support the recruitment and retention of more representative samples. These findings also highlight the need for continued community and location-based efforts as HIV research and interventions are increasingly delivered online. Collectively, our findings underscore community calls for multilevel, combination approaches specific to transgender women. Such approaches should support social and structural determinants of health and other health concerns, including survival, alongside HIV prevention. A singular focus on HIV prevention is a missed opportunity to address other threats to the lives of people prioritised in HIV services and programming.

excluded by geographical or other barriers to facilities;[11,12] however, the trade-offs of such transitions in relation to cohort implementation are poorly understood.

Sustained cohorts provide essential opportunities to monitor trends in other health outcomes that align with community and public health priorities, such as mortality, mental health, violence and safety, and resilience.[13] However, few cohorts report mortality rates for populations not living with HIV, and none have reported mortality rates for transgender women in the USA. Internationally, mortality rates among transgender women were reported from an Amsterdam cohort,[13] which found that standardised mortality rates were 2·8-times higher among transgender women for all causes of death and 6·1-times higher for non-natural causes compared with national estimates for cisgender women.

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Our research team established a multisite cohort study exclusively among transgender women in the eastern and southern USA. This study aimed to assess HIV incidence and risks for infection that are unique to transgender women. We also evaluated how digital methods could be integrated to support participation. Throughout follow-up, we observed several premature deaths among participants. We report mortality rates alongside HIV incidence in this Article, given the urgency and importance of identifying how comprehensive HIV prevention programmes can optimally support improvements in health and wellbeing beyond reducing HIV incidence.

Methods

Study design and participants

In this multisite cohort study, we informed and refined cohort design and methods by use of formative, qualitative research.[14–16] We have previously described our methods.[17,18] Briefly, the cohort included two modes of participation: a site-based, technology-enhanced mode in collaboration with research and clinical institutions in Atlanta, Baltimore, Boston, Miami, New York City, and Washington, DC, and an exclusively digital (online) mode.[17,18] This mode was geotargeted to 72 eastern and southern US cities that matched the six site-based cities in terms of population size and demographics.

The modes of participation differed in the following ways. The site-based mode used a quarterly assessment schedule, including HIV testing and questionnaires. Participants completed in-person assessments at baseline, 6 months, 12 months, and 24 months to foster rapport and to complete annual laboratory-based sexually transmitted infection (STI) testing. Participation in the digital mode was entirely remote. We scheduled digital assessments semi-annually because of resource constraints, and STI testing was unavailable.

Enrolment launched on March 22, 2018, and Jan 18, 2019, for the site-based and digital modes, respectively, and continued until Aug 31, 2020. 36 participants enrolled after March 13, 2020, when the COVID-19 pandemic was declared a national emergency.

We recruited participants via a mix of technology-based and non-technology-based methods.[17,18] Individuals from the six site-based cities could enrol in either mode of participation. Screening and consent were completed in person for site-based participants and remotely for digital mode participants. Participants were required to complete electronic verification procedures to prevent fraudulent enrolment.[17]

Study inclusion criteria included age 18 years or older, identification on the trans feminine spectrum as determined with a two-step measure of assigned sex at birth and current gender,[19] speaking or understanding English or Spanish, and residing within 50 miles of one of the study cities. We restricted cohort enrolment to individuals with negative baseline HIV tests. Individuals currently enrolled in a PrEP clinical trial were not eligible to participate.

Eligible candidates provided written consent to participate for 24 months. At the 24-month assessment, enrollees could consent to extend participation for up to 3 years. All study materials and activities were available in English and Spanish.

The Johns Hopkins Single Institutional Review Board (sIRB; IRB00142429) reviewed and approved this study. Johns Hopkins sIRB served as the IRB of record for all partner institutions in this multisite study. A community advisory board of 16 community members from study cities regularly reviewed and provided input to study methods, instruments, results, and dissemination.

Procedures

Participant retention efforts included a comprehensive locator form for current contact information, ongoing community outreach, networking, newsletters, and in-person and online events. These strategies permitted relationship building, recontact, and event ascertainment. The study team regularly contacted participants using automated and on-demand text messages, emails, and telephone calls to notify and remind them of study visits. We defined loss to follow-up as missing three or more consecutive assessments and not returning to the study by the time of data freeze. Staff initiated intensive outreach efforts when a participant missed two successive assessments.

We designed the study questionnaire for electronic self-administration. We asked site-based participants with low literacy, identified by literacy screening, or restricted capacity for self-administration to complete an interviewer-administered questionnaire.

The questionnaire spanned numerous domains of demographics; food security; immigration history; justice and carceral system involvement; gender transition-related care; sexual health history and access to or uptake of HIV services including post-exposure prophylaxis and PrEP; primary care and social services use; barriers and facilitators to care; substance use; mental health symptoms; gender pride and affirmation; sexual relationships and behaviours; and social marginalisation, stigma, discrimination, and violence victimisation.[17,18] Participants completed the questionnaire in a mean of 30 min. Affirmative responses to questions indicating violence victimisation, mental health needs, substance use, or HIV risk triggered referrals to local, gender-affirming services for the site-based mode and national resources for the digital mode.

We provided HIV testing at each assessment. In the site-based mode, participants did the OraQuick HIV self-test (OraSure Technologies; Bethlehem, PA, USA). This test was selected to enable participants to test remotely and to empower participants to feel confident using HIV self-testing outside the study. HIV test results were available within 20 min. Site-based participants

completed annual laboratory-based testing for syphilis, anorectal and vaginal gonorrhoea, and chlamydia.

We asked each digital mode participant to provide an oral fluid specimen, collected with the OraSure Oral Specimen Collection Device (OraSure Technologies) and tested at a central laboratory (Lenexa, KS, USA) with enzyme immunoassay with reflex to western blot for reactive preliminary results.[20] We used oral fluid specimen collection to ensure that study staff could receive the results and effectively provide interactive post-test counselling and support referrals for participants with reactive or indeterminate preliminary results. We based this decision on research that showed low self-reported HIV self-test results in digital research.[21]

	Site-based mode (n=734)	Digital mode (n=578)	Overall cohort (n=1312)	p value
Age, years	29 (24–37)	27 (22–34)	28 (23–35)	<0·0001
Region	..	..	..	<0·0001
North	382 (52%)	273 (47%)	655 (50%)	..
Mid-Atlantic	194 (26%)	107 (19%)	301 (23%)	..
South	158 (22%)	198 (34%)	356 (27%)	..
Race and ethnic identity	..	..	..	<0·0001
Non-Hispanic White	266 (36%)	431 (75%)	697 (53%)	..
Non-Hispanic Black	147 (20%)	26 (4%)	173 (13%)	..
Hispanic White	67 (9%)	19 (3%)	86 (7%)	..
Hispanic Black	23 (3%)	0 (0%)	23 (2%)	..
Non-Hispanic and more than one or other race	110 (15%)	73 (13%)	183 (14%)	..
Hispanic and more than one or other race	111 (15%)	22 (4%)	133 (10%)	..
Unknown	10 (1%)	7 (1%)	17 (1%)	..
Language	..	..	..	<0·0001
Spanish	57 (8%)	2 (<1%)	59 (4%)	..
English	677 (92%)	576 (>99%)	1253 (96%)	..
Born in the USA	..	..	..	<0·0001
Yes	596 (81%)	553 (96%)	1149 (88%)	..
No	132 (18%)	24 (4%)	156 (12%)	..
Unknown	6 (1%)	1 (<1%)	7 (1%)	..
Sexual orientation	..	..	..	<0·0001
Straight or heterosexual	243 (33%)	56 (10%)	299 (23%)	..
Lesbian	82 (11%)	127 (22%)	209 (16%)	..
Gay	48 (7%)	11 (2%)	59 (4%)	..
Bisexual	117 (16%)	134 (23%)	251 (19%)	..
Queer, pansexual, or other	224 (31%)	244 (42%)	468 (36%)	..
Unknown	20 (3%)	6 (1%)	26 (2%)	..
Education	..	..	..	<0·0001
High school diploma or General Educational Development tests or less	259 (35%)	103 (18%)	362 (28%)	..
Some college or higher	468 (64%)	470 (81%)	938 (71%)	..
Unknown	7 (1%)	5 (1%)	12 (1%)	..
Level of literacy (site-based mode only)*	..	..	..	..
High	634 (86%)	..	..	..
Low	76 (10%)	..	..	..
Unknown	24 (3%)	..	..	..
Current employment status				<0·0001
Unemployed	330 (45%)	193 (33%)	523 (40%)	..
Employed full-time	223 (30%)	246 (43%)	469 (36%)	..
Employed part-time	164 (22%)	117 (20%)	281 (21%)	..
Unknown	17 (2%)	22 (4%)	39 (3%)	
Income†	..	..	..	<0·0001
Above the federal poverty level	332 (45%)	366 (63%)	698 (53%)	..
Below the federal poverty level	283 (39%)	132 (23%)	415 (32%)	..
Unknown	119 (16%)	80 (14%)	199 (15%)	..

(Table 1 continues on next page)

	Site-based mode (n=734)	Digital mode (n=578)	Overall cohort (n=1312)	p value
(Continued from previous page)				
Health insurance	..	..	..	<0·0001
Uninsured	71 (10%)	54 (9%)	125 (10%)	..
Public insurance	353 (48%)	147 (25%)	500 (38%)	..
Private insurance	258 (35%)	348 (60%)	606 (46%)	..
Unknown	52 (7%)	29 (5%)	81 (6%)	..
Method of recruitment (multiple options)‡	..	..	..	..
Friend	235/724 (32%)	121/568 (21%)	356/1292 (28%)	<0·0001
Health-care organisation	304/724 (42%)	38/568 (7%)	342/1292 (26%)	<0·0001
Facebook	52/726 (7%)	54/570 (9%)	106/1296 (8%)	0·1318
Reddit§	27/192 (14%)	245/544 (45%)	272/736 (37%)	<0·0001
Google advertisement§	7/192 (4%)	104/544 (19%)	111/736 (15%)	<0·0001
Dating app	30/728 (4%)	12/570 (2%)	42/1298 (3%)	0·0417
Other	51/725 (7%)	56/570 (10%)	107/1295 (8%)	0·0702

Data are median (IQR), n (%), or n/N (%), unless otherwise indicated. Pearson's χ^2 test was used to detect differences by mode of participation. *No p value because literacy was only assessed for site-based participants. †Below the federal poverty level (using 2018 data) was classified at a monthly income ranging from US$0–999; above the federal poverty level was classified as ≥$1000 per month. ‡Options were not mutually exclusive and not all patients answered. §These recruitment methods were added later during enrolment; thus, the overall denominators differ.

Table 1: **Characteristics of LITE cohort participants at enrolment and by mode of participation**

Participants who tested outside the study within a 30-day window before or after their assessment due date could submit HIV test result documentation instead of repeating the test. We referred all participants with a positive preliminary test result for confirmatory testing and care at a local and affirming facility of their preference. We asked these participants to provide confirmatory results to verify seroconversion.

We developed a web-based Health Insurance Portability and Accountability Act-compliant digital platform hosted by the Johns Hopkins University central information technology department. The participant interface was available in English and Spanish as a hybrid app for download for Android and iOS systems and through a web app for participants without smartphones or tablets. The app was tailored to each mode and provided secure access to the participants' profiles, study timelines, and assessment activities. The platform sent automated reminders and on-demand notifications (text message and email) to participants in the participant's preferred language. Staff had role-based and mode-based access to the interface for tracking and data entry.

All incident HIV infections were laboratory-confirmed. We ascertained death through medical records, community reports, and obituaries. We attempted to confirm all deaths that were reported outside medical records through a second source; all except one were confirmed by a second source.

Statistical analysis

We estimated HIV incidence and mortality rates as the number of observed events divided by person-years accumulated. Observations were censored at date of HIV seroconversion, loss to follow-up, or data freeze on May 25, 2022, whichever came first. We visualised Kaplan-Meier estimates of the cumulative incidence of HIV and death (separately). We found no substantive effect of the competing risk of death on HIV incidence estimates nor of HIV incidence on death. We stratified data by time before (enrolment to March 1, 2020) and during the COVID-19 pandemic (March 2, 2020, to May 25, 2022) to evaluate the potential effect of that pandemic on study outcomes.

We used logistic regression models to estimate relative risks (RRs) of potential predictors of incident HIV or death from enrolment to censoring. Point estimates (ie, odds ratios) from these models are interpreted as RRs in longitudinal designs with rare outcomes. Logistic regression models were unadjusted because of the small number of events. We calculated RRs for individual, interpersonal, and structural variables that were conceptually and statistically associated with the outcome at $p<0·10$ in the appropriate test for differences. Independent variables were from the baseline assessment, with exceptions being measures of consistent telephone connection, home internet access, and PrEP use during follow-up, which were time-fixed but measured after enrolment. We classified responses as having home internet connection only if they reported such a connection at all assessments and classified responders as having "phone disconnected" if this was reported at any assessment.

Statistical analyses were done with SAS version 9.4 and R version 4.1.2 for visualisations.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between March 22, 2018, and Aug 31, 2020, we enrolled 1312 transgender women, with 734 (56%) in site-based and 578 (44%) in digital modes (appendix 2 p 1). At the 24-month assessment, 633 (59%) of 1076 eligible participants consented to extending participation. 1084 (83%) of 1312 participants were retained at this analysis based on the study definition of loss to follow-up and regardless of consent to extension. As of May 25, 2022, the cohort participants had contributed 2730 accumulated person-years to the analytical dataset.

The study population was racially and ethnically diverse (table 1) and well distributed across the eastern and southern USA (figure 1). 73 (6%) of 1312 participants (65 [11%] online) resided in a rural area. Differences in participant characteristics were observed across modes of participation.

We confirmed 15 participants had seroconversions. Overall HIV incidence was 5·5 (95% CI 2·7–8·3) per 1000 person-years (table 2). HIV incidence was higher in the site-based mode (8·7 cases per 1000 person-years, 95% CI 4·0–13·5) than in the digital mode (1·6 cases per 1000 person-years, 0·2–5·8), although the CIs overlapped (table 2). Incidence rates differed by race and PrEP indication, based on criteria adapted for transgender women,[22] and were qualitatively different by age, region, and time relative to the onset of COVID-19. Of the 15 participants who seroconverted during follow-up, seven were PrEP-naive at the time of seroconversion, seven were former PrEP users, and one declined to answer questions on PrEP use.

Nine participants died during the study. These deaths were attributed to homicide (one participant), suicide (one participant), overdose (two participants), cardiac arrest of unknown cause (one participant), other health condition (one participant), and unknown causes (three participants). The overall mortality rate was 3·3 (95% CI 1·5–6·3) per 1000 person-years. Rates were qualitatively different by cohort mode, race, and ethnicity (figure 2).

Baseline variables associated with seroconversion and death included recent sexual relationships with cisgender men, laboratory-confirmed STI infection, and region of residence (table 3, appendix 2 p 4). When we reclassified geographical location to US Census regions (ie, reclassifying mid-Atlantic to north or south by state), residence in the south was associated with a higher risk of seroconversion (RR 3·4, 95% CI 1·1–12·2) and perfectly predicted deaths (ie, all deaths occurred in the south). Cocaine or methamphetamine use was associated with increased risk of HIV seroconversion, and any stimulant use was associated with increased risk of death. Participants in the digital mode, compared with those in the site-based mode, and those who sought gender transition (compared with those who had not) had lower risks of HIV seroconversion and death.

Characteristics and experiences associated with HIV incidence included race, telephone disconnection, self-reported history of STI, number of recent sexual partners, PrEP indication, and partner PrEP use. A home internet connection, primary care provider, experience of psychological, physical, or sexual violence, and lifetime suicidal ideation were inversely associated with HIV seroconversion.

See Online for appendix 2

Characteristics and experiences associated with premature death during follow-up included Hispanic or Latinx ethnicity and recent arrest (in the past 12 months). All deaths occurred among participants who were

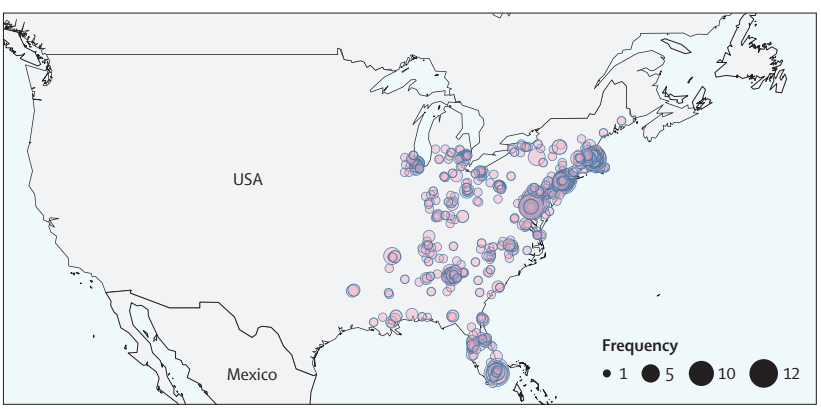

Figure 1: **Geographical distribution of cohort participants by zip code of residence reported at enrolment**

	Incident HIV per 1000 person-years (95% CI)	Mortality per 1000 person-years (95% CI)
All	5·5 (2·7–8·3)	3·3 (1·5–6·3)
Cohort mode		
Digital	1·6 (0·2–5·8)	0·8 (0·0–4·5)
Site-based	8·7 (4·0–13·5)	5·4 (2·3–10·6)
Race and ethnicity*		
White	1·6 (0·3–4·7)	3·2 (1·2–7·0)
Black	19·3 (8·4–30·2)	4·8 (1·0–14·1)
Hispanic or Latinx ethnicity	9·9 (3·2–23·1)	9·9 (3·2–23·1)
Region		
North	3·0 (0·8–7·7)	0·0 (0·0–2·8)
Mid-Atlantic	4·8 (1·0–14·1)	4·8 (1·0–14·1)
South	10·3 (4·5–20·3)	7·7 (2·8–16·8)
Age category, years		
18–24	8·5 (3·4–17·5)	3·6 (0·8–10·6)
≥25	4·2 (1·8–8·3)	3·2 (1·2–6·9)
PrEP indicated at baseline†		
No	0·7 (0·0–3·8)	..
Yes	11·2 (5·3–17·0)	..

PrEP=pre-exposure prophylaxis. *Categories are not mutually exclusive, as participants might report multiple race or ethnic identities. †PrEP indication based on an adapted version of US Centers for Disease Control and Prevention criteria for transgender women.[22]

Table 2: **Crude incidence and mortality rates among 1312 participants with 2730 person-years of follow-up**

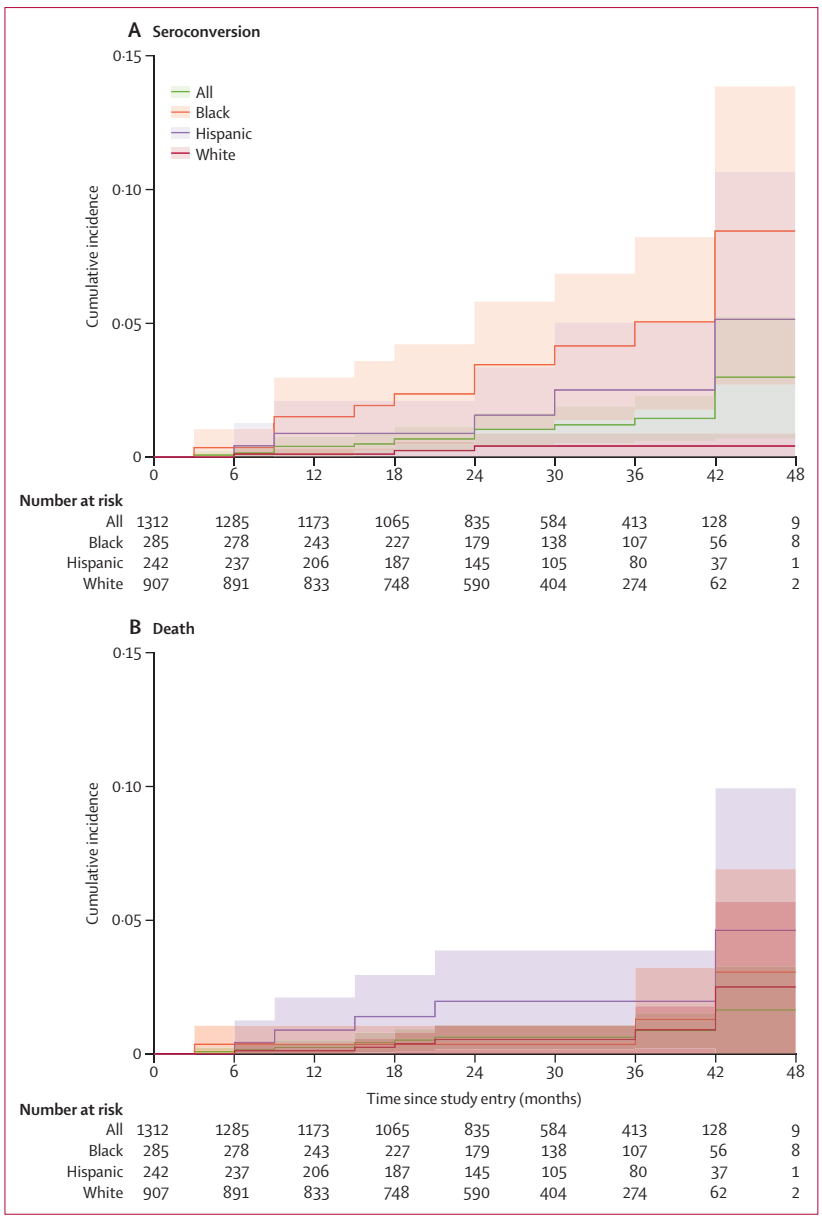

***Figure 2*: Cumulative incidence of HIV seroconversion (A) and death (B) among cohort participants, overall and by race and ethnicity**
Shaded areas represent 95% CIs.

uninsured or publicly insured. Full-time or part-time employment and stigma-related barriers to health care were inversely associated with death.

Discussion

In this study, we describe HIV incidence and mortality among a diverse, multisite cohort study that exclusively focused on transgender women in the USA. HIV incidence was high, at 5·5 cases per 1000 person-years. Unexpectedly, mortality rates were similar, at 3·3 deaths per 1000 person-years overall. HIV incidence and mortality rates were highest among Black and Latinx participants and those residing in the south. Predictors of HIV incidence and death underscored individual and contextual factors that impact health outcomes for transgender women. Notably, sexual partnerships with cisgender men and the use of stimulants were shared predictors of HIV seroconversion and death, whereas participation in the digital mode and seeking care related to gender transition were inversely associated with these outcomes.

High mortality rates and causes of death reflect the burden of violence victimisation, poor mental health, and substance misuse among transgender women, which stem from persistent stigma, discrimination, incarceration, and barriers to health care.[23,24] Despite a wealth of longitudinal data collected in HIV prevention research, mortality rates are rarely reported in scientific literature, although deaths are reported in clinical trials. During a non-inferiority trial of long-acting injectable PrEP among transgender women and cisgender men, 11 participant deaths were reported, similar to the number of seroconversions (n=13).[25] Eight of those deaths were attributed to overdose or trauma.[25] Although the primary goal of HIV observational research and trials is to evaluate HIV outcomes, these findings collectively raise ethical questions of why deaths—particularly violent and preventable deaths—are not given greater attention in HIV research. These findings also raise questions about how benefits of research participation can be enhanced to address related vulnerabilities.

Predictors of incident HIV infection and deaths point to clear intervention targets, particularly multilevel HIV prevention interventions. Structural interventions could indirectly aid in sustained access to various health services, including HIV prevention and mental and behavioural health services, and ultimately improve long-term survival. Examples of structural interventions include policy changes to reduce disproportionate arrest and incarceration, reduce employment discrimination, increase insurance access, support stable housing and safety, develop culturally competent care, and permit insurance coverage for gender-affirming care.

Individual-level interventions might include substance use and sexual health services. Substance use interventions could reduce the harmful effects of use and HIV acquisition risk associated with methamphetamines and cocaine.[12] Sexual health predictors of HIV acquisition, including STI infection and number of sexual partners, could be met with prevention strategies to increase availability of combined STI and HIV testing with linkage to PrEP services.

The non-use of PrEP observed among participants who seroconverted, specifically never initiating PrEP or discontinuing use, suggests that a thoughtful approach to PrEP delivery for transgender women is needed. Knowledge of and willingness to use PrEP are high among transgender women, but there is a gap in use.[26] To explore this, Cooney and colleagues used a group-based multitrajectory model and identified five longitudinal behavioural-risk and interpersonal-risk patterns mapped

	Overall (n=1312)	No seroconversion (n=1297)	Seroconversion (n=15)	RR* (95%CI)	Alive (n=1303)	Deceased (n=9)	RR* (95% CI)
Demographics							
Mode of participation							
Digital	578 (44%)	576 (44%)	2 (13%)	0·2 (0·0–0·7)	577 (44%)	1 (11%)	0·2 (0·0–0·9)
Site-based	734 (56%)	721 (44%)	13 (87%)	1 (ref)	726 (56%)	8 (89%)	1 (ref)
Race and ethnicity†							
White	907/1302 (70%)	904/1287 (70%)	3 (20%)	0·1 (0·0, 0·3)	901/1293 (70%)	6 (67%)	..
Black	285/1300 (22%)	273/1285 (21%)	12 (80%)	14·8 (4·7–65·4)	282/1291 (22%)	3 (33%)	..
Hispanic and Latinx	242/1301 (19%)	237/1287 (18%)	5/14 (36%)	..	237/1293 (18%)	5/8 (63%)	7·4 (1·8–36·4)
Region							
North	655 (50%)	651 (50%)	4 (27%)	1 (ref)	655 (50%)	0	..
Mid-Atlantic	301 (23%)	298 (23%)	3 (20%)	1·6 (0·3–7·5)	298 (23%)	3 (33%)	..
South	356 (27%)	348 (27%)	8 (53%)	3·7 (1·2–14·1)	350 (27%)	6 (67%)	..
Socioeconomic							
Employment status							
Currently employed full-time or part-time	750/1273 (59%)	743/1259 (59%)	7/14 (50%)	..	749/1264 (59%)	1 (11%)	0·1 (0·0–0·5)
Unemployed	523/1273 (41%)	516/1259 (41%)	7/14 (50%)	..	515/1264 (41%)	8 (89%)	1 (ref)
Telephone disconnected during follow-up							
Yes	137/983 (14%)	133/975 (14%)	4/8 (50%)	6·3 (1·5–27·1)	137/981 (14%)	0	..
No	846/983 (86%)	842/975 (86%)	4/8 (50%)	1 (ref)	844/981 (86%)	2/2 (100%)	..
Internet connection at home							
Yes	924/983 (94%)	919/975 (94%)	5/8 (63%)	0·1 (0·0–0·5)	923/981 (94%)	1/2 (50%)	..
No	59/983 (6%)	56/975 (6%)	3/8 (38%)	1 (ref)	58/981 (6%)	1/2 (50%)	..
Risk environments							
Homeless in the past 6 months							
Yes	137/1291 (11%)	135/1276 (11%)	2/15 (13%)	..	134/1282 (10%)	3/9 (33%)	4·3 (0·9–16·4)
No	1154/1291 (89%)	1141/1276 (89%)	13/15 (87%)	..	1148/1282 (90%)	6/9 (67%)	1 (ref)
Arrested in the past 12 months							
Yes	63/1281 (5%)	62/1267 (5%)	1 (7%)	..	60/1272 (5%)	3 (33%)	10·1 (2·1–39·3)
No	1218/1281 (95%)	1205/1267 (95%)	13 (93%)	..	1212/1272 (95%)	6 (67%)	1 (ref)
Lifetime sex work							
Yes	492/1295 (38%)	486/1281 (38%)	6/14 (43%)	..	486/1286 (38%)	6 (67%)	3·3 (0·9–15·7)
No	803/1295 (62%)	795/1281 (62%)	8/14 (57%)	..	800/1286 (62%)	3 (33%)	1 (ref)
Violence victimisation							
Psychological violence							
Yes	1101/1293 (85%)	1095/1280 (86%)	6/13 (46%)	0·1 (0·1–0·4)	1095/1285 (85%)	6/8 (75%)	..
No	192/1293 (15%)	185/1280 (14%)	7/13 (54%)	1 (ref)	190/1285 (15%)	2/8 (25%)	..
Sexual violence							
Yes	557/1287 (43%)	555/1274 (44%)	2/13 (15%)	0·2 (0·0–0·9)	553/1278 (43%)	4/9 (44%)	..
No	730/1287 (57%)	719/1274 (56%)	11/13 (85%)	1 (ref)	725/1278 (57%)	5/9 (56%)	..
Gender affirmation and health history							
Sought gender transition-related care in the past 12 months							
Yes	1082/1297 (83%)	1072/1282 (84%)	10 (67%)	0·4 (0·1–1·3)	1078/1289 (84%)	4/8 (50%)	0·2 (0·1–0·8)
No	215/1297 (17%)	210/1282 (16%)	5 (33%)	1 (ref)	211/1289 (16%)	4/8 (50%)	1 (ref)
Has a personal doctor or health-care provider							
Yes	919/1297 (71%)	912/1282 (71%)	7 (47%)	0·4 (0·1–1·0)	912/1288 (71%)	7 (78%)	..
No	378/1297 (29%)	370/1282 (29%)	8 (53%)	1 (ref)	376/1288 (29%)	2 (22%)	..
Health insurance							
Uninsured or public insurance	625/1231 (51%)	617/1219 (51%)	8/12 (67%)	..	616/1222 (50%)	9 (100%)	..
Private insurance	606/1231 (49%)	602/1219 (49%)	4/12 (33%)	..	606/1222 (50%)	0	..

(Table 3 continues on next page)

	Overall (n=1312)	No seroconversion (n=1297)	Seroconversion (n=15)	RR* (95% CI)	Alive (n=1303)	Deceased (n=9)	RR* (95% CI)
(Continued from previous page)							
Stigma-related barriers to care							
Yes	733 (56%)	725 (56%)	8 (53%)	..	731 (56%)	2 (22%)	0·2 (0·0–0·9)
No	579 (44%)	572 (44%)	7 (47%)	1 (ref)	572 (44%)	7 (78%)	1 (ref)
Mental and behavioural health							
Cocaine use							
Yes	136/1294 (11%)	132/1280 (10%)	4/14 (29%)	3·5 (0·9–10·6)	134/1285 (10%)	2 (22%)	..
No	1158/1294 (89%)	1148/1280 (90%)	10/14 (71%)	1 (ref)	1151/1285 (90%)	7 (78%)	..
Methamphetamine, speed, or amphetamine use							
Yes	73/1295 (6%)	70/1281 (5%)	3 (21%)	4·7 (1·1–15·5)	72/1286 (6%)	1 (11%)	..
No	1222/1295 (94%)	1211/1281 (95%)	11 (79%)	1 (ref)	1214/1286 (94%)	8 (89%)	..
Any stimulant use							
Yes	211/1294 (16%)	207/1280 (16%)	4/14 (29%)	..	207/1285 (16%)	4 (44%)	4·2 (1·0–15·9)
No	1083/1294 (84%)	1073/1280 (84%)	10/14 (71%)	..	1078/1285 (84%)	5 (56%)	1 (ref)
Lifetime suicidal ideation							
Yes	971/1269 (77%)	966/1255 (77%)	5/14 (36%)	0·2 (0·1–0·5)	966/1261 (77%)	5/8 (63%)	..
No	298 (23%)	289/1255 (23%)	9/14 (64%)	1 (ref)	295/1261 (23%)	3/8 (38%)	..
Sexual health and HIV prevention							
Laboratory-confirmed STI (site-based only)							
Yes	80/722 (11%)	75/709 (11%)	5/13 (38%)	5·3 (1·6–16·3)	76/714 (11%)	4/8 (50%)	8·4 (2·0–36·2)
No	642/722 (89%)	634/709 (89%)	8/13 (62%)	1 (ref)	638/714 (89%)	4/8 (50%)	1 (ref)
Self-reported STI							
Yes	264/1292 (20%)	258/1278 (20%)	6/14 (43%)	3·0 (1·0–8·6)	261/1283 (20%)	3 (33%)	..
No	1028/1292 (80%)	1020/1278 (80%)	8/14 (57%)	1 (ref)	1022/1283 (80%)	6 (67%)	..
Indicated for post-exposure prophylaxis based on criteria for transgender women							
Yes	619 (47%)	605 (47%)	14 (93%)	16·0 (3·2–291·0)	614 (47%)	5 (56%)	..
No	693 (53%)	692 (53%)	1 (7%)	1 (ref)	689 (53%)	4 (44%)	..
Partner characteristics							
Gender(s) of casual and regular partners (past 3 months)‡							
Cis woman or trans person only	259/867 (30%)	259/856 (30%)	0	..	259/862 (30%)	0	..
Cis man only	364/867 (42%)	356/856 (42%)	8/11 (73%)	..	359/862 (42%)	5/5 (100%)	..
Multiple genders	244/867 (28%)	241/856 (28%)	3/11 (27%)	..	244/862 (28%)	0	..
Partner PrEP use							
Yes	193/1260 (15%)	188/1246 (15%)	5/14 (36%)	3·1 (1·0–9·2)	191/1251 (15%)	2 (22%)	..
No	1067/1260 (85%)	1058/1246 (85%)	9/14 (64%)	1 (ref)	1060/1251 (85%)	7 (78%)	..

Data are n (%) or n/N (%), unless otherwise indicated. Data were missing for some variables. RR=relative risk. STI=sexually transmitted infection. *Characteristics displayed and RRs calculated for variables significant at p<0·05 using the appropriate Pearson's χ^2 test, Fisher's exact test, or Wilcoxon rank sum test for either or both outcomes (for all tested variables and p values see appendix p 3); RRs were not calculated in some cases because of 0 events in some categories. †Original select-all categories for race are used in this table to avoid creation of categories with numerators that would be too small for analytical comparison, which would otherwise occur with a combined race–ethnicity categorisation; responses to race categories might overlap for participants with multiracial identities. ‡Gender of regular and casual partners was missing for four deceased participants for the following reasons: two reported no sex in the past 12 months, one reported sex work clients only, and one reported sex in the previous 12 months, but no sex partners in the past 3 months.

***Table 3*: Predictors of HIV incidence and mortality among transgender women in eastern and southern USA, March 22, 2018, to May 25, 2022**

to daily oral PrEP use over 18 months of follow-up.[27] Two patterns showed consistent (15%) or dynamic risk for HIV (47%) but no reported PrEP use, whereas the other patterns showed PrEP use consistent with risk. Young people (aged 18–24 years) and uninsured participants were more likely to have dynamic risk and to report never using PrEP. People experiencing homelessness were more likely to have dynamic risk patterns and PrEP use.[27] These results suggest that many transgender women use PrEP during periods of risk; however, basic livelihood and survival might take priority over PrEP use and persistence, even if considered an effective HIV prevention option. More research is needed to understand how to support PrEP use among transgender women who can benefit from PrEP, particularly young people and people experiencing structural vulnerabilities. Research on whether long-acting injectable PrEP resolves these barriers is also needed.

Participants who reported PrEP use by their sexual partner at baseline were more likely to have HIV seroconversion. This finding might be due to low adherence, discontinued use by the partner, or acquisition from a different partner not using PrEP; it could also

reflect previous reports of discrepant sexual agreements among some transgender women and their cisgender male sexual partners, which were associated with intra-dyadic and extra-dyadic sexual risk.[28] One pilot study of a couples-focused HIV prevention programme for transgender women and their partners showed acceptability and improved prevention practices within sexual partnerships.[29] Because partnerships with cisgender men were associated with an increased likelihood of incident HIV and death, such partner-level interventions could be leveraged to support HIV prevention, supportive relationships, and safety.

Our findings reflect US HIV epidemic trends, although few incidence estimates are available to compare study findings. The incidence rate among the full sample in our study was lower than in the facility-based cohort in San Francisco (n=415; 1·3 cases per 100 person-years, 95% CI 0·7–2·7). However, rates are similar when comparing estimates from our site-based mode with the San Francisco cohort.[10] This comparison highlights the qualitative differences observed in HIV incidence and mortality estimates between site-based and digital modes, although with overlapping confidence intervals. Inconsistent access to communication technology was also associated with incident HIV infection in our study. These findings support the digital divide concept (ie, participants with technology access and comfort using it might have higher levels of education, social capital, and fewer economic vulnerabilities) and the need to address this divide in HIV research.

Hybrid cohort models that combine site-based and digital modes might facilitate sampling that is representative and generalisable to the target population, which is crucial to monitoring epidemiological trends. Each mode accrued and retained study populations with different profiles. However, when combined, the study population reflected the race and ethnic distributions of the 2020 US Census.[30] National survey efforts increasingly use mixed-mode approaches (eg, National Survey on Drug Use and Health) to minimise response bias and measurement error.[31] Mized-mode approaches also hold promise for alternative methods in HIV research designs. Therefore, strategies beyond online delivery could increase inclusion of people with restricted or inconsistent technology access and who might experience health vulnerabilities. Failure to recognise and address disparities in technology access within HIV research and prevention services could maintain or exacerbate health inequities.

Our findings should be interpreted in light of study limitations. First, this cohort was exclusive to the eastern and southern USA, so results might not be generalisable to transgender women in the broader USA and its territories. The observed differences across cohort mode reflect differences in characteristics of individuals reached through such strategies—digital mode participants might have lower individual, interpersonal, and structural vulnerabilities that relate to HIV acquisition risk, but site-based participants might have better access to HIV prevention and gender-affirming services. The mixed-mode approach, coupled with the inclusion of all trans feminine people regardless of reported behavioural risk, probably maximises the generalisability of our results to transgender women in the region. We interpret HIV incidence, mortality rates, and corresponding regression models with caution because of the small number of events. Incidence and mortality could be underestimated, particularly for digital mode participants, given the limited community and clinical connections, which are critical to reconnecting with participants or ascertaining events. National datasets used to verify a participant's death, such as the National Death Index, are of limited usefulness for transgender participants, given the commonality of name changes to align with gender. Limitations exist for digital research, as participants are less likely to share multiple identifiers (eg, social security number) in digital survey platforms, given security concerns. Finally, increased stigma in health facilities was inversely associated with premature death. As we report unadjusted associations, this unexpected association might be confounded by increased engagement with health facilities. Likewise, we were surprised to observe inverse associations between violence victimisation and suicidal ideation with incident infection. Epidemiologically, this might reflect survival bias; sociologically, this might reflect participants' resilience.

In conclusion, HIV incidence among a cohort study of transgender women in the eastern and southern USA underscores the importance of the prioritisation of transgender women in national HIV prevention strategies.[8,9] Mortality rates and shared predictors of HIV incidence and premature death emphasise the importance of community calls for attention to structural factors and other threats to health and wellbeing alongside HIV for transgender women, particularly Black and Latinx transgender women. National strategies,[8] such as co-located service delivery, expansion of prescribing authority to pharmacists and other providers, and telehealth might reduce barriers to effective daily oral and long-acting PrEP and other HIV prevention strategies. Partner-level and multilevel interventions delivered across digital and in-person modalities to support safety, housing, employment, and substance use treatment alongside HIV prevention could be strategies that change the trajectories of the HIV epidemic and premature death among transgender women.

Contributors

ALW, SLR, and TCP developed the study concept. TCP, AR, KNA, CMC, AJW, AER, EEC, JSS, JSH, and KHM provided extensive input to the original grant submission or the study protocol. EEC, DA, and MS oversaw study coordination. JC designed and maintained the digital platform. EH did the statistical analyses with support from KNA. EH, ALW, and EEC have accessed and verified the data. ALW wrote the first draft of the manuscript and was responsible for the decision to submit the manuscript for publication. All authors reviewed the manuscript, provided scientific input to the manuscript, and agreed with the decision to submit the manuscript. All authors had full access to all the data in

the study. The following individuals are members of the collaborative author groups, the American Cohort to Study HIV Acquisition Among Transgender Women (also known as the LITE cohort): Sari Reisner (principal investigator; Brigham and Women's Hospital); Andrea Wirtz (principal investigator; Johns Hopkins University); Keri Althoff (Johns Hopkins University); Chris Beyrer (Johns Hopkins University); James Case (Johns Hopkins University); Erin Cooney (Johns Hopkins University); Meg Stevenson (Johns Hopkins University); Dee Adams (Johns Hopkins University); Oliver Laeyendecker (National Institute of Allergy and Infectious Diseases); Charlotte Gaydos (Johns Hopkins University); Tonia Poteat (University of North Carolina); Kenneth Mayer (Fenway Health); Asa Radix (Callen-Lorde Community Health Center); Christopher Cannon (Whitman-Walker Health); Jason Schneider (Emory University and Grady Hospital); J Sonya Haw (Emory University and Grady Hospital); Allan Rodriguez (University of Miami); Andrew J Wawrzyniak (University of Miami); or the LITE Community Advisory Board: Sherri Meeks, Sydney Shackelford, Nala Toussaint, SaVanna Wanzer, and others who have remained anonymous.

Declaration of interests

KNA is a consultant for the All of Us Research Program. TCP is a consultant for ViiV Healthcare and received an honorarium for a lecture provided to Merck & Co staff. All other authors declare no competing interests.

Data sharing

Deidentified individual data and a data dictionary will be made available upon reasonable request after approval of a proposal and signing of a data use agreement. There is a formal process for external users to request access to LITE data, which involves review and approval by principal investigators from each study site and the Community Advisory Board. Further details and forms can be obtained by emailing ALW (awirtz1@jhu.edu) and SLR (sreisner@bwh.harvard.edu).

Acknowledgments

We would like to express our gratitude to the transgender women who participated in this study. This study would not have been possible without their experiences and participation. We appreciate the continued involvement and contributions of the Community Advisory Board that supports and guides this study. We also thank all the research staff who spent their time and effort to actualise this study and connect with study participants in meaningful ways: Shannon Seopaul, Chloe Jordan, Maryam Roosta, Genesis Valera, Blanca Esquivel, Ali Harris, Amiyah Guerra, Valeria Botero, Jessica Orr, Nicho Herrera, Melissa Estrada, Alexandra Beem, Jessica Castaneda, Jeffrey Herman, and Barrett Crawford. Research reported in this publication was jointly supported by the National Institute of Allergy and Infectious Diseases, the National Institute of Mental Health, and the National Institute of Child Health and Human Development of the National Institutes of Health, under award number UG3/UH3AI133669 (to ALW and SLR). Research reported in this publication was also supported by the HIV/AIDS, Hepatitis, STD, and TB Administration (HAHSTA), Washington, DC Department of Health. The LITE study also appreciates support from the Centers for AIDS Research at partner institutions, including Johns Hopkins University (P30AI094189), Emory University (P30AI050409), Harvard University (P30AI060354), DC CFAR (AI117970), and the University of Miami (P30AI073961). A predoctoral fellowship from the National Institute of Mental Health (F31MH124582) supports EEC. The content of this Article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or HAHSTA.

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