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Addressing the sexually transmitted infections epidemic in the United States: A sociomedical perspective

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Addressing the sexually transmitted infections epidemic in the United States: A sociomedical perspective

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Editorial: Addressing the sexually transmitted infections epidemic in the United States: a sociomedical perspective

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Editorial on the Research Topic
Addressing the sexually transmitted infections epidemic in the United States: a sociomedical perspective

Sexually transmitted infections (STIs) cause significant morbidity and mortality in the United States (US) and across the globe. Within the last decade, there have been substantial advances in the number and diversity of biomedical and public health interventions critical for controlling STIs. Despite these gains, incident STIs are on an upward trajectory (1). In 2022 there were ∼1.3 million new STIs equating to 3,500 new infections globally per day (2). STIs have a direct impact on acute and chronic health outcomes and are implicated in neurological and cardiovascular diseases, cancer, infertility, and pregnancy complications (3). According to a seminal report by the US National Academies of Sciences, Engineering, and Medicine, the STI epidemic exacts a deleterious medical and economic toll on individuals and society as a whole (4). And although STIs are pervasive, poor and disadvantaged populations bear a disproportionate share of disease burden (5).

The STI epidemic ranks high among the most pressing public health concerns and has captured attention across disparate research disciplines. This widespread interest is reflected in the fact that 13 peer-reviewed articles were published, which to date had 20k views and downloads. This Research Topic contains methodologically rigorous research approaches including qualitative and quantitative data analytic strategies, proof-of-concept and efficacy study designs, and systematic, meta-analytic, and bibliometric reviews. Each article advances the science in its respective field and collectively they inform hypothesis generation, encourage replication studies, and support clinical practice and public health policy decision-making. The impetus for this Research Topic stems from a recognition that the STI epidemic is driven by a complex interaction of biological, behavioral, and structural determinants of disease. As such, manuscripts involving innovative screening and diagnostic tools, high-priority populations, and public health policies and practices were prioritized.

Chlamydia, herpes, gonorrhea, and syphilis infections are key risk factors for other more consequential pathogens including HIV. Evidence from epidemiological studies has shown that ∼1 of 10 HIV infections is directly attributable to incidence of the most common STIs (6). And although there has been a number of innovations in HIV/AIDS care, it remains a serious public health threat made worse by increasing global genetic diversification. Nchinda et al. explores this diversity in their systematic review of HIV-1 recombinants among highly-vulnerable populations. They report that injection drug use was associated with the greatest odds of recombinants and circulating recombinant forms while commercial sex work was associated with increased odds of recombinants and unique recombinant forms. These findings underscore the critical need for rigorous HIV-1 molecular surveillance as pathogens and new epidemiological patterns emerge. In a second review article, Nguyen et al. employed bibliometric techniques (e.g., topic modeling) to examine knowledge gaps in HIV/AIDS research. Their work identified growing interest in research that examines the complex dynamics of intimate partner violence and HIV/AIDS as well as a dearth of research on pregnant women and at-risk adolescents.

Men who have sex with men (MSM) are another high-priority population warranting renewed multidisciplinary research consideration. "Chemsex," a type of high-risk prolonged sexual activity practiced among a subpopulation of MSM, involves intentional drug use before or during sessions with multiple known and unknown partners. Unfortunately, few harm-reduction interventions to address chemsex have been rigorously evaluated (7). In this Research Topic, Platteau et al. tested a mobile phone application for its efficacy in reducing substance use (e.g., use of GHB, methamphetamine). The app showed promise for relaying messages to and from researchers and for promoting individualized harm reduction strategies. Vallée's review paper also considered chemsex with more commonly available substances. Their analysis indicated that cannabis and alcohol use were linked to an increased number of sexual partners and decreased immune response to monkey pox infection—demonstrating the importance of rapid knowledge transfer at the earliest stage of STI outbreaks.

Widespread availability of effective screening and diagnostic tools are essential for advancing toward an end to global STI epidemics; however, adoption of innovative tools and good clinical practices has not kept pace with the dispersion and prevalence of the most common infections (8). Telehealth medicine holds significant promise toward this goal. The next three articles make important contributions in this area. For instance, Zoschke et al. assessed screening practices of healthcare providers who serve MSM—a population at increased risk for human papillomavirus-associated oropharyngeal cancer. Overall, providers reported low self-confidence and hesitancy in screening for oropharyngeal cancer; however, those who practiced in LGBTQ+ specialty healthcare reported less hesitancy and expressed more confidence and skill in conducting screenings. In a similar population, Ross et al. examined the efficacy of "selfies"—pictures taken at home by patients—of the oral cavity. Patients who submitted selfies were younger, more knowledgeable about HPV, and more likely to have had an HPV vaccine than those who did not. Furthermore, provider inter-rater agreement about image quality to screen for oral malignances was determined to be acceptable. In another study examining telehealth practices, Van Gerwen et al. assessed attitudes toward at-home collection of gonorrhea and chlamydia specimens among transgender women. Preliminary evidence suggests that participants were enthusiastic about at-home extragenital STI testing—a finding that has important implications for avoiding provider-driven stigma and mitigating gender dysphoria. Combined, these studies point to the impact of rapid, affordable, easy-to-use testing innovations that are rigorously evaluated in high-priority populations.

For cisgender reproductive-aged women, even the most common STIs can have a consequential impact. Li and Chen's work is important in this regard as it extends basic science research demonstrating the association between infertility and Pgp3AbMBA antibody levels—a scarcely-used assay for chlamydia. Their findings indicated that each standard increment in Pgp3AbMBA predicted a substantial increase in infertility and this association persisted when limiting the analysis to women who had previously given birth. Stapleton et al. also investigated chlamydia infection, but with a sample of carceral-involved men who have sex with women. Multivariate analyses revealed that having a history of incarceration was positively associated with a positive chlamydia test even after adjusting for potential confounders (e.g., insurance status). This article contributes to a growing body of research demonstrating the shared social and structural determinants of STI acquisition and incarceration.

The development of innovative behavioral interventions to reduce STIs is critical for reducing STI acquisition (4). Using a mixed-method approach including survey data and qualitative assessments, Filippone et al. found that motivational interviewing and monetary incentives were both feasible and efficacious in suppressing HIV viral load in a sample of patients from low-income backgrounds—demonstrating the value of behavioral interventions that consider financial hardship as a proximal barrier to viral load suppression.

Vaccination, a type of prevention as intervention, is an important tool in the arsenal for controlling STIs. The availability of safe and effective vaccines has increased; however, few countries have reached adequate vaccination rates (9). Dykens's et al. article is important in this regard as they critically review policies to expand gender-neutral HPV vaccination programs so that boys are vaccinated at rates comparable to girls. Their work suggests that a more comprehensive approach to HPV vaccine programing is essential for reducing morbidity and would also have the added benefit of reducing misinformation and vaccine-related stigma. In addressing HPV vaccine hesitancy, Moya et al. conducted qualitative assessments among community health workers and healthcare providers who serve Latino people. They identified financial concerns, misinformation, and entrenched cultural norms and attitudes as salient barriers to broad-scale HPV vaccination.

To effectively address STI epidemics, it is essential to develop a comprehensive sexual health approach informed by a multidisciplinary body of stakeholders. Ford et al. examined various national surveys and surveillance systems for the development of a national score card on the state of sexual health in the US. Their work identified four broad domains including knowledge, behaviors and relationships, service access and utilization, and adverse health outcomes as essential in measuring and monitoring core sexual health indicators. This

work holds promise for a national strategy to promote holistic sexual health.

Collectively, these articles highlight the complex interaction between social networks, infectious pathogens, epidemiological patterns, and a myriad of structural forces linked to STI morbidity and mortality. This Research Topic is published at a time of increasing STI incidence and eroding public health infrastructure and these factors are made worse by emergent global antimicrobial resistance. In order to achieve the World Health Organization Sustainable Development Goal of eliminating STI epidemics as major health threats, a renewed commitment to cutting-edge research and rapid transfer of innovation to practice is warranted (10). The articles presented here are an important step toward this public health imperative.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Sexual behaviors, cannabis, alcohol and monkeypox infection

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The emergence of the monkeypox virus (MPXV) outbreak in 2022 is a worldwide health issue. The rapid increase of monkeypox cases caused the WHO to designate the escalating global monkeypox outbreak a Public Health Emergency of International Concern on July 23, 2022. The WHO has called on the group currently most affected by the virus, men who have sex with men (MSM), to limit their sexual partners. The diminution in number of sexual partners not only decreases the proportion of infected MSM but could also increases the number of days needed to reach a given infection level among the general population. Several behavioral factors could be associated with high levels of different sexual partners, such as cannabis use and alcohol consumption. Firstly, this review focuses on the association between cannabis and alcohol consumption and the number of sexual partners, and their possible impact on the current MPXV outbreak by impairing the immune responses. Secondly, this review investigated in the UK Biobank cohort the relationship between alcohol and cannabis use and the number of sexual partners. Among the 115,604 participants, 1.8% declared to be MSM, 1.9% to be WSW (women having sex with women), 43.3% men heterosexuals and 53.0% women heterosexuals. MSM and WSW showed higher lifetime sexual partners ($N = 17.4$ (SD:17.52) and $N = 13.65$ (SD: 13.21), respectively) compared to heterosexual men ($N = 6.89$ (SD: 9.47) and women ($N = 5.19$ (SD:6.56), $p < 0.001$. After adjustment for age, body mass index, lifetime sexual activity, educational and income levels, tobacco and cardiovascular diseases, cannabis use and alcohol consumption remained significantly associated with increase in the number of different sexual partners in all four subgroups. Thus, cannabis use and alcohol consumption may have two detrimental effects on the MPXV outbreak: by participating in the increase of the number of sexual partners which are mainly responsible for the augmentation of the number of new MPXV infected cases and by impairing the immune response to a viral infection. Health and safety policies should address the factors and practices, including chemsex, leading to an increase in risk of sexual behaviors responsible for MPXV dissemination in the worldwide population.

KEYWORDS

sexual behavior, cannabis, alcohol, monkeypox, MSM, outbreak, chemsex, epidemic

Introduction

The emergence of the monkeypox virus (MPXV) outbreak in 2022 is a worldwide health issue (1). To date, more than 58,000 laboratory-confirmed cases and 18 deaths have been observed by the World Health Organization (WHO) from 103 territories in all six WHO Regions (2). The rapid increase in monkeypox infected cases caused the WHO to designate the escalating global monkeypox outbreak a Public Health Emergency of International Concern on July 23, 2022. Like previous infectious diseases (3), Monkeypox is a contagious disease which requires physical or sexual contact with people infected with the virus (4). Although the risk to the overall population is considered to be rather low, the WHO has responded by making this pandemic as a high priority to avoid further outbreaks (5). In a recent report, the WHO has called on the group

currently most affected by the virus, men who have sex with men (MSM), to limit their sexual partners. Recent analyses showed numerous risk determinants, such as being young men, having sex with other men (MSM), having risk behavioral attitudes and activities, including condomless sex, PrEP (pre-exposure prophylaxis) and HIV positivity (6, 7). Indeed, the transmission of MPXV has been correlated with close relationships, especially sexual contact, between men (4, 8) but also within heterosexual populations (9). Studies have suggested that gay, bisexual, and other MSM have taken steps to protect themselves and their sexual partners against MPXV, such as reducing their number of sexual relationships (10, 11). Thus, the decrease in the number of sexual partners not only decreases the percentage of infected MSM but could also increase the number of days needed to reach a given infection level among the overall population. This could allow more time for vaccination campaigns to reach targeted people (12). The decrease in sexual partners could significantly decrease the MPXV transmission rate (11) and slow down the trend toward a pandemic (13). Several behavioral comportments could be associated with high levels of different sexual partners, such as cannabis use (14) and alcohol consumption (15). Thus, this review focuses on the association between cannabis and alcohol consumption on the number of sexual partners, sexual behaviors, and their possible impact on the current MPXV outbreak.

Monkeypox virus outbreak

Monkeypox (MPX) is a zoonotic viral disease which originates from the monkeypox virus (MPXV). This disease has been known for over 50 years but was limited to a restricted number of endemic territories localized in Central and West Africa. Nevertheless, since the years 2000, sporadic reports of imported cases have been observed in North America, Europe, and the Middle East. To date, a worldwide epidemic has shown major issues as the disease is quickly spreading, mainly in young MSM, showing a classic vesicular-pustular rash along with other clinical symptoms (16). More than 65,000 laboratory-confirmed cases and 26 deaths have been observed by the World Health Organization (WHO) from all the territories in the WHO Regions (Figure 1) (2)[1]. The skin is the major source of infection and contamination (17). Although respiratory droplets are thought to diffuse the infection from person to person, the US CDC (Centers for Disease Control and Prevention) declared that the transmission requires a long face-to-face relationship due to the inability of the droplets to cover a long distance. Whereas MPXV remains not only sexually transmitted by vaginal or sperm secretions, health authorities have declared that the current epidemic is due to human-to-human sexual intercourse (4, 18). MPXV is observed in seminal fluid, genital and rectal lesions, and feces and saliva from confirmed infected people in several countries (4, 19). Thus, human-to-human propagation needs contact with lesions, respiratory droplets, or bodily fluids. MPXV infection is characterized by first, a fever associated with headaches, body aches and asthenia. Two days after the fever, a blistering rash begins with formation of scab and scarring. The vesicles are mainly localized on the hands, the palms and the face, and the soles of the feet but can also be present around the mouth and the genital area. The incubation of the MPX ranges from 5 to 21 days. The MPX usually heals spontaneously after 2 to 3 weeks (20).

Monkeypox infection and its complications

A recent French observational study found that complications affected more than a third of the patients (21). The main frequent complications were anal pain, and secondary bacterial skin infections, including cellulitis. The common neurologic symptoms were prodromal frontal headache occurring in the majority of patients (22) in association with asthenia and myalgias. Conjunctivitis can occur with corneal lesions and vision loss (23). Encephalitis has been observed in rare cases. Other complications can include pneumonitis, keratitis and secondary bacterial infections (23). Few patients were hospitalized but can represent up to 6% of them (21). From the beginning of the worldwide 2022 outbreak, the WHO reported 20 confirmed deaths for 64,290 cases in September, 2022 (24), and only six deaths have been reported in the United States for more than 25,000 cases (25). These data are consistent with the mortality rates of past MPXV outbreaks in Africa ranging from 1% in Nigeria to 10% in the Congo Basin (23). Most of the deaths have occurred in young people and people living with HIV (26).

Cannabis use

Marijuana (cannabis) is the main worldwide consumed illicit drug, with over 188 million users, or around 2.5% of the population of 15–64 years (27). Cannabis use is correlated with poor economic, social, psychosocial and health levels. The psychosocial repercussions of cannabis use have been well reviewed (27), with drop out of school, antisocial behaviors and poor school performance. The health repercussions of cannabis use implicate several physiological and biochemical processes including immune, cardiovascular, hepatic, renal, endocrine and general health issues (28). Furthermore, around 38 million people are living with HIV, 170 million with hepatitis C virus, and 10 to 20 million with T-lymphotropic virus type 1. Most of them are cannabis users (29).

Alcohol consumption

More than 100 million people worldwide are observed to have inappropriate alcohol consumption (30). Globally, 3 million deaths per years are the consequences of alcohol disorder. 5.3% of all causes of death are represented by alcohol disorder. Overall, 5.1% of the global burden of disease and injury is attributable to alcohol. Chronic alcohol consumption was associated with progression of community infections and complications in COVID-19 (31).

Cannabis, alcohol, and sexual behaviors

Several studies have shown that the relationship between alcohol and sexual behaviors increases the probability of HIV transmission

1 https://www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html

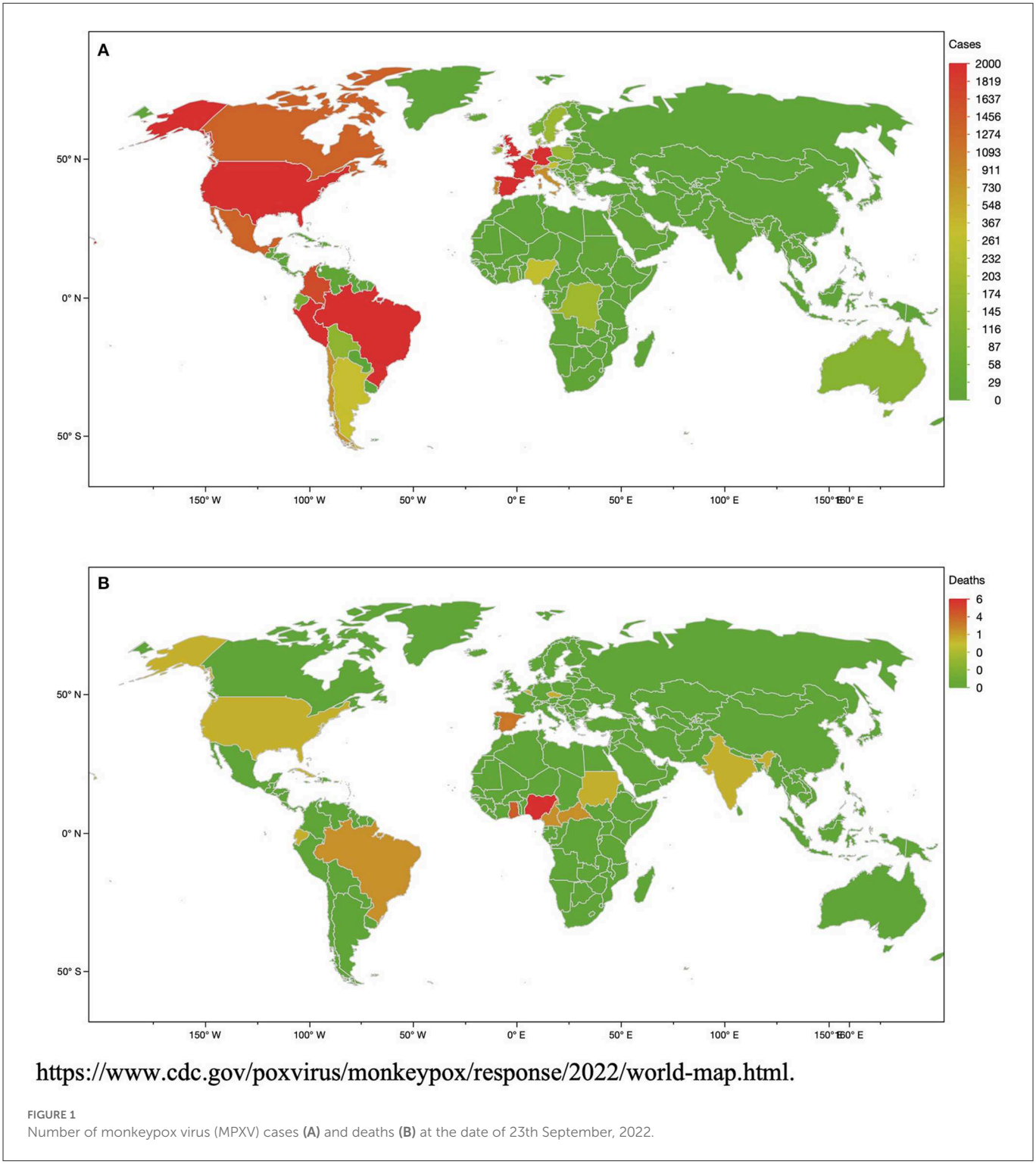

FIGURE 1
Number of monkeypox virus (MPXV) cases **(A)** and deaths **(B)** at the date of 23th September, 2022.

and the absence of use of condoms in anal sexual practice (32–34). Among MSM, the consumption of alcohol is a major determinant of viral infection, such as HIV (33, 35). Nevertheless, the information regarding the effect of cannabis is limited (36). Around 40% of MSM reported to be heavy cannabis users, in comparison to seven percent of the overall population (37). Furthermore, in young MSM, the cannabis is more consumed than alcohol (daily 23 vs. 2%) (38). Recent investigations have suggested that MSM consume cannabis before having sex as frequently as alcohol consumption (63.5 vs. 61.5%) (39). Evidence also suggested that cannabis could increase condomless sex in heterosexual people (40–43).

The delta-9-tetrahydrocannabinol (THC) which composed cannabis could generate pharmacological actions on sexual-risk decision-making as could the consumption of alcohol (44). THC can lead to euphoric mood, impulsivity, risk-taking and aphrodisiac effects and can diminish the capacity of initiating responses (45, 46). Some studies have shown that, among MSM, cannabis and alcohol consumption may affect cognitive functions (47, 48). This risk

is higher than the drug alone, with higher behavioral and social impacts and distress (34). Similar results have been observed among heterosexual young people, with higher risk of condomless sex (49, 50). In contrast, other studies have shown inconclusive results (36, 38, 51). The decision to use condoms or not may be impacted by other HIV prevention strategies, including pre-exposure prophylaxis (PrEP) and treatment-as-prevention (TasP), which could diminish the risk of sexually-based HIV infection, even in case of condomless sex (52, 53). The relationship between alcohol and sexual risk taking has been widely shown (54, 55). Alcohol consumption is correlated with disinhibition of behavioral sex comportments, leading to highly risk of exposure to sexually transmitted infections for individuals under its influence (56, 57). Alcohol consumption, especially in individuals who drink to intoxication levels, is correlated with higher risk of condomless sex (58, 59). Face to the MPXV outbreak, the WHO has called MSM to limit their sexual partners. In this review, we point the fact that several studies have shown that cannabis use was correlated with higher numbers of sexual partners for both genders (60, 61). Sexually transmitted diseases remain a major health issue, and new cases of infection are mainly attributable to the sexual relationships, among both MSM, women having sex with women (WSW) and heterosexuals (58). Thus, it is essential to investigate the role of both alcohol consumption and cannabis use with the number of sexual relationships in these different subgroups of populations.

Cannabis use, alcohol consumption and number of sexual partners, data from the UK Biobank

The objective of this part of the work was to confirm the review information by original results of the association between cannabis use and alcohol consumption and the number of sexual partners among MSM, WSW and heterosexual men and women of the UK Biobank.

Materials and methods

UK biobank population

The UK Biobank is a prospective cohort for the investigation, prevention, diagnosis, and treatment of chronic diseases, such as CV diseases in adults. 502,478 Britons aged of 40–70 years across 22 UK cities from the UK National Health Service Register were included between 2006 and 2010. The cohort was phenotyped and genotyped, with participants who responded to a questionnaire; a computer-assisted interview; physical and functional measures; and blood, urine, and saliva samples (62–64). Data included socio-economic status, lifestyle behaviors, a mental health battery, clinical diagnoses and therapies, genetics, imaging and physiologic biomarkers from blood and urine samples. The cohort protocol can be found in the literature (65).

Lifetime number of sexual partners

Sexual partners were reported by questionnaire. Participants were asked: "About how many sexual partners have you had in your lifetime?". Lifetime sexual activity was defined as the difference between age at inclusion and the age of first sexual intercourse. Men having sex with men (MSM) and women having sex with women (WSW) were defined as participants who declared having same sex intercourse.

Cannabis use

Cannabis use was reported by questionnaire. Participants were asked about their life-time cannabis use: "Have you taken cannabis (marijuana, grass, hash, ganja, blow, draw, skunk, weed, spliff, dope), even if it was a long time ago?". Those who responded "no" were classified as controls (i.e., never users) and those endorsing "yes" options were classified as cannabis users. We separated these users into three groups: those reporting initial cannabis use ("yes, 1–2 times", or "yes, 3–10 times": low users) and continued cannabis use ("yes, 11–100 times": moderate users; and "yes, more than 100 times": high users).

Alcohol consumption

Although the alcohol questionnaire has not been formally validated, several studies have shown expected associations with alcohol (66, 67). Alcohol level consumption was defined as reported in the questionnaire: high level ("daily or almost daily" or "three or four times a week"), moderate level ("once or twice a week," or "one to three times a month"), and low level ("special occasions only" or "never"). Then participants self-reported the number of alcohol units (10 ml of pure ethanol) consumed, in "units per week" or "units per month" (for less frequent drinkers), across numerous beverage categories (red wine, white wine/champagne, beer/cider, spirits, fortified wine, and "other"). The UK Biobank assessment defined units of alcohol as: a pint or can of beer/lager/cider = two units; a 25 ml single shot of spirits = one unit; and a standard glass of wine (175 ml) = two units. The number of weekly units by summing the weekly units consumed in all categories was computed. When reported monthly, the intake was converted to units per week by dividing by 4.3. The number of weekly units was divided by 7 to determine units per day (68).

Covariates

Current tobacco smokers were defined as participants who responded "yes, on most or all days" or "yes, only occasionally" to the question "do you smoke tobacco now." Smoking pack-years are calculated as the average number of packs smoked per day multiplied by the total number of years smoking during lifetime. Body mass index was calculated as weight (in kg) divided by height^2 (meters), and categorized as high (BMI $>$ 30 kg/m^2), moderate (BMI between 25 and 30 kg/m^2) and low ($<$25 kg/m^2). Cardiovascular (CV) diseases were defined by heart attack, angina and stroke, as diagnosed by a doctor and reported in the questionnaires (69). Education level was defined in three categories, high (college or university degree), intermediate (A/AS levels or equivalent, O levels/GCSEs or equivalent), and low (none of the aforementioned) (70). Income

level was defined as, high (">£52,000 per year"), moderate (between £18,000 and £51,999 per year), and low ("<£18,000 per year") (71).

Ethical considerations

All participants provided electronic informed consent and UK Biobank received ethical approval from the North-West Multi-center Research Ethics Committee (MREC) covering the whole of the United Kingdom. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the North-West–Haydock Research Ethics Committee (protocol code: 21/NW/0157, date of approval: 21 June 2021). For details: https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/about-us/ethics.

Study population

Inclusion criteria were participants who responded to the cannabis use questionnaire, to the questionnaire of number of sexual partners, and to alcohol consumption per day. Exclusion criteria

TABLE 1 Characteristics of the study population.

	MSM		WSW		Heterosexual men		Heterosexual women		*P* value
	N = 2,059		*N* = 2,243		*N* = 50,007		*N* = 61,295		
Age (years)	53.36	8.03	51.83	7.31	56.45	7.77	55.07	7.62	<0.001
Number of sexual partners	17.38	17.52	13.65	13.21	6.89	9.47	5.19	6.56	<0.001
Age first intercourse	19.50	6.13	17.99	4.45	19.75	4.88	19.04	4.10	<0.001
Lifetime sexual activity	33.85	9.82	33.84	7.86	36.69	8.66	36.02	7.94	<0.001
Average alcohol daily consumption (units/days)	3.03	3.06	2.12	2.32	2.943	2.73	1.672	1.85	<0.001
Cannabis use									<0.001
High	227	11.02%	228	10.16%	1,746	3.49%	873	1.42%	
Moderate	210	10.20%	350	15.60%	2,659	5.32%	2,159	3.52%	
Low	597	28.99%	733	32.68%	8,169	16.34%	8,500	13.87%	
Never	1,025	49.78%	932	41.55%	37,433	74.86%	49,763	81.19%	
Alcohol level									<0.001
High	639	31.05%	563	25.12%	14,580	29.16%	11,875	19.38%	
Moderate	1,160	56.37%	1,338	59.71%	30,897	61.80%	38,839	63.38%	
Low	259	12.59%	340	15.17%	4,522	9.04%	10,570	17.25%	
Educational level									<0.001
High	1,228	59.64%	1,564	69.73%	25,535	51.06%	29,682	48.42%	
Moderate	575	27.93%	512	22.83%	15,314	30.62%	23,452	38.26%	
Low	256	12.43%	167	7.45%	9,158	18.31%	8,161	13.31%	
Income level									<0.001
High	784	38.08%	882	39.32%	19,524	39.04%	19,999	32.63%	
Moderate	951	46.19%	1,055	47.04%	25,451	50.89%	32,346	52.77%	
Low	324	15.74%	306	13.64%	5,032	10.06%	8,950	14.60%	
BMI (kg/m^2)	27.13	4.52	26.60	5.26	27.26	3.95	26.31	4.88	<0.001
BMI level									<0.001
High	427	20.78%	474	21.21%	10,289	20.62%	11,269	18.42%	
Moderate	925	45.01%	746	33.38%	24,668	49.44%	21,395	34.97%	
Low	703	34.21%	1,015	45.41%	14,938	29.94%	28,518	46.61%	
Current tobacco	204	9.91%	206	9.18%	2,356	4.71%	2,479	4.04%	<0.001
Smoking pack years (pack-years)	9.87	17.31	6.88	12.07	6.76	14.14	4.07	9.81	<0.001
CV diseases	98	4.77%	27	1.21%	2,764	5.53%	1,070	1.75%	<0.001

Continuous variable as mean and standard deviation, categorical variable as number and percentage.

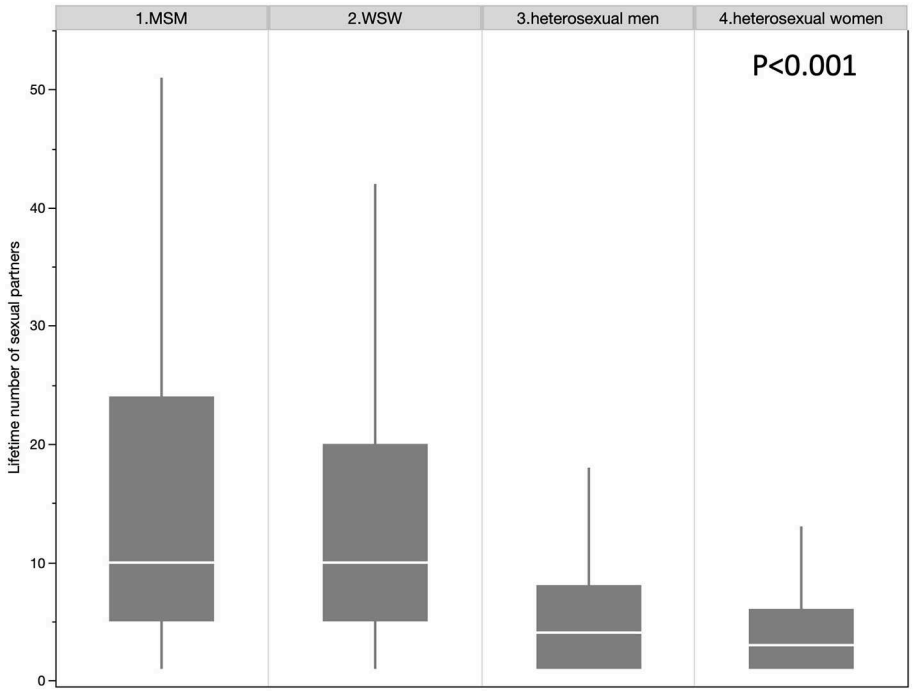

FIGURE 2
Lifetime number of sexual partners between the four groups.

were missing data for all covariates (like age, lifetime sexual activity, gender, income level, educational level, smoking pack years), 115,604 participants were included in the study.

Statistical analysis

Characteristics of the study population were described as the means with standard deviation (SD) for continuous variables. Categorical variables were described as numbers and proportions. To compare characteristics among the quartiles, we used the one-way ANOVA test for continuous variables and the chi-square test for categorical variables. Comparisons between two groups were performed using Student's test for continuous variables. Pearson's χ^2 test was performed for categorical variables. Multivariate linear regression models were performed for the relationship between cannabis use and alcohol consumption, with adjustment for age, BMI, lifetime sexual activity, education, income, smoking pack years and CV diseases. Statistics were performed using SAS software (version 9.4; SAS Institute, Carry, NC). A $p < 0.05$ was considered statistically significant.

Results

Among the 115,604 participants, 2,059 (1.78%) declared to be MSM, 2,243 (1.94%) to be WSW, 50,007 (43.26%) to be heterosexual men and 61,295 (53.02%) to be heterosexual women (Table 1). The gay population (both MSM and WSW) showed a significantly higher number of different sexual partners than the heterosexual population (15.4 vs. 6.0, $p < 0.001$). The gay population has a higher proportion of high cannabis users than the heterosexual population (10.58 vs. 2.356%, $p < 0.001$) and higher levels of alcohol consumption (27.96% vs 23.77%, p<0.001). The same results were observed by stratifying by gender (Figure 2). The number of different sexual partners increases with cannabis use in all the groups, $p < 0.001$ (Figure 3). However, as the number of different sexual partners increases with alcohol consumption in heterosexual women ($p < 0.001$) and men ($p < 0.001$), and among WSW ($p < 0.001$), but this was not the case among MSM ($p = 0.242$) (Figure 4).

After adjustment for age, BMI, lifetime sexual activity, education, income, smoking pack years and CV diseases, the number of different sexual partners was significantly higher in high cannabis users compared to never users in all the groups (MSM, $p = 0.031$; WSW, $p < 0.001$; heterosexual women, $p < 0.001$ and heterosexual men, $p < 0.001$). The same results were observed for average daily alcohol consumption (MSM, $p = 0.004$; WSW, $p < 0.001$; heterosexual women, $p = 0.002$ and heterosexual men, $p < 0.001$) (Table 2). No interactions were observed between cannabis use and alcohol consumption in MSM ($p = 0.674$) and in WSW ($p = 0.362$) but significant interactions were observed in heterosexual women ($p = 0.047$) and in heterosexual men ($p < 0.001$).

Limitations

The cross-sectional observational design limits the relationship of causality. Reverse causation cannot be ruled out. The number of sexual partners was self-reported and could be considered as a major bias. Moreover, no historical indication of sexually transmitted infections has been reported in the UK Biobank cohort and could not allow us to investigate the relationship between number of sexual partners and sexually transmitted infection prevalence.

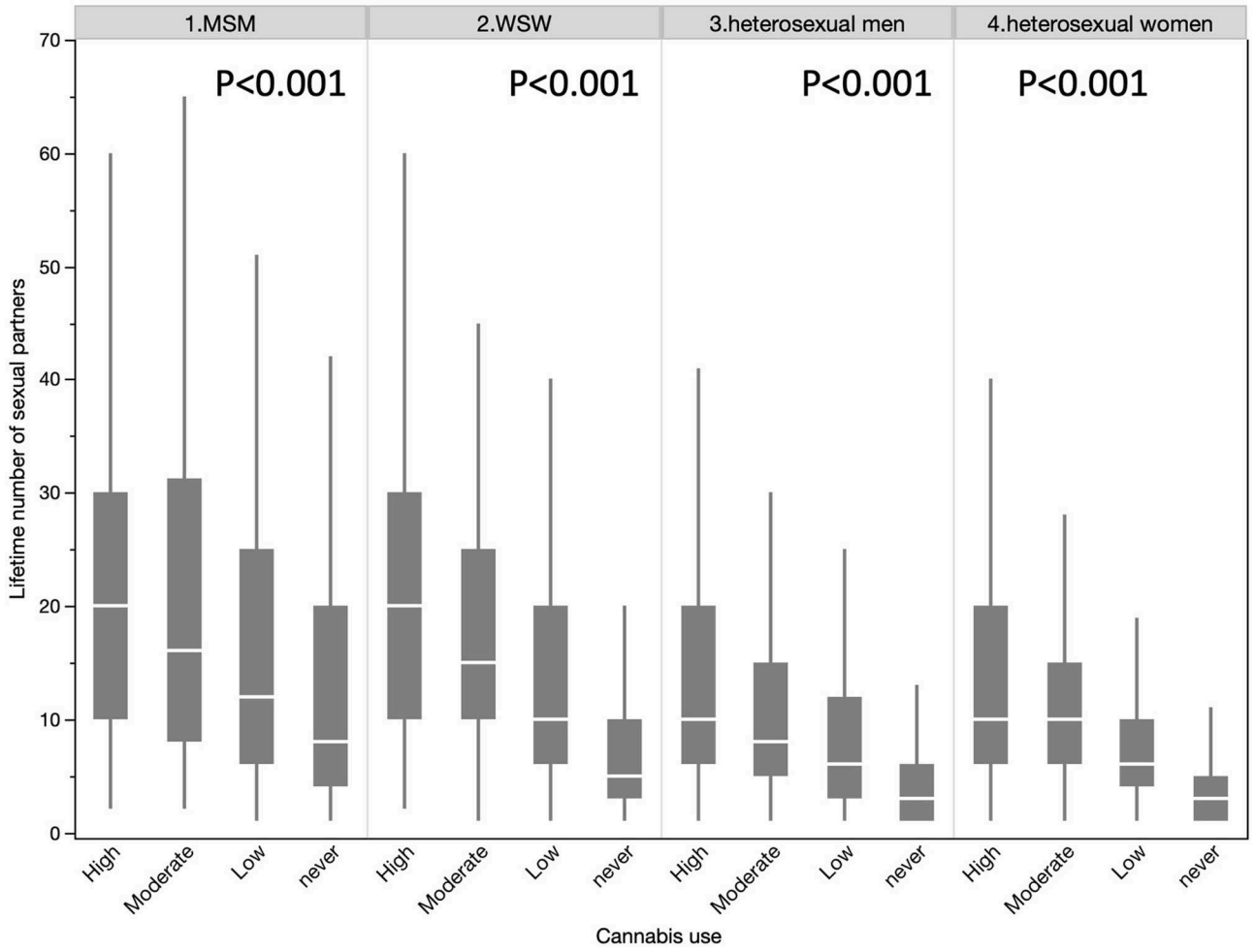

FIGURE 3
Lifetime number of sexual partners in all the subgroups according to cannabis use.

Cannabis and alcohol with immune and viral systems

It is well-known that illicit or licit substances could affect several components of the immune system, by dysregulating the function of distinct immune response cells. Numerous studies have shown that some drugs could influence lymphocytes as well as dendritic cells and macrophages. Cannabis use, as well as alcohol consumption, has been reported to damage immune responsiveness. The recreational use of such drugs has been well described to affect resistance to microorganisms and alter susceptibility to infectious diseases (72). The consumption of cannabis and alcohol simultaneously is known to dysregulate the inflammatory responses through toll-like receptors (TLRs) (73).

Cannabidiol (CBD), one of the compound of cannabis, can damage the functional roles of the immune system (74). Cannabis acts as an immune modulator, damaging T-cells, B-cells, monocytes, and microglia, leading to reduction of the production of proinflammatory cytokines and an increase in the activity of anti-inflammatory cytokines. The role of cannabis immunity has been well discussed (75, 76). Cannabis use could predispose people to pulmonary infection, in patients showing a decrease in immune defenses by HIV infection chemotherapy (77). These people show that cannabis generates a concentration-dependent diminution in the proliferation of T cells and in the production of IFN-γ through CB2 receptor-dependent signaling. At the level of gene expression, cannabis stimulates Th1 cytokines (IFN-γ/IL-2) expression and decreasesTh2 cytokine (IL-4/IL-5) expression. Thus, both consumption of cannabis and alcohol significantly stimulates the production of IL-6 cytokine and toll-like receptors, TLR5, TLR7 and TLR9s. This suggests cannabis-related action on pulmonary innate immunity promoting airway inflammation (73). People living with viral infections can consume several illegal drugs, including cannabis. With regard to its negative actions, there are investigations which support the information that cannabis is detrimental for viral infections. Recent studies have shown that cannabis could control the immune system by modulating specific receptors on immune cells and decreasing immunity (78–83). Nevertheless, several investigations have shown that cannabis could have some positive actions (27). Thus, cannabis could affect the immune system (74, 75), could stimulate inflammatory cytokine production and CRP levels (84), and could decrease resistance to viral infections (85, 86). However, the literature remains inconsistent for the alteration of T cell lymphocytes, B cell lymphocytes, macrophages or

immunoglobulin (27). Cannabis may reduce inflammation in HIV infection (87), and impairment of neurocognition of people living with HIV (88).

Similar results were observed for alcohol consumption. Alcohol may exert a dose-dependent interaction on the host response to viral infection (89). High alcohol consumption increases viral and bacterial infections (90), severity of infections (91), leads to viral infection expression, including HIV (92) and hepatitis C (93). However, moderate alcohol consumption was correlated with enhancement of immune response to infection and vaccination (94–96). The negative actions of high alcohol consumption on the immune system have been widely shown (97). Alcohol consumption can affect cell-mediated immunity and can be associated with high levels of post-operative infections (98). Ethanol diminishes cytokine production, affects macrophage responses to cytokines and LPS and stimulates the intracellular survival rate of Mycobacteria, Legionella, Salmonella or Listeria (99).

Cannabis and orthopoxvirus infection

Few investigations have reported cannabis use and orthopoxvirus infection, none with the MPXV infection (100, 101). A team from Austria reported in 2016 that a young patient infected by an unusually severe cowpox virus (CPXV) with generalized rash and fever (102), showed abused substances associated with severe symptoms and diminution of the overall anti-CPXV antibody titer (100). They also showed that a single dose of cannabinoids increased the severity of CPXV infection in animals (101). Thus, a monodose of cannabis resin or THC before infection was associated with the reduction of the anti-CPXV anti-body formation in mice. The patient viewed by this team, developed a severe and generalized CPXV infection but without antibody response (100). The production of antibodies may have a major and protective role in CPXV infections (103). However, data are not consistent for the role of cannabis in antibody formation. A recent investigation showed a correlation between the diminution of immunoglobulin G and M rates and cannabis use (104) while other studies did not observe modifications in B-cell numbers rather than augmented IgE levels (105).

In a report of CPXV infection, the patient presented levels of lymphocytes within a normal range and serum analysis showed normal levels of immunoglobulin IgM but augmented serum IgG and IgE levels (100). These observations could be mainly attributed to a cannabinoid drug action showing an augmentation of the levels of IgE (99). Cannabis use can lead to immune-suppression leading to an enhancement of susceptibility to infection (100).

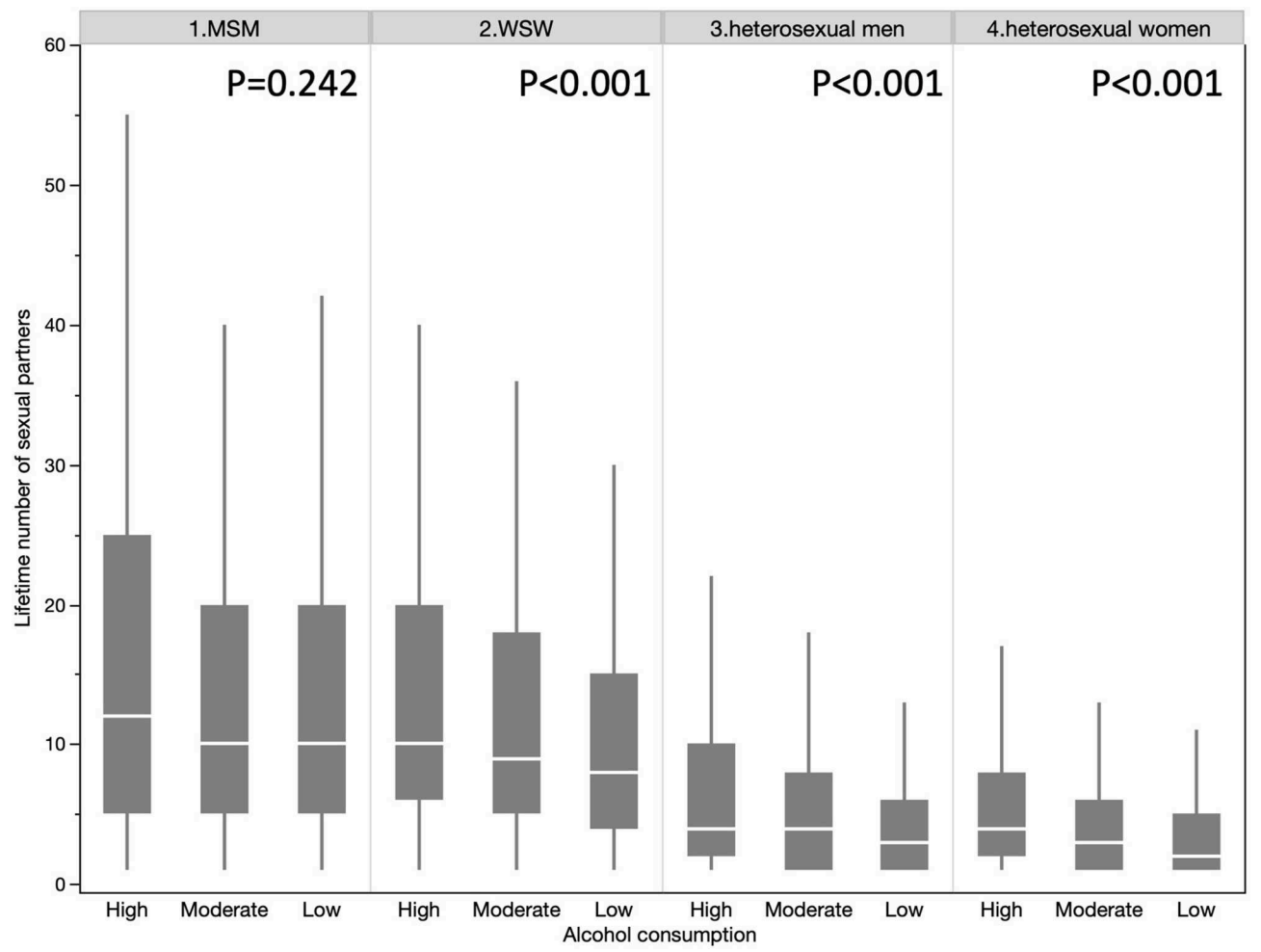

FIGURE 4
Lifetime number of sexual partners in each groups according to alcohol consumption level.

TABLE 2 Multivariate linear regression models for cannabis use and alcohol consumption with lifetime number of sexual partners, with adjustment for age, BMI, lifetime sexual activity, education, income, smoking pack years and CV diseases.

MSM	Beta (95%CI)	*P* value
Cannabis		
High	2.03 (0.18; 3.87)	0.031
Moderate	2.70 (0.84; 4.57)	0.005
Low	−0.47 (−1.81; 0.85)	0.481
Never	Ref.	
Alcohol consumption	0.37 (0.12; 0.61)	0.004
WSW	**Beta (95%CI)**	***P* value**
Cannabis		
High	6.01 (4.72; 7.29)	<0.001
Moderate	2.27 (1.19; 3.34)	<0.001
Low	−2.14 (−2.99; −1.28)	<0.001
Never	Ref.	
Alcohol consumption	0.26 (0.04; 0.48)	0.020
Heterosexual men	**Beta (95%CI)**	***P* value**
Cannabis		
High	3.99 (3.66; 4.31)	<0.001
Moderate	1.19 (0.91; 1.46)	<0.001
Low	−0.89 (−1.09; −0.69)	<0.001
Never	Ref.	
Alcohol consumption	0.32 (0.29; 0.35)	<0.001
Heterosexual women	**Beta (95%CI)**	***P* value**
Cannabis		
High	4.09 (3.79; 4.39)	<0.001
Moderate	2.13 (1.92; 2.35)	<0.001
Low	−1.11 (−1.26; −0.97)	<0.001
Never	Ref.	
Alcohol consumption	0.27 (0.25; 0.30)	<0.001

An association between cannabis use and herpes virus infections has been shown to reduce the phagocytic ability of alveolar macrophages, the NK-cell activity, interferon-gamma, and interleukin IL-12 levels (106). This observation of an increase of intracellular agent survival rate, and then of a decrease in survival rate of THC-treated mice with Legionella pneumophila infection (106).

Cannabis can influence the humoral immune response (107) and can control allergic immune responses (108) and neuro-inflammatory disorders (109). Even if no data clearly showed a negative role of cannabis in Orthopoxvirus, and its detrimental actions in viral infections, the significant reduction of Ig levels against vaccines and the reduction of complement protein in specific populations, like students, can highlight the dimension of the health problem (104).

No data linked alcohol consumption and Orthopoxvirus infection.

Chemsex, alcohol, cannabis and monkeypox infection

The incidence of STIs (sexually transmitted infections) has globally increased and continues to bear a disproportionate disease burden (110). Chemsex is sexualized drugs use and could be characterized as the intention to use illicit substances and/or drugs to enhance pleasure during sex. These substances include gamma-hydroxybutyrate (GHB), crystal meth, mephedrone, ecstasy, or cocaine (111). Chemsex is associated with a higher risk of reduction in the use of condoms (112, 113), increased risk of multiple sexual partners (114, 115) and higher risk of STI transmission, including HIV (116, 117). Face to the MPXV outbreak, chemsex practice could be a high-risk sexual practice for virus transmission. Furthermore, recent studies have observed that chemsex is often associated with cannabis use (118) and alcohol consumption (44).

Although investigations were mainly focused on LGBT (gay, lesbian, bisexual and transgender) populations, recent studies have shown that the practice of chemsex could be also frequently observed in both women and men, regardless of their sexual orientation (119, 120). Nevertheless, certain drug combinations should be considered according to the different populations. For example, alcohol and cannabis were mainly used in association with ecstasy among heterosexual sexual relationships (121, 122). To date, very few studies have investigated the role of chemsex in the MPXV outbreak. Wang et al. (123), showed that MSM using chemsex recently were less likely to perceive higher concern for MPXV infection (123). One of the explanations could be that MSM using chemsex tend to underestimate the STI risk in general (124, 125). However, Thornhill et al. (20), reported a prevalence of 20% of chemsex use among 528 infections diagnosed in 16 countries (20). Moreover, in a French cohort of patients infected by MPXV, 42% (90/216) reported having practiced chemsex in the last 3 months, and 40% (106/264) having condomless sex (21).

Conclusion

The emergence of the monkeypox virus (MPXV) outbreak in 2022 has become a worldwide health issue. Monkeypox is a contagious disease which requires physical or sexual contact with someone infected with the virus. In a recent report, the WHO has called on the group currently most affected by the virus, men who have sex with men (MSM), to limit their sexual partners. In this review, we observed that cannabis use and alcohol consumption are mainly correlated with a high number of sexual partners and at-risk sexual behaviors in both gay and heterosexual populations, which can lead to increase the dissemination of the MPXV and therefore lead to a sharp increase in this outbreak. Cannabis use and alcohol consumption may have two detrimental effects for the MPXV outbreak: by participating in the increase of the number of sexual partners which is mainly responsible for the augmentation of the number of new MPXV infected cases and by impairing immune responses to a viral infection. Health preventing policies should address the factors and practices leading to an increase

in risk of sexual behaviors responsible for MPXV dissemination in the worldwide population (126). Health professionals should be aware of all risk behaviors concerning the MPXV outbreak to implement appropriate health policies without stigmatization to prevent discrimination and optimize compliance to these messages.

Author contributions

AV: conceptualization, methodology, formal analysis, and writing—original draft preparation.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Sexual health indicators for the United States: Measuring progress and documenting public health needs

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Introduction: Today, we are facing increased and continued adverse sexual health outcomes in the United States, including high post-COVID-19 pandemic rates of sexually transmitted infections (STIs). For the past 20 years, there have been calls for a national health strategy and a more comprehensive sexual health approach to address the myriad of persistent sexual health problems in this country. Employing a sexual health approach requires shifting from a longstanding, stigmatizing focus on morbidity toward a holistic and integrated focus on health rather than disease. While strategies are being implemented by multisectoral stakeholders, it is also important to establish a core set of indicators that broadly describe the state of sexual health in the U.S. and allow for measurement across time. The development of a comprehensive scorecard with key sexual health indicators has been proposed by other entities (e.g., Public Health England, World Health Organization), but such an attempt has not been made in the U.S.

Methods: A review of national U.S. surveys and surveillance systems with items related to sexual health was conducted for years 2010–2022 to develop an inventory of existing data that yield national estimates for potential indicators of sexual health.

Results: We selected 23 sexual health indicators in four broad domains including: (1) knowledge; communication and attitudes (five indicators); (2) behaviors and relationships (four indicators); (3) service access and utilization (seven indicators); and (4) adverse health outcomes (seven indicators). Recent data for each indicator are provided.

Discussion: A growing body of evidence shows the positive effects of moving away from a morbidity focus toward an integrated, health-promoting approach to sexual health. Yet, not much has been done in terms of how we implement this national shift. We argue that measurement and monitoring are key to future change. We envision these core sexual health indicators would be published in the form of an index that is publicly available and updated frequently. These sexual health indicators could be used for ongoing monitoring, and to guide related research, programming, and policy development to help promote sexual health in coming years.

KEYWORDS

sexual health, sexual wellbeing, sexually transmitted infections, reproductive health, indicators and metrics

Introduction

During the COVID-19 pandemic, rates of sexually transmitted infections (STIs) increased substantially. This trend—driven by delays in surveillance and treatment—reminds us that sexual health matters even in the face of a pandemic (1–3). Amidst the recent overturning of Roe v. Wade we are reminded again that sexual health has profound impacts on people's lives. For the last 20 years, there have been calls for a more holistic and integrated approach

to sexual health in the U.S. (3–8). Such an approach would help combat persistent public health challenges, including HIV, STIs, unintended pregnancy, and sexual violence. "Sexual health" is defined by the World Health Organization (WHO) as "a state of physical, emotional, mental and social wellbeing in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity. Sexual health requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination, and violence." (9). Employing a sexual health approach involves shifting away from an enduring, stigmatizing focus on morbidity toward a focus on health rather than disease across the lifecourse (3, 10–12). In turn, sexual health services and funding would be less fragmented, costs lowered, stigma decreased, and health and productivity improved (3, 7, 10–14).

While we have not yet succeeded in generating a broadly integrated national approach to sexual health in the U.S., some essential efforts are already in place. For example, our National HIV/AIDS Strategy (2022–2025) (15), STI Treatment Guidelines (2021) (1), and the Center for Disease Control and Prevention (CDC's) new unintended pregnancy prevention initiative (16) have all recently been updated with a renewed focus on overall health. Yet, there is room for more progress. In this article, we present a baseline set of sexual health indicators designed as a foundation upon which to build our future sexual health.

Background

Current data provide evidence of persistent sub-optimal sexual health in the U.S. STIs such as chlamydia and gonorrhea are the most commonly reported infectious diseases and HIV and syphilis consistently rank highly on the list of notifiable diseases compiled annually by the Centers for Disease Control and Prevention (CDC) (17). Almost half of all pregnancies are unintended (18) and sexual violence is common (19). Sexual dysfunction (e.g., erectile dysfunction, painful intercourse) is reported by at least half of older Americans (20). Reproductive tract cancers affect hundreds of thousands of people annually (21).

Many of these outcomes occur in the same individuals and subpopulations, creating syndemics (overlapping epidemics of two or more health-related issues), furthering the burden of disease (22). Syndemics most commonly emerge under conditions of health inequality created by poverty, stigma, or structural violence where these factors work together to heighten vulnerability (23). HIV and viral hepatitis, for example, form a syndemic affecting vulnerable populations namely people who use drugs. Despite the accessibility of treatments, this syndemic has become of increasing concern in U.S. areas most affected by the social drivers of opioids and other substance use (24).

Adverse sexual health outcomes are not just too common, they are also costly, placing a large burden on health care systems (3, 10). The direct medical costs of STIs including sexually transmitted HIV and hepatitis B are estimated at $16 billion dollars annually (22, 25). Similarly, the social and economic impact of unintended and teen pregnancy in the U.S. is substantial, with $9 billion annually in estimated costs related to teen pregnancy alone (26). Rape and other forms of sexual assault are estimated to cause an annual minimum loss of $12 billion (27, 28); these estimates do not account for the emotional and psychological burdens of such acts.

Historically, public health efforts to address adverse sexual health outcomes have typically focused on a single outcome or disease rather than examining sexual health in a holistic and integrated manner. For example, many public health programs, such as family planning or STI/HIV prevention, are funded based on the topic area, with organizational separation (7, 10). To address this tendency toward such isolated efforts, there have been calls for a national health strategy and a more comprehensive sexual health approach to address the myriad of persistent sexual health problems. Beginning in 2001, *The Surgeon General's Call to Action to Promote Sexual Health and Responsible Sexual Behavior* was the first formal U.S. government recognition of the need to broadly promote sexual health to enhance overall population health (4). More recently, Healthy People 2030, the White House National Strategy on Gender Equity and Equality, and the World Health Organization's Global STI Strategy all echo this focus on sexual health, emphasizing health, wellbeing, prevention, and relationships (1, 6, 13, 29). The Department of Health and Human Services (HHS) recently developed a blueprint for how to include sexual health across all HHS programs, including Medicare and Medicaid (30). Finally, the National Academies of Sciences, Engineering, and Medicine (NASEM) called for moving from a narrow view of STI prevention to a broader, holistic sexual health approach that addresses the social and structural determinants of sexual behavior (7).

In dialogue with these national efforts, a novel model for action was proposed in 2013 (11) and again in 2017 (3) for public health partners to promote sexual health across the lifespan This framework—based upon an emphasis on wellness, focus on positive and respectful relationships, acknowledgment of sexual health as a component of overall health, and integrated approach to prevention—includes four primary long-term objectives: (1) Increase knowledge, communication, and respectful attitudes; (2) Increase healthy, responsible, and respectful sexual behaviors and relationships; (3) Increase use of high quality, coordinated educational, clinical, and other preventive services; and (4) Decrease adverse sexual health outcomes (detailed below) (11). To support these long-term sexual health objectives, it is essential to establish a core set of indicators that broadly describe the state of sexual health in the U.S. and allow for tracking across time. Collecting better measures of sexual health will not only help address recent rises in STI rates, it will help efforts to manage other syndemics such as HIV, substance use, and mental health disorders.

Notably, the development of a comprehensive scorecard with key sexual health indicators has been proposed by some entities [e.g., Public Health England, United Nations Population Fund (UNFPA), WHO] (31–33). Likewise, a growing number of countries have conducted national sexual health surveys (e.g., Australia, Canada,

Abbreviations: APNCU, Adequacy of Prenatal Care Utilization; GSS, General Social Survey; HEDIS, Healthcare Effectiveness Data and Information Set; HP2020/HP2030, Healthy People 2020; 2030; M, male; F, female; NAACCR, North American Association of Central Cancer Registries; NHAS, National HIV/AIDS Strategy; NIS-Teen, National Immunization Survey-Teen; NISVS, National Intimate Partner and Sexual Violence Survey; NNDSS, National Notifiable Disease Surveillance System; NPS, National Prevention Strategy; NSFG, National Survey of Family Growth; NVSS, National Vital Statistics System; Profiles, School Health Profiles; STI Plan, STI National Strategic Plan.

Flanders, France, Germany, Ireland, Latvia, Malta, The Netherlands, Portugal, Spain, and the United Kingdom) (34–37). We have not seen efforts to this extent in the U.S. At present, these countries and organizations use this type of data to monitor the sexual health of their population, to support local and national efforts, and to determine the impact of public health related systems (32, 38). We anticipate that a proposed U.S. scorecard might be used in a similar way (e.g., for monitoring, to inform related research, programming, and policy development). We elaborate on this further in the discussion.

Accordingly, we reviewed existing data systems that yield national estimates for potential indicators of sexual health (8). Although numerous high-quality data sources exist, none provided a comprehensive assessment of sexual health across the lifespan and included the domains of knowledge, communication, attitudes, service access and utilization, behaviors, relationships, and adverse health outcomes (8). Therefore, we sought to identify a core set of measures from multiple existing data systems and to characterize the current state of sexual health in the U.S.

Methods

Two sets of meetings were held to review and identify a core set of sexual health indicators. First, representatives from six CDC divisions addressing aspects of sexual health (i.e., HIV/AIDS, STD, viral hepatitis, adolescent/school health, reproductive health, sexual violence) met in 2010–2011 to review and identify a core set of sexual health indicators. Subject matter experts proposed indicators based on their understanding of their respective fields' best available measurements; all indicators were selected through a consensus decision-making process. These indicators were shared with external partners active in the CDC/Health Resources and Services Administration (HRSA) Advisory Committee's sexual health workgroup. Recognizing the critical state of sexual health during the COVID-19 pandemic, efforts to finalize indicator selection and dissemination continued: a second meeting was held in 2022 with public health representatives, including academics, non-governmental organizations, and CDC experts, to reexamine the indicators considering the current state of public health. Based off feedback provided at this meeting, we: (1) confirmed the indicators corresponded with Healthy People 2030 targets (rather than Healthy People 2020); (2) made sure the indicators aligned with 2021 CDC STI treatment guidelines and NASEM report both calling for attention to sexual health and reduction of stigma; and (3) changed one indicator measuring gonorrhea to syphilis based on current guidelines (1).

Indicators were selected to measure long-term sexual health outcomes (3, 11) and to allow for future tracking (ideally, every 1–2 years). Additionally, selection criteria included: (1) identifying a concise set of indicators; (2) focusing on the general population; (3) identifying indicators that would link policy and action; and (4) aligning these measures with existing targets or goals (e.g., Healthy People 2030).

We established a target range for number of indicators (18–23 total) for the aforementioned four primary long-term objectives for improving population sexual health: (1) Increase knowledge, communication, and respectful attitudes (3–4 indicators); (2) Increase healthy, responsible, and respectful sexual behaviors and relationships (3–4 indicators); (3) Increase use of high quality, coordinated educational, clinical, and other preventive services that improve sexual health (6–7 indicators); and (4) Decrease adverse health outcomes, including HIV/STIs, viral hepatitis, unintended pregnancies, sexual violence, sexual dysfunction, and cancers in reproductive tracts (6–7 indicators). Within each objective, we attempted to select at least one indicator per domain (domains summarized in Table 1). For example, for Objective 1, we identified at least one indicator for each domain: knowledge, communication, and attitudes. We thought 18–23 indicators could capture the range of domains covered and topics represented in sexual health while being a manageable set to track over time.

Our primary source in this process was an existing review study that identified 18 U.S.-focused nationally-representative surveys and surveillance systems that provided individual-level data, addressed elements of sexual health, and had a high likelihood of future data collection (8). We also selected indicators that best aligned with the strategic goals such as those included in Healthy People 2030 and the National Strategy on Gender Equity and Equality. When a sufficient indicator at the individual level was not available, we considered national-level data at other levels (e.g., institutional).

Results

The selected indicators of sexual health in the U.S. are described below and summarized in Table 1. We provide further information on indicators' data sources, and measurement notes including a detailed description of indicator components in Table 2. We provide recent data for each indicator in Table 3.

Objective 1. Increase knowledge, communication, and respectful attitudes regarding sexual health

Knowledge of sexual health is a complex concept that is not easily represented by the few existing items on national data sources (8). Therefore, although it is not comprehensive and may not adequately capture what youth have retained, we selected "youth (15–24 years) exposure to formal sex education (four topics) before age 18 years" (6, 39) for our knowledge indicator (Table 2, 1.A.). This indicator comes from the National Survey of Family Growth (NSFG) (40). In 2015–2019, ~54% of males and 53% of females reported receiving formal sex education on delaying sex, birth control methods, HIV/AIDS prevention, and sexually transmitted diseases before they were 18 years old (Table 3) (6, 41).

We also found measures of communication with partners, parents/family, and providers to be lacking in the existing data sources meeting our criteria. We selected the following as best available measures of parent and partner communication as sexual health indicators from the NSFG: "youth (15–19 years) who had talked with a parent or guardian about (four key) sexual health topics" (Table 2, 1.B.) and "who reported it would not be embarrassing to discuss using a condom with a new partner" (Table 2, 1.C.). NSFG data (2011–2015) show that 54% of females and 47% of males have talked with a parent or guardian about several sexual health topics (Table 3) (42). In addition, in 2011–2015, over 60% of youth reported

TABLE 1 Summary of sexual health indicators.

	CDC surveillance	GSS	HEDIS	NAACCR	NIS-Teen	NISVS	NSFG	NVSS	Profiles
1. Knowledge, communication, attitudes									
Formal sex education							X		
Communication with parents							X		
Condom communication							X		
Attitudes toward same-sex sex		X							
Presence of gay/straight alliance									X
2. Behaviors and relationships									
Sexual debut							X		
Condom use							X		
Contraceptive use							X		
Relationship happiness		X							
3. Education and services									
Sexual health course required									X
Bullying and harassment									X
Receipt of health services							X		
HIV testing	X								
Chlamydia screening			X						
HPV vaccine					X				
Prenatal care								X	
4. Adverse outcomes									
HIV	X								
Syphilis	X								
Hepatitis B	X								
Unintended pregnancy							X	X	
Teen pregnancy							X	X	
Sexual violence						X			
Reproductive cancer				X					

that they would not be embarrassed to discuss condom use with a new partner (43).

For attitudes related to sexual health, we identified several measures that could serve as potential indicators; however, it was challenging to find measures of "respectful" attitudes given concerns about value bias or misinterpretation. Thus, we decided to focus on attitudes related to sexual health that could reduce the likelihood of discrimination. CDC states that "stigma and homophobia may have a profound impact on the lives of MSM [men who have sex with men], especially their mental and sexual health" (44); therefore, we selected the following attitudinal indicator from the General Social Survey (GSS): "What about sexual relations between adults of the same sex—do you think it is always wrong, almost always wrong, wrong only sometimes, or not wrong at all" (Table 2, 1.D) (45). In 2021, ~64% of females and 60% of males agreed that same-sex relations between adults were not wrong. Additionally, an indicator was also chosen from the CDC School Health Profiles (46) to measure attitudes toward sexual minority youth: the percentage of middle and high schools with gay-straight alliances (GSAs) (Table 2, 1.E). In 2018, 36.8% of secondary schools in the United States had a GSA or similar club (46). Research shows sexual minority youth who attend schools with gay/straight alliances are less likely than sexual minority youth who attend other schools to report dating violence, harassment or skipping school because they felt unsafe (47).

Objective 2. Increase healthy, responsible, and respectful sexual behaviors and relationships

Three indicators were selected to assess healthy, responsible, and respectful sexual behaviors. As a measure of delay in initiation of sex, from NSFG we chose "adolescents aged 15–17 who had never had sexual intercourse (vaginal sex)" (Table 2, 2.A) (6). In 2017–2019, ~77% of male and 72% of female adolescents reported that they never had sexual intercourse (Table 3) (6). The remaining two indicators of healthy and responsible sexual behavior (both from NSFG) focused

TABLE 2 Selected sexual health indicators by objectives.

Sexual health indicator	Data source	Population	Alignment with existing published goals/objectives	Measurement notes[a]
Objective 1. Increase knowledge, communication, and respectful attitudes regarding sexual health				
Knowledge				
1.A. Percentage of youth that received formal sex education before they were 18 years old	NSFG	M&F, 15–24 yrs	HP2030 (FP-08) -includes separate measures for 4 topics; 15–19 yrs	Composite indicator, requiring "yes" response to all 4 topics: saying no to sex; methods of contraception; STIs; HIV/AIDS prevention (2–3 years)
Communication				
1.B. Percentage of adolescents that have talked with a parent or guardian about several sexual health topics	NSFG	M&F, 15–19 yrs	HP2020 (FP-13)	Composite indicator, requiring "yes" response to all 4 topics: how to say no to sex; methods of contraception; STIs; how to use a condom (2–3 years)
1.C. Percentage of youth that report it would not be embarrassing to discuss using a condom with a new partner	NSFG	M&F, 15–24 yrs	–	Represents youth who report there is 'no chance' a condom discussion would be embarrassing (2–3 years)
Attitudes				
1.D. Percentage of people that agree sexual relations between two adults of the same sex are not wrong	GSS	M&F, >17 yrs	–	Combines two categories: "wrong only sometimes" and "not wrong at all" (biennial)
1. E. Proportion of middle and high schools with gay-straight alliances (GSA)	School Health Profiles (Profiles)	M&F middle and high school youth	–	Based upon response that "yes" school has a GSA or similar club (biennial)
Objective 2. Increase healthy, responsible, and respectful sexual behaviors and relationships				
Sexual behaviors				
2.A. Percentage of adolescents who never had sexual intercourse (aged 15 yrs)	NSFG	M&F, 15 yrs	HP2030 (FP-04)	Sexual intercourse = vaginal sex. Slight wording change from HP2030. (2–3 years)
2.B. Percentage of sexually active unmarried persons who use condoms	NSFG	M&F, 15–44 yrs	HP2030 (FP-05; FP-06)	Based upon last vaginal sex (2–3 years)
2.C. Percentage of percent of women aged 20 to 44 years at risk of unintended pregnancy who used most effective or moderately effective methods of contraception	NSFG	F, 15–44 yrs	HP2030 (FP-10)	Based upon last vaginal sex (2–3 years)
Relationships				
2.D. Percentage of people that report happiness with marriage	GSS	M&F, >17 yrs	–	Represents adults who selected "very happy" (biennial)
Objective 3. Increase use of high-quality, coordinated educational, clinical, and other preventive services that improve sexual health				
3.A. Percentage of schools teaching 20 key HIV, STI, and pregnancy prevention topics in a required course	School Health Profiles	Middle & high schools	–	Composite indicators, requiring "yes" response to 20 age-appropriate sexual health topics, by grade level
3.B. Percentage of schools with practices in place to prevent bullying and sexual harassment	School Health Profiles	Middle & high schools	–	Composite performance indicator requiring "yes" response to 4 key practices in place to prevent bullying and sexual harassment
3.C. Percentage of sexually active persons who receive sexual and reproductive health services	NSFG	M&F, 15–44 yrs	HP2020 (FP-7), NPS	Sexually experienced men and women who received ≥ 1 reproductive health services in the past 12 months[b]
3.D. Percentage of people living with HIV who know their serostatus	HIV surveillance	>12 yrs	HP2030 (HIV-02), NHAS, NPS	Estimates derived using extended back-calculation on HIV and acquired immunodeficiency syndrome (AIDS) data at diagnosis from 40 states (with confidential name-based HIV infection reporting since at least January 2006), and AIDS data from 10 states and the District of Columbia. (annual)

(Continued)

TABLE 2 (Continued)

Sexual health indicator	Data source	Population	Alignment with existing published goals/objectives	Measurement notes[a]
3.E. Proportion of sexually active adolescent and young females enrolled in Medicaid and commercial health plans who are screened for chlamydial infections	HEDIS	F, 16–24 yrs	HP2030 (STI-01), NPS, STI Plan	Participating health plans report the annual Chlamydia screening rate measured by the proportion of sexually active women (annual)
3.F. Percentage of adolescents aged 13 through 15 years who received recommended doses of the HPV vaccine	NIS-Teen	13–15 yrs	–	Vaccination coverage estimates are available for adolescents with adequate provider data
3.G. Percentage of pregnant women who receive early and adequate prenatal care	NVSS	F, 15–44 yrs	HP2030 (MICH-08)	Uses APNCU measure combining number and timing of prenatal visits (annual)
Objective 4. Decrease adverse health outcomes, including HIV/STIs, viral hepatitis, unintended pregnancies, sexual violence, sexual dysfunction, and cancers in reproductive tracts				
4.A. New (incident) HIV infections among adolescents and adults	HIV incidence surveillance	M&F, >12 yrs	HP2030 (HIV-1), NHAS	Incidence is statistically estimated by CDC (part of NNDSS) (annual)
4.B. Rate of syphilis in women (15–44 yrs) and MSM (all ages) (per 100,000)	STD surveillance	F, 15–44 yrs; all MSM	HP2030 (STI-03; STI-05), STI Plan	Nationally notifiable STD surveillance data (part of NNDSS) (annual)
4.C. New hepatitis B infections in adults	Viral hepatitis surveillance	M&F, >17 yrs	NNDSS; HP2030 (IID-11)	New infections are statistically estimated by CDC using reported cases (part of NNDSS) (annual)
4.D. Percentage of pregnancies that are unintended	NSFG, NVSS, Guttmacher, CDC Abortion Surveillance Data	F, 15–44 yrs	HP2030 (FP-1)	Modification of HP2020 indicator. Calculated using several data sources (4–5 years)
4.E. Pregnancy rates among adolescent females (per 1,000)	Abortion Provider Survey, Guttmacher Institute; NVSS; NSFG; Abortion Surveillance Data	F, 15–19 yrs	HP2030 (FP-3), NPS	Calculated using several data sources (annual)
4.F. Prevalence of sexual violence in past 12 months (by any perpetrator)	NISVS	M&F, >17 yrs	HP2030 (IVP-05)	Rape (completed and attempted) and unwanted sexual contact involving touch but not sexual penetration. (annual)
4.H Incidence of cancers of the reproductive tract	NAACCR	M&F, >17 yrs	–	Cancers associated with genital HPV in men and women; prostate cancer and cervical, ovarian, uterine, vaginal, and vulvar cancer

[a]Projected timeframe for data availability is provided in parentheses. [b]Services included by sex were: Males (received advice/counseling regarding female birth control methods, male birth control methods, getting surgically sterilized, STIs, or HIV/AIDS); Females (received birth control method or counseling, birth control check-up/medical test, sterilization counseling, emergency contraception counseling, pelvic exam, pap smear, pregnancy test, or STI counseling/treatment).

on approaches to reduce risk of HIV/STI and unintended pregnancy among sexually active adolescents and adults (15–44 years) (40). The first indicator assessed condom use: "sexually active unmarried persons who use condoms" (Table 2, 2.B) (6); the second indicator assessed contraceptive use more broadly: "percent of women aged 20–44 years at risk of unintended pregnancy who used most effective or moderately effective methods of contraception" (Table 2, 2.C) (6). In 2017–2019, during the last episode of vaginal sex, 22% of adolescent females used effective birth control and 67% of adolescent males used a condom and 62% of adolescent females (or their partners) at risk for unintended pregnancy used a most/moderately effective method of contraception (Table 3) (6).

Finally, we had particular difficulty identifying indicators of healthy, responsible, and respectful relationships in existing surveys and surveillance systems. Measures of relationships were rare and those we identified were focused on negative outcomes rather than aspects of positive relationships; therefore, we selected only one indicator for this topic: "people (>17 years) that report happiness with marriage" from the GSS (Table 2, 2.D) (45). Although limited to married persons only, it provided an initially useful measure of an important aspect of sexual health: relationship satisfaction. In 2021, 51% of married men and 49% of married women reported that they were very happy with their marriage (Table 3) (45).

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TABLE 3 Recent data for sexual health indicators.

Sexual health indicator	Year	Most recent data
Objective 1. Increase knowledge, communication, and respectful attitudes regarding sexual health		
Knowledge		
1.A. Percentage of youth that received formal sex education before they were 18 years old		
Female	2015–2019	53%
Male	2015–2019	54%
Communication		
1.B. Percentage of adolescents that have talked with a parent or guardian about several sexual health topics		
Female	2011–15	54%
Male	2011–15	47%
1.C. Percentage of youth that report it would not be embarrassing to discuss using a condom with a new partner		
Female	2011–15	63%
Male	2011–15	61%
Attitudes		
1.D. Percentage of people that agree sexual relations between two adults of the same sex are not wrong		
Female	2021	64%
Male	2021	60%
1.E. Percentage of middle and high schools with gay-straight alliances	2018	37%
Objective 2. Increase healthy, responsible, and respectful sexual behaviors and relationships		
Sexual behaviors		
2.A. Percentage of adolescents age 15–17 who never had sexual intercourse		
Female	2017–19	72%
Male	2017–19	77%
2.B. Proportion of sexually active adolescent females who used effective birth control and adolescent males who used a condom at last intercourse		
Female	2017–19	22%
Male	2017–19	67%
2.C. Percent of women at risk of unintended pregnancy who used most effective or moderately effective methods of contraception	2017–19	62%
Relationships		
2.D. Percentage of people that report happiness with marriage (very happy)		
Female	2021	49%
Male	2021	51%
Objective 3. Increase use of evidence-based education and clinical and other preventive services that improve sexual health		
Education services		
3.A. Percentage of schools teaching 20 key HIV, STIs, and pregnancy prevention topics in a required course		
Grades 6-8	2018	18%
Grades 9-12	2018	43%
3.B. Percentage of middle and high schools with 4 key practices in place to prevent bullying and sexual harassment	2018	49%
Clinical and other preventive services		
3.C. Percentage of sexually active persons who receive reproductive health services		
Female	2011–15	78%
Male	2011–15	13%
3.D. Percentage of people living with HIV who know their serostatus	2017	86%

(Continued)

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TABLE 3 (Continued)

Sexual health indicator	Year	Most recent data
3.E. Percentage of sexually active women enrolled in Medicaid and commercial plans who are screened for chlamydia		
Female	2018	56%
3.F. Percentage of adolescents aged 13–15 years received recommended doses of the HPV vaccine		
Adolescents	2020	55%
3.G. Percentage of pregnant women who receive early and adequate prenatal care	2020	75%
Objective 4. Decrease adverse health outcomes, including HIV/AIDS, STIs, viral hepatitis, unintended pregnancies, and sexual violence		
4.A. New (incident) HIV infections among adolescents and adults	2017	37,000
4.B. Cases of primary and secondary syphilis in women and men who have sex with men (MSM) (per 100,000)		
Women	2017	5.1
MSM	2018	401.1
4.C. New hepatitis B infections in adults[a]	2016	20,900
4.D. Percentage of pregnancies that are unintended	2014	45%
4.E. Pregnancy rates among adolescent females (per 1,000)	2016	20.3
4.F. Prevalence of sexual violence in past 12 months (by any perpetrator)		
Rape (completed or attempted): Female	2016–2017	2%
Unwanted sexual contact other than rape: Female	2016–2017	5%
Rape (completed or attempted): Male	2016–2017	<1%
Unwanted sexual contact other than rape: Male	2016–2017	3%
4.G Estimated Cases of Genital System Cancers		
Female	2018	110,070
Male	2018	176,320

[a]Cases adjusted for underreporting.

Objective 3. Increase use of high-quality, coordinated educational, clinical, and other preventive services that improve sexual health

The seven indicators selected for this objective assessed educational, clinical, and other preventive services for sexual health, including HIV/AIDS, STIs, viral hepatitis, and pregnancy. First, two indicators assess the percentage of schools teaching specific sexual health topics in a required course and having key violence prevention practices in place (Table 2, 3.A., 3.B.). In 2018, 18% of U.S. schools reported teaching 20 key sexual health topics to students in grade 6–8 and 43% in grades 9–12; such topics included modes of HIV/STI transmission and how to reduce the risk of HIV, STIs, and pregnancy, including the benefits of being sexually abstinent, negotiation and decision-making skills, and condom use (46). In 2018, 49% of secondary schools had policies in place to prevent bullying and sexual harassment (46). In addition, one indicator served as an overall measure of use of services: "sexually active persons (15–44 years) who receive reproductive health services" (Table 2, 3.C) (43). In 2011–2015, 78% of women received a reproductive-health service in the previous 12 months; however, only 13% of men reported the same (43). Two indicators were selected to measure the uptake of key recommendations for HIV and STI screening: (1) "people (>12 years) living with HIV who know their serostatus" (Table 2, 3.D) (6) and (2) "sexually active women (16–24 years) enrolled in Medicaid or commercial plans who are screened for chlamydia" (Table 2, 3.E) (6). In 2017, 86% of individuals living with HIV who were over the age of 12 years knew their serostatus (Table 3) (43). In 2018, the percentage of eligible women screened for chlamydia was 56% for those enrolled in Medicaid and commercial plans. For human papillomavirus (HPV), to prevent HPV-related cancers in men and women, "percent of adolescents aged 13–15 years received recommended doses of the HPV vaccine" (Table 2, 3.F) was selected as the indicator from the National Immunization Survey-Teen (NIS-Teen) (48). In 2020, 55% of adolescents received the recommended doses of the HPV vaccine (Table 3) (43). Additionally, "pregnant women (15–44 years) who receive early and adequate prenatal care" was chosen as an indicator of pregnancy care (Table 2, 3.G) from the National Vital Statistics System (NVSS) (49). In 2020, 77% of pregnant women received early and adequate prenatal services (50).

Objective 4. Decrease adverse health outcomes, including HIV/STIs, viral hepatitis, unintended pregnancies, sexual violence, sexual dysfunction, and cancers in reproductive tracts

Given the traditional public health focus on adverse outcomes, we identified several indicators focusing on health outcomes. For HIV/AIDS, the indicator selected was "new HIV infections among

adolescents and adults (>12 years)" (Table 2, 4.A) from the National HIV/AIDS Strategy (NHAS) (43). In 2017, there were an estimated 37,000 new HIV infections in the U.S. (Table 3) (51). The indicator selected for STIs was "syphilis in women aged 15–44 years and men who have sex with men (MSM)" (Table 2, 4.B) (43). Due to the variety of disease outcomes of concern for STI prevention, this indicator was selected as a complement to the service indicator (chlamydia screening). Of note, young women (ages 15–24) accounted for nearly half (45%) of the 1.7 million cases of chlamydia reported in 2017 (52). In 2017, the rate of primary and secondary syphilis (per 100,000) was 5.1 for women aged 15–44 year olds (Table 3) and 401.1 for MSM (6). Next, "new hepatitis B infections in adults (>17 years)" was selected as the indicator for viral hepatitis (Table 2, 4.C). In 2016, there were an estimated 20,900 new cases of hepatitis B infection in adults (Table 3) (43).

Three indicators were selected for pregnancy and sexual violence. For pregnancy, "pregnancies that are unintended (15–44 years)" and "pregnancy rates among adolescent (15–19 years) females" were selected as indicators (Table 2, 4.D, 4.E, respectively) (43). In 2011, 45% of pregnancies among females 15–44 years old were unintended (Table 3) (53). In 2016, 20.3 per 100,000 adolescents aged 15–19 gave birth in the United States (Table 3) (6). Finally, "prevalence of sexual violence in the past 12 months (>17 years)" was selected (Table 2, 4.F) from the National Intimate Partner and Sexual Violence Survey (NISVS) (54). In 2016–2017, 2.3% of females and 0.3% of males reported being raped in the previous 12 months (Table 3) (19). Other forms of unwanted sexual contact involving touch but not sexual penetration (e.g., being kissed in a sexual way or having sexual body parts fondled, groped, or grabbed) were more commonly reported −5.3% of females and 3.0% of males (Table 3).

A reoccurring measure of sexual dysfunction does not currently exist in the U.S. Therefore, at this point, we have not included an indicator here. To measure reproductive tract cancers, an indicator was selected from the North American Association of Central Cancer Registries (NAACCR), which monitors all cancer cases in the U.S. (21). This indicator measures the estimated annual number of: prostate, testis, and other penile cancer in men, and cervical, ovarian, uterine, vaginal, and vulvar cancer in women. In 2018, there were 110,070 new cases of genital system cancers among women and 176,320 among men (21).

Discussion

For the past 20 years, there have been calls for a national health strategy and a more comprehensive sexual health approach to address the myriad of persistent sexual health problems in the U.S. Employing a sexual health approach requires shifting toward a holistic and integrated focus on health rather than disease. While strategies are being implemented by multisectoral stakeholders to support sexual health, reduce gender inequality, and combat stigma (e.g., HHS, The White House, CDC) (1, 6, 13, 15, 30), it is essential to establish a core set of national sexual health indicators that allow for measurement across time. The U.S. currently has an array of national surveys and surveillance systems with items related to sexual health. We argue that these indicators could be utilized to produce a baseline measure of national sexual health.

To be clear, we are not suggesting the indicators be used to form composite score. Rather, we envision these core sexual health indicators would be published in the form of an index that is publicly available and updated frequently. The Human Rights Campaign (HRC), for example, currently published an equality index "an annual comprehensive state-by-state report that provides a review of statewide laws and policies that affect LGBTQ+ people" (55). Similar to this HRC index (55) and other national sexual health indices (31–37), a U.S. sexual health scorecard could be used for: (1) monitoring purposes (e.g., to target areas for improvement); (2) research efforts (e.g., to examine associations with other structural drivers); (3) program design (e.g., to justify interventions); (4) policy guidance that entities such as CDC and HHS use to inform strategies and services to help promote sexual health in coming years.

To this end, we identified 23 indicators of sexual health that both highlight the current state of sexual health in the U.S. and also allow for future tracking. We were able to identify a set of indicators aligned with long-term sexual health objectives relevant to individuals, relationships, and communities. Each of these can be measured on a regular basis and used to monitor a breadth of issues relevant to sexual health. We conceive of these indicators as a baseline measure of the state of U.S. sexual health. It is our hope that these estimates will only improve in coming years and decades. The use and further refinement of these indicators is an essential aspect of resurgent national efforts to address sexual health (3, 11).

Our efforts were more successful for some objectives than others. Traditional public health measures—clinical services and adverse outcomes (Objectives 3 and 4)—tended to be collected frequently and consistently. This finding was not surprising given that surveillance of adverse outcomes is a primary, long-standing activity in U.S. public health systems. We found fewer measures of knowledge, communication (particularly with providers), attitudes, and behaviors and relationships related to sexual health (Objectives 1 and 2); and many of the measures that we did identify were limited in different ways. For example, in the absence of data on specific aspects of knowledge, we used exposure to education as an indirect measure; yet as a result, these indicators remain more focused on youth than young and older adults. Additionally, our measure of partner communication addresses a hypothetical situation rather than an actual event and is limited to adolescents and young adults. Finally, we were least successful in identifying measures of healthy relationships as our measure (i.e., "happiness in marriage") is restricted to marriage and only an estimated 45% of women and 43% of men aged 15–44 years old in the U.S. are currently married (56). We were unable to identify a measure of sexual dysfunction (or its inverse, sexual function, or even sexual satisfaction), but we hope to do so in the future. One important national survey, the National Survey of Sexual Health and Behavior (NSSHB) could serve as a possible source for some of these measures if it were ongoing (57). Thus, it is our hope that proposed indicators will be reviewed and revised overtime to ensure usefulness—moving away a narrow focus on the specific (e.g., youth and marriage) toward a general focus on the life course.

Communication about sexual health with partners and parents was low: over 60% of youth would be embarrassed to discuss condom use with a new partner and roughly half of adolescents have talked to their parents/guardians about all four important sexual health topics. Formal sex education is limited, with roughly one-half of adolescents receiving it. Attitudes demonstrated the potential for discrimination, with around 36–40% of American adults agreeing that same-sex sexual relations between adults is wrong on some level.

Stigmatizing attitudes toward homosexual populations may impact the sexual health of MSM, who are disproportionately impacted by HIV and other syndemics (14).

Additionally, findings for clinical and other preventive services were mixed. More females used reproductive-health services than men; however, 50-60% of young sexually active females did not receive recommended STI testing. Findings for sexual behaviors were also mixed. Less than 15% of youth aged 15 and under have had sexual intercourse. Only 67% of adolescent males used a condom at last sex. Finally, the burden of adverse outcomes remains high. Overall HIV incidence has been flat over the past 5 years but has increased substantially in young MSM (6, 43) while rates of STI such as gonorrhea remain far above Healthy People targets (6, 43). Although adolescent pregnancy has declined substantially over the past 20 years, the U.S. teen birth rate remains one of the highest of any industrialized country (58). Finally, for sexual violence, there are limited trend data, but current national estimates are cause for concern (19).

There are several limitations to our selected set of sexual health indicators. First, some indicators are imperfect matches to the constructs we want to measure. The use of education as an indicator for knowledge is a drawback. Measuring happiness in relationships should not be confined to marriage. Additionally, there is a lack of national data that address the sexual health of adults older than 49 years; thus, our indicators ignore the needs of older adults (8). We also found few quality measures of stigma-related to sexuality. The percentage of GSAs in schools taps into broader stigma but better measures are needed. Additional gaps in our set of indicators include limited available measures of communication (with providers and partners), attitudes, sexual dysfunction, sexual pleasure and satisfaction, and healthy relationships in national data sources. Finally, several of the selected indicators are not collected annually or biennially limiting frequent tracking of prevention efforts for some domains.

Public health implications

As emphasized in the National Prevention Strategy, "healthy reproductive and sexual practices can play a critical role in enabling people to remain healthy and actively contribute to their community" (59). We identified a set of 23 sexual health indicators that allowed us to characterize the current state of sexual health in the U.S. as measured by breadth of issues related to sexual health knowledge, attitudes, service access and utilization, behaviors, relationships, and adverse health outcomes. These data are selected from an inventory of existing data systems that yield national estimates and allow for measurement across time. By tracking these indicators, we can measure progress made by larger national efforts, as well as multisectoral actors. There is potential for these indicators to have broad reaching impact beyond the STI epidemic or unintended pregnancy prevention—they could provide needed insight related to how social inequality is reproduced. For instance, these indicators can help us understand how syndemics encompassing HIV, viral hepatitis, substance use, maternal-child health, sexual violence, and reproductive health make it more difficult for some individuals and communities to protect their sexual health. Overall, our findings regarding the current state of sexual health in the U.S. provide broad evidence of sub-optimal sexual health in all domains measured, indicating the need for new approaches to address this important area of health and meet goals of national initiatives. Additionally, available indicators contain crucial gaps. Considerations for addressing these gaps include adding new measures (although we recognize the difficulty of doing this), creating research partnerships across disciplines, and developing a new comprehensive survey of sexual health as other countries have done (34–37).

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

EC contributed to the framing and conceptualization of this article. JVF contributed to the framing, background, analysis, writing, and analysis as well as organizing the 2022 meeting. MBI contributed to the article's conceptualization, data review, literature, writing, organization of the paper, and also led 2010–2012 meetings. All authors contributed to the article and approved the submitted version.

Conflict of interest

MBI was employed by Population Reference Bureau.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Gender neutral HPV vaccination programs: Reconsidering policies to expand cancer prevention globally

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Human papillomavirus (HPV) infection is responsible for many cancers in both women and men. Cervical cancer, caused by HPV, is the fourth most common cancer among women worldwide, even though it is one of the most preventable cancers. Prevention efforts include HPV vaccination, however these programs remain nascent in many countries. In 2020 the World Health Assembly adopted the Global Strategy for cervical cancer elimination including a goal to fully vaccinate 90% of girls with the HPV vaccine by the age of 15. However, very few countries have reached even 70% coverage. Increased vaccine availability in the future may allow the opportunity to vaccinate more people. This could add to the feasibility of introducing gender-neutral HPV vaccination programs. Adopting a gender-neutral HPV vaccine approach will reduce HPV infections transmitted among the population, combat misinformation, minimize vaccine-related stigma, and promote gender equity. We propose approaching programmatic research through a gender-neutral lens to reduce HPV infections and cancers and promote gender equality. In order to design more effective policies and programs, a better understanding of the perspectives of clients, clinicians, community leaders, and policy-makers is needed. A clear, multi-level understanding of these stakeholders' views will facilitate the development of target policy and programs aimed at addressing common barriers and optimizing uptake. Given the benefit of developing gender-neutral HPV vaccination programs to eliminate cervical cancer and address other HPV associated cancers, we must build knowledge through implementation research around this topic to inform policy-makers and funders for future policy shifts.

KEYWORDS

HPV, cervical cancer, cancer prevention, policy, vaccine program

Introduction

Human papillomavirus (HPV) affects both women and men and is the most common sexually transmitted infection in the world (1). There are more than 100 HPV types of which 13 are classified as oncogenic. HPV is highly prevalent globally, with an estimated 80%–90% of women and men acquiring infection in their lifetime (2, 3). Oncogenic HPV types are responsible for anogenital and cutaneous warts and several cancers including oropharyngeal, anogenital, cervical, anal, vulvar, vaginal, and penile (1).

Cervical cancer is the predominant HPV-related cancer and is the fourth most common cancer among women worldwide, despite effective prevention strategies (4). Global estimates show that cervical cancer occurred in 604,127 new cases and led to 341,831 deaths in 2020 (5). It is the most common type of cancer-related mortality among women in 42 countries, the majority living in Sub-Saharan Africa (4).

While cervical cancer incidence rates are declining or stagnating in high-income countries, the absolute number of cases continue to rise in low- and lower-middle-income countries (LMIC) (4). Models show that cervical cancer burden will increase by 17% to 708,000 cases and mortality will increase by 42% to 442,926 deaths in the year 2030 (6, 7). The most significant rise will be in LMICs, where 84% of incident cervical cancer cases and 90% of cervical cancer deaths occur (4).

Virtually all cases of invasive cervical cancer are caused by infection with high-risk (oncogenic) HPV infection types (8). Most infections (90%) are cleared through a normal immune-response within 1 year, with ∼10% of all infections with an oncogenic HPV type progressing to a precancer or invasive cervical cancer (9). HPV 16 and 18 are responsible for about 70% of cervical cancer worldwide (10) while >90% of cases worldwide are caused by HPV types 16, 18, 31, 33, 45, 52, and 58 (11).

The higher rates of cervical cancer incidence and mortality in LMICs is attributable to the relative lack of high-quality cervical cancer screening and lack of widespread high-quality treatment of preinvasive/invasive cervical cancer in LMICs rather than significant differences in HPV infection rates (12). Higher rates, however, do not appear to be broadly associated with differences in cervical infection with oncogenic HPV types (10) (though there are higher rates of HPV among women infected with human immunodeficiency virus).

HPV vaccination programs remain nascent in several countries, particularly LMICs. Globally, there are 122 World Health Organization (WHO) countries and territory member states, and 27 non-members with HPV vaccination on the national routine immunization schedule. As of 2022, eight of 29 (28%) low-income countries and 22 of 51 (43%) lower-middle income countries had introduced HPV vaccine programs (13). Meanwhile, 72% of low-income countries and 57% of lower-middle income countries are yet to include HPV vaccination into their national immunization programs (14). Cost is a significant factor in a country's ability to initiate and maintain a program (15). The actual cost of the vaccine, which increases over time, initially accounts for 51% of total program costs (16). Other direct medical costs which tend to decrease over time include cold chain, workforce education, monitoring and evaluation, community education, and vaccination campaigns (14, 17).

Current global HPV vaccination program guidance and progress

In 2020 the World Health Assembly adopted the Global Strategy for the Elimination of Cervical Cancer. This strategy includes targets for HPV vaccination, and cervical cancer screening and treatment. Specifically, that 90% of girls will be fully vaccinated by the age of 15; that 70% of women will be screened using a high-performance test by the age of 35, and again by the age of 45; and that 90% of women with pre-cancer or invasive cancer will be treated or managed. Achieving these targets by 2030 will ensure that all countries reach and maintain a cervical cancer incidence rate of below four per 100,000 women (10).

Many transmission-dynamic models developed by the WHO Cervical Cancer Elimination Modeling Consortium show that 70% coverage through a girls-only HPV vaccination approach at 15 years of age leads to disease reduction (18). However, very few countries have reached 70% coverage. LMIC HPV vaccination coverage is 16% (8%−31% among 51 countries) for the first dose and 12% (5%−24% in 43 countries) for the second dose. Likewise, in Gavi eligible countries in 2018 (14 countries), 12% (4%−32%) of the population received one dose, and 7% (1%−21%) received the second dose in six countries (19). Based on these deficient coverage levels, neither disease reduction nor herd immunity will occur. In order to bolster the beneficial effects of the HPV vaccine, we must consider a gender-neutral approach. Recent models have shown that vaccinating boys in an environment of female coverage below 50% may be cost-effective, depending upon the prevalence of HPV-related disease and available resources (20). In addition, a systematic review that primarily included studies from high income countries showed that as long as vaccine price remained low, a gender neutral vaccination program was cost-effective if coverage was low. The same review did reinforce earlier findings that gender-neutral vaccination was less cost-effective than when targeting only girls aged 9–18 years if coverage for females was above 75% (21), however achieving this level of coverage in some LMICs is challenging.

The WHO has recently expanded recommended ages among females and added males within a secondary target group for HPV vaccination (22). Of the 141 global HPV vaccination programs, there are 43 countries and 4 territories that have gender-neutral HPV vaccine schedules (23). All of these programs are in high income countries and upper middle-income countries (19) except for a single program. Bhutan became the first LMIC and the first country in South East Asia to adopt gender-neutral vaccination policy in September 2020 (24).

Female-only HPV vaccination programs have several shortcomings (25) including the consideration of only cervical cancer as a HPV transmission outcome (21) and multiple additional assumptions: (1) of monogamy or serial monogamy with few lifetime partners without the consideration of polygamous societies (20); (2) of heterosexual relationships, thus discounting the potential for HPV spread through bisexual contact and by way of men who have sex with men (26); (3) of penile-vaginal intercourse, thus minimizing the consideration of digital and oral spread of HPV; (4) of the presence of gender equity without consideration of women's structural barriers (such as lack of autonomy, early marriages, and lack of education); and (5) of a uniform geographic and other social determinant acceptability of HPV vaccination. These assumptions may contribute to inequities as well as mistrust and misinformation.

One dose HPV vaccination approach

There is mounting evidence that a one-dose approach may prove effective (27–32). Currently, ongoing studies (33) through the Costa Rica Vaccine Trial (31), a multicenter cohort study in

Abbreviations: HPV, human papillomavirus; WHO, World Health Organization; LMIC, low- and lower-middle-income country.

India (32), and the industry-sponsored PATRICIA trial (28) will inform future guidelines. Recently, The WHO Strategic Advisory Group of Experts on Immunization (SAGE) recommended updating the dosing schedule to one or two doses for girls aged 9–14 and women 15–20 years and concluded that a single dose is comparable to a 2-dose schedule (34). Compared with a two-dose HPV vaccination schedule, one-dose HPV vaccination could reduce many barriers. For instance, studies highlight program costs, ease of administration, multi-cohort vaccination delivery, and increased HPV vaccine program adoption in populations with limited access to healthcare and a high burden of cervical cancer (33).

With growing evidence of the potential efficacy of a one-dose approach, new predictive modeling is underway. Additional simulation models suggest that one-dose vaccination has similar health benefits to a two-dose regimen but also simplifies vaccine delivery, reduces costs, and helps to alleviate vaccine supply constraints (35, 36). Countries that have yet to implement an HPV vaccination program or have low coverage but a high burden of HPV-related diseases may benefit by implementing one-dose vaccination (37). Available resources in LMICs favor a one-dose approach, but data are needed to support adoption (38). Evidence may be sufficient to alter existing guidelines by 2025 (39).

Considering gender-neutral vaccination programs

Eliminating cervical cancer means reducing the incidence to <4/100,000. The current approach, with sustained vaccination for girls only, will change disease rates in 70 years if 100% coverage occurs (40–43). If it is impossible to reach 70% coverage for girls, superior cancer control will need gender-neutral immunization in order to more rapidly impact disease rates (44). Recent modeling assumes HPV vaccine efficacy is >85% and confers lifelong protection. Extending the target-age range of girls and women and focusing on boys is more cost-effective than giving a second dose to girls aged 9–14 when the outcomes are the maximum ICER (incremental cost-effectiveness ratio) and the minimum NNT (number needed to treat). This result applies to India, Vietnam, Uganda, and Nigeria, the countries under study (33).

The epidemiological and economic considerations about vaccinating boys should focus on the benefits in terms of disease reduction, the feasibility and incremental marginal costs of increasing vaccination coverage among girls vs. introducing a gender-neutral program (41, 45). Importantly, gender-neutral HPV vaccination programs will also depend on population acceptability (14, 36, 46, 47) and political viability (47–50).

Discussion

Forward perspective

It is time to reconsider a gendered approach to vaccination to best respond to the WHO's call to eliminate cervical cancer. To date, modeling has primarily been driven by reconciling constraints (vaccine availability and financial barriers) with consideration of cost-effectiveness. With advancing knowledge that potentially reinforces a single-dose approach, the potential to vaccinate more people with current vaccine supplies emerges (i.e., the transition to single dose looks to be promising and is a reasonable expectation to be considered). Other possibilities that may alter vaccine availability include: (1) vaccine cost decline, (2) increased production, and (3) changes in licensing policy. With these considerations, a shift in resource availability may result in opportunities to transition global HPV vaccine programs to alternative approaches. There is a need to continue reworking HPV vaccination models and inform potential approaches through implementation research. Currently, research on implementing a gender-neutral HPV vaccination approach is lacking, and understanding the context in which gender-neutral programs will be successfully adopted is critical.

A gender-neutral HPV vaccination approach will advance the health of both male and female populations. In women, HPV vaccination must include at least one primary HPV screening test in the woman's mid-life. HPV vaccines are incomplete in their genotype prevention, and screening is necessary to reduce the incidence to achieve the WHO elimination goal of <4/100,000. The screening services are likely to be more effective in a population already vaccinated as the underlying prevalence of HPV infection will be lower. Likewise, the treatment services will go to fewer numbers of women who still develop CIN 3 or early cervical cancers.

Knowledge gaps informing a gender neutral approach in LMICs

Adopting a gender-neutral HPV vaccine approach will reduce HPV infections transmitted among the population. We must plan for HPV vaccine uptake, combat misinformation, minimize vaccine-related stigma, and promote gender equity (46). HPV is not a virus that only infects female epithelium; instead, it is a gender-neutral infection. We propose approaching programmatic research through a gender-neutral lens to reduce HPV infections and cancers and promote gender equality (51).

To achieve these goals, we must begin to understand the local community-based customs that will affect the acceptability of gender-neutral vaccination programs in LMICs. Having male and female population endorsement is critical to a gender-neutral approach to HPV vaccination. Once a community-based agreement pushes for gender-neutral vaccination, we must have the data to show the effectiveness of a single HPV vaccine dose in males, as we currently do for females. Designing and supporting variable dose HPV vaccine studies in males is critical for long-term follow-up. There is little literature monitoring male serologic titers and HPV-related outcomes (52).

In addition, implementation research is needed to inform the acceptability, adoption, appropriateness, feasibility, fidelity, implementation cost, penetration, and sustainability of transitioning to a gender neutral approach. There is some recent literature describing the barriers toward HPV vaccinations for boys. However these reports are mostly in high-income countries or upper middle-income countries (53). We are not aware of literature on this topic in the LMIC context. Given the benefit of developing gender neutral HPV vaccination programs in the effort to eliminate cervical cancer, it is imperative that we build knowledge around this topic in order to inform policy-makers and funders in consideration of the possibility for future policy shifts.

Limitations

There are some limitations to the stated argument in favor of advancing research in order to inform the consideration of developing gender neutral HPV vaccination programs. Foremost, there is a noted distinction between the WHO goal of elimination of cervical cancer and individual country-level health ministry considerations regarding research evaluating cost effectiveness of HPV vaccination strategies. It is not always possible to compare all variables across these perspectives. Therefore, these goals may not align in many cases and contextual considerations may weigh certain variables in lieu of others. Secondly, given that resources are currently limited and arguments relative to future availability of the HPV vaccine are, ultimately, conjecture, the current modeling limitations create gaps in our ability to precisely estimate the effects of any potential change in resources. Thirdly, our call to action does not fully consider currently unknown, or unconsidered, repercussions of a significant change in vaccination strategy such as effects on supply chains and distribution channels of the HPV vaccine between and within countries. Our hope is that implementation research would help to shine light on these types of challenges, thus informing future policy-makers at all levels. In addition, it is noted that there is a lack of effective HPV screening methods in men and research exploring male HPV infection is deficient (54). Additional studies assessing the cost-effectiveness of HPV testing in men and modeling studies to assess the effects in females of adding males to existing HPV vaccination programs are needed (55). Lastly, a major unaccounted shift in vaccine technology could also significantly alter these considerations. Ultimately, these limitations may also be concurrently viewed as additional evidence of the need for more research.

Conclusion

HPV and HPV vaccination are sensitive topics and are commonly associated with misinformation, rumors, and stigma (56–58). In order to design more effective policies and programs, a better understanding of the perspectives of clients, clinicians, community leaders, and policy-makers is needed. A clear, multi-level understanding of these stakeholders' views will facilitate the development of target policy and programs aimed at addressing common barriers and optimizing uptake. Given the benefit of developing gender-neutral HPV vaccination programs to eliminate cervical cancer, we must build knowledge around this topic to inform policy-makers and funders for future policy shifts.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Past incarceration and chlamydia infection among young Black men in New Orleans

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Background: Young Black men are disproportionately and adversely affected by incarceration and sexually transmitted infections (STIs), both of which share common social and structural determinants. It is well documented that incarcerated individuals, including youth, are more likely to acquire STIs in the carceral setting compared to the general population. However, the effects of imprisonment on sexual health outcomes after imprisonment are not well-understood. The relationship between incarceration history (having ever spent time in a correctional institution such as prison, jail, or juvenile detention) and chlamydia positivity was examined in this study.

Methods: A secondary analysis of the *Check it* Program, a *Chlamydia trachomatis* (Ct) community-based seek, test, and treat screening program for Black men aged 15–24 who have sex with women in New Orleans was conducted. Participants completed a computer-assisted self-administered questionnaire on relevant sexual and social histories and provided a urine specimen for a Ct urine nucleic acid amplification test. Bivariate and multivariable regressions were used to estimate the association between incarceration history and chlamydia positivity.

Results: Participants (N = 1,907) were enrolled from May 2017 to March 2020. Of those, 351/1,816 (19.3%) reported past incarceration and 203/1,888 (10.8%) tested positive for Ct. When adjusted for age, insurance status, and condom use, having a history of incarceration was positively associated with a positive Ct test (adjusted odds ratio (95% confidence interval):1.61 (1.12, 2.31), p = 0.0095).

Conclusions: Interacting with the carceral system is associated with a positive Ct test post-incarceration. Incarceration may be an important marker for Ct acquisition in young Black men who have sex with women and those with a history of incarceration should be prioritized for Ct screening after release.

KEYWORDS

jail, prison, incarceration, young Black men, Deep South, post-release

Introduction

Caused by the *Chlamydia trachomatis* (Ct) bacterium, Ct accounts for the largest proportion of reportable STIs in the United States (US) with 1.6 million cases reported in 2020 (1). Untreated Ct infections in men can lead to proctitis, urethritis, and infertility and can serve as a reservoir of infection in women (2). In 2018, Ct cases among Black men were 6.8 times the rate compared to White men (952.3 and 140.4 cases per 100,000 population, respectively) (3). Among males aged 15–19 years, reported Ct cases among Black men were 9.1 times the rate among White men (2,668.6 and 293.0 cases per 100,000 population, respectively). Reported Ct cases among Black males aged 20–24 years were 5.3 times the rate among White males of the same age group (3,867.1 and 732.6 cases per 100,000 population, respectively) (3).

In Louisiana, a state in the Deep South, the Ct diagnosis rate was 777.2 cases per 100,000 population with a 5% increase in males from 11,068 cases in 2018 to 11,599 cases in 2019 (4). In the same year, 70% of all Ct cases with reported race were Black individuals, a rate that demonstrates a significant racial disparity as Black people comprise only 32% of Louisiana's population (5). Additionally, 69% of all cases were among youth younger than 25 years old, with the highest rates among youth aged 15–19 and 20–24 (4). Even after adjusting for individual-level factors that impact risk, such as the number of sexual partners or condomless sex, disparities in Ct outcomes still remain. This suggests that other community- or structural-level factors may play a role in the observed disparities.

Structural racism is an important social determinant of population health in the United States (6, 7) as racial minorities bear a disproportionate burden of general morbidity (8). Literature on the sexual risk behaviors of youth of color describes several pathways through which racism leads to unhealthy conditions. Consequently, these unhealthy conditions can facilitate the observed elevated risks of STIs in youth of color (9). Boutrin and Williams organize the three key mechanisms of racism into institutional/structural racism, cultural racism, and differential treatment (discrimination) by both institutions and individuals (9). Structural racism can affect stress and behaviors through residential segregation, criminal justice system policies, and incarceration (9).

It is well documented that those incarcerated are more likely to acquire STIs in the carceral setting compared to the general population due to drug use, high-risk sexual behaviors, densely populated settings, and reduced access to screening (10). In a systematic review of STI prevalence among prisoners, the prevalence of STIs among prisoners was higher than the general population with drug use, low educational levels, and unsafe sexual activities as major risk factors (11). However, it is not well understood if interacting with the carceral system influences post-incarceration Ct rates.

Mass incarceration is an institutional driver of racial inequality (12). The US has the largest prison population and the highest rates of imprisonment and incarceration in the world (13). In 2021, Louisiana had the highest incarceration rate in the US, with 1,094 people per 100,000 population in state prisons, local jails, federal systems, and other systems of confinement (14). By race, Black people are overrepresented in prisons and jails in Louisiana with 1,411 incarcerated Black people per 100,000 Black people in the state in 2019. This is a 3.8 to 1 disparity ratio to White people (15). As of June 2021, 95.4% of the prison population were men, 6,490 individuals were admitted between the ages of 18 and 24, and 1,182 inmates of the same age were released the same year (16).

Research examining the relationship between incarceration rates and STI rates and incidence has been scarce. High rates of STIs often occur in communities where incarceration rates are also high. Initial cross-sectional county-level studies have found positive correlations between incarceration rates and STI rates in the general population (17–19). These studies examined incarceration in men and women collectively and demonstrated that the relationship was strongest with correlating STIs occurring in the year after the incarcerations. In a longitudinal analysis using census tract-level data of male incarceration rates in a south-eastern city, census tracts with higher baseline male incarceration rates had higher baseline rates of incident STIs (20). Among men in the US, incarceration has also been associated with high-risk sex partnerships, such as multiple partners and condomless sex, which are known risk factors for STIs (21). In another study of incarceration and risky sexual behavior, men reporting incarceration in the past 12 months were 1.8 times as likely to experience multiple new sexual partnerships and transactional sex in the past 4 weeks (22). However, the effects of imprisonment on sexual health outcomes after imprisonment are not well-understood.

In a retrospective cohort study of having a positive Ct, gonorrhea, or syphilis test or incident-positive HIV test in the year following arrest or incarceration, test positivity rates were highest for chlamydia and rates of positive STIs and HIV were between 2.7 and 6.9 times higher for Black people than White people with an arrest or incarceration between 2003 and 2008. Compared to those without an arrest or incarceration, those with arrest or incarceration had a relative risk of 3.9 for Ct (23). Furthermore, Black race for men and younger age for Ct and gonorrhea were among the characteristics that were most associated with increased risk for positive STI in a cohort of individuals released from jail (24). These few existing studies motivated this present study since incarceration history and STI outcomes have not been studied specifically among young Black men.

Given the high and ever-increasing incarceration rates in the US and high rates of STIs, which disproportionately affect young Black men in the Deep South, incarceration may be an important social determinant of Ct risk in young Black men. At the intersection of race-based incarceration and disparities in sexually transmitted infections, this study investigates Ct outcomes in young Black men with and without exposure to prior incarceration. The relationship between incarceration history (having ever spent time in a correctional institution such as prison, jail, or a juvenile detention center) and Ct positivity in New Orleans, Louisiana was examined in this study. It is hypothesized that Ct positivity will be greater in those with a history of incarceration.

Methods

The *Check It* Program was a *Chlamydia trachomatis* (Ct) community-based seek, test, and treat screening program for Black men aged 15–24 who have sex with women in New

Orleans, Louisiana. Methods have been described elsewhere, but briefly, the program was developed to evaluate the effect of screening and treating men for chlamydia and gonorrhea in communities with high STI prevalence (25). Participants were recruited through venue-based recruitment and via print and social media marketing. Venues included barbershops, historically Black colleges or universities, Black-owned businesses, or other locations where young Black men frequented. At physical venues, field staff approached participants about the study. Eligible participants provided informed consent, completed a computer-assisted self-administered survey that elicited relevant sexual and social histories, provided a urine sample, and received a wide variety of monetary or in-kind compensation. In-kind compensation consisted of vouchers for services or gift cards for community partners and venues valued at $25. This study was approved by Tulane University's Institutional Review Board.

Participation in *Check It* was limited to those who met the following inclusion criteria: identified as African American or Black, were assigned male sex at birth (based on the question "do you have a penis?"), were 15–24 years of age, had lived or spent most of their time in Orleans Parish, had reported having had vaginal sex with a woman in their lifetime, were able and willing to consent to study activities, spoke and understood English, had not taken azithromycin in the 2 weeks before enrollment, and had not been previously enrolled in *Check It* (25).

This analysis was restricted to participants enrolled from the beginning of the study in May 2017 until March 2020, when the COVID-19 stay-at-home mandate was implemented in New Orleans. After restricting to account for the impact of this secular trend on sexual behavior and consequently Ct infections, the final dataset had 1,907 young men. Of those participants, 94.9% (1,809/1,907) had both complete information on incarceration history and conclusive chlamydia screening results. After removing participants with missing covariate data, the sample size for the primary complete case analysis was 1,616 participants. To assess the impact of missing data, multiple imputation was conducted in a sensitivity analysis to address the missing data.

Respondents were asked about their experiences with the criminal justice system. The primary exposure of ever having spent time in jail was reported retrospectively when respondents were asked, "Have you ever spent time in a correctional institution such as a prison, jail, or juvenile detention?" Response options included "yes", "no", or "refuse to answer". The survey instrument only captured data on lifetime incarceration (ever incarcerated) and did not capture data on when the incarceration occurred, such as in the last 6 months. Cases in which respondents selected "refuse to answer" were recoded as missing.

The outcome measure of chlamydia was assessed using a nucleic acid amplification test (NAAT) from a first-catch urine sample from the participant. Results of the screening were categorized as "negative", "positive", or "specimen error". Respondents whose samples resulted in a specimen error were recoded as missing.

Age was constructed as a continuous variable calculated based on the date of birth and the date of enrollment and then categorized into two groups (15–18 and 19–24). Dichotomous variables were also constructed for insurance status, condom use, and binge drinking. For the age at sexual onset, participants were asked, "How old were you the first time you had any kind of sex? That includes vaginal, oral, or anal sex." and responses ranged from <14 years old to 25 years (categorized as ≤14–25 in one-unit increments). Participants were asked about the number of female sexual partners in the previous 2 months and lifetime male and female partners and responded with a whole number.

Descriptive analysis was performed to describe the prevalence of incarceration, chlamydia, and other characteristics of the entire cohort. The median and range were provided for continuous variables and a count and percentage were provided for categorical variables. The cohort characteristics were stratified by the participants' incarceration history and chlamydia test result for bivariate analyses. Inferential statistics (p-values) were obtained using Mann-Whitney U tests for continuous variables and Pearson Chi-Squared tests for categorical variables. Descriptive and bivariate analyses were conducted using IBM SPSS Statistics Version 28.0. (26).

In the primary analysis, bivariate and multivariable logistic regressions were used to estimate the crude and adjusted associations (odds ratios, 95% confidence intervals, and p-values) between history of incarceration and chlamydia positivity. Respondents who selected "refuse to answer" were recoded as missing. Observations with missing values for the outcome, exposure, or covariate data were not included in the complete case primary analysis. Covariates associated with both incarceration and chlamydia at a two-tailed significance level of 0.05 or less were tested as potential confounders. These variables were categorical age, insurance status, age at sexual debut, condom use, binge drinking, number of lifetime female sexual partners, and parental incarceration. Forward, backward, and stepwise selections were used to determine which covariates to include in the final model. The significance level for entering or staying in the model was 0.05. Categorical age, insurance status, and condom use were consistently selected across all three selection methods and were retained for the final adjusted model. The Hosmer-and-Lemeshow goodness of fit test was used to assess model fit. Bivariate and multivariable logistic regressions were performed using SAS Version 9.4. (27).

A sensitivity analysis was conducted to assess the impact of missing values. From examining missingness among the variables of interest, age at sexual debut, the number of lifetime female sexual partners, and condom use were identified as auxiliary variables. They were correlated (correlation coefficient <0.4) with the participants' incarceration history. Mean comparisons via statistical testing revealed that the total number of female sexual partners were associated with the missingness of participants' incarceration history and chlamydia test results. The mean number of lifetime female sexual partners was significantly higher among respondents who had missing data on incarceration history ($p < 0.001$) and chlamydia test results ($p = 0.0139$). The mean age at sexual debut was significantly higher among respondents who had missing data on incarceration history ($p < 0.001$). Condom use was also associated with missingness of participants' incarceration history ($p = 0.0111$). As such, these variables were included in the imputation model to address missing values. The fully conditional specification method was used to impute missing values. Dichotomous variables

were imputed under a logistic distribution and continuous variables were imputed using the predictive mean matching method. Fifteen imputed datasets were created. Binary logistic regression analyses were conducted on the imputed datasets and those results were synthesized for inference using SAS Version 9.4. (27). Table 5 reports crude and adjusted associations (odds ratios, 95% confidence intervals, and *p*-values) obtained using the multiply imputed datasets with missingness in the data addressed, for reference (27).

Results

Table 1 presents the descriptive statistics of the participants (N = 1,907) enrolled through March 2020. The median age was 19.8 years (range of 9.9), and all participants identified as Black/African American with 3.3% (62/1897) identifying as two or more races, and 3.1% (58/1897) identifying as Hispanic. Based on the analytical sample, 60.6% (1156/1885) were high school students or graduates and 38.2% (729/1885) had higher than a high school education. Having a form of health insurance was reported by 80.3% (1442/1795) of participants. Money or services from government assistance programs were received by 35.3% (674/1907) of the participants or a member of their household. About 19% (351/1816) of the participants reported having spent time in prison, jail, or a juvenile detention center. Previous chlamydia (Ct) test results were reported for 40.6% (762/1879) of participants and 10.8% (203/1888) had positive Ct test results during the study.

In the 2 months prior to enrollment, binge drinking was reported by 27.2% (512/1369) of the participants, 60.6% (1120/1849) used at least one type of drug, and 52.4% (975/1860) used marijuana only (87.1%, 975/1120 of those using drugs). The median age of sexual debut was 15.0 (range of 11). Nearly half of the participants (43.0%, 741/1723) used condoms consistently with all female partners, 64.6% (1207/1869) of participants had one female partner only, and 35.4% (662/1869) had two or more female partners 2 months prior to enrollment. The median number of lifetime female partners was 5 (range of 90). A few participants (5.3%, 97/1828) reported at least one male partner in their lifetime.

Table 2 presents the distribution of demographic and behavioral characteristics by the participants' own history of incarceration. Time spent in jail was reported by 19.3% (351/1816) participants and was associated with older age ($p < 0.001$), having no health insurance ($p < 0.004$), use of government assistance ($p < 0.001$), younger age at sexual debut ($p < 0.001$), inconsistent condom use ($p < 0.001$), binge drinking ($p = 0.009$), at least one type of drug use ($p < 0.001$), marijuana use ($p < 0.001$), and more lifetime female sexual partners ($p < 0.001$), parental incarceration ($p < 0.001$), previous Ct tests ($p < 0.001$), and positive Ct test results ($p = 0.002$). Participants' own history of incarceration was not associated with the number of male sexual partners in the prior 2 months or lifetime.

Table 3 presents the bivariate analysis of demographic and behavioral characteristics by Ct positivity. About a tenth of the participants (10.8%, 203/1888) tested positive for Ct, and positive results were associated with older age ($p = 0.002$), having no health insurance ($p = 0.011$), the participant's own history of incarceration ($p = 0.002$), younger age at sexual debut ($p = 0.016$), inconsistent condom use ($p = 0.004$), binge drinking ($p = 0.006$), having two or more female sexual partners in a lifetime ($p < 0.001$), and more lifetime female sexual partners ($p < 0.001$). Positive Ct test results were not associated with the use of government assistance, any drug use, marijuana use, the number of male sexual partners, and previous Ct screening.

Table 4 presents the bivariate and multivariable logistic regression analyses for the participants' own history of incarceration and Ct positivity. There was a positive crude association between having a history of incarceration and testing positive for Ct using the primary complete case analysis [OR (95% CI): 1.71 (1.22, 2.39), $p < 0.0020$)]. In the multivariable logistic regression model, categorical age, insurance status, age at sexual debut, consistent condom use, binge drinking, number of lifetime female sexual partners, and parental incarceration were examined for potential confounding effects. Categorical age, insurance status, and condom use were consistently selected across all three selection methods and were retained for the final adjusted model. The final adjusted model [aOR (95% CI): 1.61 (1.12, 2.31), $p = 0.0095$] was assessed for the goodness of fit and the results of the Hosmer-and-Lemeshow goodness-of-fit test supported that the model fitted the data well ($p = 0.4254$). The results of the sensitivity analysis, as seen in Table 5, were similar to the results based on the primary analysis. As such, the primary results remain robust.

Discussion

In this study, incarceration history was associated with chlamydia (Ct) positivity in young Black men who have sex with women in New Orleans, as hypothesized. Those who had a history of incarceration had a 61% increased risk in testing positive for Ct compared to those who did not have a history of incarceration, after accounting for the effects of age, insurance status, and condom use. The positive trend for crude and adjusted associations remained with the more stringent sensitivity analysis and supports the conclusions of the primary analysis. These findings demonstrate that past incarceration is associated with Ct risk in young Black men. It also supports that incarceration is an important social determinant of sexual health outcomes that negatively impact vulnerable populations including young Black men.

Incarceration can have devastating effects on sexual networks of young Black men by modifying their composition in a manner that can contribute and even accelerate the spread of STIs (28). Removing men from a community can disrupt existing sexual relationships during and after incarceration (18, 29, 30). During incarceration men may engage in same-sex sexual behavior, such as condomless anal sex, which increases the risk of STI transmission (18, 28). Moreover, recently released men may return to previous sexual relationships without disclosing sexual activities during incarceration

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TABLE 1 Characteristics of the *Check It* cohort enrolled through March 2020 ($n = 1,907$).

	Sample size	Participants enrolled through March 2020 ($n = 1,907$)
Age (median years, range)	1,899	19.8 (9.9)
Categorical age		
15–18		722 (38%)
19–24		1,177 (62%)
Race	1,897	
Black/African American only		1,835 (96.7%)
Two or more races		62 (3.3%)
Ethnicity	1,897	
Hispanic		58 (3.1%)
Non-Hispanic		1,835 (96.7%)
Education	1,885	
High school graduate or less		1,156 (60.6%)
More than high school		729 (38.2%)
Insurance	1,795	
No insurance		353 (19.7%)
Some type of insurance		1,442 (80.3%)
Participant or household used government assistance in the past 12 months	1,907	
Yes		674 (35.3%)
No		1,233 (64.7%)
Binge drinking in the past 2 months	1,369	
At least once		512 (27.2%)
No		1,369 (72.8%)
Any drug use in the past 2 months	1,849	
At least one type of drug		1,120 (60.6%)
No		729 (39.4%)
Only marijuana used in the past 2 months	1,860	
Only marijuana		975 (52.4%)
No drugs or drugs other than marijuana		885 (47.6%)
Age at sexual debut (median years, range)	1,855	15.0 (11)
Consistent condom use with all partners in past 2 months	1,723	
Yes		741 (43.0%)
No		982 (57.0%)
Sexual partners in the past 2 months	1,869	
Only one female partner		1,207 (64.6%)
Two or more female partners		662 (35.4%)
Total female sexual partners in lifetime (median, range)	1,855	5 (90)
Male partners in lifetime	1,828	
At least one male partner		97 (5.3%)
No male partners		1,731 (94.7%)
Own incarceration	1,816	
Yes		351 (19.3%)
No		1,465 (80.7%)

(Continued)

TABLE 1 (Continued)

	Sample size	Participants enrolled through March 2020 ($n = 1,907$)
Ever booked or charged	1,821	
Yes		373 (20.5%)
No		1,448 (79.5%)
Ever convicted (not minor traffic)	1,820	
Yes		211 (11.6%)
No		1,609 (88.4%)
Previous chlamydia test	1,879	
Yes		762 (40.6%)
No		1,117 (59.4%)
Chlamydia test results	1,888	
Positive		203 (10.8%)
Negative		1,685 (89.2%)

and may also form new concurrent sexual relationships (18, 31). These factors may help to explain the mechanism by which male incarceration may contribute to increased STI incidence and prevalence in the population after release from incarceration.

There were strengths to this study. Firstly, it allowed us to examine a minoritized subgroup of the Black population. Where previous studies have stratified analyses by race, this study elicited within race differences among a group of young Black men. Furthermore, this was as a relatively large sample of young Black men. Additionally, participants' urine was tested for Ct during the study; thus, avoiding reporting bias, which STIs has been known to be under-reported in minorities who experience additional stigma (32).

There were also some limitations that must be considered. Incarceration was self-reported and those who did not report a history of incarceration may have been subject to social desirability bias since incarceration is highly stigmatized. Arrest records were not accessed to verify incarceration history; however, there is no reason to suspect recall bias in participants that reported a history of incarceration because recalling traumatic or adverse experiences such as their own incarceration has reliable estimates (33). As with all cross-sectional data, establishing a temporal relationship is challenging because the data does not allow us to discriminate between infection acquisition. That is, it is unknown whether the infection was acquired during incarceration and persisted post-release or was acquired during post-release. This is important to note as Ct infection is generally asymptomatic and can be harbored for a long time. We also do not know how long ago the incarceration occurred. It is possible that incarceration is a proxy for all the other factors that were more common among the formerly incarcerated group, such as having no health insurance, use of government assistance, younger age at sexual debut, and parental incarceration. However, many factors known to be associated with both incarceration and Ct positivity were measured and adjusted for, minimizing the likelihood that the observed results were due to a proxy related to incarceration. Additionally, the study may be vulnerable to sampling bias because the sample was a convenience sample of sexually active young Black men. As such, it may not be generalizable to the target population of young Black men in New Orleans. Since data on community-level characteristics (such as neighborhood segregation and social capital) were not collected, it is possible that residual confounding may have remained after adjusting for confounding in the analysis.

The effects of age at incarceration, duration of incarceration, multiple incarcerations (recidivism) and duration of time since release were not captured in the *Check It* survey and should be investigated in future studies that include longitudinal analysis. Duration of incarceration and time since release from incarceration may provide nuanced insights and help to identify a critical period of heightened risk for incident STI cases. This can inform prevention and intervention programs that target formerly incarcerated young men as the duration of incarceration and the one-year period from incarceration represent a high-impact opportunity to reduce STIs (23, 34, 35). Furthermore, the exposure measure could be disaggregated (jail, prison, and juvenile detention separately) to discern the relationship between the various carceral settings as the relationship between STIs and incarceration have been shown to be stronger with prison than jail incarceration (18). Certain community-level variables could not be obtained such as gender-ratio imbalances, which are linked to the number of opposite-sex sexual partners post-release and could be an important covariate for future work in understanding correlates of STI burden in young Black men (36, 37).

The present study contributes to emerging evidence that incarceration may function as a driver for Ct incidence and prevalence. It strengthens support that mass incarceration, perpetuated by structural racism, has negative consequences for sexual health outcomes in formerly incarcerated young Black men, a group already marginalized, in a southern US city.

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TABLE 2 Characteristics by participants' incarceration history ($n = 1,816$).

Characteristic	Spent time in jail ($n = 351$) n (%)	No time spent in jail ($n = 1,465$) n (%)	p-value
Age (median years, range) ($n = 1,816$)	20.6 (10.0)	19.7 (10.0)	**<0.001**[a]
Categorical age			
15–18	113 (32.2)	572 (39.0)	**0.017**[a]
19–24	238 (67.8)	893 (61.0)	
Race ($n = 1,816$)			
Black/African American only	340 (98.9)	1,417 (96.7)	0.892[a]
Two or more races	11 (3.1)	37 (3.1)	
Ethnicity ($n = 1,814$)			
Hispanic	12 (3.4)	44 (3.0)	0.689[a]
Non-Hispanic	339 (96.6)	1,419 (97.0)	
Education ($n = 1,809$)			
High school graduate or less	243 (69.6)	864 (59.2)	**<0.001**[a]
More than high school	106 (30.4)	243 (40.8)	
Insurance ($n = 1,724$)			
No insurance	84 (24.9)	251 (18.1)	**0.004**[a]
Some or other type of insurance	253 (75.1)	1,136 (81.9)	
Participant or household used government assistance in the past 12 months ($n = 1,816$)			
Yes	152 (43.3)	501 (34.2)	**<0.001**[a]
No	199 (56.7)	964 (65.8)	
Age at sexual debut (median years, range) $n = 1,798$	14 (11.0)	15 (11.0)	**<0.001**[b]
Consistent condom use ($n = 1,699$)			
Yes	106 (32.1)	631 (46.1)	**<0.001**[a]
No	1,076 (73.8)	738 (53.9)	
Binge drinking in the past 2 months ($n = 1,808$)			
No	234 (66.9)	1,076 (73.8)	**0.009**[a]
At least once	116 (33.1)	382 (26.2)	
Any drug use in the past 2 months ($n = 1,785$)			
No	91 (26.1)	619 (43.1)	**<0.001**[a]
At least one type of drug	257 (73.9)	818 (56.9)	
Only marijuana used in the past 2 months ($n = 1,785$)			
No drugs or drugs other than marijuana	137 (39.4)	706 (49.1)	**0.001**[a]
Only marijuana	211 (60.6)	731 (50.9)	
Sexual partners in the past 2 months ($n = 1,789$)			
Only one female partner	212 (61.1)	952 (66.0)	0.084[a]
Two or more female partners	135 (38.9)	490 (34.0)	
Total female sexual partners in lifetime (median, range) $n = 1,747$	7.0 (90.0)	5.0 (90.0)	**<0.001**[b]
At least one male partner in lifetime ($n = 1,775$)	17 (4.9)	75 (5.2)	0.822[a]
No male partners in lifetime	327 (95.1)	1,356 (94.8)	
Previous chlamydia test ($n = 1,808$)			
Yes	179 (51.1)	546 (37.4)	**<0.001**[a]
No	171 (48.9)	912 (62.6)	
Chlamydia test results ($n = 1,809$)			
Positive	54 (15.4)	141 (9.7)	**0.002**[a]
Negative	296 (84.6)	1,318 (90.3)	

[a]Pearson Chi-Square Test. [b]Mann-Whitney U-Test.
Bold values represent statistical significance at or below $p = 0.05$.

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TABLE 3 Characteristics by chlamydia test results ($n = 1,888$).

	Positive test ($n = 203$) *n* (%)	Negative test ($n = 1,685$) *n* (%)	*p*-value
Age (median years, range)	20.4 (9.9)	19.7 (9.9)	**0.002**[b]
Categorical age			
15–18	57 (28.1)	656 (39.0)	**0.002**[a]
19–24	146 (71.9)	1,024 (61.0)	
Race ($n = 1,883$)			
Black/African American only	200 (98.5)	1,621 (96.5)	0.125[a]
Two or more races	3 (1.5)	59 (3.5)	
Ethnicity ($n = 1,804$)			
Hispanic	6 (3.0)	51 (3.0)	0.956[a]
Non-Hispanic	196 (97.0)	1,626 (97.0)	
Education ($n = 1,871$)			
High school graduate or less	108 (53.7)	1,039 (62.2)	**0.020**[a]
More than high school	93 (46.3)	631 (37.8)	
Insurance ($n = 1,782$)			
No insurance	50 (26.6)	300 (18.8)	**0.011**[a]
Some or other type of insurance	138 (73.4)	1,294 (81.2)	
Own incarceration ($n = 1,809$)			
Yes	54 (27.7)	296 (18.3)	**0.002**[a]
No	141 (72.3)	1,318 (81.7)	
Participant or household used government assistance in the past 12 months ($n = 1,888$)			
Yes	63 (31.0)	605 (35.9)	0.170[a]
No	140 (69.0)	1,080 (64.1)	
Age at sexual debut (median years, range) ($n = 1,843$)	14 (11)	15 (11)	**0.016**[b]
Consistent condom use ($n = 1,713$)			
Yes	62 (33.2)	676 (44.3)	**0.004**[a]
No	125 (66.8)	850 (55.7)	
Binge drinking in the past 2 months ($n = 1,868$)			
No	129 (64.5)	1,230 (73.7)	**0.006**[a]
At least once	71 (35.5)	438 (26.3)	
Any drug use in the past 2 months ($n = 1,837$)			
No	70 (35.2)	653 (39.9)	0.201[a]
At least one type of drug	129 (64.8)	985 (60.1)	
Only marijuana used in the past 2 months ($n = 1,842$)			
No drugs or drugs other than marijuana	86 (43.2%)	784 (47.7%)	0.230[a]
Only marijuana	113 (56.8%)	859 (52.3%)	
Sexual partners in the past 2 months ($n = 1,856$)			
Only one female partner	110 (54.2%)	1,092 (66.1%)	**<0.001**[a]
Two or more female partners in lifetime	93 (45.8%)	561 (33.9%)	
Total female sexual partners in lifetime (median, range) ($n = 1,783$)	8 (89)	5 (90)	**<0.001**[b]
At least one male partner in lifetime ($n = 1,819$)	9 (4.7%)	87 (5.4%)	0.686[a]
No male partners in lifetime	184 (95.3%)	1,539 (94.6%)	
Previous chlamydia test ($n = 1,866$)			
Yes	82 (41.0%)	673 (40.4%)	0.869[a]
No	118 (59.0%)	993 (59.6%)	

[a]Pearson Chi-Square Test. [b]Mann-Whitney U-Test.
Bold values represent statistical significance at or below $p = 0.05$.

TABLE 4 Crude and adjusted associations for chlamydia outcomes and history of incarceration from primary complete case analysis.

	Crude model OR (95% CI)	*p*-value	Adjusted model[a] OR (95% CI)	*p*-value
History of incarceration				
No	Reference		Reference	
Yes	1.71 (1.22, 2.39)	0.0020	1.61 (1.12, 2.31)	0.0095
Consistent condom use				
Yes	Reference		Reference	
No	1.60 (1.16, 2.21)	0.0038	1.43 (1.02, 2.01)	0.0374
Categorical age				
15–18	Reference		Reference	
19–24	1.64 (1.19, 2.26)	0.0025	1.47 (1.02, 2.10)	0.0383
Insurance				
Some or other type of insurance	Reference		Reference	
No insurance	1.56 (1.11, 2.21)	0.0117	1.46 (1.01, 2.10)	0.0450

[a]Adjusted for categorical age, insurance status, and condom use.

TABLE 5 Crude and adjusted associations for chlamydia outcomes and history of incarceration from sensitivity analysis.

	Crude model OR (95% CI)	*p*-value	Adjusted model[a] OR (95% CI)	*p*-value
History of incarceration				
No	Reference		Reference	
Yes	1.66 (1.52,1.80)	<0.0001	1.51 (1.38, 1.65)	<0.0001
Consistent condom use				
Yes	Reference		Reference	
No	1.59 (1.47,1.72)	<0.0001	1.42 (1.31, 1.54)	<0.0001
Categorical age				
15–18	Reference		Reference	
19–24	1.65 (1.52,1.79)	<0.0001	1.48 (1.36, 1.61)	<0.0001
Insurance				
Some or other type of insurance	Reference		Reference	
No insurance	1.55 (1.42, 1.69)	<0.0001	1.44 (1.32, 1.57)	<0.0001

[a]Adjusted for categorical age, insurance status, and condom use.

Establishing criminal justice policies that prioritize community re-entry for formerly incarcerated individuals, promoting community health services that focus on screening individuals recently released from carceral systems, and preventing criminal justice involvement can mitigate these unintended negative effects of poor sexual health outcomes in the southern US, which is burdened by high rates of incarceration and STIs in young Black men.

Data availability statement

The datasets presented in this article are not readily available per the determination of the Tulane University Institutional Review Board. Requests to access the datasets should be directed to kissing@tulane.edu.

Ethics statement

The study involving human participants were reviewed and approved by Tulane University Institutional Review Board. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with national legislation and the institutional requirements.

Author contributions

JS drafted the manuscript, supported the conception, and performed data analysis and interpretation. AR and PK reviewed and edited the manuscript, supported the conception, and supported data analysis and interpretation. GG and PK developed the data collection instrument and GG oversaw data collection

under the supervision of PK. HH supported the analytic methodology and reviewed data analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association between serum *Chlamydia trachomatis* antibody levels and infertility among reproductive-aged women in the U.S.

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Introduction: *Chlamydia trachomatis* infection, the most prevalent sexually transmitted bacterial infection worldwide, is a significant cause of infertility. Many countries have introduced the widespread use of serologic assays for IgG seropositivity to chlamydial plasmid gene product 3 (Pgp3). However, data on the association between the level of Pgp3-IgG in the multiplex bead array assay (Pgp3AbMBA) and female infertility are still scarce.

Methods: This cross-sectional analysis included 1,425 women from the National Health and Nutrition Examination Survey (NHANES) from 2013 to 2016.

Results: In the fully adjusted logistic regression model, each standard deviation increments of Pgp3AbMBA (SD = 17,079.63) led to a 28% increase in the risk of infertility. The relationship remained consistent in women who had been pregnant and women who gave birth. Smooth curve fitting revealed that the association was linear across the entire range of Pgp3AbMBA. Subgroup analysis suggested that the association was significantly stronger in women who had ever used marijuana and lived in poverty.

Conclusions: This study revealed a linear and independent association between the level of Pgp3AbMBA and self-reported infertility in U.S. women. Furthermore, we found that women who had ever used marijuana and lived in poverty were at the highest risk of infertility upon chlamydial infection.

KEYWORDS

***Chlamydia trachomatis*, infertility, NHANES, Pgp3, association**

Introduction

Infertility is a serious global medical concern. Over 186 million people worldwide have infertility problems, affecting 8–12% of reproductive-aged couples (1). Infertile couples have high economic costs associated with treatments, such as intrauterine insemination and *in vitro* fertilization. Female infertility has a complex, multifactorial set of causes, including tubal pathology (2), ovulation dysfunction (3) and unexplained causes. Furthermore, an important risk factor for infertility is exposure to pathogenic microorganisms such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae* (4).

C. trachomatis is the most prevalent sexually transmitted bacterial infection in the United States and worldwide (5) and is a significant cause of infertility. From 2013 to 2016, ∼30% of U.S. women showed serological evidence of current or past infection with *C. trachomatis* (6). In 2020, 1.6 million cases of chlamydial infection were reported by the Centers for Disease Control and Prevention (CDC) (7). *C. trachomatis*-induced ascending uterine infections may result in adverse reproductive complications, such as

salpingitis, pelvic inflammatory disease, tubal scarring, ectopic pregnancy and infertility (8–11). Moreover, ∼50–70% of infected women are asymptomatic and undiagnosed (12–14). Untreated *C. trachomatis* infections in the genital tract may impair immune function (15–17), which was related to biological processes after semen deposition, including sperm capacitation, fertilization, embryo implantation, embryogenesis and maintenance of pregnancy.

Over recent years, the role of chlamydial infection in promoting the development of infertility has been part of an ongoing scientific debate (8, 18). A large retrospective cohort study from Denmark reported that the risk of infertility was 37% higher in women with positive *C. trachomatis* infection tests than in women with only negative tests (19). Another cross-sectional study revealed that *C. trachomatis* was one of the prevalent pathogens in patients with primary infertility (20). In addition, a report from Dutch showed that higher risk for tubal factor infertility in chlamydia-positive women (21). However, coinfections with other sexually transmitted infection (STI) are common (22); such as bacterial vaginosis in chlamydial infection (23, 24). Whether bacterial vaginosis-associated bacteria facilitate STI ascension and pelvic inflammatory disease, or whether they are the cause of STI, is difficult to determine (16). Besides, a retrospective cohort study of women in Sweden (aged <25 in 1985) was followed up for 15 years to investigate the association between chlamydial infection and infertility (25). The cumulative incidence of infertility was reported between 3 and 7% depending on whether a woman had ever tested for or been treated for chlamydia, which was lower than expected (26). To better design interventions and policies aimed at preventing adverse trends in reproductive health, more research is needed to verify the association and to search for high-risk subpopulations.

Many countries have introduced the widespread use of *C. trachomatis* serologic assays, especially for IgG seropositivity to chlamydial plasmid gene product 3 (Pgp3) (26–28). Pgp3 has been well-recognized as the most reliable and specific marker of a previous *C. trachomatis* infection due to its high degree of conservation among clinical strains (29). Of the methods currently utilized in Pgp3-IgG testing, the multiplex bead assay (MBA) is the most sensitive (30–32). However, most of the studies investigating the relationship between chlamydial infection and infertility were based on nucleic acid amplification test, which only reported negative or positive results. Pgp3-IgG was reported to last for more than 12 years after infection and its level may reflect cumulative exposure to chlamydia (33). The risk of infertility following chlamydial infection that is identified by the quantitative Pgp3-IgG level has been scarcely reported.

Further estimates of the risk of infertility upon chlamydial infection are essential to provide needed information for clinical counseling and chlamydia surveillance of high-risk populations. Therefore, the aim of this study was to identify the association between the level of Pgp3-IgG in the multiplex bead array assay (Pgp3AbMBA) and female infertility based on the U.S. nationally representative NHANES data from 2013 to 2016.

Abbreviations: BMI, body mass index; CDC, Centers for Disease Control and Prevention; CI, confidence interval; MBA, multiplex bead assay; MFI, median fluorescence intensity; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; PBST, Phosphate Buffered Saline + 0.05% Tween 20; Pgp3, chlamydial plasmid gene product 3; Pgp3AbMBA, Pgp3-IgG in the multiplex bead array assay; PIR, poverty-income ratio; SD, standard deviation; STI, sexually transmitted infection.

Materials and methods

Study design and population

In the present study, the data were from NHANES 2013–2014 and NHANES 2015–2016, as the reproductive health questionnaires that included infertility were carried forward only for these two cycles. Using a complex multistage and stratified sampling design (34), NHANES is a biennial, nationally representative, cross-sectional survey of civilian non-institutionalized residents in the U.S. All NHANES data and more detailed information are publicly available on the CDC website (https://www.cdc.gov/nchs/nhanes/). A total of 1,726 women, aged 18–39 years, with chlamydia Pgp3AbMBA results were enrolled for NHANES 2013–2016. Participants with missing infertility data ($n = 182$), pregnant women ($n = 82$) and women with a history of oophorectomy or hysterectomy ($n = 36$) were excluded. The final analytic sample comprised 1,425 subjects (Figure 1). The NHANES study protocol was reviewed and approved by the NCHS Ethics Review Board (35). NHANES was approved by the CDC Institutional Review Board, and no written consent was required, as we conducted secondary analysis using NHANES data. Ethical approval was granted by the Ethics Committee of Huizhou Central People's Hospital (Date.20210801/No. KYLL202108). Methods adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies (36).

Pgp3AbMBA

The Pgp3AbMBA assay was performed by the Laboratory Reference and Research Branch in the Division of Sexual Transmitted Diseases Prevention at the CDC. After assays were verified in-house, the serum specimens were analyzed by the MAGPIX Luminex MBA system, as described previously in the literature (31, 37, 38). Briefly, beads coupled to Pgp3 antigen were incubated with 1:400 diluted serum for 1.5 h. After washing in PBST (Phosphate Buffered Saline + 0.05% Tween 20), the beads were incubated with 50 ng biotinylated mouse anti-human IgG/Fc-specific antibody (Southern Biotech, Birmingham, Alabama) and 20 ng biotinylated mouse anti-human IgG4 (Southern Biotech, Birmingham, Alabama) for 45 min. After washing in PBST, the beads were incubated with 250 ng phycoerythrin-labeled streptavidin for 30 min, washed in PBST and incubated in Buffer A (1 × PBS, 0.5% bovine serum albumin, 0.05% Tween-20 and 0.02% sodium azide) for 30 min. After washing in PBST once, the beads were suspended in 100 µl of 1 × PBS and analyzed by optical density at 511 nm. Pgp3AbMBA assays were performed only once. In the case of unreadable data or instrument error occurring the first time, the sample was rerun in a second run, and the second

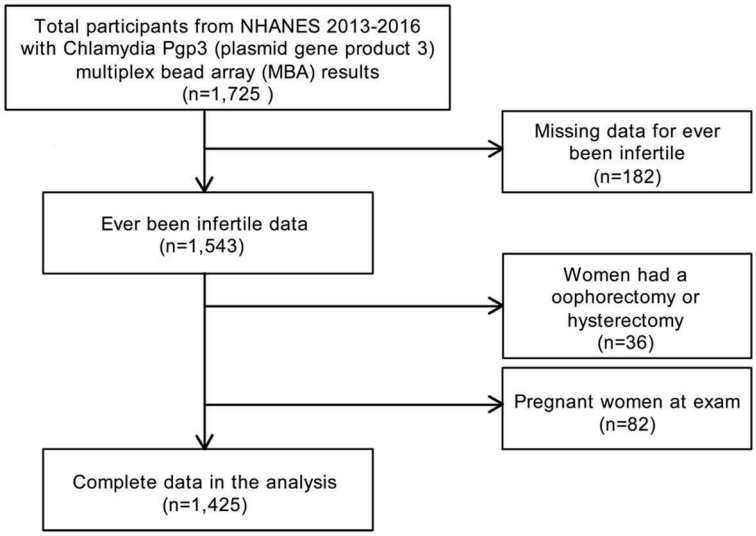

FIGURE 1
Flow chart of participant selection from the NHANES 2013–2016.

reading was used as the result. The results of the Pgp3AbMBA assay are expressed as median fluorescence intensity (MFI) units. Positive and negative cut-offs for the Pgp3AbMBA assays were established by testing a receiver operating characteristic panel on Pgp3-coupled beads. The MFI units above 551 were judged to be positive. Values equal to or below the cut-off were negative.

Infertility

The outcome variable was self-reported infertility from the reproduction health questionnaires. The question was "Have you ever attempted to become pregnant over a period of at least a year without becoming pregnant?" Participants who answered "yes" were considered infertile. If the answer was "no", then they were categorized as fertile. Otherwise, the data were regarded as missing.

Covariates

A number of sociodemographic, lifestyle behaviors and reproductive-related variables were assessed as potential covariates. Sociodemographic variables included age, race/ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American, or other Hispanic), educational levels (high school or less, some college or AA degree, or college graduate or above), poverty-income ratio (PIR) and marital status (married, never married, living with partner or divorced/separated). A PIR is calculated by dividing family income (or individual income) by poverty guidelines for the survey year. The variables of lifestyle behaviors included smoking status (current, former, or never), alcohol drinking status (had at least 12 alcohol drinks in 1 year), physical activity (moderate or vigorous work activity), energy intake (kcal per day) and drug use (ever used marijuana/hashish, ever used cocaine/heroin/methamphetamine). Anthropometric variables included body mass index (BMI) and waist circumference. Reproductive variables were based on women's self-report questionnaires. Reproductive factors included age when first menstrual period occurred, had ever taken birth control pills, had ever been pregnant, had ever gave live birth, age at first live birth, age at last live birth, ever treated for a pelvic infection (yes or no), recent gonorrhea (in the past 12 months, has a doctor or other health care professional told you that you had gonorrhea) and recent chlamydia (in the past 12 months, has a doctor or other health care professional told you that you had chlamydia).

Statistical analysis

In the current cross-sectional analysis, Pgp3AbMBA was severely skewed toward the right. Thus, the MFI value of Pgp3AbMBA were log 10-transformed before analysis. The MFI value of Pgp3AbMBA were categorized into quintiles according to the weighted distributions of the study population. Continuous variables were tested for normal distribution using the Anderson-Darling normality test. Continuous variables are expressed as the mean ± SD, and categorical variables are expressed as percentages. We conducted weighted chi-square tests for categorical variables and weighted regression models for continuous variables. Bonferroni correction was applied to all multiple comparisons. The association of variables and self-reported infertility was first evaluated using univariate logistic regression analysis. Covariates were included as potential confounders if: (1) they changed the estimate of Pgp3AbMBA on self-reported infertility by more than 10%, (2) were known or suspected risk factors for infertility, or (3) were statistically significant in univariate analysis. We then built the logistic regression models to investigate the relationship between Pgp3AbMBA and infertility, both unadjusted and adjusted for covariates. The adjusted odds ratios (ORs) and their 95% confidence intervals (95% CIs) were calculated to evaluate the

TABLE 1 Baseline characteristics of study participants by quintiles of Pgp3AbMBA.

Variables	Total	Quintiles of Pgp3AbMBA					*P*-value
		Q1	Q2	Q3	Q4	Q5	
Sociodemographic variables							
Age (years)	28.33 ± 6.25	27.37 ± 6.19	28.15 ± 6.30	28.15 ± 6.28	29.41 ± 5.99	28.65 ± 6.30	0.0030
Race/ethnicity (%)							
Mexican American	13.10	10.45	11.07	16.58	14.82	13.11	<0.0001
Other Hispanic	18.17	21.15	16.90	18.70	15.68	18.96	
Non-Hispanic White	57.99	63.45	68.09	59.27	58.05	33.94	
Non-Hispanic Black	10.74	4.95	3.94	5.46	11.45	33.99	
Education (%)							
High school or less	26.00	20.57	21.45	18.74	34.34	38.44	<0.0001
Some college or AA degree	36.45	44.02	32.17	30.33	35.19	43.14	
College graduate or above	29.37	25.18	37.93	40.12	25.50	12.45	
Marital status (%)							
Married	39.20	44.48	43.58	43.99	35.65	24.44	<0.0001
Never married	32.67	32.29	34.27	24.27	27.91	46.75	
Living with partner	12.99	7.53	7.65	17.75	20.54	12.92	
Divorced/separated	7.00	5.75	6.06	3.18	10.93	9.92	
Poverty-income ratio (PIR)	2.56 ± 1.60	2.64 ± 1.61	2.75 ± 1.61	2.92 ± 1.60	2.47 ± 1.56	1.83 ± 1.35	<0.0001
Anthropometric variables							
BMI (kg/m^2)	28.46 ± 7.84	27.69 ± 7.01	27.68 ± 7.64	28.27 ± 8.21	29.45 ± 8.54	29.61 ± 7.46	0.0033
Waist circumference (cm)	93.29 ± 17.49	92.05 ± 16.24	91.67 ± 16.43	93.19 ± 18.66	94.54 ± 18.51	95.92 ± 17.35	0.0253
Lifestyle variables							
Smoke status (%)							
Current	44.86	38.14	35.66	48.50	49.03	50.97	0.0457
Former	17.01	29.38	12.92	15.92	15.45	16.94	

(Continued)

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TABLE 1 (Continued)

Variables	Total	Quintiles of Pgp3AbMBA					*P*-value
		Q1	Q2	Q3	Q4	Q5	
Never	38.13	32.47	51.42	35.59	35.51	32.09	
Had at least 12 alcohol drinks/1 year—yes (%)	70.06	63.19	72.55	69.11	71.82	73.46	0.0596
Vigorous work activity-yes (%)	16.53	16.49	11.49	12.86	23.74	20.21	0.0020
Moderate work activity-yes (%)	44.04	46.32	43.63	41.20	45.45	43.74	0.7794
Energy intake (kcal/d)	1,963.24 ± 769.62	1,901.87 ± 773.72	1,978.09 ± 785.36	1,971.64 ± 778.41	1,964.11 ± 729.36	2,002.19 ± 772.31	0.6445
Ever used marijuana/hashish-yes (%)	54.06	40.61	52.35	51.59	59.15	69.62	<0.0001
Ever used cocaine/heroin/methamphetamine-yes (%)	11.58	8.09	6.73	12.88	13.93	18.92	<0.0001
Reproductive factors							
Age when first menstrual period	12.62 ± 1.70	12.62 ± 1.52	12.69 ± 1.71	12.68 ± 1.76	12.55 ± 1.74	12.50 ± 1.76	0.6520
Had ever taken birth control pills -yes (%)	70.15	69.23	70.91	69.12	71.62	69.55	0.9691
Ever pregnant (%)	59.09	50.46	53.67	49.84	32.50	25.80	<0.0001
Had ever gave live birth (%)	54.62	53.51	57.14	53.68	38.38	33.42	<0.0001
Age at first live birth	22.28 ± 4.82	23.57 ± 4.36	23.28 ± 4.44	24.14 ± 4.89	21.28 ± 4.69	20.00 ± 4.41	<0.0001
Age at last live birth	26.64 ± 5.16	27.23 ± 4.42	27.65 ± 4.82	27.87 ± 4.58	26.03 ± 5.47	24.77 ± 5.52	<0.0001
Ever treated for a pelvic infection -yes (%)	3.36	0.42	1.38	2.93	5.75	7.64	<0.0001
Recent gonorrhea (%)	0.42	0	0	0	0.7	1.4	<0.0001
Recent chlamydia (%)	2.31	0.39	0	0.35	2.81	7.02	<0.0001
Sexual behaviors							
Age at first sex (years)	17.26 ± 3.05	17.83 ± 2.96	17.60 ± 3.07	17.97 ± 3.35	16.88 ± 2.95	15.63 ± 2.06	<0.0001
No. of lifetime male sex partner	7.53 ± 11.62	5.51 ± 8.02	5.73 ± 7.12	6.02 ± 6.99	9.29 ± 12.26	12.50 ± 19.95	<0.0001
Sex without condom in last year							<0.0001
Never	35.60	38.54	31.29	32.47	36.59	41.47	
<50%	11.13	9.08	14.24	8.33	9.40	14.28	
50–100%	40.47	33.27	41.23	44.50	44.81	37.67	
Always	12.80	19.12	13.24	14.70	9.20	6.59	

95% CI of Pgp3AbMBA quintiles: Q1 (13.31, 13.86), Q2 (20.58, 21.34), Q3 (39.27, 43.44), Q4 (3,184.55, 4,459.11), and Q5 (37,911.41, 41,587.24). Mean ± SD for continuous variables. The *P*-value was calculated by a weighted linear regression model. Percentage (%) for categorical variables. The *P*-value was calculated by weighted chi-square test. All data are weighted using pooled Medical Examination Center (MEC) survey weights provided by the National Center for Health Statistics.

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degree of association. In addition, we evaluated the linearity of the association between Pgp3AbMBA and infertility using a fully adjusted generalized additive model with a spline function. Subsequently, according to the covariates in the full model, we performed several secondary analyses, including interaction and stratified analysis. Missing values for covariates were treated as dummy variables in the models, including BMI, PIR, male sex partners, and age at first sex, and the missing ratios were 0.70, 5.82, 0.70, and 8.21%, respectively. Missing values for categorized covariates were included as an additional category. The *P*-values for interactions were tested by the likelihood-ratio test. The data were analyzed using R (http://www.R-project.org) and EmpowerStats software (X&Y Solutions). All analyses took sampling weights into account (39). A combined 4-year weight was calculated by dividing the MEC exam weight (wtmec2yr) by two. $P < 0.05$ indicated statistical significance.

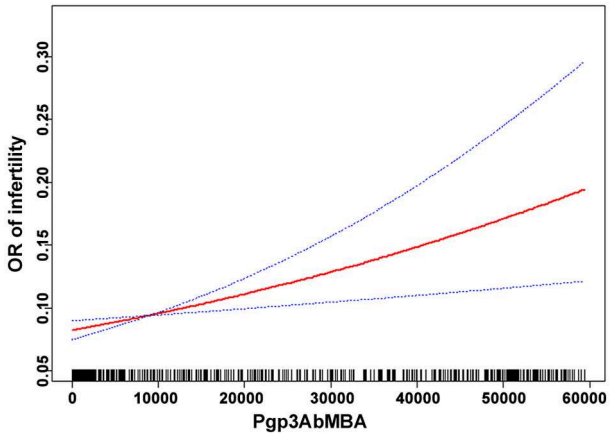

FIGURE 2
The relationship between Pgp3AbMBA and infertility by smooth curve fitting.

Results

Characteristics of subjects

In total, 1,425 women were included in the study (Figure 1). When dividing Pgp3AbMBA into quintiles, a higher Pgp3AbMBA level was associated with older age, non-Hispanic black ethnicity, lower education level, unmarried status, lower PIR, higher BMI and larger waist size. In addition, higher levels of smoking, alcohol use, vigorous work activities, marijuana/hashish use, and cocaine/heroin/methamphetamine use were in quintile 5 of Pgp3AbMBA. Regarding fertility-related conditions, women with higher serology results had a lower occurrence of pregnancy and childbirth, were younger at first and last live birth, had a higher frequency of pelvic infection, had more recent history of gonorrhea prevalence, had a more recent history of chlamydia prevalence, were younger when they first had sex, had more male sex partners and engaged in less unprotected sex in the last year (Table 1). A total of 54.62% of the subjects in this study were pluriparous, and 59.09% had been pregnant at some point (Table 1).

Association between Pgp3AbMBA and self-reported infertility

First, univariate logistic regressions were performed to analyze associations between collected variables and infertility (Supplementary Table 1). The univariate analysis showed that age, BMI, waist circumference, ever pregnant, had given live birth, age at first live birth, age at last live birth, number of lifetime male sex partners and Pgp3AbMBA were significantly positively associated with infertility. Never married, alcohol consumption, pelvic infection, age at first sex, and dangerous sex in the last year were significantly negatively associated with infertility.

Then, we used a logistic regression model (Table 2) to explore the association between Pgp3AbMBA and self-reported infertility. In the crude model, each SD increment (SD = 17,079.63) of Pgp3AbMBA led to a 36% increase in the risk of infertility. After adjusting for age, BMI, race, marital status, PIR, education level, alcohol consumption, number of lifetime male sex partners, age at first sex, ever pregnant, pelvic infection and recent chlamydia, each SD increment of Pgp3AbMBA resulted in a 28% increase in the risk of infertility. Quintile 5 had two times the risk of quintile 1 in the fully adjusted model. We further restricted the logistic regression analysis to the women who had been pregnant and who gave birth. The linear relationship remained consistent in these subgroups. A Pgp3AbMBA cut-off value above 551 was used to categorize participants into a positive group and a negative group. However, the correlation was not significant in the positive group (Supplementary Table 2).

Linear association

Smooth curve fitting was performed after adjusting for confounding factors in model 2. The results indicated that the association between Pgp3AbMBA and self-reported infertility was linear over the entire range of Pgp3AbMBA (Figure 2). This finding agreed with the stepwise increased aOR in the logistic regression analysis (Table 2).

Subgroup analysis

To determine whether the association between Pgp3AbMBA and infertility was consistent across the population groups, we conducted a subgroup analysis by numerous variables, as summarized in Figure 3. The results indicated that the association was consistent in the subgroups of age, BMI, race, education level, PIR, male sex partners, sex without condoms in the last year, ever pregnant, had ever given live birth, alcohol consumption, and ever used cocaine/heroin/methamphetamine ($P > 0.05$ for all interactions). We found that there was an interaction in the subgroup of ever used marijuana/hashish ($P = 0.0010$). The association between Pgp3AbMBA and infertility was significantly stronger in women who ever used marijuana/hashish than in those who never used marijuana/hashish (OR = 1.33; 95% CI: 1.07–1.66)

TABLE 2 Logistic regression of Pgp3AbMBA for the risk of infertility.

	Crude	Model 1[a]	Model 2[b]	Women had been pregnant*	Women gave birth*
Variables	$n = 1,425$, 100%	$n = 1,425$, 100%	$n = 1,425$, 100%	$n = 780$, 59.09%	$n = 721$, 54.62%
	(OR, 95% CI)	(OR, 95% CI)	(OR, 95% CI)	(OR, 95% CI)	(OR, 95% CI)
Pgp3AbMBA per 1 SD	1.36 (1.17, 1.58)	1.34 (1.15, 1.57)	1.28 (1.03, 1.58)	1.20 (1.00, 1.44)	1.28 (1.01, 1.62)
Quintiles of Pgp3AbMBA					
Q1 (0.95, 1.22)	Reference	Reference	Reference	Reference	Reference
Q2 (1.23, 1.41)	1.32 (0.69, 2.52)	1.23 (0.64, 2.38)	1.23 (0.63, 2.42)	1.04 (0.48, 2.28)	1.08 (0.48, 2.45)
Q3 (1.42, 1.97)	1.20 (0.61, 2.36)	1.13 (0.57, 2.25)	1.13 (0.56, 2.29)	0.81 (0.35, 1.89)	0.78 (0.32, 1.88)
Q4 (1.99, 4.19)	1.71 (0.91, 3.23)	1.30 (0.68, 2.49)	1.14 (0.58, 2.25)	1.16 (0.55, 2.45)	1.08 (0.49, 2.41)
Q5 (4.20, 4.77)	2.69 (1.47, 4.90)	2.24 (1.21, 4.14)	2.02 (1.02, 4.00)	1.62 (0.74, 3.55)	1.57 (0.68, 3.63)
P for trend	<0.001	0.008	0.048	0.184	0.265

[a]Model 1 adjusted for age and BMI.
[b]Model 2 adjusted for age, BMI, race, marital status, PIR, education level, alcohol drinking, male sex partners, ever pregnant, age at first sex, pelvic infection and recent chlamydia.
*Covariates adjusted in the two subgroups as in Model 2, except for the stratifying variable.

(Table 3). Smooth curve fitting representing the linear association between Pgp3AbMBA and infertility in the subgroup of ever used marijuana/hashish was shown in Supplementary Figure 1.

We found that there was an interaction between marijuana/hashish use and PIR ($P = 0.0463$, data not shown). Thus, the population was further divided into 8 groups according to the combination of marijuana/hashish use (yes or no) and PIR quartiles (Table 3). PIR values were classified by quartile: quartile 1 (Q1) ≤ 0.95; quartile 2 (Q2) 0.96–1.93; quartile 3 (Q3) 1.94–3.27; quartile 4 (Q4) 3.28–5. We found that in women who reported ever using marijuana/hashish, the risk of infertility after chlamydial infection was highest in quartile 1 of PIR (OR = 2.15; 95 CI%: 1.12–4.14).

Discussion

In this study, we found an independent association between chlamydial infection and infertility that persisted after adjustment for confounders related to demographics, health behaviors and reproductive issues. We further revealed that the association was linear over the entire range of Pgp3AbMBA. Furthermore, the subgroup analysis indicated that people who had ever used marijuana/hashish and lived below the poverty line were more vulnerable than their counterparts. To our knowledge, this report is the first study on the independent linear association between infertility and chlamydial infection, as measured by quantitative Pgp3AbMBA levels. High risk of infertility population upon chlamydial infection was first reported in our study.

Our results agreed with a cohort study that included 857,324 UK women. Compared with women whose chlamydia testing status was negative, women whose test was positive had an 85% increased risk of infertility (40). In a study screening of chlamydia antibodies in 890 women visiting fertility clinics, chlamydia antibodies were present significantly more often in tubal factor infertility (27). However, those studies were based on qualitative data of chlamydial infection and not quantitative. In a previous relevant study utilizing NHANES data, a 2-fold higher risk of infertility was found among women with high levels of Pgp3Ab than women with negative Pgp3Ab results (41). Based on expert opinion and the assumption that the highest level of Pgp3Ab has the strongest association with infertility, they defined high-positive Pgp3Ab with two standards: MFI $\geq$ 50,000 or MFI $\geq$ 25,048. However, this cut-off was defined artificially and these grouping did not seem plausible. Besides, their analysis did not include confounding factors, which could significantly affect female infertility. In the present study, twelve confounders were adjusted in the regression model and Pgp3AbMBA was treated as a continuous variable. Our study is the first to report an independent and linear correlation between quantitative Pgp3AbMBA levels upon chlamydial infection and infertility in fully-adjusted regression model. Serological surveillance may be especially useful to estimate the cumulative risk of chlamydial infection (37, 42, 43), unlike PCR positivity, which may be more transient. In addition, our results showed that a cut-off value above 551, as suggested by the CDC as chlamydia positive, did not predict an increased risk of infertility. Smooth curve fitting revealed that the prominent association was linear across the entire range of Pgp3AbMBA, and hence, no saturation or threshold effect was present. Therefore, future studies on the relationship between chlamydial infection and infertility should be cautiously interpreted.

To check the stability of the association between Pgp3AbMBA and infertility in numerous subpopulations, we carried out subgroup analysis. The results revealed that the association remained robust in the subgroups of age, BMI, race, education level, PIR, male sex partners, sex without condoms in the last year, alcohol consumption, and ever used cocaine/heroin/methamphetamine. However, we found that some vulnerable groups were of particular interest. First, women who reported ever using marijuana/hashish were more vulnerable than their counterparts. Marijuana is the world's most common illicit drug. A retrospective study found that women who were marijuana smokers at enrolment had a higher risk of miscarriage during infertility treatment (44). Several studies have reported

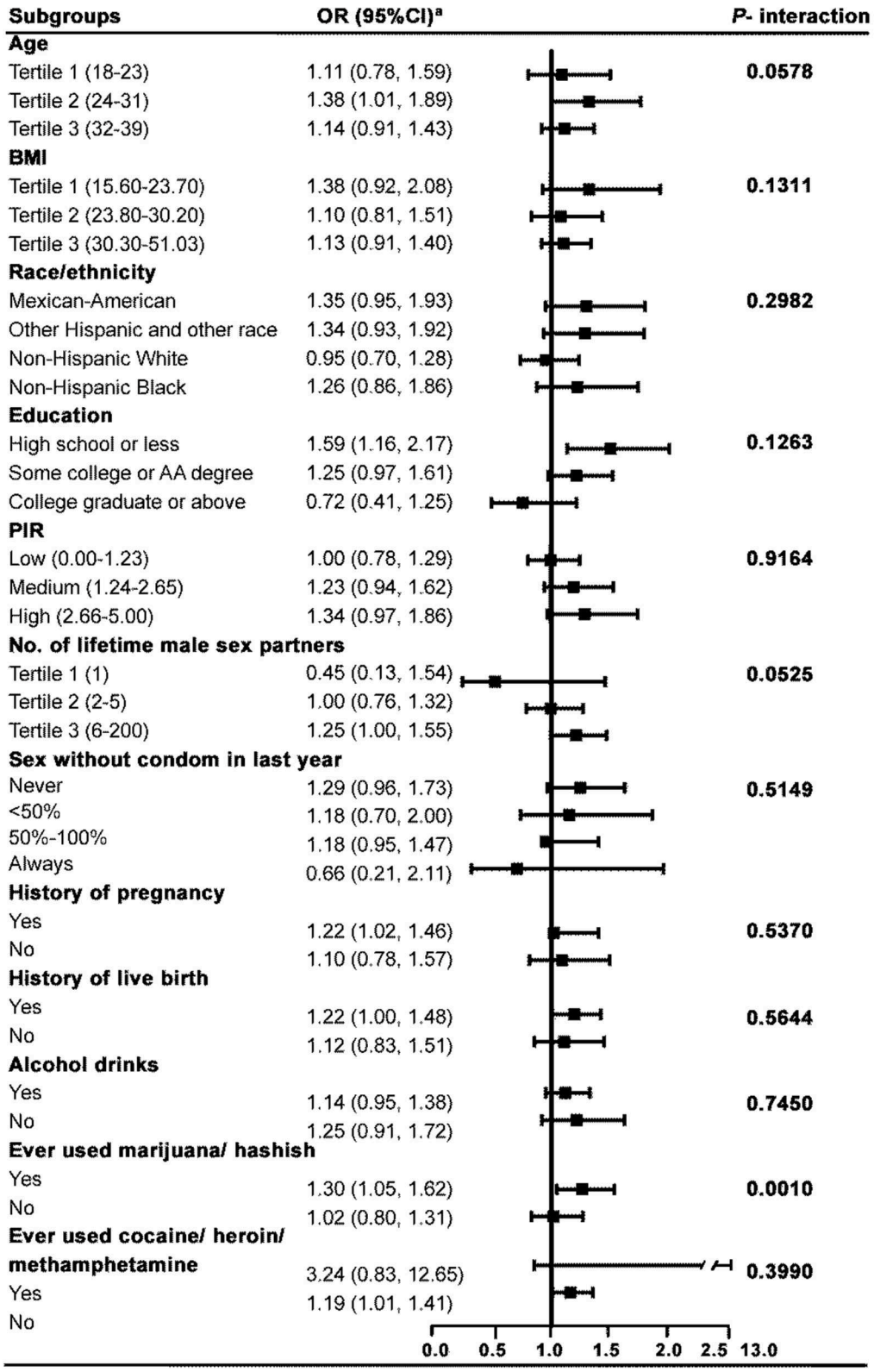

FIGURE 3
Subgroup analysis for the association between Pgp3AbMBA and infertility. [a]Model adjusted for age, BMI, race, marital status, PIR, education level, alcohol consumption, male sex partners, ever pregnant, age at first sex, pelvic infection and recent chlamydia, except for the stratifying variable.

TABLE 3 Comparison of risk of infertility following chlamydial infection in subgroups of women stratified by PIR and ever marijuana/hashish use.

Variables	Crude model		Model 1[a]		Model 2[b]	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Ever used marijuana/hashish-yes						
PIR Q1 (≤0.95)	1.51 (1.04, 2.19)	0.0314	1.49 (0.97, 2.27)	0.0655	2.15 (1.12, 4.14)	0.0216
PIR Q2 (0.96, 1.93)	1.45 (1.05, 2.01)	0.0243	1.45 (1.05, 2.02)	0.0247	1.18 (0.74, 1.88)	0.4890
PIR Q3 (1.94, 3.27)	1.18 (0.82, 1.72)	0.3707	1.14 (0.78, 1.66)	0.5053	1.39 (0.81, 2.37)	0.2331
PIR Q4 (3.28, 5.00)	1.67 (1.12, 2.49)	0.0126	1.47 (0.96, 2.26)	0.0770	1.40 (0.82, 2.41)	0.2163
Total	1.44 (1.20, 1.72)	<0.0001	1.39 (1.16, 1.68)	0.0005	1.33 (1.07, 1.66)	0.0114
Ever used marijuana/hashish-no						
PIR Q1 (≤0.95)	1.15 (0.78, 1.71)	0.4725	1.04 (0.68, 1.59)	0.8689	0.92 (0.49, 1.73)	0.7937
PIR Q2 (0.96, 1.93)	1.19 (0.83, 1.69)	0.3472	1.11 (0.77, 1.62)	0.5727	1.28 (0.76, 2.15)	0.3471
PIR Q3 (1.94, 3.27)	0.88 (0.54, 1.43)	0.5992	0.75 (0.44, 1.26)	0.2777	0.78 (0.36, 1.69)	0.5289
PIR Q4 (3.28, 5.00)	1.68 (1.12, 2.50)	0.0112	1.38 (0.86, 2.24)	0.1851	2.01 (0.82, 4.90)	0.1247
Total	1.20 (0.98, 1.46)	0.0772	1.06 (0.85, 1.30)	0.6138	1.01 (0.79, 1.30)	0.9130

[a]Model 1 adjusted for age and BMI.
[b]Model 2 adjusted for age, BMI, race, marital status, education level, alcohol drinking, male sex partners, ever pregnant, age at first sex, pelvic infection and recent chlamydia.

that anandamide and other components of the endocannabinoid system, such as cannabinoid receptors, are detectable in the fallopian tube (45, 46). Moreover, anandamide was reported mostly concentrated in the isthmus (47), where sperm capacitation and early embryogenesis occur (48). Therefore, the use of marijuana was reported to associate with female infertility, as well as abnormal embryo implantation and development (49, 50).

Second, when the study population was further classified into 8 groups based on the combination of marijuana/hashish use and PIR quartiles (Table 3), the highest risk of infertility upon chlamydial infection was seen in women who ever used marijuana/hashish and lived below poverty. PIR is calculated as the ratio of the family's income to the poverty threshold guidelines, which is specific to the appropriate year and state. A PIR under 1.0 (income less than the poverty level) represents a person living below the poverty line (51). Poverty has been demonstrated to substantially increase the risk of infertility in many aspects: limited access to health services and nutrition increases susceptibility to genital infection (52). Moreover, a recent study based on 2005 to 2018 NHANES data reported that the prevalence of past-year marijuana use significantly increased among those with income below the poverty level (53). Marijuana use and poverty promote each other and may impair health and fertility. Women living below poverty may experience increase vulnerability to the adverse effects of marijuana. In our analysis, those women with these two risk factors could be more at risk for developing a more severe genital chlamydial infection leading to infertility. Taken together, these findings indicated that marijuana, particularly coupled with substantial economic problems, may be detrimental to fertility upon chlamydial infection. Our findings emphasized that chlamydia prevention should be targeted at high-risk populations and that diagnosis must be followed by optimal treatment to reduce the burden of chlamydial infection. Overall, our study showed that marijuana users and poverty-stricken women were most likely to develop infertility following chlamydial infection. To our knowledge, such relationship has never been reported hitherto.

There were limitations to this study. First, this was a cross-sectional study, and we could not ascertain temporality or causation. Second, with a median age of ∼28 years, our study cohort was relatively young; therefore, some women would not have wanted to become pregnant at this age. This could have led to an underestimation of the associations that we found. However, the association remained consistent between the two groups, which were women who had been pregnant and who gave birth. Finally, although this analysis controlled for some confounders, the findings may have been influenced by factors not accounted for, such as the reproductive factors of males, coinfection of other sexually transmitted disease and variability in Pgp3AbMBA assay.

Conclusions

Our study revealed a positive and linear association between the Pgp3AbMBA level and self-reported infertility in U.S. women. Furthermore, we found that women who had ever used marijuana and lived in poverty were most at risk of infertility upon chlamydial infection. This indicates the need for adequate diagnosis and effective treatment for chlamydia infection, particularly for high-risk populations, and to maintain good reproductive health.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes/.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Huizhou Central People's Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

PL and ZC contributed to the study conception and design. ZC participated in data analysis. PL prepared the figure and tables and wrote the manuscript text. Both authors reviewed and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1117245/full#supplementary-material

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HPV-related oropharyngeal cancer early detection in gay and bisexual men is an "orphan" practice: A qualitative analysis among healthcare providers

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Introduction: Among US men, oropharyngeal cancer (cancer of the back of the mouth and throat) is the 8th most common cancer. If detected early, human papillomavirus (HPV)-16-associated oropharyngeal cancer has a high 5-year survival rate. Risk factors such as high numbers of oral sex partners, disparities in smoking and drinking, and low rates of HPV vaccination may put gay and bisexual men at even higher risk for oropharyngeal cancer.

Methods: We recruited 21 healthcare providers in Minneapolis-St. Paul, Minnesota and Houston, Texas to participate in semi-structured interviews. Nurses, physician assistants, dental hygienists, and dentists were asked about their clinical experiences serving gay and bisexual men and opinions on potential interventions for the early detection of oropharyngeal cancer.

Results: Providers typically did not tailor health screenings and examinations for gay and bisexual men. Participants lacked confidence in their ability to effectively implement routine screening for oropharyngeal cancer. The extent to which oropharyngeal cancer screening was incorporated into clinical practice varied by specialty, and practices necessary to detect it were scattered across clinical environments. HIV- and LGBTQ-focused healthcare providers were more aware of HPV-associated oropharyngeal cancer in gay and bisexual men, and appeared readier to act and lead on this issue.

Discussion: Further studies should (1) evaluate protocols for oropharyngeal cancer detection; (2) identify and assess the acceptability of screening in the community; and (3) study how to best close gaps in health services for gay and bisexual men which might contribute to low early detection rates of oropharyngeal cancer.

KEYWORDS

HPV, oropharyngeal, cancer, detection, gay, bisexual, men, qualitative analysis

1. Introduction

Oropharyngeal cancer (OPCa) is the 8th most common cancer in men in the US, with one of the highest increases in rates of any cancer (1). The oropharynx includes the back one-third of the tongue, the soft palate and uvula, tonsillar pillars and tonsils, and oropharyngeal walls. Much of this at least partially is visible on an oral inspection (2). The Human Papillomavirus (HPV) is responsible for most cases of OPCa, outpacing carcinogen-induced OPCa (3). Among all HPV-associated cancers, the greatest number of annual cases is attributed to oropharyngeal cancer (3). As of 2018, the number of cases per year of HPV-associated OPCa among men (N = 10,600) surpassed the number of cases per year of HPV-associated cervical cancer among women (N = 8,100) (4). In the US, OPCa is highly gender-linked; between 2001 and 2017, among men, OPCa incidence increased 2.7% per year (95% CI, 2.5% to 2.9%) to a total of 8.9 cases per 100,000, while no change in incidence occurred among women (a total of around 1.6 cases per 100,000) (5). The rise in OPCa cases is accounted for by HPV-associated OPCa. Among OPCa patients, 91.1% had human papillomavirus (HPV)-16 positive tumors compared to 3.3% of oral cavity (lips, gums, teeth, hard palate, floor of mouth, cheeks, and front of the tongue) cancer cases (6).

Classic OPCa occurs in heavy smokers and alcohol users, while HPV-associated OPCa is associated with oral sexual risk behaviors. HPV-associated OPCa is now recognized as a separate entity with a well-defined risk population: young adult men who do not smoke or drink but engage in high-risk sexual behavior (7). Oral HPV infection risk increases with the number of recent oral sex partners, and data suggests that high rates of oral HPV infection lead to increased rates of OPCa (8). In the US, oral HPV-16 prevalence was six times higher in men (1.8%) than in women (0.3%) (9). In men who reported having two or more same-gender oral sex partners in their lifetime, high-risk oral HPV infection (including HPV 16, 18, and other cancer-causing types), prevalence was 22.2%, compared to 6.8% of men with no lifetime same-sex oral sex partners ($P = 0.038$), representing an enormous health disparity for gay and bisexual men (GBM) (9).

Patients with HPV-positive oropharyngeal cancer have significantly superior survival over those with non HPV-positive oropharyngeal cancer, with half the risk of death (10). In the US, 65% of people with HPV-associated OPCa tumors survived 5 years compared to only 28% of patients with OPCa tumors not associated with HPV ($p < 0.0001$) (11). Because detecting HPV-associated OPCa before it has metastasized leads to reduction in morbidity and mortality, early detection and treatment can have a major impact on psychosocial distress and reduced quality of life from cancer diagnosis (2). Therefore, HPV-associated OPCa is ripe for screening, especially considering its rising incidence.

Early vaccination against carcinogenic HPV (16 and 18) types is critical, too. The Centers for Disease Control and Prevention routinely recommends HPV vaccination for people of all genders, including GBM, from ages 9 to 26, as well as for those who did not receive the vaccine, up to the age of 45 (12). Recent incidence models project vaccine-associated reductions in OPCa will not be realized until 2060, considering current vaccination rates (13). Further, the shift in the burden of OPCa from a younger cohort (35–54 years of age) to an older vaccine-ineligible cohort (65–84 years of age) will continue, due to age and birth cohort effects with a 50% increase in incidence among those 70 years of age and older between 2018 and 2045 (13, 14). Notably, HPV vaccination rates among GBM are below Healthy People 2030 targets (80% adolescents aged 13–15 years) to minimize excess healthcare costs [Increase the Proportion of Adolescents Who Get Recommended Doses of the HPV Vaccine — IID-08 - Healthy People 2030 | health.gov[1]; (15)]. A recent meta-analysis including 78 studies conducted mostly in the US demonstrated that HPV vaccine completion among GBM was 47%, leaving much room to improve (15). This study also demonstrated that GBM under 25 years of age and over 40 were less likely to initiate vaccination than other age categories (15). These data suggest that there may be a window, which narrows with age, for vaccination of GBM to prevent acquisition of carcinogenic HPV types. However, for unvaccinated men or men infected with HPV, the focus must be on early detection, diagnosis, and treatment to improve outcomes.

Currently, there is no approved screening test for HPV-associated OPCa (16). Therefore, it is critical to develop new techniques to identify OPCa early (16). One opportunity may be improving visual inspections, typically involving the inspecting the oropharynx and palpating the lymph nodes in the neck (17) and increasing the frequency of such inspections. Physicians and nurses anecdotally appear less likely to carry out oropharyngeal examinations unless there are specific cancer-associated symptoms. Furthermore, a recent study demonstrated that only about one of four US adults over the age of 30 who get oral healthcare receive oral and oropharyngeal cancer screening (18). In general, there is little information on what healthcare providers are aware of, and practice, with regard to routine examinations to detect OPCa, particularly among GBM. Thus, the purpose of this study was to understand how healthcare workers in two US cities use visual inspection of the oral cavity and specifically the oropharynx in GBM for early detection of OPCa.

2. Research design and methods

2.1. Methods

We recruited healthcare providers from Houston, Texas and Minneapolis-St. Paul, Minnesota from January to September 2021. Five types of healthcare providers were recruited, including dentists, dental hygienists, physicians, physician assistants, and nurses. In each location, we searched print and social media for healthcare providers that cared for GBM and collected word of mouth recommendations. Clinics, practices, and individual healthcare providers were contacted *via* email, phone, and flyers. After initial contact, interested individuals were directed to complete an eligibility and consent form programmed in Qualtrics©. Eligible and consenting participants then scheduled a 1-h virtual appointment from the study calendar. Participants were not given specific details about the topic prior to beginning the interview but were informed they would be discussing their

1 https://health.gov/healthypeople/objectives-and-data/browse-objectives/vaccination/increase-proportion-adolescents-who-get-recommended-doses-hpv-vaccine-iid-08

work with GBM and thoughts on disease screening. Prior to the scheduled interview, participants were emailed a reminder and a link to the virtual appointment.

The interview guide included five questions and several optional probes to explore participants' knowledge of OPCa, care for GBM, screening protocols, education, and opinions toward novel screening methods. See Supplementary material for the full interview guide. All interviews were recorded with participant consent. Participants were compensated for their time and effort with a $100 Amazon gift card. Interview recordings were transcribed then uploaded to Atlas.ti©, a computer-assisted qualitative data analysis software, for analysis.

Saturation was assessed by comparing provider responses across three central interview guide questions. Two coders independently examined provider transcripts to record brief statement summaries and poignant quotes. Finally, the coders compared provider responses for similarities and differences that would indicate saturation. It was determined that the qualitative data was cohering around central themes and that contradicting quotations were sufficiently contextualized for the research team to draw conclusions.

2.2. Analysis

We applied a deductive coding approach to generate provisional codes for the final transcripts (19). Two independent coders reviewed transcripts and created a preliminary codebook of code titles, definitions, specific uses, and relevant quotations. The two coders then compared codebooks and merged or expanded codes to generate a final codebook, which was re-applied to all transcripts. A total of 45 codes were developed. The research team then applied thematic analysis to the coded data (20). This process involved examining the coded data, looking for patterns, commonalities, divergences, highlights, special cases, and outcomes that were not anticipated by the literature review (20). These patterns were then closely examined by the research team to determine if the emerging concepts were rooted in the ideas and perspectives of the researchers or embedded in the language and experiences of the study participants, or both. Phenomena that seemed authentically rooted in both the qualitative data and literature review (either as complementary or divergent) emerged as themes.

3. Results

3.1. Participant demographic characteristics

The demographic characteristics for participants are displayed in Table 1. Participants had an average age of 43.8 years and an average of 18 years in practice. There was a fairly even split between cisgender men and cisgender women participants. A just over a third of participants identified as a sexual minority. While a majority of participants were white, three participants were Asian and five were Hispanic/Latino. Participants worked in a range of healthcare settings.

TABLE 1 Participant demographic characteristics.

Participant demographics	Mean	Range
Age (years)	43.8	28–70
Years in practice	18	4–47
Gender	**N**	**%**
Female	12	54.5
Male	9	40.9
Missing	1	4.5
Sexual minority status		
Yes	8	36.4
No	14	63.6
Race		
White	16	72.7
Asian	3	13.6
Missing	3	13.6
Ethnicity		
Hispanic/Latino	5	22.7
Not Hispanic/Latino	16	72.7
Missing	1	4.5
Practice Information	**N**	**%**
Provider type		
Physician (MD/DO)	4	18.2
Dentist (DDS/DMD)	4	18.2
Nurse (RN/NP/LPN/CNM)	7	31.8
Dental Hygienist (RDH)	4	18.2
Physician Assistant (PA-C)	2	9.1
Other	1	4.5
Practice type		
Federally Qualified Health Center	7	31.8
Hospital/Medical Center	1	4.5
Practice Network/HMO	3	13.6
Private Practice	5	22.7
Academic Center/School	2	9.1
Community Health Clinic	1	4.5
Public Health	2	9.1
Other	1	4.5%
Practice location		
Minnesota	11	50.0
Texas	10	45.5
Not currently practicing	1	4.5

FQHC, Federally qualified health center.

3.2. Supporting themes

Seven themes emerged during analysis: (1) *treating patients the same*, (2) *Healthcare providers of all types are aware of HPV-associated cancers, but can't always address the problem; patients are less aware,* (3) *guidance on OPCa screening and prevention is lacking, especially among GBM,* (4) *lack of funding and time are barriers to comprehensive oral health examinations,* (5) *discomfort with talking about sex can be a barrier to OPCa detection,* (6) *screening for OPCa is an "orphan,"* and (7) *HIV- and Lesbian, Gay, Bisexual, Transgender, and Queer (LGBTQ)- specific clinicians are at the forefront of OPCa screening and prevention.*

3.2.1. Treating patients the same

When participants were asked whether they tailor HPV or OPCa prevention services for GBM patients, most said they did not. For example, one Registered Dental Hygienist working at a Minneapolis-St. Paul private practice said:

> "Actually, no [we don't tailor screenings for GBM]. I was thinking about that when you had sent me a little preview on that. I was like, "Do we?" It's interesting because it only comes up organically. We don't have a box that's checked, "what is your interest?" No, I think we do just the same general screenings we do with every patient because... Like oral cancer screenings, those are the kinds of things that would show up any way if there was an association with anything. Not really anything different."

This quotation illustrates a sentiment shared by many of the participants from all professions that providing uniform services to all patients, ensuring everyone receives equal treatment, was the best practice. Some physicians, physician assistants, and nurses asked more in-depth sexual health history questions if they knew the patient was a GBM. For example, when patients reported to nurses they had oral sex with men, it prompted oral swabs for chlamydia and gonorrhea. Patient HPV vaccination status was a key indicator prompting physicians, physician assistants, and nurses to discuss the risks of HPV and associated cancers with patients. Some participants justified treating all patients the same because they were concerned about making GBM feel singled out, as all patients who are sexually active are at risk for HPV. This fact led one participant to report they believed all patients should receive the same OPCa prevention services.

3.2.2. Healthcare providers of all types are aware of HPV associated cancers, but can't always address the problem; patients are less aware

Healthcare professionals of all types were aware that HPV causes cancer. The majority of participants reported recommending GBM patients apply safer sex practices to prevent HPV. However, among the nurses and physicians interviewed, cervical cancer was more commonly discussed than OPCa. Due to gaps in training and service, opportunities for prevention beyond vaccination were missed. For example, two nurse participants stated they were not equipped to screen for OPCa. Additionally, participants in general reported that their patients were less aware of HPV-associated cancers. For example, one Doctor of Dental Surgery working at a Houston Federally Qualified Health Center (FQHC) said:

> "That's something that I have been mentioning more now to patients. We talked a lot about HIV pretty openly and frequently with my patients, and we also talked a lot about other STIs in general. I feel like HPV has been something that has not been talked about. For the most part, a lot of patients don't really know what it is or that it even exists."

This quotation, combined with the experience of another nurse participant who said their patients never ask about OPCa, demonstrates the level of awareness about HPV and the perception of resultant risk to health among patients is low.

3.2.3. Guidance on OPCa screening and prevention is lacking, especially among GBM

Clearly, dentists and dental hygienists routinely looked inside patients' mouths and throats to screen for diseases. However, physicians, physician assistants, and nurses expressed they may only look inside a patient's mouth if a specific symptom is presented. Participants in general commonly reported that a lack of training, institutional guidance, education, and standard screening practices on OPCa was a barrier to effective prevention. For example, one nurse practitioner at a Minneapolis-St. Paul medical center said, "I need to check into that, what the clinical outcomes are in that arena. Is it really worth our time doing? Is it something that's needed to do? I know the USPSTF [United States Preventive Services Task Force] doesn't have any recommendations for that." This quotation demonstrates the common experience that the lack of clinical recommendations makes prevention approaches unclear. Additionally, only a few participants reported receiving adequate training to address OPCa concerns unique to GBM.

3.2.4. Lack of funding and time are barriers to comprehensive oral health examinations

Physicians, physician assistants, and nurses reported that HIV and STI prevention and treatment were central to their work because of emphasis from their clinics, funders, and qualifying patient healthcare coverage. Screenings that were not recommended by national institutions were typically not covered in a regular check-up due to time and resource constraints. Generally, participants reported being tight on time with patients, occupied with existing routine screenings. For example, one Minneapolis-St. Paul-based dentist mentioned that between their practices' dentist and dental hygienist, no more than 5 min is spent looking inside the oral cavity for signs of cancer. Another Minneapolis-St. Paul-based dentist stated they often tried to fit an hour's worth of care into a 20-min visit. Additionally, one nurse practitioner working in a Houston public health setting said, "We don't have [the] ability [for full-body screening]. We don't have that ability, funding, or the clinical… [sic] to get that done. Like I said, we were very limited. We're working toward that to do the full screening, but otherwise, we can't do that." Combined, these experiences demonstrate that

time and money are major barriers to detecting OPCa early when it is most critical.

3.2.5. Discomfort with talking about sex can be a barrier to OPCa detection

Participants reported that in some cases, GBM patients had guilt and shame about their sexual identity and sexual practices, which can prevent healthcare utilization and impede discussions on oral health. However, competency and comfort talking about these issues varied across participants' roles and healthcare settings. For example, several physicians, physician assistants, and nurses reported having developed skills to discuss sexual health, particularly with GBM. But one dental hygienist in Minneapolis-St. Paul stated that discussing HPV prevention with youth and their families can be difficult. Another Minneapolis-St. Paul-based nurse participant stated that even though their practice had come a long way in destigmatizing discussions on sex and sexuality with patients, these approaches didn't appear common. This participant said that a number of patients report not being able to talk about same sex behaviors because of histories of trauma and judgment. Lastly, another dental hygienist working in a Minneapolis-St. Paul private practice said, "It is a bit of a tough... It is a weird, tough topic to, like, talk about." Together these experiences underscore that discomfort with discussions about sex serves as a critical barrier to effective OPCa screening and examination.

3.2.6. Screening for OPCa is an "orphan"

Participants reported that healthcare providers in general were missing opportunities to prevent OPCa. Only a few participants reported being sure their practice had a written protocol for OPCa screening, each working in dentistry in either private practice or a practice network. Only one participant, a physician assistant working in an FQHC, reported having a written protocol for general health screenings for GBM. Participants stated that HPV-associated cancer prevention and detection requires a number of activities that are scattered across general practice, dentistry, and specialized oral healthcare. To illustrate this point, one doctor at a Minneapolis-St. Paul community health clinic said, "So I think [OPCa education and screening is] a little bit of an orphan and I'm guessing that's part of why this research is being done." This comment represents a prevailing notion among participants that OPCa prevention doesn't have a single clinical home. For example, dentists and dental hygienists sometimes viewed discussions about oral sex as not their purview, yet physician assistants, and nurses lack the training to detect cancers of the mouth and oropharynx. Additionally, the separation between general healthcare and dentistry may create gaps in OPCa prevention. The separation can manifest in several ways; physicians, physician assistants, and doctors, typically refer oral health concerns to dentists. But dentists and dental hygienists don't typically see sexual health prevention as in their scope of work. Furthermore, dentists and dental hygienists lack the specialized equipment to examine deep in the throat and study participants were concerned that OPCa in the throat may go undetected prior to referral to an ear, nose, and throat specialist.

3.2.7. HIV-and LGBTQ-specific clinicians are at the forefront of OPCa screening and prevention

Healthcare providers that work in HIV- and LGBTQ-specific healthcare settings appeared more prepared and readier to bridge the gap between providing sexual health services and OPCa screening. For example, among the few participants who reported receiving adequate training about addressing OPCa among GBM, most identified as sexual minorities themselves. Perhaps lived experience and familiarity with LGBTQ issues cues healthcare providers off to address these concerns. One Houston-based dentist who worked in HIV-centered care suspected that dentists who serve the general population may find candid discussions about GBM sexual behaviors difficult to foster, even though their own practice was very open with patients about these issues. This candor allows for patients to be open and honest about sexual practices and other risk factors for OPCa. The experiences of professionals in HIV- and LGBTQ-specific healthcare settings could be leveraged to improve practice, as well. For example, another Houston Doctor of Dental Surgery working in the same HIV-focused practice referenced earlier said, "[Our HIV-focused training] could easily be expanded to talk about HPV, right? Because we do talk a lot about HPV with HIV. And all of these people [in our training center] are very gay friendly, if not gay themselves. All the dentists here."

Another nurse practitioner in Houston indicated that they were more aware of HIV-associated oral diseases, and paid close attention to oral lesions because of awareness surrounding GBM sex practices. Additionally, one Minneapolis-St. Paul-based doctor indicated that patients living with HIV may be getting more screening for OPCa due to routine HIV-associated oral health visits. Similarly, one nurse practitioner working in Minneapolis-St. Paul said that young people living with HIV receive aggressive preventive treatment and therefore may have oral health issues like OPCa detected earlier.

4. Discussion

4.1. Discussion of findings

The key findings of this study are that frontline healthcare providers were not confident in conducting OPCa assessments among GBM, and few medical and dental practices had written protocols for conducting such assessments. Additionally, we found that healthcare providers believe patients don't know that oral HPV infection, and therefore oral sex, are risk factors for OPCa. This finding is consistent with, and extend, what has previously been reported in research on OPCa. Williams et al. (21) found public awareness for OPCa is low and most people are not aware that HPV can cause OPCa. Our study on healthcare provider experiences suggests that gay and bisexual men are similar to other members of the general public in having low awareness of OPCa and knowledge of HPV as a causative agent.

Additionally, we found that healthcare providers view patient stigma associated with being GBM as a barrier to effective OPCa prevention. Several study participants stated that hesitancy to discuss sex and sexuality between healthcare providers and patients may prevent important conversations which may reveal risk for HPV-associated OPCa. This hesitancy goes both ways; in some

cases, patients are hesitant to disclose same sex activity. In other cases, healthcare providers, such as dentists and dental hygienists, are uncomfortable asking patients about sex practices. These impressions correspond to literature on the subject. Whitehead et al. (22) found that being closeted to healthcare providers may lead to lower rates of healthcare use among GBM, and Facione and Facione (23) demonstrated that prejudice against LGBTQ people is associated with reduced rates of cancer screening. However, Rindal et al. (24) demonstrated that among a group of 36 dental healthcare providers, 90% reported being highly comfortable with asking patients about sexual behaviors during oral HPV screening, and 69% of patients surveyed ($N = 1{,}025$) reported being comfortable if asked about them. Perhaps the findings in Rindal et al. (24) indicate that conversations about sexual activity are becoming more commonplace in dentistry.

Appropriate practices to detect HPV-associated OPCa in general are unclear (16). Furthermore, most participants in this study stated they didn't tailor screening services to GBM, which aligns with recommendations that HPV-associated cancer prevention services be promoted to all patients regardless of sexual orientation (25). These conditions may explain why participants lack confidence in approaching OPCa prevention specifically among GBM. However, there is clear evidence that oral HPV infections are more prevalent among GBM (9), and that early detection can prevent excess OPCa morbidity (26). This appears to be a critical concern as GBM already experience cancer disparities (27). Treating all patients equally may fail to equitably address a potential health disparity among GBM which OPCa may represent. Therefore, future epidemiologic studies should investigate whether special attention to detect OPCa early among GBM decreases disparities in OPCa morbidity and mortality.

Some of the results of this study were unexpected and address an important gap in the literature surrounding GBM OPCa disparities. For example, we did not anticipate the central theme of the qualitative outcomes: OPCa early detection and prevention services may be an "orphan" in healthcare, meaning that no single healthcare venue houses all the services necessary to address the problem. Frontline healthcare providers like nurses and physician assistants commonly gather sexual health histories and may tailor assessment questions based on sexual activity to learn more about disease risk such as HPV. However, nurses and physician assistants lack the specialized training to conduct an OPCa examination. These skills usually reside among doctors and dentists. Dentists and dental hygienists said that tailored conversations with GBM patients about their sexual activity was not within their purview, and they may lack training on how to ask these questions. Dentists and dental hygienists have the skills to detect OPCa, but may not pay special attention to GBM who may be at higher risk for HPV-associated OPCa. A study by Stull et al. (28) suggested to improve comfort and confidence of dental providers in having HPV-related conversations, skills-based training and multiple opportunities to practice communication technique are needed. Furthermore, dentists and dental hygienists lack the training and specialized equipment that ear, nose, and throat specialists have available to look for OPCa deeper in the throat. Integrating dental and medical practices, such as conducted in many FQHCs, may improve collaborative OPCa prevention, availing the expertise of each healthcare provider (29).

Healthcare providers who work in HIV- and LGBTQ- specific healthcare settings appear to be strongly positioned to lead in closing critical gaps in OPCa early detection and prevention among GBM. Because these specialized healthcare providers lead destigmatized clinical environments, services are more comprehensive and individualized. This environment may enable healthcare professions to ask about individual risk factors and ultimately to look more closely for oral lesions, which may indicate OPCa. Our findings add to the evidence that dentists and dental hygienists are well positioned to develop protocols for oral HPV detection and that such procedures are feasible and acceptable to both dental healthcare providers and patients (24).

HIV- and LGBTQ- specific healthcare centers represent an important opportunity for increasing healthcare system capacity for OPCa early detection and prevention. In a similar context, dozens of interventions have aimed to integrate cervical cancer screening into HIV treatment services, and while outcomes data are scarcely reported, such interventions are deemed acceptable and feasible among women living with HIV (30). Furthermore, researchers who conducted a qualitative study on social support among GBM living with prostate cancer recommend healthcare providers account for the unique support networks GBM have when referring them for support for their diagnosis (31). It is likely that clinicians who specialize in providing healthcare to LGBTQ patients can integrate new OPCa prevention activities into their workflows, assist GBM to identify tailored cancer survivor networks, and make key recommendations on how to institute such processes broadly across health and dental care.

4.2. Limitations

Findings from this analysis should be understood given three limitations. The study sample was drawn from only two cities in the US potentially limiting transferability to other regions. Additionally, because we interviewed physicians, physician assistants, nurses, dentists and dental hygienists, our findings may not represent healthcare providers in other categories. Lastly, because we interviewed a total of 22 participants among five separate professions, examining differences between specific professions was challenging. Despite these limitations, this analysis highlights gaps in OPCa early detection and prevention and identifies opportunities to leverage the experiences of HIV- and LGBTQ- specific healthcare providers to improve OPCa screening.

4.3. Conclusion

Methods to best prevent OPCa among GBM are not well understood. Findings from this analysis highlight an opportunity to train primary care and dental providers on how to identify GBM in their practice and to screen these men for abnormalities indicative of possible OPCa. Healthcare providers who specialize in serving people living with HIV or who identify as GBM are well positioned to lead practice-based recommendations and design training for how to systematically detect HPV-associated OPCa. Further studies

should (1) better characterize rates of OPCa among GBM; (2) evaluate protocols for OPCa detection; (3) identify and assess the acceptability of screening in the community; and (4) study how to best close gaps in health services for GBM which might contribute to low early detection rates of OPCa. Informed by findings from this analysis and additional research, screening guidelines should be formalized and incorporated into routine preventative care.

Data availability statement

The datasets presented in this article are not readily available because it may contain identifying details even if redacted. Participants were assured we would not share the data beyond the interviewers and PI. Requests to access the datasets should be directed to mwross@umn.edu.

Ethics statement

The studies involving human participants were reviewed and approved by University of Minnesota Human Research Protection Program, UTHealth Committee for the Protection of Human Subjects. The patients/participants provided their written informed consent to participate in this study.

Author contributions

IZ: first authorship, primary data collection, data analysis, and primary authorship. SB: equal contribution, data collection, and data analysis. JW and CS: equal contribution and senior authorship, data interpretation, and revision. AN, SK, and CN: equal contribution, data interpretation, and revision. BR: equal contribution and senior authorship, conception and design, data interpretation, and revision. MR: equal contribution and last authorship, conception and design, data interpretation, and revision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1165107/full#supplementary-material

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A virtual pilot optimization trial for African American/Black and Latino persons with non-suppressed HIV viral load grounded in motivational interviewing and behavioral economics

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Introduction: Virtual and low-touch behavioral interventions are needed for African American/Black and Latino persons living with HIV (PLWH) with barriers to HIV viral suppression, particularly during COVID-19. Guided by the multiphase optimization strategy, we explored three components for PLWH without viral suppression, grounded in motivational interviewing and behavioral economics: (1) motivational interviewing counseling, (2) 21-weeks of automated text messages and quiz questions about HIV management, and (3) financial rewards for viral suppression (lottery prize vs. fixed compensation).

Methods: This pilot optimization trial used sequential explanatory mixed methods to explore the components' feasibility, acceptability, and preliminary evidence of effects using an efficient factorial design. The primary outcome was viral suppression. Participants engaged in baseline and two structured follow-up assessments over an 8-month period, and provided laboratory reports to document HIV viral load. A subset engaged in qualitative interviews. We carried out descriptive quantitative analyses. Then, qualitative data were analyzed using directed content analysis. Data integration used the joint display method.

Results: Participants (N = 80) were 49 years old, on average (SD = 9), and 75% were assigned male sex at birth. Most (79%) were African American/Black, and the remainder were Latino. Participants were diagnosed with HIV 20 years previously on average (SD = 9). Overall, components were feasible (>80% attended) and acceptability was satisfactory. A total of 39% (26/66) who provided laboratory reports at follow-up evidenced viral suppression. Findings suggested no components were entirely unsuccessful. The lottery prize compared to fixed compensation was the most promising component level. In qualitative analyses, all components were seen as beneficial to individual wellbeing. The lottery prize appeared more interesting and engaging than fixed compensation.

However, structural barriers including financial hardship interfered with abilities to reach viral suppression. The integrated analyses yielded areas of convergence and discrepancy and qualitative findings added depth and context to the quantitative results.

Conclusions: The virtual and/or low-touch behavioral intervention components tested are acceptable and feasible and show enough potential to warrant refinement and testing in future research, particularly the lottery prize. Results must be interpreted in the context of the COVID-19 pandemic.

Trial registration: NCT04518241 (https://clinicaltrials.gov/ct2/show/NCT04518241).

KEYWORDS

HIV care continuum, multiphase optimization strategy (MOST), mixed methods, motivational interviewing, behavioral economics, low-touch, HIV viral suppression, financial incentive

1. Introduction

Ending HIV transmission in the United States hinges on preventing new HIV infections (1, 2). This, in turn, requires assisting those already living with HIV to achieve and sustain HIV viral suppression through linkage to HIV primary care, engaging in care regularly, and taking HIV medication with high levels of adherence, a sequence of steps called the HIV care continuum (3–5). As HIV systems of care and treatment improve in the United States, some subpopulations of persons living with HIV (PLWH) benefit from these advances more than others. Although overall rates of HIV care continuum engagement have increased, subgroups of PLWH still experience longstanding and complex barriers to sustained engagement. In particular, racial/ethnic inequities in care continuum engagement and health outcomes are striking. For example, most PLWH are virally suppressed (66%) (1). However, African American/Black and Latino persons living with HIV, who are mainly from socioeconomically disadvantaged backgrounds, experience disproportionately lower rates of engagement along the HIV care continuum compared to White PLWH, including in HIV viral suppression and sustained HIV viral suppression (6–10). Only an estimated 40% of African American/Black and 50% of Latino PLWH sustain HIV viral suppression, compared to 56% of their White counterparts (7). The reasons for these racial/ethnic inequities are multifaceted and include barriers at the structural (e.g., chronic poverty, food insecurity, housing disadvantages, challenges accessing high-quality services), social (e.g., complex stigma, discrimination), cultural (e.g., medical distrust), and individual levels of influence (e.g., substance use and mental health challenges, unstable housing) (11–13). The complexity of barriers that impede access to the HIV care continuum and the fact that racial/ethnic inequities in HIV are serious and persistent signal the need for continued improvement and innovation at all levels, including in behavioral intervention strategies, particularly for subpopulations of PLWH with the greatest impediments to optimal HIV health outcomes.

The COVID-19 pandemic has complicated HIV management and exacerbated existing barriers to HIV care, including for African American/Black and Latino PLWH. Although the Centers for Disease Control and Prevention (CDC) reported expanding measures to support the continuity of HIV care, particularly in high HIV prevalence settings, the COVID-19 pandemic has caused substantive disruptions to engagement along the HIV care continuum (14, 15). Concerns about COVID-19 transmission rates and related social distancing mandates had the effect of constricting access to HIV care by way of reduced clinic hours and provider availability, frequent cancellation of healthcare appointments by both patients and providers, and an increased reliance on telehealth (16). While telehealth visits were useful for PLWH overall, for more disadvantaged PLWH, inadequate access to computer and smartphone technology and internet services precluded such remote visits (17–19). For many PLWH, the stress and emotional toll of social isolation adversely affected mental health, and commonly served as a catalyst for problematic levels of alcohol and drug use, along with increased contact with other people who use drugs, which further impeded engagement along the HIV care continuum (20, 21). Common long-standing structural barriers to HIV management, such as housing instability, food insecurity, and financial hardship, worsened due to the COVID-19 pandemic, related to its economic fallout, and these barriers further obstructed engagement along the care continuum (16, 22). Overall, the COVID-19 pandemic amplified the preexisting racial/ethnic health and economic inequalities so prevalent among African American/Black and Latino PLWH (23–25).

Abbreviations: AA, Alcoholics Anonymous; CAPI, Computer-assisted personal interview; CDC, Centers for Disease Control and Prevention; CI, Confidence interval; CONSORT, Consolidated Standards of Reporting Trials; FU, Follow-up (assessment); HCSUS, HIV Cost and Services Utilization Study; HIPAA, Health Insurance Portability and Accountability Act; MI, Motivational interviewing; MOST, Multiphase optimization strategy; NA, Narcotics Anonymous; PLWH, Persons living with HIV; S-CAP, Silver Community Action Project; S-CAP2, Silver Community Action Project 2; TM, Text message; TMQQ, Text messages and quiz questions; QQ, Quiz question; REDCap, Research Electronic Data Capture; WHO ASSIST, World Health Organization Alcohol, Smoking, and Substance Involvement Screening Test.

The field of intervention science had focused on virtual and "low-touch" interventions prior to the COVID-19 pandemic, and the COVID-19 pandemic, during which travel on public transportation and in-person contact in professional settings was curtailed, highlighted the importance of such approaches (11, 19). Virtual interventions include those conducted on the phone or a Voice over Internet Protocol (e.g., Webex). Low- and lower-touch interventions consist of those requiring limited staff time for facilitation; for example, because they are technology-based and/or automated (26).

In prior research we developed and explored the acceptability and feasibility of a "lower-touch" intervention for African American/Black and Latino PLWH with non-suppressed HIV viral load. The intervention was called the Silver Community Action Project (S-CAP) and was grounded in motivational interviewing (MI) and behavioral economics and designed to be culturally and structurally relevant by attending to the main barriers to HIV viral suppression experienced by this population, as described above (11, 27). The S-CAP intervention was grounded in work by Linnemayr and colleagues (28–30) and was a multi-component program comprised of a MI counseling session, and 16-weeks of automated text messages (TMs) about HIV management followed by quiz questions, where participants earned points by answering quiz questions (QQs). This aspect of the study was intended to foster engagement in the period during which participants might increase HIV medication use to reach HIV viral suppression, if they wished to and were able to do so. Consistent with behavioral economics (described below), this was followed by a lottery prize, the amount of which was based on viral suppression status (with higher prize amounts for those virally suppressed), number of points earned in the TM component, and chance (max. $275).

The S-CAP intervention was grounded in a conceptual model that integrates critical race theory, harm reduction, and self-determination theory, as described in more detail elsewhere (27, 31). As such, the S-CAP intervention prioritized support of participants' own health decisions and their autonomy overall, reinforced any steps toward positive change, and attended to and sought to resolve structural barriers to HIV management. The S-CAP intervention was designed to be low-touch, in that most activities did not require staff facilitation. It was not designed to be virtual but switched from requiring in-person contact (for enrollment and the MI session) to virtual participation in response to COVID-19 during the study. In a modest pilot study using a pre-test/post-test design and mixed methods, we found the S-CAP intervention was acceptable and feasible, and although it was not powered to examine efficacy, quantitative and qualitative results suggested it had utility and was worth further study (11). The behavior change techniques and approaches that underpin the S-CAP intervention components are incorporated into the present study.

First, MI is an evidence-based directive and collaborative counseling approach for behavior change that elicits participants' values, perspectives, and questions, identifies ambivalence and discrepancies, and corrects misinformation with permission, to thereby foster durable intrinsic motivation and readiness for change (32, 33). MI interventions have been found effective at clinically significant levels across a range of health outcomes (34–36). Moreover, MI has been found highly effective with African American/Black and Latino populations compared to White populations (34). This may be because while MI supports personal decisions and autonomy, such autonomy is often restricted in larger societal and institutional systems in which African American/Black and Latino populations engage (37–39). In the context of the present study, since not all PLWH may wish to or be able to achieve HIV viral suppression, the MI approach, which supports participants' personal decisions about HIV management without pressure or judgment, has utility.

Galarraga and colleagues carried out a substantive review of programs that used conditional economic incentives to improve HIV treatment adherence, mainly programs in clinical settings and including those grounded in behavioral economics (40). The review found that when appropriately implemented, conditional economic incentives can help PLWH improve their adherence to HIV treatment in the short-term, while incentives are in place. However, mechanisms to increase habit formation or maintain effects in the longer term warrant more investigation (40). Behavioral economics uses rewards and/or "nudges" to alter behavior and circumvent cognitive biases (41). Nudges are subtle and often indirect reminders that attempt to influence behavior through the way choices are made, taking into consideration behavioral biases. Ideally, a conditional economic incentive for behavior change (such as reaching HIV viral suppression) will align with an individual's own intrinsic motivation for behavior change, allowing the individual to build durable habits. Nudges are most effective when they are provided immediately after the desired behavior is carried out (41–44). However, it can take several months for PLWH who wish to increase HIV medication use and reach HIV viral suppression to do so (45). Thus, we use a text message and quiz question (TMQQ) component to foster engagement in the study over time and serve as a reminder about the larger goal of achieving viral suppression (described in more detail in Methods).

Financial rewards in the form of lottery prizes or fixed compensation amounts have been used in past research to reward longer-term behavior change. Prize drawings leverage the cognitive bias of overestimating small probabilities (leading individuals to participate in the prize drawing because they overestimate their chance of winning) and also increase salience (prizes keep a behavior high on a person's mental priority list) (43). On the other hand, participants in low-income contexts may actually prefer a fixed compensation amount over a lottery prize (11).

Overall, the results from our past study highlighted that the conceptual approach taken and the intervention activities in the S-CAP intervention warranted further exploration. We also identified a number of ways the intervention could be improved. For example, results indicated that the lottery prize structure was overly complicated, some participants would have preferred a fixed compensation amount for viral suppression over a lottery prize (although fixed compensation vs. a lottery prize have not yet been directly compared in the literature), participants requested additional MI counseling sessions, and the TMQQ period may have been too brief. We applied these lessons learned to the present study.

As is common in intervention research, the S-CAP intervention tested in the previous study consisted of a number of intervention

components that were combined into a single "packaged" intervention. One disadvantage of testing packaged interventions in what is often called the classical approach (generally using the randomized controlled trial design) is that, if found efficacious/effective, it is not possible to determine which of the components contributed to its efficacy, if some components performed better than others, or if some components had counter-productive effects on others. Further, when packaged interventions are not found efficacious/effective in a randomized controlled trial, it is not possible to determine if any of the components showed promise, or to determine what the next steps in the program of research should be. The multiphase optimization strategy (MOST) framework solves these problems through the systematic testing of individual intervention components and their interactions using a variety of designs (46).

The MOST framework is inspired by engineering and has three stages: preparation (identifying intervention components, developing a conceptual model, and identifying the "optimization objective" to guide future decisions about whether or how to combine components), optimization (evaluating the effects of components, applying the optimization objective to create a new multi-component intervention, if appropriate), and evaluation (testing the new optimized intervention in a randomized controlled trial) (46). The present study is grounded in the MOST framework. It is a pilot optimization trial that uses mixed methods and an efficient factorial design to examine the acceptability, feasibility, and preliminary evidence of effects of three separate intervention components derived from the results of the previous S-CAP intervention study, described in more detail elsewhere (11). Because the present study is exploratory and not powered for efficacy, it aligns most closely with the MOST framework's preparation phase. The three components explored in the present study are: (1) a financial reward for viral suppression (fixed compensation vs. a lottery prize), (2) weekly TMQQs for 21 weeks, and (3) three MI counseling sessions (the components are described in more detail below.) The factorial design permits a more precise exploration of each intervention component than the classical approach to testing packaged interventions allows.

2. Methods

2.1. Overview

The present mixed methods study is a pilot optimization trial, grounded in the MOST framework. The proposed study took place between 9/2020 and 1/2022 in the New York City metropolitan area, a COVID-19 epicenter. The study was carried out entirely virtually, as in-person activities with human subjects were prohibited at our institution due to COVID-19 restrictions. The study's primary outcome was HIV viral suppression, and viral load levels were a secondary outcome. We used an efficient factorial design to explore three behavioral intervention components, each designed to address specific barriers to HIV viral suppression in this population. The goals of the present study are to examine the acceptability and feasibility of the intervention components and explore preliminary evidence of their effects on factors believed to mediate changes in the primary outcome and on the primary and secondary outcomes, in order to inform future research. We enrolled 80 African American/Black and English-speaking Latino PLWH with non-suppressed HIV viral load (>200 copies/mL). Participants received a baseline assessment and follow-up assessments at 4- and 8-months post-baseline. With support of the study team, they provided a recent laboratory report including HIV viral load levels at each of the three assessment periods. Participants were randomly assigned to one of 8 experimental conditions, each comprised of a unique combination of intervention components or component levels. Consistent with the sequential explanatory mixed methods design, we used the quantitative results to develop a set of research questions that could be addressed using qualitative data, and then results from the two analyses were integrated using the joint display method. The study used the field name "Silver Community Action Project 2" (S-CAP2). Results were interpreted in the context of the COVID-19 pandemic, which impeded HIV management and other aspects of participants' lives, and the fact that all activities were carried out virtually, almost always by phone, since participants generally did not have smartphones or computers that would allow for Telehealth. Compensation was provided to participants using the Greenphire ClinCard system, a refillable debit card for research compensation. The study was approved by the Institutional Review Board at New York University and participants gave verbal informed consent for study activities.

2.2. Eligibility criteria

Inclusion criteria were: 1. age 18–65 years, 2. living with HIV, 3. resides in the New York City metropolitan area, 4. can participate in research activities in English, 5. has a phone and can receive text messages, 6. has not participated in a local conditional economic incentive program for HIV viral suppression in the past month, 7. has not been enrolled in the research team's two most recent research studies (the first S-CAP study and another previous study), 8. willing to provide a recent lab report showing HIV viral load (lab test completed in the past 2 months), and 9. the lab report at screening indicates non-suppressed HIV viral load (≥200 pp/mL). Although race/ethnicity were not eligibility criteria, it was anticipated that >90% of participants would be African American/Black or Latino given trends in past studies and the demographic characteristics of PLWH in New York City (>75% African American/Black or Latino; (47, 48). As shown in Table 1, all participants were either African American/Black or Latino.

2.3. Preparation for the present study

In preparation for the present study, the research team and a Community Advisory Board created separate intervention components from the original packaged S-CAP intervention and made minor modifications to them, based on past study findings. We increased the number of MI counseling sessions from one to three, increased the length of the TMQQ period from 16 to 21 weeks, changed some specific TMs that were unclear or that

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TABLE 1 Sociodemographic and background characteristics and HIV-related health factors ($N = 80$).

	Mean (SD) or %
Age in years (M, SD)	49.0 (9.42)
Age range [min, max], in years	29.0, 62.0
Sex, sexual orientation, and gender identity	
Male sex assigned at birth	75.0
Female sex assigned at birth	25.0
Sexual minority (bisexual, homosexual, queer, gay, lesbian)	38.8
Transgender, gender fluid, gender identity	15.0
African American/Black (non-Latino/Hispanic)	78.8
Latino/Hispanic	16.3
High school graduate/equivalent or higher	61.3
Homeless over the lifetime	93.8
Homeless in the past year	56.3
Currently stably housed	48.8
Indications of poverty	
Currently employed full- or part-time	1.3
Ran out of funds for basic necessities at least monthly in the past year	58.9
Any indication of food insecurity	86.3
Receives public health insurance (e.g., Medicaid)	96.3
Receives public entitlements/assistance (e.g., food stamps, cash benefits)	100
HIV History and HIV Health Status Indicators	
Years living with HIV/years since HIV Diagnosis (M, SD)	20.1 (9.50)
Range of years living with HIV [min, max]	<1, 37.0
Perinatally infected with HIV	0.0
Has taken HIV medication in the past	95.0
Years since first initiated HIV medication	17.2 (9.12)
Range of years since initiated ART [min, max]	0, 38.0
Number of HIV medication starts (range 0–288 times)	7.49 (13.2)
Longest duration of sustained HIV medication over the lifetime, in months (range 2–204 months)	36.2 (45.0)
Adherence to HIV medication—past month (range 0–100)	64.0 (37.0)
Taking any HIV medication at enrollment	81.3
If not on any HIV medication at enrollment, number of months since last dose	5.29 (5.14)
Satisfaction with HIV care (range 0–100)	77.1 (22.8)
Substance use	
Alcohol use at a moderate-to-high risk level	37.5
Cannabis use at a moderate-to-high risk level	51.3
Cocaine use at a moderate-to-high risk level	66.3
Polysubstance use (2+ substances excluding tobacco and alcohol) at a moderate-to-high risk level	51.3
Any substance use treatment lifetime	75.0

participants did not find acceptable, and added a comparison between fixed compensation and a lottery prize.

2.4. Component levels

In this design, components have two "levels," such as "on" (the participant receives the component) or "off" (the participant does not receive the component). In the present study, the component levels were: (A) financial rewards (fixed compensation vs. lottery prize); (B) TMQQ (on/off), and (C) MI counseling sessions (on/off). All participants also received a brief core orientation session. The core session is not evaluated, since all participants receive it.

2.5. Design

A full factorial experiment with three components (also called factors), each comprising two levels, contains 2^3 unique combinations of component levels. Thus, the factorial design comprises every possible combination of the component levels. In this case, each of the eight unique combinations of component levels constitutes a different experimental *condition*. Participant are randomly assigned to an experimental condition (Figure 1) (49). For example, in condition 1, participants receive the core session, fixed compensation for viral suppression, TMQQs, and MI counseling sessions. In condition 8, participants receive the core session and the lottery prize for viral suppression, but no other components.

2.6. Description of intervention components

2.6.1. Core orientation session (<60 min)

This session comprised an introduction to the study and its ethos grounded in the conceptual model described above (e.g., emphasizing support for personal decisions about HIV management and any positive change, no pressure, no judgment, and structural and cultural salience) (27, 31), a brief needs assessment, and referrals to needed services (e.g., HIV care, food pantries, housing, or clothing) to help overcome structural barriers to HIV care or medication. Participants were informed about the type of financial reward they were eligible to receive and the structure and duration of other components they were randomly assigned to receive during the core session.

2.6.2. Component A: financial reward for HIV viral suppression

All participants could become eligible for a financial reward at the first follow-up (FU) assessment by achieving HIV viral suppression. The financial reward was either a fixed compensation amount or lottery-type prize. The fixed compensation amount was $300, based on the literature, input from community partners, and our previous research (11). For those randomly assigned to receive

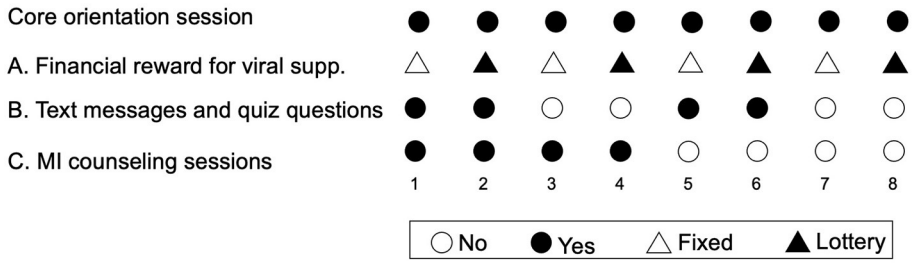

FIGURE 1
Experimental conditions in the factorial design.

the lottery prize level, prize amounts were determined by chance. Participants had a 3/10 chance of winning $500 and a 7/10 chance of winning $250. Thus, the average lottery prize amount was $325, comparable to the fixed compensation amount. The lottery prize was determined by spinning an electronic prize wheel, similar to a roulette wheel. This was done virtually. Participants had the option of delaying receiving the financial reward until the second follow-up assessment, for example in cases where they were increasing their HIV medication adherence, but had not yet achieved viral suppression. Those who did not achieve HIV viral suppression in the study period or who were unable to provide a lab report with their HIV viral load results received a $50 participation bonus. The primary mediator for the financial reward component was motivation for HIV viral suppression.

2.6.3. Component B: TMQQs

Those randomized to an experimental condition that included the "on" level of this component received TMQQs over a 21-week period (a reasonable length of time during which to engage in care, re-initiate HIV medication, change adherence patterns, and achieve HIV viral suppression, if so desired). Each week a TM was sent to participants' phones, containing health and general HIV-related information including a hyperlink to more information, as appropriate, or a motivational message (see Supplementary Table 1). Two days later, a second TM was sent with a true/false QQ based on the first TM. The QQs were not intended to be difficult but instead were designed to keep participants engaged in the study and serve as a reminder that the ultimate goal of the study was to support HIV viral suppression. The TMQQ component was implemented by the Telerivet program, which sent TMs and QQs automatically. After participants responded to the QQ, Telerivet sent additional TMs indicating whether the response was correct or not. Participants received five points for answering the true/false QQ correctly and two points if they answered, but incorrectly. They were informed they would receive $1 per point earned. The maximum compensation amount was $105 if participants answered every QQ correctly. The primary mediator for the TMQQ component was motivation, and engagement in the study, assessed as the proportion of QQs answered, to foster retention, was a secondary mediator and mechanism of action.

2.6.4. Component C: MI counseling sessions (30–40 minutes each)

The component focused on eliciting participants' decisions regarding reaching HIV viral suppression and how that might be achieved if participants wished to do so. The three sessions were guided by manuals that were developed by the research team and a Community Advisory Board for the present study. The written manuals note the overall goal for the component, techniques recommended as part of MI (e.g., developing discrepancy, readiness ruler, encouraging change talk), and guidance on training on habit formation. Then, each session was guided by a sequence of activities, with sample language provided as a guide. Further, interventionists were instructed to think of the component as flexible and individualized in order to meet participants' needs and to use the manuals in that context. Session one guided participants to identify HIV-related goals, barriers, and facilitators of goals, and introduced participants to the idea of habits for HIV medication. Session two took place ∼2 weeks later and reviewed goals, habits, successes, and barriers, and discussed the perceived value of sustained HIV medication adherence at levels sufficient to achieve viral suppression. The final session took place ∼2 weeks after that and focused on gains made and sustaining achievements after the financial reward was received. The primary mediator for MI counseling sessions was motivation for HIV viral suppression. (Manuals are available from the corresponding author.).

2.7. Recruitment

Participants were recruited using a hybrid method that included advertisements placed in the medical research section of a local free newspaper, flyers posted in local community-based organizations, and peer-to-peer recruitment, where participants were compensated $15 for referring peers to the study. Peer recruiters were also able to receive a bonus of $15 in compensation per peer who provided a laboratory report to the study, as a means of using peer influence, support, and reminders to encourage the timely provision of such laboratory reports, which were challenging for participants to obtain. Most participants were recruited from peer referral 72.5% (58/80), and a minority from newspaper advertisements (25.0%, [20/80]), and through flyers posted in community-based organizations or other means (2.5%, [2/80]).

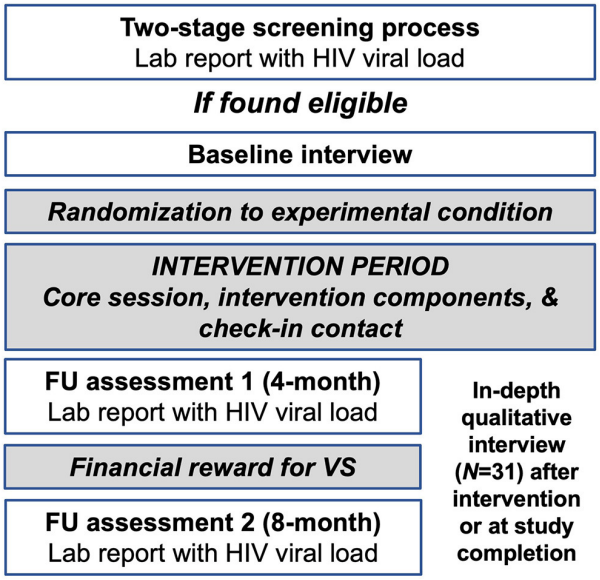

FIGURE 2
Sequence of study activities.

2.8. Study procedures)

The study was managed in the Research Electronic Data Capture (REDCap) platform. REDCap is a cloud-based platform for data capture designed for clinical research (50, 51). Assessment batteries were programmed in REDCap and administered to participants by trained interviewers. The sequence of study activities have been outline in Figure 2.

2.8.1. First screening interview

Screening for study eligibility took place in two stages. For the first screening interview, potential participants contacted the study directly by phone. Because all activities were virtual, we obtained verbal informed consent following an IRB-approved script, and then study staff led participants through a brief structured assessment in the computer-assisted personal interview (CAPI) format on the REDCap platform that assessed eligibility criteria. Gender identity, sex assigned at birth, and race/ethnicity were assessed but were not eligibility criteria.

2.8.2. Second screening interview

Those found preliminarily eligible at this stage were told they might be eligible for the research study, pending confirmation of non-suppressed HIV viral load on a recent laboratory report (HIV viral load assessed in the past 2 months). If potential participants were interested, the research staff discussed strategies participants could use to obtain new or existing laboratory reports without cost. Participants were asked to provide the laboratory report in an electronic format prior to the second screening interview (e.g., a photograph or screenshot sent electronically to a password-protected computer) or have their healthcare facility provide the report to the study electronically. Electronic faxes from health care settings were received by a computer-based application on a password-protected computer. Challenges to obtaining laboratory reports were common and included participants not recently attending HIV care visits and therefore not having a recent lab report, their having inconsistent access to cell phones or cell phone service being cut off, not being certain how to request or not feeling comfortable requesting a lab report from the provider, or not knowing how to create a screenshot or take a photograph to send lab results to the study electronically. These barriers were overcome by walking participants through the process of obtaining records, helping them take a problem-solving approach to barriers, and offering to contact the provider directly (with participants' signed consent). Participants typically required assistance obtaining the laboratory report (>90% of the time).

During the second screening interview, HIV viral load values were entered into REDCap and we then determined study eligibility based on HIV viral suppression status. Lab reports were scanned as needed and the electronic version was loaded into REDCap. No paper copies were retained, nor were electronic copies of records stored on computer hard drives, to protect participant confidentiality. Because participants generally requested their own records from providers or provided their records to the study, they were not required by the study to sign a Health Insurance Portability and Accountability Act (HIPAA) consent form. However, participants did sign a HIPAA form in cases where we were asked to contact the providers directly (we contacted providers in ~10% of cases). Participants received $30 for providing the laboratory report to the study and $10 for the second screening interview.

2.8.3. Enrollment and baseline assessment

Those found eligible provided verbal informed consent and completed a structured baseline assessment battery in the CAPI format on the REDCap platform lasting ~60 min. Participants received $30 for the baseline assessment.

2.8.4. Randomization to an experimental condition

After completing the baseline assessment, participants were randomly assigned to one of the eight different experimental conditions, using a randomization table created by the study's biostatistician and programmed in REDCap. Regarding the order in which components were delivered, the core session was provided first. MI sessions were provided next for those assigned to receive that component, followed by the TMQQs for those assigned to receive it. Financial rewards were provided last for all participants.

2.8.5. Check-in contact

At ~8 weeks post-baseline, participants engaged in a check-in call (<30 min). The goal of the check-in contact was to identify and solve any problems preventing engagement in the study.

Participants received $25 for the check-in contact along with any TMQQ compensation earned thus far, for participants assigned to the TMQQ component.

2.8.6. First FU assessment (~4-months post-baseline)

Prior to the first FU assessment, participants were contacted and asked to provide a recent lab report with HIV viral load levels (regardless of whether they were HIV virally suppressed or not). When laboratory reports were obtained, the FU assessment was scheduled and carried out in CAPI in the REDCap platform (lasting ~60 min). Participants received $40 for providing the laboratory report and $30 for the FU assessment.

2.8.7. Determination of financial reward

Participants who were assigned to the fixed compensation category received the appropriate compensation based on whether they achieved HIV viral suppression. Participants assigned to the lottery prize were able to hear or watch (if on a Voice over Internet protocol) study staff spin a virtual prize wheel for them and earned the lottery prize based on whether they achieved HIV viral suppression, and chance. Otherwise, the participation bonus was provided.

2.8.8. Second FU assessment (~8-months post-baseline)

Procedures for the second FU assessment were similar to the first: participants were contacted in advance to obtain the laboratory report, and then the FU assessment was scheduled and carried out. Participants received $40 for providing the laboratory report and $30 for the second FU assessment.

2.9. Procedures for qualitative interviews

Participants were recruited for in-depth qualitative interviews at one of two-time points. The first in-depth qualitative interview was conducted after the first FU assessment and the second in-depth interview took place after the second FU interview. Those who engaged in the first in-depth interview were not recruited for the second interview. Interviews lasted between 60 and 90 min, and were conducted virtually. Trained interviewers used a semi-structured interview guide as a template for the interview. Interviews were audio-recorded and professionally transcribed. Participants were compensated $30 for participating in an interview. For both interviews, participants were purposively sampled for maximum variability on key indices including sex, whether they achieved HIV viral suppression, time living with HIV, and experimental condition assigned to. A total of 16 participants were interviewed after the first FU and a total of 15 participants were interviewed after the second FU (total qualitative sample size was 31). Participants were compensated $30 for the in-depth interview.

2.10. Quantitative measures

2.10.1. Sociodemographic and background characteristics

Structured instruments developed specifically for HIV-affected populations in high-risk contexts such as the population under study here were used to assess relevant quantitative domains, including age, sex assigned at birth, gender identity, sexual minority status (identifies as gay, lesbian, bisexual, queer, or other non-heterosexual), race/ethnicity, education level (high school graduate or equivalent or higher), history of homelessness (homeless over the lifetime, homeless in the past year), and whether currently stably housed (that is, the residence is not temporary [such as a single-room occupancy hotel] or a location unfit for human habitation, including living on the streets). We assessed indications of poverty such as frequency of running out of funds for basic necessities at least monthly in the past year, any indication of food insecurity on a three-item scale, any receipt of public benefits such as food stamps or cash assistance, whether receives public health insurance (e.g., Medicaid), and whether currently employed full- or part-time (52). We assessed a range of HIV indices using a version of the HIV Cost and Services Utilization Study instrument (HCSUS) (53) including: years since first HIV diagnosis, whether perinatally infected with HIV, whether has taken HIV antiretroviral therapy in the past, years since first initiated HIV antiretroviral therapy, number times has stopped and started HIV antiretroviral therapy (a numerical response), the longest duration of sustained HIV antiretroviral therapy use in months (a numerical response), adherence to HIV antiretroviral therapy doses over the past 4 weeks on a visual analog scale (VAS; range 0–100% of prescribed doses taken), if not on HIV antiretroviral therapy at enrollment, number of months since last dose (a numerical response), and satisfaction with HIV care (range 0–100). Patterns of substance use were assessed using the World Health Organization Alcohol, Smoking, and Substance Involvement Screening Test (WHO ASSIST) which provides scoring algorithms to distinguish substance use at moderate-to-high risk vs. low-risk levels (54). We assessed engagement in any substance use treatment in the past (e.g., outpatient drug treatment, detox, inpatient drug treatment, methadone maintenance treatment program, 12-step or self-help meetings like Alcoholics Anonymous [AA] or Narcotics Anonymous [NA]), an indicator of past concerns about substance use (recoded as yes if any substance use treatment was reported). Physical and mental health were assessed using the SF-12 measure, a self-reported outcome measure assessing the impact of health on an individual's everyday life (55). We created T-scores from the SF-12 items; namely, weighted linear composite scores using weights presented by Ware and colleagues (55). The normative mean for composite scores in the 1995 general U.S. population was 50. In addition to physical and mental health composite scores, we also used the SF-12 items to create the SF-6D preference-based measure of health described by Brazier and Roberts (2004) (56). We used the SF-12 items (57) to create the SF-6D preference-based measure of health described by Brazier and Roberts (2004) (58). SF-6D scores can range from 0.35 to 1.0 with higher values indicating better health. The recent median SF-6D score for the adult United States population is 0.8 (59).

2.10.2. Motivation

We assessed motivation for (1) HIV care attendance and motivation to (2) take HIV antiretroviral therapy (if taking HIV antiretroviral therapy at all at the time of enrollment) or increase HIV antiretroviral therapy adherence (if taking HIV antiretroviral therapy but not at a sufficient level to achieve viral suppression), and motivation for (3) undetectable viral load. Based on past research, motivation was conceptualized as how important a behavior or outcome is to an individual and how confident they are they can engage in the behavior or achieve the outcome (60). Importance of the behavior was rated on a 1–10 scale (e.g., On a scale of 1–10, how important is it to you today to significantly increase how often you take HIV medication, where 1 is not important at all, and 10 is extremely important?), followed by the participant's confidence that they could engage in the behavior (e.g., On a scale of 1–10, how confident are you that you could significantly increase how often you take HIV medication, where 1 is not at all confident and 10 is extremely confident?). Thus, "motivation" for a behavior was operationalized as the mean of the importance score and the mean of the confidence score and ranged from 1 to 10; higher values indicated higher motivation for the behavior (60).

2.10.3. HIV treatment engagement

We assessed HIV treatment engagement by (1) assessing HIV medication adherence (range 0–100) and we assessed (2) the amount of HIV medication taken in the past 4 weeks using a visual analog scale ranging from 0 to 100% (53).

2.10.4. Acceptability

A version of the Client Satisfaction Survey (61) was adapted to the present study by the research team and reviewed by the community advisory board for comprehensiveness and clarity. The revised Client Satisfaction Survey was used to assess the acceptability of the study overall and of aspects of the intervention components. A total of 19 items were assessed such as "the S-CAP2 staff understand the treatment needs of people of my racial, ethnic, or cultural group," and "the chance to win a financial reward as part of the S-CAP2 study played a role in my recent HIV medication decisions." Items were rated on two types of Likert scales depending on the item (poor, fair, good, very good, excellent, rarely or never, sometimes, most times, and all of the time) and coded to reflect the proportion who endorsed the item as "very good to excellent" or "most times to all of the time." An activity was considered acceptable if 70% or more of participants endorsed it as "very good to excellent" or "most times to all of the time." Some questions were asked at the second follow-up assessment only.

2.10.5. Feasibility

Study feasibility was defined as the proportion of participants attending assigned components. The study or a component was considered feasible if 70% or more of the participants engaged in the activity.

2.10.6. Primary and secondary outcomes

HIV viral suppression ($\leq$200 copies/mL) and $\log_{10}$ HIV viral load level were assessed by laboratory reports provided by the participant's HIV primary care site.

2.10.7. Confidence intervals

We calculated 95% confidence intervals (CIs) for the main effect of each intervention component in a model for $\log_{10}$ HIV viral load at the second FU. Missing data were imputed 80 times with a chained equation approach where baseline HIV viral load, first FU HIV viral load, and all intervention components were included in the imputation model.

2.11. Qualitative interview guides

We used a semi-structured guide developed by the research team, which included experts on African American/Black and Latino PLWH, sexual and gender minorities, behavioral economics, and the HIV care continuum. The interview guide was structured as a series of suggested questions and prompts. The guide directed the interviewer from general to more specific questions in each of the following sections and was divided in two parts. Part 1 of the interviews focused mainly on participants' views on the intervention components: (1) general overview of the participant's experience in the project (e.g., What stands out to you most about the S-CAP2 project?); (2) experiences with fixed compensation or prize (e.g., Was the idea of receiving [fixed compensation or lottery prize] based on undetectable viral load fair? Motivating? Interesting? Confusing? Did the [compensation/prize] make you feel pressured in any way?); (3) views on sustaining viral load, where relevant (e.g., Do you plan to continue taking HIV medication and/or sustain an undetectable viral load after the [compensation/prize]? Why or why not? (4) experiences with the TMQQ component, for those assigned to receive it (e.g., What do you think about the text messages you have received? Are they easy to read? Hard to read? Too long? Too short? Are they helpful in any way? If so, how? Are they unhelpful in any way?); (5) the TMQQ component's potential effects on HIV decisions and behavior (e.g., Did the TMQQs have any influence or effect on your decision to take HIV medication or not? Why or why not?); (6) experiences with MI counseling sessions for those assigned to receive that component (e.g., Were the sessions helpful for you? Were you able to create habits around your HIV medication?); (7) effects of MI counseling sessions on HIV decisions and behavior (e.g., Did the sessions play a role in your decisions to take HIV medication or create any other health goals? Why or why not?).

Part 2 of the interview guides focused on the context of HIV management and experiences in the S-CAP2 study more generally. Questions included: (1) acceptability, feasibility, and safety (e.g., Has there been anything about S-CAP2 that you think has been particularly unhelpful? Helpful? What do you think should be included that was not included?); (2) the experience of virtual intervention (e.g., S-CAP2 was conducted on the phone because of COVID, was that OK for you? Do you feel you had a connection to

or relationship with S-CAP2 even though you never met the team in person?); (3) lab reports (e.g., How was the process of getting your lab reports? What got in the way of getting your lab reports? Was the S-CAP2 project helpful with respect to getting lab reports?); and (4) COVID-19 (e.g., Looking back, in what ways did the COVID pandemic influence your HIV management? Did you get tested for COVID? Have you been vaccinated?).

2.12. Quantitative data analysis

Descriptive statistics were presented by the time of assessment (baseline, FU1, and FU2) and by the levels of each intervention component, with percentages for categorical variables and means and standard deviations for continuous variables. Following recommendations from NIH (62) and in the methods literature (63), we did not perform null-hypothesis significance testing with these pilot data. All analyses were conducted with the R statistical computing environment (64).

2.13. Qualitative data analyses

Analyses of qualitative data followed a directed content analysis approach that was both inductive and theory-driven (65). Analyses were carried out in the Dedoose platform. We started with an initial list of "start codes" and their operational definitions that was generated by the primary qualitative analyst, who is a medical anthropologist. This initial start code list was informed by the theories and perspectives framing the study. Codes were generated that reflected structural barriers (e.g., quality of housing, poverty), culture and race/ethnicity (e.g., experiences of discrimination, medical distrust); and substance use management; autonomy, competence, relatedness, and other factors known to promote or impede engagement along the HIV care continuum (e.g., mental health distress). Using this scheme, the primary analyst coded interview transcripts along with an additional trained qualitative researcher. During the coding process, codes were refined, clarified, and/or broadened; for example, when new codes were identified. Discrepancies in codes and coding between the data analysts were resolved by consensus. Then, the interview transcripts were recoded using the final coding frame. Further, a subset of transcripts were coded using the final coding frame by three other members of the research team. Codes were then combined into larger themes and sub-themes in an iterative process led by the two main data analysts and in collaboration with an interpretive community of research team members, which included people who identify as cisgender men and women, people who are transgender, gender non-binary, or gender-fluid, people from White, African American/Black, Asian, and Latino backgrounds, and PLWH (66, 67). Methodological rigor of the analysis was monitored continually in several ways. An audit trail of process and analytic memos was maintained (68). Analysts engaged in debriefing sessions approximately monthly with the interpretive community. The primary analysts and the interpretive community attended to the potential effects of the team's positionality related to power and privilege, sex, gender, race/ethnicity, health, and socioeconomic status throughout the data collection process through reflection and training that focused on how these factors might affect interviewing and data analytic processes (69, 70).

2.14. Data integration procedures

Data integration followed procedures outlined by Fetters and colleagues (71) and used the joint display method (71). A joint display is a state-of-the-art visual tool (i.e., a side-by-side visual presentation of results) to integrate data sources. The process brings about new insights beyond the information gained from the separate quantitative and qualitative results. Data integration was carried out by the interpretive community made up of research team members in an iterative process in which each joint display table revealed insights about the merged findings that shaped subsequent iterations. Thus, joint displays are both a method and a cognitive framework for data integration and facilitate the production of new inferences (71). Beginning with the major quantitative findings, the interpretive community assessed areas of convergence and divergence between the quantitative results and the primary themes in the qualitative data. To do so, we used an informational matrix to compare results at a granular level (finding-by-finding) (71). Then, we explored primary qualitative findings that may not be present in the quantitative results. The results from this data integration effort were summarized and presented in a joint display table.

3. Results

3.1. Demographics and other characteristics at baseline

We recruited 80 participants who had a mean age of 49 years, were 75% cisgender men, 15% transgender, 79% non-Hispanic African-American/Black, and 39% sexual minority (Table 1). Approximately 61% had completed high school or equivalent secondary education. Almost none were employed (1%) and the majority (59%) ran out of funds for basic necessities at least monthly in the past year. Participants had been diagnosed with HIV for an average of 20 years. Most (81%) reported taking HIV medication at baseline, but self-reported adherence on the 0–100 visual analog scale was modest (mean = 64). About half (51%) had use of two or more substances other than tobacco or alcohol at moderate-to-high risk levels, and most (75%) had been in substance use treatment in the past. Other sociodemographic and background characteristics are presented in Table 1.

3.2. Enrollment and feasibility

Figure 3 provides data on study screening, enrollment, and participation in study activities, consistent with the Consolidated Standards of Reporting Trials (CONSORT) model. Among potential participants who completed the two-stage screening process, 84 were eligible and 80 (95% of eligible) went on to enroll and were randomly assigned to an experimental condition.

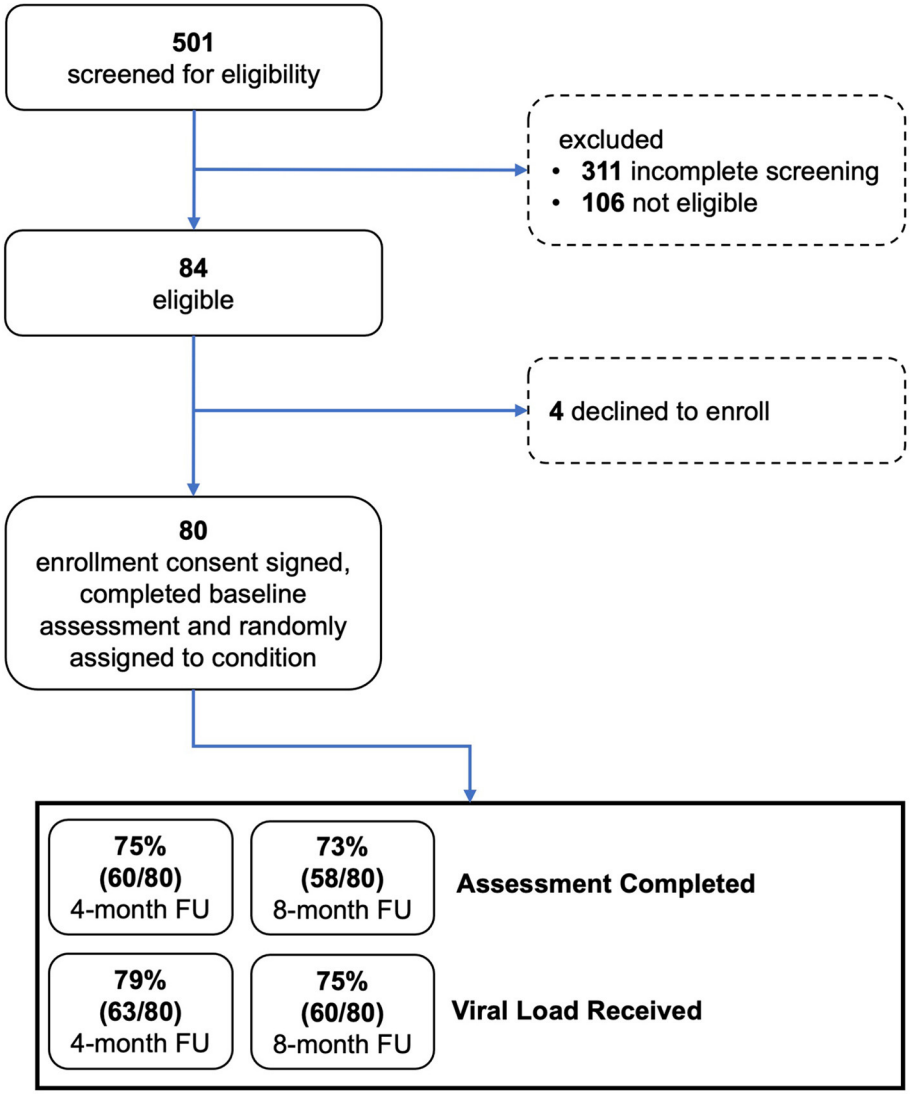

FIGURE 3
CONSORT diagram.

Approximately 75% of participants completed an assessment and viral load testing at the 4- and 8-month FU assessments. As shown in Table 2, most enrolled participants (96%) completed the core intervention session. Most participants assigned to MI sessions completed all three of those sessions (38 of 40, 95%). Most participants assigned to the TMQQ component (32 of 39, 82%) answered at least one QQ, on average responding to 11 of the 21 QQs.

TABLE 2 Feasibility of study activities.

	N (%) or M (SD)
Completed core intervention session	78/80 (97.5)
Completed all three MI counseling sessions	38/40 (95.0)
Check-in contact completed	74/80 (92.5)
Text messages (TM) and quiz questions (QQ)	
Answered at least one QQ	32/39 (82.1)
Number QQs answered (of 21 max.) [Mean, SD]	*10.7 (8.0)*

3.3. Acceptability and self-reported influence of S-CAP2 as a whole and intervention components

Table 3 shows responses to items assessing acceptability of the overall project as well as specific intervention components. Overall, most participants rated the activities and services of the project as very good or excellent at the 4-month (82%) and 8-month (69%) FUs. Participants also rated the information received as helpful or very helpful. Being treated like an individual, respect for privacy, and understanding of the needs of racial, ethnic, or cultural groups

were all rated favorably as well. Most participants indicated the project increased their desire to take HIV medication, and planned to continue taking HIV medication after the end of the project.

TMQQs were designed in part to support engagement in the study. Among participants assigned to the TMQQ component, more than half found the messages very good or excellent at the 4-month (66%) and 8-month (63%) FUs. More than half of participants assigned to this component said the TMQQs played a role in HIV medication decisions and led them to take more medication at the 4-month FU, but ratings of the importance of TMQQs seemed to decrease at the second, 8-month FU.

Regardless of whether a participant was assigned to the fixed compensation or lottery prize, about half said the financial reward played a role in decisions about HIV medication or led them to try achieving undetectable viral load. Nearly all participants said they planned to continue taking HIV medication after receiving the financial reward at the end of the project.

Most participants assigned to the MI counseling sessions component said the sessions played a role in their HIV medication decisions and led them to take more medication at both FUs. Most participants assigned to this component also said the MI counseling sessions led them to try achieving undetectable viral load.

3.4. Motivation

Regardless of assignment to components, ratings of motivation for taking HIV medication, attending HIV care, and having an undetectable viral load were high at baseline and increased from baseline to FU (Tables 4a–c). Variability in ratings of motivation also generally decreased as more participants approached or reached the ceiling of the 0–100 scale in follow-ups.

3.5. Health-related quality of life

Health utility, physical health, and mental health scores on the SF-12 are presented in Tables 4a–c. Physical and mental health T-scores indicate participants' health was lower than for the average adult (normative mean = 50). Health was generally stable over time and similar regardless of intervention components assigned, with any differences between groups or time points small relative to the standard deviations of each health variable.

3.6. HIV treatment engagement and HIV medication adherence

The percentage of participants taking any medication in the past 4 weeks was high at baseline and increased in FUs, regardless of intervention components assigned (Tables 4a–c). Self-reported HIV medication adherence was ∼64 on the 0–100 scale at baseline. Participants assigned to the lottery prize started with lower adherence (50 vs. 66%) and increased more than participants assigned to fixed compensation. At the second FU, adherence was 80 (sd = 21) among those assigned to the lottery prize and 68 (sd = 25) among those assigned to receive fixed compensation. At each FU point, medication adherence was similar regardless of assignment to the TMQQ and MI counseling sessions components.

3.7. HIV Viral Load by laboratory report

HIV viral load decreased from baseline to FU and the percentage of participants with suppressed viral load increased from baseline to FU (Tables 4a–c). Overall, $\log_{10}$ viral load was ∼4.0 at baseline (sd ≈ 0.9). A total of 39.4% (26/66) of those who provided laboratory reports at FU evidenced viral suppression (32.5% [26/80] among the full sample; data not shown in Table 4).

At the second FU, participants assigned to the lottery prize had a viral load about 0.6 $\log_{10}$ lower than participants assigned to receive fixed compensation. At the second follow-up, participants assigned to the lottery prize were more likely to have viral suppression (42%) than those assigned to the receive fixed compensation (24%). When considering TMQQ and MI counseling sessions components, about one-third of participants had viral suppression at FUs and $\log_{10}$ viral load was substantially reduced relative to baseline (∼0.75 $\log_{10}$ reduction) regardless of whether these components were assigned or not. We also examined the relationship between the TMQQ component and participation in post-baseline activities: check-in contact, FU1, and FU2. A total of 64% of those assigned to receive the TMQQ component engaged in all three of these activities compared to 61% of those who were not assigned to receive the TMQQ component (data not shown in Table 4).

As noted above, we calculated 95% CIs for the main effect of each intervention component in a model for $\log_{10}$ viral load at the second FU (data not shown in Table 4). In the pooled analysis model with baseline viral load as a covariate, all confidence intervals for intervention component main effects included values below zero, indicating potential benefit in reducing viral load. Evidence for the potential benefit of the lottery prize vs. fixed compensation was strongest, as most of the interval for the lottery prize was below zero (95% CI: −0.67–0.14). Evidence for the potential benefit of the TMQQ component was weakest, as most of the interval was above zero (95% CI: −0.07–0.76).

3.8. Developing research questions for the qualitative analysis

The sequential explanatory mixed methods design is a two-phase process where quantitative data are collected and analyzed first, then qualitative data are collected and analyzed based on the quantitative results (72). In the present study, quantitative and qualitative data were collected concurrently, but the research questions for the qualitative aspect of the study were developed after quantitative analyses were complete, so the qualitative data could be used to add richness, meaning, and context to the quantitative findings. To develop the research questions, the interpretive community comprised of members of the research team met to review and interpret quantitative results and articulate questions that could plausibly be answered by the qualitative data. Then, in the interest of parsimony, we selected two research

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TABLE 3 Intervention acceptability and participant perspectives ($N = 80$).

Acceptability	FU1 ($N = 60$)	FU2 ($N = 58$)
Overall, I think that the activities and services in the S-CAP2 project are Very Good/Excellent	49 (81.7%)	40 (69.0%)
The information I have received in the S-CAP2 project has been Helpful/Very Helpful	59 (98.3%)	58 (100%)
The S-CAP2 staff here treat me like I am an individual with unique needs and concerns	51 (85.0%)	51 (87.9%)
The S-CAP2 staff respect my privacy All of the Time	58 (96.7%)	57 (98.3%)
The S-CAP2 staff here understand the treatment needs of people of my racial, ethnic, or cultural group	57 (95.0%)	56 (96.6%)
Participant perspectives on the study and components		
The S-CAP2 project increased my desire to take HIV medication	52 (86.7%)	46 (79.3%)
Do you think you will continue to take HIV medication after the S-CAP2 project ends? (yes)	57 (95.0%)	58 (100%)
Lottery prize	**FU1 ($N = 29$)**	**FU2 ($N = 30$)**
The chance to win a prize for achieving undetectable viral load as part of the S-CAP2 project played a role in my recent HIV medication decisions	15 (51.7%)	15 (50.0%)
Because of the chance to win a prize as part of the S-CAP2 project, I tried to achieve HIV undetectable viral load	18 (62.1%)	13 (43.3%)
Fixed compensation	**FU1 ($N = 31$)**	**FU2 ($N = 28$)**
The chance to receive compensation for achieving undetectable viral load in the S-CAP2 project played a role in my recent HIV medication decisions	15 (48.4%)	13 (46.4%)
Because of the chance to receive compensation in the S-CAP2 project, I tried to achieve HIV undetectable viral load	13 (41.9%)	11 (39.3%)
Text messages and quiz questions (TMQQ)	**FU1 ($N = 32$)**	**FU2 ($N = 27$)**
Overall I think that the text messages I received as part of the S-CAP2 project are Very Good/Excellent	21 (65.6%)	17 (63.0%)
Receiving TMQQs to earn points as part of the S-CAP2 project played a role in my recent HIV medication decisions	22 (68.8%)	14 (51.9%)
Because of the TMQQs, I took HIV medication more often than I did in the past	19 (59.4%)	11 (40.7%)
MI counseling sessions	**FU1 ($N = 30$)**	**FU2 ($N = 25$)**
Meeting with the S-CAP2 staff to discuss my goals and learn about habits as part of the S-CAP2 project played a role in my recent HIV medication decisions	22 (73.3%)	19 (76.0%)
Because of meeting with the S-CAP2 staff to discuss my goals and habits, I took HIV medication more often than I did in the past	25 (83.3%)	21 (84.0%)
Because of the meetings with the S-CAP2 staff, I tried to achieve HIV undetectable viral load	26 (86.7%)	20 (80.0%)

questions to address in the present study. First, we found in the quantitative analyses the S-CAP2 intervention components were acceptable to participants and feasible, as noted above. However, we did not know participants' views on which aspects of the intervention components were useful, whether for supporting HIV management or other behaviors. This included perspectives on fixed compensation or the prize received for viral suppression, given quantitative results presented above. Second, we wished to examine how the COVID-19 pandemic affected HIV-related health decisions and behaviors during the study. Other research questions identified in this process were determined to be outside the scope of the present study, but could be addressed in future qualitative or mixed methods research.

3.9. Overview of qualitative results

As noted above, the present study was carried out in the early stages of the COVID-19 pandemic in a major COVID-19 epicenter. Overall, participants discussed both ongoing multi-level challenges to HIV management, along with the complexity of managing feelings of anxiety and helplessness related to COVID-19, the general uncertainty of daily living during this time, and the ways in which COVID-19 affected their capacity to manage their HIV treatment. Most participants in the present study had been living with HIV for many years. Although participants did not evidence HIV viral suppression at the time of enrollment, the majority were taking HIV medication at some level prior to enrolling, and most of those who were not on HIV medication at the time of enrollment had taken HIV medication within the last 6 months. Thus, they could be considered long-term HIV survivors, and as such had extensive prior experiences taking HIV medication and engaging in HIV care. Quantitative data highlighted that participants were located in the lower socio-economic strata, and less than half the sample was stably housed. Therefore, we addressed the qualitative research questions in the context of the COVID-19 pandemic, the experience of long-term HIV survivorship, and chronic poverty. In the next section we provide an overview of the qualitative study findings, followed by results for the two qualitative research questions and a joint display (Table 5) summarizing the integrated findings.

TABLE 4a Motivation, health-related quality of life, HIV treatment engagement, and HIV viral load over time (Mean [SD] or percent).

	Baseline		Follow-Up One		Follow-Up Two	
	Fixed ($n = 41$)	Lottery ($n = 39$)	Fixed ($n = 31$)	Lottery ($n = 29$)	Fixed ($n = 28$)	Lottery ($n = 30$)
Motivation (0–100)						
Motivation for HIV Care	88.7 (19.0)	92.4 (13.1)	95.0 (8.37)	95.4 (6.21)	94.3 (10.2)	97.2 (4.63)
Motivation for High HIV Medication Adherence	81.5 (24.7)	83.7 (21.0)	91.3 (9.97)	95.7 (7.53)	94.7 (11.1)	95.9 (5.80)
Motivation for Undetectable Viral Load	86.8 (22.1)	91.3 (13.5)	90.4 (18.5)	92.8 (9.52)	92.1 (12.7)	93.0 (12.7)
SF-12 health-related quality of life						
SF-6D Health Utility score	0.705 (0.188)	0.684 (0.187)	0.742 (0.188)	0.742 (0.197)	0.761 (0.207)	0.698 (0.174)
SF-12 Physical Health T-score	44.4 (12.2)	43.4 (10.8)	46.6 (11.4)	43.8 (10.5)	47.5 (11.0)	45.1 (11.4)
SF-12 Mental Health T-score	46.5 (12.7)	44.9 (12.2)	48.2 (10.9)	49.6 (10.2)	47.0 (10.3)	44.7 (11.7)
HIV treatment engagement						
HIV Medication Adherence (0–100)	66.1 (38.3)	50.3 (40.1)	65.3 (28.3)	72.8 (26.3)	67.9 (24.9)	79.8 (21.0)
HIV Medication Taken in Past 4 Weeks	34 (82.9%)	28 (71.8%)	30 (96.8%)	27 (93.1%)	28 (100%)	30 (100%)
HIV viral load						
$\log_{10}$ HIV viral load†	4.06 (0.90)	3.78 (0.91)	3.40 (1.61)	3.26 (1.34)	3.44 (1.64)	2.85 (1.44)
Suppressed (viral load < 200)	0 (0%)	0 (0%)	9 (29%)	7 (22.6%)	7 (24.1%)	13 (41.9%)

† At Follow-Up One, viral load was available for 31 participants assigned to fixed compensation and 31 participants assigned to lottery prize. At Follow-Up Two, viral load was available for 29 participants assigned to fixed compensation and 31 participants assigned to lottery prize.
Available for 29 participants assigned to fixed compensation and 31 participants assigned to lottery prize.

TABLE 4b Motivation, health-related quality of life, HIV treatment engagement, and HIV viral load over time (Mean [SD] or percent).

	Baseline		Follow-Up One		Follow-Up Two	
	No TMQQ ($n = 41$)	Yes TMQQ ($n = 39$)	No TMQQ ($n = 28$)	Yes TMQQ ($n = 32$)	No TMQQ ($n = 31$)	Yes TMQQ ($n = 27$)
Motivation (0–100)						
Motivation for HIV Care	89.1 (19.7)	92.0 (12.1)	96.0 (6.05)	94.5 (8.35)	95.6 (6.83)	95.9 (9.06)
Motivation for High HIV Medication Adherence	82.0 (26.0)	83.2 (19.3)	93.9 (8.95)	92.8 (9.35)	96.0 (6.03)	94.5 (11.2)
Motivation for Undetectable Viral Load	89.2 (19.8)	88.7 (17.1)	91.8 (17.0)	91.4 (12.8)	90.3 (15.4)	95.2 (7.86)
SF-12 health-related quality of life						
SF-6D health utility score	0.671 (0.188)	0.719 (0.184)	0.682 (0.196)	0.794 (0.172)	0.729 (0.203)	0.728 (0.182)
SF-12 Physical health T-score	42.2 (12.3)	45.8 (10.4)	42.8 (11.5)	47.3 (10.2)	45.8 (11.8)	46.8 (10.5)
SF-12 Mental health T-score	44.4 (14.0)	47.1 (10.6)	45.7 (12.3)	51.7 (7.77)	46.1 (12.0)	45.5 (10.1)
HIV treatment engagement						
HIV Medication adherence (0–100)	62.0 (40.8)	54.6 (38.8)	71.3 (25.7)	66.8 (29.0)	74.6 (23.4)	73.4 (24.1)
HIV Medication taken in Past 4 Weeks	33 (80.5%)	29 (74.4%)	27 (96.4%)	30 (93.8%)	31 (100%)	27 (100%)
HIV viral load						
$\log_{10}$ HIV viral load†	4.01 (0.87)	3.83 (0.96)	3.35 (1.45)	3.30 (1.51)	2.84 (1.45)	3.45 (1.63)
Suppressed (viral load < 200)	0 (0%)	0 (0%)	8 (25.8%)	8 (25.8%)	11 (35.5%)	9 (31.0%)

† At Follow-Up One, viral load was available for 31 participants assigned to TMQQ and 31 participants not assigned to TMQQ. At Follow-Up Two, viral load was available for 29 participants assigned to TMQQ and 31 participants not assigned to TMQQ.
Assigned to TMQQ and 31 participants not assigned to TMQQ.

Participants discussed a number of significant barriers and interruptions to healthcare access in response to COVID-19, which in turn interfered with their sustained HIV medication use. As we describe throughout this section, some of these barriers pre-dated the COVID-19 pandemic, some were exacerbated by COVID-19, and others were specific to COVID-19. Further, the COVID-19 pandemic certainly served as the backdrop for how the intervention components were experienced with respect to

TABLE 4c Motivation, health-related quality of life, HIV treatment engagement, and HIV viral load over time (Mean [SD] or percent).

	Baseline		Follow-Up One		Follow-Up Two	
	No MI ($n = 40$)	Yes MI ($n = 40$)	No MI ($n = 30$)	Yes MI ($n = 30$)	No MI ($n = 33$)	Yes MI ($n = 25$)
Motivation (0–100)						
Motivation for HIV Care	95.6 (6.25)	85.4 (21.3)	95.3 (6.69)	95.1 (8.06)	96.0 (6.49)	95.4 (9.53)
Motivation for High HIV Medication Adherence	89.1 (16.5)	76.1 (26.5)	91.8 (9.21)	95.1 (8.82)	95.9 (5.67)	94.5 (11.6)
Motivation for Undetectable Viral Load	93.0 (13.1)	84.9 (22.0)	91.6 (9.45)	91.5 (18.8)	91.5 (14.5)	94.0 (9.63)
SF-12 health-related quality of life						
SF-6D Health utility score	0.704 (0.188)	0.685 (0.187)	0.759 (0.183)	0.725 (0.199)	0.761 (0.170)	0.685 (0.212)
SF-12 Physical Health T-score	45.2 (10.6)	42.7 (12.3)	46.7 (11.3)	43.7 (10.6)	48.4 (9.98)	43.4 (12.1)
SF-12 Mental Health T-score	45.3 (11.9)	46.1 (13.1)	48.7 (9.35)	49.1 (11.7)	46.2 (10.2)	45.3 (12.2)
HIV treatment engagement						
HIV medication adherence (0–100)	61.4 (41.2)	55.4 (38.6)	70.1 (24.1)	67.7 (30.7)	73.2 (26.3)	75.2 (19.7)
HIV medication taken in past 4 weeks	31 (77.5%)	31 (77.5%)	28 (93.3%)	29 (96.7%)	33 (100%)	25 (100%)
HIV viral load						
$\log_{10}$ HIV viral load[†]	3.80 (0.87)	4.04 (0.94)	3.26 (1.38)	3.41 (1.59)	2.96 (1.43)	3.36 (1.71)
Suppressed (viral load < 200)	0 (0%)	0 (0%)	8 (24.2%)	8 (27.6%)	12 (35.3%)	8 (30.8%)

[†] At Follow-Up One, viral load was available for 29 participants assigned to MI sessions and 33 participants not assigned to MI sessions. At Follow-Up Two, viral load was available for 34 participants assigned to MI sessions and 26 participants not assigned to MI sessions.

promoting HIV care engagement. In exploring the disconnect between reported high levels of motivation for HIV medication adherence and viral suppression found in the quantitative results, common barriers to HIV management reported by participants included structural impediments such as financial insecurity, housing instability, safety concerns within housing circumstances, and other factors that limited material resources. Importantly, participants underscored the cumulative, synergistic effects of these and other related structural barriers on their mental health and/or substance use patterns, which in turn, frequently diminished HIV treatment as a priority in participants' lives. Some participants expressed complicated perspectives about their individual HIV care, often affected by their state of wellbeing, but also the pressure they felt to attain viral suppression, particularly during periods of elevated stress, which, in turn, exacerbated feelings of stress.

Chronic poverty contributed to some participants selling (or diverting) their HIV medication doses to pharmacies operating outside the law, an opportunity to receive financial resources that participants typically found very challenging to decline. Study findings made evident aspects of the intervention components that were experienced as positive, as described below. Findings demonstrated key aspects of the intervention components that were useful in supporting HIV management, as well as ways the intervention components could be improved. One goal of the study was to allow participants to engage in the components even if they could not or did not achieve HIV suppression, and we attended to positive effects of components on behaviors other than HIV management. Names used below are pseudonyms and identifying details have been removed or obscured to protect participants' confidentiality. Participants were queried about their preferred pronouns (e.g., he, she, they, other) at enrollment, and the appropriate pronoun is used below in the description of each participant.

3.10. RQ1: what aspects of the S-CAP2 intervention components were useful, including in supporting HIV management, and how could they be improved?

3.10.1. Overview of results for RQ1

Despite the structural and other challenges to HIV management that were common among participants, including related to COVID-19 as described in more detail below, the majority viewed engagement in the S-CAP2 intervention components as markedly beneficial to their individual wellbeing, whether they achieved HIV viral suppression or not. In particular, supportive and nonjudgmental interactions between study team members and participants often prompted participants to reflect on and, in some cases, reconsider or even modify their personal attitudes toward and behaviors regarding HIV medication adherence. In the sections that follow we describe participants' perspectives on each of the three intervention components, with an emphasis on the ways each component influenced HIV management, and other factors that may have contributed to the satisfactory-to-high levels of acceptability and feasibility as described in the quantitative results.

TABLE 5 Joint display summarizing the integrated results.

Domain	Quantitative results	Qualitative results	Findings were concurrent, complementary, or discrepant, and comments
Feasibility	Components and assessments were feasible Having participants obtain their own lab reports from HIV care settings was feasible but challenging (e.g., because participants lacked smartphones and had lower levels of technical abilities). This was complicated by the COVID-19 pandemic. These challenges reduced the number of lab reports provided for analysis.	Compensation for study visits was the main reason participants initially enrolled in the study, but they continued in the study at high rates mainly because of their positive experiences in the study. Compensation overall led participants to feel respected and valued, and this, in turn, promoted retention and engagement.	Qualitative and quantitative results were complementary. Compensation is likely necessary but not sufficient for retention and engagement. The quality of the participant experience drives feasibility. The ClinCard system we used to provide compensation virtually and quickly likely played a role in participants' positive study experiences. We recommend similar studies support participants in obtaining lab reports, and if possible, provide multiple ways for them to do so with minimum burden and hassle, along with cell phones.
Acceptability overall	The study was acceptable to participants overall in a number of respects (e.g., information was helpful, privacy was respected, needs pf racial/ethnic group were understood). Overall acceptability dropped from 82 to 69% at the second FU. Almost all noted they would continue to take HIV medication after the study ended.	Project was acceptable overall. Qualitative results rarely highlight negative or unacceptable experiences in the study.	Lower rates of acceptability at the second FU suggest some participants may not have gotten their needs met in the study. Qualitative results may over-estimate acceptability since those with less positive experiences may decline to be interviewed or to comment.
Evidence of efficacy on viral load and suppression	Viral load levels decreased, and rates of viral suppression increased at FU1 and FU2. This suggests some or all of the components may be "active."	Some participants discussed ways the project fostered the desire and ability to take HIV medication at higher levels and achieve HIV viral suppression, as well as barriers they experienced. Not all participants wished to achieve viral suppression at this time.	Findings were congruent, with qualitative results perhaps presenting a more favorable view of the effects of the components compared to quantitative findings.
Financial rewards (overall)	NA (see below)	We found both fixed compensation and lottery prizes enhanced positive experiences related to study participation, were not seen as coercive or pressuring, and were seen as a form of encouragement to achieve viral suppression, but not necessarily a primary motivating factor or reason in and of themselves to achieve viral suppression. There were three themes: the financial reward was sufficient to motivate changes in HIV medication adherence behavior, the reward was appreciated but not necessarily a primary motivating factor or reason to achieve viral suppression, or it increased desire to achieve viral suppression but this was not sufficient to overcome serious structural and individual-level barriers to HIV medication adherence. Both levels of this component are acceptable, and feasible if participants provide lab reports and present for FU.	Financial rewards require relatively less emotional and cognitive effort for participants compared to counseling components. Financial rewards require relatively less effort for staff compared to counseling components. Financial rewards for viral suppression hold promise but the type (fixed vs. lottery), amount, and timing warrant further study.
Lottery prize	Feasibility was high since the component is not labor intensive to administrate. At FU1, 62% said the prize prompted them to achieve HIV undetectable viral load, dropping to 43% at FU2. Almost all intended to continue to take medication after the prize was received. Approximately 20% achieved HIV viral suppression at FU1 and 40% at FU2. CIs indicate the lottery prize was the most promising of the component levels with respect to reducing HIV viral load.	The lottery prize appeared more interesting, memorable, and engaging than fixed compensation, consistent with behavioral economic theory. See above re: themes related to the effects of financial rewards on behavior.	Quantitative and qualitative findings are largely congruent: prizes can encourage or support behavior but may not be a primary motivator. It is possible the effects of prizes operate largely outside conscious awareness, consistent with behavioral economic theory. Qualitative results provide insights into the ways the prize was seen and its effects. Taken together, findings suggest the lottery prize may be more promising than fixed compensation for viral suppression, consistent with behavioral economic theory.
Fixed compensation	Equivalent to findings for lottery prize with respect to acceptability and feasibility. Approximately 30% achieved HIV viral suppression at FU1 and 25% at FU2.	See above section on financial rewards.	See above

(Continued)

TABLE 5 (Continued)

Domain	Quantitative results	Qualitative results	Findings were concurrent, complementary, or discrepant, and comments
TMQQ	Feasibility was high: 82% answered at least one QQ and on average responded to 11 of 21 questions. Acceptability was modest (< 70%). Approximately 25% achieved HIV viral suppression at FU1 and 30% at FU2, with no difference between those who received TMQQ or not. In addition to influencing viral suppression, this component was intended to foster engagement in the study. Quantitative results suggest this component had the smallest effect on reducing HIV viral load, but may be useful as a low-touch engagement tool.	TMs were seen as informational, but the information provided was quite basic. Some were frustrated by how easy the QQs were. But, participants reported it "felt good" to get the answers correct. Frequency of TMQQs was acceptable and more frequent TMQQs would be acceptable and feasible. TMs were not necessarily connected to motivation to take HIV medications. TMQQs became reminders to take HIV medication that day for some. The information about HIV was found to be interesting and useful by most. TMQQs were commonly experienced as a form of positive connection with the study. TMQQs were experienced as an aspect of the participant's overall, generally positive, relationship with the study.	Qualitative findings add rich description and context to understanding this component, which was intended in part to foster engagement in the study in the period during which participants might seek to achieve viral suppression. Reminders of HIV status and HIV medication can induce negative feelings. The TMQQs did not appear to do so. Thus, providing short, easy, and private intervention content that does not directly refer to the need to take HIV medication that that yielded compensation may induce positive emotions, or at least no negative emotions. This may be valuable and may support study engagement over time. Findings suggest this component is promising and warrants further study, including regarding more challenging questions and/or individualized messages, and more frequent messages. The TMQQ component requires relatively less emotional and cognitive effort for participants compared to counseling components. Quantitative questions may need refinement to better assess perspectives on this component.
MI counseling sessions	The component was feasible: 95% completed all three sessions, despite sessions being virtual and problems with phones being common. It was also highly acceptable and participants reported it influenced their decisions to take HIV medication (Table 3). Approximately 25% achieved HIV viral suppression at FU1 and 33% at FU2, with no large difference between those who received the component or not.	Highly acceptable and associated with insights and various types of behavior change, such as substance use challenges. It is not clear whether the habit-formation aspect of this component was useful.	Few MI interventions have been carried out virtually (on the phone, not a Voice over Internet Protocol) and during COVID-19. Participants had very high levels of motivation at entry into the study, which may have reduced the need for this component. It is possible serious structural and individual-level barriers to HIV medication adherence including those related to COVID-19 impeded behavior change even when sessions were provided.
Motivation (mediator of component effects)	Motivation for HIV viral suppression is high at study enrollment (~90/100).	Motivation was assessed indirectly in the qualitative results (e.g., goals for viral suppression). Some components increased motivation for viral suppression, as noted above, but in many cases, motivation was not sufficient to overcome serious structural and individual-level barriers to HIV medication adherence.	We cannot explain with precision why motivation for HIV viral suppression is very high at enrollment (although it may be related to COVID-19), but participants were not virally suppressed (despite taking HIV medication in some cases) and many did not achieve viral suppression during the study. There is a large literature on multi-level barriers to viral suppression, but we do not yet understand participants' perspectives on this phenomenon.
Diverting (selling) HIV medication	Not assessed	Diverting HIV medications is common and a power structural impediment to achieving HIV viral suppression for some.	Pharmacies eliciting illegal medication diversion were a serious barrier to HIV management for some.
Effects of COVID-19	Not assessed	COVID-19 overall created impediments to HIV management but also increased motivation to manage HIV in some cases.	Understanding COVID-19 as a contextual factor was vital to interpreting study findings.
How to improve procedures and components	Some measures may need refinement for more precise estimates of effects.	Various improvements to components and study procedures (regarding laboratory reports) were identified.	Having both quantitative and qualitative data and integrating results was useful. Quantitative data captured experiences of participants as a whole and qualitative data provided richness, detail, and context but seemed skewed toward more positive experiences with the study. Quantitative data required us to not over-estimate the positive aspects of participants' experiences.

3.11. Component A: financial reward for viral suppression, and compensation in general

As noted above, participants received compensation for study activities such as assessments and providing laboratory reports, and all participants could receive a financial reward if they achieved HIV viral suppression at the first FU assessment: fixed compensation ($300) or a lottery prize (maximum prize $500). Those who did not achieve viral suppression received $50. Overall, compensation for study activities was viewed as highly acceptable among participants, was the primary reason they joined the study, and for many, led them to feel respected and valued in the study ("They [S-CAP2] don't give you pressure, they give you encouragement. [Compensation] did play a role as part of the encouragement I felt. Because I feel like they understood the fact that you don't live life for free and your time is valuable"). Compensation in general was described as promoting study engagement and participants commonly reported that it, along with a positive experience with staff and study activities, encouraged them to remain active for the duration of the study. We found both fixed compensation and lottery prizes enhanced these positive experiences related to study participation and were not seen as coercive or pressuring.

Participants' views on the attitudinal and behavioral effects of financial rewards could be organized into three main themes: in some cases, the financial reward was seen as sufficient to motivate changes in HIV medication adherence behavior (that is, serving as "nudge" and a source of hope and encouragement), and in other cases, it was appreciated but not necessarily a primary motivating factor or reason to achieve viral suppression. Third, some participants reported the financial reward increased their motivation to achieve viral suppression, but this motivation was not sufficient to overcome serious structural and individual-level barriers to HIV medication adherence. Qualitative results did not yield evidence of any major differences in participants views on financial rewards based on whether they received fixed compensation or a lottery prize, although the lottery prize came across as more exciting and memorable than fixed compensation. Regarding the first theme where the financial reward served as a nudge, Bryant, a 40-year-old cisgender, heterosexual Black man who was diagnosed with HIV <10 years ago, was assigned to an experimental condition that included the lottery prize and noted:

> It encourages me to reach the goal of becoming undetected and also just a reminder. Like listen, you know, I should stay on taking my meds every time I should be taking them.

Mark was a 60-year-old cisgender, heterosexual Black man who as diagnosed with HIV 30 years ago, who was also assigned to an experimental condition that included the lottery prize. He did achieve viral suppression, and won the largest possible prize. While the funds were appreciated, and the experience of spinning the prize wheel was exciting, he noted that the prize was not the actual reason for his change in behavior.

> She spins the wheel, you can hear it. […] So, listen to it. So, she's spinning it and I'm hearing it. I kept saying, "Oh man, I want to win this money. I want to win this money." She says, "Mr. [name redacted], you won." I was like, "Thank you." But I'm not doing it for the money. […] I try not to look at it like that. I try to look at this as a beneficial thing. It's a helpful thing for me. Like you all kept me on track with this, and I'm just continue on being on track, you know, when the study is over. You know, I'm continue on, you know, staying on track with it. I'm not doing this for that. You know, I'm doing it to benefit me health-wise, not financial-wise. Health-wise, you know, because money doesn't mean anything for me. You know what I mean? I grew up poor. We didn't have anything. So when, you know, when I get a little few dollars every now and then, I put it toward my apartment or I treat myself or something or I help somebody out that's less fortunate.

Mark continued:

> It wasn't about the money, it was about the hope that you all gave me, the encouragement, man, to stay on time and take the medications on time. You know what I mean? Because, you know, for a long time, I used to get real depressed, being detected [having detectable viral load].

Jason, a 35-year-old cisgender, gay Black man, described a 20-year history living with HIV during which he had achieved viral suppression only once, in part because of concerns about HIV medication side effects and because he sold his medication to meet financial needs. Yet, during his time in the study, he seriously considered taking HIV medication, and began to explore his fears about the adverse health consequences of not doing so. The chance to win a lottery prize increased his motivation for viral suppression, but ultimately, financial constraints prevented him from doing so. Yet, he also believed that if he achieved undetectable HIV viral load, he would continue taking HIV medication.

> I have a serious issue with the medication as a whole, regarding long term. Short term is great. Long terms is not so great to continue to that medicine in your body once you have leveled off and get the virus out of the body due to the fact of the kidney and the liver damage. […] I can tell you right now, I actually have a desire to take my meds. I'm currently trying to get over this mental health hump and financial crunch. […] The fact of I need to take my meds or I'm going to die. Or it's either choosing to take the meds and stay financially twisted, because that $350– that's my biggest check, is the medicine I sell. […] That final end to the bonus of possibly getting $500 for the undetectable almost made me take my bottle. I'll pop the pill, because I knew, I know if I pop the pill in about 40 days my body bounces like right back [to undetectable viral load]. […] I almost did it. But then—I did it but then I didn't. […] It's all finances for me.

Thus, Jason highlights the complexities of HIV management in the context of chronic poverty.

In summary, the COVID-19 pandemic intensified existing financial strains for many participants. Study compensation was

a release valve for financial pressures for most and even offered positive experiences during periods of sustained stress. The financial reward component was acceptable to participants, no adverse effects were detected, and the component influenced attitudes and behaviors in a number of ways.

3.12. Component B: TMQQs

In the present study, TM reminders were paired with QQ each week to assess knowledge gained and to generate points for which participants earned compensation. Participants reported TMQQs were appreciated, it was generally enjoyable to answer the QQ and receive correct answers, and the TMQQ component served a number of functions. First, those currently taking HIV medication experienced the TMQQs as a reminder to take HIV medication. Although HIV knowledge was relatively high for the majority of respondents, particularly those who had lived with HIV for a decade or more, TMQQs served a function of keeping HIV medication adherence in the foreground of their daily activities and decisions, even though the TMs did not focus on medication or adherence. ("Yeah, it's just a constant reminder, the constant influx of information flying in someone's phone…I think it's a great reminder."). Second, the information provided about HIV was found to be interesting and useful for the most part. Third, the TMQQs were commonly experienced as a form of positive connection with the study. Overall, TMQQs were seen as fostering study engagement.

Participants noted TMQQs could be improved in two main ways: they could be more challenging (as they were too easy in most cases, since participants were generally expert on HIV) and should be sent more frequently than once a week. Nonetheless, one of the aims of the TMQQ component were to support continued engagement, and as such they were not intended to be difficult to answer. In most cases, TMQQs were not associated in participants' minds with *changes* in motivation to take HIV medication with high levels of adherence, but in some cases the reminders did support existing adherence patterns ("At first, I was undetectable, but then I started reading those text messages and one of them came in one week and that one motivated me to just continue to take the medication"). As Jason, introduced above, noted:

> Would [TMQQs] get people to take their medicine? No. No, I think—I'm not sure it would get people to take their meds. I just think it would be a little bit more challenging. For someone like me, when I saw those questions, I wasn't learning anything. You've got to think about the people that have been sick for a little bit and know the knowledge. So I didn't learn anything new on the questions. It was just a reminder to take my meds. So asking the questions became reminders. I guess that's the first thing I—and that really, I could say that that's cool. The questions did become reminders. […] The fact that the questions were coming to me and things, it keep the HIV medication thing in my head all the time.

Participants reported that receiving HIV-related information, such as in medical settings, was not typically associated with positive emotions, and was commonly avoided. However, the TMQQs were a positive experience for most. This was largely related to the fact that information was brief and limited, received by text message, compensation was provided for correct responses on the TMQQs, and TMQQs were associated with the larger generally positive experience of engaging in the S-CAP2 study.

3.13. Component C: MI counseling sessions

As a reminder, all intervention components were informed by the conceptual model that incorporates critical race theory and that includes autonomy support and harm reduction and aligns with MI, but the counseling session component also used specific MI techniques such as identifying discrepancy, a "readiness ruler," and training on habit formation. Participants described themselves as knowledgeable about HIV and reported they did not require training on how to manage HIV. In general, MI counseling sessions were experienced as acceptable and useful in that they provided a supportive and non-judgmental experience in which to reflect on behavior patterns. Importantly, this commonly prompted participants to reflect on and/or reconsider their attitudes toward HIV medication adherence and adherence patterns. The supportive, non-judgmental approach engendered participants' feelings of connectedness with the S-CAP2 study while also centering participants' individual health needs, which may or may not have included HIV medication adherence and HIV viral suppression. Further, the sessions allowed for open and honest sharing of their experiences, which further promoted participants' health decision making. This was notable, because participants commonly reported concerns or fears about discussing potentially stigmatized issues such as declining to take HIV medication, along with behaviors such as drug use, selling medications, and other "hustles" in the context of a research study ("I've been selling my medication for so long. I know that this is all confidential, right? Right?" and "I'm being pretty open with you and because, what are you going to do? I'm [not] going to see helicopters over my roof tomorrow, I mean"). Ultimately, participants were clear they made their own decisions about HIV management, consistent with the MI approach. Further, as noted above, taking HIV medication was not a precondition for study participation.

One participant who had been living with HIV for over 20 years shared how MI counseling sessions helped maintain a focus on his health. In sessions, the participant shared that, within the context of the staff member-participant relationship, he engaged in self-reflection, and was open and honest with the interventionist, which, in turn, appeared to have played a role in his continuing to avoid heavy drug use and begin to take HIV medication with high levels of adherence ("I'm trying to be undetectable as before"), in conjunction with improvement in his housing placement. Daniel, a 56-year-old cisgender, heterosexual Black man diagnosed with HIV 20 years ago, described:

> Well, [MI Counseling Sessions] helped me to stay focused on my physical health. You know what I'm saying? My mental health, as far as me, you know, living, living with a medical condition, the one I have. […] I'm not going to be in denial; you know, 20 some years I've been medically disabled. So I look at

> it like this. If I live this long, I can live longer. Just keep focused, pray, ask God to help me. You know, take my medication, do the right thing, and stay off the drugs. You know what I'm saying? I drink here and there, I smoke a little weed. I don't do all that other shit. You know? I've been there, done that. You know, them days are over with. [. . .] [With staff member], it was like I talked to her like a sister. Anything she wanted to know, I tell her. Whatever's going on in my life, I kick it to her. You know, the only way to get answers, get help, you've got to be honest with yourself. [. . .] Right. I can trust her.

Importantly, staff and participants were generally able to construct productive working relationships, despite being unable to meet in-person due to COVID-19, as described by Daniel.

A typical constellation of serious barriers to HIV medication adherence for participants comprised persistent mental health issues, substance use challenges, and sub-optimal housing, which, not surprisingly, reduced HIV care and HIV medication as priorities in their lives and interfered with participants' capacity to effectively manage their HIV treatment. MI counseling sessions, which were flexible and individualized and could attend to such barriers along with HIV care engagement and HIV medication served the purpose of supporting participants in centering or re-centering wellbeing along with HIV-related health, with the potential to interrupt periods of distress, heavy substance use, and/or sub-optimal HIV management or solidify a commitment to behaviors and relationships that could support wellbeing. Mary, a 54-year-old Black heterosexual, cisgender woman diagnosed with HIV 25 years ago, described the importance of an improved housing situation in her HIV management, and the role MI counseling sessions played in her articulating and carrying out her own health-related decisions.

> [I stopped taking HIV medication] because of depression, my mother passing away, me moving from shelter to shelter. And then when I do get the medication at times I just say [forget it] you know? And now I'm staying [. . .] in one place now and I know I'm not going nowhere no time so, yeah. [. . .] I can get back on my program as far as [taking medication] every time—because I used to wake up in the morning—before I put my feet on the ground, I'd take all my medications you know? [S-CAP2 helped with that stability]. And I said now that I've got my place, I could start back taking my medication like I was taking it. [. . .] You know that's what I choose to want to do? Yes. [S-CAP2] encouraged me and it was me that was encouraged to want to do it, you know?

3.14. RQ2: how did the COVID-19 pandemic affect HIV-related health decisions and behaviors during the study?

Participant narratives reflected emotional challenges (fear, loneliness, depression, stress) and clear obstacles to accessing healthcare and social services during the COVID-19 pandemic ("I used to [go to social service center], but now with this Corona nothing is going on. It's horrible. And that made me in a deep depression too because there's nothing to do"). As in many other locations, participants were under stay-at-home orders and physical distancing protocols, which contributed to a disruption in care and services, including medication delivery and drug program groups. Some participants stopped taking HIV medication during the COVID-19 pandemic, and experienced reduced access to substance use treatment and social services. Others increased their HIV medication adherence rate to better protect themselves from the effects of COVID-19. Tracey, a 60-year-old cisgender, heterosexual woman diagnosed with HIV 15 years ago, noted that HIV medication use was abruptly interrupted by the COVID-19 pandemic.

> I mean I would take them [HIV medication] if I could. [. . .] Coronavirus came out, which hurt me from having my medical [home health aide] to come out to my house and work with me. They used to come out, [check my] pill box, stuff like that. That would help me a lot. And if they weren't here, yeah it caused a lot of problems. And after that hopefully we'll get back in our regiment and be able to come out to my house and things like that. So, we're working closely, hopefully we'll get this thing settled, and I'll be on my meds regularly.

These disruption to relationships and services, and the tumultuous sociopolitical context in which COVID-19 occurred, commonly had adverse effects on mental health. Participants reported feeling isolated during COVID-19, and recounted reports of social unrest and violence in the news related to the consolidation of the racial justice and Black Lives Matter movements. Thus, the COVID-19 pandemic often led to or exacerbated depression and sadness. Others found in-person therapy and medical visits difficult to manage because of anxieties about COVID-19, especially being around strangers. In fact, concerns about contracting COVID-19 when living with a compromised immune system combined with the fall-out of managing health needs with COVID-19 were palpable among participants. One participant talked about his struggle in deciding whether or not to continue taking HIV medication while sick with COVID-19. He described the shared decision-making process that unfolded during a phone contact with a nurse who followed up with him as part of outreach. The participant, Mark, introduced above, revealed the uncertainty and stress that health decision-making engenders, particularly when living with chronic illness such as HIV.

> Well, I had it [COVID-19] back in February, right and when I had it. . . I had to quarantine in a hotel in New York. My first 3 days being in a hotel and having this COVID, I was like, "I'm not taking this HIV medication. I'm not taking shit." So, after that day passed, I'm sitting in that hotel room and I'm like literally crying and my mind went back to 1998 and I said to myself, "If I don't take this medication, right, and me having this COVID, my T-cells going to drop." Because now the COVID is attacking my immune system. I have nothing to fight the virus and I have COVID. A nurse calls me on the phone, and she said, "How you doing, Mr. [name redacted], with the COVID?" I said, "I'm not doing well." And we talked about HIV medication. She said, "Let me explain something to

> you, OK? Take the HIV medication because it will help you. Because if you stop taking the HIV medication, the COVID is going to attack your immune system.

The risk of contracting COVID-19 commonly motivated participants to resume HIV medication use, if possible, for fear of the effects of COVID-19 on health while living with HIV. The S-CAP2 study was a source of information for participants to better understand the potential effects of not taking HIV medication. Mark noted how support from a health care professional became the catalyst for improved medication adherence, which helped him reach HIV viral suppression.

In general, participants' narratives demonstrated the challenges of HIV-related health decisions particularly in a disrupted healthcare environment. Although the desire and motivation for HIV viral suppression were generally high, participants discussed how barriers to and interruptions in HIV care may derail their HIV management efforts, but also how they often reprioritized HIV medication and their HIV care with ongoing support and encouragement, including through the S-CAP2 project activities.

4. Discussion

The goal of ending the HIV epidemic in the United States cannot be reached without addressing the complex impediments that African American/Black and Latino PLWH experience to consistent engagement along the HIV care continuum. Clearly, efficient and effective behavioral interventions are an essential aspect of supporting these populations of PLWH in making use of and benefitting from HIV care and medications (73). The present study seeks to advance the portfolio of low-touch and virtual behavioral intervention approaches for the large and growing population of African American/Black and Latino PLWH, the vast majority of whom are located in the lowest socioeconomic strata. As we describe above, this population of PLWH experiences barriers to the HIV care continuum at structural, social/cultural, and individual levels of influence, and these barriers also can impede their participation in research (74, 75). Thus, they are under-studied compared to PLWH well-engaged in HIV care settings (74, 75). Further, since 2020, the COVID-19 pandemic has complicated HIV management in many locations (16). The present study was carried out in the relatively early stages of the COVID-19 pandemic when PLWH experienced disruptions to access to HIV care and services, social relationships, and their livelihoods. Further, the COVID-19 pandemic precluded in-person activities with research participants at our institution during this time and study activities were carried out over the phone or virtually, since participants rarely had computer or smartphone access (19).

We apply the MOST framework and use an efficient factorial design to explore three behavioral intervention components directed at African American/Black and Latino PLWH with non-suppressed HIV viral load. All three components are delivered virtually, and two of them (TMQQ and financial rewards for viral suppression) are low-touch and require minimal staff time to administrate. The factorial design used in the present study allows for a more precise understanding of the components' acceptability, feasibility, and preliminary evidence of effects compared to the classical approach of testing multi-component "packaged" interventions in randomized controlled trials. This factorial design, combined with the mixed methods approach, produced findings that advance research on low-touch and virtual interventions for American/Black and Latino PLWH with serious barriers to the HIV care continuum. In particular, the sequential explanatory mixed-method approach provided vital richness, depth, and context to the study results, and also enhanced the study's validity (72, 76). The present study highlights the acceptability, feasibility, and in some cases, preliminary evidence of effects of novel behavioral intervention components to improve HIV self-management for this population at-risk for poor HIV outcomes, and suggests directions for the next stage of this program of research.

The challenges inherent in managing HIV in the context of structural violence, including chronic poverty, cannot be overstated, as the present study highlights. Structural violence is defined as the social forces that harm certain groups of people, producing and perpetuating inequality in health and wellbeing (77). Consistent with past literature, financial insecurity, lack of financial and material resources, housing instability, and safety concerns within housing circumstances are common barriers to HIV management among African American/Black and Latino PLWH (78, 79). We found these types of barriers appear to function in cumulative and synergic ways to thereby exacerbate mental health and/or harmful substance use, which then generally diminishes HIV self-management abilities. In addition, participants commonly describe being approached by pharmacies that sought to purchase their HIV medication from them, called medication diversion (80). These actions by pharmacies are illegal, and certainly a serious impediment to PLWH with financial constraints, as immediate material needs will generally take priority over longer-term health outcomes (81). The present study was carried out in this challenging context.

As noted above, and contrary to expectations, participants' motivation to reach HIV viral suppression was high at the time they were enrolled in the study and increased during the study. In our previous study, motivation for high HIV medication adherence was somewhat lower at enrollment (Mean = 73.1 on a 0–100 scale, SD = 26.6) (11). It is possible that motivation for HIV viral suppression was elevated in the present study due to the COVID-19 pandemic, which triggered health concerns for many PLWH. Yet, none evidenced viral suppression at the time of enrollment. This may be due to the severity of structural barriers to HIV management and their downstream effects on mental health and substance use management, both long-standing barriers and those related to COVID-19. The factors that impede PLWH reaching HIV viral suppression even when motivation to do so is very high warrants further study, along with how such factors operate and how they can be ameliorated. While the present study sought to identify and circumvent some structural barriers to HIV care, clearly, mitigating structural violence would have powerful positive downstream effects on HIV management (82, 83). Such efforts could include universal basic income, improving housing quality, and providing easy access to high-quality HIV care (84–87).

While reaching HIV viral suppression may be difficult in the context of structural violence, and complicated by the COVID-19 pandemic, behavioral interventions are clearly an essential aspect of ending the HIV epidemic (84). And, a substantial proportion of participants during the present study (up to ∼40%) moved from unsuppressed to suppressed viral load. As noted above, the present study focuses on a population of PLWH who reside in high-risk contexts and are not well-embedded in medical settings. In fact, many behavioral intervention studies in the field of HIV focus on assisting participants who are initiating HIV medication with achieving HIV viral suppression (88), those at risk for stopping medication (89), or are focused on strategies to allow those who evidence viral suppression to sustain it (90, 91). Fewer studies focus on the population of PLWH examined here: mainly long-term HIV survivors who do not evidence HIV viral suppression and who experience serious barriers to engagement along the HIV care continuum (92). Rates of viral suppression reached among participants in the present study are comparable to past studies with similar subpopulations of PLWH (93, 94), and, notably, the intervention components in the present study were virtual and/or low-touch, suggesting the promise of cost-effective interventions for this population that faces serious challenges.

The field of behavioral economics, including the study of the types, magnitude, duration, and timing of conditional economic incentive approaches to supporting HIV management and "nudging" participants toward their personal health goals, are relatively new areas of study. In general, financial incentives work best when applied close in time to the desired behavior (95, 96). Designing effective financial rewards for HIV viral suppression is complicated by a number of factors including that self-reported adherence may not be sufficiently accurate to allocate rewards, laboratory testing for viral suppression is not usually done on a frequent basis, and PLWH must take HIV medication at high levels for months before reaching suppression (97). Nonetheless, past research has highlighted the utility of providing a financial reward for viral suppression (98, 99). Our own past S-CAP study suggested that lottery prizes were acceptable and feasible, but that some participants might have preferred a fixed level of compensation (11). However, these two types of financial rewards had not yet been directly compared.

The present pilot study provides evidence for the acceptability and feasibility of both types of financial rewards, and we did not find any social harms or negative effects related to this component. About half the participants said the financial reward played a role in decisions about HIV medication or led them to try achieving undetectable viral load, regardless of whether a participant was assigned to the fixed compensation or lottery prize. Qualitative results were consistent with behavioral economic theory in that PLWH generally did not experience the financial reward as directly causing their decisions and behavior. But, the financial reward could align with participants' intrinsic motivation and goals to support HIV management behavior, consistent with behavioral economic theory (100, 101). Further, financial rewards and compensation in general were experienced by participants as a form of respect for their time and contribution to the study, or even a form of emotional support in some cases ("It wasn't about the money, it was about the hope that you all gave me, the encouragement … to take the medications on time.") Qualitative data suggest that the use of a prize wheel for the lottery prize was engaging, exciting, and memorable in comparison to the fixed compensation (i.e., made the receiving the reward more 'salient'), consistent with behavioral economic theory (100, 102, 103). The financial reward component may have promoted engagement in the study, and did not require extensive staff time to administer. Further, the financial reward did not "crowd out" intrinsic motivation for health, again consistent with behavioral economic theory (100, 102, 103). Overall, study findings indicate that financial rewards for HIV viral suppression hold promise for this population of PLWH, particularly lottery prizes, and yielded many important research questions regarding the optimal type, size, duration, and timing of financial rewards for HIV viral suppression, along with how to sustain behavior change after rewards conclude (98).

The TMQQ component was automated and intended in motivate viral suppression, to support engagement in the study during the period where participants might increase HIV medication use to reach viral suppression, and to foster study retention. The feasibility of this component was reasonable. Acceptability was moderate in quantitative results and appeared high in qualitative results, highlighting the utility of the mixed methods approach for enhancing validity of findings. One major factor affecting this component was participants' severe financial hardship, which interfered with consistent access to a working cell phone that could receive the TMQQs. Thus, many participants wished to complete the TMQQ component but were unable to, reducing participation rates. In some cases, the TMs were experienced positively, perhaps as a form of connection to the study, and served as a reminder to take HIV medications. We found it is challenging for research teams, even in collaboration with a Community Advisory Board, to create TMQQs with the right level of difficulty for participants. Although as an engagement tool, the QQs were not intended to be difficult, some participants reported the TMQQs were too simplistic given their extensive experiences living with HIV, suggesting that advanced HIV information is needed and welcomed. It is possible that allowing participants to choose between a set of basic vs. advanced messages would have utility in future research, along with providing cell phones, as we note below. Alternately, messages could vary in level of difficulty, and participants can receive more difficult messages if they respond correctly to easier ones.

As noted above, the intervention components are grounded in a conceptual model that incorporates critical race theory and that includes autonomy support and harm reduction. Participants' views on the MI counseling session component were consistent with the elements of this model. For example, they reported the component provided an opportunity to reflect on and/or reconsider their attitudes toward HIV management and the non-judgmental, pressure-free approach that stimulated participants' feelings of connectedness with the study. The MI sessions component was highly acceptable and feasible, even virtually and carried out over the phone. Most participants assigned to the MI counseling sessions component said in the acceptability ratings that the sessions played a role in their HIV medication decisions and led them to increase HIV medication adherence. Most participants

assigned to this component also said the MI counseling sessions led them to try achieving undetectable HIV viral load. However, quantitative results (Table 4) did not reflect these findings.

MI is designed in large part to strengthen personal motivation for and commitment to a specific goal by eliciting and exploring the person's own reasons for change within an atmosphere of acceptance and compassion (33). In the present study, as noted above, motivation for viral suppression was very high at the time participants enrolled in the study and increased, and was somewhat higher at enrolment than in past studies, perhaps in part related to the COVID-19 pandemic. Yet, despite this high level of motivation, the majority of participants did not reach viral suppression during the study. This suggests the main aspects of MI—to build durable, intrinsic motivation for behavior change—were not salient for most participants in this particular context. This finding contrasts with the large literature on the effects of MI interventions in a range of contexts and for a variety of health outcomes, as described above.

These findings have implications for the design of this MI component: it should be flexible and individualized to spend little time on strengthening personal motivation for change in cases where such motivation is strong, and more time on uncovering, understanding, and resolving barriers to related behavioral concerns such as mental health treatment and substance use patterns. Indeed, these were important barriers to viral suppression in the present study and MI approaches are effective with such behaviors (104). The MI sessions component included a focus on habit formation, but results did not indicate whether participants found this useful. However, counseling intervention components are costly to administer compared to low-touch components (105), suggesting the need for future cost-effectiveness analyses. These findings provide support for a fully-powered efficient factorial design that can both ascertain the potential of intervention components in both implementation and cost-effectiveness.

As interventionists, in addition to exploring acceptability and feasibility in early-stage research, we are interested in whether intervention components "work." The main purpose of conducting a pilot study such as this pilot optimization trial is to examine the acceptability and feasibility of an approach that is intended to be used in a larger scale study (63, 106). But, the efficacy or effectiveness of interventions cannot be evaluated in a pilot study because of insufficient statistical power to detect effects (63). On the other hand, it is challenging to move a program of research from a pilot study to larger scale studies without some "signal" that the interventions tested show promise. So, despite constraints related to low statistical power, we can look for preliminary evidence of effects of components, as we have done here, a type of "non-futility." (107). In other words, we have explored whether any of the components show evidence of effects, with the understanding that the lack of effects does not necessarily mean the component is futile or completely inactive. We examined confidence intervals for each component's main effect on $\log_{10}$ viral load at FU2 and found that none of the components would be considered futile, but that the TMQQ component had the weakest effect on HIV viral load and may not be an optimal component for improving viral suppression in this population. Nonetheless, the TMQQ component appears to have utility as an engagement tool. The study findings taken together, and considering the larger literature, suggest that all three components warrant further study and that, consistent with behavioral economics theory, financial rewards in the form of lottery prizes may hold greater promise than fixed compensation of similar value.

5. Limitations

Strengths of this pilot optimization trial include the factorial design, mixed methods approach, and evaluation of the primary outcome by laboratory report, an objective measure. It also has limitations. The sample did not include monolingual Spanish-speaking participants, which limits the generalizability of study findings to the population of Latino PLWH as a whole. The sampling method and study procedures (such as the requirement for participants to provide their own laboratory reports and to have their own phones to receive TMQQs) may have introduced bias by reducing participation rates among those PLWH with the greatest barriers to HIV care and the least material resources. Further, inconsistent access to cell phones appeared to reduce participation in the TMQQ component. In future research, we can help reduce these potential biases by providing HIV viral load testing and cell phones to participants as part of the study. We will also explore factors that predict higher vs. lower levels of participation in the TMQQ component. Last, since African American/Black and Latino PLWH tend to stop and start HIV medication, as shown in past research (12), a proportion of the sample could be expected to reach HIV viral suppression during the study for factors unrelated to the intervention components. A fully-powered trial is needed to estimate the effects of each intervention component with precision. Results must be interpreted within the context of the COVID-19 pandemic and may not generalize to other contexts.

6. Conclusion

A range of intervention approaches are needed for African American/Black and Latino PWLH who are poorly or inconsistently engaged along the HIV care continuum in order to achieve the public health goal of ending the HIV epidemic. In particular, lower-touch interventions that reduce the burden on health care systems and that can be carried out virtually are needed (108, 109). The relatively low-touch intervention components grounded in behavioral economics and MI tested in the present study are acceptable and feasible and warrant further refinement and study in future research. Further, these approaches can be carried out outside the traditional health care settings to which this population of African American/Black and Latino PLWH experiences serious barriers. The MOST framework and the factorial design have an important role to play in the development of future efficient multi-component interventions.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board, New York University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

PF, MG, CC, and SL conceptualized the purpose and design of the present study, contributed to the data analysis, and wrote much of the manuscript. CC was the principal statistician. SS directed the study and served as a member of the interpretive community that analyzed, interpreted, and integrated data. CR-D was a study co-Investigator and advisor on study procedures. RF and SC were the main qualitative methodologists and analysts, and served as leaders of the interpretive community. SC and KI carried out study procedures and intervention components and critiqued the manuscript. SC was a member of the interpretive community. All authors commented on previous versions of the manuscript and read and approved the final manuscript.

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Conflict of interest

RF and SC was employed by Independent Consultant.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

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Drug behaviors, sexually transmitted infection prevention, and sexual consent during chemsex: insights generated in the Budd app after each chemsex session

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Chemsex refers to the intentional use of drugs before or during sex in a specific context, typically involving prolonged sex sessions with multiple partners. Engaging in chemsex is associated with a wide range of health risks and related risk behaviors. We developed a mobile phone application ('Budd-app') to support and inform chemsex participants, reduce potential negative impacts associated with chemsex (e.g., physical, psychological and social health harms), and encourage more reasoned participation. During Budd's development process, 11 participants completed a survey after each chemsex session they attended. This data collection approach provided precise experiences on drug related behavior, prevention measures for sexually transmitted infection and sexual consent on 63 chemsex sessions. The mean duration of chemsex sessions was 17.5h. Polydrug use was reported during 95% of chemsex sessions with an average of 3.5 agents per session. Unsafe dosing occurred at 49% of chemsex sessions, and 9/11 participants dosed unsafely at least once. Seven participants did not consistently take measures to prevent STI transmission. Nine had experienced peer pressure, both regarding drug use and sexual health. The same number reported sex without consent, not respecting others' boundaries as well as their own boundaries not being respected. Many participants experienced negative impact of their chemsex behavior during (7/9) and after (8/9) chemsex. Through participants' behavior assessment during multiple chemsex sessions, 'within-person' variability can be clarified. This clarification provides valuable insights in personal, emotional and contextual vulnerabilities. These insights can direct an individualized care and support trajectory aimed at addressing those vulnerabilities.

KEYWORDS

chemsex, drug use, sexual health, STI prevention, sexual consent

1. Introduction

The term chemsex refers to the use of psychoactive substances—such as methamphetamine, γ-hydroxybutyrate (GHB), γ-butyrolactone (GBL), or mephedrone—in sexualized settings (1). Although the practice of sexualized drug use has been observed across a diversity of people (2), chemsex is primarily observed among gay, bisexual, and other men who have sex with men (GBMSM) (1). Chemsex is characterized by its specific context, with the use of digital technologies to meet for sessions that may last for several days. Moreover, GBMSM who engage in chemsex experience adverse impact from their chemsex use (3). Throughout this paper we will use the term 'chemsex participants' to refer to GBMSM who engage in chemsex in an effort to increase readability.

In scientific literature, there is no consensus definition of the term 'chemsex', in terms of substances used. Substances can be categorized by toxicology, or their effect during sex. As not all drug use during sex is considered chemsex, Strong et al. categorized drugs used in a sexual context into three distinct categories (4). The first category consists of 'universally' considered chemsex drugs, such as metamphetamine, GHB/GBL and mephedrone ("reported in many studies … triggering a particular intensity of sexual interaction that is qualitatively different from other drugs included in the table"; p. e717). The second category contains chemsex drugs in some regions but not in others, such as ketamine, cocaine and MDMA ("drugs that are considered part of the chemsex scene in some countries," p. e717). The third category consists of drugs that are consumed by users during chemsex events, but that are not considered chemsex drugs, such as poppers, marijuana, and erectile dysfunction drugs ("substances commonly used alongside, but not typically constituting, chemsex drugs themselves"; p. e717).

The 2017 European Internet Survey has shown that 11 % of Belgian male respondents who reported to have sex with men (MSM), have used stimulant drugs in the past four weeks to make sex more intense or last longer (5). Beside, over 40 % (40.63%) of 1,549 chemsex participants in four European countries reported 'unwanted side effects' of their chemsex use (6). Lastly, substantial increases in chemsex related deaths are observed in France and the UK (7, 8).

In July 2022, the World Health Organization (WHO) highlighted the need for novel and tailored approaches to the growing phenomenon of chemsex (9). In answer to that, we developed a mobile phone application ('app') with the aim to improve care and support for chemsex participants by facilitating harm reduction strategies. The app, called 'Budd', was developed using the Intervention Mapping Protocol (IMP), in co-design with stakeholders and chemsex participants and was launched in April 2022. A dedicated article describing the three-year process of development was published elsewhere (10).

During Budd's development process, chemsex participants were consulted three times. During a first consultation round, twenty chemsex participants provided insight in their needs and adhered risk reduction practices (before, during and after a chemsex session) via in-depth interviews (11). The identified needs could be translated into content and features in the app to optimize its relevance. Adhered risk reduction practices were integrated as app components in order to improve the use and acceptability of the app. A second consultation round was organized among eight chemsex participants to pilot-test the proof of concept version of the app on usability and acceptability (10). In a third consultation, prior to launching the app, 11 chemsex users tested the final version of the app on its effectiveness. The results of this effectiveness study will be submitted for publication later.

During their eight-week participation in this effectiveness study, participants filled out a survey on their chemsex related behavior after each chemsex session they attended. The analysis of these data is presented in the current manuscript, implying that this is a sub-analysis using data collected during the effectiveness study. The data provide very concrete information per session and per participant. This may complement the perspective of interviews or cross-sectional survey studies, where people reflect and describe their behavior over a period of time, following a chemsex event. Results stemming from studies using these qualitative (interviews) and cross-sectional study designs are potentially very interesting yet limited in their validity by recall bias that may occur. The goal of this paper is to describe very precisely chemsex participants' experiences with drug use, STI prevention and sexual consent when participating in chemsex sessions.

2. Methods

2.1. Study design

The data presented below describe participants' behavior during chemsex sessions before and during their access to the Budd-app, regardless their use of the app. Therefore, for the data-analysis presented here, case study or descriptive analysis may fit the design. The overarching effectiveness study however had a single case design with the introduction of an intervention (access to the Budd-app) during the study period. Using a single-case design is nowadays becoming more common in psychology, to study behavior and behavior change (12). It is characterized by the systematic and repeated measurement of a dependent variable in a small group of participants. It is especially useful in small or heterogeneous populations (where a randomized controlled trial is not feasible), for behavior that does not occur very often and/or for intervention studies with a limited study period, as it provides insights in the personal use and effect per participant in a relatively small sample size. Therefore, a single case design seemed the most appropriate way to describe drug behaviors, STI prevention and sexual consent during chemsex sessions.

2.2. Study setting

The study was conducted at the Institute of Tropical Medicine (ITM) in Antwerp, Belgium. The outpatient clinic at ITM consists of an HIV treatment center, PrEP consultation and low-threshold HIV/STI testing center. Participants were recruited via these channels. Although participants needed to visit the clinic for enrolment, the data we present here were collected during the study period, and were self-collected in the app. Therefore, a specific visit to the clinic was not required to fill in the information.

2.3. Study participants

GBMSM who reported to engage in chemsex were eligible for participation. Additional inclusion criteria were age above 18 years, identification as member of the LGBTQ+ community, intentional combination sex and drugs in the previous two months, understanding English or Dutch well, and owning a smartphone.

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A convenience sample of patients attending ITM's HIV/STI clinic were approached to participate in the study. Participants were selected by health care providers who consult in the clinic. Additionally, a leaflet was sent out via social media (by Sensoa, the Flemish center of expertise on sexual health); no participants were recruited via the latter approach. In order to generate solid results from our SCD, we aimed to include 10 participants for the full study period. Twelve participants had been enrolled. One participant was excluded during the study as he did not fill in the required surveys. Data from 11 participants who completed the study were used for this analysis, who provided detailed information on their drug-related behavior, STI preventions measures and consent when having sex during 63 unique chemsex sessions.

The participants age ranged between 25 and 59 years old. The educational level of the participants was diverse and ranged from: no secondary school diploma ($n=2$), secondary school diploma ($n=3$), professional bachelor ($n=3$), and master ($n=3$). The vast majority of participants ($n=10$) were full-time employed. Most participants participated in chemsex on a weekly ($n=5$) or monthly ($n=4$) basis during the three months prior to their enrollment in the study (Table 1).

TABLE 1 Characteristics of the study participants $n=11$.

Variable	Categories	Number of participants
Age		
	25–29	3
	30–39	3
	40–49	2
	50–59	3
Educational status	No secondary school diploma	2
	Secondary school diploma	3
	Bachelor	3
	Master	3
	PhD	0
Employment status	Unemployed	1
	Employed (fulltime)	10
	Retired	0
Frequency chemsex	Daily	0
	More than once per week	1
	Weekly	5
	Monthly	4
	Less than once a month	1

2.4. Measures

Chemsex risk behavior was assessed via a risk-taking behavior questionnaire. This questionnaire was based on the chemsex-related risk behaviors that resulted from the needs assessment as part of the first consultation round in the app development process. The health problem of 'participating in chemsex' was conceptualized through previous research (literature study), a brainstorm with a large group of stakeholders, project team and advisory board, as well as via own research (in-depth interviews) (11).

The risk-taking behavior questionnaire contained 14 questions, divided into two overarching categories: high-risk drug use and high-risk sexual practices. For this analysis, we select answers on ten questions reflecting seven variables: (1) which drugs participants use, (2) duration of chemsex session, (3) dosing products safely, (4) avoiding STI transmission, (5) experiencing negative effects (during and after chemsex), (6) experiencing peer pressure (sexual and drug-related), and (7) consent (reciprocal). The complete 'risk-taking behavior questionnaire', and how we computed the answers for this analysis is described in Supplementary Table S1.

The participant was asked to complete the questionnaire at least twice during the study period. Each participant completed the questionnaire in the Budd app the day after having had participated in a chemsex session.

2.5. Statistical analysis

For this analysis, data are descriptive only, no statistical analysis was carried out.

2.6. Ethical statement

Ethical clearance was obtained from the Institutional Review Board of the Institute of Tropical Medicine in Antwerp (reference 1520/21; September 8th, 2021).

3. Results

In total, 11 participants provided information on 63 chemsex events. Participants reported behavior when participating in chemsex during a period of median 11 weeks and 5 days (ranging between 8 weeks, 5 days and 13 weeks). In this period, participants attended a mean of 5.7 chemsex sessions (median 4), ranging between 2 and 11 sessions. The mean duration of a chemsex session was 17.5 h (median 13 h), ranging between 2 and 48 h per session. Per session, participants used a mean of 3.5 different substances (median 4; range: 1–7). During three events (5%) one drug was used. In 95% of the events, different drugs were combined ('polydrug use').

Below, in Table 2, we present the results from the substances used during the chemsex sessions in the study, from the perspective of the used substance (which product is used how many times?; Table 2) (4, 13).

We additionally created a table where we present the results from the substances used during the study from the perspective of the participant (which participant used which product?). We categorized the substances according to the review article by Strong and colleagues (4). We included the cathinone 3MMC, also referred to as 'metaphedrone', in category 1 as it is very similar to mephedrone (4MMC) (14). We add this table as Supplementary Table S2.

In Table 3, we present the detailed behaviors with regards to dosage of substances, STI prevention measure people take, experienced peer pressure (both sexual and substance-related pressure) and reciprocal sexual consent during chemsex sessions. With regards to the participants, we categorize a specific behavior if

the participant reported this behavior at least once. This does not imply that this participant reports this behavior for every chemsex session he has attended.

4. Discussion

This study is the first where men who engage in chemsex systematically report their behavior for each separate chemsex event during a specified period of time. Although the number of participants in the study is too small to make absolute statements and their profile is heterogeneous, the information on the total number of chemsex sessions ($n = 63$) is considerable.

In our study, the two most commonly used products were GHB/GBL (used during 75% of the events) and the cathinone 3MMC (70%). The latter, also referred to as 'metaphedrone' is related to mephedrone (4MMC), which falls first category described above (4), as well as within the 'narrow' chemsex definition from the UK (1). Although in recent years this narrow definition has been broadened (to other substances), GHB/GBL and cathinones seem to remain the 'core' of chemsex use in our studied population, together with crystallized metamphetamine ('crystal meth'). Metaphedrone (3MMC) seems to have replaced mephedrone when the latter became illicit. When we sum both cathinones mephedrone and 3MMC, it becomes the most commonly used drug ($n = 52$; used during 83% of the events). When considering the 'number of participants' as denominator (instead of the number of events), all participants reported the use of at least one 'category 1' substance: 2 participants report the use of one of these substances (18%), 7 used two (64%), and 2 (18%) all three of the 'category 1' drugs (GHB/GBL, 3MMC/4MMC, crystal meth).

Although the number of participants in our study is small, our findings are in line with results from recent qualitative and cross-sectional studies in our surrounding countries. Cathinones were found to be the most commonly used drug during chemsex research in France, followed by GHB and cocaine (7). In a study in the UK, mephedrone was the most common reported drug, followed by GBL and crystal metamphetamine (13). In a study in The Netherlands, Ecstasy/MDMA was most reported drug, followed by GHB (15). The frequent use of mephedrone and Ecstasy/MDMA may not be surprising as their effect is similar: alertness, feeling more empathic, and a positive effect on sexual desire (14).

In other European countries, methamphetamine (Spain), GHB/GBL (Norway, Spain, The Netherlands), and cocaine (Norway, France and Italy) were reported as frequently used drugs in a sexual context (16–18). Polydrug use is also very prevalent in our study: all participants reported the use of more than one substance, during 95% of all events. This is higher compared to studies in The Netherlands, United Kingdom and France (7, 15, 19, 20).

While being under the influence of drugs, chemsex participants seem to pose multidimensional 'risky' behavior: drug-related, related to their sexual health and related to their social situation. By crossing boundaries, people may experience adverse impact from their chemsex participation. The majority (9/11) reported their own boundaries were crossed, resulting in non-consensual sex; the same number of participants reciprocally did not respect others' boundaries (9/11). This aspect of consent is particularly concerning, and requires more attention in chemsex research as findings show that sex without consent (or sexual violence) is reported in different studies. In the Netherlands, 58 of 273 men who participate in chemsex (21.1%) reported a non-consensual sexual experience in the past 5 years (21). In studies in the United Kingdom, the United States and Germany, the number of respondents who reported sexual violence and sex without consent was even more prevalent, with percentages between 43 and 48%. Moreover, participants who engaged in chemsex were up to 12.5

TABLE 2 Frequency of use, per product.

Product	Number of occasions used (%)
Category 1	
GHB/GBL	47 (74.6)
3MMC	44 (69.8)
Crystal meth	8 (12.7)
Mephedrone	8 (12.7)
Category 2	
Amphetamine	30 (47.6)
Ketamine	15 (23.8)
Ecstasy/MDMA	11 (17.5)
Cocaine	9 (14.3)
Category 3	
Poppers	26 (41.3)
Alcohol	17 (27.0)
Weed/hash	8 (12.7)
Total	223

TABLE 3 Reported behaviors, number of participants, and events.

		Participants (%)	Events (%)
Dosage and impact	Unsafe dosage	9 (81.8)	31 (49.2)
	Negative impact *during* event	7 (63.6)	21 (33.3)
	Negative impact *after* event	8 (72.7)	21 (33.3)
STI prevention	No preventive measures	7 (63.6)	20 (31.8)
Peer pressure	Peer pressure sex	9 (81.8)	31 (49.2)
	Peer pressure chems	9 (81.8)	36 (57.1)
Consent	Personal boundaries were not respected by other people	9 (81.8)	24 (38.1)
	I did not respect other peoples' boundaries	9 (81.8)	19 (30.2)

times more likely to experience sexual violence than their counterparts who did not engage in chemsex (22–24).

The majority of participants in the study reported dosing the substances 'unsafe', and experienced peer pressure and negative impact, including physical, psychological and social health harms, during and after the chemsex session. Related to their sexual health, the majority experienced peer pressure, and reported not having taken necessary preventive measures on at least one occasion. Of course, not every participant experiences all aspects (e.g., non-consensual sex, peer pressure) during each and every event. Nevertheless, peer pressure is experienced with regards to drug use during 57% of the events, peer pressure for sex in 49% of the events. Unsafe dosage is also reported in almost half of the events (49%). All other aspects (experiencing negative impact during and after the event, no preventive measures taken, and not respecting personal boundaries in two directions) are reported in 30–38% of the events (data not shown). These results confirm that, although similarities are obvious (e.g., polydrug use), chemsex can be experienced differently (e.g., frequency of participation, duration of a chemsex session, substances used).

We can identify some limitations in the study: we enrolled a convenience sample, thereby insufficiently controlling for participation bias. Moreover, the limited number of participants implies that the findings from this study cannot be generalized. Lastly, the limited number of variables assessed may obscure a multi-faceted picture of one's individual situation and experiences. However, as participants were requested to provide information repeatedly, we balanced the comprehensiveness of the questionnaire with participants' repetitive efforts to provide the same information. Despite these limitations, our study provides a snapshot of drug related behavior, sexual behavior and consent among a group of men engaging in chemsex using a study design that prevents recall bias. By assessing behavior during multiple chemsex sessions, 'within-person' variability can be clarified (one person can do different things during different chemsex sessions). This clarification may give insight in personal, emotional and contextual vulnerabilities which can be tackled during an individual care and support trajectory.

5. Conclusion

We consider a better insight in how people behave during chemsex events an important research question. First, to help in closing the scientific knowledge gap on the actual behavior during chemsex. The development of the Budd-mobile health intervention (10) was scientifically supported via the Intervention Mapping Protocol (25). Secondly, and potentially more relevant than the scientific knowledge, we hope that our findings support the improvement and optimization of care and support for people who engage in chemsex.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of the Institute of Tropical Medicine in Antwerp (reference 1520/21; September 8th, 2021). The patients/participants provided their written informed consent to participate in this study.

Author contributions

TP and CH collaborated equally in the set-up, execution of the study, analysis of the results, and writing the manuscript. EF, KP, and HV were involved in setting up and executing the study and provided valuable feedback on the manuscript. PV provided statistical and methodological advice in the set-up and analysis of the study and provided feedback on the manuscript. LA was involved in the enrolment of the participants and provided valuable feedback on the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1160087/full#supplementary-material

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Sexual healthcare and at-home STI test collection: attitudes and preferences of transgender women in the Southeastern United States

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Background: HIV and sexually transmitted infections (STIs) disproportionally affect transgender women in the United States, particularly in the Southeast where rates of HIV and bacterial STIs are especially high. Despite the high HIV/STI burden among transgender women, their engagement in sexual healthcare services, including HIV/STI testing, is low. Understanding reasons for this disconnect is essential in developing HIV/STI prevention efforts for this population, especially in the Southeastern US, where access to affirming sexual healthcare providers and resources is limited. We aimed to perform an exploratory qualitative study to describe the attitudes and preferences of transgender women living in Alabama with regards to sexual healthcare and at-home STI test collection.

Methods: Transgender women ≥18 years old residing in Alabama were invited to participate in virtual individual in-depth interviews via Zoom. The interview guide explored participant experiences engaging with sexual healthcare services as well as preferences related to extragenital (i.e., rectal, pharyngeal) and at-home STI testing for gonorrhea and chlamydia. A trained qualitative researcher coded transcripts after each interview and iteratively amended the interview guide as themes emerged. Data were coded and thematically analyzed using NVivo qualitative software.

Results: Between June 2021-April 2022, 22 transgender women were screened and 14 eligible women enrolled. Eight participants were white (57%), and six were black (43%). Five participants (36%) were living with HIV and engaged with HIV care services. Interview themes included preference for sexual healthcare environments specializing in LGBTQ+ care, enthusiasm toward at-home STI testing, an emphasis on affirming patient-provider interactions in sexual healthcare settings, a preference for sexual healthcare providers involved in STI testing who were not cisgender men, and gender dysphoria around sexual health discussions and testing.

Conclusion: Transgender women in the Southeastern US prioritize affirming provider-patient interactions, however resources in the region are limited. Participants were enthusiastic about at-home STI testing options, which have the potential to mitigate gender dysphoria. Further investigation into development of remote sexual healthcare services for transgender women should be performed.

KEYWORDS

at-home testing, qualitative research, sexually transmitted infections, transgender, sexual health

Introduction

In the United States, it is estimated that between 14% and42% of transgender women are living with HIV (1, 2). Despite this immense disease burden, uptake of effective HIV prevention strategies such as Pre-Exposure Prophylaxis (PrEP) remain low in this population, especially in the Southeastern US (3). Reasons for this are multifactoral, including limited access to gender-affirming healthcare providers and services, intersecting stigma associated with PrEP and transgender identity, and concern for drug-drug interactions between PrEP and hormone replacement therapy (4, 5). Furthermore, the Southeastern US accounts for the most of the new HIV infections annually and is home to a growing population of transgender individuals (6). Thus, a better understanding of how to increase PrEP uptake among transgender women in the Southeastern US is essential in efforts toward ending the HIV epidemic.

One crucial component of PrEP care is routine bacterial STI (i.e., gonorrhea, chlamydia, syphilis) screening, because individuals taking PrEP experience an increased incidence of STI infection and bacterial STIs are also common among transgender women (7–9). The risk of HIV transmission may double in the setting of a bacterial STI co-infection, making frequent STI screening a priority for patients on PrEP to optimize its efficacy (10). Depending on sexual practices, extragenital STI testing (i.e., testing at rectal and/or pharyngeal sites) for bacterial STIs is also an important consideration for transgender women taking PrEP. Despite this, clinicians frequently limit specimen collection to urogenital sites, which can miss a large proportion of extra-genital STI infections (11).

Routine STI testing is also an essential part of sexual healthcare for transgender women living with HIV. A retrospective cohort study found that chlamydial infection from extra-genital sites in 312 transgender women living with HIV accounted for 80% of positive results and extra-genital gonorrhea accounted for 82% of positive results (12). Given that the sexual behaviors of some transgender women (i.e., receptive anal intercourse) may lead them to be at risk of extragenital STIs, developing inclusive and acceptable means of STI screening/testing in this population are essential to promote engagement in HIV prevention and sexual healthcare services.

Access to trans-affirming STI screening/testing is not only an essential component of PrEP care for transgender women, but is also a necessary service for transgender women who are sexually active, regardless of their HIV status. Unfortunately, a major barrier to access to sexual healthcare for this population is the stigma and discrimination transgender women often experience in healthcare settings (13). In the Southeastern US, these issues are further compounded by limited sexual healthcare resources serving LGBTQ+ populations. As such, transgender women may have unique preferences related to STI screening/testing in this setting. In a pilot study previously conducted by our team (4), transgender women in the Southeastern US identified STIs to be a major concern in their communities. In the current qualitative study, we explored community-specific considerations among transgender women living in Alabama regarding receipt of sexual healthcare services including STI screening/testing in general and as a part of HIV PrEP care.

Methods

The purpose of this exploratory qualitative study was to describe the experiences of transgender women living in Alabama. This study asked how transgender women's general experiences in health care settings shape their openness to seeking sexual health care as well as their perceptions of at-home STI testing, given their previous health care experiences. A phenomenological approach was adopted for this study due to the limited information available in the existing literature that describes transgender women's experiences with sexual health care in their own words (14).

Eligible participants were ≥18 years old, identified as transgender women (i.e., assigned male at birth and identify as female) and resided in the state of Alabama. Exclusion criteria included not speaking English and being unable to participate in an individual virtual interview using Zoom (because the study was conducted during the COVID-19 pandemic). Given both the high prevalence of HIV within this population as well as the high STI burden experienced by transgender women, regardless of HIV status, all transgender women were allowed to enroll. Participants were recruited through flyers posted in locations around the Birmingham and Huntsville, Alabama metropolitan areas, including local clinics and community organizations serving transgender individuals, bars, clubs, art galleries, and locations across the University of Alabama at Birmingham (UAB) campus. Participants were also recruited via referrals form clinicians at the UAB Gender Health Clinic (GHC). Participants received a $50 Visa gift card for their participation in the study.

This study was approved by the UAB Institutional Review Board (IRB) (protocol #IRB-300005085). Participants provided verbal consent, including consent for audio recordings, before beginning of the in-depth individual interviews. The participants were emailed a copy of the consent form prior to the interview for review. Participants verbally consented with study staff who documented this on a printed version of the consent form. This consent process was approved by the UAB IRB and was completed prior to participation in any study-related activities.

In-depth interviews

After verbal informed consent and permission for audio recording were obtained via Zoom, participants completed an interviewer-administered socio-demographic survey, which included questions on age, race/ethnicity, insurance status, sexual history, STI history, details regarding gender transition, and history of PrEP use. Transgender women living with HIV were not asked questions pertaining to PrEP.

Following completion of the questionnaire, an in-depth individual interview (IDI) was conducted using a script to facilitate discussion (Figure 1); the interviewer (author OVG) is a cisgender women and sexual health care provider with 9 years of experience working with LGBTQ+ populations. Participants were asked about their experiences in sexual health care settings, particularly related to obtaining HIV/STI testing. They were also be asked about their impressions of at-home self-collected STI testing kits and materials, specifically the acceptability and appropriateness for use

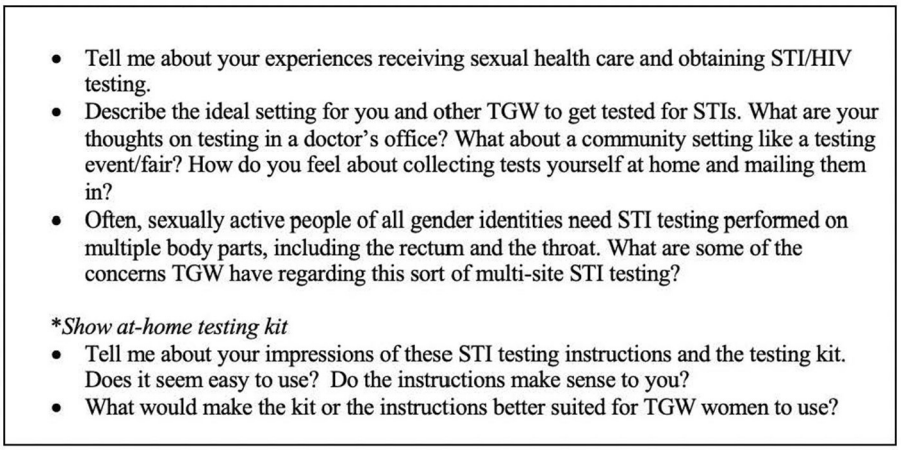

FIGURE 1
IDI script.

by transgender women. Sample at-home self-collected STI testing kits, including the collection materials and instruction documents, were also shown to participants (Supplementary Figure 1). These kits included extragenital and urine specimen collection materials as well as lancets and dried blood spot cards to be used for HIV testing. This was both to provide a visual reference for participants for this type of testing and to ensure that all instructions and infographics were acceptable for use by transgender women. All interviews were audio recorded via Zoom and uploaded to UAB Box on an encrypted, password-protected computer. They were later transcribed verbatim by a professional transcription service.

Qualitative data analysis

A descriptive phenomenological approach was used in this work (15, 16). The initial in-depth interview script was developed based on the lead author's experience as a physician providing sexual health care to transgender women; this script was iteratively revised throughout the data collection process to explore emerging themes and to further examine conflicting perspectives. Memos of emerging issues and discussions within the research team were used to document the initial stages of data analysis. Once data collection was completed, the lead author conducted a review of all interview transcripts and began developing thematic codes. Using NVivo qualitative software, all transcripts were coded; these initial codes were further reviewed by a second member of the research team (author ELA) to ensure reliability and to check for potential bias resulting from the lead author's identity as a health care provider (17).

Results

Sample characteristics

Between June 2021 and April 2022, 22 transgender women were screened for eligibility in this project. Those who were not enrolled were either lost to follow up or no longer wished to participate when they were contacted to schedule an IDI. A total of 14 transgender women enrolled in the study and completed an IDI. Sociodemographic characteristics of the enrolled participants are described in Table 1. The mean age of participants was 33 years old (SD 10 years). Eight participants were white (57%), and six were black (43%). Five participants (36%) were living with HIV and all of them were engaged with HIV care services. Participants reported a variety of genders of their sexual partners, with the most reporting sex with cisgender men (71.4% [$n = 10$]). Of note, participants could select multiple options when reporting the genders of their sexual partners. In addition to genders of sexual partners, participants reported the following sexual orientations: gay/homosexual ($n = 7$), pansexual ($n = 5$), bisexual ($n = 1$), straight/heterosexual ($n = 1$). More than half reported having a history of an STI ($n = 8$) and 28.6% ($n = 4$) reported having participated in transactional sex at some point in their lives. One participant reported having a gender-affirmation surgery, which was an orchiectomy. Of the participants who were not living with HIV ($n = 9$), all had heard of PrEP, but only one (11.1%) reported a history of PrEP use.

Major themes

Preference for sexual healthcare environments specializing in LGBTQ± care

Participants reported that care environments with specialization in LGBTQ+ healthcare services were preferred when pursuing their sexual healthcare needs. Given this type of provider expertise in queer health, participants reported more affirming experiences than with other types of healthcare providers. They cited trauma associated with going to clinical spaces in general, particularly related to being blatantly discriminated against by staff at all levels (i.e., receptionists, nurses, physicians, etc.). Many recounted experiences they had had in non-LGBTQ+ specializing healthcare venues as being cold and insensitive.

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TABLE 1 Sociodemographic data for transgender women participants in the Southeastern U.S. ($n = 14$).

	N (%) or Mean ± SD
Age	33 ± 10 years
Race/ethnicity	
Black, Hispanic	1 (7.1%)
Black, non-Hispanic	5 (35.7%)
White, non-Hispanic	8 (57.1%)
Gender of sexual partners	
Transgender women	4 (28.6%)
Transgender men	2 (14.3%)
Cisgender women	5 (35.7%)
Cisgender men	10 (71.4%)
Genderfluid individuals	1 (7.1%)
Self-reported sexual orientation	
Gay/homosexual	7 (50.0%)
Pansexual	5 (35.7%)
Bisexual	1 (7.1%)
Straight/heterosexual	1 (7.1%)
Self-reported STI history	8 (57.1%)
Living with HIV	5 (35.7%)
Participation in transactional sex	4 (28.6%)
Currently using HRT	11 (78.6%)
History of gender-affirmation surgery	1 (7.1%)

HIV, human immunodeficiency disease; HRT, hormone replacement therapy; SD, standard deviation; STI, sexually transmitted infection.

> *"[the workers at non-LGBTQ+ focused clinics] are just not educated on trans people or gay people, but I just feel like they're insensitive and just like rude. Like even when they took my blood they kind of just like stuck me and it was very like aggressive; it wasn't like empathetic or anything like that."*
>
> *"So [at a local LGBTQ+ focused clinic], I'm not as worried about because I don't feel threatened, but if I were outside [that clinic in the main healthcare system] like in a different hospital room, you know, and it was something real sensitive like I was doing bottom surgery or discussing something about that may be different on a cis person I would rather not be in a room with someone overhearing all that."*
>
> *"I would say by virtue of being at [a local LGBTQ+ focused clinic], like I just feel like it's sort of like a self-selecting thing like you're not going to be volunteering or working there if you have negative ideas about trans people, you know, which is what sort of led me to wanting to go there and, you know, maybe even deal with a less efficient and profession, I guess, like operation because I knew like no matter what nobody's gonna look at me weird, everybody's gonna be like affirming and accepting…"*

Many participants reflected specifically on negative experiences in non-LGBTQ+ focused care environments related to being misgendered, often intentionally, by clinic staff.

> *"So I kept getting called 'he', I kept getting called by my real name. It was like they was stating facts about me that I already knew. It was just… I don't know, it was just… it wasn't a pleasant… pleasant experience."*
>
> *"Interviewer: So they misgendered you.*
>
> *Respondant: A lot, even after it was corrected they still… well, they was like, well, I'm goin' by what I see in the computer and what I see in the books. But I'm like… but look at me… you know, but-…*
>
> *Interviewer: Yeah, I'm a person in front of you, telling you that's not my name."*

They also endorsed appreciating the LGBTQ+ representation in these focused care environments. Particularly, they acknowledged feeling more comfortable receiving sexual healthcare in a place with visible signs of transgender allyship (i.e., flags, posters, displays of staff pronouns) as well as openly LGBTQ+ staff. LGBTQ+ representation was seem as reassuring that participants would be cared for in an affirming manner.

> *"… it's as simple as like just seeing the pronouns in someone's bio or like their display name or something, just in and of itself like, you know, virtue signaling in like a good way."*
>
> *"But they have been super welcoming. When you first walk in the area… the lobby is very welcoming. There's two queers behind the counter doing all the intake and paperwork, so I automatically feel very, uh… one of them is actually trans feminine, so that, you know, made me feel a lot more comfortable."*

Enthusiasm toward at-home STI testing

When presented with the option of self-collection of STI test specimens in the home, namely for urogenital and extragenital gonorrhea and chlamydia, participants were enthusiastic. They also cited that the kits seemed easy to use. Several participants did acknowledge, however, apprehension around performing STI testing that requires a finger stick using a lancet or needle (i.e., syphilis and HIV testing). However, they cited both privacy and convenience as appealing aspects of an at-home testing option. Participants expressed that their desires for these attributes came from a long history of mistrust of the medical system and fear of being in physical danger in sexual healthcare settings. In addition, participants expressed that the option of at-home test collection removes the need for transgender women to discuss the details of their anatomy, sexual behaviors, or other potentially uncomfortable details directly with a healthcare provider.

> *"I hate to say it, but like especially with the trans community, we have like typically such a large distrust with doctors because… or the medical field in general, that if we are given the slightest chance to do it ourselves instead and like be maybe within the comfort of our own homes or whatever to do that kind of thing, we will do that because that is much nicer than like having to go out and do it."*

> *"I personally would like doing it either at home or doing it myself and… just don't wanna be like naked around a stranger and how much of it is, you know, would actually be a worry of some sort of like negative interaction because I was trans or something."*
>
> *"…people are nervous and anxious when it comes to sharing the intimacy of those details with people they don't know, especially a medical provider, and, you know, just the physical of having someone swab in places like that is a little discomforting. I personally think that at-home testing could be and may as well, already is, revolutionary in terms of making sure people are being tested correctly."*

Participants also stated that having access to at-home STI testing provided a sense of empowerment around sexual health promotion. They stated that they may be more likely to utilize this resource than if an at-home testing option were not available.

> *"And it would be convenient to know what type of testing you can have done, whether you need to go through a doctor or whether it's something you could approach the clinic and just have simply done yourself, and then have that information readily disseminated out into the population in some sort of public awareness."*

Emphasis on affirming interactions between providers and patients in sexual healthcare settings

Participants not only sought to receive sexual healthcare services in LGBTQ+-focused care environments, but also emphasized the importance of certain characteristics of the clinician-patient relationship. Preference was expressed for providers who demonstrated warmth and passion about their job. It was important to participants to feel genuinely cared for by their providers. This was especially important given the potential for discussion of sensitive topics such as sexual history and behaviors as well as exams involving genitalia. Some participants discussed negative experiences they had had in sexual health care settings which involved staff being rude and judgmental, especially when a visit was specifically for STI testing. Participants preferred providers who treated sexual health care and STIs as normal parts of the human experience as opposed to stigmatizing patients who may present for such testing.

> *"… I feel like that they actually do care about your health instead of just doing their job; it's more than just their job to them. They actually do care."*
>
> *"And it does mean a lot to me to be able to go into a doctor's office and be able to have a conversation with the person who's sticking needles in me and taking my blood instead of just kind of it being a very clinical thing and then I leave."*
>
> *"I feel like in a field like [sexual health] you kind of have to be empathetic and compassionate and not like rude, and a lot of them are just very rude. Like going [to a local health department] I just feel like you walk in and just all eyes on you, like, oh, they have an STD, and it's a very uncomfortable environment, at least for me."*
>
> *"So I feel like at UAB they make you feel human and like, you know, things happen. It's not like, oh, you did this to yourself; it's just, you know, stuff happens, gotta move forward, we'll teach you, you know, what to do to keep yourself protected, give you condoms."*

Preference for sexual healthcare providers who were not cisgender men

When having STI testing done in the clinic setting, participants overwhelmingly preferred female providers to male providers. In fact, they cited that one of the benefits of being able to do at-home, self-collected STI testing was avoiding encountering male health care providers or clinic staff. Several themes emerged as to why female providers were preferred. One was that transgender women feel sexually fetishized by men, even in clinical settings. Participants expressed unease with the potential for a male provider deriving sexual pleasure from providing sexual health services such as STI testing to transgender women patients.

> *"We are typically seen as like only doing it for sex or sexual pleasure or whatnot, and so it kind of, um… we kind… we, again using we instead of me… I kind of fear that like a cisgender heterosexual man might feel that way about me and think that he can use me for sexual pleasure."*
>
> *"…not because I necessarily would think that they're a bad person, but in the back of my head, trans women in particular are fetishized in pornography and it's a large percentage of online pornography consumption, and even in a clinical environment in the back of my head I would probably have this question of is this some kind of weird thrill for them."*

Participants also expressed a preference for female providers for several reasons. They noted that, in general, female providers tend to have a more natural understanding of the female experience. Several participants also cited that female providers tend to be more affirming and understanding in terms of gender diverse patients.

> *"Respondent: No, with a female doctor it's not a problem, but with a male, yeah.*
>
> *Interviewer: Okay. Tell me more about that. What are the concerns there?*
>
> *Respondent: My concern is a male doctor … they don't understand what I go through. Now with a woman, they're more like… like they understand, they do. And they talk to me more better because they can relate to me what I'm stressin' about, but with a male I become scared because they don't know what I go through, they don't know how I'm feelin', they don't know half the stuff I've dealt with."*
>
> *"Respondent: … I would always feel more comfortable with like a woman doing it, yeah.*
>
> *Interviewer: Okay. Can you speak more as to why that is?*
>
> *Respondent: Yeah, maybe just my own personal biases, honestly, I just generally that expect of the two options that the odds are the woman is going to be more understanding and it's*

> *more likely that she's either going to be like directly affirming or just also has experiences as a woman and so it's more likely that it will be a positive interaction from my experience."*

Gender dysphoria exacerbated by sexual healthcare encounters

Gender dysphoria associated with various components of receiving sexual healthcare were also described by participants. Feelings of dysphoria around sexual healthcare environments were viewed as negative and, therefore, made participants apprehensive about engaging with such services. Specifically, participants cited conversations referring to tests in a gendered way that were particularly dysphoric. For example, labeling testing materials for men or for women based on the test needing to be performed on a penis or a vagina, respectively, was not preferred. Instead, emphasis was placed on making testing and sexual health discussions center around a patient's specific anatomy. Participants also said that discussing their genitalia and anatomy on an as-needed basis only was important to them. They said that if such information was not needed to provide optimal sexual health care, then discussions of their genitalia should be avoided. Reasons for this included the acknowledgment that many transgender people experience genital dysphoria if they have not yet undergone any gender-affirming surgeries and that clinicians inquiring about their genitalia are often viewed as curiosity on the behalf of the provider as opposed to necessary for their medical care.

> *"…One of my worries… and it goes back to the anatomy and stuff… some part of that interaction sort of like triggering some sort of dysphoria, like I guess I would say the big thing is not saying… this is the test for women or something like that… [but instead] maybe making it anatomy specific and not gendered at all."*
>
> *"I think trying to strip away all of that until it becomes absolutely necessary, so, you know, what do you need to be tested for… let them describe the symptoms instead of asking them do you have this coming out of this, because that person sitting in front of you might not have those, and now you've just put them in an uncomfortable position because what if they have genital dysphoria and you've just really hammered home that you thought they had so and so."*

Participants also acknowledged that sexual health care differs from other sorts of routine care in its content and that because of this, transgender patients may feel more discomfort or dysphoria discussing their bodies or having invasive examinations performed that involve their genitalia.

> *"I think a lot of trans people to start with, even before transition, are uncomfortable with their bodies and so they may be more hesitant to take part in exams that are more personal and more invasive than the standard tongue depressor in your mouth sort of a thing, only because there's that extra level of dysphoria that you may not be dealing with, with a regular patient."*

Discussion

This study augments previous work done by our team exploring the preferences of transgender women in Alabama regarding how they receive sexual healthcare (4). In the wake of the COVID-19 pandemic, telehealth and at-home healthcare technologies are now a permanent fixture in care delivery, both in the US and worldwide (18). Acceptability and development of such technologies for PrEP and STI testing have been promising in recent years (19–22). Thus, understanding how these options can be implemented to suit the unique needs and preferences of populations who may access PrEP or frequently need STI testing, including transgender women, is essential.

In this study, a sample of transgender women in Alabama expressed insights regarding best practices in the provision of sexual healthcare services to their community. Specifically, they highlighted the need for genuine relationships with affirming providers in LGBTQ+ dedicated spaces as well as enthusiasm (excitement) for at-home STI testing. Their reasons for desiring at-home STI testing underscore several ways in which health care in the Southeastern US is currently failing this population. The transgender women in our study desired to test at home because of privacy and the ability to avoid potential negative interactions with health care staff and providers. Previous studies of providers working with transgender patients, including those with HIV, have noted perceived barriers including lack of care accessibility and security, providers' misunderstanding of the transgender community, and lack of cultural competency of information systems and staff (23). Stigma toward this community, particularly transgender women living with HIV, is also prevalent (24). Although participants acknowledged the existence of some exemplar gender-affirming care providers in the region, such resources are limited in the state of Alabama. The results of our study should serve as a call to action for improved provision of gender-affirming care for transgender people, including sexual health services. Most notably, a patient-centered approach to transgender care where patients are treated with compassion and understanding is desired by patients, especially in sexual healthcare settings. In addition, given the need for routine STI testing for patients on PrEP, these approaches may also serve to increase uptake of PrEP and its consistent use among this population.

Participants also cited that the sample at-home STI testing kits appeared to be both easy to use and acceptable for use among transgender women. Overall, when developing such resources, investigators and manufacturers should avoid using gendered language in the patient facing instructional materials used for testing. Community involvement and vetting of language and schematics should be prioritized. Stakeholders of the transgender experience offer the most accurate and informed perspective on how such materials should be developed.

Finally, these results highlight the need for comprehensive, gender-affirming healthcare services for transgender people in the sexual healthcare setting. This not only entails the clinician-patient interactions that take place, but the overall culture and atmosphere of clinical spaces in which transgender women receive care. Representation and celebration of transgender identity by clinic staff at all levels play an integral role in patients engaging

in sexual healthcare services. While at-home testing for STIs is a promising and important option for patients, there are still times when patients need to access in-person services. Enhanced medical education and LGBTQ+ cultural competency training for all providers and staff are key first steps to creating such a culture. Enhancing patient engagement in sexual health services through the creation of such environments will help to combat the STI epidemic faced by gender diverse populations.

This study had several limitations. Given that interviews were conducted during the COVID-19 pandemic, our recruitment period was delayed and IDIs were conducted virtually over Zoom. While use of Zoom was helpful in terms of including transgender women from various parts of the state outside of the Birmingham, AL metropolitan area and allowing participants to discuss sensitive topics in the comfort of their homes where they felt the safest, the dynamics of in-person interactions were missing. Specifically, detailed reading of body language cues and more interactive demonstration of testing kits was not possible. One important point that was not discussed in these IDIs was the role of cost regarding at-home STI testing. There were some mentions from participants that affordable testing was preferred, but this theme was not explored in this study and should be investigated in future work. We also recognize that the healthcare landscape for transgender individuals in Alabama is not nationally or globally representative. Currently, the transgender people and the healthcare providers caring for them in Southeastern US experience unique culture and legal challenges in providing gender-affirming healthcare that are clearly reflected by the limited resources and in-person interactions expressed by participants. These include ongoing legislative efforts aimed at limiting, banning, or criminalizing the provision of gender-affirming healthcare for transgender individuals in this area (25, 26).

In conclusion, transgender women prioritize affirming provider-patient interactions; however, gender-affirming sexual health resources in the Southeastern US are limited. Given these regional limitations and enthusiasm for at-home STI testing options, further investigation into developing remote sexual healthcare services for transgender women are of interest.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by University of Alabama at Birmingham Institutional Review Board. Written informed consent was obtained from all participants for their participation in this study and was approved by the University of Alabama at Birmingham Institutional Review Board.

Author contributions

Study conception and design: OV, EA, PS, and CM. Data collection and draft manuscript preparation: OV and CB. Analysis and interpretation of results: OV and EA. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

OV has received research grant support from NIH/NIAID, Abbott Molecular, and Gilead Sciences, Inc and also served on a scientific advisory board for Scynexis, for which she received honoraria. CM has received research grant support from NIH/NIAID, Lupin Pharmaceuticals, Gilead Sciences, Inc., Visby Medical, and Abbott Molecular, is a consultant for Lupin Pharmaceuticals, BioNTech, Scynexis, and Cepheid, and has received honoraria from Visby Medical, Elsevier, Abbott Molecular, Cepheid, Roche Diagnostics, and Lupin Pharmaceuticals.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1187206/full#supplementary-material

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A global bibliometric analysis of intimate partner violence in the field of HIV/AIDS: implications for interventions and research development

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This study aimed to explore the research landscape of intimate partner violence (IPV)—harm-induced behavior in an intimate relationship and HIV/AIDS to determine lessons learnt and gaps that may be filled by future research. Publications related to IPV, and HIV/AIDS published from 1997 to 2019 were collected from Web of Science (WoS). STATA and VOSviewer software tools were used for bibliometric analysis. Content analysis, common topics, and the map of co-occurrence terms were structured by Latent Dirichlet allocation and VOSviewer software tool. 941 studies were included. Factors associated with domestic violence and interventions to reduce IPV were the two most common themes. Meanwhile, mental health illness among pregnant women affected by HIV and IPV, and HIV-risk among youth suffering from IPV have not received adequate attention. We suggest that more research focusing on adolescents and pregnant women affected by HIV and IPV. In addition, the development of collaborative networks between developed and developing countries should also be addressed.

KEYWORDS

global mapping, intimate partner violence, domestic violence, HIV/AIDS, bibliometric analysis, IPV

1. Introduction

Intimate partner violence (IPV) is defined as a "behavior within an intimate relationship that causes physical, sexual or psychological harm, including physical aggression, sexual coercion, psychological abuse and controlling behaviors" perpetrated by a significant other (1). According to WHO, the global burden of IPV is often borne by women while the majority of perpetrators being males (1). While approximately 30% of women globally are victims of IPV (2), it may also

occur against males and in same-sex relationships. The prevalence of IPV among bisexual women, lesbian, bisexual men, and homosexual men were 61.1%, 43.8%, 37.3%, and 26.0%, respectively (3).

HIV/AIDS and IPV are major public health challenges with close intersection with each other. IPV is associated with HIV transmission, as indicated by lower rates of condom use among people with IPV (4). Furthermore, male perpetrators are more likely to engage in HIV-risk sexual behaviors, such as multiple partners, condomless sex, and/or drug use (5). For people living with HIV/AIDS (PLHA), IPV was significantly associated with poor adherence to antiviral therapy (ART) (6), negative impact on the engagement of women with HIV health care services (7–11), and heightened risk of poorer mental and physical health outcomes (12, 13).

Since IPV has been linked to significant challenges for HIV care, treatment adherence, and overall quality of life for PLHA, there have been recent efforts to characterize research trends and findings on the topic of IPV and HIV/AIDS. For example, a systematic review by Kouyoumdjian et al. evaluated 101 articles, including both qualitative and quantitative studies on the relationship between IPV and HIV (14). There have also been reviews focused on characterizing IPV and HIV interventions among women in sub-Saharan Africa (15), as well as a more recent review by Marshall et al. examining the efficacy of 14 international studies on interventions that address both IPV and HIV among women (16). While the previous systematic reviews provided in detail reliable and accurate summaries, they consume time and human resources (17). Meanwhile, some authors have used bibliometrics to explore the trend of research in IPV from 2005 to 2014 (18), or gender-based violence from 1982 to 2012 (19). Both studies showed an increase in the number of papers related to IPV and indicated new research topics, such as the relationship between IPV and HIV infection among pregnant women, during the study period. However, these studies did not include publications from 2015 up to 2019, and may not fully reflect the current trend. Also, they did not use context analysis to explore research topics and research disciplines.

To the best of our knowledge, there are currently no studies that examine the existing literature on IPV in HIV/AIDS studies using a combination of topic modelling and scientometrics approach. This study aims to evaluate the productivity of research quantitatively, examine the trend and research areas, and determine a visual network of international collaboration globally as well as explore research topics and research disciplines on IPV in HIV/AIDS publications. Our results could aid researchers, health care providers, and policymakers by informing them of the direction for future studies and interventions worldwide.

2. Methods

2.1. Database and keywords

In this scientometrics study, Web of Science Core Collection (WoS) was used for data collection. It has several advantages compared with other databases, including (1) allowing for the extraction of a large number of records with fundamental information (titles, abstracts, number of citations, number of download times, and research area), and (2) coverage of references since 1900 from high impact journals worldwide. The search strategy included two steps.

First, Topic search (Title, abstract, authors' keywords, and keywords plus) and Boolean logic AND/ OR were used for the keywords: "HIV," "HIV and AIDS," "Human immunodeficiency virus," and "Acquired Immune Deficiency Syndrome." Scientific papers from January 1, 2020 onward were excluded because the search process was conducted on March 28, 2020, and the papers up to March 2020 may not fully reflect the trend of that year. Hence, in this study, we included publications related to IPV, and HIV/AIDS published from 1997 to 2019. The publications chosen were research articles and research reviews in English. Other documents such as books, book chapters, or data papers and in any other language were excluded. The data were downloaded manually and independently by two researchers. Any inconsistencies in the results were checked by a senior researcher (e.g., missing records or missing information of data) and the downloads of the data were re-entered.

Secondly, we transferred text data into STATA for further filtering. Title and abstract search containing the phrase "Intimate partner violence" OR "domestic violence" OR "spouse violence" were extracted. Keywords for HIV and "Intimate partner violence" were contributed by health experts, Mesh terms (20), and previous studies (21). A final sample of 941 papers was used for further analysis.

2.2. Bibliometric analysis, text mining, and topic modelling

In this study, the bibliometric analysis was used to explore the trend in this research field. The final dataset was analyzed using STATA (version 15, StataCorp LLC, Texas, United States) by the following indicators: publication year, an annual number of publications, total and average counts of citation and download times per 6 months and 5 years. A network graph showing the collaboration among countries sharing co-authorships was visualized using VOSviewer software tool (22).

To explore the hidden topics of the dataset, a visualization tool by VOSviewer and topic modelling by Latent Dirichlet allocation (LDA), were used. In this study, the VOSviewer (version 1.6.8, Center for Science and Technology, Leiden University, Netherlands) was applied to illustrate the relationship between the most frequent terms in titles/ abstracts of selected publications. Additionally, a co-occurrence network and a country network were created using this software (Table 1). The dendrogram was applied to identify the hierarchical clustering of major research disciplines from selected papers. Analytical techniques for each data type were presented in Table 1.

In addiction, topic modeling was utilized by using the LDA technique to identify 10 latent topics from the titles and abstracts of

TABLE 1 Analytical techniques and outcomes of each data type.

Type of data	Unit of analysis	Analytical methods	Presentations of results
Keywords, countries	Words	Frequency of co-occurrence	Map of keywords clusters, countries
Abstracts	Papers	Latent Dirichlet allocation	10 classifications of research topics
WOS classification of research areas	WOS research areas	Haberman distance	Dendrogram of research disciplines

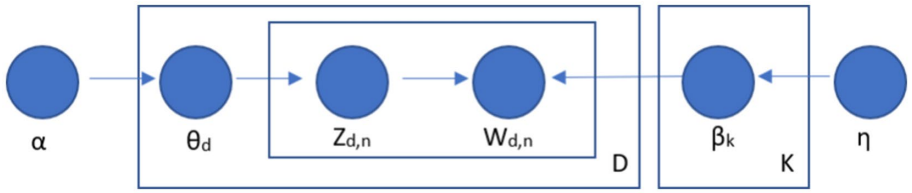

FIGURE 1
LDA's algorithm in topic modeling. Where: *K*, number of topics; α, prior weight of topic k by document based on Dirichlet distributions, identifying θ; η, prior weight of word w by document based on Dirichlet distributions, identifying β; θ_d, ratios of topics as per document; β_k, probability that word w is created by topic; $Z_{d,n}$, topic of the *n*th word in document d, created from θ_d; $W_{d,n}$, *n*th word in document d, determined by $Z_{d,n}$.

selected documents (23–26). Particularly, a set of words with relevant meanings might be grouped together according to this algorithm to reflect a certain topic. LDA is a Bayesian probabilistic topic model and one of the most common techniques for topic modeling. Up until now, LDA had been defined as a state-of-art or the most common method for topic modeling (27). In particular, the LDA considers all pooled publications (e.g., Intimate partner violence and HIV/AIDS publications in this study) representing K latent topics, and each topic is also represented by a set of words (27). The LDA generative process is illustrated in Figure 1 (28).

In this study, STATA's LDA command was applied (29). In the initial stage, STATA was used to decompose the titles and abstracts into individual words. The words are then given to one of the n themes at random with equal probability. A new subject is assigned for words with a similar theme after the burn-in time (every 50 iterations). After LDA is completed, the file in Excel format containing allocated topics was exported (30). After obtaining the outputs of the LDA model, we invited HIV and IPV experts to discuss and label the topics by providing them with words (after sorted) with the highest probability appear within each topic and titles/abstracts of papers within each topic.

3. Results

Table 2 reveals the characteristics of the dataset. The first paper was published in 1997. Since then, there has been a gradual increase in the number of studies on IPV among HIV/AIDS studies during 1997–2019, contributing to a total of 941 papers. Notably, the total number of download times (total usage) and the average number of downloads times (the mean use rate) in the last 5 years shows the middle-term interest of readers. These highest figures belonged to that of papers published in 2013. Also, total usage and mean use rate in the last 6 months were highest for papers published in 2019, which shows the recent increased interest by readers.

Figure 2 shows the collaboration of countries in HIV/AIDS research mentioning intimate partner violence. There were 65 countries with at least one paper in the figure. There were four main groups in this research field, including (1) the U.S and sub-Saharan African countries (red cluster), (2) South Africa and North European countries (green cluster), and (3) England, Brazil, and Southeast Asia countries (blue cluster).

By using the text mining function of VOSwiver, the co-occurrence of terms was visualized, with the most frequent groups of terms displayed in Figure 3. There were two major clusters, (1) Cluster 1 (red) refers to interventions to reduce intimate partner violence and (2) Cluster 2 (green) focuses on factors associated with IPV. The two minor clusters included IPV and sex workers (yellow cluster), and gender inequity in IPV (blue cluster).

Table 3 shows the most cited papers with more than 200 citations among all papers in the analysis. The titles and abstracts of the publications were carefully reviewed and assigned to a suitable topic based on LDA. Among those 10 papers, gender inequity, and factors associated with domestic violence were the most common topics. The two most cited papers in our dataset addressed the high risk of HIV infection among women suffering from violence from male partners (31), especially among young South African women (32). The third paper in our list evaluated the risk factors affecting IPV against women (33).

Latent Dirichlet allocation classified titles and abstracts of the dataset into 10 research topics (Table 4). Each topic was identified upon careful review of the titles and abstracts as well as the most frequently appearing words. After that, based on experts' opinions, it was decided to merge topic 2, topic 4, and topic 7 into one new topic (topic 2), and topic 1 and topic 3 into topic 1, as they share the same theme. Factors associated with domestic violence among people living with HIV had the highest number of papers during 1997–2019 and in the last 5 years, with 272 papers and 145 papers, respectively. Additionally, interventions to reduce domestic violence and health care services for women with domestic violence also received high concern from scientists. Youth and pregnant women suffered a large impact on domestic violence, particularly in families affected by HIV/AIDS (34). The number of papers concerning these two subjects in the last 5 years contributed 65.2% and 74.6%, respectively, showing an increased research interest in these topics.

Figure 4 shows the hierarchical clustering of research areas in IPV in HIV/AIDS research. The dissimilarity between research areas was shown by the horizontal axis; meanwhile, research areas were presented by the vertical axis. The red lines show the depth of the cut-off for each cluster. There were three main categories of research areas regarding domestic violence among HIV/AIDS publications. They were (1) social sciences and environment-related health issues, (2) criminological psychology and family, and the third with six sub-clusters: (a) Psychology, respiratory healthcare, and health policy, (b) Immunology of Infectious Diseases, (c) Obstetrics, Gynecology, and Women's Health, (d) Social Sciences, and Psychology, (e) Healthcare, and (f) Mental health and substance misuse. As can be seen, the research areas of Psychology, Psychiatry, Social Sciences, and Women's Health garnered great concern among researchers. However, there was limited research in areas focusing on children or health care services for those suffering from domestic violence, as well as on economic aspects of these studies.

TABLE 2 General characteristics of publications (total 941).

Year published	Total number of papers	Total citations	Mean cite rate per year	Total usage last 6month	Total usage last 5years	Mean use rate last 6month	Mean use rate last 5year
2019	105	100	1.0	182	372	1.7	0.7
2018	103	352	1.7	63	552	0.6	1.1
2017	91	570	2.1	34	714	0.4	1.6
2016	107	1,072	2.5	41	1,213	0.4	2.3
2015	87	1,786	4.1	57	1,619	0.7	3.7
2014	77	1,710	3.7	33	1,397	0.4	3.6
2013	75	1,732	3.3	29	1,555	0.4	4.1
2012	41	1,440	4.4	17	724	0.4	3.5
2011	50	1,881	4.2	18	750	0.4	3.0
2010	40	2,095	5.2	9	600	0.2	3.0
2009	33	1,217	3.4	12	419	0.4	2.5
2008	33	2,251	5.7	11	459	0.3	2.8
2007	19	1,349	5.5	9	332	0.5	3.5
2006	18	1,673	6.6	3	257	0.2	2.9
2005	16	736	3.1	3	99	0.2	1.2
2004	11	1,185	6.7	16	247	1.5	4.5
2003	10	908	5.3	4	106	0.4	2.1
2002	5	272	3.0	0	34	0.0	1.4
2001	4	222	2.9	0	28	0.0	1.4
2000	8	725	4.5	3	72	0.4	1.8
1999	5	73	0.7	0	16	0.0	0.6
1998	2	205	4.7	0	21	0.0	2.1
1997	1	156	6.8	0	33	0.0	6.6

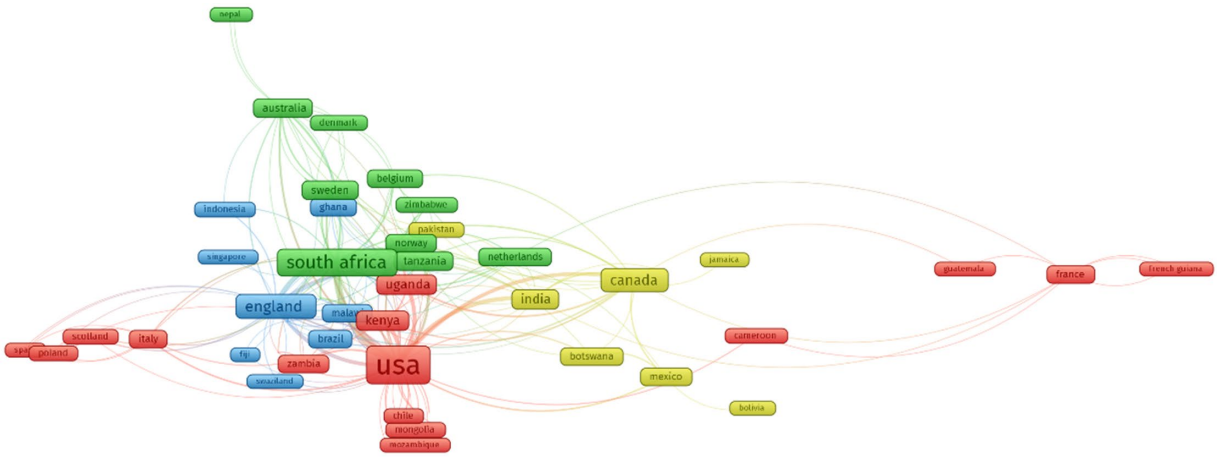

FIGURE 2
Collaboration of countries regarding intimate partner violence among people living with HIV during 1997–2019 (Red cluster: the US and sub-Saharan African countries; green cluster: South Africa and North European countries; blue cluster: England, Brazil, and Southeast Asia countries).

4. Discussion

This study provides an overview of the trend in published works as well as common topics regarding intimate violence studies in HIV/AIDS publications from 1997 to 2019. The findings showed that most papers are published and conducted in developed countries, led by the US. Two most common research themes were factors associated with domestic violence and intervention and prevention to reduce domestic

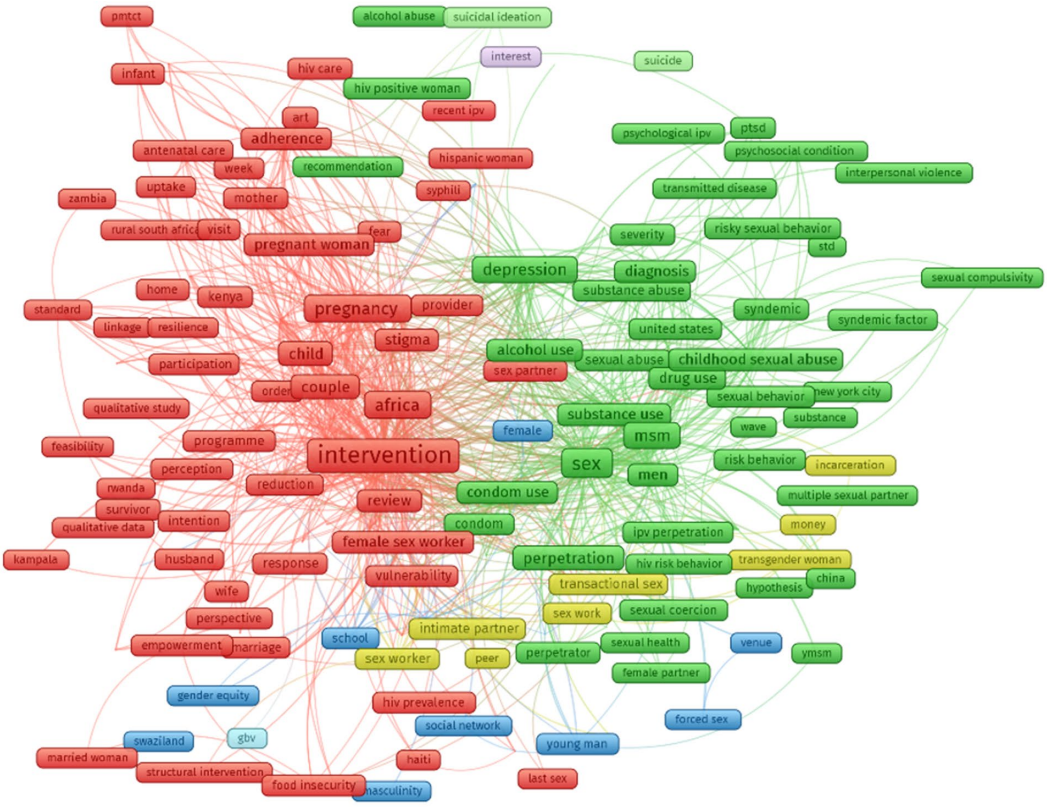

FIGURE 3
Co-occurrence of most frequent terms in titles and abstract (The size of the term was calculated based on its weight. The color was determined by its cluster. The length of lines showed the relatedness between two terms; red cluster: interventions to reduce intimate partner violence; green cluster: factors associated with IPV; yellow cluster: IPV and sex workers; blue cluster: gender inequity in IPV).

violence. This study emphasized that more research collaboration should be conducted between developed and developing countries. Also, more research and attention should be paid to mental health issues and domestic violence among pregnant women infected with HIV/AIDS, as well as the relationship between HIV risks and domestic violence among youth.

In accordance with the results of other studies, research on domestic violence in HIV/AIDS publications has increased gradually during the 1997–2019 period (35, 36). In addition, most published works were contributed by developed countries and led by the U.S, in line with results from previous studies (37, 38). Up until now, Intimate partner violence (IPV) and HIV/AIDS are complex issues that affect individuals and communities worldwide, but they may manifest differently in developed and developing countries. Particularly, it should be noted that there has been a great burden of HIV/AIDS and IPV in developing countries, especially in sub-Saharan Africa (39). The prevalence of IPV among PLHA in developing countries was shown to be particularly high compared with HIV-negative populations (14, 40–44). For example, the prevalence of violence among women with HIV in Nepal was 93% (45). This number was much higher than that of Uganda (44.2%) (41), Nigeria (23.6%) (42), or the US (35%) (43). This finding suggests that the contribution of developing countries in research did not meet the need to address IPV. This dearth is likely due to the lack of resources, funding, or facilities in poor-resource countries (46). Although this gap cannot be filled in a short time, poor-resource settings should be active in research collaboration with developed countries, as well as increase internal funding and spending for HIV/AIDS research (47).

From the results of the term co-occurrence map and the research topic tables, our study affirms previous reviews which show various approaches related to HIV/AIDS and IPV research, including prevalence and associated factors, gender inequity, and domestic violence (48), and studies focused on interventions or prevention of intimate partner violence (15). With the high burden of disease due to the intersection of HIV and IPV, it is no doubt that research addressing the prevention of IPV, as well as evaluation of the effectiveness of interventions, are needed. In our dataset, most studies focused on some intervention that addresses IPV and women affected with HIV/AIDS, such as the Women's Health CoOp (WHC) (49), SASA! Activist kit (50), or microfinance intervention (51). A similar conclusion was reached by Marshall KJ et al. (16). The above interventions addressed HIV and IPV with different approaches, target populations, and outcomes. For example, a group that received microfinance and training intervention showed better economic well-being, reducing HIV risk behavior compared with the control group (51). Similarly, Wechsberg et al. showed that the Women's Health CoOp brief peer-facilitated intervention was effective in promoting drug abstinence among women using drugs in South Africa.

In addition, the results show evidence of the limited number of papers mentioning mental health illness and domestic violence among

TABLE 3 Most cited papers.

No	Topic	Authors	Title	Journal	Total cite	Publication year	Cite rate per year
1	Topic 5	Dunkle KL et al.	Gender-based violence, relationship power, and risk of HIV infection in women attending antenatal clinics in South Africa	Lancet	781	2004	48.8
2	Topic 5	Jewkes RK et al.	Intimate partner violence, relationship power inequity, and incidence of HIV infection in young women in South Africa: a cohort study	Lancet	627	2010	62.7
3	Topic 2	Abramsky T et al.	What factors are associated with recent intimate partner violence? findings from the WHO multi-country study on women's health and domestic violence	BMC Public Health	428	2011	47.6
4	Topic 2	Jewkes R et al.	Impact of steppingstone on incidence of HIV and HSV-2 and sexual behavior in rural South Africa: cluster randomized controlled trial	BMJ-British Medical Journal	426	2008	35.5
5	Topic 5	Jewkes R et al.	Gender and sexuality: emerging perspectives from the heterosexual epidemic in South Africa and implications for HIV risk and prevention	Journal of The International Aids Society	334	2010	33.4
6	Topic 2	Kim JC et al.	Understanding the impact of a microfinance-based intervention on women's empowerment and the reduction of intimate partner violence in South Africa	American Journal of Public Health	268	2007	20.6
7	Topic 5	Jewkes RK et al.	Gender inequalities, intimate partner violence and HIV preventive practices: findings of a South African cross-sectional study	Social Science & Medicine	241	2003	14.2
8	Topic 6	Cohen M et al.	Domestic violence and childhood sexual abuse in HIV-infected women and women at risk for HIV	American Journal of Public Health	238	2000	11.9
9	Topic 2	Coker AL	Does physical intimate partner violence affect sexual health? A systematic review	Trauma Violence & Abuse	228	2007	17.5
10	Topic 7	Dunkle KL et al.	Perpetration of partner violence and HIV risk behavior among young men in the rural Eastern Cape, South Africa	AIDS	207	2006	14.8

Topic 2: prevalence and factors associated with domestic violence; Topic 5: health services and women suffered intimate partner violence; Topic 6: mental health illness and domestic violence among pregnant women infected with HIV/AIDS; Topic 7: prevalence and factors associated with domestic violence.

pregnant women infected with HIV/AIDS, compared to other topics. However, 74.6% of published works mentioning this vulnerable population were conducted in the last 5 years. This phenomenon indicates that the concern of scientists and policymakers has been transferred from HIV high-risk populations, such as sex workers, to this vulnerable population (52). This could be partially explained by the serious health problems which IPV poses to pregnant women affected by HIV, such as mental health issues, poor child health outcomes (53), or depression and suicidal ideation. A study from Kapetanovic S, et al. also confirmed this result (53). Moreover, 65% (15/23 studies) of studies concerning adolescents, HIV infection, and domestic violence were conducted in the last 5 years. This result highlights that there has been a growing recognition that adolescents are vulnerable to HIV risks and domestic violence (54). Most of the studies regarding these two vulnerable populations were conducted in sub-Saharan Africa countries, where women and youth face higher risks of HIV infection when they have suffered violence, compared with those who have not (31, 55). Furthermore, the thematic map showed that there was a limitation in the number of studies mentioning violence among sex workers, although the relationship between IPV and HIV risk among sex workers has been well-documented in previous studies (56, 57).

Some implications can be derived from this study. First, future research may benefit from viewing IPV and HIV/AIDS as an intersecting healthcare challenges when assessing related factors and interventions for these two problems (58). For example, future research may focus on the cost-analysis of interventions targeting IPV and HIV-related outcomes (59). Secondly, support and research collaborations between developed countries and developing countries could bring more fruitful results to increase the health status of PLWHA and IPV, especially in regions with a high prevalence of HIV. Moreover, due to the growing number of PLWHA and the association between HIV and IPV, comprehensive research should be conducted not only on prevalence, associated factors and interventions or prevention, but also focused on healthcare service, which is a priority in public health, especially among pregnant women and adolescents with HIV who suffer IPV (60). Although women and girls experience a higher risk for IPV, many boys also suffer from

TABLE 4 Ten research topics classified by LDA.

Topic	Research areas	Frequency	Percent (of total 832 papers)	Frequency (2014–2019)	Percent (% total of each topic)
Topic 1	Interventions and preventions domestic violence	79	9.5	50	61.6
Topic 2	Prevalence and Factors associated with domestic violence	78	9.4	57	53.3
Topic 3	Interventions and preventions domestic violence	85	10.2	51	–
Topic 4	Prevalence and Factors associated with domestic violence	6	0.7	3	–
Topic 5	Health services and women suffered intimate partner violence	70	8.4	32	45.7
Topic 6	Mental health illness and domestic violence among pregnant women infected with HIV/AIDS	59	7.1	44	74.6
Topic 7	Prevalence and Factors associated with domestic violence	188	22.6	85	–
Topic 8	Relationship power inequity, social norms, and intimate domestic partner	102	12.3	55	53.9
Topic 9	Youth, HIV risks and domestic violence	23	2.8	15	65.2
Topic 10	Perpetration of intimate partner violence and sexual risk behaviors	142	17.1	50	35.3
		832	**100**	**442**	

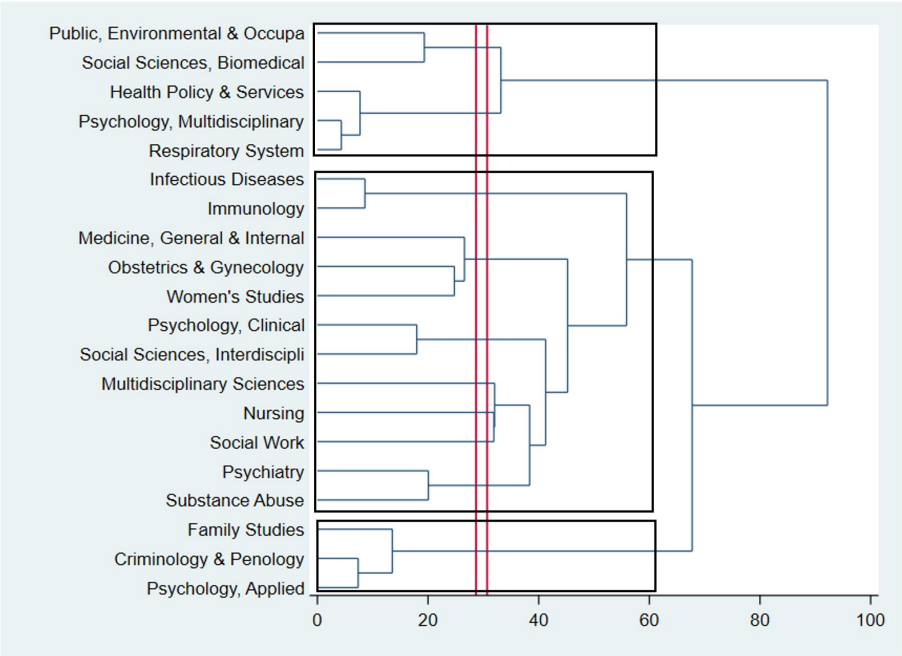

FIGURE 4
Dendrogram of coincidence of research areas using the WoS classifications.

physical, sexual, and emotional domestic violence (61). Future studies thus may consider taking a focus on male victims of IPV. In addition, further research is required to access for post-traumatic stress disorder as well as mental health conditions among the victims.

Considering these findings, several limitations of the study should be considered. Firstly, the shortcoming of this study was that only one database from the Web of Sciences was used. Despite a number of journals in the field of HIV indexed in the Web of Science database, we acknowledge that it is still not fully representative of all databases. And this might restrict our ability to cover all relevant publications as well as certain disciplines may not be included in this study. Secondly, only English-language publications were selected in this study, which may not fully reflect the trend of the research field because in some developing countries, publications may not have been not written in English. Also, only titles and abstracts were used for text mining. However, different levels of data, including countries, text data visualization, topic modelling, and research disciplines, were used to increase the results of this research. Finally, 10 topics from the LDA

model were labeled based on HIV and IPV experts. This may exist some biases as well as can be affected the subjectivity of the results.

5. Conclusion

Our study highlighted a gradual increase of publications regarding IPV research in HIV/AIDS studies during the 1997–2019 period. Associated factors of IPV and prevention and intervention to reduce IPV among HIV/AIDS were the most common topics. Meanwhile, there was a limitation in the number of published works related to mental health illness, pregnant women, adolescents, and sex workers who suffer from IPV. More future studies should focus on these l topics with the interdisciplinary collaboration of research fields. In addition, support and research collaboration between developed countries and developing countries might be a key element to reduce the global burden of this overlapping health issue.

Author contributions

TN, LH, LN, and CL: conceptualization. LN and RH: methodology. TN, LV, HD, and CH: formal analysis and investigation. LH, LN, TN, LV, HD, LB, GF, PA, CL, CH, and RH: writing—original draft preparation and writing—review and editing. LB, GF, PA, CL, CH, RH, LH, and HD: supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Global associations of key populations with HIV-1 recombinants: a systematic review, global survey, and individual participant data meta-analysis

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Introduction: Global HIV infections due to HIV-1 recombinants are increasing and impede prevention and treatment efforts. Key populations suffer most new HIV infections, but their role in the spread of HIV-1 recombinants is unknown. We conducted a global analysis of the associations between key populations and HIV-1 recombinants.

Methods: We searched PubMed, EMBASE, CINAHL, and Global Health for HIV-1 subtyping studies published from 1/1/1990 to 31/12/2015. Unpublished data was collected through a global survey. We included studies with HIV-1 subtyping data of key populations collected during 1990-2015. Key populations assessed were heterosexual people (HET), men who have sex with men (MSM), people who inject drugs (PWID), vertical transmissions (VERT), commercial sex workers (CSW), and transfusion-associated infections (BLOOD). Logistic regression was used to determine associations of key populations with HIV-1 recombinants. Subgroup analyses were performed for circulating recombinant forms (CRFs), unique recombinant forms (URFs), regions, and time periods.

Results: Eight hundred and eighty five datasets including 77,284 participants from 83 countries were included. Globally, PWID were associated with the greatest odds of recombinants and CRFs (OR 2.6 [95% CI 2.46–2.74] and 2.99 [2.83–3.16]), compared to HET. CSW were associated with increased odds of recombinants and URFs (1.59 [1.44–1.75] and 3.61 [3.15–4.13]). VERT and BLOOD were associated with decreased odds of recombinants (0.58 [0.54–0.63] and 0.43 [0.33–0.56]). MSM were associated with increased odds of recombinants in 2010–2015 (1.43 [1.35–1.51]). Subgroup analyses supported our main findings.

Discussion: As PWID, CSW, and MSM are associated with HIV-1 recombinants, increased preventative measures and HIV-1 molecular surveillance are crucial within these key populations.

Systematic review registration: PROSPERO [CRD42017067164].

KEYWORDS

HIV, key populations, recombinant, CRF, URF, molecular epidemiology

1. Introduction

In 2021, 38.4 million people were living with HIV worldwide and 1.5 million people became newly infected (1). The HIV pandemic remains a major global health challenge, and its extreme global genetic diversity impedes treatment and prevention efforts (2). Global temporal analysis indicates that the HIV-1 pandemic is diversifying, with increases in both the numbers of distinct HIV-1 variants and proportions of recombinant strains (3–5). Increasing diversity impacts HIV diagnosis and treatment, drug resistance, viral load measurement, transmission, disease progression, immune responses, and vaccine development (2, 6–10).

After zoonotic transmission from chimpanzees to humans in Central Africa around 1900, the HIV-1 group M epidemic rapidly diversified into distinct subtypes, designated by the letters A–D, F–H, and J–L (11, 12). HIV-1 subtypes spread across the globe throughout the 20th century, resulting in HIV-1 subtype distributions that greatly vary by region (3, 13). The genetic complexity of the HIV pandemic continues to increase over time, largely driven by the high mutation and recombination rates of the error-prone reverse transcriptase enzyme (14). Recombination occurs when an individual is co-infected with multiple strains which combine into a new variant (15). The resulting variants are designated as circulating recombinant forms (CRFs) or unique recombinant forms (URFs). CRFs, which are characterized by community spread, must be fully sequenced and found in at least three epidemiologically unlinked individuals. More than 120 distinct CRFs have been described to date, and more CRFs continue to be identified (16). URFs are unique recombinant sequences without evidence of onward transmission. The proportion of recombinants has been increasing over time, both globally and in most regions, and recombinants now constitute nearly a quarter of all HIV-1 infections globally (4). In addition to increasing the genetic complexity of the HIV pandemic, recombination may confer an evolutionary advantage, leading to altered transmission and/or virulence (17, 18).

In 2021, 70% of new HIV infections occurred within key populations and their sexual partners, though these populations account for <5% of the global population (1). It is estimated that men who have sex with men (MSM) have 28 times the risk of HIV infection relative to heterosexual (HET) adult men, female commercial sex workers (CSW) have 30 times the risk relative to other adult women, and people who inject drugs (PWID) have 35 times the risk compared to those who do not inject drugs (1). Additionally, people in areas without comprehensive blood screening are particularly vulnerable to HIV infection through transfusions with infected blood (BLOOD) (19), and children born to mothers with HIV can become infected via vertical transmission (VERT) during pregnancy, labor, delivery, or breastfeeding (20). Prior work indicates that HIV can follow a chain of transmission among these groups, spreading from PWID to CSW who transmit the virus to their HET clients. The virus can then be transmitted to the client's female sexual partner before VERT transmission of HIV infection to children (20, 21). Transmission among MSM and during blood transfusions has also played a major historical role in the spread of HIV, particularly across Asia, Europe, and North America (19, 21, 22).

Though these key populations are known to play a role in HIV transmission, it is unclear what role they play in the spread of HIV-1 recombinants. Since these populations often face difficulties accessing HIV services and have an increased risk of infection (1), potentially by multiple strains, they may be more likely to develop novel HIV strains. These recombinant strains may cross from key populations into the general population, making the overall HIV epidemic more complex.

The global proportion of HIV infections with recombinants is increasing and key populations globally account for most new HIV infections. However, there is an evidence gap regarding the global association of key populations with HIV-1 recombinants. To address this gap, we conducted a global analysis of the association between multiple key populations and HIV-1 recombinants using the largest global HIV-1 molecular epidemiology database assembled to date.

2. Materials and methods

2.1. Data collection

Data on the global distribution of HIV-1 subtypes and recombinants among key populations were obtained through a systematic literature review (PROSPERO: CRD42017067164), review of specialist journals and reports, and global survey of experts (3). We searched PubMed (29,825 citations retrieved), Embase (Ovid) (25,914 citations), CINAHL (Ebscohost) (451 citations), and Global Health (Ovid) (9,707 citations) for studies reporting HIV-1 subtyping data published from Jan 1, 1990 to Dec 31, 2015. This time period covers the period for which reliable estimates of national HIV prevalence were available. Search terms were Medical Subject Headings (MeSH) and Emtree terms, free text words, and synonyms, including "HIV," "Subtype," "recombinant," "CRF," and "URF" (Appendix pp2–5). No language or methodology filters were used. All references retrieved were combined in Endnote reference manager, and duplicates removed (Endnote X9; Clarivate Analytics, Philadelphia, PA). Authors RE, JY, LD-T and JH screened titles and abstracts, retrieved relevant full text articles, and assessed articles against the eligibility criteria. Additional published data were derived from the WHO HIV Drug Resistance Report 2012 (23), published reviews and reports on HIV diversity, and papers indexed on Scopus that referenced previous publications on global HIV-1 diversity (Appendix pp6–8). Additionally, four specialist journals (*AIDS, Journal of AIDS, Journal of Virology, AIDS Research and Human Retroviruses*) were screened for relevant articles published between January 1990 and February 2016. Using a data collection template, unpublished original HIV-1 subtyping data was collected through a global survey of members in the WHO-UNAIDS Network for HIV Isolation and Characterisation.

2.2. Eligibility criteria and data extraction

Studies were eligible for inclusion if they were prevalence studies of key populations living with HIV with original HIV-1 subtyping data, known country and year of sample collection

(1990–2015), and a minimum of 20 participants. Studies that only contained incident infections or untyped samples were excluded. Full-length genomes or any genome segment could be used for subtyping, no minimum sequence length was specified, all online subtyping tools were accepted, and subtyping data from each included dataset was assumed to be correct.

Authors RE, JY, LD-T, and JH extracted the following information for each data set: country, city or region, sample collection year(s), study type, key population, HIV-1 subtyping method(s), and genome segment(s) analyzed. The primary outcome was the number of each key population designated by the original authors as each HIV-1 subtype (A, B, C, D, F, G, H, J, K), CRFs, and URFs. Country designation was based on where samples were taken. One subtype/CRF/URF was assigned to each participant. Subtyping methods included sequencing, heteroduplex mobility assay, and serotyping. The vast majority of data was acquired by sequencing (100% in 2010–2015), mostly of partial genome sequences, mainly pol (94.4% in 2010–2015) (3). Contributing researchers were assumed to have obtained consent from participants, and no personal identifiable information was retrieved. Formal assessment of individual study quality was not performed. Discrepancies were resolved by the senior reviewer (JH).

2.3. Key populations

Based on the populations specified by each study, participants were categorized as heterosexual (HET), men who have sex with men (MSM), people who inject drugs (PWID), vertical transmissions (VERT), commercial sex workers (CSW), and transfusion-associated infections (BLOOD) by author NN and confirmed by JH. Studies involving multiple key populations were assigned to the key population comprising at least 95% of data or excluded if no single key population met the 95% threshold. Studies with unspecified or indeterminate key populations were excluded. Any discrepancies or ambiguities were resolved by JH.

2.4. Meta-analysis

As most studies provided data on a single key population, one-stage meta-analysis of individual-participant data of different studies was performed. For logistic regression, HIV-1 variants were categorized as "Subtype" or "Recombinant" (CRF/URF). A univariate binomial logistic regression model was constructed to analyse the global association of each key population with HIV-1 recombinants. To assess the global association of key populations with CRFs and URFs separately, logistic regression was repeated using a multinomial model.

Countries were grouped into 14 regions (Appendix p9) and data were assigned to four periods: 1990–1999, 2000–2004, 2005–2009, and 2010–2015 (Appendix p10). All participants in each dataset were assigned to periods based on the midpoint year of the reported sample collection period. Datasets of which sampling years were evenly split between two periods (e.g., 2003–2006) were excluded from time-stratified analyses. To assess temporal and geographic differences in the associations with recombinants, the binomial logistic model was separately stratified into subgroups by time period and region.

For all logistic models, "Subtype" was used as the reference group. Odds Ratios (ORs) were reported with 95% confidence intervals. In the Appendix, pairwise ORs are reported globally and for each region (pp11–13) and period subgroup analyses were repeated for the multinomial logistic regression model (pp14). Statistical analyses were performed using STATA 17.0 (StataCorp LLC, College Station, TX). This systematic review is reported according to the PRISMA guidelines, as applicable.

3. Results

3.1. Data collection

A total of 885 datasets including 77,284 participants from key populations from 83 countries were included (Figure 1). The systematic literature search yielded 208 datasets comprising 23,988 participants. Six hundred and seventeen datasets with 48,984 participants were collected from the global survey, and 60 datasets with 4,312 participants were obtained from other published sources.

Most included participants were heterosexual people (58.2%) and MSM (25.7%), with smaller proportions of participants representing PWID (8.1%), VERT (5.3%), CSW (2.2%), and BLOOD (0.6%) (Table 1). Data from the HET population was the largest in each time period, while there was no data for CSW in the most recent period. Most participants were derived from Western and central Europe, and North America (WCENA) followed by East, West, and Southern Africa. HET data was available in every geographic region while all BLOOD participants were derived from East Asia and WCENA. HET was selected as the reference group as it was the only population represented in all regions and time periods.

3.2. Global association of key populations with recombinants

The global distribution of HIV-1 subtypes, CRFs and URFs among key populations in 1990–2015 is shown in Table 2. During 1990–2015, the largest proportion of recombinant infections was found among PWID (52.8%) and CSW (40.5%), followed by HET (30.1%), MSM (29.4%), VERT (19.9%), and BLOOD (15.6%). PWID had the highest proportion of CRFs (49.1%) and CSW had the highest proportion of URFs (17.6%). The proportion of recombinant infections grew consistently across periods for HET, MSM, and BLOOD and across the first three periods for PWID. Global proportions of individual CRFs for each key population are included in the Appendix p16.

PWID were associated with the greatest odds of recombinants relative to all other key populations (Figure 2A; Table 3). Relative to HET, PWID and CSW were associated with increased odds of recombinants [OR 2.6 (95% CI 2.46–2.74) and 1.59 (1.44–1.75)], while VERT and BLOOD were associated with decreased odds [0.58 (0.54–0.63) and 0.43 (0.33–0.56)]. MSM did not have a significant

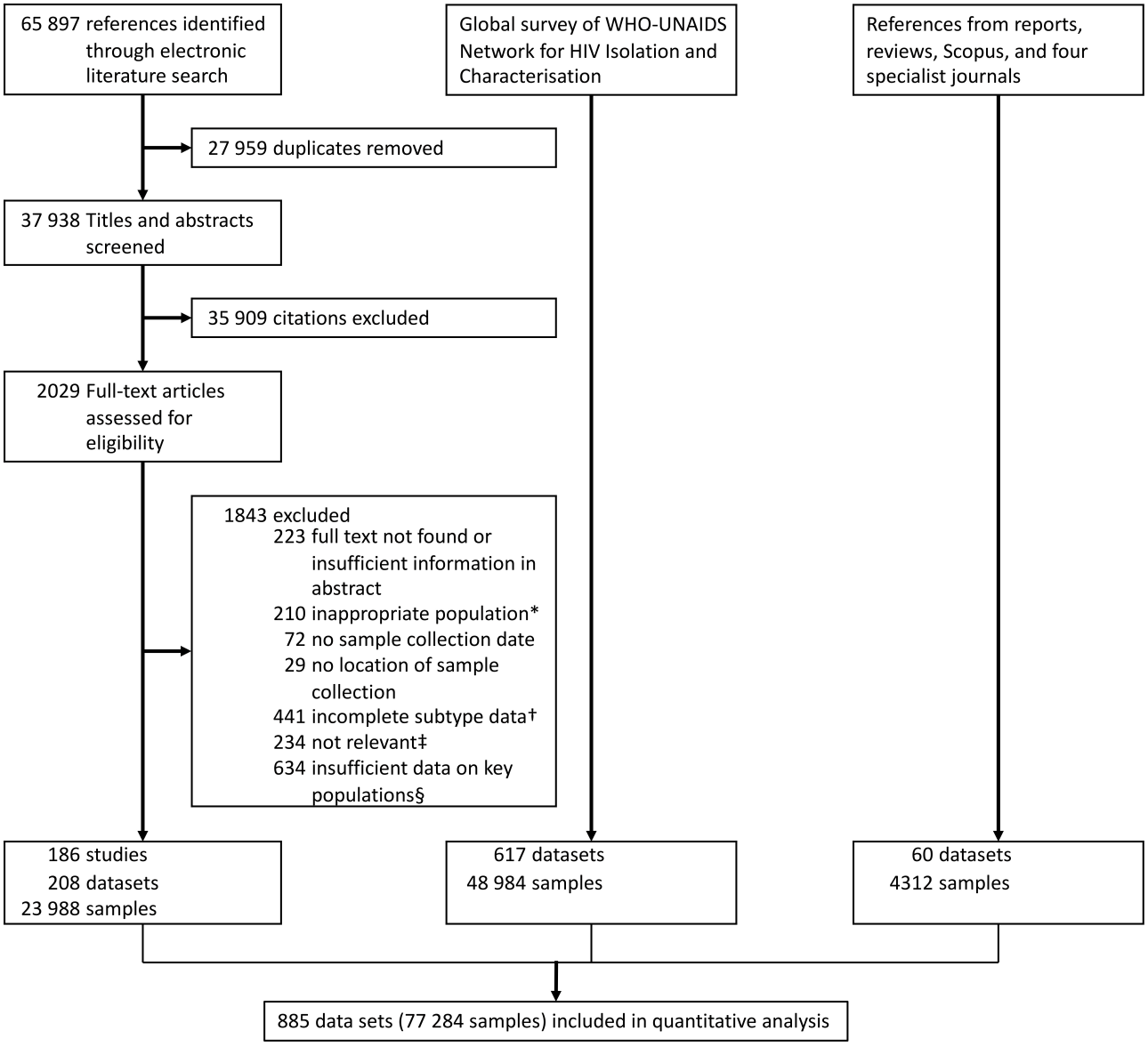

FIGURE 1
Data collection flowchart. *For example, HIV-positive immigrants only. †For example, data only provided for subtype B and non-B participants. ‡For example, subtypes referred to disease states, not HIV subtypes. §For example, HIV subtyping data could not be assigned to a specific key population, as multiple key populations were present in the study.

association with recombinants relative to HET [0.97 (0.93–1.01)] (Figure 2A; Table 3).

Relative to HET, independent associations of each key population with CRFs and URFs varied substantially (Figure 2A; Appendix p15). PWID were significantly associated with increased odds of CRFs [2.99 (2.83–3.16)], while CSW were significantly associated with increased odds of URFs [3.61 (3.15–4.13)]. VERT was associated with decreased odds of CRFs [0.49 (0.44–0.53)], and BLOOD was associated with decreased odds of both CRFs and URFs [0.43 (0.32–0.56) and 0.45 (0.26–0.77)]. MSM were associated with slightly increased odds of CRFs [1.09 (1.05–1.14)], but decreased odds of URFs [0.44 (0.40–0.48)] (Figure 2A; Appendix p15).

Relative to HET, the strength of associations with recombinants across time differed by key population (Figure 2B; Appendix pp14, 15). PWID were associated with increased odds of recombinants across all periods. CSW were initially associated with increased odds of recombinants, but the strength of the association decreased with time before leading to decreased odds in the 2005–2009 period. VERT alternated from increased to decreased odds of recombinants across time. BLOOD was associated with decreased odds of recombinants during 2000–2009 but was not significant in the most recent period. MSM had decreased odds of recombinants during 1990–2009 but trended upwards and were associated with increased odds in 2010–2015 [1.43 (1.35–1.51)].

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TABLE 1 Data collection on key populations and HIV-1 subtypes and recombinants, 1990–2015.

	HET	MSM	PWID	VERT	CSW	BLOOD	Total
Number of datasets							
GLOBAL (1990–2015)	**538 (60.8%)**	**110 (12.4%)**	**98 (11.1%)**	**86 (9.7%)**	**20 (2.3%)**	**33 (3.7%)**	**885 (100%)**
1990–1999	109 (56.5%)	18 (9.3%)	36 (18.7%)	18 (9.3%)	4 (2.1%)	8 (4.1%)	193 (100%)
2000–2004	106 (55.5%)	22 (11.5%)	28 (14.7%)	16 (8.4%)	10 (5.2%)	9 (4.7%)	191 (100%)
2005–2009	230 (73.0%)	35 (11.1%)	17 (5.4%)	19 (6.0%)	6 (1.9%)	8 (2.5%)	315 (100%)
2010–2015	86 (49.1%)	32 (18.3%)	17 (9.7%)	32 (18.3%)	0 (0.0%)	8 (4.6%)	175 (100%)
Caribbean	10 (76.9%)	3 (23.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (100%)
Latin America	18 (40.0%)	8 (17.8%)	4 (8.9%)	12 (26.7%)	3 (6.7%)	0 (0.0%)	45 (100%)
Western and central Europe, and North America (WCENA)	56 (23.5%)	66 (27.7%)	44 (18.5%)	40 (16.8%)	0 (0.0%)	32 (13.4%)	238 (100%)
Eastern Europe and central Asia (EECA)	6 (27.3%)	2 (9.1%)	13 (59.1%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	22 (100%)
South Asia	8 (61.5%)	0 (0.0%)	2 (15.4%)	0 (0.0%)	3 (23.1%)	0 (0.0%)	13 (100%)
Southeast Asia (SE Asia)	28 (50.0%)	1 (1.8%)	21 (37.5%)	5 (8.9%)	1 (1.8%)	0 (0.0%)	56 (100%)
East Asia	2 (6.2%)	16 (50.0%)	12 (37.5%)	1 (3.1%)	0 (0.0%)	1 (3.1%)	32 (100%)
Oceania	3 (30.0%)	7 (70.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (100%)
Middle East and North Africa (MENA)	1 (50.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (100%)
West Africa	137 (90.1%)	4 (2.6%)	0 (0.0%)	6 (3.9%)	5 (3.3%)	0 (0.0%)	152 (100%)
East Africa	91 (83.5%)	0 (0.0%)	1 (0.9%)	9 (8.3%)	8 (7.3%)	0 (0.0%)	109 (100%)
Ethiopia	7 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (100%)
Central Africa	39 (95.1%)	0 (0.0%)	0 (0.0%)	2 (4.9%)	0 (0.0%)	0 (0.0%)	41 (100%)
Southern Africa	132 (91.0%)	3 (2.1%)	0 (0.0%)	10 (6.9%)	0 (0.0%)	0 (0.0%)	145 (100%)
Number of participants							
GLOBAL (1990–2015)	**44,952 (58.2%)**	**19,835 (25.7%)**	**6,236 (8.1%)**	**4,128 (5.3%)**	**1,685 (2.2%)**	**448 (0.6%)**	**77,284 (100%)**
1990–1999	10,021 (71.1%)	1,071 (7.6%)	2,333 (16.5%)	370 (2.6%)	277 (2.0%)	27 (0.2%)	14,099 (100%)
2000–2004	9,369 (57.5%)	3,602 (22.1%)	1,829 (11.2%)	406 (2.5%)	965 (5.9%)	131 (0.8%)	16,302 (100%)
2005–2009	13,845 (62.1%)	5,487 (24.6%)	1,510 (6.8%)	754 (3.4%)	443 (2.0%)	242 (1.1%)	22,281 (100%)
2010–2015	10,768 (46.4%)	9,293 (40.0%)	564 (2.4%)	2,539 (10.9%)	0 (0.0%)	48 (0.2%)	23,212 (100%)
Caribbean	662 (61.1%)	421 (38.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1,083 (100%)
Latin America	3,146 (60.3%)	883 (16.9%)	241 (4.6%)	828 (15.9%)	121 (2.3%)	0 (0.0%)	5,219 (100%)
Western and central Europe, and North America (WCENA)	6,485 (31.8%)	11,726 (57.5%)	1,390 (6.8%)	516 (2.5%)	0 (0.0%)	269 (1.3%)	20,386 (100%)
Eastern Europe and central Asia (EECA)	263 (25.3%)	75 (7.2%)	694 (66.7%)	8 (0.8%)	0 (0.0%)	0 (0.0%)	1,040 (100%)
South Asia	541 (73.6%)	0 (0.0%)	80 (10.9%)	0 (0.0%)	114 (15.5%)	0 (0.0%)	735 (100%)
Southeast Asia (SE Asia)	3,649 (54.1%)	425 (6.3%)	2,195 (32.5%)	319 (4.7%)	157 (2.3%)	0 (0.0%)	6,745 (100%)
East Asia	763 (10.3%)	4,885 (66.1%)	1,537 (20.8%)	22 (0.3%)	0 (0.0%)	179 (2.4%)	7,386 (100%)
Oceania	93 (10.1%)	826 (89.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	919 (100%)
Middle East and North Africa (MENA)	71 (64.0%)	0 (0.0%)	40 (36.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	111 (100%)
West Africa	9,286 (91.1%)	333 (3.3%)	0 (0.0%)	110 (1.1%)	465 (4.6%)	0 (0.0%)	10,194 (100%)
East Africa	9,347 (85.3%)	0 (0.0%)	59 (0.5%)	730 (6.7%)	828 (7.6%)	0 (0.0%)	10,964 (100%)
Ethiopia	230 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	230 (100%)
Central Africa	2,673 (93.5%)	0 (0.0%)	0 (0.0%)	186 (6.5%)	0 (0.0%)	0 (0.0%)	2,859 (100%)
Southern Africa	7,743 (82.3%)	261 (2.8%)	0 (0.0%)	1,409 (15.0%)	0 (0.0%)	0 (0.0%)	9,413 (100%)

BLOOD, blood/plasma transfusion associated infections; CSW, commercial sex workers; HET, heterosexual; MSM, men who have sex with men; PWID, people who inject drugs; VERT, vertical transmission (mother to child).

TABLE 2 Global distribution of HIV-1 subtypes, CRFs, and URFs among key populations, 1990–2015.

	HIV-1 subtypes									CRFs			URFs	Total CRFs*	Total recombinants†	Total‡
	A	B	C	D	F	G	H	J	K	CRF01_AE	CRF02_AG	Other				
Global (1990–2015)																
HET	8,340 (18.6%)	5,889 (13.1%)	11,408 (25.4%)	3,222 (7.2%)	580 (1.3%)	1,729 (3.8%)	182 (0.4%)	64 (0.1%)	22 (0.0%)	4,140 (9.2%)	4,995 (11.1%)	1,807 (4%)	2,574 (5.7%)	10,942 (24.3%)	13,516 (30.1%)	44,952 (100%)
MSM	157 (0.8%)	12,937 (65.2%)	561 (2.8%)	12 (0.1%)	219 (1.1%)	104 (0.5%)	4 (0.0%)	1 (0.0%)	7 (0.0%)	3,154 (15.9%)	446 (2.2%)	1,730 (8.7%)	503 (2.5%)	5,330 (26.9%)	5,833 (29.4%)	19,835 (100%)
PWID	794 (12.7%)	1,846 (29.6%)	169 (2.7%)	8 (0.1%)	116 (1.9%)	13 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1,363 (21.9%)	8 (0.1%)	1,691 (27.1%)	228 (3.7%)	3,062 (49.1%)	3,290 (52.8%)	6,236 (100%)
VERT	578 (14%)	824 (20%)	1,627 (39.4%)	152 (3.7%)	71 (1.7%)	45 (1.1%)	5 (0.1%)	3 (0.1%)	0 (0.0%)	328 (7.9%)	136 (3.3%)	96 (2.3%)	263 (6.4%)	560 (13.6%)	823 (19.9%)	4,128 (100%)
CSW	439 (26.1%)	47 (2.8%)	367 (21.8%)	72 (4.3%)	19 (1.1%)	56 (3.3%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	155 (9.2%)	196 (11.6%)	36 (2.1%)	296 (17.6%)	387 (23%)	683 (40.5%)	1,685 (100%)
BLOOD	11 (2.5%)	270 (60.3%)	19 (4.2%)	5 (1.1%)	70 (15.6%)	3 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (4%)	25 (5.6%)	13 (2.9%)	14 (3.1%)	56 (12.5%)	70 (15.6%)	448 (100%)
1990–1999																
HET	4,229 (42.2%)	462 (4.6%)	1,832 (18.3%)	1,607 (16.0%)	239 (2.4%)	321 (3.2%)	80 (0.8%)	24 (0.2%)	8 (0.1%)	609 (6.1%)	245 (2.4%)	38 (0.4%)	327 (3.3%)	892 (8.9%)	1,219 (12.2%)	10,021 (100%)
MSM	3 (0.3%)	1,041 (97.2%)	17 (1.6%)	1 (0.1%)	3 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.3%)	0 (0.0%)	0 (0.0%)	3 (0.3%)	3 (0.3%)	6 (0.6%)	1,071 (100%)
PWID	383 (16.4%)	979 (42.0%)	30 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	792 (33.9%)	0 (0.0%)	138 (5.9%)	11 (0.5%)	930 (39.9%)	941 (40.3%)	2,333 (100%)
VERT	68 (18.4%)	86 (23.2%)	73 (19.7%)	32 (8.6%)	11 (3.0%)	4 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	43 (11.6%)	3 (0.8%)	16 (4.3%)	34 (9.2%)	62 (16.8%)	96 (25.9%)	370 (100%)
CSW	72 (26.0%)	3 (1.1%)	35 (12.6%)	1 (0.4%)	0 (0.0%)	12 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	154 (55.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	154 (55.6%)	154 (55.6%)	277 (100%)
BLOOD	1 (3.7%)	25 (92.6%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	27 (100%)
2000–2004																
HET	1,351 (14.4%)	1,143 (12.2%)	2,840 (30.3%)	714 (7.6%)	82 (0.9%)	232 (2.5%)	11 (0.1%)	10 (0.1%)	3 (0.0%)	1,164 (12.4%)	1,024 (10.9%)	335 (3.6%)	460 (4.9%)	2,523 (26.9%)	2,983 (31.8%)	9,369 (100%)
MSM	22 (0.6%)	3,399 (94.4%)	82 (2.3%)	0 (0.0%)	12 (0.3%)	10 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	28 (0.8%)	25 (0.7%)	3 (0.1%)	21 (0.6%)	56 (1.6%)	77 (2.1%)	3,602 (100%)
PWID	246 (13.4%)	568 (31.1%)	21 (1.1%)	0 (0.0%)	17 (0.9%)	6 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	340 (18.6%)	5 (0.3%)	488 (26.7%)	138 (7.5%)	833 (45.5%)	971 (53.1%)	1,829 (100%)

(Continued)

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TABLE 2 (Continued)

	HIV-1 subtypes									CRFs			URFs	Total CRFs*	Total recombinants†	Total‡
	A	B	C	D	F	G	H	J	K	CRF01_AE	CRF02_AG	Other				
VERT	85 (20.9%)	215 (53.0%)	31 (7.6%)	11 (2.7%)	16 (3.9%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	25 (6.2%)	3 (0.7%)	19 (4.7%)	28 (6.9%)	47 (11.6%)	406 (100%)
CSW	126 (13.1%)	21 (2.2%)	291 (30.2%)	25 (2.6%)	18 (1.9%)	38 (3.9%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	1 (0.1%)	189 (19.6%)	35 (3.6%)	219 (22.7%)	225 (23.3%)	444 (46%)	965 (100%)
BLOOD	5 (3.8%)	35 (26.7%)	7 (5.3%)	1 (0.8%)	70 (53.4%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (3.8%)	5 (3.8%)	0 (0.0%)	2 (1.5%)	10 (7.6%)	12 (9.2%)	131 (100%)
2005–2009																
HET	2,030 (14.7%)	1,769 (12.8%)	4,194 (30.3%)	691 (5.0%)	154 (1.1%)	473 (3.4%)	78 (0.6%)	26 (0.2%)	5 (0.0%)	842 (6.1%)	1,757 (12.7%)	848 (6.1%)	978 (7.1%)	3,447 (24.9%)	4,425 (32%)	13,845 (100%)
MSM	37 (0.7%)	4,218 (76.9%)	105 (1.9%)	2 (0.0%)	20 (0.4%)	13 (0.2%)	1 (0.0%)	1 (0.0%)	0 (0.0%)	740 (13.5%)	87 (1.6%)	134 (2.4%)	129 (2.4%)	961 (17.5%)	1,090 (19.9%)	5,487 (100%)
PWID	79 (5.2%)	209 (13.8%)	91 (6.0%)	3 (0.2%)	5 (0.3%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	219 (14.5%)	1 (0.1%)	849 (56.2%)	52 (3.4%)	1,069 (70.8%)	1,121 (74.2%)	1,510 (100%)
VERT	35 (4.6%)	260 (34.5%)	181 (24.0%)	10 (1.3%)	1 (0.1%)	5 (0.7%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	146 (19.4%)	19 (2.5%)	14 (1.9%)	82 (10.9%)	179 (23.7%)	261 (34.6%)	754 (100%)
CSW	241 (54.4%)	23 (5.2%)	41 (9.3%)	46 (10.4%)	1 (0.2%)	6 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (1.6%)	1 (0.2%)	77 (17.4%)	8 (1.8%)	85 (19.2%)	443 (100%)
BLOOD	1 (0.4%)	189 (78.1%)	8 (3.3%)	4 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (5.0%)	10 (4.1%)	10 (4.1%)	8 (3.3%)	32 (13.2%)	40 (16.5%)	242 (100%)
2010–2015																
HET	553 (5.1%)	2,505 (23.3%)	2,526 (23.5%)	164 (1.5%)	100 (0.9%)	548 (5.1%)	10 (0.1%)	2 (0.0%)	5 (0.0%)	1,344 (12.5%)	1,789 (16.6%)	553 (5.1%)	669 (6.2%)	3,686 (34.2%)	4,355 (40.4%)	10,768 (100%)
MSM	91 (1.0%)	4,200 (45.2%)	159 (1.7%)	9 (0.1%)	180 (1.9%)	73 (0.8%)	1 (0.0%)	0 (0.0%)	7 (0.1%)	2,383 (25.6%)	334 (3.6%)	1,517 (16.3%)	339 (3.6%)	4,234 (45.6%)	4,573 (49.2%)	9,293 (100%)
PWID	86 (15.2%)	90 (16.0%)	27 (4.8%)	5 (0.9%)	94 (16.7%)	5 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (2.1%)	2 (0.4%)	216 (38.3%)	27 (4.8%)	230 (40.8%)	257 (45.6%)	564 (100%)
VERT	390 (15.4%)	252 (9.9%)	1,303 (51.3%)	99 (3.9%)	42 (1.7%)	35 (1.4%)	4 (0.2%)	3 (0.1%)	0 (0.0%)	139 (5.5%)	89 (3.5%)	63 (2.5%)	120 (4.7%)	291 (11.5%)	411 (16.2%)	2,539 (100%)
BLOOD	4 (8.3%)	21 (43.8%)	3 (6.2%)	0 (0.0%)	0 (0.0%)	2 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.1%)	10 (20.8%)	3 (6.2%)	4 (8.3%)	14 (29.2%)	18 (37.5%)	48 (100%)

Global distribution of HIV-1 subtypes, CRFs, and URFs within key populations in 1990–2015 and each of four time periods (1990–1999, 2000–2004, 2005–2009, 2010–2015).

*Total CRFs is the sum of CRF01_AE, CRF02_AG, and Other CRFs.

†Total recombinants is the sum of total CRFs and URFs.

‡Total is the sum of total recombinants and all HIV-1 subtypes.

BLOOD, blood/plasma transfusion associated infections; CRF, circulating recombinant form; CSW, commercial sex workers; HET, heterosexual; MSM, men who have sex with men; PWID, people who inject drugs; URF, unique recombinant form; VERT, vertical transmission (mother to child).

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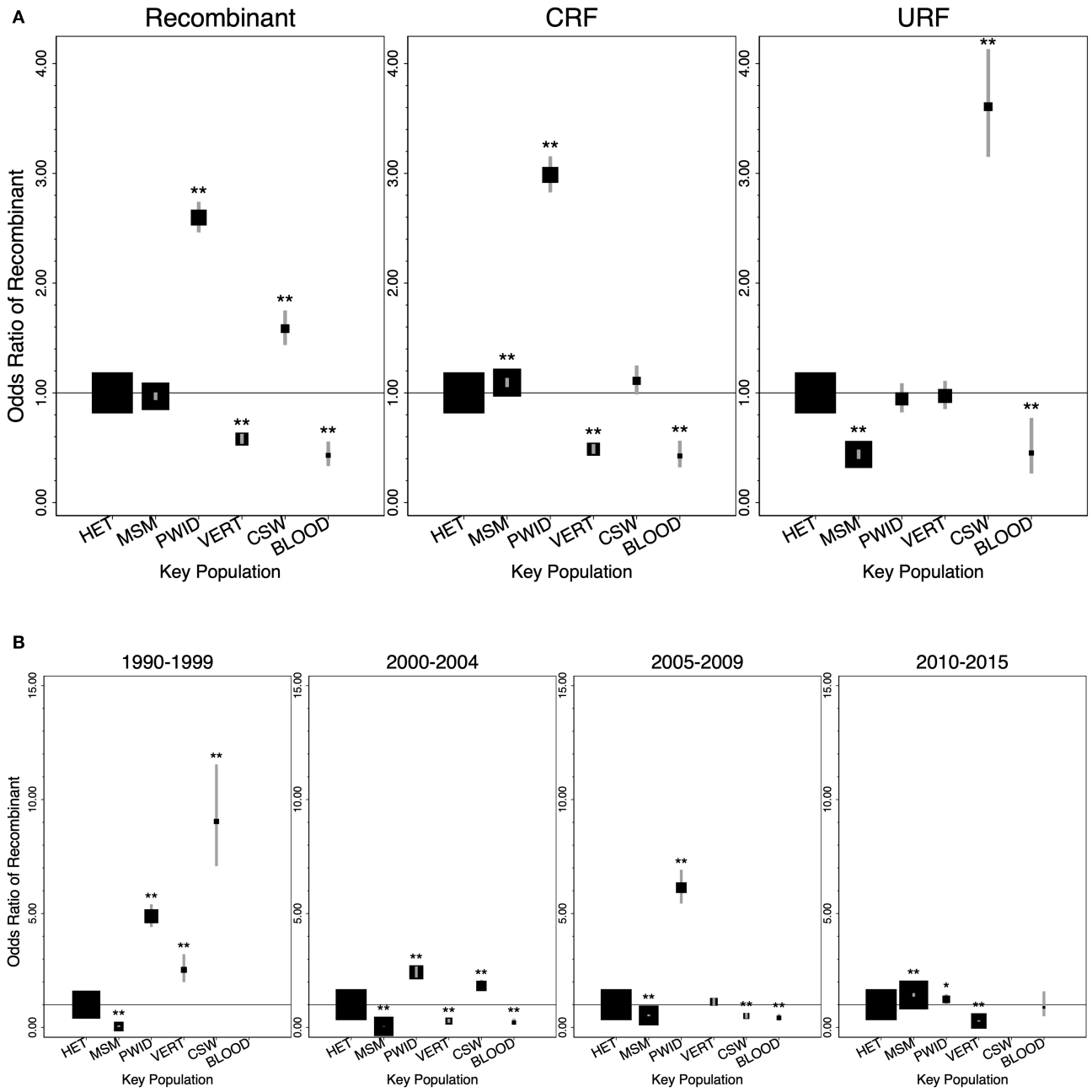

FIGURE 2
Global associations of key populations with HIV-1 recombinants, CRFs, and URFs relative to heterosexual people (1990–2015). **(A)** Odds ratios for HIV-1 recombinants, CRFs, and URFs, compared to HIV-1 subtypes, of key populations relative to heterosexual people (1990–2015). **(B)** Odds ratios for HIV-1 recombinants, compared to HIV-1 subtypes, of key populations relative to heterosexual people in each time period (1990–1999, 2000–2004, 2005–2009, 2010–2015). No data on recombinants was available for BLOOD in 1990–1999, and no data was available for CSW in 2010–2015. Error bars represent the 95% confidence intervals. Square areas are proportional to the number of participants in each key population analyzed. Odds ratios and 95% CI are provided in the Appendix p15 (*$P < 0.05$, **$P < 0.01$). BLOOD, blood/plasma transfusion associated infections; CRF, circulating recombinant form; CSW, commercial sex workers; HET, Heterosexual; MSM, men who have sex with men; PWID, people who inject drugs; URF, Unique Recombinant Form; VERT, vertical transmission (mother to child).

3.3. Regional association of key populations with recombinants

The regional distribution of HIV-1 subtypes, CRFs, and URFs for each key population is included in the Appendix pp17–19. The association of key populations with recombinants varied by region (Table 3). Compared to HET, PWID had the greatest odds of recombinants in Eastern Europe and central Asia [EECA; OR 19.98 (95% CI 6.30–63.34)], followed by Latin America [4.16 (3.02–5.74)] and East Asia [3.20 (2.50–4.09)]. PWID were significantly associated with CRFs in EECA [54.89 (7.62–395.26)] and East Asia [3.26 (2.55–4.18)], and both CRFs and URFs in Latin America

[2.72 (1.45–5.11) and 4.80 (3.36–6.85)]. In contrast, PWID had a strong negative association with recombinants in Southeast Asia [0.06 (0.05–0.07)].

CSW had the largest odds of recombinants in Latin America [15.58 (10.63–22.85)] and East Africa [3.36 (2.85–3.97)]. In both regions, CSW were significantly associated with URFs [22.46 (15.17–33.23) and 3.81 (3.22–4.51)]. However, in West Africa, CSW had decreased odds of recombinants [0.68 (0.56–0.82)], CRFs [0.77 (0.64–0.93)], and URFs [0.06 (0.01–0.23)].

VERT was associated with decreased odds of recombinants in Southern Africa [0.14 (0.03–0.56)] and WCENA [0.69 (0.55–0.88)]. VERT was not independently associated with CRFs or URFs in Southern Africa, but had decreased odds of both CRFs [0.74 (0.58–0.94)] and URFs [0.51 (0.28–0.91)] in WCENA. In Latin America [3.10 (2.50–3.85)], West Africa [3.39 (2.04–5.63)], and SE Asia [12.12 (1.69–86.98)] VERT was associated with increased odds of recombinants. In Latin America, VERT was significantly associated with increased odds of both CRFs [1.85 (1.20–2.86)] and URFs [3.65 (2.86–4.66)], but it was only associated with increased odds of CRFs in West Africa [3.40 (2.03–5.68)] and SE Asia [12.28 (1.71–88.12)].

BLOOD was associated with decreased odds of recombinants in East Asia [0.04 (0.02–0.06)] and WCENA [0.70 (0.51–0.96)]. In both regions, BLOOD was also associated with decreased odds of CRFs [0.04 (0.02–0.06) and 0.65 (0.45–0.92)].

In East Asia, MSM were associated with increased odds of recombinants [1.94 (1.60–2.34)] and CRFs [1.92 (1.59–2,32)]. In West Africa, MSM were associated with increased odds of recombinants [1.44 (1.14–1.82)] and URFs [2.44 (1.80–3.30)]. In Latin America and WCENA, MSM had decreased odds of recombinants [0.46 (0.31–0.67) and 0.18 (0.16–0.20)] and URFs [0.66 (0.45–0.97) and 0.18 (0.15–0.23)].

4. Discussion

A strong association between PWID and recombinants and CRFs was observed globally across all periods and in most regions. Only in SE Asia, where CRF01_AE has a prevalence of ∼70–80% (3), were PWID associated with decreased odds of recombinant strains. The prevalence of recombinant epidemics among PWID in most regions, where "pure" HIV-1 subtypes are typically the most prevalent overall (3), and subtype-based epidemics among PWID in SE Asia, where recombinant strains are highly prevalent, indicates that HIV-1 circulates among PWID via transmission networks distinct from the HET population. This finding extends previous studies suggesting that HIV is transmitted among independent PWID networks across multiple continents (24, 25). Furthermore, the association with recombinants across all periods indicates that PWID play a major role in the global diversification of HIV-1.

CSW were associated with increased odds of recombinants and URFs, particularly in the periods 1990–1999 and 2000–2004. Across East Africa and Latin America, CSW were significantly more likely to be infected with URFs than the HET population. These findings highlight that novel HIV strains frequently arise within the CSW population. URFs arise independently and lack evidence of transmission, minimizing the likelihood that the observed association is due to reverse causation. The decreased odds of CRFs in West Africa may be related to the high prevalence of CRF02_AG (3), similarly to the case of PWID and CRF01_AE in SE Asia. Additional data is required to identify factors contributing to the diminishing global association of CSWs with recombinants across time.

Though VERT was associated with decreased odds of recombinants and CRFs, results greatly varied across times and regions. While biological differences in recombinant strains may cause increased rates of vertical transmission relative to "pure" subtypes (26), high levels of heterogeneity indicate that VERT is not a major driver of increasing HIV-1 diversity.

BLOOD was associated with decreased odds of recombinants and CRFs in both East Asia and WCENA. Particularly in East Asia, where CRF01_AE is highly prevalent, blood transfusion recipients were significantly less likely to have a recombinant strain of HIV than the heterosexual population, which may reflect the geographical origins of the blood donor base. However, the small number of datasets means that the observed association is subject to limitations of power and representativeness. Additional data is required to clarify the association between BLOOD and recombinants.

MSM did not have a significant global association with recombinants overall, likely due to a positive association with CRFs and negative association with URFs. The positive association between MSM and CRFs was strongest in East Asia where the prevalence of CRFs has grown from 25.9 to 75.5% during 1990–2015 (3). Within this region, MSM had nearly double the odds of CRFs as HET, indicating that MSM may be at the forefront of the growing epidemic across East Asia. Similar results were seen in West Africa where the proportion of URFs grew from 3.4 to 15.5% over the same period (3), and findings indicated that MSM had 2.44 times the odds of being infected with URFs. These associations suggest that MSM likely play a major role in the spread of new strains in some regions. Despite an overall association with recombinants that was not significant and historical associations with HIV-1 subtype B (27), the significant association in 2010–2015 and increasing trend across time indicate that MSM may be associated with an increased risk of recombinants.

A key strength of this study is its unprecedented large size, including 77,284 participants from 83 countries, collected from key populations globally during 1990–2015. To our knowledge, this is the first comprehensive analysis of the association between key populations and HIV-1 subtypes and recombinants at a global and regional level. Additionally, data was collected through both a literature search and a global survey, with the inclusion of unpublished data enabling increased regional coverage and improved coverage of recent time periods.

The study also had some limitations. Estimates of associations of key populations with HIV-1 variants are dependent on the underlying data. There was notable variation in coverage by key population, geographic region, and time period. Although the numbers of participants were generally high, the limited number of datasets included from BLOOD means that results must be interpreted with caution. Conclusions could not be independently

TABLE 3 Regional associations of HIV-1 recombinants, CRFs, and URFs with key populations relative to heterosexual people, 1990–2015.

	GLOBAL*	Latin America	Western and central Europe, and North America	Eastern Europe and central Asia	South Asia	Southeast Asia	East Asia	West Africa	East Africa	Central Africa	Southern Africa
Recombinants											
MSM	0.97 (0.93–1.01)	**0.46 (0.31–0.67)**	**0.18 (0.16–0.20)**	–	–	0.67 (0.42–1.05)	**1.94 (1.60–2.34)**	**1.44 (1.14–1.82)**	–	–	1.13 (0.35–3.60)
PWID	**2.60 (2.46–2.74)**	**4.16 (3.02–5.74)**	0.94 (0.82–1.08)	**19.98 (6.30–63.34)**	4.18 (0.98–17.83)	**0.06 (0.05–0.07)**	**3.20 (2.50–4.09)**	–	–	–	–
VERT	**0.58 (0.54–0.63)**	**3.10 (2.50–3.85)**	**0.69 (0.55–0.88)**	–	–	**12.12 (1.69–86.98)**	0.79 (0.30–2.04)	**3.39 (2.04–5.63)**	1.08 (0.85–1.38)	0.80 (0.58–1.10)	**0.14 (0.03–0.56)**
CSW	**1.59 (1.44–1.75)**	**15.58 (10.63–22.85)**	–	–	–	1.96 (0.62–6.21)	–	**0.68 (0.56–0.82)**	**3.36 (2.85–3.97)**	–	–
BLOOD	**0.43 (0.33–0.56)**	–	**0.70 (0.51–0.96)**	–	–	–	**0.04 (0.02–0.06)**	–	–	–	–
CRFs											
MSM	**1.09 (1.05–1.14)**	–	**0.18 (0.16–0.20)**	–	–	**0.59 (0.37–0.92)**	**1.92 (1.59–2.32)**	1.21 (0.94–1.55)	–	–	–
PWID	**2.99 (2.83–3.16)**	**2.72 (1.45–5.11)**	1.03 (0.89–1.19)	**54.89 (7.62–395.26)**	–	**0.05 (0.05–0.07)**	**3.26 (2.55–4.18)**	–	–	–	–
VERT	**0.49 (0.44–0.53)**	**1.85 (1.20–2.86)**	**0.74 (0.58–0.94)**	–	–	**12.28 (1.71–88.12)**	0.77 (0.29–2.02)	**3.40 (2.03–5.68)**	0.58 (0.24–1.43)	0.72 (0.47–1.09)	0.29 (0.07–1.22)
CSW	1.11 (0.98–1.25)	–	–	–	–	1.98 (0.62–6.29)	–	**0.77 (0.64–0.93)**	–	–	–
BLOOD	**0.43 (0.32–0.56)**	–	**0.65 (0.45–0.92)**	–	–	–	**0.04 (0.02–0.06)**	–	–	–	–
URFs											
MSM	**0.44 (0.40–0.48)**	**0.66 (0.45–0.97)**	**0.18 (0.15–0.23)**	–	–	**11.98 (7.91–18.13)**	1.19 (0.78–1.82)	**2.44 (1.80–3.30)**	–	–	2.12 (0.65–6.89)
PWID	0.95 (0.82–1.09)	**4.80 (3.36–6.85)**	**0.52 (0.35–0.75)**	2.54 (0.56–11.52)	**5.22 (1.15–23.78)**	**6.61 (4.62–9.47)**	**0.53 (0.31–0.89)**	–	–	–	–
VERT	0.97 (0.85–1.11)	**3.65 (2.86–4.66)**	**0.51 (0.28–0.91)**	–	–	–	1.50 (0.19–11.84)	0.98 (0.53–1.80)	1.15 (0.89–1.47)	0.90 (0.59–1.35)	–

(Continued)

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TABLE 3 (Continued)

	GLOBAL*	Latin America	Western and central Europe, and North America	Eastern Europe and central Asia	South Asia	Southeast Asia	East Asia	West Africa	East Africa	Central Africa	Southern Africa
CSW	**3.61 (3.15–4.13)**	**22.46 (15.17–33.23)**	–	–	–	–	–	**0.06 (0.01–0.23)**	**3.81 (3.22–4.51)**	–	–
BLOOD	**0.45 (0.26–0.77)**	–	0.97 (0.54–1.76)	–	–	–	2.37 (0.52–10.76)	–	–	–	–

Odds ratios and 95% confidence intervals by region for binomial/multinomial logistic regression between key populations and recombinants, CRFs, and URFs compared to HIV-1 subtypes. Significant results are in bold.

*Regions with insufficient data on key populations to fit a logistic regression model for recombinants (Caribbean, Ethiopia, Middle East and North Africa, Oceania) were included in the global association, but not as independent regions.

Additional data on global and regional odds ratios of key populations and HIV-1 recombinants is included in the Appendix pp11–13.

BLOOD, blood/plasma transfusion associated infections; CRF, circulating recombinant form; CSW, commercial sex workers; HET, heterosexual; MSM, men who have sex with men; PWID, people who inject drugs; URF, unique recombinant form; VERT, vertical transmission (mother to child).

drawn for any key populations in the Caribbean, Ethiopia, Oceania, and Middle East and North Africa (MENA) due to persistent data gaps that have been previously noted (1, 28). Similarly, the absence of data for certain key populations in some regions (e.g., MSM data in Central Africa, East Africa, and MENA) may reflect limited access to healthcare due to sociolegal restrictions (29). Most data were not drawn from nationally representative surveys and we were unable to weigh country-level data according to relative numbers of people of key populations living with HIV in each country, as comprehensive global data on key populations is not available. Hence, reported distributions of HIV-1 variants should not be interpreted as representative of key populations in each region or globally. As HIV subtyping data for most studies was primarily based on *pol* sequencing rather than the whole genome (3), recombination outside of this genome region was likely missed, leading to an underestimation of recombinants. Seventy four CRFs were described at the time of data collection (up until 2015), contributing to the discrepancy between the 48 CRFs identified within the datasets contributing to this study and the >120 CRFs that have been described to date (16). Findings could be subject to bias due to heterogeneity in study design, inclusion/exclusion criteria, subtyping methods, and rates of treatment and migration across regions. In particular, differences in participant recruitment and the definition of key populations between studies could affect observed associations with recombinants. Lastly, insufficient data was available to conduct analysis for transgender women.

Among key populations, increased risk of HIV infection, potentially by multiple strains, and difficulty accessing treatment, potentially leading to increased viral loads, may contribute to the formation and onward spread of HIV-1 recombinants (18, 30). The increasing diversity of the HIV pandemic has implications across diagnosis, treatment, and prevention (2, 6–10). Efforts to prevent the spread of novel HIV strains should consider approaches for key populations such as PWID, CSW, and MSM that are at increased risk of developing and transmitting recombinants. In the case of PWID, this may require prevention-based approaches such as distribution of sterile injection equipment (31, 32), opiate substitution treatment (33), and increased access to antiretroviral therapies (34). For CSW and MSM, prevention efforts should focus on increasing availability of the dapivirine vaginal ring for cisgender women, oral TDF-based pre-exposure prophylaxis (PrEP), and long-acting injectable cabotegravir (1, 35, 36). Increased HIV testing among key populations will help detect and treat new HIV infections early. These efforts can help limit the spread of traits from newly-emergent, highly virulent strains (18). Structural reform may also be necessary as the criminalization of these three key populations is associated with worse HIV outcomes and inadequate viral suppression (37, 38), potentially accelerating HIV-1 diversification.

In summary, this is the first study to comprehensively analyse the global association of key populations with HIV-1 recombinants. PWID, CSW, and MSM were significantly associated with recombinants globally and across multiple regions. As key populations and their partners account for 70% of new HIV infections (1), it is apparent that key populations are driving the genetic diversification of the global HIV-1 pandemic, posing a challenge to diagnostics, treatments, and vaccines against

HIV. Therefore, additional surveillance of HIV-1 molecular epidemiology and increased preventative measures should be targeted toward these key populations.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

NN assessed eligibility of manuscripts, conducted the analyses, designed figures and tables, interpreted the data, and wrote the manuscript. RE, JY, and LD-T screened the electronic literature search results for relevant manuscripts, assessed their eligibility, extracted data, and collected additional published data. SK designed and did the electronic literature search. JH conceived, designed, coordinated the study, wrote the systematic review protocol, assisted with the literature search, assessed eligibility of manuscripts, collected additional published data, conducted the global survey, extracted data, designed the analysis plan, interpreted the data, and wrote the manuscript. All authors read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1153638/full#supplementary-material

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Oral/oropharyngeal "selfies" in gay and bisexual men: a pilot study exploring oropharyngeal screening for HPV-related possible malignancies

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Objectives: This study aims to determine the potential uptake and quality of oropharyngeal "selfies" taken by gay/bisexual men as a screening approach for HPV-associated oropharyngeal cancer.

Methods: From 1,699 gay/bisexual men in the US, surveyed about knowledge and attitudes to HPV-associated oropharyngeal cancer, a random sample of 320 men were invited to take an oropharyngeal "selfie" by smartphone and send it to the study website: 113 (35.5%) did so. Images were rated for quality by three healthcare professional raters blinded to each other's rating, with an otolaryngologist as the gold standard. In the second wave, those whose images were rated as unacceptable were sent a short instructional video and asked to send another image. Of the 65 invited, 46 did so. An additional 15.2% sent acceptable images, and a total of 28.3% of the sample was acceptable.

Results: A total of 1,121 men willing to participate in the future study who believed they could take a quality "oral selfie" were potentially eligible for this activity. A random sample of 320 participated: 153 participants started (47.8%) and 113 participants (35.3%) submitted an image. Responders were more likely to be younger, have higher knowledge scores on oropharyngeal HPV-related cancer, and have had HPV vaccination. There was high agreement between the three raters. Images of good/acceptable quality were 22.1%; oropharynx partially occluded images were 29.2%; oropharynx not visible images were 18.6%; images too dark were 21.2%; and images too small were 8.8%. From the second wave of requests with instructional videos, an additional 15.2% sent in quality images, with the remaining issues being partial occlusion of the tonsils by the tongue.

Conclusion: One-third of the invited gay and bisexual men sent oropharyngeal selfie images to the study website and a total of 28.3% were of clinically acceptable quality. Following an instructional video on poorer-quality images, additional quality images were received. One barrier, i.e., partial occlusion of the oropharynx by the tongue remained. Quality oropharyngeal "selfies" are obtainable online.

KEYWORDS

human papillomavirus (HPV), gay, oropharyngeal cancer, screening, online, telemedicine, oral sex

Introduction

Oropharyngeal squamous cell cancers (OPSCC) associated with human papillomavirus (HPV) 16 infection are increasing in incidence and exceeded the incidence of high-risk HPV infection of the cervix in 2020 (1). HPV-related oropharyngeal malignancies differ from classic oropharyngeal malignancies by having a significantly better prognosis and lower associations with tobacco and alcohol use (1, 2). However, Heck et al. reported that the strongest risk factor for HPV markers in OPSCC in men was sex with another man in the past 5 years (OR = 8.89, 95% CI: 2.14–36.8) (3); furthermore, oral sex is also implicated (4).

The very significantly increased survival rates of HPV-related OPSCC, compared with non-HPV-associated OPSCC, have highlighted the importance of screening and early diagnosis. In a large US study of the National Cancer Database, 2-year overall survival rates for HPV-positive (caused by HPV) cases vs. HPV-negative cases (not caused by HPV) were 93.1 vs. 77.8% ($p < 0.001$) with an adjusted hazard ratio of 0.44 (95% CI: 0.36–0.53; $p < 0.001$) (5, 6). New approaches for screening and early detection in populations at high risk of developing HPV-related OPSCC are warranted.

Oropharyngeal malignancies have the potential diagnostic advantage of being visible to the inspection of the oropharynx (depending on the exact sub-site) by healthcare professionals including physicians, dentists, dental hygienists, and nurses. The use of visual images to diagnose cancer has been successfully utilized in Australia, where self-screening using smartphone images of potentially malignant skin lesions (including malignant melanoma) occurs (7). It was previously demonstrated that the diagnostic and treatment accuracy of store-and-forward malignant melanoma images is close to that of face-to-face clinical consultation (8).

In Western Europe, there have been reports of oral cancer rates significantly declining in men, while oropharyngeal cancer significantly increases (9). *Oral* inspections (of the oral cavity including the floor of the mouth, buccal surfaces, palate, and front two-thirds of the tongue) provide an opportunity for dental screening for oral malignancies, although only a very small proportion of these *oral* lesions are HPV related. We specifically differentiate here between *oral* (mouth, cheek, gums, and front of tongue) and *oropharyngeal* (including tonsils, uvula, back of the throat, and back of the tongue) cancers, and focus on *oropharyngeal* cancers because of the high proportion that are caused by HPV (9).

The combination of tobacco use, alcohol use, and HPV prevalence, which are all known risk factors for oropharyngeal cancer, puts GBM men at the intersection of several heightened risk factors. Tobacco use and alcohol use also add to the elevated risk of oral cancers, and tobacco-related and alcohol-related disorders are significantly more common among gay and bisexual men (GBM) than heterosexual men in nationally representative samples in the US (10, 11). It is also a reason to consider that the approaches investigated here may also apply to *oral* cancers, although that is not the focus of this study.

Artificial intelligence (AI) approaches have established that oral images depicting potentially malignant lesions can be identified with sensitivity and specificity approaching that of experienced clinicians (12). Information technology approaches to potentially malignant oral lesions have shown promise. Welikala et al. (12) used convolutional neural networks (CNNs), which are designed for processing structured arrays of data, including images, for referral for clinical decision-making. They demonstrated precision levels of 84.8% for lesion detection, and 67.5% for identifying the need to make referrals for conventional diagnosis. More recently, Tanriver et al. (13) used deep networks to develop second-stage classification analyses for the classification of oral lesions into benign lesions, potentially malignant lesions, and carcinomas.

Visual inspections of *oropharyngeal* sub-sites (palatine tonsils, tongue base, soft palate/uvula, and posterior oropharyngeal wall), where HPV-associated OPSCC occurs, however, have never been reported on images. Telemedicine advances during COVID-19 have shown that oral and oropharyngeal images can be taken in a clinical setting by patients with good results and are acceptable to patients (14, 15).

However, recent previous research with practitioners (16) has indicated that clinical screening for OPSCC in the US is an "orphan" practice, with physicians infrequently screening GBM for OPSCC unless symptoms are reported, while dentists may limit their inspection to the oral cavity but not the oropharynx. This is despite practitioners with significant numbers of GBM patients being aware of the heightened risk of HPV-associated OPSCC in GBM.

In view of the reported epidemic increase in HPV-associated and sexually transmissible cancer in the oropharynx, particularly in gay and bisexual men (1, 3, 4), we investigated whether smartphone "oral selfies," of sufficient quality for screening, could be taken by GBM following online instruction.

Methods

This cross-sectional study aimed to recruit 1,700 GBM from two online dating portals (Scruff and Jack'd; Perry Street Software Inc., New York, NY) used by GBM. In February–March 2022, GBM with a profile on either portal was shown a single advertisement with an embedded link to the online survey. The recruitment criteria were (a) GBM aged ≥18 years, who self-reported to be (b) living in the USA, (c) having sex with a man in the past 5 years, and (d) self-identified as men. Trans men, non-binary individuals, and other individuals self-identifying as men could participate. Interested individuals were directed to a screening questionnaire (Qualtrics, Provo, UT) to determine eligibility. If eligible, they were directed to the consent process, after which they could access the main survey.

All active users meeting eligibility criteria, who logged in during the 5-day campaign period saw the advertisement. Recruitment continued until the institutional review board (IRB) approved the number of participants who had responded and provided full consent (participants could pause the survey and continue later). Of the 9,264 total clicks, 4,192 were unique clicks on Scruff and 5,072 were unique clicks on Jack'd. Among these, 4,464 people commenced the consent process, 1,836 people completed the consent process (19.86% of unique clicks), and 114 participants were removed during the deduplication process. After validation,

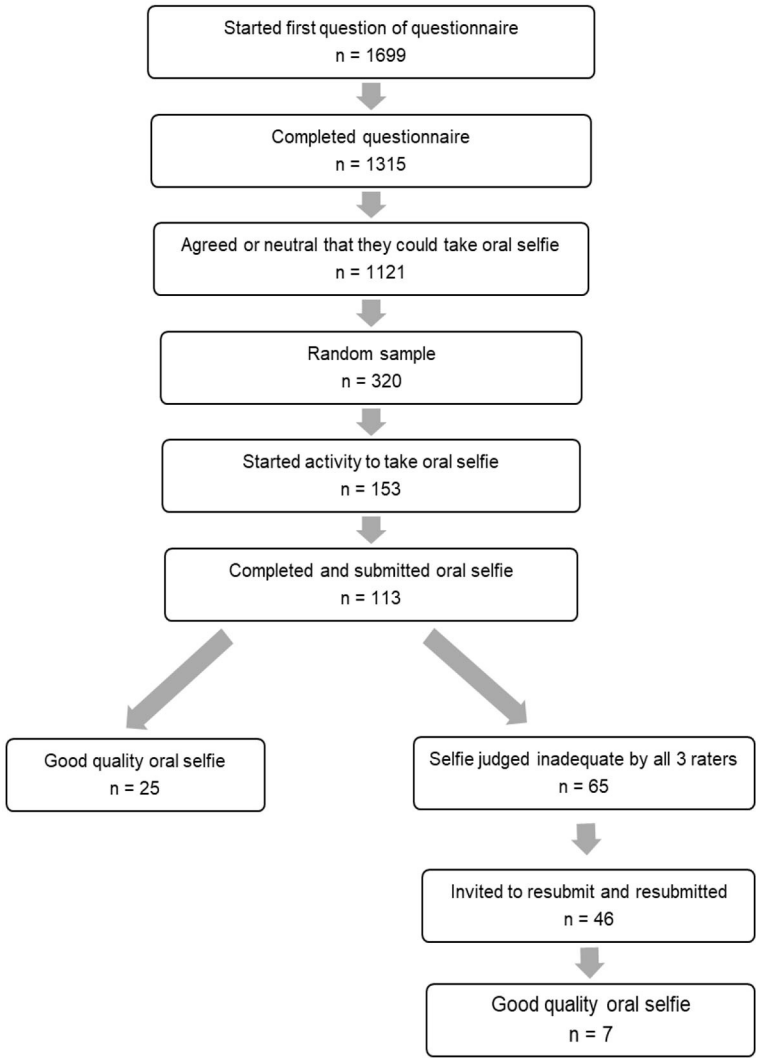

FIGURE 1
Flow of study design.

deduplication, and internal consistency protocols, 1,722 consenting participants remained eligible, and 1,699 completed the first question of the main survey.

All users in the US and its territories who logged in would see the ad, which could be saved as an inbox message to check later. The link could only be accessed by Scruff/Jack'd users. Scruff had a reach of 185,257 with 417,296 total impressions, whereas Jack'd had a reach of 120,409 with 247,956 impressions. Individuals who completed the survey were recompensed $50 for their effort.

After the recruitment period, all surveys were reviewed to determine uniqueness using a modified validation and deduplication protocol (17). Study materials were reviewed and approved by the University of Minnesota IRB.

Participants from the survey who were willing to participate in future studies and "strongly agreed," "somewhat agreed," or "neither agreed nor disagreed" that they could take a quality "oral selfie" were potentially eligible ($n = 1{,}121$) for this activity. A random sample of 320 of these individuals was invited to participate. A total of 153 participants started the activity (47.8%) and 113 participants (35.3%) submitted an "oral selfie," based on written instructions and an illustration of an ideal image, for rating. Figure 1 illustrates the sampling chain.

Participants who submitted one best "oral selfie" (multiple attempts possible) were compensated with a $30 Amazon gift card. Three clinicians blinded to each other's ratings (an otolaryngologist/head and neck surgeon, a dentist with a large GBM and HIV practice, and a medical researcher without clinical experience in the area) rated the photos. These photographs, in random order, were first rated for quality (good, acceptable, or unacceptable), and those considered not acceptable were additionally classified for one or more reasons: too dark, too small or unfocused, oropharynx partially occluded, or oropharynx not visible at all.

A second wave of those men whose images had not been rated by all of the raters as good or acceptable quality (to have no possibility that the selection of inadequate photos was a function

TABLE 1 Differences between participants who completed an "oral selfie" and those who did not.

Variable mean ± SD	Completed	Did not complete	*p*
Age (years)	38.55 ± 11.44	42.62 ± 12.95 years	$t = 2.80$, df = 318, $p = 0.006$
HPV and oropharyngeal cancer knowledge scores*	5.20 ± 0.23	5.97 ± 0.29	$t = 2.05$, df = 317, $p = 0.01$
Had HPV vaccination (%)	45.53%	33.33%	$\chi^2 = 4.61$, df = 1, $p = 0.03$
Compared to other early cancer screenings, I believe that the benefits of checking for oropharyngeal cancer early are:**	3.97 ± 0.89	3.63 ± 0.90	$\chi^2 = 12.88$, df = 4, $p = 0.012$

*Possible range 0–12.

**1 = Much lower; 2 = Somewhat lower; 3 = About the same; 4 = Somewhat higher; 5 = Much higher.

of rating uncertainty, $n = 65$) was invited to watch a commercially produced 3-min video created for this purpose (https://vimeo.com/manage/videos/780429315) and take another oral selfie. The compensation was again $30. This study was approved by the University of Minnesota IRB. Differences between those who uploaded or did not upload a photo after being invited to participate in taking an "oral selfie" were computed using 2-tailed *t*-tests for interval data and χ^2 tests for nominal or ordinal data.

Results

Oropharyngeal oral selfies were received on the study website from 113 GBM. Comparing those who completed the request with those who did not (Table 1), those who completed the request were more likely to be younger, had higher HPV and oropharyngeal cancer knowledge scores, were more likely to have had HPV vaccination, and were more likely to have answered the question "Compared to other early cancer screenings, I believe that the benefits of checking for oropharyngeal cancer are higher." There were no significant differences in race, ethnicity, sexual identity, or education.

The great majority (93.80%) had taken the photos themselves, and a few were taken by their partners or spouses. The mean ± SD number of photos that had to be taken to get 1 uploaded was 8.28 ± 6.55, range 1–34. Time taken was a mean of 6.80 ± 6.41 min, range 1–45. The majority (75.20%) reported using Apple phones, 15.9% Samsung, and the remainder a variety of Android smartphone makes. Figure 2 illustrates the reported difficulty of obtaining the photograph, with a mean, median, and mode of "slightly difficult."

Figure 3 illustrates that high-quality oropharyngeal selfies can be obtained from men through limited instruction such as that provided here (Figure 3A). Figure 3B illustrates that one of the participants had bilateral tonsillitis, and that enlarged tonsils are clearly visible. There were also a number of unsuccessful images, for reasons of being too dark (Figures 3C, D), having the oropharynx occluded by the tongue (Figure 3D), and being poorly focused (Figure 3D).

There were significant correlations between the quality ratings of the three reviewers blind to each other's ratings. The otolaryngologist was the "gold standard" reviewer and gamma coefficients with the medical researcher were 0.88, $p < 0.001$, and the dentist, 0.72, $p < 0.001$.

Quality ratings by the otolaryngologist were as follows: good or acceptable quality, 22.1%; oropharynx partially occluded, 29.2%; oropharynx not visible, 18.6%; image too dark, 21.2%; and image too small, 8.8%. For these last two categories, an additional secondary code of partial or complete occlusion was registered for 12.

In the second wave, of the 65 whose images were rated as unacceptable by all the three raters in the first wave, 49 commenced the second wave exercise and 46 (70.8%) completed the exercise. The orolaryngologist's blinded ratings on the same scale were of an additional 7 (15.2%) rated good or acceptable quality. However, 36 (78.3%) remained partially obscured. Combining the participant results for the first and second waves, 28.3% of the 113 were rated as good or acceptable images.

Discussion

These data indicate that GBM will respond to a request for a smartphone oral selfie with email instructions and that oral selfies of high enough quality to identify potentially malignant oropharyngeal lesions can be obtained. Oral selfies of sufficient quality for potential diagnosis can be obtained from GBM. Younger men who were HPV vaccinated, better informed about HPV-related oropharyngeal cancer, and agreed that the benefits of screening for oropharyngeal cancer were higher than for other early cancer screenings and were more likely to return images. This feasibility study indicates that for 28% of SGM, taking oral "selfies" of a quality to potentially observe the potential malignancies and returning them to a study website is feasible with minimal training. However, some participants could do this efficiently while others took significant time. Research that further explores more detailed approaches to training and guided telemedicine to explore oropharyngeal images is clearly warranted.

A serendipitous data image that shows bilateral tonsillitis (Figure 3B) illustrates the level of detail which may be obtained. Relatively simple modifications (an instruction video, using flash in dark photos or better positioning of the camera to improve focus and image size) can increase the proportion of quality oral selfies to over 28% in total by improving some second-wave previously unacceptable quality images.

It is clear that these quality images may be obtained by oropharyngeal selfies, using only online instructions, or as in the second wave, a video demonstration with instructions. The most difficult image modification is to prevent the tongue from occluding the palatine tonsils, which, along with the tongue base, constitute the majority of potentially malignant lesions. Those which were too dark could be remedied by the use of flash; and too small,

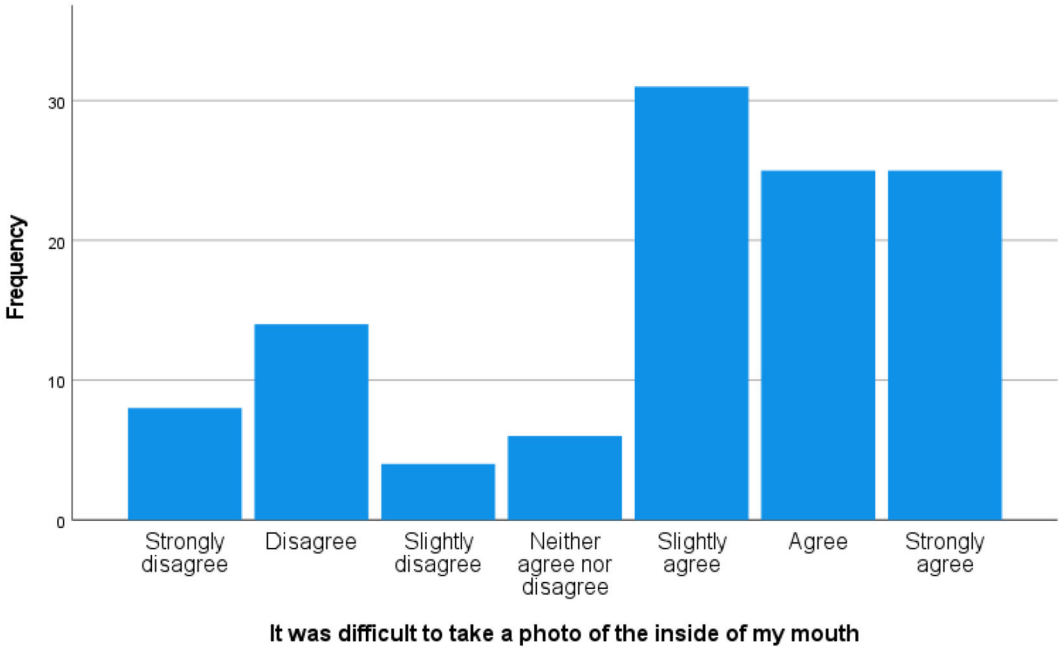

FIGURE 2
Reported difficulty of taking an "oral selfie."

by better positioning of the camera. Clearer instructions, using an instructional oral selfie video for those whose oral selfie was judged inadequate by any of the 3 raters of the first wave, resulted in an additional 15.2% of the second wave being judged acceptable by the otolaryngologist. In this second wave, the fault remaining was partial occlusion of the palatine tonsils by the tongue. Clear video instructions do appear to raise the proportion of quality images by 15%, in those who previously had inadequate images. The total number of acceptable images of the first and second waves, by the participant, was 28.3%.

Inter-individual variability in tongue bulk and "size" of the oral cavity will likely mean that some subjects will not benefit from this approach. Furthermore, given that most tongue base tumors are not readily visible via trans-oral view, our approach will not allow screening for this sub-site. However, given that the bulk of HPV-related oropharyngeal tumors occurs in the palatine tonsils and visible oropharynx, oral "selfies" do appear to provide an opportunity to economically screen online, without having to rely on clinic attendance, which may be geographically or economically challenging for GBM, many of whom may not wish to "come out" to a clinician or who may anticipate stigma or discrimination, have heightened concerns about confidentiality, or not want to discuss their sexual behavior or identity.

In potentially malignant HPV-associated oropharyngeal lesions, their significantly improved outcomes over classic oropharyngeal lesions (5, 6) make screening attractive, especially in high-risk populations such as GBM. Progress in using AI to identify oral lesions requiring referral suggests that may be possible to identify suspicious oropharyngeal lesions in GBM.

While HPV vaccination will over time reduce the incidence of HPV-related cancers, it is calculated that the full effect of HPV vaccination will not occur until the year 2045 (1). Interventions to obtain oropharyngeal "selfies" can also be used to encourage HPV vaccination, but HPV vaccinations (a course of 3 over 6 months) are costly in the US, and not recommended for men over the age of 45 years. Potentially, oral "selfies" may open the possibilities of online screening for those who fall through the gaps of receiving HPV vaccination.

While this study was limited to oropharyngeal selfies to identify possible HPV-related malignancies, they do also suggest that *oral* selfies of the oral cavity and buccal mucosa, palate, and gingiva may be possible. Given that GBM report relatively high rates of alcohol and tobacco use, both related to higher rates of oral malignancies (10, 11), it may be possible to screen for *oral* lesions, although this was not explored in the present study.

These pilot data are limited by being a random sample of a larger study in the US. There are inadequate geographic data on the rise in HPV-related oropharyngeal cancer in men, and so these findings may not be generalizable beyond Western countries (18). Furthermore, few major cancer registries ask questions on sexual behavior or sexual identity, severely limiting data available for epidemiological analysis. Nevertheless, it appears that although not all oral selfies in this study are of a quality to make diagnoses, the potential of oral "selfies" as a screening tool for HPV-associated oropharyngeal lesions is worth further exploration.

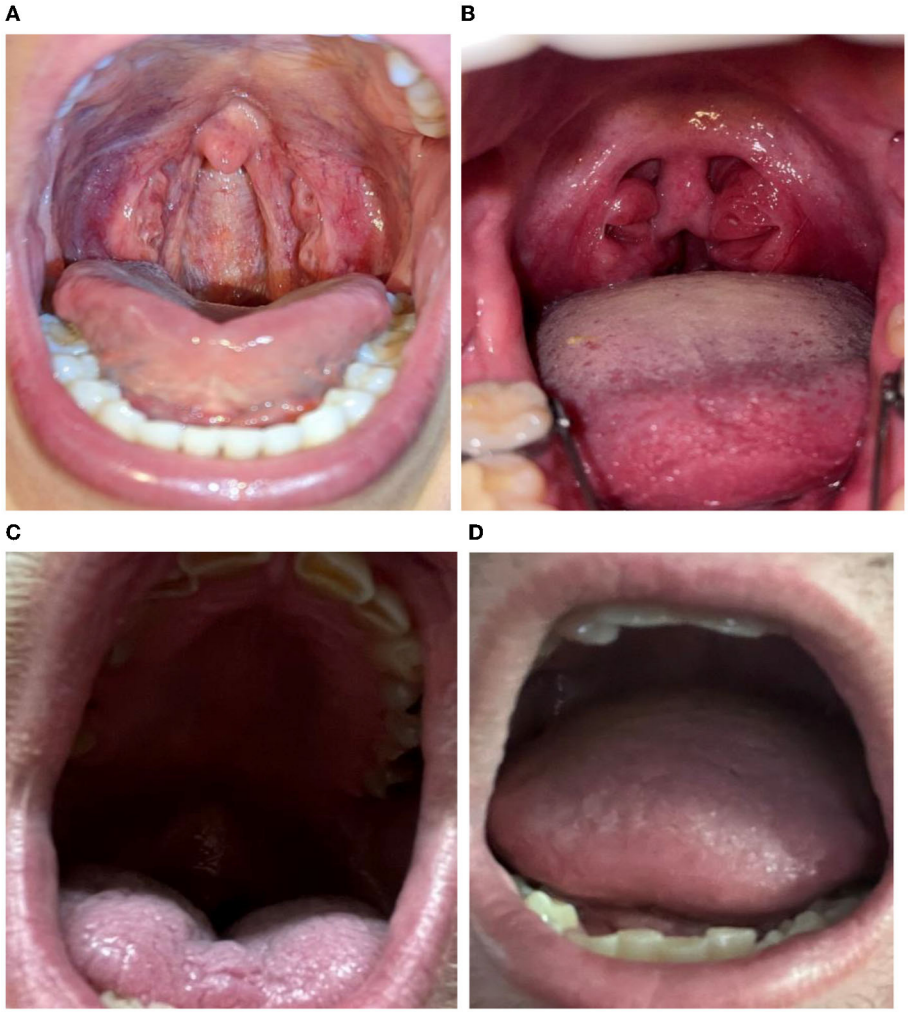

FIGURE 3
"Oral selfie" examples. **(A)** Good quality. **(B)** Good quality, inflamed tonsils. **(C)** Too dark. **(D)** Occluded oropharynx, poor focus.

Data availability statement

The datasets presented in this article are not readily available because, the study is still ongoing. Requests to access the datasets should be directed to mwross@umn.edu.

Ethics statement

The studies involving human participants were reviewed and approved by University of Minnesota IRB. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MR: wrote draft, conducted data analysis, and grantee. SB: curated data and conducted data analysis. CN, SK, and MR: rated clinical images. IZ, JW, BR, CS, AN, CF, CN, SK, and SB: reviewed and edited versions of the drafts. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Addressing knowledge gaps: the key role of community health workers and healthcare providers in human papillomavirus prevention and vaccine uptake in a border community

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The Human Papillomavirus (HPV) is the most common sexually transmitted infection and nearly every person who is sexually active will get HPV at some point in their lifetime without having the HPV vaccine. Healthcare Providers (HCPs) and Community Health Workers (CHWs) play an essential role in promoting the HPV vaccine and providing education about HPV in communities. Three focus groups with CHWs (n = 17) and HCPs (n = 7) were conducted and led by trained facilitators. In addition to participating in the focus group, CHWs and HCPs completed a brief questionnaire. Focus groups were voice recorded and transcribed for qualitative analysis. Independent coders conducted content analysis to identify the salient themes of the focus groups. Several important findings emerged from this study highlighting the barriers to HPV knowledge, gaps in the self-perceived role of HPV cancer prevention, and opportunities to action. Financial, knowledge, patriarchy, behaviors, attitudes, and fears were identified as the perceived patient-related barriers to promoting HPV cancer prevention. Both CHWs and HCPs explained that their female patients are often discouraged by their husbands from seeking out sexual health-related healthcare. Finding suggest the need for community tailored education on HPV and "best practice" trainings for HPV prevention that is applicable to both CHWs and HCPs.

KEYWORDS

human papillomavirus, community health workers, Hispanics, healthcare providers, sexual health

Introduction

The Human Papillomavirus (HPV) is the most common sexually transmitted infection with as many as 43 million infections in 2018 (1). Nearly every person who is sexually active will get HPV at some point in their lifetime without the vaccine (2). HPV contains more than 150 different DNA related strains. Most HPV strains are asymptomatic and the infections will resolve on their own and will not cause health problems. However, some HPV strains

be considered "low risk" and result in genital warts, while other HPV strains can be considered "high risk" and have been associated with cancer or other health problems if unnoticed. The HPV vaccine protects individuals from the high-risk strands that cause genital warts and various HPV-related cancers (1). Cervical cancer among cancer of the vulva, vagina, penis, anus, throat, tongue, and tonsils have been attributed to HPV (1). Screening and vaccination are the safest and most effective ways to be protected against HPV-related illness (3). Proper screening differs by age, gender, and previous screening results (4–6). Screenings are gender specific in detection, with women being able to get an HPV test to look for the virus and a Pap test for precancers cell changes, men do not have any approved test of HPV (7, 8). For early detection of cancer, diagnosis and treatment, the public needs to be educated on prevention efforts, health promotion, and the administration of the HPV vaccine (9). Without the education and knowledge on what HPV is and how to be protected against it, HPV infections can lead to more serious issues and go undetected until a cancer diagnosis which could lead to a poorer prognosis.

The U.S.-Mexico border region, where HPV prevalence for any subtype has been found to be 53.2%, is reported to have the highest cervical cancer rates in the United States, with 8.4 cases of cervical cancer for 100,000 females (10). This number is higher for Hispanic women as compared to their White, non-Hispanic counterparts at 6.5 per 100,000 (11). (El Paso, Texas), is one of the largest metropolitan cities on the U.S.-Mexico border, with 82% of its 839,238 inhabitants of Hispanic origin (12). Adolescents in (El Paso, Texas), have the highest rate of first-dose HPV vaccine uptake in Texas and one of the highest in the country (13). This suggests the presence of facilitators for first-dose HPV vaccine uptake in the population of predominantly Mexican origin in (El Paso, Texas) and indicates that this specific location may provide important information in the study of first-dose vaccine uptake in children and young adults. However, it is important to recognize that the COVID-19 pandemic has been identified as a significant barrier in health-seeking and obtaining non-COVID-19 related medical services (11). Data is needed to understand how COVID-19 has specifically affected HPV vaccine uptake and HPV-related education.

To further understand the barriers to HPV education delivery and HPV vaccine uptake in (El Paso, Texas), it is important to understand that sexual health education plays a key role in both. Sexual health education in Texas is focused on abstinence-only education. Health literacy is essential in lowering STI rates, including HPV (14). The (El Paso, Texas) Independent School District (EPISD) is the 12th largest district in Texas, with nearly 50,000 students. The sexual education curriculum in EPISD, which is State mandated, focuses solely on abstinence, considered by the State to be 100% effective in preventing pregnancies, STIs, and any emotional trauma (15). The curriculum used at EPISD as well as the lack of sexual health resources outside of the school setting may present barriers to increasing health literacy in the community (16). With 80.3% of the (El Paso, Texas) community reporting only having a high school degree, this abstinence-focused education provided by school districts may be the only sexual health education (El Paso, Texas) residents will encounter in their lives (12). The public health care system, through Community Health Workers (CHWs) and other healthcare providers, therefore, may be left the task of increasing health literacy by supplementing the knowledge of people in the community.

CHWs, also known as promotors/as de salud, play an essential role in educating the community, promoting healthy behaviors, and providing resources. These individuals have been referenced as paraprofessionals who have a deep understanding of the community they are serving and whose primary goal is to provide healthcare resources and education to said community (17). CHWs are trusted individuals in their respective communities and act as a bridge between the public and health providers (18). Their role is integral in removing barriers that prevent the community from seeking out resources and connecting them with the proper health care services (17, 19). CHWs promote meaningful changes in the health behaviors of the community, as they are in close contact and provide education to the communities they serve (20). The low economic and health insurance rates in communities have further increased the need for CHWs and their connection to health-related services (21). CHWs are doing essential work for health promotion and prevention in these communities with different and special needs (22, 23).

CHWs act as vital links to the health care system by providing referrals, transportation, food assistance, social support, and removing situational barriers, among other services. Texas is one of 16 states in the U.S. where CHWs are required to follow a state-wide training requirement through state government programs, colleges, or training centers that emphasize health education and community outreach (24). Programs have diverse curricula, require different durations of training, and vary in methods (24). To obtain this certificate in Texas, individuals must complete an approved 160-h training program. Their education does not stop here as they are also required to renew their certification every 2 years with continuing education credits. CHWs' efficacy is debated in the field, but their contributions are well documented and have been seen to improve access, the education and behaviors of their communities for specific conditions (asthma, hypertension, diabetes, HIV/AIDS, cancer screening, vaccines, maternal and child health) (25). CHWs have a long history as salient links for low-income members of the border community to health services and information.

Other barriers traditionally overcomed by CHWs are language differences between providers of services and clients. The U.S. Census has a poverty threshold of $31,661, and (El Paso, Texas), has a poverty rate of 18.8%, with a per capita income average of $21,683 (12). Texas also reports having 18.4% uninsured individuals, of which 10% are Hispanic (12). (El Paso, Texas), reports having 22.1% uninsured individuals, which is estimated to have risen after the COVID-19 pandemic (26). (El Paso, Texas) is one of the 22 cities where Spanish is predominantly spoken to English by 70–80% of the population (27). The role of the CHWs in this community is not only to educate the community and provide resources, but to make sure they are linguistically and culturally appropriate for the individual (28, 29). CHWs are often found in locations where healthcare is limited, and this being a community made up of majority Hispanics and immigrants, with high poverty rates, low rates of education, and low insurance rates.

Healthcare providers (HCPs) (i.e., physicians, nurses, nurse practitioners) are other key figures in health care education who receive a different education and training than CHWs. Curricula vary as they are based on the degree being obtained. HPV education and training is inconsistent with knowledge gaps across the various healthcare professions as it is not often a focus in the various curricula (30). Both CHWs and HCPs deliver care in the community in two

different and complementary ways. While CHWs take on the first contact with the individual, build rapport, gain trust, and connect individuals to services who otherwise would not receive these services, HCPs have the role of service delivery. HCPs are the next line of contact with individuals, and they have the responsibility of not only delivering the services but of providing their patients with a more extensive health education. It is this provider-patient relationship that makes patients gain more trust in the healthcare system, perceive a greater quality of care, and increase frequency of visits (31).

HPV vaccinations have been received with low enthusiasm and acceptance by different communities. The latest vaccination rates from 2020 report that only 54% of adolescents have received two or three doses at the recommended time (52% for males; 56% for women) (32). Hispanic adolescents between ages 13–15 have received two or three doses of the HPV vaccine at 58% while Non-Hispanic Whites report a 51% vaccination rate (32). Due to this low reception of the HPV vaccine, it is important for the public health sector to identify the barriers to vaccine uptake and understand the different roles CHWs and HCPs play in increasing the rates of the vaccine.

The (El Paso, Texas), a border town with an 80% Hispanic population, is a prime location for exploring the barriers to HPV vaccination uptake. HPV-data and research are prominent in the health care field yet the frequency with which they reach the community may not be sufficiently efficient to improve knowledge gaps or change attitudes and perceptions (33). Gaps in knowledge include topics about HPV strains that lead to cancer, HPV-related cancers, information on vaccine effectiveness, vaccine side effects, abnormal pap smear tests, and sexual promiscuity stigmas (34). The HCP's role in the HPV-vaccine uptake is key in closing the gaps in knowledge of the individuals they serve. Literature indicates that HPV-vaccine uptake can have up to a foldfold increase if there is a strong provider recommendation to the parents (35).

The current study is part of a 5-year behavioral research project that will assess HPV-related knowledge, attitudes, and practices in a Hispanic community, identify barriers and facilitators of vaccine uptake, and develop and utilize interventions to improve vaccination, screening, and health literacy. The project follows three aims: (1) Identify predictors of HPV vaccine acceptability, knowledge, and screenings (VAKs) among Hispanic adults, (2) assess the practices and behaviors of emerging and current healthcare providers, followed by an intervention to improve provider recommendation and patient communication strategies, and (3) develop, implement, and deploy a culturally-tailored, bilingual, intervention to increase HPV vaccine uptake, screenings, and critical health literacy across a broad age range (26–45).

This focus group falls under aim 3 and is one of three focus groups (HPV-associated cancer survivors and caregivers; CHWs/HCPs; youth and adult males) that will be used to inform the intervention (36). These three focus groups in combination with the VAKs community sample study will come together to inform the intervention of a Randomized Clinical Trial (RCT) that will attempt to vaccinate 400 Hispanic adults during Fall 2023. The aim of this focus group is to understand perceptions about the roles of CHWs and HCPs in increasing HPV-vaccine uptake. Knowledge, attitudes, and practices related to Human Papillomavirus (HPV), the HPV vaccine, and HPV-related cancers were examined among CHWs and healthcare providers HCPs in a U.S.-Mexico border city. The goals of the current study were to: (1) assess HPV-related knowledge, attitudes, and practices, (2) identify barriers and facilitators of vaccine uptake; and (3) assess the practices and behaviors of CHWs and HCPs.

Methods

The study was cross-sectional and qualitative in nature. Data was collected through three online focus groups of CHWs and HCPs. Focus groups are considered effective research methods, and, in their online modality, online focus groups remain effective and provide a convenient flexibility (37). During a focus groups, participants are invited to come together and increase understanding of experiences. Interactions among groups members can provide invaluable insight, ideas, and bring new questions and issues not previously explored. Therefore, focus groups are a strong methodological tool used in health promotion and especially helpful in planning, designing, and implementing interventions geared to health promotions efforts. The study utilized purposive sampling, selecting these two groups due to their shared characteristics and relevance to the end goal of the project.

CHWs and HCPs were recruited to participate by local partner agencies in (El Paso, Texas), the project manager, and CHWs working with the research team through flyers and word of mouth. These local agencies included federally qualified health center, community-based organizations, local department of public health, the Mexican consulate, local cancer care centers, and the primary institution. These agencies are committed to understanding the health needs of the community and to increasing health access, and they supported the aims of the research project. Willing participants were invited to take part in a brief survey followed by a focus group through the online service Zoom (2020). The initial survey asked participants to answer demographic questions and questions about their HPV knowledge, attitudes, and practices. Upon completion, participants were given the focus group information and invited to participate. During these Zoom sessions, participants were first introduced to the research team and to the navigation tools that would be used for the group discussions; ground agreements for the discussion were established; and a detailed explanation of the informed consent was given, after which participants submitted them electronically. Once consent forms were submitted, the recording of the session began with the participant's permission, and facilitator began asking the focus group questions to facilitate discussion. Participants were asked about their knowledge about HPV, their knowledge about the HPV vaccine, their HPV health messaging, and recommendations to improve HPV vaccination uptake. Their participation was voluntary and anonymous and had an average duration of 1.5 h. Two researchers trained in Public Health and Social Work facilitated the groups using a structured open-ended question guide. Data were gathered between April and June 2020.

The first two focus groups were conducted in Spanish and in total included 17 CHWs ($n = 17$). Both groups were combined in data analysis due to similarity in scope and group characteristics. The third focus group was with HCPs and was conducted in English. The third focus group occurred over the span of two different dates. On the first date, seven HCPs (nurses, physicians, health professionals) ($n = 7$) were part of the focus group with the same online modality. Due to time constraint and interest for the participants to finish the entirety of the questions, a second date was added for the focus group. On the second date, only four ($n = 4$) of the original participants were able to

come back and finish the study. After the focus groups the recordings were transcribed by trained transcribers from the research team, who protected the anonymity of the participants. Upon completion of the focus groups, participants were given $30 gift cards to compensate for their time and participation.

Data analysis

A qualitative coding manual adapted from Saldaña (38) was prepared by project research assistants to facilitate and standardize the team coding process of the qualitative data. Participant responses were organized in a template created through Microsoft Excel to facilitate manual coding. Three coders from the research team independently employed a pre-coding technique to help filter important information through highlighting, underlining, or coloring salient words and/or phrases in individual participant responses (39). This process is important to facilitate the coding process to follow. Coding was done manually on an excel sheet as well as with the use of NVivo Software, a qualitative and mixed methods data analyzing software which permits for the identification of themes, visualization tools, and draw conclusions (40). Data were then interpreted through the creation of preliminary codes using affective methods (i.e., emotion and value coding) and elemental methods (i.e., descriptive and NVivo coding). An emotion code included participant's sentiments, feelings, reactions, excitements, and sensations. Value codes included coding participant values, attitudes, and beliefs. Descriptive codes were short phrases or words that described the content. And finally, NVivo codes were coded in the software program to identify if participant's own words seemed to be an important direct quote. Pre-coding was the first stage to data analysis, in which coders would listen to the audio-recording while reading along the transcription. Coders were instructed to retain from coding and use this stage to make notes of areas they thought were relevant and would require further attention during the coding rounds. During coding rounds, coders were instructed to code comment by comment, look for salient sections, quotes, and/or sentences that stuck our to them. All of their codes were tracked through Microsoft Excel. After a pre-coding round and two independent coding rounds, coders would share their codes and work simultaneously to identify differences in codes. This process, known as triangulation, was used to reduce bias and enhance intercoder reliability and reduce error in the coding process. During this process, the coders would work together to analyze the final codes for patterns, identify which connections and create categories. Final codes and categories were presented to the project research team for theme extraction. Disagreements were discussed and resolved during coding meetings. Qualitative analysis focused on four domains: (1) general HPV knowledge; (2) access to healthcare services related to HPV prevention; and (3) HPV health promotion efforts.

Results

For participant demographics (see Table 1).

Reporting focuses on these CHWs and HCPs regarding the salient similarities and differences in their roles, knowledge, and challenges related to promoting HPV cancer prevention in the Hispanic U.S-Mexico border community of (El Paso, Texas),

TABLE 1 Participant demographics.

Community health workers (n = 17)		
Gender, n (%)	Female	14 (82)
	Male	3 (18)
Ethnicity, n (%)	Hispanic/Latino/Mexican-Origin	15 (86)
	Non-Hispanic/Latino	2 (14)
Primary language spoken at home, n (%)	Spanish	10 (59)
	English	2 (12)
	Both	5 (29)
Time employed as CHW, n (%)	Less than 1 year	6 (35)
	1–4 years	8 (47)
	5–9 years	2 (12)
	Prefer not to answer	1 (6)
Population served, n (%)	Children (<18)	3 (18)
	Young adults (18–24)	4 (25)
	Adult ages (25–64)	6 (36)
	Older adults (65+)	4 (21)
Health care professionals (n=7)		
Gender, n (%)	Female	6 (86)
	Male	1 (14)
Ethnicity, n (%)	Hispanic/Latino/Mexican Decent	7 (100)
	Non-Hispanic/Latino	0 (0)
Primary language spoken at home, n (%)	Spanish	1 (14)
	English	5 (72)
	Both	1 (14)
Time employed as health professional, n (%)	1–4 years	1 (14)
	5–9 years	1 (14)
	10+ years	5 (72)
Current role, n (%)	Nurse	5 (72)
	Medical doctor/Physician	1 (14)
	Health professional	5 (14)

The roles CHWs and HCPs saw for themselves in HPV cancer prevention shared similarities, however, were distinct in some of their approaches (see Table 2). Additionally, both CHWs and HCPs identified the need for HCPs to be more proactive and intentional in their role in HPV health promotion. HCPs are viewed as authority figures by the community and could play an active role in providing information to patients. HCPs recognized that they need to take an active role, and mentioned community partnerships and educational campaigns as a good avenue for this. Regarding the HPV vaccine, all CHWs (n = 17) and HCPs (n = 7) stated that they would recommend that patients receive it. Two HCPs reported:

> "If we make strong recommendations on the provider side, if the provider and the staff is knowledgeable, it's up to date with the most current information, then we are making those really strong recommendations and not be so lackadaisical: 'well there is a

TABLE 2 Self-perceived roles in HPV cancer prevention.

Community health workers	Healthcare providers
Educate—first self, then community	Educate—first self, then healthcare workers, then community
Education strategy: (a) debunk myths, (b) clarify misinformation, (c) "spread fear" about consequences of HPV (to motivate parents to vaccinate their children)	Education strategy: (a) build rapport with patients, (b) create friendly, caring clinical environment (to encourage patients to ask questions and be open to communication about HPV and sexual health)
No mention of recommending HPV vaccine	Make "strong recommendations" to get the HPV vaccine

> vaccine if you want it, if not…' you know… because… they come to us, they come to us because we are the professionals. We were supposed to know this stuff."

> "Having advanced practitioners or nurse practitioners go out to the community and educate patients and geared towards schools, maybe some sort of school age children, High Schools, elderly, adults, parents, let's have something for the parents, education for the parents, go into the community."

CHWs displayed a range of awareness and knowledge about HPV, some evidencing strong knowledge of HPV-associated risks, such as cervical, uterine, and oral cancers, and others having only basic or very little knowledge of HPV stating "It is one of the most common STI's. I do not really know too much about it besides that."

CHWs gained their knowledge of HPV in different ways, the majority learning of it through HPV-affected family, friends, or clients; some gaining awareness through school or work-related trainings or courses; and one learning about HPV through a gynecologist. During the initial pre-focus groups survey, when asked "Do you believe you are properly informed about HPV?" one CHW strongly agreed, five agreed, nine were not certain, and two did not agree.

HCPs displayed clinical knowledge of HPV, stressing its association with cancer and genital warts. They reported a variety of ways of having learned about HPV, including experience in school and clients with HPV infections, pediatricians or pharmaceutical representatives, or self-education. "I first learned of HPV when the pharmaceutical company started coming around and talking about it, but further than that, I went ahead, and I educated myself with the content." When asked, "Do you feel adequately informed about HPV?" during the initial pre-focus group survey, one HCP strongly agreed, three agreed, three were undecided.

CHWs and the HCPs identified many similar perceived obstacles in their efforts to prevent HPV cancer in the Hispanic community of (El Paso, Texas). These obstacles related to the community members'/patients' financial situations, knowledge of HPV, influence of patriarchy, and attitudes. Additional patient-related barriers mentioned by HCPs were behavior and fear (see Table 3).

Non-patient-related obstacles mentioned by HCPs were high cost of HPV vaccines, vaccine accessibility, and inconsistency in practices and information provided by HCPs, which causes distrust in patients and results in patients not seeking out medical care, including HPV-related care. One HCP mentioned Providers giving unnecessary pap smears as an example of this last obstacle.

> "Primary care providers do not carry the vaccine, so now they have to out to either a pharmacy or try to seek it somewhere else which to me, if you don't have it there, you don't capture them when they are at the visit. How likely are they to follow up, or how soon are they likely to seek out this vaccine and get it done?"

Discussion

The current study provides unique insight into the barriers that CHWs and HCPs perceive are faced by Hispanic communities they serve. These include financial challenges, knowledge about HPV, and socio-cultural factors such as patriarchy (e.g., Machismo). Several important findings emerged from this study which highlight the need for community-tailored interventions. For example, CHWs and HCPs both expressed financial concerns related to patients lacking health insurance and other resources to obtain services. These findings were expected given that (El Paso, Texas), has a poverty rate of 18.8% (12), and recent estimates suggest that 22.1% of (El Paso, Texas residents), are uninsured (25). These findings also reflect similar findings from literature which report financial barriers as the most significant barriers to care in underserved populations (39). Identifying resources to counter financial barriers to HPV vaccination and to improve access to HPV education and healthcare is warranted.

Another important finding that emerged was that both CHWs and HCPs discussed knowledge barriers related to countering misinformation and misperceptions about HPV and the HPV vaccine. These findings are congruent with a review by Zimmet et al. (41) reporting that most fears associated with the HPV vaccine are associated with false information or fabrications and suggests that interventions should focus on educating HCPs to improve their approaches toward communicating the safety and benefits of HPV vaccination to parents and patients, as well as the risks of non-vaccination. Communicating the benefits and risks associated with vaccinations is challenging and must be approached with caution. For example, paradoxical effects were reported by Betsch and Sachse (42) when investigating strategies to debunk vaccine untruths. That is, the authors found that messages that strongly deny the risks associated with vaccination were associated with increased perceived vaccine risks (e.g., vaccine-adverse events). This finding highlights the critical need for testing messaging techniques prior to deployment to ensure that boomerang effects do not emerge.

Culture emerged as an important fact that contributes to sexual health-related healthcare. The cultural barriers of women's sexual health not being openly discussed within Hispanic communities fosters feelings of shame and embarrassment. Furthermore, there is a notion of strong adherence to gender roles in the Hispanic community. Hispanic males are often associated with the term "machismo" which can be defined as an over masculine character that is often reported as "possessive of women" and women playing a submissive role in their relationship. Notably, our findings revealed that both CHWs and HCPs explained that their female patients are often discouraged by their husbands from seeking out sexual health-related healthcare, "The wives that could not go get the Pap smears because they were

TABLE 3 Patient-related barriers to promoting HPV cancer prevention according to CHWs and HCPs.

	Community health workers	Healthcare providers
Financial	(a) Lack of health insurance, (b) lack of resources to pay for services. "Basically where [vaccines] are free… only certain ages are included like 9–21 years if you are older than 21 they do not have it for free. This is when a lot of people do not get it because they do not have money to pay for it."	(a) Lack of health insurance, (b) lack of resources to pay for services. "If you do not have insurance the price is really high."
Knowledge	(a) Lack of information about HPV and HPV vaccine, (b) misconceptions about HPV and the HPV vaccine, (c) lack of information on community resources that offer sexual health services. "I have even had some talks with parents of patients in the health department and they said not to give their children the vaccine because for them it was inviting their children to start a sexual life." "*Platicando con una señora… ella me decia 'pero la vacuna solamente es para mujeres.' Ella pensaba que era solamente para mujeres, no para los hombres tambien*." ("Talking with a lady… she told me 'but the vaccine is only for women.' She thought it was only for women, not for men as well.")	(a) Lack of information about HPV and HPV vaccine, (b) misconceptions about HPV and the HPV vaccine. "…it's not treated as a vaccine like we do now with measles and chickenpox or anything like that. It's more like a morality, it's more of my child you know… is now gonna be sexually active"
Patriarchy	*Machismo* (seen in male partner refusing to let female partner go to doctor because her intimate parts would be seen by doctor). "I have heard that they do not get the pap-smear because they are embarrassed or their husband does not let them."	Strong adherence to gender roles (women submitting to male partners who do not want them to see doctor and having to go in secret for sexual health-related care).
Behaviors	No mention of behaviors.	(a) Practice of not openly discussing women's sexual health, (b) Practice of not seeking out healthcare unless already sick.
Attitude	Stigma (associating HPV as a condition that only occurs in "promiscuous" women). "I have heard that this only happens to people who have a lot of sexual partners, specifically women."	Stigma (associating HPV prevention with sexual activity—especially in children/youth—and sexually transmitted infection).
Fear	No mention of fear.	Fear about side effects (of vaccine) that they have heard about through non-reliable sources. "…they are skeptical, they are afraid to go out …they are not at school, it's not a required vaccine you know"

afraid of their spouse finding out." This left women needing to keep Pap smear appointments in secret to avoid conflict with their partner.

Similarly, Guerra-Rodríguez et al. (43) investigated factors influencing HPV management in young Mexican women and reported that both men and women have erroneous knowledge about the transmission of HPV and suffer the negative psychosocial effects of the stigma of HPV including guilt and shame. Moreover, the authors reported that prescribed gender roles occur in both men and women and may reduce the likelihood of disclosing HPV infection status for fears of being seen as promiscuous.

Limitations

This study explored small sample sizes, thus findings are not generalizable. Bias may have been introduced due to the use of self-selection of focus group members. Responses may have been impacted by the historical underpinnings of the study—it was being done during COVID-19 and via technology due to COVID-19—in that the pandemic milieu may have prevented respondents from being able to focus on the intent of certain questions, and the technology-mediated nature of the groups may have been distracting and intimidating for some. Although current literature supports the use of Zoom based focus groups. In addition, one focus group was not able to finish in one session, necessitating the reconvening of the group to finish, which resulted in the loss of three members of the group due to scheduling conflicts.

Conclusion

The themes of this study highlight the barriers that CHWs and HCPs perceive are experienced by the community members they serve when these people are trying to access health and social services. The overarching finding points to a lack of knowledge and education surrounding HPV and preventative measures among Hispanic communities. This lack of knowledge is many times replaced by erroneous information and myths about HPV, both of which are exacerbated by stigma and cultural factors that further prevent individuals from adopting preventive practices. Another important barrier is the lack of access to health care. There is limited knowledge about the community resources available due to a lack of health insurance and finances. A high rate of uninsurance is another important obstacle that was identified. Lower rates of insurance come with medical outcomes such as being more likely to die from health-related problems, unwillingness to seek treatment regardless of the severity of symptoms, and increased emergency room services as an only option.

Identifying missed opportunities can make the difference on quality of health care services. Utilizing routine health care visits to

educate about HPV, sexual health, and the vaccine to parents, youth, and children can further close the gaps of HPV vaccine uptake. However, these opportunities are being missed due to self-reported lack of knowledge from CHWs and HCPs, as well as not being fully comfortable initiating these conversations. Education is important both for the health professionals and the community, and it must be culturally tailored to meet the needs of the communities.

The perceived barriers show a need for tailored messaging and interventions for different populations. This study evidenced the need for both CHWs and HCPs to be more literate in HPV health. Although all CHWs and HCPs stated they would recommend HPV vaccination for increasing vaccine uptake, they will need to be thoroughly versed in HPV health, including an effective, community-tailored method for responding to misconceptions and myths about HPV and the vaccine. Without an increase in knowledge and available resources, CHWs and HCPs will miss opportunities to make strong recommendations for the HPV vaccine and narrow the gaps in vaccine uptake.

Additionally, HCPs everywhere need to maintain up-to-date practices and messaging regarding sexual healthcare--including preventive care and treatment--to give the best care and to engender trust in their patients, who have experienced distrust and lack of confidence in HCPs due to inconsistent messaging and practices. The Health Care System needs to address the need to develop a complimentary approach to educating for CHWs and HCPs to strengthen their ability to challenge barriers like gender roles and improves their capacity to improve community HPV health literacy that respects and draws from strengths in their community and challenges misinformation that impedes health literacy.

The health messaging and recommendations given By CHWs and HCPs Are important To consider while developing educational programs and interventions. These educational programs and interventions should Use different methods To target different Age groups, including But Not limited To social media, media outlets, and health fairs. Talking about HPV and sexual health In a Hispanic community needs To Be normalized To invite members of The community To take preventive practices and remove The myths that surround The virus. CHWs and HCPs need To continue To spread information and resources As well As encourage individuals To seek health care despite these interruptions. Closing The HPV vaccine uptake gaps will require The health care system To work together with The community.

Next steps

As part of the 5-year behavioral research project, this focus group will inform the intervention of a RCT that will be launched during Fall 2023 to attempt to vaccinate 400 Hispanic adults. Participants will go from being unvaccinated or having an incomplete vaccination series, to be fully vaccinated during a 9-month time period where they will be followed-up by the researchers to understand how their knowledge, attitudes, and practices change over the time of the study.

With Hispanic adults being the audience, the RCT intervention will be culturally tailored. The perspectives of CHWs and HCPs will be essential in the development of these interventions, particularly as they are familiar with this population's strengths and weaknesses.

Research should continue to be done beyond this study and continue to enrich the knowledge we have on diverse communities and their specific needs. In order to create change in health prevention and services, the different barriers that are preventing access need to be understood from a close or direct perspective. CHWs and HCPs are at the forefront of advocating and educating the community about preventive health measures and consequences associated with HPV-related illnesses. To do a better job at closing gaps and creating positive change, health care provider education needs to become a priority across settings and disciplines.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the University of Texas at El Paso Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

EM designed the study and obtained IRB approval, was instrumental in the development and revision of the manuscript. AJ analyzed the qualitative data and reported on the findings. AG helped with the qualitative data analysis and drafted the introduction and methods of the study. GF drafted the discussion and revised the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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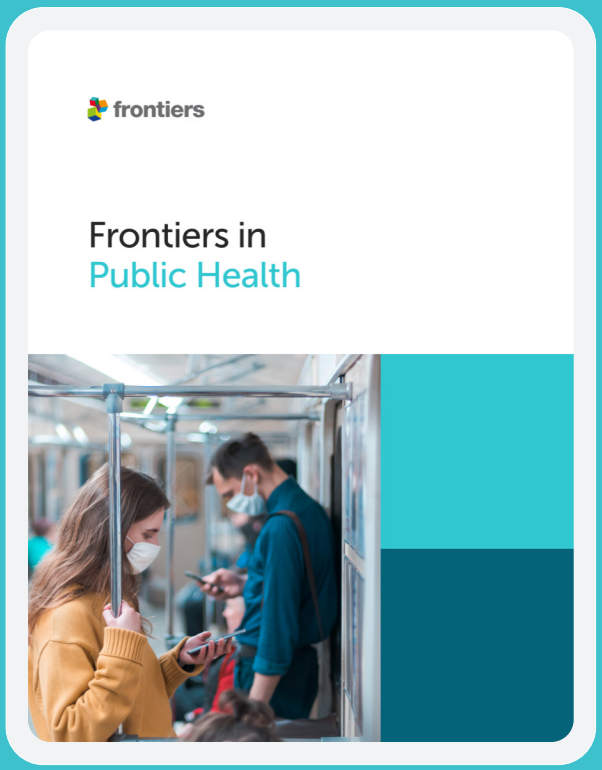

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