Investigating the sexual partnerships of transgender women in Lima, Peru to improve targeted HIV interventions

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Abstract

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Background: Transgender women (TW) have a high burden of HIV but remain understudied in HIV research. One poorly understood aspect of HIV risk among TW is the source of HIV infection in epidemics driven by sexual transmission. TW primarily report sexual partnerships with hetero- or bisexual cisgender men, populations that generally have a low HIV prevalence and therefore limited potential to transmit. This dissertation investigated the characteristics and behavior of partners of TW (PTW), as well as the sexual and HIV transmission networks of TW, to determine if sexual networks of TW overlap with those of men who have sex with men (MSM) and if HIV is transmitted between the populations.

Methods: Three distinct methods were used to answer these questions. Previously collected data from a study conducted among MSM and TW in Lima were used to compare partnership behavior among TW, PTW, and MSM, focusing specifically on sexual concurrency (Aim 1). A modified respondent-driven sampling study was conducted in Lima to collect data from a large sample of TW and their sexual partners (Aim 2). Finally, HIV sequences were used to complete a molecular epidemiology study examining overlap in HIV transmission clusters of TW and MSM (Aim 3).

Results: In Aim 1, we found that PTW engage in risky partnership behavior, and have higher rates of concurrent partnerships than either MSM or TW. In Aim 2, we found that partners differed in identity and behavior from MSM, that only 7% of PTW reported male partners, and that those with male partners were more likely to identify as homosexual, sell sex, and engage in receptive condomless anal intercourse (CAI). These results suggested little overlap in TW and MSM sexual networks. In Aim 3, we found that HIV transmission networks of MSM and TW do overlap, with over 50% of TW who were found in molecular transmission clusters also clustering with MSM.

Conclusions: PTW are a unique population, separate in sexual identity and sex-seeking behavior from MSM, and may engage in behavior that puts their partners at risk for HIV. A majority of PTW do not report male sexual partners, however, overlap in TW and MSM HIV transmission networks indicates that HIV is transmitted between the two sexual networks. This work highlights the need for further research to understand who is driving HIV transmission between TW and MSM, and if those with both male and TW partners are a distinct group that could be targeted by HIV prevention and treatment interventions.

Table of Contents

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List of Tables

List of Supplementary Tables

List of Figures

Chapter 1: Introduction

Transgender women (TW) are among those most at risk for HIV infection worldwide. Globally, an estimated 19% of TW are living with HIV, and the chance of acquiring HIV is 49 times higher for TW when compared to all adults of reproductive age (1,2). In Lima, Peru, HIV prevalence among TW is estimated to be 30%, compared with 12-18% among men who have sex with men (MSM), and <1% in the general population (3–5). Despite this disparity, TW are routinely conflated with MSM in HIV research. When they are included in studies, their data are often aggregated with data from MSM, limiting our understanding of the different risk profiles of these two populations (6–9). TW face many unique social, cultural, and psychological challenges that increase vulnerability to HIV. Compared with MSM, TW face higher rates of perceived stigma, family rejection, homelessness, lack of protection in jobs and education, social isolation, violence, and criminalization (1,3,10–14). TW are also more likely to engage in high-risk sexual behavior, including having a high number of sexual partners, alcohol use during sex, and having unprotected receptive anal sex, a sexual position that carries a high HIV risk (1,8,12,13,15). Sex work is extremely common in this population as well, with up to 70% of TW in Peru relying on transactional sex as a primary source of income (3,16).

As a consequence of the conflation of MSM and TW, little work has been done to understand how TW acquire HIV infection and how this likely differs from epidemics among MSM. In Peru, injection drug use is uncommon (17,18), so sexual behavior is the presumed driver of HIV epidemics within subpopulations. In HIV epidemics among MSM, HIV can spread rapidly through sexual networks in the absence of safe sexual practices (19–21). Condomless anal intercourse (CAI), high number of sexual partners, and sexual concurrency (temporal overlapping of sexual partnerships) all contribute to the efficient spread of HIV through the sexual network (19,22–24). In these epidemics, both the transmitting partner and the partner at risk for HIV acquisition are primarily MSM (19).

In contrast, TW primarily partner outside of their demographic group, largely reporting their sexual partners to be cisgender men (persons assigned male sex at birth who identify as men) who identify as bi- or heterosexual (25–27). However, HIV prevalence in bi- and heterosexual men in the general population is relatively low; in Peru, an estimated 2-16% of bisexual men and <1% of heterosexual men are living with HIV (5,28,29). HIV prevalence specifically among partners of TW (PTW) in Peru is currently unknown, though one recent estimate found a self-reported HIV prevalence among PTW across 17 countries in South America to be 9% (27). If HIV prevalence among sexual PTW is low, it remains unclear why HIV burden among TW is so high.

More information about the identities and behaviors of PTW is needed to fully understand the HIV epidemic among TW. A small number of studies have begun investigating PTW to better understand this population and how they contribute to HIV infection among TW (25–27,30–33). However, much of this research is qualitative, includes small sample sizes, or uses samples of primarily MSM to identify men who also have sex with TW. As a result, PTW remain vastly understudied, particularly in low- and middle-income countries (LMICs) (27).

The purpose of this dissertation is to investigate the sexual networks and sexual partners of TW in Peru to better understand the burden of HIV in this network. Specifically, this work was designed to test the hypothesis that the sexual networks of TW and MSM overlap due to sexual partners of TW also having sex with men, and that this overlap may drive the HIV epidemic among TW. We aimed to address three primary objectives to examine this. First, to examine the partnership-level behavior of PTW, focusing on behaviors that contribute to spread of HIV within networks, such as number of partners and sexual concurrency (Aim 1). The primary purpose of this aim is to understand the degree to which these behaviors in PTW may drive HIV transmission in TW populations. Second, to characterize PTW, to better understand their gender identity, sexual orientation, HIV prevalence, and sexual and risk-taking behavior, and how these behaviors of TW partners differ from behaviors of MSM and TW (Aim 2). The primary purpose of this aim is to describe TW partners and understand their risk for acquiring HIV. Third, to use phylogenetics to examine the HIV transmission networks of TW, PTW, and MSM to identify if HIV transmission occurs between these groups and what drives that transmission (Aim 3). This provides information about overlap between sexual networks of TW and MSM, and potential bridging of HIV between these groups.

To conduct this research, three distinct methods were employed. For Aim 1, we use previously collected partnership questionnaires to calculate sexual concurrency and other partnership behavior among TW, PTW, and MSM. In Chapter 2 we describe the results of this analysis, and examine behavior that is associated with sexual concurrency. For Aim 2, we used a modified respondent-driven sampling design to collect data from a sexual network of TW and their partners in Lima. PTW do not constitute a community or social network, so this novel method was designed to reach a large and representative group of this hidden population. Chapter 3 describes the results of this study, specifically characterizing the demographics, sexual and gender identities, and sexual behaviors of PTW in Lima. For Aim 3, we use HIV sequences obtained from HIV-infected TW, PTW, and MSM in Lima to identify if sequences from these groups are found in the same clusters, which would indicate transmission events between groups. Chapter 4 describes the outcome of this analysis, as well as analyses to determine if any demographic or behavioral characteristics predict co-clustering of MSM with TW.

The ultimate objective of this work is to improve our understanding of the HIV epidemic among TW and their sexual partners to allow for improved targeted HIV interventions to these populations. TW have been identified by the World Health Organization as a key population in the global HIV epidemic (34), but TW remain underserved, and the risk behaviors and characteristics of their sexual partners are virtually unknown. Understanding how HIV is being transmitted to and between TW and their partners will allow us to better tailor interventions to most effectively reduce transmission within this sexual network, and in doing so reduce viral spread while providing treatment to a hidden population.

Chapter 2: Characterizing men who have sex with transgender women in Lima, Peru: Sexual behavior and partnership profiles

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Introduction

Transgender women (TW), persons assigned male sex at birth who identify as women, are among those most at risk for HIV infection, with an estimated global HIV prevalence of 19% (2). The high burden of HIV among TW is attributed to multi-level disease drivers, including factors on structural (e.g. lack of legal protection for employment, education, and housing rights), societal (e.g. stigma and discrimination), and interpersonal (e.g. family expulsion, partner violence) levels (1,3,10). These drivers may also be linked to a greater prevalence of homelessness, alcohol abuse, and depression among TW (1,35–38). The downstream effects of these factors are widespread, and have demonstrable associations with behaviors that transmit HIV, such as participation in sex work, receptive condomless anal intercourse (CAI), and high numbers of sexual partners (3,35,36,39,40).

While many in the global health community, including the World Health Organization, identify TW as a distinct population, many researchers conceive TW as a subpopulation of men who have sex with men (MSM) (2,6,13,34,41), largely because the primary mode of transmission in both groups is anal intercourse. Conflating these populations overlooks distinctions between them that are central to HIV prevention. A fundamental, but underappreciated dissimilarity between TW and MSM communities lies in the compositions and structures of their sexual networks. Important work is underway on other factors driving high HIV prevalence among TW, among these, reliance on sex work due to job discrimination, power imbalances in sexual relationships, and the role of stigma and discrimination in driving risk behavior (6,37,42). However, these factors must be understood within the context of their network attributes.

Characteristics of sexual networks, such as number of partners, types of partnerships, and spacing of partnerships are known to contribute to HIV epidemics among heterosexual and MSM populations (20–22,43). MSM represent a largely distinct sexual network, in which partners are primarily other MSM, permitting HIV to spread rapidly in the absence of safe sexual practices. In contrast, TW partner outside of their demographic group, largely partnering with cisgender men (persons assigned male sex at birth who identify as men) who identify as bi- or heterosexual (26,32,40). Evidence suggests that TW sex workers are more likely to have CAI with stable partners compared to clients (40,44–46), but less work has been done to understand who these non-client partners are, or to characterize their sexual network (27).

Concurrency (sexual partnerships that overlap in time), is a recognized network attribute that contributes to HIV transmission (23,43,47). An individual may have multiple, monogamous partnerships over time; this is termed sequential monogamy. Should that individual acquire HIV from a partner, they expose subsequent partners to infection. If an individual has the same number of partners over time, but those partnerships are concurrent (overlapping), the individual may expose a greater number of partners than they would under sequential monogamy. Furthermore, under concurrency partners are more likely to be exposed in the weeks following HIV acquisition, when infectivity is highest (23,43,47–49). As a result, concurrency increases the likelihood of HIV transmission to partners, fueling HIV epidemics in populations with high concurrency (22,23,43). Evidence of high concurrency has been shown among MSM sexual networks (20,21,24). If overlap is commonplace among the TW and their partners, in the presence of CAI, concurrency could be an important contributor to the HIV burden among TW.

Characterizing the sexual identities and sex-seeking behavior of PTW can help determine the degree to which they overlap with MSM networks, and to clarify their role in HIV transmission to TW populations. In addition, understanding the individual-level characteristics of PTW, their behavior, and the extent to which they form partnerships outside of the TW population, is crucial to designing appropriate HIV prevention and treatment interventions.

This analysis used data from a large study in Lima, Peru that enrolled MSM, TW, and men who reported TW as sexual partners. This analysis aims 1) to describe and compare individual and sexual partnership characteristics of PTW to those of TW and MSM, and 2) to examine whether concurrency is more prevalent among PTW than among MSM and TW, and 3) to describe factors associated with concurrency.

Methods

Sample and Data Collection Procedures

This cross-sectional analysis used data collected at the screening visit for *Sabes*, an expanded treatment-as-prevention study in Lima. Detailed methods of the *Sabes* study have been published previously (50). Participants were recruited into *Sabes* using peer outreach and were enrolled at four participating clinics in community-based organizations or non-governmental organizations. Eligibility criteria included being ≥18 years of age, assignment of male sex at birth, self-report of a male or TW sexual partner in the previous 12 months, lack of awareness of HIV status, and elevated risk for HIV based on previously described criteria, such as sex work, having an HIV-positive sex partner, or having a sexually transmitted disease in the past six months (50,51). Because one of the aims of *Sabes* was to measure the impact of HIV treatment on viral load in semen, TW were excluded if they were taking gender-affirming hormone treatment at the time of screening. At enrollment, participants completed an extensive computer-assisted self-interview (CASI) questionnaire and biological testing for HIV and syphilis, using methods previously described (50). Informed consent was obtained from all individual participants included in the study, and all study activities were approved by IRBs at the participating research sites in Lima (IMPACTA, Epicentro, Via Libre) and Fred Hutchinson Cancer Research Center in Seattle.

Measures

Participant Identity: Transgender identity was assessed using both *Sabes* questionnaire data and medical records. In the *Sabes* questionnaire, gender identity was assessed using a single question: "*¿Se considera una travesti/transgénero/transsexual*?" (Do you consider yourself a transvestite/transgender/transsexual?" Note: prior research in this population in Lima indicated that all these terms are understood as referring to transgender woman identity). In medical records, a yes/no "transgender" checkbox was completed by the care provider during patient intake. In prior analyses, these two measures were found to be discordant for 40% of participants who identified as transgender at *Sabes* screening (unpublished data). While fear of disclosure of transgender status is common, the reason for such high discordance is unknown, thus primary analyses were conducted using a conservative definition of TW including only those who identified as transgender in both self-report and the medical record, and all other TW participants were excluded. Sensitivity analyses, described below, were conducted with all TW (see Supplementary Materials). Participants missing questionnaire data on gender identity were excluded from analysis.

PTW were defined as *Sabes* participants who did not identify as transgender and reported having any TW as a sexual partner in the sexual history questionnaire. MSM were defined as *Sabes* participants who did not identify as transgender on the study questionnaire and did not report a TW partner.

Individual Characteristics: Baseline characteristics potentially associated with HIV risk that were included in this analysis were sociodemographic characteristics, use of alcohol and other drugs, sexual behavior, social venue attendance, and HIV and syphilis test results. Sociodemographic data included age, income (earned minimum wage or higher), and education level (any post-secondary education or vocational training). Use of alcohol and other drugs was collected by self-report. Heavy alcohol use was assessed using the Alcohol Use Disorders Identification Test (AUDIT), with alcohol dependency defined as having a score ≥20 (52). Sexual behavior (including condom use and history of exchanging money, gifts, favors, or a place to sleep for sex) and venue attendance (bars, clubs, saunas, plazas) were assessed using self-report. HIV and syphilis prevalence were reported based on results of baseline testing (50).

Partnership Characteristics: As part of the CASI, participants nominated up to three most recent sexual partners in the previous three months. For each nominated partner, participants indicated the type of partnership (stable, casual, one-time, client, and sex worker), the partner's gender (cisgender man, transgender woman, cisgender woman), and the dates of first and most recent sexual encounter with the partner. Duration of partnerships was calculated in days using date of first and last sex. Any participant who did not nominate a sexual partner in the previous three months was excluded from this analysis.

Concurrency: The primary indicator of a participant having concurrent partnerships was three-month cumulative concurrency, defined as any overlapping partnerships during the previous three months, calculated using standardized methods (23,47). Relationship timelines were collected using calendar recall of date of first sex and most recent sex with each partner. Only sexual partnerships for which first or last sex fell within the three months prior to the date of interview were retained for this analysis. Concurrency was defined as any overlap in nominated partners, based on the start or end date of one partnership falling between the start and end date of another partnership, resulting in a binary measure (yes/no). In the case of missing data on end dates of sexual partnerships, dates were imputed based on the reported partnership type (stable, casual, one-time, client, sex worker) and whether future sex was expected. Full description of imputation rules and sensitivity analyses to assess the impact of imputation can be found in the Supplementary Materials.

We employed a second measure of concurrency, point prevalence concurrency, which measured ongoing partnerships that were concurrent at the time of data collection (47). Participants were asked whether they expected to have sex with each partner in the future (yes/no). Partnerships were considered ongoing at the time of interview if future sex was expected, or if reported date of last sex was the day of data collection. Point prevalence concurrency was defined as having more than one ongoing partnership at the date of survey completion (yes/no). Point prevalence concurrency did not rely on start and end date and there were no missing data regarding future sex, so this was reported without imputation.

Statistical Analysis

Individual and partnership characteristics were compared using Pearson's chi-squared test and the Kruskal-Wallis test (α level of 0.05). Poisson regression with robust standard errors was used to calculate unadjusted and adjusted prevalence ratios and 95% confidence intervals (CI) for associations between sexual concurrency and potential correlates (53). Any covariate associated with concurrency at $p < 0.10$ in unadjusted models was entered into multivariate models with *a priori* confounders (age, income, education, and number of sexual partners). In adjusted models, Wald testing was used to detect statistically significant differences in associations between groups (PTW, TW, and MSM). Sensitivity analyses were conducted to assess impact of including all those indicating transgender identity in the study survey, and impact of data imputation (see Supplementary Material). All statistical analyses were performed using Stata version 15.1 (College Station, TX, USA, 2017).

Results

Of the 3,336 participants who completed the screening questionnaire for *Sabes* from July 2013 – September 2015, 1,814 met the inclusion criteria for this analysis, including 1,526 MSM, 142 TW, and 146 PTW. Of those Sabes participants excluded, 1,430 participants either did not nominate a partner in the sexual history questionnaire or did not report dates of one or more relationships in the previous three months, and 92 participants were discordant on transgender identity or missing gender identity. Three TW reported another TW as a partner; these participants were classified as TW for this analysis.

Individual Characteristics

Fewer than 10% of PTW participants identified as homosexual, with 75% identifying as bisexual, and the remaining 16% identifying as heterosexual (Table 1.1). PTW were more likely to report CAI than were TW and MSM; fewer than a third reported using a condom at last sex and 87% reported CAI in the last three months. TW partners were primarily the insertive partner when engaging in CAI, with fewer than a third of PTW reported receptive CAI. HIV prevalence was lowest among PTW, with 8% testing positive, in contrast to 15% of TW and 21% of MSM. Alcohol dependency (AUDIT scores ≥20) in PTW and TW (31% and 32%, respectively) was higher than among MSM (18%). Sex under the influence of alcohol was significantly more common among PTW than other groups. PTW fell between TW and MSM in education and income with fewer than half of PTW reporting any post-secondary education or vocational training, or income above the Peruvian minimum wage.

TW had the least educational attainment and the lowest income (Table 1.1). TW were most likely to report receptive CAI (83%) and reported the highest number of partners in the past three months. Sex work was far more common among TW, with 65% self-identifying as sex workers compared to 31% of PTW and 8% of MSM. A significantly higher percentage of TW reported HIV testing in the prior 12 months compared to PTW and MSM.

Partnership Characteristics

Most participants in this study reported a high number of partners; median number of male partners in the last three months was 5 among PTW, 10 among TW, and 4 among MSM (Table 1.1). Detailed partnership data were collected on only the three most recent partners (Table 1.2). Gender of partners was more variable among PTW. While by definition all PTW had at least one TW partner, two-thirds of PTW reported *only* TW as partners, while 16% reported both TW and cisgender male partners, 19% reported TW and cisgender female partners, and 3% reported TW, cisgender male, and cisgender female partners. Both TW and MSM reported almost exclusively cisgender male partners (97% and 94%, respectively), and only 1.8% of cisgender men overall reported TW partners (inclusive of MSM and PTW).

Cumulative concurrency over the prior three months was appreciably more common among PTW (38%), in contrast to 30% in TW and 30% in MSM (p=0.097). Point prevalence at time of interview was significantly different between groups, with 28% concurrency among TW and 26% among PTW, compared to 17% among MSM (p<0.001).

Partnership type differed across the groups. Among PTW and MSM, both one-time and stable partnerships were reported by approximately half of participants. A majority of TW reported stable partnerships (67%), but far fewer TW reported one-time partnerships compared to PTW and MSM. Over 10% of PTW purchased sex (reported as exchanging money, gifts, favors, or a place to sleep), compared to only 2% of MSM. Sex was sold to a client by 10% of PTW and 3% of MSM. TW reported a significantly higher proportion of clients among partnership types (20%) compared to MSM and PTW, and did not report purchasing sex. In all groups, almost half of partnerships were single encounters (regardless of reported relationship to the partner), and duration of partnerships lasting more than one day did not differ significantly among the groups (Table 1.2). Across groups, there was no significant difference in CAI by partnership type; CAI was more common in stable partnerships, and least common with transactional or one-time partnerships in all groups.

Of the 72 stable partnerships reported by 66 PTW participants, 51 (71%) were with TW, 14 (19%) were with cisgender women, and 7 (10%) were with cisgender men. Among instances of purchased sex among PTW, 15 (83%) were with TW partners and 3 (17%) were with cisgender male partners. TW reported on 105 stable partners, of whom 103 (98%) were cisgender men and 2 (2%) were TW. Of the 42 client partnerships reported by 28 TW, all were cisgender men.

Correlates of Concurrency

Few individual characteristics showed significant associations with cumulative concurrency in PTW (Table 1.3). Among MSM and TW, concurrency was more prevalent among those aged 25 years or older than younger participants; concurrency did not differ by age among PTW. Post-secondary education or vocational training was associated with higher prevalence of concurrency in MSM (aPR 1.36, 95% CI 1.12, 1.64) but no association was found among TW and PTW.

For MSM, meeting a sex partner at a social venue (aPR 1.23, 95% CI 1.01, 1.50) and sex while under the influence of alcohol (aPR 1.21, 95% CI 1.03, 1.41) were associated with concurrency; these associations were not found among PTW and TW. Reporting one or more stable partner(s) was negatively associated with concurrency among TW (aPR 0.46, 95% CI 0.28, 0.76) and MSM (aPR 0.84, 95% CI 0.72, 0.98); no statistically significant association was found among PTW (aPR 0.78, 95% CI 0.51, 1.20). Among all groups, reporting a casual, one-time, or client partner was associated with higher likelihood of concurrent partnerships. We could not ascertain whether there was an association between concurrency and purchasing sex due to sparse data.

Comparing groups, the association between stable partnerships and concurrency was the only estimate that differed significantly by group, showing a stronger association in TW compared to MSM (aPR 0.55, 95% CI 0.32, 0.93, Table 1.3 footnote). Sensitivity analyses found that data imputation and use of a conservative definition of transgender identity did not substantially affect the results (see Supplementary Material for full results).

Discussion

The PTW participating in this study were mainly bi- or heterosexually identified men who reported behavior and partnerships markedly distinct from those reported by MSM and TW. Over two-thirds of PTW reported only TW as partners, 81% reported no cisgender male partners, and fewer than 10% identified as homosexual. While prevalence of HIV and syphilis were lower among PTW than among the other two groups, PTW more commonly reported practices associated with HIV transmission, such as alcohol use indicative of dependency and having sex under the influence of alcohol (15,54–56). In contrast to MSM and TW, few PTW had tested for HIV in the prior 12 months. PTW had the highest rates of cumulative concurrency, and a high percentage reported CAI, particularly with stable partners. Taken in aggregate, this evidence suggests that PTW are a distinct population from MSM and TW communities, are engaging in risky sexual behavior with primarily TW partners, and may be less likely than MSM and TW to receive interventions like HIV testing.

In recent years, researchers in high-income settings have begun to focus on PTW to better understand the HIV epidemic among TW (25,26,31,32,40,57,58). One study conducted among TW and their partners in San Francisco demonstrated that PTW in this region identified mainly as bi- or heterosexual, had high alcohol use, were likely to engage in CAI, and reported mostly TW partners (25,40). Two recent studies investigated clients of TW sex workers and cisgender men with TW partners in Latin America (27,33). The findings from these studies, as well as prior research conducted among TW (30,46,59), suggest that the sexual identities and gender of preferred partners of PTW may be largely similar in high vs. low- or middle-income countries (LMIC). Our findings aligned with this prior research, with 75% of PTW identified as bisexual and 15% as heterosexual, and over 60% reporting solely TW partners. This is markedly different from our findings among MSM, who identified largely as homosexual and had only cisgender male partners.

In our analysis, concurrency was common across groups, with over a third of PTW reporting concurrent partnerships in the previous three months. Practicing concurrency confers greater risk of HIV transmission to partners, so high concurrency among PTW could contribute to the high burden of HIV in TW. Only one study, to our knowledge, has measured concurrency among PTW. Operario *et al*. found that among 174 PTW in San Francisco, 14% reported sex outside their partnership in the previous three months (40). While this was lower than our findings, this study was conducted among PTW with stable partners, and less than half of our PTW population reported having a stable partner. In our analysis, having a stable partner was protective against concurrency, though this did not reach significance in PTW. This result may indicate that those in stable partnerships are more likely to be monogamous. Further research is needed to understand patterns of concurrency in PTW, how behavior differs with different types of partners, and how this relates to HIV risk in TW.

Notable among these results is the lower HIV prevalence found among TW compared to other studies in Lima (3,4). Several factors could be contributing to these results. First, this analysis only included participants who nominated at least one partner in the sexual history questionnaire; when including those with no nominated partners, the HIV prevalence among TW in *Sabes* was 19.7%, which is more in line with previous studies (results not shown). This suggests that those with higher HIV prevalence were either less likely to have had a partner in the previous three months or less likely to nominate their partners. Furthermore, this study only enrolled TW who were not using gender-affirming hormone treatment. It is possible that this resulted in a group of TW that are less likely to publicly identify as transgender, and therefore may be less susceptible to harmful consequences of discrimination and at lower risk for HIV.

In this analysis, HIV prevalence among PTW was far lower than that among MSM. To our knowledge there is no prior estimate of HIV prevalence among PTW in Peru, though Reisner et al. found a self-reported HIV prevalence of 9.4% among 106 men in Latin America reporting TW partners, which aligns with our findings (27). HIV prevalence among heterosexual men in Lima is <1%, and studies among bisexual men in Lima have estimated their HIV prevalence to be 2%-16% (5,28,29). However, these studies examined men who have sex with cisgender men and cisgender women, so these populations are likely to be different than bisexually identified men in our study. A recent study of partners of transgender people in San Francisco also found high risk behavior but low HIV prevalence; however in this population injection drug use was high and overall HIV prevalence was low, indicating that HIV risk may not be comparable to the population in our study (26). Lower HIV prevalence among PTW is plausible given their role as a primarily insertive partner in CAI. One hypothesis to explain the high HIV prevalence among TW but relatively low prevalence among their partners could be that fewer PTW are HIV-positive, but high concurrent behavior at the time of seroconversion could mean those that are HIV positive are effective transmitters to their sexual partners. The low HIV testing rate found among PTW indicates that they may be less likely to receive HIV prevention interventions than other groups, and therefore may not be aware of their risk. Reisner et al. found that the PTW in their sample were both less likely to have recently tested and less likely to perceive themselves to be high risk for HIV (27). Future research should be conducted purposely targeting PTW in Peru and other LMICs, both to evaluate the validity of our estimates and to better understand HIV burden, knowledge, and prevention practices in this population.

This analysis had several strengths. The size of the *Sabes* baseline cohort was sufficient to stratify the analysis into three groups, and collect data specific to PTW in Lima. *Sabes* employed standardized data collection instruments (AUDIT and sexual history items), permitting comparison of our results to those of other studies. Use of CASI helped minimize social desirability bias and improve validity given the sensitivity of questionnaire topics and stigma facing the study population.

There were a number of limitations in this analysis. First, censoring of partnership timeline data was likely a limitation in the assessment of concurrency. All groups reported a median of >3 male partners in the last three months, and our instrument collected data on a maximum of three partnerships. While this could underestimate the prevalence of concurrency, we expect it would do so for all groups. Second, despite large sample size, the analysis of correlates of concurrency had limited power to detect associations among PTW and TW due to small cell sizes. Sensitivity analyses demonstrated that given a larger sample, more correlates would have been identified as associated with concurrency among TW (Supplementary Material, Table S1.3). Third, generalizability of our results may be limited, as our study sample was recruited based on their elevated risk for HIV. Additionally, study recruitment involved peer outreach targeting MSM and TW, so PTW in this study only include those that were captured in this recruitment and may not represent general PTW populations. Lastly, this analysis used a conservative criterion for classification as TW due to fairly low corroboration (60% agreement) between identification as transgender to their provider and questionnaire response. Stigma and fear of discrimination may have resulted in reluctance to self-identify as transgender to health care providers, which has been recorded in other settings (4). However, this could not be confirmed, and due to concerns about possible confusion in the CASI regarding the meaning of transgender identity, the conservative estimate was chosen *a priori* for this analysis. Results did not significantly differ in sensitivity analyses that include all participants who identified as transgender on the CASI (see Supplementary Materials). Future research should use two-step question structures to define gender (e.g. sex assigned at birth and current gender identity) to improve data collection in this population (60,61).

This study provides the first estimates of HIV prevalence among PTW in Lima, and is among the first studies to examine partnership characteristics and sexual behavior of this population in LMICs. Our findings align with growing evidence from high-resource settings suggesting that PTW are a population distinct from MSM. These results suggest that existing prevention and outreach models, which combine MSM and TW as one target group, may not be an effective approach to reduce the HIV burden among TW. Not only do PTW have distinct behavior and sexual networks compared to MSM, but HIV prevention activities may not be reaching PTW, resulting in less frequent HIV testing and less condom use. In Peru, outreach and prevention is largely targeted to gay communities, and therefore may underserve TW and PTW.

Understanding the partners and sexual networks of TW is imperative to understanding the alarmingly high HIV prevalence among TW and to identify how to effectively intervene. Future research and outreach should actively include PTW to better serve this sexual network and address HIV risk among TW and their partners.

Tables

Table 1.1: Sociodemographic and behavior characteristics among partners of transgender women, transgender women, and men who have sex with men who reported at least one partner in the three months preceding interview.

Characteristic	Partners of transgender women (n=146)	Transgender women (n=142)	Men who have sex with men (n=1,526)	Test Statistic (χ^2)[a]	p-value
Post-secondary education	62 (42.5%)	56 (39.4%)	1,087 (71.2%)	99.8	<0.001
Income above min wage	67 (45.9%)	51 (35.9%)	752 (49.3%)	9.6	0.008
Age (mean, SD)	29.8 (9.3)	29.6 (8.4)	27.6 (7.9)	14.9	<0.001
Sexual identity[b]				202.96	<0.001
Homosexual man	14 (9.6%)	-	1,027 (67.3%)		
Bisexual man	109 (74.7%)	-	452 (29.6%)		
Heterosexual man	23 (15.8%)	-	47 (3.1%)		
HIV positive	12 (8.2%)	21 (14.8%)	318 (20.8%)	15.7	<0.001
HIV test in last 12 months	40 (27.4%)	68 (47.9%)	538 (35.3%)	13.7	0.001
Active untreated syphilis	4 (2.7%)	12 (8.5%)	128 (8.4%)	5.9	0.053
Condom use at last sex	44 (30.1%)	66 (46.5%)	628 (41.2%)	8.8	0.012
Sex at a social venue[c]	104 (71.2%)	110 (77.5%)	1,055 (69.1%)	4.4	0.110
Alcohol dependency (AUDIT ≥20)	46 (31.5%)	44 (31.0%)	277 (18.2%)	25.8	<0.001
Sex while drinking[c]	79 (54.1%)	72 (50.7%)	667 (43.7%)	7.8	0.020
Sex with drinking and drugs	22 (15.1%)	16 (11.3%)	59 (3.9%)	43.7	<0.001
Male or TW partners[c] **(median, IQR)**	5 (3, 8)	10 (4, 40)	4 (2, 7)	75.0	<0.001
Sex worker	45 (30.8%)	92 (65.2%)	125 (8.2%)	373.5	<0.001
Insertive CAI[c]	124 (87.3%)	62 (50.8%)	984 (70.2%)	41.8	<0.001
Receptive CAI[c]	42 (29.6%)	101 (82.8%)	898 (64.1%)	88.5	<0.001
Any CAI[c]	124 (87.3%)	101 (82.8%)	1,177 (84.0%)	1.3	0.530

[a]Chi-squared test statistics were calculated to compare each variable across the groups. For categorical variables, the Pearson's chi-squared test was used. For continuous variables (age, number of male partners) the Kruskal-Wallis equality-of-populations rank test was used.
[b]Sexual identity was not collected for participants who indicated "transgender" as a gender identity
[c]Behavior reported for the last 3 months with any partner (not limited to sexual history recall partners).
SD: standard deviation; IQR: inter-quartile range; CAI: condomless anal intercourse

Table 1.2: Partnership characteristics among partners of transgender women compared to transgender women and men who have sex with men.

Characteristic	**Partners of transgender women** (n=146)	**Transgender women** (n=142)	**Men who have sex with men** (n=1,526)	Test Statistic (χ^2)[a]	p-value
Total number of dyads	282	231	2,702		
Mean dyads per participant (SD)	1.9 (0.9)	1.6 (0.8)	1.8 (0.9)	9.6	0.010
3-month cumulative concurrency[b]	56 (38.4%)	43 (30.3%)	454 (29.8%)	4.7	0.097
Point prevalence concurrency	38 (26.0%)	40 (28.2%)	255 (16.7%)	17.6	<0.001
Single encounter partnerships[b]	133 (47.5%)	105 (45.5%)	1259 (46.6%)	0.2	0.920
Median days duration for partnerships >1 days (IQR)[b]	148 (46, 725)	220 (61, 722)	122 (31, 700)	3.9	0.140
Reported partnership type[c]:					
Stable	66 (45.2%)	95 (67.0%)	885 (57.9%)	14.3	0.001
Casual	42 (28.7%)	25 (17.6%)	432 (28.3%)	7.6	0.022
One-time	69 (47.3%)	36 (25.4%)	727 (47.6%)	26.1	<0.001
Client	14 (9.6%)	28 (19.8%)	46 (3.0%)	86.3	<0.001
Sex Worker	16 (10.9%)	0 (0.0%)	28 (1.9%)	50.7	<0.001
Any unprotected sex by partner type[d]					
Stable	36 (54.5%)	50 (52.6%)	522 (59.0%)	1.8	0.410
Casual	20 (47.6%)	10 (40.0%)	179 (39.8%)	1.0	0.620
One-time	22 (31.9%)	8 (22.2%)	201 (27.6%)	1.1	0.570
Client	3 (21.0%)	9 (32%)	15 (33.0%)	0.7	0.720
Sex Worker	6 (38.0%)	0 (0.0%)	7 (25.0%)	0.8	0.380
Gender of partners:					
Transgender women only	94 (61.6%)	1 (0.7%)	N/A		
Cisgender men only	N/A	138 (97.2%)	1,430 (93.7%)		
Cisgender women only	N/A	0 (0.0%)	71 (4.7%)		
Cisgender men and women	N/A	1 (0.7%)	25 (1.6%)		
TW and cisgender women	28 (19.2%)	0 (0.0%)	N/A		
TW and cisgender men	23 (15.8)	2 (1.7%)	N/A		
TW, cisgender men and women	5 (3.4%)	0 (0.0%)	N/A		

[a]Chi-squared test statistics were calculated to compare each variable across the groups. For categorical variables, the Pearson's chi-squared test was used. For continuous variables (number of dyads, single encounter partnerships, days duration of partnership) the Kruskal-Wallis equality-of-populations rank test was used.
[b]Includes data imputation described in the methods.
[c]Inclusive, participants could report more than one type of partner
[d]Reported any unprotected sex with each partner type within the sexual history questionnaire of three most recent partners. Only among those who reported that partner type
SD = standard deviation IQR = inter-quartile range

Table 1.3: Independent associations between 3-month cumulative concurrency and covariates at baseline among partners of transgender women, transgender women, and men who have sex with men.

Characteristic	Partners of transgender women		Transgender women		Men who have sex with men	
	PR (95% CI)	aPR[a] (95%CI)	PR (95% CI)	aPR[a] (95%CI)	PR (95% CI)	aPR[a] (95%CI)
Age						
<25 years	1		1	1	1	1
25-35 years	1.06 (0.66, 1.71)		2.56 (1.20, 5.47)**	2.22 (1.04, 4.72)**	1.38 (1.15, 1.65)***	1.24 (1.03, 1.50)**
>35 years	1.13 (0.66, 1.93)		2.74 (1.24, 6.08)**	2.95 (1.36, 6.41)**	1.94 (1.60, 2.35)***	1.70 (1.39, 2.09)***
Income						
>minimum wage	1		1		1	1
< minimum wage	1.46 (0.97, 2.21)*	1.15 (0.76, 1.76)	0.77 (0.44, 1.34)		1.20 (1.02, 1.40)**	1.05 (0.90, 1.24)
Education						
>secondary school	1		1		1	1
>Secondary school	1.02 (0.67, 1.54)		1.00 (0.60, 1.67)		1.34 (1.11, 1.62)**	1.36 (1.12, 1.64)**
Total partners (3 mos)						
1-3	1		1		1	1
4+	1.51 (0.83, 2.73)		1.88 (0.88, 4.04)		2.06 (1.70, 2.49)***	1.99 (1.65, 2.41)***
HIV positive						
No	1		1		1	1
Yes	0.41 (0.11, 1.50)		0.59 (0.24, 1.49)		0.84 (0.68, 1.03)*	0.88 (0.71, 1.07)
Met for sex at a venue[b]						
No	1		1		1	1
Yes	1.48 (0.87, 2.52)		1.79 (0.83, 3.88)		1.54 (1.27, 1.87)***	1.23 (1.01, 1.50)**
Alcohol use disorder						
No (AUDIT<20)	1		1		1	
Yes (AUDIT ≥20)	1.03 (0.66, 1.60)		1.02 (0.62, 1.68)		1.01 (0.83, 1.23)	
Sex while drinking[b]						
No	1		1		1	1
Yes	1.41 (0.92, 2.18)		1.07 (0.63, 1.83)		1.37 (1.17, 1.60)***	1.21 (1.03, 1.41)**
Sex while drinking & drugs[b]						

No	1		1		1	
Yes	1.23 (0.73, 2.05)		1.80 (1.02, 3.17)**	1.46 (0.86, 2.47)	1.09 (0.74, 1.59)	
Any insertive CAI[b]						
No	1		1		1	
Yes	1.48 (0.68, 3.22)		1.12 (0.68, 1.85)		0.97 (0.82, 1.15)	
Any receptive CAI[b]						
No	1		1		1	
Yes	1.32 (0.88, 2.00)		0.86 (0.46, 1.59)		1.06 (0.89, 1.25)	
1+ stable partner[c]						
No	1		1		1	1
Yes	0.73 (0.47, 1.12)		0.39 (0.24, 0.64)***	0.46 (0.28, 0.76)**[d]	0.73 (0.63, 0.85)***	0.84 (0.72, 0.98)**
1+ casual partner[c]						
No	1		1		1	1
Yes	2.48 (1.69, 3.63)***	2.05 (1.39, 3.03)***	2.77 (1.78, 4.32)***	2.20 (1.40, 3.48)**	2.58 (2.23, 2.98)***	2.16 (1.85, 2.53)***
1+ one-time partner[c]						
No	1		1		1	1
Yes	1.72 (1.12, 2.65)**	1.74 (1.14, 2.65)**	2.12 (1.32, 3.41)**	2.27 (1.44, 3.58)***	2.23 (1.88, 2.63)***	2.07 (1.75, 2.45)***
1+ client partner[c]						
No	1		1		1	1
Yes	2.05 (1.36, 3.08)**	1.88 (1.18, 3.00)**	2.93 (1.88, 4.57)***	1.95 (1.19, 3.18)**	1.95 (1.50, 2.55)***	1.41 (1.04, 1.91)**

[a]All adjusted analyses include *a priori* confounders of age (continuous), number of partners (log transformed), income (above or below minimum wage), and college (any secondary education).
[b]Behavior reported for the last 3 months with any partner (not limited to sexual history recall partners).
[c]Behavior reported among the last 3 sexual partners as reported in the sexual history recall questionnaire
[d]Statistically significant difference compared to MSM (reference): TW aPR: 0.55, 95% CI (0.32, 0.93)
PR: prevalence ratio; CI: confidence interval; aPR: adjusted prevalence ratio; CAI: condomless anal intercourse
*p<0.10; **p<0.05; ***p<0.0001

Supplementary Materials: Sensitivity Analyses

Methods

Analysis 1: Primary analyses were conducted using a conservative definition of TW including only those who identified as transgender in both self-report and the medical record, and all other TW participants were excluded. For this sensitivity analysis, the same methods described in the Statistical Analysis section were used, but TW were defined as any *Sabes* participant who reported transgender identity in the *Sabes* baseline questionnaire. This analysis was conducted to assess if using the conservative definition of TW in the primary analysis effected the outcomes of this study. Data on PTW and MSM did not change from those used in the primary analysis. All analyses reported in the primary results (individual characteristics, partnership characteristics, and correlates of concurrency) were repeated for this analysis.

Analysis 2: Primary analyses of cumulative concurrency were conducted with imputed dates of most recent sex when these data were missing. Imputation was performed for partnerships in which date of first sex was reported, and additional data were provided about the partner to inform imputation. The following imputation rules were used: for partners reported as stable, if future sex was anticipated, sex was considered ongoing and the end date was imputed as date of the interview. If the participant responded “no” or “I don’t know” to the question about future sex, a midpoint between first sex and date of interview was imputed as the end date. For partners reported as casual, clients, or sex workers, the date of last sex was imputed as the date of the interview if the participant indicated “yes” for future sex. For all other answers, sex was classified as one-time and missing end dates were imputed as the start date. Some end dates were reported as prior to the start date; in these instances, the dates were transposed.

In the second sensitivity analysis, partnership characteristics and correlates of concurrency were examined without imputation or transposition. Only partnerships in which the participant reported complete data on start and end dates of the partnership were included, to assess the impact of imputation for missing date of last sex on interpretation of the results. Only partnerships that were ongoing within the 3 months prior to interview were included. Partnerships that did not have complete data on start and end dates were therefore dropped from analyses; if no partner for a given participant fit these criteria, that participant was dropped from analysis. Analysis of partnership characteristics and correlates of concurrency were assessed using this subgroup.

Results and Interpretation

Analysis 1: The *Sabes* baseline data included 510 TW participants. Based on the inclusion criteria of this study, 234 TW were included in sensitivity analyses (276 were excluded due to absent or incomplete data in the sexual history questionnaire). Minimal differences were found in individual and partnership characteristics between TW in the full group (Supplementary Material Tables S1.1 and S1.2) compared to the conservative group (Primary results Tables 1.1 and 1.2). Most individual level characteristics varied by less than 10%. Among individual characteristics, the largest differences were found in prevalence of alcohol dependency (27.4% in sensitivity analysis vs 31.0% in primary analyses), identifying as a sex worker (54.1% vs 65.2%, respectively) and both insertive (56.7% vs. 50.8%) and receptive CAI (75.9% vs 82.8%) (Table S1.1, Table 1.1).

Comparing partnership data, concurrency was very similar in primary and sensitivity analyses (Table S1.2 vs Table 1.2). Differences between the two analyses were found in the median duration of partnerships that lasted longer than a day (153 days in sensitivity analyses vs. 220 in primary analysis), and reporting giving money, goods, or services in exchange for sex (4 participants in sensitivity analyses vs. none in primary). TW in the full cohort were more likely to report TW as sexual partners (13 in sensitivity analyses vs non in primary).

Table S1.3 shows the results of the analysis of correlates of concurrency. A number of correlates were significantly associated with concurrency in unadjusted sensitivity analyses but not in primary analysis. After adjusting for confounders, income and number of partners remained significantly associated. However, point estimates in unadjusted analyses are very similar in primary and sensitivity analyses, suggesting that significance resulted from narrowing of the confidence intervals due to larger sample size.

These results show that while some small differences exist between the full TW group and the conservative group chosen *a priori* for primary analyses, these are likely due to a larger sample size included in the sensitivity analyses and do not reflect meaningful differences between the groups.

Analysis 2: This analysis included 133 PTW, 141 TW, and 1,522 MSM. One TW, one PTW and four MSM were dropped from analysis due to no eligible partners; 12 PTW were dropped from analyses because their transgender partners were no longer eligible partnerships. Overall, cumulative concurrency calculated without imputation was found to be somewhat lower across the groups when compared to primary analyses (Table S1.4 vs Table 1.2). Due to few partnerships being excluded from analyses, all other partnership data remained very similar to those found in the primary analysis. Percent of single encounter partnerships was lower in sensitivity analyses when compared to primary analysis, and median days of partnerships were longer. This suggests that imputation led to a higher inclusion of one-off and short-term partnerships. Differences between the groups remained the same in both analyses, with the exception of casual partners; a significant difference in the percentage of casual partners was found in sensitivity analyses but not the primary analysis (Table S1.2). The analysis of correlates of concurrency found fewer significant associations among TW and PTW than those found in primary analyses; point estimates were similar but likely lacked power due to small sample size (Supplementary Material Table S1.4).

These results suggest that imputation did not significantly change interpretation of results, but provided additional power to observe statistically significant associations between concurrency and correlated behaviors.

Supplementary Tables

Table S1.1: Sociodemographic and behavior characteristics among partners of transgender women, transgender women, and men who have sex with men who reported at least one partner in the three months preceding interview including all participants who identified as TW in *Sabes*.

Characteristic	**Partners of transgender women** (n=146)	**Transgender women** (n=234)	**Men who have sex with men** (n=1,526)	Test Statistic (χ^2)[a]	p-value
Post-secondary education	62 (42.5%)	97 (41.5%)	1,087 (71.2%)	116.1	<0.001
Income above min wage	67 (45.9%)	85 (36.3%)	752 (49.3%)	13.8	0.001
Age (mean, SD)	29.8 (9.3)	28.9 (8.2)	27.6 (7.9)	11.1	<0.001
Sexual identity[b]				203.0	<0.001
Homosexual man	14 (9.6%)	-	1,027 (67.3%)		
Bisexual man	109 (74.7%)	-	452 (29.6%)		
Heterosexual man	23 (15.8%)	-	47 (3.1%)		
HIV positive	12 (8.2%)	37 (15.8%)	318 (20.8%)	15.7	<0.001
HIV test in last 12 months	40 (27.4%)	104 (44.4%)	538 (35.3%)	12.3	0.002
Active untreated syphilis	4 (2.7%)	19 (8.2%)	128 (8.4%)	5.9	0.054
Condom use at last sex	44 (30.1%)	105 (44.9%)	628 (41.2%)	8.6	0.014
Sex at a social venue[c]	104 (71.2%)	177 (75.6%)	1,055 (69.1%)	4.2	0.12
Alcohol dependency (AUDIT ≥20)	46 (31.5%)	64 (27.4%)	277 (18.2%)	22.9	<0.001
Sex while drinking[c]	79 (54.1%)	116 (49.6%)	667 (43.7%)	7.9	0.020
Sex with drinking and drugs	22 (15.1%)	21 (9.0%)	59 (3.9%)	39.9	<0.001
Male or TW partners[c] **(median, IQR)**	5 (3, 8)	8 (3, 30)	4 (2, 7)	73.6	<0.001
Sex worker	45 (30.8%)	126 (54.1%)	125 (8.2%)	351.6	<0.001
Insertive CAI[c]	124 (87.3%)	115 (56.7%)	984 (70.2%)	37.5	<0.001
Receptive CAI[c]	42 (29.6%)	154 (75.9%)	898 (64.1%)	82.7	<0.001
Any CAI[c]	124 (87.3%)	169 (83.3%)	1,177 (84.0%)	1.2	0.540

[a]Chi-squared test statistics were calculated to compare each variable across the groups. For categorical variables, the Pearson's chi-squared test was used. For continuous variables (age, number of male partners) the Kruskal-Wallis equality-of-populations rank test was used.
[b]Sexual identity was not collected for participants who indicated "transgender" as a gender identity
[c]Behavior reported for the last 3 months with any partner (not limited to sexual history recall partners).
SD: standard deviation; IQR: inter-quartile range; CAI: condomless anal intercourse

Table S1.2: Partnership characteristics among partners of transgender women compared to transgender women and men who have sex with men, including all participants who identified as transgender women in *Sabes*.

Characteristic	**Partners of transgender women** (n=146)	**Transgender women** (n=234)	**Men who have sex with men** (n=1,526)	Test Statistic (χ^2)[a]	p-value
Total number of dyads	282	381	2,702		
Mean dyads per participant (SD)	1.9 (0.9)	1.6 (0.8)	1.8 (0.9)	12.2	0.003
3-month cumulative concurrency[b]	56 (38.4%)	68 (29.1%)	454 (29.8%)	4.9	0.088
Point prevalence concurrency	38 (26.0%)	65 (27.8%)	255 (16.7%)	21.7	<0.001
Single encounter partnerships[b]	133 (47.5%)	163 (42.8%)	1259 (46.6%)	2.1	0.360
Median days duration for partnerships >1 days (IQR)[ab]	148 (46, 725)	153 (54, 715)	122 (31, 700)	2.1	0.350
Reported partnership type[c]**:**					
Stable	66 (45.2%)	151 (64.5%)	885 (58.0%)	13.9	<0.001
Casual	42 (28.7%)	40 (17.1%)	432 (28.3%)	13.2	0.001
One-time	69 (47.3%)	70 (29.9%)	727 (47.6%)	25.9	<0.001
Client	14 (9.6%)	39 (16.7%)	46 (3.0%)	83.0	<0.001
Sex Worker	16 (10.9%)	5 (2.1%)	28 (1.9%)	44.5	<0.001
Any condomless sex by partner type[d]					
Stable	36 (54.6%)	83 (55.0%)	522 (59.0%)	1.2	0.540
Casual	20 (47.6%)	15 (37.5%)	172 (39.8%)	1.1	0.570
One-time	22 (31.9%)	15 (21.4%)	201 (27.7%)	2.0	0.370
Client	3 (21.4%)	11 (28.2%)	15 (32.6%)	0.7	0.710
Sex Worker	6 (37.5%)	4 (80.0%)	7 (25.0%)	5.7	0.057
Gender of partners:					
Transgender women only	94 (61.6%)	13 (5.6%)	N/A		
Cisgender men only	N/A	214 (91.5%)	1,430 (93.7%)		
Cisgender women only	N/A	3 (1.3%)	71 (4.7%)		
Cisgender men and women	N/A	1 (0.4%)	25 (1.6%)		
TW and cisgender women	28 (19.2%)	1 (0.4%)	N/A		
TW and cisgender men	23 (15.8)	2 (0.9%)	N/A		
TW, cisgender men and women	5 (3.4%)	0 (0.0%)	N/A		

[a]Chi-squared test statistics were calculated to compare each variable across the groups. For categorical variables, the Pearson's chi-squared test was used. For continuous variables (number of dyads, single encounter partnerships, days duration of partnership) the Kruskal-Wallis equality-of-populations rank test was used.
[b]Includes data imputation described in the methods.
[c]Inclusive, participants could report more than one type of partner
[d]Reported any unprotected sex with each partner type within the sexual history questionnaire of three most recent partners. Only among those who reported that partner type
SD: standard deviation; IQR: inter-quartile range

Table S1.3: Independent associations between 3-month cumulative concurrency and covariates at baseline among transgender women, transgender women, and men who have sex with men, including all participants who identified as transgender women in *Sabes*.

Characteristic	Partners of transgender women		Transgender women		Men who have sex with men	
	PR (95% CI)	aPR[a] (95%CI)	PR (95% CI)	aPR[a] (95%CI)	PR (95% CI)	aPR[a] (95%CI)
Age						
<25 years	1		1	1	1	1
25-35 years	1.06 (0.66, 1.71)		1.75 (1.06, 2.89)**	1.31 (0.82, 2.45)	1.38 (1.15, 1.65)***	1.24 (1.03, 1.50)**
>35 years	1.13 (0.66, 1.93)		1.63 (0.91, 2.93)		1.94 (1.60, 2.35)***	1.70 (1.39, 2.09)***
Income						
>minimum wage	1		1		1	1
< minimum wage	1.46 (0.97, 2.21)*	1.15 (0.76, 1.76)	0.68 (0.43, 1.08)*	0.54 (0.34, 0.87)**	1.20 (1.02, 1.40)**	1.05 (0.90, 1.24)
Education						
>secondary school	1		1		1	1
>Secondary school	1.02 (0.67, 1.54)		1.18 (0.79, 1.77)		1.34 (1.11, 1.62)**	1.36 (1.12, 1.64)**
Total partners (3 mos)						
1-3	1		1		1	1
4+	1.51 (0.83, 2.73)		1.89 (1.06, 3.36)**	1.86 (1.05, 3.28)**	2.06 (1.70, 2.49)***	1.99 (1.65, 2.41)***
HIV positive						
No	1		1		1	1
Yes	0.41 (0.11, 1.50)		0.52 (0.24, 1.10)*	0.82 (0.41, 1.62)	0.84 (0.68, 1.03)*	0.88 (0.71, 1.07)
Met for sex at a venue[b]						
No	1		1		1	1
Yes	1.48 (0.87, 2.52)		1.67 (0.94. 2.96)*	1.36 (0.74, 2.47)	1.54 (1.27, 1.87)***	1.23 (1.01, 1.50)**
Alcohol use disorder						
No (AUDIT<20)	1		1		1	
Yes (AUDIT ≥20)	1.03 (0.66, 1.60)		0.97 (0.62, 1.52)		1.01 (0.83, 1.23)	
Sex while drinking[b]						
No	1		1		1	1
Yes	1.41 (0.92, 2.18)		1.08 (0.72, 1.61)		1.37 (1.17, 1.60)***	1.21 (1.03, 1.41)**

Sex while drinking & drugs[b]						
No	1		1		1	
Yes	1.23 (0.73, 2.05)		1.75 (1.06, 2.88)**	1.29 (0.79, 2.12)	1.09 (0.74, 1.59)	
Any insertive CAI[b]						
No	1		1		1	
Yes	1.48 (0.68, 3.22)		0.98 (0.65, 1.48)		0.97 (0.82, 1.15)	
Any receptive CAI[b]						
No	1		1		1	
Yes	1.32 (0.88, 2.00)		1.14 (0.69, 1.87)		1.06 (0.89, 1.25)	
1+ stable partner[c]						
No	1		1		1	1
Yes	0.73 (0.47, 1.12)		0.52 (0.35, 0.77)***	0.57 (0.38, 0.85)**	0.73 (0.63, 0.85)***	0.84 (0.72, 0.98)**
1+ casual partner[c]						
No	1		1		1	1
Yes	2.48 (1.69, 3.63)***	2.05 (1.39, 3.03)***	2.32 (1.59, 3.39)***	2.63 (1.78, 3.88)***	2.58 (2.23, 2.98)***	2.16 (1.85, 2.53)***
1+ one-time partner[c]						
No	1		1		1	1
Yes	1.72 (1.12, 2.65)**	1.74 (1.14, 2.65)**	2.64 (1.79, 3.88)***	2.12 (1.45, 3.09)***	2.23 (1.88, 2.63)***	2.07 (1.75, 2.45)***
1+ client partner[c]						
No	1		1		1	1
Yes	2.05 (1.36, 3.08)**	1.88 (1.18, 3.00)**	2.07 (1.75, 2.44)***	2.00 (1.33, 3.00)***	1.95 (1.50, 2.55)***	1.41 (1.04, 1.91)**

[a]All adjusted analyses include *a priori* confounders of age (continuous), number of partners (log transformed), income (above or below minimum wage), and college (any secondary education).
[b]Behavior reported for the last 3 months with any partner (not limited to sexual history recall partners).
[c]Behavior reported among the last 3 sexual partners as reported in the sexual history recall questionnaire
PR: prevalence ratio; CI: confidence interval; aPR= adjusted prevalence ratio; CAI: condomless anal intercourse
*p<0.10; **p<0.05; ***p<0.0001

Table S1.4: Partnership characteristics among transgender women, transgender women, and men who have sex with men, among only those with full data on start and end dates.

Characteristic	**Partners of transgender women** (n=133)	**Transgender women** (n=141)	**Men who have sex with men** (n=1,522)	Test Statistic (χ^2)[a]	p-value
Total number of dyads	230	190	2333		
Mean dyads per participant (SD)	1.6 (0.8)	1.4 (0.6)	1.5 (0.3)	10.5	0.005
3-month cumulative concurrency[b]	38 (28.6%)	26 (18.4%)	366 (24.1%)	3.9	0.140
Point prevalence concurrency	32 (24.1%)	40 (28.4%)	253 (16.6%)	15.5	<0.001
Single encounter partnerships[b]	86 (41.1%)	71 (38.2%)	955 (41.6%)	0.9	0.650
Median days duration for partnerships >1 days (IQR)[a]	182 (61, 727)	244 (92, 727)	153 (46, 705)	8.4	0.015
Reported partnership type[c]**:**					
Stable	61 (45.9%)	94 (66.7%)	883 (58.0%)	12.3	0.002
Casual	37 (27.8%)	25 (17.7%)	430 (28.3%)	7.2	0.027
One-time	60 (45.1%)	35 (24.8%)	725 (47.6%)	27.1	<0.001
Client	11 (8.3%)	28 (19.9%)	45 (3.0%)	86.8	<0.001
Sex Worker	13 (9.8%)	0 (0.0%)	28 (1.8%)	38.1	<0.001
Any condomless sex by partner type[d]					
Stable	35 (57.4%)	50 (53.2%)	520 (58.9%)	1.2	0.560
Casual	17 (45.9%)	10 (40.0%)	170 (39.5%)	0.6	0.750
One-time	21 (35.0%)	8 (22.9%)	201 (27.7%)	1.9	0.380
Client	3 (27.3%)	9 (32.1%)	14 (31.1%)	0.1	0.960
Sex Worker	5 (38.5%)	0 (0.0%)	7 (25.0%)	0.8	0.380
Gender of partners:					
Transgender women only	99 (74.4%)	1 (0.7%)	N/A		
Cisgender men only	N/A	137 (97.2%)	1432 (94.1%)		
Cisgender women only	N/A	0 (0.0%)	71 (4.7%)		
Cisgender men and women	N/A	1 (0.7%)	19 (1.2%)		
TW and cisgender women	18 (13.5%)	0 (0.0%)	N/A		
TW and cisgender men	13 (9.8%)	2 (1.7%)	N/A		
TW, cisgender men and women	3 (2.3%)	0 (0.0%)	N/A		

[a]Chi-squared test statistics were calculated to compare each variable across the groups. For categorical variables, the Pearson's chi-squared test was used. For continuous variables (number of dyads, single encounter partnerships, days duration of partnership) the Kruskal-Wallis equality-of-populations rank test was used.
[b]Includes data imputation described in the methods.
[c]Inclusive, participants could report more than one type of partner
[d]Reported any unprotected sex with each partner type within the sexual history questionnaire of three most recent partners. Only among those who reported that partner type
SD: standard deviation; IQR: inter-quartile range;

Table S1.5: Independent associations between 3-month cumulative concurrency and covariates at baseline among transgender women, transgender women, and men who have sex with men, among only those with full data on start and end dates

Characteristic	Partners of transgender women		Transgender women		Men who have sex with men	
	PR (95% CI)	aPR[a] (95%CI)	PR (95% CI)	aPR[a] (95%CI)	PR (95% CI)	aPR[a] (95%CI)
Age						
<25 years	1		1	1	1	1
25-35 years	1.07 (0.58, 1.99)		1.66 (0.61, 4.53)		1.39 (1.13, 1.70)**	1.24 (1.00, 1.53)*
>35 years	1.15 (0.57, 2.34)		3.02 (1.15, 7.93)**	3.16 (1.24, 8.01)**	1.87 (1.49, 2.36)***	1.59 (1.25, 2.03)***
Income						
>minimum wage	1		1		1	1
< minimum wage	2.20 (1.23, 3.93)**	1.71 (0.96, 3.07)*	0.67 (0.30, 1.49)		1.28 (1.07, 1.53)**	1.13 (0.94, 1.37)
Education						
>secondary school	1		1		1	1
>Secondary school	1.33 (0.78, 2.28)		1.15 (0.57, 2.32)		1.35 (1.09, 1.68)**	1.31 (1.05, 1.63)**
Total partners (3 mos)						
1-3	1		1		1	1
4+	1.01 (0.54, 1.90)		2.29 (0.73, 7.13)		1.89 (1.53, 2.33)***	1.83 (1.48, 2.26)***
HIV positive						
No	1		1		1	1
Yes	0.56 (0.15, 2.05)		0.79 (0.26, 2.39)		0.77 (0.61, 0.99)**	0.82 (0.64, 1.05)
Met for sex at a venue[b]						
No	1		1		1	1
Yes	1.50 (0.76, 2.98)		1.61 (0.60, 4.36)		1.39 (1.13, 1.73)**	1.13 (0.90, 1.40)
Alcohol use disorder						
No (AUDIT<20)	1		1		1	
Yes (AUDIT ≥20)	1.00 (0.52, 1.94)		1.10 (0.48, 2.53)		1.06 (0.89, 1.28)	
Sex while drinking[b]						
No	1		1		1	1
Yes	1.45 (0.82, 2.56)		1.58 (0.77, 3.24)		1.49 (1.24, 1.78)***	1.34 (1.11, 1.61)**
Sex while drinking & drugs[b]						

No	1		1		1	
Yes	0.91 (0.41, 2.04)		1.86 (0.81, 4.26)		1.23 (0.82, 1.85)	
Any insertive CAI[b]						
No	1		1		1	
Yes	1.12 (0.46, 2.72)		1.03 (0.51, 2.08)		0.96 (0.79, 1.17)	
Any receptive CAI[b]						
No	1		1		1	
Yes	1.11 (0.62, 1.96)		0.79 (0.34, 1.87)		1.00 (0.83, 1.22)	
1+ stable partner[c]						
No	1		1		1	1
Yes	0.69 (0.39, 1.21)		0.58 (0.29, 1.16)		0.80 (0.67, 0.95)**	0.91 (0.76, 1.10)
1+ casual partner[c]						
No	1		1		1	1
Yes	4.64 (2.45, 8.78)***	2.11 (1.26, 3.57)**	4.64 (2.45, 8.78)***	3.56 (1.88, 6.73)***	2.80 (2.36, 3.33)***	2.36 (1.96, 2.84)***
1+ one-time partner[c]						
No	1		1		1	1
Yes	1.50 (0.87, 2.59)		1.89 (0.95, 3.79)*	1.93 (0.99, 3.75)*	2.25 (1.86, 2.74)***	2.09 (1.72, 2.54)***
1+ client partner[c]						
No	1		1		1	1
Yes	1.69 (1.29, 2.21)***	1.92 (0.96, 3.85)*	1.66 (1.11, 2.49)**	1.10 (0.50, 2.44)	1.58 (1.29, 1.94)***	1.34 (0.89, 2.02)***

[a]All adjusted analyses include *a priori* confounders of age (continuous), number of partners (log transformed), income (above or below minimum wage), and college (any secondary education).
[b]Behavior reported for the last 3 months with any partner (not limited to sexual history recall partners).
[c]Behavior reported among the last 3 sexual partners as reported in the sexual history recall questionnaire
PR: prevalence ratio; CI: confidence interval; aPR: adjusted prevalence ratio; CAI: condomless anal intercourse
*p<0.10; **p<0.05; ***p<0.0001

Chapter 3: Little to no overlap in sexual networks of transgender women and MSM in Lima, Peru

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Introduction

The global prevalence of HIV among transgender women (TW; persons assigned male sex at birth who identify as women) is estimated to be 19% (2). Despite this high prevalence, TW remain understudied in HIV research and under-prioritized in HIV interventions. Data from TW are often aggregated with data from men who have sex with men (MSM), limiting our understanding of how HIV transmission and pathogenesis differs between the two groups (6,8,9). This conflation is attributed to the common modality of transmission between MSM and TW (anal sex), difficulty finding and enrolling TW in research, and lack of recognition of differences between MSM and TW (6,8). However, research focused on TW have found that, compared to MSM, they are more susceptible to family expulsion, homelessness, and legal discrimination in jobs and education, are more likely to rely on sex work as a primary or sole income source, and are more likely to experience violence and power imbalances in relationships, impacting their ability to negotiate condom use (1,3,10,41,62–64).

While these social and cultural factors place TW at higher risk for HIV acquisition, it remains unclear why HIV prevalence in TW is higher than other high-risk groups, and how HIV is entering this population. Among MSM, HIV has been documented to spread quickly within intra-group sexual networks (20,21). TW sexual networks are more heterogenous, however, with TW in many settings reporting their partners as primarily cisgender (persons who identify as the gender that corresponds to the sex assigned at birth) men who identify as hetero- or bisexual (26,27,65). In many settings, HIV prevalence among cisgender heterosexual and bisexual men is relatively low, raising questions about the role they play in fueling the HIV epidemic among TW. One potential explanation for the high prevalence of HIV among TW is sexual network overlap between TW and MSM. This could allow bridging of HIV between MSM and TW directly or indirectly through people who have sex with both MSM and TW. Partners of TW (PTW) have been minimally characterized (26,27,30–32,46,65), and very little is understood about PTW living in low- and middle-income countries (LMICs) (27). Furthermore, there is a worldwide dearth of research examining the degree to which HIV is transmitted between these distinct, yet historically conflated groups.

In Peru, the HIV prevalence among TW is estimated to be 30%, significantly higher than the prevalence among the general population and heterosexual men (<1%), MSM (12-18%), and bisexual men (2-16%) (4,5,28,29). Injection drug use in Peru is low (17,66), so the primary mode of transmission is through sexual contact. Few studies have examined PTW in Latin America (27,30,33), and little is understood about their HIV risk. This is due in part to practical challenges in engaging PTW in research. First, PTW are not necessarily a community, and may not have unifying characteristics beyond their sexual partners, limiting our ability to find research participants. Second, due to stigma and discrimination against sexual and gender minorities, engaging in sexual relationships with TW is a hidden behavior and this may limit willingness of PTW to participate in research about their sexual behavior.

The objective of this research is to characterize the sexual network, and in particular the sexual partners, of TW in Lima to better understand the demographic and sexual characteristics of people who are potential sources of HIV infection and identify possible overlap between TW and MSM sexual networks. To do this, we used a novel modified method of respondent-driven sampling, in which we recruited participants through the sexual network and allowed for semi-anonymous study participation. These data could have implications for HIV prevention and outreach strategies, as well as our understanding of HIV transmission dynamics among sexual and gender minority groups.

Methods

Sampling and Procedures

We conducted a cross-sectional chain-referral study of TW and their sexual partners in Lima, Peru. Formative research, including focus groups and key informant interviews, were conducted prior to the study start to assess feasibility and acceptability of study design.

Participants were invited to join the study using a modified respondent-driven sampling scheme. Respondent-driven sampling is a chain-based recruitment method that operates through social networks, starting with “seed” participants selected through convenience sampling (67–69). This recruitment method has been used extensively to sample hard to reach populations, including sexual and gender minorities (3,67,70–77). For this study, the primary target population was PTW, who are not necessary a social network and therefore would be difficult to enroll using traditional respondent-driven sampling methods. To reach this population, we instead began with TW as seeds and asked them to recruit their sexual partners, allowing for recruitment through a sexual network. Ten TW who had participated in previous research or attended clinical services at Epicentro Salud, a community health center serving sexual and gender minorities in Lima, were selected as seeds. Seeds were purposefully selected based on HIV status, geographic location of residence, socio-economic status, and participation in sex work to ensure a range of these characteristics were represented in the sample. Each seed was asked to complete the survey and invite up to three recent (three months or less) sexual partners. Each sexual partner who joined the study was then given the same survey and asked to invite three of their sexual partners; forward recruitment continued in waves until the desired sample size was reached. Study staff tracked data in real time to assure eligibility criteria were met by each survey participant. Recruitment chains that did not include a TW or a PTW for two consecutive waves were censored (not allowed to recruit further).

Study Population

Eligibility criteria for this study were described in the consent form, and included being 18 years of age or older, living in Lima, reporting their recruiter to be a current or past sexual partner, and not having already participated in the study. Survey responses that were in violation of these criteria were removed from analysis and the survey participant was not permitted to recruit. For recruitment, sexual partner was defined as anyone the participant had sex with in the last three months; the type of sex was not specifically defined. TW were defined as anyone who was born male sex and identified as either a transgender woman or a woman. PTW were defined as anyone who reported a TW as a sexual partner in the previous three months. MSM were defined as anyone born male sex, identified their current gender as male, reported a man as a sexual partner in the previous three months, and did not report a TW as a sexual partner in the previous three months. For analyses, TW who also reported a TW partner were analyzed as PTW, and therefore were not included in the TW category to allow for mutual exclusivity across groups.

Data Collection

As a result of concerns about safety and confidentiality, the survey was self-administered online using a REDCap survey platform (ITHS, Seattle, WA) (78), and WhatsApp (WhatsApp Inc., Mountain View, CA) was used for recruitment. Previous studies using web-based respondent-driven sampling have found this to be a feasible and acceptable way to reach stigmatized populations, while producing comparable results to traditional in-person methods (79–82). Each time a survey was completed, survey responses were assessed by study staff to confirm eligibility, and phone numbers were checked against the study database to ensure the participant was not previously enrolled. Those found ineligible (due to age or reporting their recruiter as a non-sexual contact) and those already enrolled were called and notified that their survey results would not be used in the study. Eligible participants were each linked within the REDCap database to three new randomly generated participant identification numbers (PTIDs), which served as the PTIDs of their study recruits. For each PTID, REDCap also generated a survey link that could only be used one time, and was automatically linked to that PTID to ensure tracking of the recruitment structure. Eligible participants were contacted, provided further explanation of recruitment and compensation, then given three recruitment "coupons" in the form of a WhatsApp message with the unique PTIDs and survey URL links to send to each sexual partner recruit.

Participants could complete the survey on any device that connected to the internet. The survey assessed demographics, sexual and gender identity, sexual behavior, and alcohol and drug use. Gender identity was assessed using a two-step method (sex at birth and current gender identity) (60,61) and sexual preferences were assessed as both self-identified sexuality and reported attraction to each gender option (cisgender man, cisgender women, transgender man, transgender women).

Ethics

Participants completed online consent prior to survey completion, including consent to be contacted by study staff. Phone numbers were the only identifying information collected in the online survey. Most contact with participants was conducted by phone, aside from an in-person cash reimbursement for study participation. Participants were reimbursed using a dual payment method (67), receiving 40 soles (approximately $12 USD) for survey completion and 20 soles ($6 USD) for each successful recruitment. At the time of compensation, national identification numbers were collected in compliance with requirements of the ethics review board at la Asociación Civil Impacta Salud y Educación (IMPACTA) in Lima, which serves as the ethics review for both IMPACTA and Epicentro Salud, and approved the study protocol. All study activities, including procedures for ineligible survey respondents, were approved by the ethics committee at IMPACTA and the Fred Hutchinson Cancer Research Center in Seattle.

Statistical Analysis

Diagrams showing recruitment chains were created using NetDraw (83), and RDS Analyst (84) was used to generate variables related to recruitment structure (seed group and recruitment wave). RDS weights were not applied to the results because recruitment was conducted through sexual networks rather than social networks. This recruitment led to violations of the random recruitment assumption, as well as resulting in a different definition of degree (number of eligible sexual partners) than found in standard respondent-driven sampling studies, limiting our ability to derive accurate weights. Instead, multilevel modeling with mixed effects was used to adjust for two levels of correlation: cluster correlation (e.g. which seed group each participant was in), and wave, which was categorized into wave groups (waves 1-2, 3-6, 7-10).

Descriptive characteristics of PTW, TW, and MSM were compared across the groups using Pearson's chi-squared test and the Kruskal-Wallis test (α level of 0.05). Mixed effects models were used to generate crude and adjusted prevalence ratios and 95% confidence intervals for the association of knowledge of HIV status and predictors of interest separately for TW and PTW. Covariates associated with knowledge of HIV status at $p< 0.10$ in univariate models were entered into multivariable models alongside *a priori* determined confounders (age, education, and number of sexual partners) and random effects (seed, wave group). Finally, correlates of reporting a male sexual partner were assessed among PTW using mixed effects logistic regression modeling to produce odds ratios adjusted for random effects. Stata version 15.1 (College Station, TX, USA, 2017) was used for all analyses.

Results

Recruitment

This study enrolled 10 seeds in February 2018, and an additional 3 seeds in March 2018. A total of 529 surveys were completed between February – July 2018, with 442 included in this analysis. Surveys were excluded from analysis if the participant did not meet eligibility criteria (n=50), was a seed (n=13), or did not fit into the target groups (TW, PTW, and MSM) for this analysis (n=24). Of the seed participants, two were unproductive (no recruits joined the study) and two recruited 84% of study participants (Figure 2.1). Analysis includes 196 TW, 203 PTW, and 43 MSM. The longest chain of recruitment reached 10 waves. In the two dominant seed groups, TW (green circles and diamonds) primarily recruited cisgender men (blue circles and diamonds), who then recruited TW. Of note, few TW partners (blue diamonds) invited male sexual partners (blue circles) into the study.

Population Characteristics

PTW were primarily cisgender men who identified as bisexual (72%) or heterosexual (15%) and reported sexual attraction to cisgender women (68%) and TW (83%) (Table 2.1). Of 203 PTW, 7% reported a cisgender male partner in the previous three months, 9% reported sexual attraction to men, and 6.3% identified as homosexual. Conversely, 99% of TW and 100% of MSM reported male partners (note: MSM had a male partner by study definition). PTW primarily reported being the insertive partner for anal intercourse (88%), while TW reported primarily being the receptive partner for anal sex (84%) and MSM reported a mix of insertive (35%), receptive (28%) and versatile (37%) sex. 56% of partners reported condomless insertive sex, and 64% of TW reported condomless receptive sex. Transactional sex differed by group; a majority of TW reported a client partner in the past three months (66.3%) while purchasing sex was less common (7.1%), while in PTW a majority reported purchasing (52.7%) but not selling (6.9%) sex. MSM reported few transactional sex partners.

Correlates of Knowing HIV Status

Self-reported HIV-positive status was low across the groups, with MSM reporting the highest HIV prevalence at 14%, compared to 6% of TW and 4% of partners. However, MSM were also much more likely to know their HIV status; 42% of TW and 54% of PTW reported not knowing their status, compared to only 22% of MSM. Among 335 TW and PTW with non-missing data and controlling for age, number of partners, and education, TW were more likely to know their HIV status compared to PTW (58% versus 46%, aPR 1.48, 95% CI 1.19, 1.84, Table 2.2).

Correlates of HIV status knowledge were different for TW and PTW. Among PTW, having a male partner was associated with nearly double the likelihood of knowing one's status (aPR 1.92, 95% CI 1.42, 2.59). PTW were also more likely to know their HIV status if they reported having a stable partner (aPR 1.43, 95% CI 1.09, 1.88) and receptive (aPR 1.45, 95% CI 1.27, 1.66) or versatile (aPR 1.79, 95% CI 1.39, 2.31) anal sex when compared to insertive sex. PTW who reported buying sex (aPR 0.45, 95% CI 0.39, 0.52), having 16 or more sex partners compared to 5 or fewer (aPR 0.31, 95% CI 0.21, 0.44), and seeking sex partners at venues (aPR 0.73, 95% CI 0.55, 0.96) were less likely to know their HIV status in adjusted analyses. Among TW, similar factors were correlated with knowledge of HIV status, including reporting a steady partner and seeking sex at venues. However, receptive anal sex (aPR 0.63, 95% CI 0.67, 0.92) was associated with a lower likelihood of knowing their HIV status.

Predictors of having a male partner among PTW

Only 14 of 203 PTW reported a cisgender male partner in the previous three months. PTW who reported male partners were more likely to identify as homosexual (OR 9.1, 95% CI 2.33, 35.21) and sell sex (OR 17.1, 95% CI 3.92, 74.54), and were less likely to buy sex (OR 0.06, 95% CI 0.01, 0.55). In this small sample, those who had male partners in the last three months had over 40-fold increased odds of ever buying sex from (OR 48.95, 95% CI 10.17, 235.70) or selling sex to (PR 40.45, 95% CI 10.92, 149.89) a man. Condomless receptive anal sex was also more likely to be reported among those with recent male partners (OR 6.75, 95% CI 1.06, 42.83).

Discussion

This study found that PTW largely identified as bi- or heterosexual cisgender men, who reported attraction mainly to trans- and cisgender women. In line with this, PTW reported primarily trans- and cisgender female partners, with only 7% of these partners reporting a cisgender male partner in the previous three months. Thus, we found almost no overlap between TW and MSM sexual networks in Lima, Peru. Additionally, PTW appear to be a distinct population, with characteristics that differ from both MSM and TW, and that may put them at high risk for both acquiring and transmitting HIV, including condomless anal intercourse and frequently not knowing their HIV status. Taken together, the results of this study support the hypothesis that PTW are almost entirely separate from the MSM community, may not be receiving HIV testing at the same rate as MSM and TW, and may engage in behavior that puts TW at risk for HIV acquisition.

PTW reported sexual identifies and behaviors that differ from those of the men who did not report TW partners. Sexual orientation and reported attraction differ drastically between the groups, and align with reported gender of sexual partners. Of the partners who identify as bisexual, only 4% reported a male partner, indicating that “bisexual” may refer to their preference for both cis- and transgender women, and that bisexual men in this sample are likely markedly different from men who identify as bisexual and have sex with cisgender men and women. While few studies have characterized PTW, the sexual and gender identities of partners in this study align with previous research conducted in high-income settings (26,40,65) and Latin America (27,30,33), which have reported the majority of PTW to identify as bi- or heterosexual cisgender men. To our knowledge, no previous study in Latin America has characterized the sexual partners of PTW, so it is unknown how the reported gender of sexual partners in our sample may differ from other settings. In this sample, the few PTW that did report male partners appeared to be somewhat distinct from other PTW, and were more likely to know their HIV status, identify as homosexual, engage in condomless receptive sex, and sell sex.

The finding that PTW are unlikely to know their HIV status, but are more likely to know it if they have a male partner, has important public health implications. While an imperfect measure, knowledge of HIV status could serve as a proxy for access to HIV testing. Previous work in South America has found that HIV testing is low among PTW (27) and that they have low to moderate perceived risk of HIV (33). Based on our findings, those who are engaged in MSM sexual networks may have more access to HIV testing, and by extension other HIV prevention tools. HIV prevention interventions and peer outreach in Peru are heavily targeted to gay men, and to a lesser extent TW, so it is possible that PTW without male partners are less likely to access these services and be aware of their HIV risk. Addressing this disparity is important, as our study found that some behaviors associated with HIV risk, such as having many sexual partners and buying sex, were more likely among PTW who did not know their HIV status. One potential intervention point is to target sex seeking behavior at bars, clubs, and plazas. A majority of TW and PTW reported seeking sexual partners at social venues, some of which are unlikely to be frequented by MSM (data not shown), so interventions using peer outreach at these sites could be effective in reaching PTW.

HIV prevalence was likely under-reported in all groups, but was lowest among PTW, consistent with prior research conducted in Latin America (27,33). This could be partially explained by the strong preference for insertive anal intercourse among PTW, which inherently carries lower risk of HIV acquisition. This, combined with the high reported rate of condomless insertive sex, could result in few PTW acquiring HIV, but high risk of transmission to their TW partners among those who are infected. However, it is unclear if this fully accounts for the high prevalence of HIV found among TW in Lima in other studies (3). More work needs to be done to understand what drives transmission to TW, and more effort is needed to conduct HIV testing among partners to determine whether HIV prevalence is truly low in this group.

This study had several strengths. While a number of recent studies have collected data about PTW (27,30,32,33,44,46,59,65), few in Latin America have directly contacted the partners (27,33), and, to our knowledge, our study is the first in Latin America to enroll a cohort intentionally targeting partners. The existing literature on PTW in Latin America are primarily secondary analyses of TW partners found within studies targeting MSM or sex work population, which may produce more biased samples (27,33). In addition, the large sample size of this study is a strength, as partners are an extremely hard to reach population, both due to issues in identifying them, and stigma and violence associated with having TW sex partners in many settings, including many Latin America countries.

However, to achieve this large sample, a number of methodological modifications were made to our study design that limit the interpretation of the results. First, while the relatively anonymous online data collection was helpful in providing confidentiality, encouraging participation, and reducing social desirability bias, it limited our ability to conduct longitudinal analyses or HIV testing. Second, there may be bias in our non-population-based sampling design, and the results may not fully represent the general population of PTW. Taking the recruitment and self-reported behavior together, there is evidence of bias in recruitment. Cisgender men in the study recruited TW partners almost exclusively, despite 55% reporting cisgender women as sexual partners in addition to TW partners. Additionally, joining the study was contingent on having a recent sexual partner, and those with more partners were more likely to be invited into the study. Finally, respondent-driven sampling studies are generally weighted to account for differences in size of social network to derive population estimates, and we were not able to apply this weighting to our sample. Despite these limitations, given the hidden nature of this population and dearth of existing data, we believe the methods used provided a launching point for future research to validate our findings and further investigate HIV prevalence and access to HIV prevention services in this population.

Conclusions

This study provided new insight into the sexual networks of TW and their partners, and suggests little overlap with MSM sexual networks and a potential gap in HIV testing and prevention services for PTW. However, the source of HIV infection among TW remains unclear, as is the burden of HIV among PTW. More work needs to be done to engage PTW in both research and outreach for HIV prevention. Understanding the HIV transmission dynamics between TW and their partners could be an important step toward targeted HIV intervention among these populations.

Tables and Figures

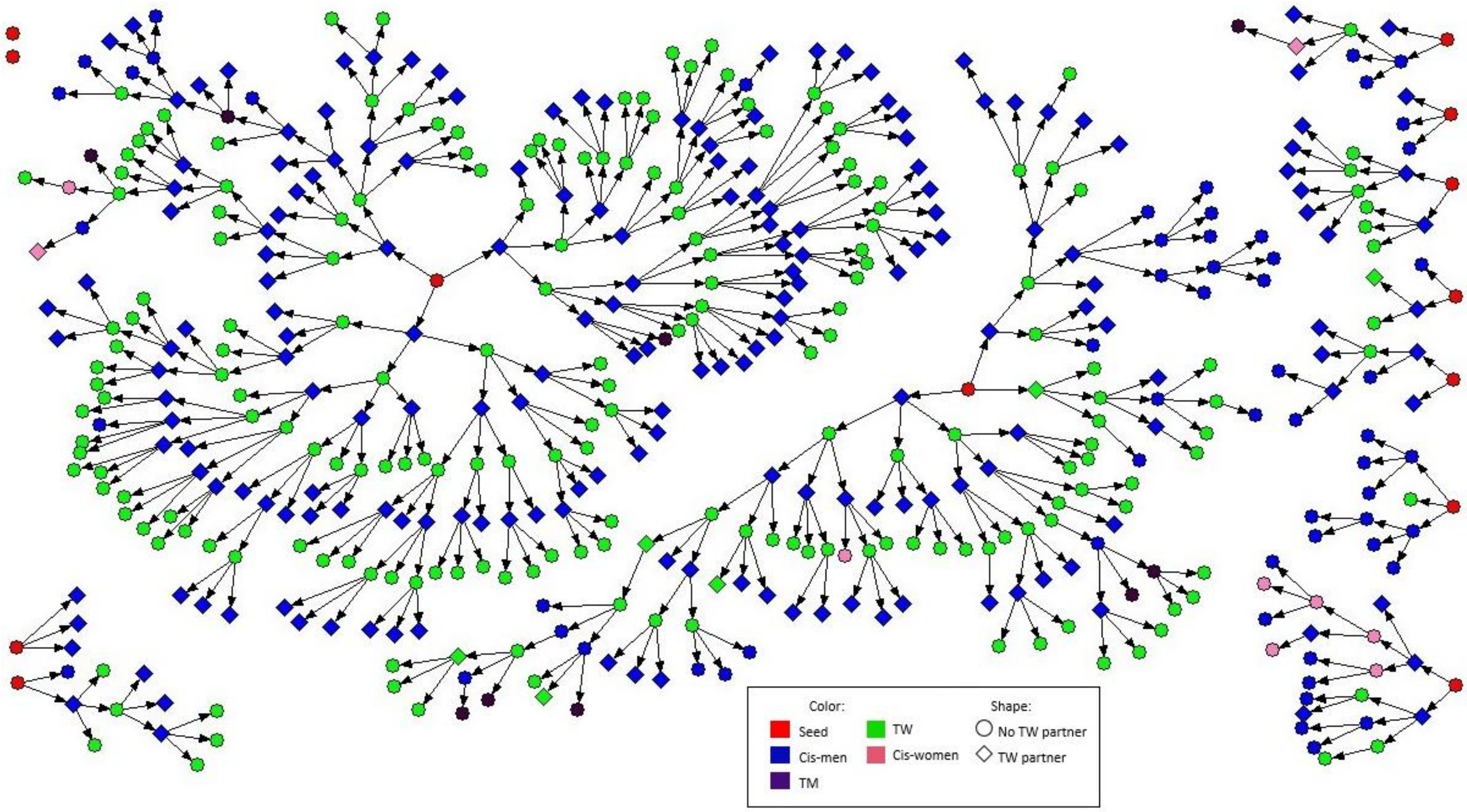

Figure 2.1: Diagram of recruitment of all eligible participants, including those not shown in analysis because they do not belong to the target groups of this analysis (n=24). Each node represents a participant, and each arrow shows who they recruited into the study, up to three recruits per participant. Colors represent genders, and shape represents whether that participant reported a TW as a sexual partner in the survey (see Key). Red dots represent TW seeds who were purposefully selected into the study. The two dominant seed groups demonstrate a pattern of TW seeds recruiting cisgender men who report TW as sexual partners, who then recruit TW. Each participant could only join the study one time, and therefore can only be one node in the diagram.

TW: transgender women; Cis-men: cisgender men; cis-women: cisgender women; TM: transgender men

Table 2.1: Characteristics of transgender women, partners of transgender women, and men who have sex with men within the sexual network.

Characteristic	Partners of transgender women (n=203)	Transgender women[a] (n=196)	Men who have sex with men (n=43)	p-value[b]
Age, mean (SD)	32.1 (9.2)	30.0 (7.9)	25.9 (8.7)	<0.001
Education (any post-secondary school)	70 (36.1%)	34 (18.1%)	27 (62.8%)	<0.001
Work status				
Full or Part time	115 (61.8%)	83 (46.9%)	21 (50.0%)	0.011
Informal	52 (28.0%)	70 (39.5%)	11 (26.2%)	
No work	19 (10.2%)	24 (13.6%)	10 (23.8%)	
Housing status				
Rent or own	61 (31.3%)	79 (42.0%)	8 (19.5%)	<0.001
With sexual partner	8 (4.1%)	10 (5.3%)	2 (4.9%)	
With parent	107 (54.9%)	65 (34.6%)	29 (70.7%)	
With friend	19 (9.7%)	33 (17.6%)	2 (4.9%)	
Street or car	0 (0.0%)	1 (0.5%)	0 (0.0%)	
Gender				
Cisgender man	196 (96.6%)	0 (0.0%)	43 (100.0%)	<0.001
Transgender woman	5 (2.5%)	196 (100.0%)	0 (0.0%)	
Cisgender woman	2 (1.0%)	0 (0.0%)	0 (0.0%)	
Sexuality				
Heterosexual	29 (15.3%)	22 (12.2%)	2 (4.7%)	<0.001
Bisexual	136 (72.0%)	5 (2.8%)	8 (18.6%)	
Homosexual	12 (6.3%)	140 (77.8%)	26 (60.5%)	
Pansexual	8 (4.2%)	4 (2.2%)	5 (11.6%)	
Attraction				
Cisgender women	138 (68.0%)	1 (0.5%)	10 (23.3%)	<0.001
Cisgender men	18 (8.9%)	192 (98.0%)	41 (95.3%)	<0.001
Transgender women	169 (83.3%)	4 (2.0%)	1 (2.3%)	<0.001
Transgender men	18 (8.9%)	0 (0.0%)	1 (2.3%)	<0.001
Sexual role				
Insertive	171 (88.1%)	5 (2.6%)	15 (34.9%)	<0.001
Receptive	5 (2.6%)	160 (83.8%)	12 (27.9%)	
Versatile	18 (9.3%)	26 (13.6%)	16 (37.2%)	
Gender of partners (past 3 mos)				
Cisgender woman	111 (54.7%)	1 (1.0%)	4 (9.3%)	<0.001
Cisgender man	14 (6.9%)	194 (99.0%)	43 (100%)	<0.001
Transgender woman	203 (100%)	0 (0.0%)	0 (0.0%)	<0.001
Transgender man	1 (0.5%)	2 (1.0%)	1 (2.3%)	0.50
Reported partnership type (past 3 mos)				
Stable/spouse	35 (17.2%)	22 (11.2%)	17 (39.5%)	<0.001
Casual/one-time	170 (83.7%)	154 (78.6%)	27 (62.8%)	0.008
Client[b]	14 (6.9%)	130 (66.3%)	3 (7.0%)	<0.001
Bought[b]	107 (52.7%)	14 (7.1%)	1 (2.3%)	<0.001

Number of partners (past 3 mos), median (IQR)	8 (4, 16)	15 (6, 22)	3 (2, 5)	<0.001
Sought sex at venues (past 3 mos)	107 (55.7%)	172 (90.5%)	20 (47.6%)	<0.001
Ever met partners online	174 (90.6%)	170 (92.4%)	38 (90.5%)	0.81
Insertive CAI (past 3 mos)	120 (59.1%)	58 (29.6%)	17 (39.5%)	<0.001
Receptive CAI (past 3 mos)	15 (7.4%)	126 (64.3%)	14 (32.6%)	<0.001
HIV status				
Negative	74 (42.8%)	85 (52.5%)	24 (64.9%)	0.002
Positive	6 (3.5%)	9 (5.6%)	5 (13.5%)	
Don’t know status	93 (53.8%)	68 (42.0%)	8 (21.6%)	
Ever use of drugs	21 (10.3%)	27 (13.8%)	5 (11.6%)	0.57
Ever injected drugs or medicine	7 (3.4%)	3 (1.5%)	3 (7.0%)	0.14
Alcohol frequency	20 (11.4%)	11 (6.4%)	3 (7.1%)	0.42
<=1 per month	48 (27.4%)	44 (25.7%)	16 (38.1%)	
2-3 per month	66 (37.7%)	68 (39.8%)	15 (35.7%)	
1+ per week	41 (23.4%)	48 (28.1%)	8 (19.0%)	
Binge drinking (past 3 mos)	94 (46.3%)	92 (46.9%)	17 (39.5%)	0.67

[a]TW category only includes TW who did not report a TW as a partner; those that did (n=5) were categorized as PTW.
[b]P-values reported for chi-squared test statistics calculated to compare each variable across the groups. For categorical variables, the Pearson’s chi-squared test was used. For continuous variables (age, number of male partners) the Kruskal-Wallis equality-of-populations rank test was used.
[c]Buying and selling sex was defined as exchanging sex for money, goods, or services.
SD: standard deviation; IQR: interquartile range; mos: months; CAI: condomless anal intercourse

Table 2.2: Characteristics associated with knowledge of HIV status among transgender women and partners of transgender women.

Characteristic	Partners of transgender women		Transgender women[a]	
	PR[b] (95% CI)	aPR[c] (95%CI)	PR[b] (95% CI)	aPR[c] (95%CI)
Age[d]				
<25 years	1		1	1
25-35 years	0.93 (0.70, 1.24)	0.96 (0.66, 1.38)	0.92 (0.65, 1.33)	0.96 (0.74, 1.24)
>35 years	0.74 (0.38, 1.45)	0.83 (0.43, 1.62)	0.79 (0.65, 0.95)	0.80 (0.68, 0.94)**
Education[d]				
>secondary school	1		1	
>Secondary school	1.85 (0.96, 3.57)	1.68 (1.16, 2.42)**	0.97 (0.76, 1.24)	0.92 (0.85, 1.00)*
Total partners (past 3 mos)[d]				
1-5	1		1	
6-15	0.55 (0.38, 0.79)	0.55 (0.35, 0.85)**	0.75 (0.62, 0.90)	0.78 (0.67, 0.92)**
16+	0.29 (0.19, 0.45)	0.31 (0.21, 0.44)***	0.48 (0.27, 0.87)	0.50 (0.31, 0.80)**
Sexual role				
Insertive	1		1	
Receptive	1.99 (0.83, 4.79)	1.45 (1.27, 1.66)***	0.68 (0.56, 0.83)	0.63 (0.42, 0.94)*
Versatile	1.80 (1.06, 3.05)	1.79 (1.39, 2.31)***	0.91 (0.64, 1.29)	0.70 (0.44, 1.10)
Sold[e] sex (past 3 mos)				
No	1		1	
Yes	1.39 (0.71, 2.72)	1.66 (0.84, 3.27)	0.61 (0.35, 1.08)	0.77 (0.52, 1.13)
Bought[e] sex (past 3 mos)				
No	1		1	
Yes	0.36 (0.26, 0.50)	0.45 (0.39, 0.52)***	1.07 (0.95, 1.20)	1.08 (0.97, 1.20)
Reported a stable partner (past 3 mos)				
No	1		1	
Yes	1.78 (1.12, 2.82)	1.43 (1.09, 1.88)*	1.35 (1.28, 1.42)	1.20 (1.02, 1.42)*
Reported cisgender male partner				
No	1		1	
Yes	1.74 (1.11, 2.74)	1.92 (1.42, 2.59)***	0.62 (0.39, 0.98)	0.54 (0.36, 0.80)**
Insertive CAI (past 3 mos)				
No	1		1	
Yes	1.01 (0.68, 1.48)	1.09 (0.72, 1.66)	0.62 (0.36, 1.05)	0.56 (0.24, 1.29)
Receptive CAI (past 3 mos)				
No	1		1	
Yes	1.38 (0.83, 2.30)	1.35 (0.88, 2.07)	0.61 (0.41, 0.90)	0.73 (0.57, 0.94)
Sought sex at social venue				
No	1		1	
Yes	0.56 (0.31, 1.03)	0.73 (0.55, 0.96)*	0.59 (0.38, 0.91)	0.61 (0.52, 0.72)***
Met partner online				
No	1		1	
Yes	0.72 (0.56, 0.92)	0.84 (0.56, 1.26)	0.73 (0.65, 0.84)	0.81 (0.58, 1.13)
Binge drinking (past 3 mos)				

No	1		1	
Yes	0.86 (0.61, 1.23)	0.98 (0.59, 1.63)	0.83 (0.71, 0.98)	0.90 (0.78, 1.04)

[a]TW category only includes TW who did not report a TW as a partner; those that did (n=5) were categorized as PTW.
[b]All univariate analyses adjusted for random effects (seed group, wave category).
[c]All adjusted models include *a priori* confounders of age (continuous), number of partners (log transformed), and secondary education (completed any university or other secondary education) as well as random effects (seed group, wave category).
[d]Variables selected a priori as confounders are presented in the table in their descriptive form for reference. Each is adjusted for the other *a priori* confounders in adjusted analysis.
[e]Buying and selling sex defined as trading sex for money, goods, or services.
*less than 0.05, ** less than 0.01, *** less than 0.001
PR: prevalence ratio; aPR: adjusted prevalence ratio; CI: confidence interval; mos: months; CAI: condomless anal intercourse

Table 2.3: Correlates of having a cisgender male partner among PTW (n=203)

Characteristics	Male partners (n=14)		No male partners (n=189)		OR[a]	95% CI	P-value
	n	(%)	n	(%)			
Identify as homosexual	4	(28.6)	8	(4.2)	9.05	(2.33, 35.21)	0.001
Know HIV status	11	(78.6)	69	(43.4)	4.78	(1.28, 17.81)	0.020
HIV positive (self-report)	1	(7.1)	5	(2.7)	2.83	(0.31, 26.05)	0.358
Bought sex (past 3 mos)[b]	1	(7.1)	106	(56.1)	0.06	(0.01, 0.55)	0.013
Sold sex (past 3 mos)[b]	7	(50.0)	7	(3.7)	17.09	(3.92, 74.54)	<0.001
Ever sold sex to a man	10	(71.4)	11	(5.8)	40.45	(10.92, 149.89)	<0.001
Ever bought sex from a	7	(50.0)	4	(2.1)	48.95	(10.17, 235.70)	<0.001
Stable partner (past 3 mos)	4	(28.6)	31	(16.4)	2.04	(0.60, 6.92)	0.253
Receptive CAI (past 3 mos)	9	(81.8)	6	(40.0)	6.75	(1.06, 42.83)	0.043
Insertive CAI (past 3 mos)	9	(75.0)	111	(60.7)	1.95	(0.51, 7.43)	0.330

[a]Adjusted for random effects (seed and level)
[b]Buying and selling sex was defined as exchanging sex for money, goods, or services.
OR: odds ratio; CI: confidence interval; mos: months; CAI: condomless anal intercourse

Chapter 4: Estimating overlap in the HIV transmission networks of transgender women and MSM using molecular epidemiologic analysis

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Introduction

Transgender women (TW), persons assigned male sex at birth who identify as women, have a disproportionally high burden of HIV, with an estimated global prevalence of 19% (2). In many settings, stigma and discrimination act as drivers of HIV risk among TW and increase vulnerability to disease, through avenues such as high reliance on sex work, power imbalances in sexual relationships, and dependencies on alcohol and drugs (1,35,37,41,85). While these factors increase the likelihood of HIV acquisition and transmission, the source of HIV in TW sexual networks is not well understood. Little is known about the sexual partners of TW (PTW), and most data on this population are from studies conducted among TW (30,40), in small qualitative studies among PTW (25), or through convenience samples of TW or bi- and homosexually identified men (27,32,33).

Based on research conducted among TW in North and South America, a majority of PTW are cisgender men (person assigned male sex at birth who identify as men) who identify as hetero- or bisexual (25–27,32,33,40,58). However, HIV prevalence among hetero- and bisexual men is generally low, limiting their potential to transmit HIV to TW. One hypothesis to explain high HIV prevalence among TW is that male PTW also have sex with men, leading to “bridging” of HIV between sexual networks of TW and men who have sex with men (MSM). Few studies provide quantitative data on sexual behavior among PTW, but these suggest that PTW are distinct from MSM populations and report few male partners, lending little support to this hypothesis (27,40,86).

Molecular epidemiology using HIV viral genetic sequences can serve as a tool to better understand transmission dynamics between populations (87–89). Due to the rapid evolution of HIV, viral samples from HIV-positive individuals can be sequenced and compared to determine the genetic distance, measured as the number of nucleotide substitutions between sequences

(88–91). Genetic distance can be used to identify clusters of viral sequences that are highly related, which are presumed to represent recent HIV transmission events, either between the individuals identified or through additional unidentified intermediaries (89,92). Analyzing cluster membership, compared to non-membership, can provide inference about potential drivers of transmission in local epidemics (89,93–95). Genetic distance analyses can be combined with epidemiologic data to identify patterns in HIV transmission that may not be evident using traditional epidemiologic methods alone (96–101).

The objective of this analysis is to use molecular epidemiology to better understand transmission dynamics between TW, MSM, and PTW in Lima, Peru. HIV prevalence is high among these populations, with an estimated 30% of TW and 12-18% of MSM living with HIV in Lima (3,4). Few studies have examined HIV prevalence among PTW, but it is estimated to be between 4-9% in Latin America (27,86). Injection drug use is low (17,66), so sexual transmission is presumed to account for HIV spread among MSM and TW in Peru. Due to this, understanding HIV transmission networks would provide insight into the sexual networks in these populations. We aim to use HIV sequences from blood samples collected in research settings to examine if TW and MSM are found in the same viral clusters, indicating overlap in HIV transmission networks. Additionally, we aim to use epidemiologic data to identify if any demographic or behavior characteristics predict clustering overall, as well as co-clustering of cisgender men (both MSM and PTW) and TW.

Methods

Genetic Data

Data for this analysis were collected from three research studies conducted in Lima, Peru between 2013 and 2018. Information about the data collected from each study is shown in Table 3.1. The Sabes study accounts for 78% of participants in this analysis. Details about enrollment and follow up in Sabes have been previously published (51). Briefly, an initial screening visit was conducted with 3,336 high-risk MSM and TW, including HIV testing and a questionnaire assessing demographic and risk behavior. Eligibility criteria included being ≥18 years of age, assignment of male sex at birth, self-report of a male or TW sexual partner in the previous 12 months, lack of awareness of HIV status, and elevated risk for HIV based on previously described criteria, such as sex work, having an HIV-positive sex partner, or having a sexually transmitted disease in the past six months. Those who were HIV-negative at baseline were followed to capture incident HIV infection, with HIV testing conducted every four weeks to allow for early diagnosis and treatment. This analysis includes 106 participants from the initial screening and 261 participants with incident infection during study follow up.

The Feminas study enrolled 216 HIV-positive and negative TW to test an integrated care package combining HIV services, social support, and provision of feminizing hormones. Inclusion criteria included age ≥18 years, assignment of male sex at birth, identifying as TW or on the trans-feminine continuum (e.g. trans, travesty, transgender, or transsexual), and being unaware of their HIV status, or HIV positive but not engaged in HIV care. HIV-positive TW received HIV treatment and HIV-negative participants received HIV prevention education. Feminas participants in this analysis were enrolled between 2016 – 2017, and include 37 participants who were HIV positive at baseline and three who seroconverted during follow up.

Finally, the Microepidemics study was a sub-study within Sabes that sought to identify hotspots for incident HIV infection using geospatial and phylogenetic data. In this study, HIV point-of-care testing and pre- and post-test counseling was conducted at social venues that were identified in previous research as being popular among MSM and TW. Data for the Microepidemics study were collected over a 6-month period in 2017 and did not include a questionnaire. The only data collected were blood samples, national identification numbers, sex, gender, and if they had male or TW sexual partners. We obtained HIV viral sequences from 63 HIV-positive MSM, TW, and PTW who were tested through this study.

This analysis incudes only one viral sequence from each participant. If multiple samples were collected within a study, the first available sample was sequenced. National identification numbers were checked across all participants to identify those enrolled in more than one study cohort. In the case of multiple enrollment (n=8 participants), only the first available sample was used, and the study in which it was collected was assigned to that participant (Sabes in 6 cases, Feminas in 2 cases). This analysis includes a mix of sequences from samples collected within 6 months of HIV acquisition (termed "early diagnoses") (102) and sequences from known or presumed prevalent cases (samples collected >6 months after presumed HIV infection, or samples for which no data were available about HIV infection date) (Table 3.1).

Epidemiologic Data

Viral sequences were linked to epidemiologic data collected at baseline in the Sabes and Feminas studies. Both Sabes and Feminas administered baseline questionnaires assessing demographic characteristics, gender and sexual identity, sexual behavior, and alcohol and drug use. Characteristics that were assessed using questions with nearly or fully identical wording between the two studies were merged allowing both studies to be included in the analyses to determine predictors of cluster membership. To examine predictors of cisgender men being found in clusters with TW, epidemiologic data were only assessed among cisgender men, so only Sabes data were used.

Groups of interest for this analysis include TW, MSM, and PTW. Definitions used for gender identities differed slightly across studies; for this analysis, all participants were categorized based on their identity in the parent study. TW identity was assessed in both Sabes and

Microepidemics through a single question asking if they self-identify as transgender. Feminas defined gender using a two-step method assessing both sex assigned at birth and current gender identity. MSM in Sabes were defined as eligible participants who did not identify as transgender. In Microepidemics, MSM were defined as cisgender men who reported male partners. PTW were defined in Sabes as participants who reported a TW as one of three most recent sexual partners in the last 6 months. Microepidemics defined PTW as anyone who identified having a TW partner by self-report.

Phylogenetic Analysis

For each sample used in analysis, the HIV *pol* region was sequenced using Sanger sequencing and aligned to a HXB2 reference sequence using the MAFFT algorithm (103) and manual removal of phylogenetically noninformative regions (91). A transmission network and phylogenetic tree were constructed using all study sequences as well as all available South American HIV *pol* sequences from the Los Alamos HIV Database (n=552; available from www.hiv.lanl.gov). A maximum likelihood phylogenetic tree was reconstructed in RaxML (104) in Geneious software (105) and visualized using R v3.4.1. Molecular clusters were identified within the transmission network, with cluster membership defined as ≥2 sequences linked to each other based on a pre-defined genetic distance threshold. For primary analyses, clusters were created using Tamura-Nei 1993 (TN93) (106) pairwise distance and a genetic distance threshold of 1.5%, corresponding to 0.015 nucleotide substitutions per base site. Codons associated with drug resistance were not removed, as previous research has found removal has minimal effect in similar analyses using pairwise clustering techniques (92,107,108). These are standard measures and thresholds, and were chosen to allow comparability with other studies (107,109,110). Sensitivity analyses were conducted defining cluster membership using pairwise genetic distance with a less conservative threshold of 3%. Additionally, analyses were repeated using patristic distance, which measures distance based on the sum of branch lengths between two branches on a phylogenetic tree. Cluster membership was again defined as ≥2 linked sequences, with distance thresholds of 1.5%. Results of the sensitivity analyses can be found in the Supplementary Material.

Statistical Analysis

To understand overlap in HIV transmission networks, we examined percent clustering within and between groups of interest (TW, MSM, and PTW). Correlates of clustering among all groups were assessed using univariate Poisson regression with robust standard errors to calculate unadjusted prevalence ratio with 95% confidence intervals (CI) and p-values (α level of 0.05). For this analysis, data from all studies were used to assess the relationship between clustering and diagnosis year, study, interest group, and early vs prevalent HIV infection. For all other potential correlates, data from Sabes and Feminas were used for analyses. Univariate Poisson regression was also used to identify predictors of co-clustering with TW among cisgender men. This subset analysis was conducted only among cisgender men, and therefore the Sabes study was the only source for demographic and behavior correlates in this analysis.

The frequency of in-group versus between-group clustering across groups (MSM, TW, and PTW) was explored using descriptive statistics of cluster membership. Among those who were found in clusters, we calculated in each group the percent who co-clustered with members of their own group, compared to the percent who co-clustered with members of other groups. No data were available about the identities of the people contributing sequences to the Los Alamos Database, so these sequences were not used for descriptive or analytic purposes. Due to this, clusters were excluded if they include only one study participant linked to one or more sequence from the Los Alamos Database. All analyses were conducted in R version 3.4.1 and Stata version 15.1 (College Station, TX, USA, 2017).

Results

Of the 467 participants included in this analysis, 303 were MSM, 139 TW, and 25 PTW. Overall, 200 (42.8%) study participants were found in a cluster with ≥1 other participant using a genetic distance threshold of 0.015 substitutions per site. Three participants were dropped from analysis due to clustering only with Los Alamos Database sequences. The remaining clustered participants were found in 62 clusters containing between 2 and 27 study participants (Figure 3.1). Of the clusters identified, 48% contained TW, 79% contained MSM and 15% contained PTW. The likelihood of appearing in a cluster did not differ significantly based on group; 44% of MSM appeared in clusters, compared to 40% of TW (PR 0.91, 95%CI 0.72, 1.16) and 40% of PTW (PR 0.90, 95% CI 0.55, 1.49) (Table 3.2). We found no meaningful differences in likelihood of clustering by study, year of diagnosis, or whether the HIV diagnosis was early (≤6 months after HIV infection) or presumed prevalent (>6 months after HIV infection or no data available on previous testing). In analyzing possible demographic or behavioral predictors of being found in a cluster, no observed characteristics were associated with cluster membership (Table 3.2).

To explore HIV transmission between interest groups, we examined the frequency and types of co-clustering between TW, MSM, and PTW among the subset of participants found in clusters. In total, 57% of clustered TW were found in a cluster with MSM and 37% of clustered MSM were found in a cluster with TW (Table 3.3). Compared to the distribution of each group in the sample, the percentage of TW clustering with MSM was slightly lower than may be expected, as MSM accounted for 67% of the sample population. Clusters containing both TW and MSM accounted for 27% (17/62) of all clusters found in this analysis (Table 3.4). Among MSM and TW, in-group clustering was more common than between-group clustering; 77% of TW clustered with TW and 91% of MSM clustered with MSM (Table 3.3). We had a limited sample of PTW who were found in clusters (n=10), but this group was more likely to cluster with TW (50%) or MSM (60%) than with each other (20%). MSM were the most likely to be found in an exclusively in-group cluster, with 51% (80/134) of MSM found in MSM-only clusters compared to 36% (20/56) of TW in TW-only clusters and no PTW in PTW-only clusters.

We sought to identify characteristics associated with co-clustering of MSM and TW to determine if men found in HIV transmission networks with TW differed from men not found in these networks. To examine this, we assessed if any demographic or behavioral characteristics of cisgender men were predictive of clustering with TW (Table 3.5). No characteristics were significantly associated with clustering with TW at alpha=0.05. However, the results show some evidence that those who identify as bisexual were more likely to cluster with TW compared to those who identify as homosexual (PR 1.52, 95% CI 0.98, 2.35). Data trends suggested that those who reported a TW partner may be more likely to be found in a cluster with a TW, and those who engage in receptive or versatile anal intercourse may be less likely, however none of these results were statistically significant.

Discussion

In this sample, TW and MSM were highly likely to be found in clusters together. Of TW found in clusters, over half were in a cluster with MSM. While this clustering may be less than would be expected given random mixing, it still indicates meaningful overlap of HIV transmission networks between the two groups. Given the low reported injection drug use in this population, overlap in HIV transmission networks is presumed to highly correlate with overlap in sexual networks. Likelihood of clustering did not differ when comparing TW, MSM, and PTW, and no identified demographic or behavioral characteristics predicted clustering. Additionally, no characteristics were found to be predictive of co-clustering of TW with cisgender men in this sample, though the small sample size may have limited the interpretations of some variables of interest, such as sexual role and sexual orientation.

The clustering patterns between MSM and TW observed in this analysis align with recent research conducted in Los Angeles County using sequences collected through the Los Angeles Department of Public Health for drug resistance testing (110). Ragonnett-Cronin et al. found that TW were highly likely to cluster with MSM, but had lower odds of clustering with MSM than would be expected based on the gender distribution in the sample. While that analysis did not include data on who reported sexual partnerships with TW, they did find that cisgender men who did not have sex with men or inject drugs were more likely to be found in a cluster with TW compared to MSM. Similarly, a phylogenetic analysis among a population with high injection drug use in San Francisco found high likelihood of clustering between TW and MSM (111). This study called into question the categorization of MSM when using public health surveillance data, suggesting that men may be labeled MSM for having sexual partnerships with TW. However, this would not present an issue in our dataset due to collection of self-reported data on sexual identity and partnerships, and disaggregation of PTW and MSM in our analysis.

While our analysis and those in the United States suggest similar trends in co-clustering of TW and MSM, these results are somewhat at odds with self-reported data from PTW. TW and their partners are understudied, and the limited literature investigating PTW rarely report on their sexual behavior with cisgender men. However, a study conducted in San Francisco in 2011 found 21% of male PTW reported a male partner in the past three months (40). Similarly, analysis of the full Sabes cohort reported in Chapter 2 found that of men who reported TW as sexual partners, 19% reported sex with cisgender men. In Chapter 3, we reported on the 2018 study of over 400 TW and their sexual partners in Lima, Peru, which found only 7% of PTW reported sex with a man in the past three months, and only 9% reported attraction to men (86). Based on these self-reported behaviors, MSM should constitute a small proportion of the sexual network of TW, and we would not expect to see the level of significant overlap in HIV transmission networks that was found in this analysis.

One potential hypothesis to explain the lack of agreement in self-reported behavior and molecular analysis results is that PTW who have sex with men are more likely to engage in high risk behavior. As a result, PTW who have sex with men may have a higher HIV prevalence than other PTW, and as a result are over-represented in HIV transmission networks compared to other PTW. There is some evidence to support this hypothesis. The 2018 study in Lima found that PTW who have sex with men had 7-fold higher odds of receptive condomless anal intercourse (CAI) than other PTW, as well as 17-fold higher odds of selling sex (86). Further, the few current studies assessing HIV status among PTW in South America suggest that HIV prevalence is 4-9%, much lower than that of TW or MSM, supporting the idea that the HIV transmission network may only be a subset of the overall sexual network (27,33,86).

The overlap in sexual networks between MSM and TW found in this study may provide insight into the source of HIV infection among TW, however this should be interpreted with caution. This cluster analysis is not able to distinguish directionality in transmission events between two linked sequences. Moreover, it is unknown if linked sequences indicate direct transmission between two members of a cluster, or transmission through an intermediary. Therefore, it is not known if transmission occurs directly between MSM and TW, or through a partner that has sex with both men and TW but may not identify as part of the MSM social or sexual network. Despite these limitations, these results suggest that some bridging of HIV is occurring between MSM and TW, and this may contribute to high HIV prevalence among TW. TW are more likely to be the receptive partner in anal sex, a sexual position that poses a higher HIV acquisition risk, and therefore may be at high risk of HIV acquisition from partners that bridge between the two populations. Further research is needed to better understand the HIV prevalence in PTW, how these partners contribute to HIV bridging between MSM and TW, and possible directionality of HIV transmission between these populations.

This analysis had a number of strengths. The availability of linked epidemiologic data allowed us to explore possible predictors of clustering, which is not readily available in surveillance cohorts used in the United States. Further, the majority of samples included in this study were collected during early infection. Sampling from early infection, before the virus has gone through intra-host mutation, is more likely to indicate recent, rapid transmission events (88,90,91), and in this study improved the likelihood of identifying clustering of sequences from participants in the same HIV transmission network. Further, this sample included a large population of HIV viral sequences from MSM and TW in Peru. These data are difficult and expensive to obtain in low- and middle- income countries (LMIC) where routine sequencing does not occur, and allows us to compare these data with results from established surveillance systems where HIV *pol* sequencing is routine.

Our results should be interpreted in light of the following limitations. First, this sample included only a small fraction of the target populations, and PTW in particular, which makes cluster detection difficult (93,112) and reduces power in statistical analysis. As a result, we were underpowered to detect possible associations of interest in some analyses, but these data still provide valuable insight that can be used to formulate hypotheses for future research. Second, cluster membership has been found to be biased, with higher clustering among those with early diagnosis of HIV infection or higher sampling fraction of a particular subgroup, generally MSM (99,101,113,114). However, our analysis found no statistical difference in clustering by gender despite differences in sample size across groups. Further, our finding that early diagnosis was not predictive of clustering was likely due to our narrow definition of early HIV diagnosis. We categorized prevalent diagnosis as those occurring >6 months after presumed HIV infection; however, participants in this group may have acquired HIV within the prior 2 years, which previous research suggests may still be early enough to increase the likelihood of being found in a cluster (88,101,102,115). Finally, in our analyses using linked epidemiologic data, we did not have demographic and behavior data for Microepidemics participants, and the data available from Sabes and Feminas were combined from two different questionnaires administered up to four years apart. Further, the data were entirely from baseline, while 71% of HIV-positive Sabes participants were seroconversions which occurred during study follow up. While this does create the possibility that the data do not reflect behavior at the time of seroconversion, we focused the analysis on characteristics that are expected to be relatively stable over time, such as education level, gender and types of partners, and self-identifying as a sex worker.

Conclusion

The results of this study build on growing use of genetic data and molecular epidemiology to study drivers of transmission in specific subpopulations. Our findings align with those of research conducted in the United States in identifying co-clustering of MSM and TW, indicating overlap in the HIV transmission network. These findings, while somewhat at odds with self-reported epidemiologic data, provide important evidence that could help to better understand drivers of the HIV epidemic among TW. This work highlights the need for more data on PTW, a population that is nearly absent from HIV research and may play a critical role in these epidemics. Understanding the HIV prevalence among PTW and identifying subpopulations driving HIV transmission within these sexual networks are important steps in determining how to best target HIV prevention and treatment interventions.

Tables and Figures

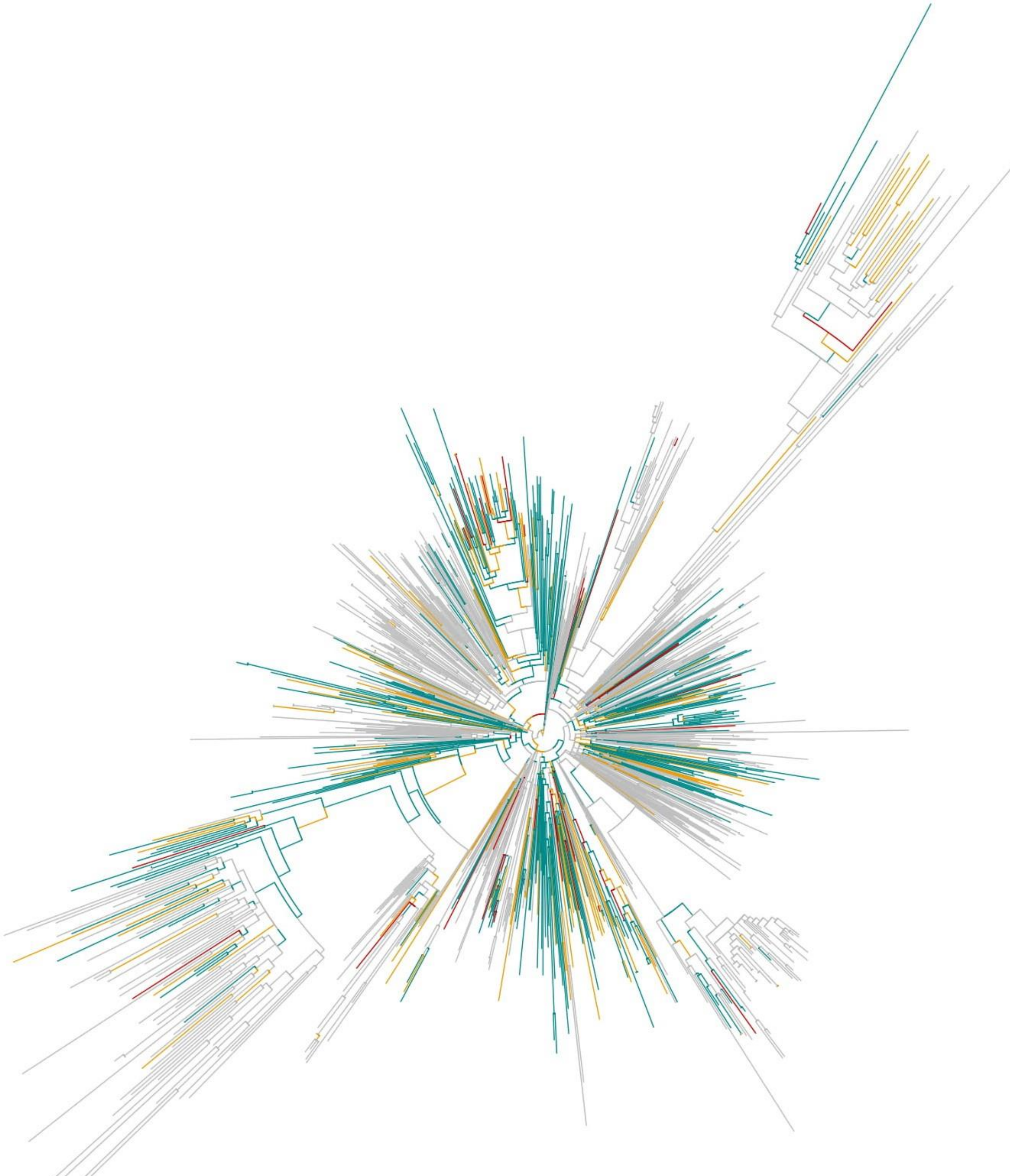

Figure 3.1: Phylogenetic tree of clustering including data from three study populations (Sabes, Feminas, and Microepidemics) and South American pol sequences from the Los Alamos National Database. Colors indicate group (Blue: MSM; Yellow: TW; Red: PTW; Gray: Los Alamos sequences, group unknown).

Table 3.1: Source and types of data used in molecular epidemiology analysis

	Sabes	Feminas	Microepidemics
Number of participants in study	3,336	216	568
Number included in this analysis	367	40	63
Dates of data collection	7/2013 – 9/2015	10/2016 – 3/2018	1/2017 – 6/2017
HIV diagnosis			
Early	302	3	0
Presumed prevalent	65	37	63
Gender of participants			
Cisgender men	284	0	46
Transgender women	82	40	17
Epidemiologic data available	Yes (baseline)	Yes (baseline)	No

Table 3.2: Predictors of being found in a cluster at cluster size ≥2 using TN93 1.5%

Characteristic[a]	N	Clustered n (%)	PR	95% CI	p-value
Diagnosis year	467	200 (42.8)	0.98	(0.90, 1.06)	0.555
Study					
Sabes	364	157 (43.1)	1		
Feminas	40	19 (47.5)	1.10	(0.78, 1.56)	0.586
Microepidemics	63	24 (38.1)	0.88	(0.63, 1.23)	0.470
Group					
MSM	303	134 (44.2)	1		
TW	139	56 (40.3)	0.91	(0.72, 1.16)	0.444
PTW	25	10 (40.0)	0.90	(0.55, 1.49)	0.692
HIV Diagnosis					
Prevalent	165	67 (40.6)	1		
Early (<6 months)	302	133 (44.0)	1.08	(0.87, 1.36)	0.478
City[b]					
Lima	342	151 (44.2)	1		
Callao	56	22 (39.3)	0.89	(0.63, 1.26)	0.510
Age category[c]:					
<25	196	89 (45.4)	1		
25-34	155	66 (42.6)	0.94	(0.74, 1.19)	0.598
≥35	38	15 (39.5)	0.87	(0.57, 1.33)	0.516
Any post-secondary school[d]					
No	158	68 (43.0)	1		
Yes	245	107 (43.7)	1.01	(0.81, 1.28)	0.900
Sexual Orientation[e]					
Homosexual	193	92 (47.7)	1		
Bisexual	91	38 (41.8)	0.88	(0.66, 1.16)	0.362
Heterosexual	10	6 (60.0)	1.26	(0.74, 2.13)	0.393
Housing status[f]					
Own place/alone	88	37 (42.1)	1		
With sexual partner	44	20 (45.5)	1.08	(0.72, 1.62)	0.707
With parent or family	222	98 (44.1)	1.05	(0.79, 1.40)	0.739
With friend	30	11 (36.7)	0.87	(0.51, 1.48)	0.613
Sexual role[g]					
Insertive	53	22 (41.5)	1		
Receptive	161	68 (42.2)	1.02	(0.70, 1.47)	0.926
Versatile	185	82 (44.3)	1.07	(0.75, 1.53)	0.720
Sex Worker[h]					

No	308	132 (42.9)	1		
Yes	79	32 (40.5)	0.95	(0.70, 1.27)	0.710
Gender of partners reported[i]					
Cisgender man	231	198 (42.4)	0.98	(0.80, 1.21)	0.862
Transgender woman	16	7 (43.8)	1.02	(0.58, 1.80)	0.939
Cisgender woman	7	0 (0.0)	N/A		
Reported partnership type[i]					
Stable/spouse	151	68 (45.0)	1.05	(0.84, 1.32)	0.644
Casual	66	28 (42.4)	0.97	(0.71, 1.32)	0.840
One time/anonymous	102	42 (41.2)	0.93	(0.71, 1.21)	0.580
Sold/client[j]	19	6 (31.6)	0.72	(0.37, 1.40)	0.328
Purchased[j]	9	4 (44.4)	1.02	(0.49, 2.14)	0.957

[a]Year of diagnosis, study, group, and HIV diagnosis (early vs prevalent) are reported for all three studies. All other data is reported from Sabes and Feminas.
[b]City data missing for n=5 Feminas participants and n=1 Sabes participant.
[c]Age data missing for n=1 Feminas participant and n=14 Sabes participants.
[d]Education data missing for n=1 Feminas participant. Education defined as any post-secondary or vocational training
[e]Sexual orientation data was not collected among TW in the Sabes study (n=82). In Feminas, n=28 TW identified their sexual orientation as transgender and are counted as missing for this analysis.
[f]Housing status data missing for n=6 Feminas participants and n=14 Sabes participants
[g]Sex role data missing for n=5 Feminas participants
[h]Sex worker data missing for n=15 Feminas participants and n=2 Sabes participants.
[i]Partnership data reported from the last three sexual partners, beginning with the most recent.
[j]Purchasing and selling sex defined as exchange goods, services, a place to sleep, or money for sex.
PR: prevalence ratio; CI: Confidence Interval; MSM: men who have sex with men; TW: transgender women; PTW: partners of transgender women

Table 3.3: Summary results of frequency of participants within each group in the sample, as well as clustering within each group, shown by group

Group	Frequency in sample	Clustered with TW	Clustered with MSM	Clustered with PTW
TW	56 (28%)	43 (77%)	32 (57%)	5 (9%)
MSM	134 (67%)	50 (37%)	122 (91%)	7 (5%)
PTW	10 (5%)	5 (50%)	6 (60%)	2 (20%)

Table 3.4: Description of cluster membership and co-clustering among groups

Cluster Type	Number of Clusters	Number of participants found in cluster type		
		TW	MSM	PTW
Only in-group clustering	37	20	80	0
Co-clustering with other groups:				
TW and MSM	16	31	47	0
TW and PTW	4	4	0	4
MSM and PTW	4	0	4	5
MSM, TW, PTW	1	1	3	1
Total:	**62**	**56**	**134**	**10**

Table 3.5: Correlates of clustering with TW among cisgender men (n=144)

Characteristics	N	TW in cluster[a] n	(%)	PR	95% CI	P-value
		n	(%)			
Reported TW partner						
No	134	50	(37.3)	1		
Yes	10	5	(50.0)	1.34	(0.69, 2.59)	0.385
Sexual Orientation						
Homosexual	88	29	(33.0)	1		
Bisexual	38	19	(50.0)	1.52	(0.98, 2.35)	0.062
Heterosexual	3	1	(33.3)	1.01	(0.20, 5.18)	0.989
HIV diagnosis						
Presumed prevalent	28	13	(46.4)	1		
Early (<6 months)	116	42	(36.2)	0.78	(0.49, 1.24)	0.297
Age category						
<25	66	24	(36.4)	1		
≥25	78	31	(39.7)	1.09	(0.72, 1.67)	0.679
Any post-secondary[b]						
No	40	18	(45.0)	1		
Yes	89	31	(34.8)	0.77	(0.50, 1.21)	0.261
Sexual role						
Insertive	21	9	(42.9)	1		
Receptive	34	12	(35.3)	0.82	(0.42, 1.62)	0.572
Versatile	74	28	(37.8)	0.88	(0.50, 1.57)	0.672
Purchased sex[c] (6 months)						
No	109	42	(38.5)	1		
Yes	18	7	(38.9)	1.01	(0.54, 1.89)	0.977
Sold sex[c] (6 months)						
No	99	38	(38.4)	1		
Yes	28	11	(39.3)	1.02	(0.60, 1.73)	0.931

[a]Data on reporting a TW partner and HIV diagnosis are from both Sabes (n= 129) and Microepidemics (n= 15) participants. All other variables include cisgender men from the Sabes study. TW found in the cluster could be from Sabes, Feminas, or Microepidemics.
[b]Post secondary education defined as any school after secondary school, or vocational training.
[c]Purchasing and selling sex defined as exchange goods, services, a place to sleep, or money for sex. Data on purchased and sold sex missing for n=2 Sabes participants.
TW: transgender women; PR: prevalence ratio; CI: confidence interval.

Supplementary Materials: Sensitivity Analyses

Sensitivity Analysis Methods

In primary analyses, pairwise genetic distances were calculated using the TN93 model, and cluster membership was defined using a relatively conservative genetic distance threshold of 1.5%. To examine if these methods of calculating genetic distance or cluster definition affected the results of these analyses, sensitivity analyses were conducted using two alternative methods to define cluster membership. For the first sensitivity analysis, pairwise genetic distance was again used to define cluster membership, but with the distance threshold set to 3% to determine the impact of using a less conservative definition of cluster membership. For the second sensitivity analysis, we used an alternative method to define genetic distance. Patristic distance measures distance based on the sum of branch lengths between two branches on a phylogenetic tree. Patristic distance measures were created using the TN93 nucleotide substitution method and a phylogenetic tree built in RaxML software (104) using maximum likelihood. With this measure of genetic distance, analyses were repeated at a genetic distance threshold of 1.5% to allow comparability with primary analyses. For both sensitivity analyses, we examined correlates of clustering, and correlates of cisgender men clustering with TW, using the same methods described in the Statistical Analysis section.

Results

Analysis 1: Using pairwise genetic distance, 302 of 470 (65%) study participants were found in clusters (of ≥2 participants) using a genetic distance threshold of 0.03 substitutions per site. Three participants were dropped from analysis due to being clustered only with Los Alamos Database sequences. The 467 remaining participants were found in 59 clusters with between 2 and 48 participants. In this analysis, the likelihood of appearing in a cluster did differ somewhat between the groups. We found 70% of MSM appearing in clusters, compared to 55% of TW and 52% of PTW. Compared to MSM, TW were 21% less likely to appear in a cluster (PR 0.79, 95%CI 0.66, 0.93) and PTW were 26% less likely, however the difference in cluster membership between MSM and PTW was not statistically significant (PR 0.74, 95% CI 0.51, 1.09) (Table S3.1).

With this wider definition of cluster membership, we found that having an early HIV diagnosis (≤6 months after HIV infection) was associated with an 18% increase in likelihood of appearing in a cluster (PR 1.18, 95% CI 1.01, 1.37) compared to prevalent diagnoses (>6 months after HIV infection or no data available on previous testing). In analyzing possible demographic or behavioral predictors of being found in a cluster, age 35 years or older was associated with reduced likelihood of being found in a cluster (PR 0.60, 95% CI 0.42, 0.87) compared to age <25 years.

In this sensitivity analysis, 72% of clustered TW were found in a cluster with MSM and 71% of clustered MSM were found in a cluster with TW. Clusters containing both TW and MSM accounted for 42% of all clusters found in this analysis. Among MSM and TW, in-group clustering was more common than between-group clustering; 80% of TW clustered with TW and 95% of MSM clustered with MSM. We had a limited sample of PTW who were found in clusters (n=13), but this group was more likely to cluster with TW (77%) and MSM (77%) than with each other (15%). In the analysis of predictors of cisgender men clustering with TW, when using a genetic distance of 3% bisexual identity was significantly associated with clustering with TW compared to homosexual identity (PR 1.22, 95% CI 1.01, 1.47). No other characteristics were predictive of clustering with TW in this analysis.

Analysis 2: Using patristic distance, 131 of 470 (28%) study participants were found in clusters (of ≥2 participants) using a genetic distance threshold of 0.015 substitutions per site. Six participations were dropped for clustering only with sequences from the Los Alamos Database. The 464 remaining participants were found in 52 clusters which included between 2 and 11 participants. The likelihood of appearing in a cluster did not differ based on group; 28% of MSM appeared in clusters, compared to 28% of PTW (PR 1.0, 95%CI 0.52, 1.93) and 29% of TW (PR 1.03, 95% CI 0.75, 1.41) (Table S3.3). We found no meaningful differences in likelihood of clustering by study, year of diagnosis, or whether the HIV diagnosis was early (≤6 months after HIV infection) or presumed prevalent (>6 months after HIV infection or no data available on previous testing). In analyzing possible demographic or behavioral predictors of being found in a cluster, no observed characteristics were associated with cluster membership (Table S3.3).

In this sensitivity analysis, 35% of clustered TW were found in a cluster with MSM and 19% of clustered MSM were found in a cluster with TW. Clusters containing both TW and MSM accounted for 19% of all clusters found in this analysis. Among MSM and TW, in-group clustering was more common than between-group clustering; 75% of TW clustered with TW and 88% of MSM clustered with MSM. We had a limited sample of PTW who were found in clusters (n=7), but this group was similarly likely to cluster with TW (43%) or MSM (57%), while no PTW were found clustered with other PTW.

In the analysis of predictors of cisgender men clustering with TW, education was predictive of cluster membership, with a 69% reduced likelihood of clustering with TW among those with post-secondary education (PR 0.31, 95% CI 0.13, 0.77). Men with early diagnosis of infection were less likely to be found in clusters with TW (PR 0.37, 95% CI 0.17, 0.79). The results suggest that having reported a TW as a partner was predictive of having a TW in a cluster, but this did not reach statistical significance (PR 2.25, 95% CI 0.85, 5.92).

Interpretation

Varying the method to calculate genetic distance and the threshold to define cluster membership did not meaningfully change the inference from this analysis. While we found some variability in statistical significance of correlates in these analyses compared to the primary analysis, this is likely due to a difference in power to detect associations, and not a difference in scientific meaning between the analyses. In all analyses, no correlates strongly predicted either being found in a cluster, or cisgender men clustering with TW. When observing clustering of TW and MSM with each other, results found in sensitivity analyses did not change inference. While the prevalence of clustering changed as we used a wider definition of clustering, we still observed patterns of cluster overlap between MSM and TW. The patterns observed in the primary analysis are likely more meaningful than those observed in the first sensitivity analysis, because primary analyses captured more genetically similar links, and therefore are more likely to infer recent transmission between identified sequences or through intermediaries not identified. The primary analysis is preferable over the second sensitivity analysis, because use of pairwise genetic distance allows us to compare our results to analyses conducted using HIV-TRACE, which also measures pairwise distance using the TN93 method and is widely used for molecular analyses in the United States (107,116).

Supplementary Tables

Table S3.1: Predictors of being found in a cluster at cluster size ≥2 using TN93 3%

Characteristic[a]	N	Clustered n (%)	PR	95% CI	p-value
Diagnosis year	467	302 (64.7)	0.98	(0.93, 1.03)	0.385
Study					
Sabes	365	241 (66.0)	1		
Feminas	39	23 (59.0)	0.89	(0.68, 1.17)	0.416
Microepidemics	63	38 (60.3)	0.91	(0.74, 1.13)	0.407
Group					
MSM	304	213 (70.1)	1		
TW	138	76 (55.1)	0.79	(0.66, 0.93)	0.005
PTW	25	13 (52.0)	0.74	(0.51, 1.09)	0.128
HIV Diagnosis					
Prevalent	164	95 (57.9)	1		
Early (<6 months)	303	207 (68.3)	1.18	(1.01, 1.37)	0.033
City[b]					
Lima	342	225 (65.8)	1		
Callao	56	35 (62.5)	0.95	(0.76, 1.18)	0.643
Age category[c]:					
<25	196	141 (71.9)	1		
25-34	154	99 (64.3)	0.89	(0.77, 1.03)	0.133
≥35	39	17 (43.6)	0.61	(0.42, 0.88)	0.008
Any post-secondary school[d]					
No	157	97 (61.8)	1		
Yes	246	166 (67.5)	1.09	(0.94, 1.27)	0.251
Sexual Orientation[e]					
Homosexual	195	141 (72.3)	1		
Bisexual	90	59 (65.6)	0.91	(0.76, 1.09)	0.268
Heterosexual	10	8 (80.0)	1.11	(0.80, 1.53)	0.539
Housing status[f]					
Own place/alone	87	57 (65.5)	1		
With sexual partner	44	27 (61.4)	0.94	(0.71, 1.24)	0.647
With parent or family	224	149 (66.5)	1.02	(0.85, 1.21)	0.868
With friend	30	18 (60.0)	0.92	(0.66, 1.27)	0.601
Sexual role[g]					
Insertive	52	36 (69.2)	1		
Receptive	162	100 (61.7)	0.89	(0.72, 1.11)	0.303
Versatile	185	124 (67.0)	0.97	(0.79, 1.19)	0.760

Sex Worker[h]					
No	309	206 (66.7)	1		
Yes	79	45 (57.0)	0.85	(0.69, 1.05)	0.137
Gender of partners reported[i]					
Cisgender man	232	149 (64.2)	0.99	(0.86, 1.13)	0.842
Transgender woman	16	7 (43.8)	0.67	(0.38, 1.17)	0.159
Cisgender woman	6	3 (50.0)	0.77	(0.35, 1.72)	0.526
Reported partnership type[i]					
Stable/spouse	151	100 (66.2)	1.02	(0.88, 1.18)	0.774
Casual	66	37 (56.1)	0.83	(0.67, 1.05)	0.118
One time/anonymous	103	64 (62.1)	0.94	(0.79, 1.11)	0.442
Sold/client[j]	18	9 (50.0)	0.76	(0.47, 1.21)	0.243
Purchased[j]	9	5 (55.6)	0.85	(0.47, 1.53)	0.583

[a]Year of diagnosis, study, group, and HIV diagnosis (early vs prevalent) are reported for all three studies. All other data is reported from Sabes and Feminas.
[b]City data missing for n=5 Feminas participants and n=1 Sabes participant.
[c]Age data missing for n=1 Feminas participant and n=14 Sabes participants.
[d]Education data missing for n=1 Feminas participant. Education defined as any post-secondary or vocational training
[e]Sexual orientation data was not collected among TW in the Sabes study (n=82). In Feminas, n=27 TW identified their sexual orientation as transgender and are counted as missing for this analysis.
[f]Housing status data missing for n=5 Feminas participants and n=14 Sabes participants
[g]Sex role data missing for n=5 Feminas participants
[h]Sex worker data missing for n=15 Feminas participants and n=2 Sabes participants.
[i]Partnership data reported from the last three sexual partners, beginning with the most recent.
[j]Purchasing and selling sex defined as exchange goods, services, a place to sleep, or money for sex.
PR: prevalence ratio; CI: Confidence Interval; MSM: men who have sex with men; TW: transgender women; PTW: partners of transgender women

Table S3.2: Correlates of clustering with TW among cisgender men using TN93 3% (n=226)

Characteristics	N	No TW in cluster[a]		PR	95% CI	P-value
		n	(%)			
Reported TW partner						
No	213	142	(66.7)	1		
Yes	13	10	(76.9)	1.15	(0.84, 1.58)	0.371
Sexual Orientation						
Homosexual	136	87	(64.0)	1		
Bisexual	59	46	(78.0)	1.22	(1.01, 1.47)	0.037
Heterosexual	5	2	(40.0)	0.63	(0.21, 1.85)	0.396
HIV diagnosis						
Presumed prevalent	41	29	(70.7)	1		
Early (<6 months)	185	123	(66.5)	0.94	(0.75, 1.17)	0.585
Age category						
<25	109	72	(66.1)	1		
≥25	117	80	(68.4)	1.04	(0.86, 1.24)	0.711
Any post-secondary[b]						
No	59	44	(74.6)	1		
Yes	141	91	(64.5)	0.87	(0.71, 1.05)	0.143
Sexual role						
Insertive	35	23	(65.7)	1		
Receptive	55	37	(67.3)	1.02	(0.76, 1.39)	0.879
Versatile	110	75	(68.2)	1.04	(0.79, 1.36)	0.790
Purchased sex[c] (6 months)						
No	174	118	(67.8)	1		
Yes	24	16	(66.7)	0.98	(0.73, 1.33)	0.912
Sold sex[c] (6 months)						
No	162	107	(66.1)	1		
Yes	36	27	(75.0)	1.14	(0.91, 1.41)	0.256

[a]Data on reporting a TW partner and HIV diagnosis are from both Sabes (n= 129) and Microepidemics (n= 15) participants. All other variables include cisgender men from the Sabes study. TW found in the cluster could be from Sabes, Feminas, or Microepidemics.
[b]Post secondary education defined as any school after secondary school, or vocational training.
[c]Purchasing and selling sex defined as exchange goods, services, a place to sleep, or money for sex. Data on purchased and sold sex missing for n=2 Sabes participants.
TW: transgender women; PR: prevalence ratio; CI: confidence interval.

Table S3.3: Predictors of being found in a cluster at cluster size ≥2 using patristic distance 1.5%

Characteristic[a]	N	Clustered n (%)	PR	95% CI	p-value
Diagnosis year	464	131 (28.2)	1.02	(0.91, 1.14)	0.779
Study					
Sabes	362	102 (28.2)	1		
Feminas	40	14 (35.0)	1.24	(0.78, 1.96)	0.349
Microepidemics	62	15 (24.2)	0.86	(0.54, 1.37)	0.526
Group					
MSM	300	84 (28.0)	1		
TW	139	40 (28.8)	1.03	(0.75, 1.41)	0.866
PTW	25	7 (28.0)	1.00	(0.52, 1.93)	1.0
HIV Diagnosis					
Prevalent	164	45 (27.4)	1		
Early (<6 months)	300	86 (28.7)	1.04	(0.76, 1.42)	0.780
City[b]					
Lima	340	99 (29.1)	1		
Callao	56	16 (28.6)	0.98	(0.63, 1.53)	0.934
Age category[c]:					
<25	196	63 (32.1)	1		
25-34	154	40 (26.0)	0.81	(0.58, 1.13)	0.214
≥35	37	10 (27.0)	0.84	(0.48, 1.48)	0.550
Any post-secondary school[d]					
No	157	47 (29.9)	1		
Yes	244	69 (28.3)	0.94	(0.69, 1.29)	0.721
Sexual Orientation[e]					
Homosexual	192	59 (30.7)	1		
Bisexual	90	22 (24.4)	0.80	(0.52, 1.21)	0.287
Heterosexual	10	5 (50.0)	1.63	(0.84, 3.14)	0.146
Housing status[f]					
Own place/alone	87	23 (26.4)	1		
With sexual partner	44	16 (36.4)	1.38	(0.81, 2.33)	0.235
With parent or family	221	59 (26.7)	1.01	(0.67, 1.53)	0.963
With friend	30	10 (33.3)	1.26	(0.68, 2.34)	0.461
Sexual role[g]					
Insertive	52	15 (28.9)	1		
Receptive	159	49 (30.8)	1.07	(0.66, 1.74)	0.790
Versatile	186	50 (26.9)	0.93	(0.57, 1.52)	0.777
Sex Worker[h]					

No	306	86 (28.1)	1		
Yes	79	20 (25.3)	0.90	(0.59, 1.37)	0.625
Gender of partners reported[i]					
Cisgender man	231	67 (29.0)	1.06	(0.79, 1.41)	0.713
Transgender woman	16	4 (25.0)	0.88	(0.37, 2.09)	0.775
Cisgender woman	7	0	N/A		
Reported partnership type[i]					
Stable/spouse	151	46 (30.5)	1.09	(0.80, 1.49)	0.580
Casual	66	19 (28.8)	1.00	(0.66, 1.51)	0.989
One time/anonymous	102	30 (29.4)	1.03	(0.72, 1.46)	0.886
Sold/client[j]	19	5 (26.3)	0.91	(0.42, 1.96)	0.806
Purchased[j]	9	3 (33.3)	1.16	(0.45, 2.96)	0.757

[a]Year of diagnosis, study, group, and HIV diagnosis (early vs prevalent) are reported for all three studies. All other data is reported from Sabes and Feminas.
[b]City data missing for n=5 Feminas participants and n=1 Sabes participant.
[c]Age data missing for n=1 Feminas participant and n=14 Sabes participants.
[d]Education data missing for n=1 Feminas participant. Education defined as any post-secondary or vocational training
[e]Sexual orientation data was not collected among TW in the Sabes study (n=82). In Feminas, n=27 TW identified their sexual orientation as transgender and are counted as missing for this analysis.
[f]Housing status data missing for n=5 Feminas participants and n=14 Sabes participants
[g]Sex role data missing for n=5 Feminas participants
[h]Sex worker data missing for n=15 Feminas participants and n=2 Sabes participants.
[i]Partnership data reported from the last three sexual partners, beginning with the most recent.
[j]Purchasing and selling sex defined as exchange goods, services, a place to sleep, or money for sex.
PR: prevalence ratio; CI: Confidence Interval; MSM: men who have sex with men; TW: transgender women; PTW: partners of transgender women

Table S3.4: Correlates of clustering with TW among cisgender men using patristic distance 1.5% (n=91)

Characteristics	N	TW in cluster[a]		PR	95% CI	P-value
		n	(%)			
Reported TW partner						
No	84	16	(19.1)	1		
Yes	7	3	(42.9)	2.25	(0.85, 5.92)	0.100
Sexual Orientation						
Homosexual	57	11	(19.3)	1		
Bisexual	22	4	(18.2)	0.94	(0.33, 2.66)	0.911
Heterosexual	3	1	(33.3)	1.73	(0.32, 9.42)	0.528
HIV diagnosis						
Presumed prevalent	16	7	(43.8)	1		
Early (<6 months)	75	12	(16.0)	0.37	(0.17, 0.79)	0.010
Age category						
<25	47	9	(19.2)	1		
≥25	44	10	(22.7)	1.19	(0.53, 2.66)	0.677
Any post-secondary[b]						
No	28	10	(35.7)	1		
Yes	54	6	(11.1)	0.31	(0.13, 0.77)	0.012
Sexual role						
Insertive	15	3	(20.0)	1		
Receptive	23	7	(30.4)	1.52	(0.46, 5.02)	0.490
Versatile	44	6	(13.6)	0.68	(0.19, 2.41)	0.552
Purchased sex[c] (6						
No	68	14	(20.6)	1		
Yes	13	2	(15.4)	0.75	(0.19, 2.93)	0.676
Sold sex[c] (6 months)						
No	65	12	(18.5)	1		
Yes	16	4	(25.0)	1.35	(0.50, 3.67)	0.551

[a]Data on reporting a TW partner and HIV diagnosis are from both Sabes (n= 82) and Microepidemics (n= 9) participants. All other variables include cisgender men from the Sabes study. TW found in the cluster could be from Sabes, Feminas, or Microepidemics.
[b]Post secondary education defined as any school after secondary school, or vocational training.
[c]Purchasing and selling sex defined as exchange goods, services, a place to sleep, or money for sex. Data on purchased and sold sex missing for n=1 Sabes participants.
TW: transgender women; PR: prevalence ratio; CI: confidence interval.

Chapter 5: Conclusions

Discussion

This dissertation contributes to a small but growing body of evidence about the sexual networks and the sexual partners of TW. This work targeted three primary goals. First, to describe the partner-level behavior of PTW, including concurrency and types of partnerships reported, to better understand their risk of transmitting HIV to their partners. Second, to characterize PTW, a currently understudied population, to better understand their identity, behavior, and risk of acquiring HIV. Third, to describe HIV transmission clusters of MSM and TW, and identify co-clustering that is indicative of HIV transmission between these two networks. This work was designed to assess if the sexual networks of TW and MSM overlap, with bridging of HIV occurring through sexual partners who have sex with both TW and MSM.

To address the first two goals, Aims 1 and 2 characterized partners of transgender women from two different studies. One addressed this through a study designed specifically to reach this population, while the other used previously collected data from a study targeting MSM and TW. In these studies, we found that PTW are a unique population, who differ in sexual orientation, sexual attraction, and sexual behavior when compared to MSM. The results of these analyses showed that PTW mainly identify as bi- or heterosexual, report attraction mainly to cis- and transgender women, and report primarily cis- and transgender women as sexual partners. They also engage in behavior associated with risk of both acquiring and transmitting HIV, including condomless anal intercourse, alcohol use, and low reported HIV testing. The findings from Aim 1 suggest that some partnership behaviors, including condomless insertive anal intercourse and high rates of concurrent partnerships, may make them effective transmitters to their sexual partners, putting TW at increased risk. Interestingly, partners appeared to have a low prevalence of HIV, based on self-reported HIV status in Aim 2, and HIV testing in Aim 1, despite high-risk behavior being an inclusion criterion for the Aim 1 study population.

Both Aims 2 and 3 targeted the third goal of identifying overlap with MSM networks. In Aim 2, recruiting through sexual networks allowed us to identify how frequently PTW both invited male sexual partners into the study, and reported men as sexual partners. In both recruitment and self-reported partnerships, the results of this study suggested few PTW had recent male partners, and few reported attraction to men. To understand how these PTW may be different from other TW partners, we examined correlates of reporting a male partner among TW partners. We found that PTW who also had male partners were more likely to sell sex, have condomless receptive anal sex, and identify as homosexual. In Aim 3, we then focused specifically on the HIV transmission network by examining genetic distances between HIV sequences collected from TW, MSM, and PTW. In this analysis, we found over half of TW who were found in transmission clusters were found in a cluster with an MSM, signifying significant overlap in HIV transmission networks. We then examined if cisgender men who are found in clusters with TW differ from other men. In this analysis, the only variable that was significantly associated with clustering with TW was lower education among men.

The results of these analyses present somewhat conflicting findings. The results of Aim 3 clearly show overlap in HIV transmission between TW and MSM, either directly or through intermediary partners that were not included in our analysis. In the context of low injection drug use, this overlap in transmission is indicative of overlap in sexual networks. However, the results of Aims 1 and 2 suggest that few PTW have male partners, identify as homosexual, or are attracted to men. This raises the question, how is HIV being transmitted between MSM and TW sexual networks if so few PTW report having sex with men?

In the discussion section of Aim 3, we present one potential hypothesis to explain these findings. Based on our results in Aims 1 and 2, as well as two other studies conducted in Latin America, HIV prevalence in PTW is between 4-9%, which is significantly lower than the HIV prevalence among MSM and TW populations in Peru (27,33,86). It also appears that compared to PTW who report sexual activity with cis- or transgender women alone, those who also report sexual activity with men are more likely to have receptive CAI and sell sex, including to men. Given this, it is possible that bridging is occurring between TW and MSM sexual networks, but that this overlap is being driven by a core group of high-risk men who have sex with both TW and men in MSM sexual networks. These men may engage in riskier behavior than other PTW, and as a result may contribute to HIV spread in both TW and MSM communities. For example, behavior such as receptive CAI and selling sex to men may put them at risk of HIV acquisition from MSM partners, and high rate of concurrent partnerships may put them at risk of transmitting to both TW and MSM. Under this hypothesis, the majority of PTW may not be responsible for bridging between populations, but may instead be at risk for acquiring HIV from their TW partners and could still contribute to HIV spread within the TW sexual network.

Next Steps

At this time, there is not enough evidence to draw conclusions about how HIV is entering TW sexual networks, or the primary drivers of HIV spread in networks. Our molecular analysis shows clear evidence of overlap in transmission networks, indicating overlap in sexual networks. However, this does not provide insight on who is driving this overlap, or directionality of transmission between the groups. More work is needed to explore hypotheses like the one above and investigate transmission dynamics of HIV in these populations.

Work is underway to explore a number of questions raised by this dissertation. First, further research is needed to better understand the identities of PTW, what motivates risky sexual behavior, and how well they understand their HIV risk and engage in HIV testing and prevention. A first step in addressing this will be an analysis of the in-depth interviews collected in parallel to the respondent-driven sampling study described in Aim 2. These data will be analyzed in 2019, and will provide further context regarding the behavior of these partners, and what role they may play in HIV transmission.

Second, research indicating directionality of HIV transmission between MSM and TW networks could help to understand how HIV is moving through these populations, and better contextualize drivers of HIV transmission. One potential avenue is to use viral genetic information to conduct a source attribution analysis. Source attribution analyses allow for paired sequences to be weighted based on an estimated probability that the putative transmitting partner infected the recipient (117,118). These analyses can be linked with epidemiologic data to determine if transmission differs across a given characteristic (e.g., if transmission is more likely from MSM or TW) (119). I will be investigating the potential to use this technique with the viral sequences used in Aim 3 of this dissertation.

Third, a reliable estimate of HIV prevalence among PTW, and PTW who also have sex with men, would allow for an understanding of possible differences between these groups and their potential to contribute to the high HIV prevalence in TW. To address this, the chair of this dissertation, Dr. Ann Duerr, has submitted an NIH proposal to target PTW for HIV testing using a number of methods, including a follow up respondent-driven sampling study, to provide a baseline measure that could inform a number of future research efforts in this population.

Finally, regardless of the drivers of HIV among TW, the results of this analysis indicate that PTW may not be accessing HIV testing at the same frequency as TW and MSM, and it is possible they do not receive the same HIV prevention and treatment messaging as TW and MSM. Research is needed to identify ways to target PTW for HIV testing, pre-exposure prophylaxis (PrEP), education, and linkage to care for those who are HIV-positive. Dr. Duerr's grant would provide a first step for this effort in Lima, by using a mobile-health app and social media as tools to provide education and encourage testing and linkage to care specifically among PTW.

Public Health Implications

The results of these analyses have direct public health implications, both for these communities in Peru and for other TW sexual networks. While the prevalence of HIV among PTW is still unknown, it is likely higher than in the general population, making this an important population for public health intervention. Further, it is clear from these studies that PTW are a unique population, differing dramatically from MSM, and therefore care needs to be taken to include them in public health outreach efforts. A majority of PTW in our studies did not identify as homosexual or report attraction to men, and their attendance at social venues better aligned with behavior of TW than MSM (results not shown). Our analyses found evidence of low HIV testing among TW partners, with PTW from both Sabes and the respondent-driven sampling study reporting significantly lower HIV testing than MSM or TW. It is possible this low rate of testing is related to lack of HIV education and low perceived risk; a 2018 study in Lima suggested that male clients who buy sex from TW judge their HIV risk to be low to moderate (33). Finally, formative research conducted prior to Aim 2 suggested that in Peru, identifying as a sexual partner of a TW can be potentially dangerous for men, as sexual and gender minorities can face stigma, discrimination, and violence in Peru (results not published).

These findings collectively suggest that successfully reaching and engaging this key group in HIV prevention and treatment efforts will require intentional intervention design. As a result of this dissertation, we have identified two important recommendations for successful inclusion of PTW in HIV interventions.

First, a successful intervention will require formative research and community engagement to reach PTW. PTW are not a social network, share no characteristics that would make them easy to find by researchers, and may be hesitant to identify as PTW. Due to this, the primary way to reach them is likely through their sexual partners, and therefore engaging them in HIV interventions will require collaboration with the TW community. Additionally, it will require outreach in spaces where PTW would feel safe and comfortable discussing their sexual behavior, and provide services that allow for confidentiality. In Peru, the data collected in this dissertation identified social venues popular among TW and PTW, which may lead to successful outreach to PTW with help from TW community members affiliated with our research team. Similar work could be done in other communities, by using ethnographic and qualitative research techniques to identify places where PTW may be identifiable and feel safe to engage in research.

Second, it is important to use an intervention design that is inclusive, non-alienating, and safe. In Peru, HIV interventions are heavily focused on gay communities, and to a lesser degree TW and sex workers. This is reflected in a wide range of intervention designs, including marketing materials featuring gay men, peer outreach at bars and clubs popular among gay communities, and non-profit clinics that specifically target sexual and gender minorities for HIV services. However, this dissertation found that the majority of PTW likely do not identify with any of these communities. As a result, PTW may either not be exposed to the interventions at all, or be resistant to interventions because they don’t want to be associated with the highly stigmatized groups that the interventions target. Marketing and outreach should therefore be specifically designed to target PTW demographics, to prevent further alienation of these groups and improve engagement in HIV services.

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