Substance Use, Sexual Networks, and HIV risk among men who have sex with men and transgender women in Peru

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Abstract

Substance Use, Sexual Networks, and HIV risk among men who have sex with men (MSM) and transgender women (TGW) in Peru

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Background: In Peru, the HIV epidemic is concentrated among men who have sex with men (MSM) and transgender women (TGW) in whom HIV incidence rates are as high as 4.2 per 100 person-years with HIV prevalence reported to be as high as 22% in MSM and up to 30% in TGW. This dissertation seeks to add to the knowledge of the structure of sexual networks, namely the level and predictors of sexual concurrency among MSM and TGW in Peru (*Aim 1),* and the understanding of risk factors for HIV acquisition in MSM and TGW with high levels of substance use in Lima (*Aim 2)*.

Methods: Data are from the 2011 Peruvian Biobehavioral Surveillance survey (*Aim* 1) and the *Sabes* cohort study conducted in Lima from 2013-2016 (*Aim 2*). Data were collected with the computer assisted self-interview (CASI) (*Aim 1 & 2*); HIV testing was performed with Determine 1/2 rapid antibody tests (*Aim 1 & 2*), pooled nucleic acid amplification test (NAAT), and Western Blot to determine Fiebig Stage at HIV diagnosis. Statistical methods used include Poisson regression and generalized estimating equations (GEE) (*Aim 1)*, and Pearson's Chi-square, Poisson regression estimated with GEE, and stratified Cox proportional hazards survival analysis with time-varying covariates (*Aim 2)*.

Results: Concurrency is a common practice among MSM and TGW in Peru with a 3-month cumulative prevalence of over 23%. There was evidence of negotiated safety—those with a stable partner were less likely to have condomless anal intercourse (CLAI) with a concurrent non-stable partner. In the *Sabes* cohort, HIV incidence was 11.7 per 100 person-years of follow-up. Those with alcohol use disorders (AUD) were significantly more likely to attend a venue that served alcohol, binge drink, and use marijuana or amyl nitrites. AUD modified the association between the time-varying behavioral factors and HIV; behavioral risk factors (binge drinking, marijuana use, sex with a casual partner, client, or one-time partner) were most strongly associated with HIV acquisition amongst those with dependent drinking patterns.

Conclusion: This study suggests that AUD is linked to HIV risk in two important ways: first, through CLAI with non-stable partners and second, through amplifying the impact of other HIV risk behaviors. These studies suggest that harm reduction approaches, such as negotiated safety with concurrent partners, and treatment of AUDs to decrease alcohol intake could decrease the HIV risk associated with these behaviors.

Table of Contents

Acknowledgments 5

Abbreviations 6

Chapter 1: Introduction 7

- **Specific Aims** 8

Chapter 2: Compounded risk: condomless sex, alcohol use disorder and concurrency among men who have sex with men and transgender women in Peru 10

- **Introduction** 10
- **Methods** 13
  - *Study population* 13
  - *Data Collection* 13
  - *Outcomes of interest* 14
  - *Missing data and data imputation* 15
  - *Covariates* 15
- **Results** 18
  - *Participant Characteristics* 18
  - *Prevalence and correlates of cumulative concurrency* 18
  - *Condom use and concurrent partners* 19
- **Discussion** 20
- **Conclusions** 24
- **Tables and Figures** 25

Chapter 3: Alcohol use disorder and HIV risk among men who have sex with men and transgender women in Lima, Peru: Results from the *Sabes* Study 29

- **Introduction** 29
- **Methods** 31
  - *Study Design* 31
  - *Assessments* 32
  - *Statistical Analysis* 34
  - *Protection of human subjects/informed consent* 37
- **Results** 37
  - *Cohort Characteristics by AUD* 37
  - *AUD and risk behaviors* 38
  - *Baseline Predictors of HIV Acquisition* 38
  - *Time-varying risk behaviors associated with HIV acquisition* 39
- **Conclusions** 44
- **Tables and Figures** 45

References 51

Appendix 56

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Abbreviations

AI Anal intercourse

ART Antiretroviral therapy

AUD Alcohol use disorder

AUDIT Alcohol use disorders identification test

CI Confidence interval

CASI Computer assisted self-interview

CLAI Condomless anal intercourse

ELISA Enzyme-linked immunosorbent assay

FHCRC Fred Hutchinson Cancer Research Center

HIV Human immunodeficiency virus

HR Hazard ratio

MSM Men who have sex with men

NAAT Nucleic acid amplification test

OR Odds ratio

PR Prevalence ratio

PrEP Pre-exposure prophylaxis

RR Relative risk

SD Standard deviation

STI Sexually transmitted infection

TGW Transgender woman/women

UAI Unprotected anal intercourse

UNAIDS Joint United Nations Programme on HIV/AIDS

UW University of Washington

Chapter 1: Introduction

HIV incidence remains unabated and unacceptably high in key populations throughout the world [1]. In Lima, Peru, the HIV epidemic is concentrated among men who have sex with men (MSM) and transgender women (TGW) in whom HIV incidence rates are as high as 4.2 per 100 person-years with HIV prevalence reported to be as high as 22% in MSM and up to 30% in TGW [2-4]. Individual-level factors, such as unprotected anal intercourse (UAI), drug and alcohol use, and co-infection with other sexually transmitted infections (STI) are known HIV risk factors. Research has shown that features of a sexual network—including the level of partner concurrency—govern how quickly and to what extent a disease will spread [5].

Sexual concurrency, or the practice of having sex with a partner in between two acts of sex with another partner, increases connectivity in a sexual network. Because it increases the risk of onward transmission of sexually transmitted infections, it is likely an important component in propagating the HIV epidemic [5-13]. This has been shown in substantial research on concurrency in the context of heterosexual HIV epidemics in Sub-Saharan Africa [5, 12-16], but the prevalence and types of concurrent relationships among MSM and TGW are less documented. Given the other risks associated with MSM and TGW, such as higher lifetime numbers of partners, the existence of highly sexually active core groups (a population subgroup that plays an important role in then spread of HIV epidemic, e.g. sex workers) , and a higher per-act probability of transmission of HIV during anal versus vaginal sex, it remains unclear whether sexual concurrency also drives the epidemic in MSM and TGW populations [17].

The association between alcohol use and HIV risk behaviors is well-established among MSM and TGW in Peru [18-22], but its association with HIV acquisition is less clear with global measures of alcohol disorder (i.e. Alcohol use disorders identification test (AUDIT)) [23]. Alcohol is the most commonly abused drug in Peru with a lifetime prevalence of 83% and alcohol use disorder is nearly five times more common in MSM and TGW than in the general male population (63% vs. 12.2%) [24]. Social drinking is common among MSM and TGW in Peru with over 80% reporting at least occasional attendance at a social venue, places where alcohol and sex commonly intersect [25-28]. Studies of Peruvian MSM and TGW have shown that the use of alcohol and/or illegal substances before sex is common [29-32] and is associated with risky sexual behaviors including sex with a casual partner, unprotected casual sex, and multiple sex partners [23]. Convincing arguments have been made to suggest that personality factors, such as impulsivity and sensation seeking are likely associated with AUD, risky sex, and HIV, and therefore confound the alcohol and sex relationship [33]. However, more research is needed to understand the complex relationships between alcohol use, risky sexual behaviors, and HIV incidence.

Specific Aims

This dissertation adds to the knowledge of the structure of sexual networks among MSM and TGW in Peru and of risk factors for HIV acquisition in a high-risk cohort of MSM and TGW in Lima. The specific aims of this dissertation are as follows:

1. Describe the structure of sexual networks among MSM and TGW in Peru by estimating the cumulative prevalence of concurrent partnerships in MSM and TGW, identifying correlates of sexual concurrency, and identifying predictors of condomless anal intercourse (CLAI) with stable and non-stable partners.

   Hypothesis: Concurrency is a common practice among MSM and TGW in Lima, but those with a stable partner will be less likely to have CLAI with concurrent non-stable partners.

2. Identify risk factors associated with newly acquired HIV infection using baseline and time-varying data from a cohort study of high-risk MSM and TGW. Specifically, investigate the role of alcohol use disorders (AUD) in HIV acquisition by describing characteristics associated with AUDs, quantifying the association between AUD and behavioral risk factors, and calculating the HIV risk associated with behavioral risk factors stratified by level of AUD.

Hypothesis: MSM and TGW with AUDs will be more likely to participate in risky behaviors including drug use, CLAI, and one-time partners. Time-varying measures of substance use and CLAI will be positively associated with HIV acquisition.

Chapter 2: Compounded risk: condomless sex, alcohol use disorder and concurrency among men who have sex with men and transgender women in Peru

Introduction

Worldwide, men who have sex with men (MSM) and transgender women (TGW) are disproportionately burdened by HIV. In Peru, the HIV prevalence in MSM and TGW is as high as 22-30%, with prevalence in the general population below 0.2% [2-4, 34, 35]. Extensive research has been conducted to determine why these disparities in HIV prevalence persist in MSM and TGW populations [36]. The differences in the structure of sexual networks, namely variation in the level of sexual partner concurrency, offer a plausible explanation for this disparity [37]. Compared with heterosexual men, MSM are 2-3 times more likely to report sexual concurrency, and MSM are more likely to be in open-relationships with a primary partner or to have an agreement in place that one or both partners may have other sex partners [38, 39]. Given the additional risks associated with MSM and TGW, such as higher lifetime numbers of partners, the existence of highly sexually active core groups, and a higher per-act probability of transmission of HIV during anal versus vaginal sex (1.4% vs 0.08%), it remains unclear whether sexual concurrency drives the epidemic in MSM and TGW populations or if these other factors are sufficient [17, 40].

Sexual concurrency, or having sex with one partner in between two acts of sex with another partner, can increase HIV prevalence by increasing the risk of onward HIV transmission above and beyond the risk associated with having multiple serial partners. Concurrency eliminates the protective sequencing associated with serial monogamy because early partners remain connected to the subject and can be exposed if the subject becomes infected by a later partner. Once an individual with concurrent partners acquires infection from one partner, transmission to the other partner can occur without the potential delay involved in ending the previous relationship and starting a new one that is required in serial monogamy [7]. This increases the number of partners who can be exposed during acute HIV infection, when infectivity is high due to high viremia, which often occurs before an individual knows he or she is infected [5, 41-44]. Mathematical models provide evidence that concurrency is essential in propagating heterosexual HIV epidemics; inference from these models show that under real-world conditions, concurrent partnerships exponentially increase the growth rate of the epidemic [5, 9, 14, 15, 43, 45-48].

Data regarding the prevalence of concurrency among MSM and TGW are predominately from the United States and other more economically developed countries and estimates vary substantially across studies. An estimate from a United States national web-based survey suggests that six-month cumulative concurrency (concurrency within a given period of time) is as high as 45% [49]. A cross-sectional study in New York found that 63% of MSM had concurrent partners in the past three months [50] and in a time-location study in San Francisco, 78% of MSM reported 12-month cumulative concurrency [51]. In Australia, a national community-based survey estimated 12-month cumulative concurrency among MSM and TGW to be slightly under 23% [52]. Clearly, there is evidence that concurrency is common, but variation in the time period of measurement makes it challenging to compare these results. The level of concurrency differs by geographic location, and data on concurrency are lacking for some populations, such as MSM and TGW in Peru where there is an ongoing high-incidence HIV epidemic largely concentrated in this population. The paucity of data and the disparity in reports from different populations of MSM and TGW suggest the need for further study of the prevalence of concurrency in these key populations, along with standardized procedures for measurement.

Individuals in concurrent partnerships who engage in condomless anal intercourse (CLAI) compound the risk of onward HIV transmission in a sexual network. There is some evidence that condoms are less likely to be used with stable partners than with new and casual partners and it is estimated that the majority of incident HIV infections among MSM occur within the context of main partnerships or within persistent casual partnerships [53-56]. Despite these data, qualitative [57-59] and limited quantitative research [60, 61] suggest that some MSM in main partnerships have adopted behavioral strategies such that CLAI, even in the context of concurrent partnerships, carries little risk of HIV transmission. These agreements, termed "negotiated safety," typically require two conditions that result in CLAI between main partners constituting a lower-risk behavior: first, both partners must test negative for HIV and disclose their status, and second, any sex outside the main partnership will be safe (e.g. use of condoms, refrain from anal sex) [57]. Many studies address negotiated safety in MSM couples in resource-rich settings, but this hasn't been explored in MSM and TGW in Peru.

Empirical estimates of the levels of sexual concurrency in key populations, correlates of concurrency, and information about the interaction of concurrency with risky sexual behaviors are needed to inform HIV prevention activities in Peru because current prevention efforts are failing to reduce HIV incidence. The purpose of this paper is to describe concurrency and CLAI patterns among Peruvian MSM and TGW by 1) quantifying the level of concurrency reported by Peruvian MSM and TGW, 2) describing individual-level characteristics associated with concurrent partnerships, and 3) identifying factors associated with condomless anal intercourse (CLAI) within the context of concurrent partnerships with or without a stable partner.

Methods

Study population

This paper presents a secondary analysis of data collected in the 2011 Peruvian Biobehavioral Survey, a nationwide survey conducted semi-regularly. Recruitment for the Peruvian Biobehavioral Survey occurred in five Peruvian cities between June and October 2011. A total of 5,575 Peruvian MSM and TGW were recruited and 5,137 (92.1%) were enrolled. Inclusion criteria for the survey were being 18 years of age or older, assigned male at birth, reporting at least one male sexual partner in the previous 12 months, and the ability to provide informed consent. There was no attempt to oversample HIV-positive individuals in this study. This was a convenience sample that included modified snowball recruitment strategies and time and space sampling (TSS) with recruitment for TSS done by peer educators at venues frequented by MSM (e.g. saunas, adult movie theaters, video arcades, nightclubs, bars, beauty parlors, and sporting arenas) and areas frequented by sex workers and cross-dressers. Recruitment strategies also included the use of posters, distribution of flyers, and informational meetings. For results that were generalizable to the sexually active population, the analysis is limited to the 3,949 MSM and TGW who reported at least one male or TGW partner in the previous three months.

Data Collection

All participants underwent HIV testing and answered a questionnaire in the form of a 45-minute computer assisted self-administered interview (CASI). Pre-and post-test HIV counseling, risk reduction counseling, condoms, and lubricant were provided. HIV testing was conducted with Determine HIV-1/2 third generation rapid antibody test (Alere Inc., MA, USA) confirmed with western blot. Participants with sexually transmitted infections (STI) were managed according to

Peruvian STI treatment guidelines and those diagnosed with HIV received standard health care following Peruvian HIV and AIDS health care management guidelines [62].

The CASI questionnaire assessed demographics, alcohol and drug use, and sexual risk behaviors including the total number of male or TGW sex partners in the 3 months preceding their interview and specific questions regarding their three most recent male or TGW sex partners in the previous three months. These questions included sexual role with the partner, the partner type (stable, casual, or anonymous), condom use during anal intercourse, the date of first and most recent sex with the partner, and whether they expected to have sex again in the future.

Outcomes of interest

Concurrency was calculated using methods recommended by the UNAIDS Reference Group on Estimates, Modeling, and Projections employing a calendar method in which each respondent reported up to three of their most recent sex partners within the previous three months [37]. For each dyad, the date of first and most recent sex was reported (day, month, and year). The 3-month prevalence of concurrency and corresponding 95% confidence intervals were calculated as the proportion of respondents with any overlap of the first and most recent dates of sex between any two dyads.

For each of the three most recent partners, respondents identified whether they were a stable partner ("a person you live with or with whom you feel a special connection"), a casual partner ("a person with whom you've had or are having sex, but you don't consider him/her your stable partner"), or a one-time partner ("a person with whom you've had sex only once"). Partner type was dichotomized to consider stable partners (SP) or non-stable partners (NSP). Casual and anonymous partners were both considered NSPs in this analysis. Any instance of insertive or receptive anal intercourse without a condom within the past 3 month was considered CLAI within a given partnership.

Missing data and data imputation

For dyadic partnerships in which the date of first sexual encounter with a partner was reported but there was no date of most recent sexual encounter, date of most recent sex was imputed based on the type of partner (stable, casual, or anonymous) and whether or not the respondent reported that he thought sex would occur again in the future. Imputation assumptions were as follows: the sexual partnership was considered ongoing for stable and casual partners for whom it was unknown whether sex would occur in the future; the date of most recent sex was imputed as the midpoint between date of first sex and the date of their interview for SPs with whom sex would not occur again; for anonymous partners and for casual partners whose relationship status was not ongoing, sex was considered a one-time event.

Covariates

Covariates considered in the bivariate and multivariate analyses of predictors of concurrency included HIV-related variables, sociodemographic characteristics, measures of alcohol use, and characteristics of each dyadic sexual partnership. HIV-related variables included HIV status at time of survey, history of a previous HIV test, and awareness of HIV status for those who tested HIV-positive. Sociodemographic characteristics included residence (Lima vs. non-Lima), age measured in quartiles, education (any post-secondary education vs. none), self-reported sexual orientation (homosexual, heterosexual, or bisexual), gender (male-identified or transgender), sexual role (self-identity as insertive, receptive, or versatile), and self-identification as a sex worker. Alcohol use disorder (AUD) was identified using the Alcohol Use Disorders Identification Test (AUDIT) and an AUDIT score greater than or equal to 8 indicated an alcohol use disorder (AUD) [63]. The total number of male and TGW sexual partners in the previous three months was log transformed to achieve normality, and a value of 0.0001 was added before log transformation to avoid undefined values. An indicator variable was created to identify participants who reported only one SP (referent group = those with multiple or no SPs) in the previous three months. For each of the three possible dyads, participants reported whether each partner was a SP or NSP and if they engaged in insertive or receptive anal sex without a condom at any time during the relationship. The same variables were considered in the bivariate analysis of CLAI with SPs and NSPs.

Statistical analysis

Proportions are presented to describe characteristics of the population. Bivariate analyses using Poisson regression with a log link and corresponding 95% confidence intervals were used to estimate the association between participant characteristics and concurrent partnerships. Stepwise backward multivariate Poisson regression was used to estimate the adjusted prevalence ratio of concurrency associated with each variable. Covariates were considered for the full multivariate analysis if they were associated with concurrency in bivariate analyses (p-value <0.10) and maintained in the multivariate model if p≤0.05. In order to maintain all participants in the analysis, characteristics that were dependent upon HIV-positive status (being unaware of HIV-positive status) or having a partner of a specific type (CLAI with a SP or NSP) were not considered in multivariate analysis. In an attempt to identify characteristics associated with concurrency above and beyond those associated with having multiple partners, the multivariate analysis was adjusted for total number of male or TGW partners in the previous three months. The final model was constructed by selecting the covariates that

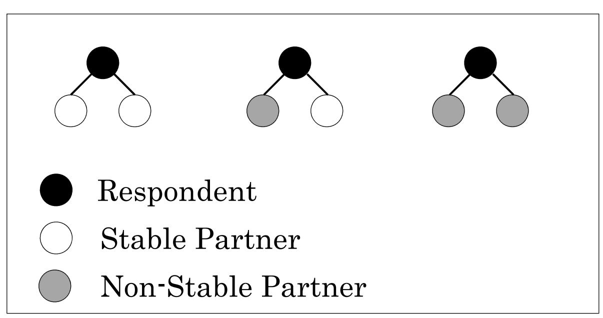

Figure 1. Overlapping dyads could be comprised of two stable partners, two non-stable partners, or a stable and non-stable partner. In this diagram, the respondent only has two simultaneous partners, but data was available to measure up to three overlapping partnerships.

minimized both the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). Prevalence ratios with corresponding 95% confidence intervals were calculated for each covariate maintained in the multivariate model.

To assess condom use with SPs and NSPs among those with concurrent partners, we first described the proportion of respondents with each overlapping combination of two dyads (two SPs, two NSPs, or one SP and one NSP) (Figure 1) and the proportion reporting CLAI in concurrent partnerships consisting of a SP and a NSP. We then conducted bivariate analyses using Poisson regression with a log link using generalized estimating equations (GEE) to estimate the association between participant characteristics and CLAI with a SP and a NSP. Since up to three dyads were possible for each respondent, estimates were adjusted for this correlation structure. Covariates were considered significant if they were associated with CLAI in bivariate analyses with a p-value less than 0.05. Significant variables were assessed for confounding by sociodemographic variables of age, education, income, role, and sex worker status and because adjustment did not change the point estimate of the significant predictors, no adjustment was made in the final analysis.

Software

All statistical analysis was performed using Stata 14 software [64].

Protection of Human Subjects

This research was determined to be exempt from Institutional Review Board (IRB) approval by the Fred Hutchinson Cancer Research Center IRB (Seattle, WA, USA) because it was secondary analysis of de-identified data.

Results

Participant Characteristics

Of the 5,137 men included in the bio-behavioral survey, 3,949 (76.9%) reported at least one male partner in the previous three months and are included in this analysis (Table 1). Nearly 9% (N=338) screened positive for HIV, of whom 302 (89.4%) were unaware of their status; 2,423 (61.4%) reported testing for HIV at least once previously. The average age was 28.4 years with a median age of 26 (IQR: 21-33). Nearly 54% were from Lima, 15% identified as a transgender woman, 62% self-identified as homosexual, and 22% self-identified as sex workers. There was a median of 3 male sex partners in the previous three months (IQR: 1-6). Within the three months preceding interview, 1,423 (36.0%) had a SP and 3,018 (76.4%) had a NSP. Over 42% had CLAI with their SP and 38% had CLAI with their NSP.

Prevalence and correlates of cumulative concurrency

The cumulative 3-month prevalence of concurrency among eligible MSM and TGW was 23.2% (N=918; 95% CI: 21.9-24.6%). The total number of male partners in the previous three months was positively associated with having concurrent partners. The bivariate analysis showed that there was significantly higher prevalence of concurrency in Lima compared to areas outside Lima (24.6% vs. 21.6%, respectively; PR=1.13, 95% CI: 1.02-1.28), but this difference was not significant after controlling for other factors (i.e. previous HIV test, age, sexual orientation, sexual role, total number of male/TGW partners, and having a stable partner) (Table 2). HIV-status was not associated with concurrency; in fact, those unaware of their HIV-positive status were less likely to have been in a concurrent partnership in the previous three months (PR=0.53, 95% CI: 0.30-0.93) CLAI with any partner was associated with having concurrent partners (PR=1.37, 95% Ci: 1.21-1.57).

In multivariate analysis, those in a concurrent partnership in the previous three months were more likely to have tested for HIV in the past (aPR=1.18, 95% CI: 1.02-1.38). Older age was associated with concurrency, with those ≥32 years having significantly higher prevalence of 3-month cumulative concurrency compared to those <22 years of age (PR=1.58, 95% CI: 1.30-1.90). Those identifying as homosexual were more likely to have concurrent partners compared to those who identified as heterosexual (aPR=1.62, 95% CI: 1.14-2.31), and those whose self-identified role was receptive or versatile were more likely to have concurrent partnerships compared to those who identified as insertive (aPR=1.31, 95% CI: 1.06-1.62; aPR=1.27, 95% CI: 1.03-1.55, respectively).

Condom use and concurrent partners

Among participants reporting any concurrency (N=918), 504 (55%) had at least one SP and 759 (83%) had at least one NSP. There were 415 total participants reporting concurrent partnerships that involved both a SP and a NSP, and condom use/non-use was generally consistent with both partners (Table 3). Nearly half (45.5%) used condoms with both the SP and NSP and a considerable proportion (20%) didn't use condoms with either their SP or NSP. Among those with inconsistent condom use behavior, CLAI only with the NSP was rare (4.9%). In contrast, many more partnerships showed behavior consistent with negotiated safety; 29.4% of participants reported CLAI with the SP but not with the NSP. Among participants with a NSP, those with a concurrent SP were significantly less likely to have CLAI with the NSP than those with two concurrent NSPs (PR=0.57, 95% CI: 0.46-0.71) (Table 4). Alcohol use disorder was associated with a 30% increased prevalence of CLAI (PR=1.31, 95% CI: 1.03-1.65) and living in Lima was associated with over 70% increased prevalence of CLAI with a NSP (PR=1.70, 95% CI: 1.36-2.12). No other sociodemographic characteristics were associated with CLAI with either a SP or NSP.

Discussion

In this large sample of Peruvian MSM and TGW, we found that the 3-month prevalence of concurrency among sexually active MSM and TGW was high (22.3%), but comparable to estimates of concurrency in other MSM populations [52, 65]. Individual-level characteristics associated with 3-month cumulative concurrency included education, sexual role, and the total number of male partners in the previous three months. This study highlights the confluence of HIV-related risk factors in this population of MSM and TGW which include concurrent sexual partnerships, alcohol use disorder, and CLAI in the context of concurrent partnerships. The majority of respondents in concurrent partnerships had consistent use/non-use of condoms regardless of whether the partners were stable (SP) or non-stable partners (NSP). There was some evidence of "negotiated safety" in this population as condoms were used preferentially with NSPs in overlapping partnerships consisting of a stable and non-stable partner.

Similar to previous studies, men and TGW with higher educational attainment were more likely to have concurrent partners [52]. This may be due to social attitudes surrounding non-monogamy; those with post-secondary education may be less socially conservative and less likely to favor traditional relationship structures [66]. Interestingly, participants identifying their sexual role as either primarily receptive or versatile had a higher prevalence of concurrency compared to those identifying as insertive. This finding is noteworthy in the context of sexual networks. The higher probability of both HIV acquisition and transmission associated with versatile positioning [17], suggests that participation in concurrent partnerships may compound the population-level risk of onward transmission. As expected, an increase in the number of total partners in the previous three months was positively associated with an increase in the prevalence of concurrency. This is likely because the more partners an individual had, the higher the probability that the 3-month measurement captured one of these partnerships overlapping in time. Similarly, having only one stable partner in the previous three months was associated with concurrency, likely because those with only one stable partner (as opposed to multiple serially monogamous stable partners) had a relationship of longer duration allowing the three-month measurement to capture any one-time partnerships that overlapped in time. Prevalent HIV infection was not associated with concurrency, which is to be expected, because traditional epidemiologic studies can detect factors associated with acquisition, but are unable to detect the population-level risk of transmission that arises in the presence of concurrency.

This study elucidated the convergence of two transmission-related risk factors: condomless anal intercourse and concurrent sexual partnerships. Nearly half of the respondents used condoms consistently with both SP and NSP and this high level of condom use with both overlapping partners should be encouraged as a risk reduction technique for individual-level protection as well as population-level control of the HIV epidemic. Still, a substantial proportion (20%) did not use condoms with either their SP or NSP. This may be because the motivation to use condoms may be separate from partner type and that those pre-disposed to CLAI may be unlikely to use condoms with any partner, even if partners occur concurrently [65].

We hypothesized that there would be evidence in this population of negotiated safety, a practice in which SPs mutually agree to use condoms with NSPs to honor a commitment to their primary partner and to protect themselves and their partner from STIs [58]. Although this survey did not ask participants directly about their motivations for condom use, this analysis suggests that negotiated safety is occurring. First, CLAI with a NSP was less common among those with a concurrent SP than those whose concurrent partner was a NSP. Second, among those who used condoms with one partner type (SP vs. NSP) but not the other, most (86%) had CLAI with the SP but used condoms with the NSP. Even though modeling studies suggest that the majority of HIV transmissions occur within the context of stable partners, negotiated safety could be an effective risk reduction technique if practiced consistently and at high levels in the population [53, 54, 57]. Clinicians and health promoters should consider this harm reduction approach, and counsel patients on "best practices" for negotiated safety agreements to most effectively protect themselves and their partners. This may include frequent HIV couples testing and consideration of PrEP for those who may fail to always use condoms with NSPs [58].

In addition to negotiated safety as a harm reduction approach, this study provides some evidence that alcohol reduction interventions may be particularly well-suited for those having CLAI with NSP. Consistent with previous studies that have shown alcohol and drug use are associated with concurrency and other sexual risk behavior, AUD was associated with CLAI with NSP [67-69]. Furthermore, it is consistent with studies from Peruvian populations that found AUDs were associated with risky sexual behavior including CLAI, anal sex in risky venues, sex with casual partners, and diagnosis of STIs [70]. Alcohol reduction interventions targeted to those with AUDs may serve as an indirect HIV-prevention strategy and may be particularly well suited for this high-risk population [71].

This study showed that those in concurrent partnerships were more likely to have been tested for HIV in the past and that those unaware of their HIV-positive status were less likely to have concurrent partners. With frequent testing, HIV-infected individuals have the opportunity to reduce their risk of transmission through suppression of viral load with antiretroviral therapy (ART) and/or increased condom use. This study provides evidence that in Peru, where concurrency is relatively common, CLAI within the context of concurrent partnerships is also common, providing opportunities for intervention to reduce the risk of onward HIV transmission associated with concurrency. Negotiated safety agreements, frequent HIV testing and treatment of AUDs should all be considered as possible prevention strategies in this high risk population.

Limitations and strengths

The results of this study should be interpreted with the following limitations in mind. First, the population included in the Biobehavioral Surveillance was a convenience sample and is therefore possibly not representative of the general MSM and TGW population in Peru. Due to the recruitment strategy—recruitment was conducted at social venues, including bars and nightclubs, and at venues frequented by sex workers and members of the transgender community—this is likely a population with higher levels of alcohol use and risky sexual behavior compared to the general MSM and TGW population. The primary outcome of interest, concurrency, was calculated based on some missing dates of most recent sex. The data was not missing at random, however, which allowed us to impute the missing dates based on a number of other informative characteristics about the partner. There was potential for recall bias in the dates of first and most recent sex with the three most recent sex partners. It is possible that participants were more likely to recall partnerships of longer duration or more accurately recall the dates of sex with their most recent partners. If participants overestimated the duration of partnerships, our calculation of concurrency is likely an overestimate; if participants underestimated the duration, our calculation is likely an underestimate. Future studies may consider adding a direct measure of concurrency (asking participants to report whether they had any overlapping sexual partners) to validate the level of concurrency estimated by the calendar method. The imputation of missing data could also have resulted in bias, particularly if those who reported they were "unsure if they would have sex again with the partner in the future" did not have sex again with that partner. If this occurred, our estimate is likely an overestimate of the true level of concurrency. A sensitivity analysis showed that assuming those who reported they were "unsure" had a date of most recent sex at the midpoint between date of first sex and interview did not decrease the point estimates by more than 5%. However, it is noted that a 5% change in concurrency could result in a substantial impact on population-level HIV prevalence.

Conclusions

This is the first study to report the prevalence of concurrency among MSM and TGW in Peru and it demonstrates that concurrency is common. It both highlights the convergence of high-risk behaviors including concurrency, CLAI, and alcohol use and provides evidence of "negotiated safety" in Peruvian MSM and TGW populations. Among those with concurrent partners, CLAI with non-stable partners was more common among those with an AUD and CLAI with non-stable partners was also more common among those who also had CLAI with their stable partners. Evidence of existing health promoting behavior was found with higher levels of HIV testing among those with concurrent partners. To reduce the risk of HIV transmission associated with concurrency, harm reduction approaches may be appropriate and these could include counseling patients on how to safely practice negotiated safety agreements, interventions to address AUD, and PrEP for those who have concurrent partners but fail to use condoms.

Tables and Figures

Table 1. Sociodemographic and behavioral characteristics of participants reporting at least one male partner in the three months preceding interview (N=3,949).

	N (%)
HIV-positive	338 (8.6)
Previous HIV test	
Yes	2423 (61.4)
No	1526 (38.6)
Unaware of HIV status[a]	302 (89.4)
Location	
Lima	2123 (53.8)
Outside Lima	1826 (46.2)
Stable Partner	
Yes	1423 (36.0)
No	2526 (64.0)
Age (years)	
Mean(SD)	28.4 (9.2)
≤21	1084 (27.5)
22-26	987 (25.0)
27-33	905 (22.9)
≥34	973 (24.6)
Any Post-Secondary Education	
Yes	1458 (36.9)
No	2491 (63.1)
Income	
< Minimum Wage	2720 (68.9)
≥ Minimum Wage	1229 (31.1)
Sexual Orientation	
Homosexual	2443 (61.9)
Heterosexual	1149 (29.1)
Bisexual	356 (9.0)
Gender	
Transgender	577 (14.6)
Cisgender	3372 (85.4)
Sexual Role	
Insertive	1345 (34.1)
Receptive	1443 (36.6)
Versatile	1159 (29.4)
Sex work	
Yes	868 (22.0)
No	3081 (78.0)
Any Alcohol Use Disorder (AUDIT≥8)	
Yes	2533 (64.1)
No	1416 (35.9)
Total Number of Male Sex Partners	
Median (IQR)	3.0 (1.0-6.0)
Only one stable partner	924 (23.4)
CLAI with stable partner[b]	604 (42.6)
CLAI with non-stable partner[c]	1133 (37.5)

[a]Among those testing HIV-positive.
[b]Among those with a stable partner.
[c]Among those with a non-stable partner.

Table 2. Prevalence ratio associated with concurrent partnerships. Results from unadjusted and adjusted Poisson regression.

	Unadjusted PR	(95% CI[b])	Adjusted[a] PR	(95% CI[b])
Log number of male/TGW partners	1.07***	(1.05-1.09)	1.06***	(1.04-1.08)
HIV-positive	1.05	(0.84-1.31)		
Previous HIV test	1.54***	(1.33-1.78)	1.18*	(1.02-1.38)
Unaware of HIV-positive status[c]	0.53**	(0.30-0.93)		
Lima (Ref.= Outside Lima)	1.13*	(1.00-1.30)		
Age (Ref.= ≤21 years)				
22-25	1.33***	(1.11-1.58)	1.22*	(1.00-1.49)
26-31	1.42**	(1.19-1.69)	1.29**	(1.06-1.58)
≥32	1.78***	(1.51-2.09)	1.58***	(1.30-1.90)
Any Post-Secondary Education	1.21**	(1.06-1.38)		
Income ≥ Minimum Wage	1.31***	(1.15-1.50)		
Sexual Orientation (Ref=Heterosexual)				
Homosexual	2.51***	(1.82-3.45)	1.62**	(1.14-2.31)
Bisexual	1.46*	(1.04-2.06)	1.18	(0.83-1.67)
Gender(Ref.=Cisgender)	1.27**	(1.07-1.50)		
Sexual Role (Ref.=Insertive)				
Receptive	1.93***	(1.63-2.29)	1.31*	(1.06-1.62)
Versatile	1.73***	(1.45-2.07)	1.27*	(1.03-1.55)
Sex work	1.14	(0.98-1.32)		
Any Alcohol Use Disorder	1.00	(0.87-1.15)		
Only one stable partner	1.43***	(1.24-1.65)	1.30***	(1.13-1.50)
Any CLAI	1.37***	(1.21-1.57)		

***p<0.001, **p<0.01, *p<0.05

[a]Adjusted for all other terms in the multivariate model.

[b]CI=Confidence interval.

[c]Among those with an HIV-positive test.

Table 3. Frequency and percent of overlapping dyads, detailed by partner type.

	Partner 1, Partner 2 (N=2,822)[a]		Partner 2, Partner 3 (N=2,557)[a]		Partner 1, Partner 3 (N=2,495)[a]	
	N	(%)	N	(%)	N	(%)
Total Concurrent	571	(20.2)	275	(10.8)	464	(18.6)
Stable/Stable	118	(20.7)	13	(4.7)	78	(16.8)
Non-stable/Non-stable	255	(44.7)	205	(74.6)	226	(48.7)
Stable/Non-stable	198	(34.7)	57	(20.7)	160	(34.5)
CLAI with stable only	61	(30.8)	16	(28.1)	45	(28.1)
CLAI with non-stable only	10	(5.0)	2	(3.5)	8	(5.0)
CLAI with both	34	(17.2)	13	(22.8)	37	(23.1)
CLAI with neither	93	(46.9)	26	(45.6)	70	(43.8)

[a]Total number of respondents reporting both partners listed (i.e. 1 and 2, 2 and 3, 1 and 3).

Table 4. Factors associated with CLAI with stable and non-stable partners among those in concurrent partnerships.

	CLAI with a SP[a] (N=504)		CLAI with a NSP[b] (N=759)	
	PR	(95% CI)	PR	(95% CI)
HIV-positive	1.04	(0.73-1.50)	0.71	(0.45-1.10)
Previous HIV test	1.16	(0.90-1.48)	0.86	(0.69-1.08)
Unaware of HIV status	1.25	(0.48-3.29)	1.75	(0.41-7.43)
Lima (Ref=outside Lima)	1.05	(0.85-1.30)	1.71	(1.36-2.12)
Age (Ref ≤21 years)				
22-25	1.17	(0.82-1.67)	1.15	(0.83-1.58)
26-31	0.98	(0.66-1.47)	1.10	(0.79-1.52)
≥32	1.02	(0.71-1.46)	1.07	(0.79-1.45)
Any Post-Secondary Education	1.03	(0.83-1.27)	1.06	(0.86-1.31)
Income ≥Min Wage	1.16	(0.94-1.43)	0.95	(0.77-1.17)
Sexual Orientation (Ref=Heterosexual)				
Homosexual	1.08	(0.58-2.02)	0.84	(0.52-1.36)
Bisexual	1.00	(0.51-1.97)	1.22	(0.66-2.24)
Gender (Ref.=Cisgender)	0.77	(0.57-1.04)	0.8	(0.59-1.08)
Sexual Role (Ref=Insertive)				
Receptive	1.07	(0.77-1.48)	0.84	(0.52-1.36)
Versatile	1.27	(0.91-1.76)	0.90	(0.54-1.50)
Sex work	0.86	(0.67-1.12)	0.98	(0.76-1.28)
Any Alcohol Use Disorder	1.19	(0.95-1.51)	1.31*	(1.03-1.65)
Dyad type (Ref=SP, SP)				
SP, NSP	1.10	(0.89-1.38)		
Dyad type (Ref=NSP, NSP)				
SP, NSP			0.57**	(0.46-0.71)

*p<0.05, **p<0.001

[a]SP=stable partner; among those with a stable partner

[b]NSP=non-stable partner; among those with a non-stable partner.

Chapter 3: Alcohol use disorder and HIV risk among men who have sex with men and transgender women in Lima, Peru: Results from the *Sabes* Study

Introduction

In Peru, the HIV epidemic is concentrated in men who have sex with men (MSM) and transgender women (TGW). Although HIV prevalence in the general population is estimated to be below 0.2% [35], HIV prevalence has been reported to be up to 22% and 30% among MSM and TGW, respectively [2-4, 34]. There is strong evidence that alcohol use is associated with increases in risky sexual behavior that is associated with HIV (e.g. multiple sex partners and condomless anal intercourse) through disinhibition, decreased risk perception, impaired decision-making, and diminished capacity to negotiate condom use [72-79]. In Peru, alcohol use disorder (AUD) is five times higher in MSM and TGW compared to the general male population (12.2% vs 63%) [24, 79]. Social drinking is common among MSM and TGW populations in Peru and alcohol-serving venues have contributed to the social cohesion of gay, bisexual, and transgender communities by providing a safe and non-judgmental space for gathering (e.g. bars and nightclubs) [80]. However, these social venues are also places where alcohol and sex commonly intersect, increasing the use of alcohol in sexual contexts [26-28].

The association between alcohol use and HIV risk behaviors is well-established among MSM in Latin America in general [81] and in Peru, specifically [18-22]. A prospective study among Peruvian MSM indicated a high prevalence of condomless anal intercourse (CLAI), alcohol use at last sex, and anal sex in risky venues amongst those with AUDs [70]; a cross-sectional study of young adult shantytown residents in Lima found an association between sex with a casual partner, sex with a sex worker, and a diagnosis of a STI [82], and a case-control study of adults in Lima found that HIV-infected people were more likely to be alcoholics [83]. However, there is limited evidence regarding the direct association between alcohol use disorders and HIV incidence [19, 24]. Further characterization of the constellation of risk behaviors associated with incident HIV are needed to inform HIV prevention strategies for high-risk MSM and TGW in Lima, Peru.

One challenge to identifying behavioral risk factors for HIV acquisition is that these behaviors can vary substantially over time. Most existing knowledge about risk factors for HIV acquisition is from 1) cross-sectional studies that identify HIV risk factors at HIV diagnosis and 2) prospective studies that examine the association between HIV acquisition and characteristics measured at study enrollment or infrequently during follow-up (i.e. every 6 months) [73-76]. These approaches depend on the assumption that risk factors are stable over time, which is unlikely for sexual behavior and substance use, thus resulting in possible misclassification of exposure status. Furthermore, because of the potential for extensive time between acquisition and diagnosis of HIV in many studies, it is challenging to establish the temporal sequence between behavioral exposures and HIV acquisition. To overcome these limitations, we conducted analyses of a prospective cohort of high-risk MSM and TGW in Lima, Peru which employed frequent HIV testing in conjunction with frequent behavioral questionnaires to assess etiologically relevant HIV risk factors.

The purpose of this paper is to investigate how alcohol use disorder influences risk behaviors, and to identify the association between AUD and HIV risk in a population of MSM and TGW in whom AUD is common. We will do this by 1) characterizing the population with AUD, 2) identifying socio-demographic characteristics associated with HIV acquisition, 3) quantifying the association between AUD and time-varying risk factors, and 4) calculating the risk associated with these time-varying behaviors.

Methods

Study Design

The *Sabes* cohort study was conducted in Lima, Peru, between April 2013 and April 2016. The goal of *Sabes* was to enroll individuals soon after HIV acquisition (during the acute phase of infection) into a randomized control trial to compare early versus deferred initiation of antiretroviral therapy (ART). Overall, 3,336 MSM/TGW were screened for participation in the study; 19.6% (N=654) of those screened were HIV-infected (Figure 1). HIV-uninfected individuals enrolled in the final cohort (N=2,084) had a total of 19,291 visits and 2,623 person-years of follow-up, with a maximum of 26 monthly visits, a mean of 7.5 (SD=5.34) follow-up visits, and a median of 34 days between visits.

Clinic staff and peer health promoters from the *Impacta* clinic recruited participants at social venues and through social media (N=3,108); the 2013 Peruvian Biobehavioral Surveillance referred a small number of participants (N=228) (Appendix A-1). MSM and TGW were eligible for cohort enrollment if they were born male, 18 years of age or older, unaware of their HIV status at screening, and at high risk for acquiring HIV infection (Appendix A-2). The high risk definition includes any one of the following behaviors: inconsistent condom use during anal intercourse (AI) during the last six months, AI with more than five male sex partners during the last six months, a diagnosis with a STI in the last six months or at screening, having an HIV-infected sexual partner in the last six months, self-identification as a sex worker, having symptoms of acute retroviral infection, or having sex with a person newly-diagnosed with acute or recent HIV infection. Participants had to be willing to enroll in a 2-year study with monthly HIV testing and behavioral questionnaires and consider participation in the ART randomization study if diagnosed with HIV infection during follow-up. Exclusion criteria included the use of estrogens or anti-androgens during the past three months or any medical, psychological, or other condition that would impair a participant’s ability to provide informed consent.

Assessments

Ascertainment of HIV status and defining the relevant acquisition window

Enrolled MSM and TGW were tested monthly (approximately every 30 days) for HIV using third-generation enzyme-linked immunosorbent assay (ELISA) to detect HIV antibody, confirmed with a second positive ELISA test or immunofluorescence (Abot Inc., MA, USA). For those with a negative ELISA test, nucleic acid amplification testing (NAAT) using the Liat HIV Quant Assay (Roche Molecular Systems, NJ, USA) was used to detect HIV RNA [85]. Daily samples were combined in pools of 30 or fewer samples and amplified, and positive pools were de-convoluted to identify the infected participants. Fiebig staging (FS) was performed to calculate the most probable time of HIV acquisition for each incident case [84]. This algorithm uses tests for HIV viral RNA and HIV antibody to estimate the time since HIV acquisition (Appendix A-3). Fiebig staging utilizes the evolution of antibody responses to HIV in the months after HIV acquisition to provide estimates of the time since infection. The earliest stages (Fiebig I and II) define the period prior to the first detection of HIV antibodies; later stages mark the progressive appearance of different immune responses. The time of HIV acquisition was determined using the following rules: for those in FS I-IV, acquisition likely occurred in the previous 30 days; for those in FS V, acquisition likely occurred up to 60 days preceding diagnosis; for those FS VI, acquisition likely occurred up to 90 days preceding diagnosis (Table A). All incident HIV cases were either enrolled into the ART

Table A. Length of Fiebig stages and corresponding exposure time (days) coverage of CASI follow-up questionnaire used in Cox proportional hazards regression analysis [84].

Fiebig Stage	Length of stage	Cumulative time since acquisition	Acquisition window for Cox PH
0	~11	Eclipse	Eclipse
I/II	10.3 (7.1-13.5)	10.3 (7.1-13.5)	30
III	3.2 (2.1-4.8)	13.5 (10.0-17.0)	30
IV	5.6 (3.8-8.1)	19.1 (15.3-22.9)	30
V	69.5 (39.7-121.7)	88.6 (47.4-129.8)	60
VI	Open-ended	Open-ended	90

randomization study or referred to the Peruvian National HIV/AIDS treatment program for HIV care [86].

Baseline Data

At enrollment, participants completed computer assisted self-interview (CASI) questionnaires which collected detailed demographic and socioeconomic information including age, education level, income, self-identified sexual role, sexual orientation, gender identity, and sex worker status. Risk behavior topics included the number of male partners and condom use with male partners. Participants were asked specific questions about their last three male sexual partners in the previous three months including sexual role with each partner, partner's HIV status, condom use with the partner, and dates of first and most recent sex with the partner. Participants reported their attendance at social venues (e.g. bars, nightclubs, saunas) in the previous three months and whether or not they engaged in anal intercourse (AI) with any partners met at social venues. Substance use information included indicators of alcohol and drug use with sex in the previous three months. The baseline survery did not include drug use in the absence of sex nor specific types of drug use with sex (i.e. marijuana, amyl nitrites, or cocaine). Instead participants completed the alcohol use disorders identification test (AUDIT) to identify alcohol use disorders (AUD) [63], a series of questions related to alcohol consumption and consequences of alcohol use in the previous year. Following convention, a score of 8 or greater on the AUDIT was considered an AUD; a score of 8-15 was indicative of hazardous drinking, a score of 16-20 was indicative of harmful drinking, and a score over 20 was indicative of dependent drinking. Included in the AUDIT questionnaire was a measure of binge drinking, defined by greater than 5 alcoholic drinks at any time in the past year.

Time-Varying Risk Behavior

At each monthly visit, participants were asked about any alcohol consumption (yes/no), their level of alcohol consumption (number of standard alcoholic drinks per day), binge drinking habits (any days with >5 standard alcoholic drinks), and whether or not alcohol was consumed before or during sex in the previous 30 days. Participants reported use of illicit drugs (i.e. marijuana, cocaine, amyl nitrite, ecstasy, amphetamine, ketamine) at any time in the previous 30 days. There were an adequate number of observations to examine the association of alcohol, marijuana, cocaine, and amyl nitrites with HIV acquisition in the study population; a very small subset of participants reported use of ecstasy, amphetamine or ketamine and are therefore not included in this analysis.

To ascertain social venue attendance, participants were asked to select venues from a predetermined list. This list contained previously identified social venues frequented by MSM and TGW in Lima. For this analysis, social venue attendance was aggregated to a binary variable (participants either attended or did not attend a social venue). Information collected monthly on sex partners included partner type (main, casual, client, one-time (*i.e. "punto"*), and anonymous). For this analysis, one-time partners (anonymous and *Punto* partners) were combined as one binary indicator.

Statistical Analysis

HIV Incidence

Incident HIV infection was a positive HIV test at any follow-up visit that was preceded by a negative HIV test at the most recent prior visit. The rate of HIV incidence was calculated as number of cases per 100 person-years of follow-up.

Sociodemographic variables

Age was summarized as both a continuous (median, IQR) and categorical variable based on tertiles (18-22 years, 23-28 years, and 29 years or older); age category was used in for all analyses. Several demographic variables were categorized as binary variables: gender was self-reported as either cisgender man or transgender women; education was categorized as any post-secondary education vs. no post-secondary education; income was categorized as either above or below Peruvian minimum wage at the time of study commencement (750 Soles/month, or approximately 220 USD). Participants reported their predominant sexual role—insertive, receptive, or versatile (both insertive and receptive) and MSM participants reported their self-identified sexual orientation (heterosexual, homosexual, or bisexual). We defined sex work to include participants who self-identified as sex workers. Alcohol use disorder was considered as three categories: none, hazardous/harmful, and dependent.

Defining exposure status for time-varying covariates

The values of behavioral risk factors could vary from one 30-day interval to the next. The last-value carried forward convention was applied to time-varying covariates with missing data. The values reported at baseline for partner type, alcohol consumption, binge drinking, and drug use were considered the participant's exposure status for the 90 days prior to enrollment. For participants who became HIV-infected over the course of the study, a relevant acquisition window was set based on their Fiebig stage at diagnosis (30 days for FS I-IV, 60 days for FS V, and 90 days for FS VI). If an exposure of interest occurred at any time during the relevant acquisition window, the participant was considered exposed for the entire window.

Baseline characteristics and AUD

Sociodemographic characteristics of the cohort were stratified by AUD category, and the distribution of these characteristics was compared across AUD category using Pearson's Chi-squared statistic to detected statistical significance (defined as $p<0.05$).

Baseline predictors of HIV acquisition

To identify individual predictors of HIV acquisition, bivariate Cox proportional hazards regression with robust standard errors to account for clustering by participant was first conducted on each sociodemographic variable of interest. Hazard ratios (HR) and corresponding 95% confidence intervals were calculated for each variable. All variables associated with HIV acquisition with $p \leq 0.05$ were considered in a multivariate Cox proportional hazards regression model with robust standard errors. Models were assessed using stepwise backward elimination and variables were maintained in the model if the p-value was ≤0.05.

Alcohol use disorder and time-varying risk behaviors

We conducted Poisson regression models with a log link estimated with Generalized Estimating Equations (GEE) to calculate the relative risk of HIV acquisition associated with each risk behavior, stratified by the three AUD levels. Risk factors included venue attendance, any alcohol use, binge drinking, marijuana use, use of amyl nitrites, cocaine use, any CLAI, sex with a main, casual, client, or one-time partner. We present both unadjusted estimates and estimates adjusted for age category, income, education, sexual role, and sex worker status.

Stratified analysis of time-varying risk behaviors

To assess risk associated with HIV for each risk behavior, we used a series of Cox proportional hazards regression models with robust standard errors to calculate the HR. For each AUD stratum, we summarize separate stratum-specific models, calculating HR and 95% confidence intervals for each stratum. We present both unadjusted estimates and estimates adjusted for age category, income, education, sexual role, and sex worker status. Time-varying covariates were interacted with a linear function of time to determine trends in exposure over time; no time interactions were statistically significant (p-value≤0.05), and were not maintained in the analysis.

Sensitivity analysis

For the main analysis of the risk associated with behaviors, we assumed that risk behaviors reported at any time throughout the interval were present for the entire extended interval for those diagnosed in FS V or VI (60 days for FS V and 90 days for FS VI). In the sensitivity analysis, the exposure status for each time-varying covariate was averaged across the number of visits in the relevant time period to assess the potential bias associated with extending the window to 60 days for those in FS V and to 90 days for those in FS VI. For example, if a participant diagnosed in FS VI had one month of exposure reported over the two preceding visits within 90 days of diagnosis, that participant was given an exposure status of 0.5 for the 90 days preceding diagnosis. The analysis was re-run with these updated exposure values.

Software

All statistical analyses were performed using Stata 14 [64].

Protection of human subjects/informed consent

Protocols for the study were approved by institutional review boards (IRB) at the Fred Hutchinson Cancer Research Center, Impacta, and Via Libre, and were reviewed by the Peruvian National Institutes of Health. All study participants provided written consent in Spanish, their native language, to participate in the study.

Results

Cohort Characteristics by AUD

The median age of participants enrolled in the cohort was 26 years (range=18-73 years, mean=28 years, SD=8.5 years), with over 30% of participants being under 23 years (Table 1). Ninety-six percent of the cohort identified as either homosexual or bisexual, with nearly half of participants identifying their primary sexual role as versatile. Nearly one-fifth of the cohort self-identified as a sex worker. Drug and alcohol use was common in this population; at enrollment, the proportion reporting alcohol use or drug use before or during sex in the previous 3 months was 75% and 38%, respectively. Over 50% of participants had an alcohol use disorder (AUDIT≥8); 42% had drinking patterns consistent with hazardous or harmful drinking and 11.8% had drinking patterns consistent with alcohol dependence. The distribution of sociodemographic characteristics varied significantly by AUD. The proportion of those over 29 years of age was highest among those with dependent drinking (45.0%). Those making less then minimum wage and those with no post-secondary education were significantly more likely to have dependent drinking patterns. Transgender individuals were nearly twice as likely to be dependent drinkers compared to cisgender individuals (18% vs. 9%, respectively), and sex workers were nearly three times as likely to be dependent drinkers compared to non-sex workers (23% vs. 8%, respectively).

AUD and risk behaviors

Those with alcohol use disorders classified as hazardous/harmful or dependent were significantly more likely to attend a venue, binge drink, and use marijuana or amyl nitrites (Table 2). Those with an AUD (AUDIT≥8) were over 5 times more likely to use cocaine (RR=5.18, 95% CI 2.93-9.18; RR=6.28, 95% CI: 3.27-12.1 for hazardous/harmful and dependent patterns of drinking, respectively). Those with an AUD were also more likely to have a client, a casual partner, or a one-time partner.

Baseline Predictors of HIV Acquisition

Overall HIV incidence in the cohort was 11.7 per 100 person-years of follow-up. Forty-five people were diagnosed with acute (N=5) or recent (N=40) infection during cohort enrollment and these cases were included in cohort incidence calculations. During cohort follow-up, 262 incident HIV cases were detected, resulting in a total of 307 incident HIV cases in the study population. A log-rank test indicated incidence varied significantly by age (p<0.001). Participants aged 18-22 years had the highest HIV incidence (17.7 per 100 years of follow-up) compared to those 23-28 years (12.4 per 100 person-years) and those 29 years or older (7.3 per 100 person-years).

In bivariate analysis of demographic characteristics, self-identified sex workers were significantly less likely to acquire HIV than non-sex workers (HR=0.55, 95% CI: 0.39-0.79) (Table 3). In multivariate analysis, younger age was associated with increased HIV risk: those 18-22 years were 2.47 times more likely (95% CI: 1.84-3.30) and those 23-28 years were 1.73 times more likely (95% CI: 1.28-2.35) to acquire HIV compared to those 29 years or older (Figure 2). Those with any post-secondary education were more likely to acquire HIV than those without (aHR=1.35, 95% CI: 1.05-1.75). Self-identified sexual roles of receptive and versatile were more likely to acquire HIV compared to those identifying as insertive (aHR=1.47, 95% CI: 1.03-2.09; aHR=1.79, 95% CI: 1.30-2.46, respectively). In contrast, an alcohol use disorder was not significantly associated with HIV risk in bivariate or multivariate analysis.

Time-varying risk behaviors associated with HIV acquisition

Alcohol use disorder (none vs. harmful/hazardous vs. dependent) modified the association between the time-varying behavioral factors and HIV (Table 4). In bivariate analysis, among those with no AUD, any alcohol use in the previous 30 days was moderately associated with HIV (HR=1.55, 95% CI: 1.01-2.37), but this did not remain significant in the adjusted analysis. For those with harmful/hazardous patterns of drinking, only one risk behavior, attendance at a social venue, was associated with HIV (HR=2.22, 95% CI: 1.51-3.26; aHR=1.89, 95% CI: 1.26-2.84). There were multiple time-varying behavioral risk factors associated with HIV among those with dependent drinking patterns. Binge drinking was strongly associated with HIV acquisition (aHR: 3.01, 95% CI: 1.25-7.22) as was marijuana use (aHR: 3.05, 95%CI: 1.06-8.76). Partner type was also strongly associated with HIV; having a casual partner, client, or one-time partner were significantly associated with HIV among those with dependent drinking patterns (HR=2.91, 95% CI:1.29-6.56; HR=2.69, 95% CI:1.26-5.74; HR=4.06, 95% CI: 1.28-12.87, respectively).

Sensitivity Analysis

There was less than a 5% difference between point estimates for the covariates and the statistical significance of the covariates, determined by $p \leq 0.05$, was not altered.

Discussion

The *Sabes* cohort illustrates the complex interconnectedness of HIV risk behaviors such as substance use, venue attendance in a population of MSM and TGW with high levels of alcohol use. Fifty-three percent of the cohort had an alcohol use disorder (AUD), over four times higher than the prevalence of AUD in the general Peruvian population (12.2%) [87]. Those with an AUD were more likely than those without an AUD to participate in risky behaviors, including binge drinking, attendance at a social venue, sex without a condom, and the use of marijuana, poppers, and cocaine. Alcohol use disorder alone was not associated with HIV acquisition, but risky behaviors (e.g. CLAI, drug use, social venue attendance) were more strongly associated with HIV acquisition among those with an AUD. This study confirmed that many previously established risk factors, such as younger age, receptive sexual role, and the use of amyl nitrites, were associated with HIV risk in this population of Peruvian MSM and TGW.

Consistent with the epidemiologic literature, having low income, being transgender, and being a sex worker were all associated with AUD in this high-risk Peruvian population. Factors that predispose an individual to substance abuse are more common among those with lower socioeconomic status (i.e. low income, poverty) [88, 89] and many previous studies have shown that there is a high burden of alcohol and substance use among gender minority groups [78, 90-92]. Numerous studies have established a strong link between substance abuse and sex work [93, 94] noting that alcohol and substance use among male and TGW sex workers is associated with inconsistent condom use with clients [95]. Given the high levels of AUD among low-income individuals, TGW, and sex workers in Peru, and the fact that sex workers may be central to the structure of sexual networks that facilitate epidemic levels of HIV [96, 97], HIV prevention interventions, including treatment for AUDs, should be targeted toward these populations.

Although previous studies of MSM and TGW in Lima have shown that AUDs are associated with risky sex, including CLAI and sex at social venues [70], this is one of the first to investigate the association between alcohol use disorder and HIV incidence [19, 24]. Our findings provide evidence that the relationship between alcohol use and HIV is complex and that the associations between HIV and alcohol use may be, at least in part, accounted for by the fact that dependent drinkers are inherently different from other populations [33, 98]. We found that the AUDIT, a stable measure of alcohol dependence, was predictive of risky behavior, yet AUDIT score was not associated with incident HIV. However, individuals with AUDs who engaged in high-risk behaviors were at markedly higher HIV risk than those without AUDs who exhibited similar risks and this was observed most dramatically among dependent drinkers. Dependent drinkers had the highest risk associated with substance use (i.e. marijuana and amyl nitrites), CLAI, sex with a client, and sex with a one-time partner. This may tell us that somehow dependent drinkers are inherently different from the other two groups (no AUD and hazardous/harmful drinkers) which resulted in a differential effect of these risk factors on HIV acquisition.
It is highly probable that there is a causal pathway between alcohol use disorder and unsafe sex which leads to HIV acquisition, though this study didn't detect an association. It is possible that

that personality factors, such as impulsivity and sensation seeking are associated with both AUD and HIV and therefore obscure the AUD and HIV relationship [33] that we hypothesized would exist [28, 99].

We identified characteristics associated with incident HIV that are consistent with previous research. First, younger participants (ages 18-22) were over twice as likely to acquire HIV compared to their older counterparts (Age 29+). Studies from around the world suggest that adolescence and young adulthood is a time of increased vulnerability to HIV and other STIs, likely due to sexual experimentation, risky sexual behaviors, and power dynamics that may impede condom negotiation [100]. As expected, sexual role was associated with HIV acquisition—those identifying their role as versatile or receptive had a significantly higher risk of HIV acquisition compared to those identifying as exclusively insertive. It is well-established that the receptive partner is at greater risk of acquiring HIV due to the higher susceptibility of rectal tissue to viral infection [101-103]. The use of amyl nitrites (i.e. "poppers"), a popular sex drug, was associated with over a three-fold increase in HIV risk. Evidence suggests that the use of amyl nitrites does not make CLAI more likely, but that they increase the risk of HIV among those engaging in CLAI by increasing susceptibility to infection through increasing blood flow to rectal tissues [104, 105].

This study highlights the complex interconnectedness of substance use, risky sexual behavior, and HIV acquisition and suggests that those with AUDs, especially those with dependent drinking patterns, may be inherently different from those without AUDs. Given that alcohol use at sex may negatively impact condom negotiation and correct usage, this study highlights the utility of screening for AUDs to identify those at risk of failing to practice safer sex, which may include young MSM, TGW and sex workers [33, 70]. Due to the synergistic effect of AUD with other sexual risk behaviors noted in this study, clinicians should consider the AUDIT score when assessing eligibility for HIV prevention strategies.

Limitations and strengths

Study findings should be interpreted with the following limitations in mind. First, all data regarding risk behaviors were self-reported by the participant. Because sensitive information such as drug use and sexual behavior is prone to social desirability bias, it is likely that there was under-reporting of risk behaviors. However, we have no reason to suspect that there was any differential under-reporting of risk behaviors based on HIV status as participants were not told their HIV test results until after questionnaire completion. Second, the cohort was composed of high-risk individuals and results are likely not representative of the general MSM and TGW population in Lima. The cohort HIV incidence rate of 11.7 per 100 person-years of follow-up, nearly three times the estimated incidence in the general MSM and TGW populations, reflects the goal of recruiting a high-risk population. Individuals in the *Sabes* cohort were recruited based on high-risk criteria in order to detect a large number of incident HIV infections during the acute phase of infection.

Strengths of this study include its prospective design which provided the opportunity to measure a large number of baseline characteristics at study enrollment and subsequent time-varying behavioral data. We had the ability to determine the likely time of HIV acquisition using dates of HIV testing and the results of Fiebig staging, which reduced misclassification of the exposure status. This study's ability to measure HIV incidence and corresponding time-varying risk factors, in conjunction with assessment of alcohol use disorder using an internationally validated screening instrument (the AUDIT) shows that the association between AUD and HIV is complex and is mediated by risky behavior [63].

Conclusions

The *Sabes* cohort illustrates the complex relationships between substance use, risky sexual behavior, and HIV risk. The overall HIV incidence rate in the cohort, 11.7 per 100 person-years of follow-up, indicates that this was indeed a high-risk group of individuals. Many of the accepted and well-established risk factors for HIV acquisition, such as younger age, non-insertive sexual role, and the use of amyl nitrites, were confirmed to be risk factors in this MSM/TGW population in Lima. Individuals with AUD were more likely to participate in risky behaviors compared to those without AUD, but AUD category alone was not associated with HIV acquisition. Instead, AUD modified the relationship between risk behaviors and HIV acquisition, providing evidence of a synergistic effect of dependent drinking patterns with the use of other substances (marijuana and amyl nitrites), condomless anal intercourse, sex with clients, and sex with one-time partners. This study provides evidence that the impact of alcohol use is not the same for everyone and that the AUDIT screening tool may be helpful in identifying those most likely to be affected by risky sex and substance use. These data support ongoing discussions of multi pronged approaches to prevention which include such things as structural interventions to reduce binge drinking in places like bars and clubs, as well as individual interventions to reduce alcohol dependency.

Tables and Figures

Table 1. Sociodemographic characteristics of the *Sabes* cohort, total and stratified by AUD category[a].

Characteristic	Total	AUDIT=0-7 (N=987) N (%)[b]	AUDIT=8-20 (N=874) N (%)[b]	AUDIT > 20 (N=220) N (%)[b]	p-value[c]
Age (Median, IQR)	26 (22-34)	26 (22-34)	27 (22-35)	27 (22-33)	
Age Category					0.043
18-22 years	641 (30.1)	322 (32.6)	262 (30.0)	57 (25.9)	
23-28 years	655 (31.5)	322 (32.6)	269 (30.8)	64 (29.1)	
29+ years	785 (37.7)	343 (34.8)	343 (39.2)	99 (45.0)	
Income					0.001
<Minimum wage	921 (44.3)	425 (43.1)	373 (42.7)	123 (55.9)	
≥ Minimum wage	1160 (55.7)	562 (56.9)	501 (57.3)	97 (44.1)	
Post-secondary education					<0.001
None	762 (36.6)	285 (28.9)	346 (39.6)	131 (59.6)	
Any	1318 (63.3)	701 (71.1)	528 (60.4)	89 (40.5)	
Sexual orientation					0.18
Homosexual	1083 (60.8)	544 (62.5)	448 (60.1)	91 (54.8)	
Bisexual	620 (34.8)	283 (32.5)	268 (35.9)	69 (41.6)	
Heterosexual	79 (4.4)	43 (4.9)	30 (4.0)	6 (3.6)	
Gender					<0.001
Cisgender	1782 (85.6)	870 (88.2)	746 (85.4)	166 (75.5)	
Transgender	299 (14.4)	117 (11.9)	128 (14.7)	54 (24.6)	
Role					0.398
Insertive	562 (27.0)	262 (26.6)	241 (27.6)	59 (26.8)	
Receptive	614 (29.5)	305 (30.9)	238 (27.2)	71 (32.3)	
Versatile	905 (43.5)	420 (42.6)	395 (45.2)	90 (40.9)	
Sex worker					<0.001
No	1692 (81.3)	864 (87.5)	696 (79.6)	132 (60.0)	
Yes	389 (18.7)	123 (12.5)	178 (20.4)	88 (40.0)	

[a]Among those with a non-missing AUDIT score. AUDIT 0-7=No AUD, AUDIT 8-20=Harmful/hazardous drinking patterns, AUDIT>20=Dependent drinking patterns.

[b]Column percentages, may not add to 100 due to rounding.

[c]P-value based on a Chi-square test.

Table 2. The relative risk of each time-varying risk factor comparing individuals with no AUD to those with harmful/hazardous and dependent patterns of drinking.

Exposure / Outcome	AUDIT=8-20[a]				AUDIT>20[a]			
	Unadjusted		Adjusted[b]		Unadjusted		Adjusted[b]	
	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Venue attendance	1.13	(1.04-1.21)	1.15	(1.06-1.24)	1.21	(1.08-1.35)	1.27	(1.12-1.42)
Any alcohol use	1.24	(1.07-1.43)	1.26	(1.09-1.46)	1.28	(1.03-1.61)	1.38	(1.09-1.73)
Binge drinking	2.47	(1.89-3.23)	2.47	(1.89-3.23)	2.74	(1.92-3.91)	2.82	(1.09-4.08)
Marijuana	2.02	(1.51-2.71)	2.00	(1.49-2.70)	1.86	(1.20-2.87)	1.85	(1.18-2.91)
Amyl Nitrites	2.17	(1.11-4.24)	2.50	(1.36-4.61)	2.24	(0.87-5.77)	3.75	(1.54-9.09)
Cocaine	5.96	(3.28-10.82)	5.18	(2.93-9.18)	8.94	(4.59-17.4)	6.28	(3.27-12.09)
Any CLAI	1.23	(1.11-1.35)	1.22	(1.10-1.34)	1.33	(1.15-1.53)	1.26	(1.09-1.45)
Any main partner	0.99	(0.93-1.04)	0.99	(0.94-1.05)	0.89	(0.81-0.98)	0.92	(0.84-1.02)
Any casual partner	1.10	(1.02-1.18)	1.08	(1.01-1.16)	1.15	(1.03-1.28)	1.07	(0.96-1.20)
Any client	1.53	(1.27-1.84)	1.20	(1.04-1.41)	2.58	(2.06-3.23)	1.28	(1.06-1.55)
Any one-time partner	1.12	(1.05-1.20)	1.10	(1.04-1.18)	1.16	(1.05-1.28)	1.08	(0.98-1.20)

[a]Compared with no AUD. AUDIT 0-7=No AUD, AUDIT 8-20=Harmful/hazardous drinking patterns, AUDIT>20=Dependent drinking patterns.
[b]Adjusted for age category, income, education, role, and sex worker status.

Table 3. Baseline characteristics associated with HIV acquisition in the *Sabes* cohort.

	Bivariate Analysis		Multivariate Analysis[a]	
	HR	(95% CI)	HR	(95% CI)
Age Category (*Ref= 29+ years*)				
18-22 years	2.52***	(1.89-3.37)	2.47***	(1.84-3.30)
23-28 years	1.74***	(1.29-2.35)	1.73***	(1.28-2.35)
Income (*Ref=<min wage)*	1.15	(0.91-1.45)		
Post-secondary education *(Ref=None)*	1.40*	(1.07-1.77)	1.35*	(1.05-1.75)
Sexual orientation *(Ref=Heterosexual)*				
Homosexual	2.11	(0.87-5.13)		
Bisexual	1.90	(0.77-4.68)		
Gender (*Ref=cisgender)*	0.75	(0.52-1.07)		
Role (*Ref=Insertive*)				
Receptive	1.45*	(1.02-2.06)	1.47*	(1.03-2.09)
Versatile	1.92***	(1.39-2.63)	1.79***	(1.30-2.46)
AUD Category (*Ref=Low Risk, AUDIT 0-7*)				
Hazardous/Harmful (AUDIT 8-20)	1.19	(0.94-1.52)		
Dependent (AUDIT >20)	0.86	(0.56-1.31)		
Sex worker	0.55**	(0.39-0.79)		

[a]Adjusted for all other terms presented in multivariate model.
*p<0.05, **p<0.01, ***p<0.001

Table 4. Hazard ratio associated with HIV for time-varying risk factors, stratified by AUDIT severity categories.[a]

Exposure \ Strata	AUDIT=0-7				AUDIT=8-20				AUDIT >20			
	Unadjusted		Adjusted[b]		Unadjusted		Adjusted[b]		Unadjusted		Adjusted[b]	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Venue attendance	1.31	(0.91-1.91)	1.20	(0.83-1.75)	**2.22****	**(1.51-3.26)**	**1.89****	**(1.26-2.84)**	2.62	(0.85-8.04)	2.50	(0.81-7.64)
Any alcohol use	**1.55***	**(1.00-2.37)**	1.35	(0.87-2.09)	1.39	(0.94-2.06)	1.22	(0.81-1.83)	2.15	(0.91-5.10)	2.11	(0.89-4.95)
Binge drinking	0.19	(0.03-1.40)	0.17	(0.02-1.29)	1.40	(0.85-2.31)	1.30	(0.78-2.14)	**3.10***	**(1.25-7.65)**	**3.01***	**(1.25-7.22)**
Marijuana	0.93	(0.36-2.42)	0.79	(0.31-2.06)	1.14	(0.60-2.19)	0.98	(0.51-1.89)	**3.10***	**(1.14-8.44)**	**3.05***	**(1.06-8.76)**
Amyl Nitrites	3.28	(0.78-13.8)	**4.07***	**(1.06-15.7)**	2.18	(0.78-6.08)	2.00	(0.69-5.75)	**8.60*****	**(2.59-28.5)**	**8.99****	**(2.50-32.32)**
Cocaine	0.86	(0.13-5.73)	1.17	(0.20-6.67)	0.28	(0.07-1.10)	0.35	(0.09-1.34)	1.96	(0.60-6.35)	1.88	(0.56-6.31)
Any CLAI	1.19	(0.84-1.70)	1.18	(0.83-1.68)	0.97	(0.69-1.37)	0.96	(0.68-1.36)	**3.28***	**(1.12-9.60)**	**3.13***	**(1.01-9.66)**
Any main partner	1.04	(0.74-1.48)	1.00	(0.71-1.42)	1.13	(0.81-1.57)	0.86	(0.38-1.20)	1.17	(0.51-2.68)	1.17	(0.53-2.57)
Any casual partner	1.08	(0.76-1.54)	1.15	(0.81-1.62)	1.19	(0.85-1.66)	1.19	(0.85-1.66)	**2.65***	**(1.19-5.92)**	**2.91****	**(1.29-6.56)**
Any client	0.68	(0.36-1.30)	0.90	(0.42-1.93)	0.81	(0.51-1.29)	1.18	(0.71-1.96)	2.09	(0.98-4.48)	**2.69****	**(1.26-5.74)**
Any one-time[b] partner	1.16	(0.81-1.67)	1.20	(0.83-1.73)	0.98	(0.69-1.40)	0.99	(0.69-1.43)	**4.07***	**(1.29-12.87)**	**4.06***	**(1.28- 12.87)**

*p<0.05, **p<0.01, ***p<0.001
[a]AUDIT 0-7=No AUD, AUDIT 8-20=Harmful/hazardous drinking patterns, AUDIT>20=Dependent drinking patterns.
[b]Adjusted for age category, income, education, sexual role, and sex worker self-identification.

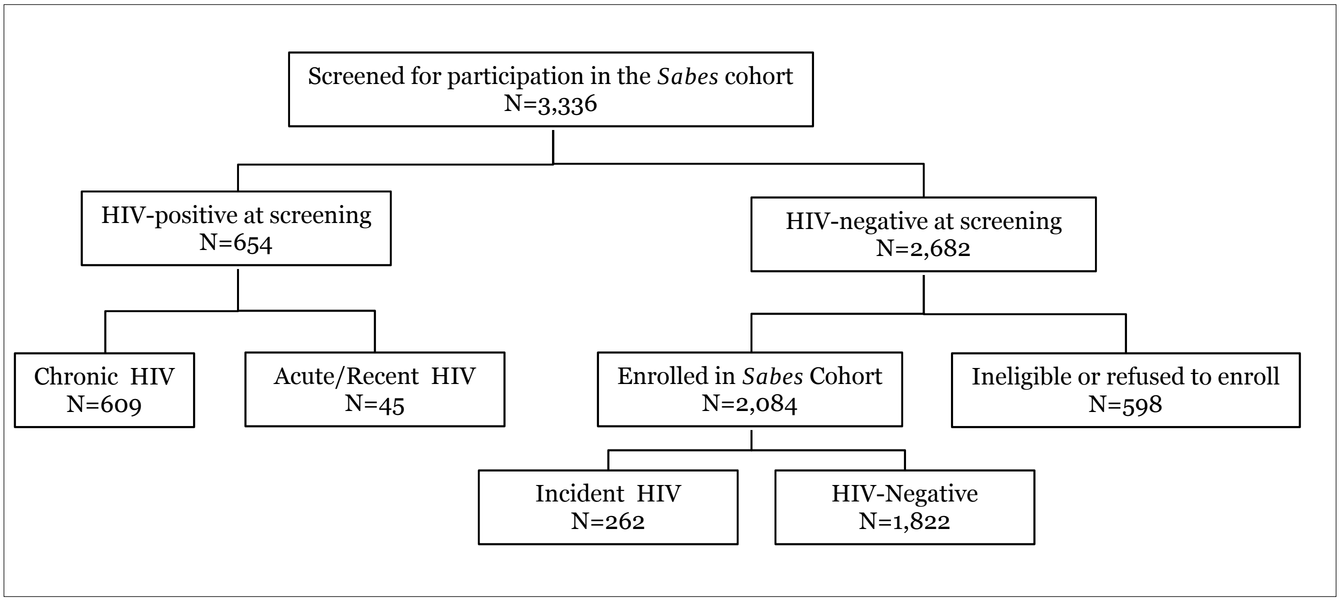

Figure 1. Consort diagram for *Sabes* participants.

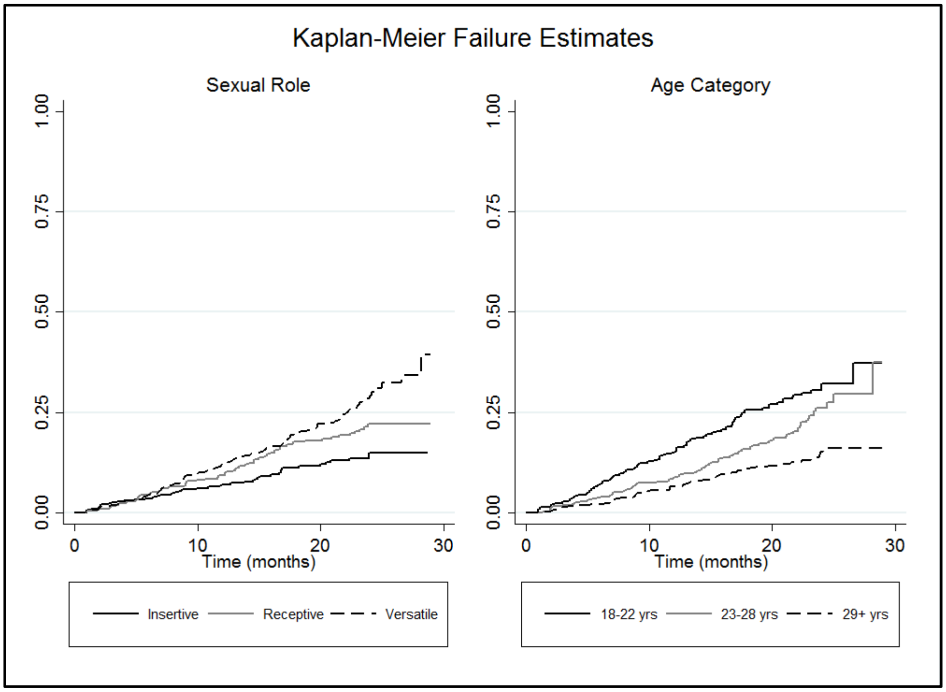

Figure 2. Kaplan-Meier failure estimates by sexual role and age category.

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Appendix

Table A-1. HIV prevalence, and demographic and behavioral characteristics of the two sample populations eligible for enrollment in the *Sabes* longitudinal cohort.

	General Screening (N=3108)		Biobehavioral Surveillance (N=228)		
	N	%	N	%	p-value[a]
HIV Prevalence	647	20.8	7	3.1	<0.001
Age (mean, SD)	27.3	7.9	30.6	8.7	<0.001
18-24	1321	45.2	68	30.0	<0.001
25-34	1045	35.8	89	39.2	
35+	556	19.0	70	30.8	
Education					0.046
No secondary	189	6.12	23	10.1	
Some secondary	990	32.1	75	33.0	
Any post-secondary	1904	61.8	129	56.8	
Monthly Income					0.016
<$400	2037	83.8	159	79.3	
$400-$799	320	13.2	30	14.8	
$800-$1199	43	1.8	7	3.5	
>$1200	30	1.2	7	3.5	
Sexuality					0.08
Homosexual	1604	61.3	120	64.9	
Bisexual	898	34.3	53	28.7	
Heterosexual	113	4.3	12	6.4	
Gender					0.141
Cisgender	2615	84.8	185	81.1	
Transgender	469	15.2	43	18.9	
Sexual Role					0.950
Insertive	780	25.3	57	25.0	
Receptive	915	29.7	70	30.7	
Both	1388	45.0	101	44.3	
AUDIT Score					0.329
0-7	1131	41.0	76	38.8	
8-15	1029	37.3	69	35.2	
16+	601	21.8	51	26.0	
Primary Reason for Clinic Visit					0.643
HIV exposure	1396	45.2	18	36.0	
Referred by a promoter	686	22.2	13	26.0	
Routine STI screening	650	21.1	15	30.0	
Felt sick	42	1.3	0	0	
Got a new partner	90	2.9	2	4.0	
Diagnosed with an STI	63	2.0	0	0	
Other reasons	87	2.8	1	2.0	
Inclusion Risk Factors					
CLAI during last AI	1767	57.3	120	52.9	0.189
AI with >5 partners in < 6 mo.	1131	41.4	88	44.9	0.335
Self-identified sex worker	578	18.8	50	22.3	0.195
Syphilis at screening	113	3.7	7	3.1	0.875
Sex partner of HIV+ male	182	6.7	12	6.1	0.770

[a]P-value based on Pearson's Chi^2 for categorical variables, t-test for continuous variables.

Table A-2. Inclusion and exclusion criteria for enrollment into the SABES cohort.

Inclusion Criteria	**Exclusion Criteria**
Male sex at birth	Any medical, psychological/psychiatric, occupational, or other condition that would interfere with, or serve as a contraindication to, protocol adherence, assessment of safety, or a participant's ability to give informed consent
18 years of age or older	Seeking HIV test behavior for routine reasons
Unaware of HIV status	Use of estrogens (or its derivatives) or anti-androgens, administered orally or intra-muscularly, during the past three months
Ability and willingness to provide informed consent for study participation, including being tested for HIV-1, for re-testing if HIV negative, and to consider enrollment in an immediate vs. deferred ART trial if diagnosed with acute or recent HIV infection after testing	
Willingness to be re-contacted if HIV seronegative by antibody analysis but with virologic evidence of acute infection HIV-1 and to be linked to care	
Evidence of high risk for acquiring HIV-1 infection, including any one of the following: 1. Sexual Behaviors: a. Inconsistent condom use during anal intercourse during the last 6 months b. Anal intercourse with more than five male sex partners during the last 6 months c. Self-identification as a sex worker d. STI diagnosis in the last 6 months or at screening e. Sexual partner of an HIV-infected man in the last 6 months 2. Partner of a newly-diagnosed person with acute or recent HIV infection 3. Seeking HIV testing because of symptoms of acute retroviral infection	
Able to provide contact information for themselves and two or more other people who would know their whereabouts during the study period	
Ambulatory performance status ≥ 80 on the Karnofsky scale.	

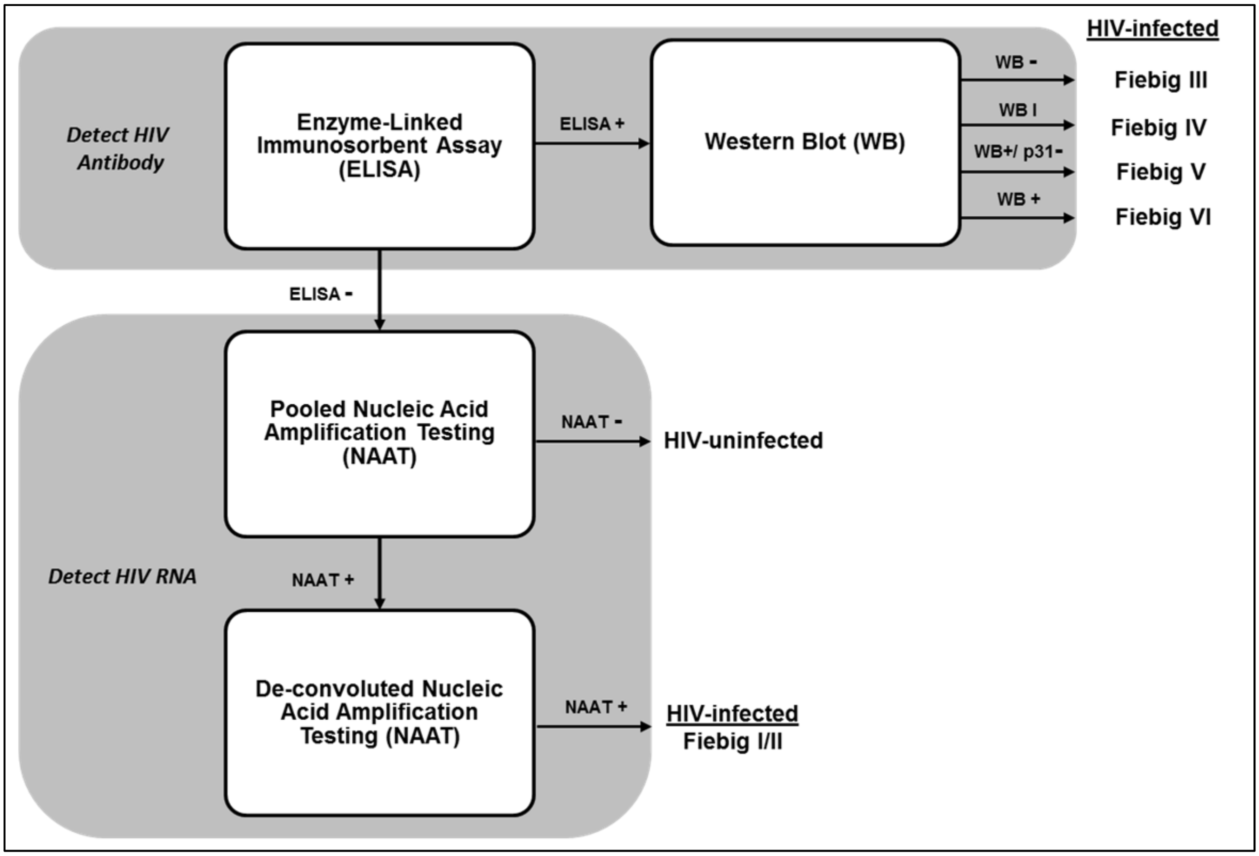

Figure A-3. Algorithm for determining likely time of HIV acquisition based on Fiebig Stages.