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Contextualizing risk: examining the impact of substance use on HIV transmission dynamics among a cohort of men who have sex with men

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Contextualizing risk: examining the impact of substance use on HIV transmission dynamics among a cohort of men who have sex with men

A dissertation submitted in partial satisfaction of the requirements for the degree of Doctor of Philosophy in Health Policy and Management

by

Cheríe Savine Blair

2021

ABSTRACT OF THE DISSERTATION

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Doctor of Philosophy in Health Policy and Management

University of California, Los Angeles, 2021

Professor Jack Needleman, Chair

Men who have sex with men (MSM) are disproportionately affected by the HIV epidemic and represent 70% of incident HIV cases in the United States, despite constituting 3.9% of the population. These disparities are particularly relevant in the context of the burgeoning stimulant use epidemic, as stimulant use is associated with increased HIV and sexually transmitted infection (STI) prevalence among MSM. Given these contexts, this dissertation consists of three studies that explored the impacts of stimulant use on HIV/STI transmission dynamics among a diverse cohort of MSM in Los Angeles, California. Study one examined the relative contributions of methamphetamine use, depression, and sexual risk behavior on rectal STIs using path analysis. Study two consisted of a latent class analysis to determine risk behaviors associated with patterns of sexualized stimulant and alcohol use. Study three used machine learning techniques, specifically least absolute shrinkage and selection operator (lasso) and elastic net, for variable selection to determine characteristics associated with increased stimulant use and whether these factors differed in relation to HIV status.

This dissertation demonstrated that the factors surrounding stimulant use and HIV/STI transmission dynamics are both nuanced and complex. Our findings reinforced the known associations between syndemic health conditions, such as depression, unstable housing, polysubstance use, and transactional sex, with stimulant use and sexual risk behaviors. However, our results highlight that the factors and contexts surrounding stimulant use and sexual risk behaviors likely differ between MSM subpopulations. For example, Black/Latinx MSM who engaged in stimulant use were more likely to experience syndemic health conditions (e.g., STIs, depressive symptoms) than their Black/Latinx counterparts who did not engage in sexualized stimulant use. Similar differences in stimulant use patterns were observed based on HIV status. Among MSM living with HIV, increased stimulant use correlated highly with reported co-substance use whereas sexual risk behaviors and sexual partnership contexts were correlated with increased stimulant use among HIV-negative MSM. This dissertation demonstrates that the contexts and factors which contribute to stimulant use patterns likely differ between MSM subpopulations and suggest that these differences should be accounted for in the design of HIV prevention and treatment interventions.

The dissertation of Cheríe Savine Blair is approved.

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Chapter 1.

Introduction to the Dissertation

Men who have sex with men (MSM) are disproportionately affected by the HIV epidemic and account for approximately 70% of incident HIV cases in the United States, despite representing only 3.9% of the U.S. population.[1, 2] MSM of color experience significant disparities with regard to HIV, representing 45% of new HIV diagnoses.[1] Furthermore, while overall HIV incidence among MSM has decreased by 7% since 2014, HIV incidence among MSM of color has remained stable,[3] suggesting that HIV prevention efforts are either not reaching certain high-risk groups or that the underlying mechanisms that contribute to ongoing HIV transmission are not being adequately addressed by current efforts. To bridge this gap, this dissertation seeks to understand factors that contribute to ongoing HIV transmission among MSM by evaluating the impact of sexually transmitted infections (STIs), risk behavior, and stimulant use on HIV transmission dynamics among a longitudinal cohort of MSM in Los Angeles, California who are living with or at high-risk for HIV.

Sexual Risk Behavior and STIs

Sexual risk behavior, STIs, and substance use are considered to be key factors that contribute to ongoing HIV transmission among MSM.[4-7] Condomless anal intercourse, particularly receptive condomless anal intercourse, represents a dominant epidemic driver for HIV within sexual networks that comprise MSM.[8-10] Receptive anal intercourse has an extremely high per-act and per-partner probability for HIV transmission, which is 18 times higher than vaginal intercourse.[11] This high transmission probability is due to the efficient transmission of HIV across the rectal mucosa, which contains high numbers of CD4 T-lymphocytes and dendritic cells that are key target cells for HIV.[12] Furthermore, unlike heterosexual networks, MSM can engage in both insertive (high risk for

transmission) and receptive (high risk for acquisition) anal intercourse, which contributes to the rapid and efficient spread of HIV within sexual networks that comprise MSM.[9, 13]

In addition to condomless anal intercourse, STIs, particularly rectal gonorrhea/chlamydia (GC/CT) and syphilis, are independently associated with HIV transmission.[7, 14-17] STI prevalence in the U.S. has been steadily rising in recent years, with the U.S. experiencing an increase of 19%, 63%, and 71% in prevalence of chlamydia, gonorrhea, and infectious syphilis, respectively, since 2014.[18] STIs promote HIV transmission through two routes: increased susceptibility of the HIV-uninfected person and increased viral shedding among individuals living with HIV.[19-21] Rectal STIs result in rectal mucosal inflammation, disrupting mucosal epithelial integrity and increasing risk for HIV infection.[22, 23] This risk is potentiated by abundant levels of CD4 T-lymphocytes and dendritic cells, key target cells for HIV, that are in the rectal mucosa.[12] These risks are compounded by the higher prevalence of mental health comorbidities, particularly anxiety and depression, among MSM, thought to be due in part to minority stress.[24-26] Higher levels of anxiety and depression symptomatology have been associated with poor linkages to healthcare, comorbid substance use disorders, antiretroviral therapy non-adherence, and increased sexual risk behavior (such as condomless anal intercourse).[24, 27, 28]

Stimulant Use and HIV Transmission Among MSM

Prevalence of methamphetamine use is substantially higher among MSM (5.9% among HIV-negative and 12.3% among MSM living with HIV) than the general population (0.7%),[29, 30] with a 707% increase in methamphetamine-related mortality in Los Angeles County in the past decade.[31] Methamphetamine has ingrained itself into the MSM party scene and is frequently consumed at sex clubs, circuit parties (music and dance parties that cater to gay- and bisexually-identified MSM), and bath houses.[32-34] Furthermore, methamphetamine use is a significant risk factor for HIV/STI transmission and is temporally related to sexual risk-taking, such as receptive condomless anal

intercourse with HIV serodiscordant partners, increased number of sexual partners, and exchange sex.[35-38]

Methamphetamine-using MSM have up to 7 times higher HIV incidence than MSM without methamphetamine use.[39] Recent stimulant use was attributed to 32.7% of HIV seroconversions among MSM in a multi-institutional cohort.[40] Bacterial STIs (e.g., GC/CT and syphilis) are independently associated with HIV seroconversion[7, 41] and linked to methamphetamine use, driven in part by increased sexual risk behavior and high-risk sexual networks.[6, 42, 43] Further compounding HIV transmission risk, methamphetamine use is associated with impaired HIV virologic control due to antiretroviral therapy non-adherence,[44, 45] impaired immune cell function,[46-48] enhanced intracellular HIV replication[49, 50] and cell entry.[51, 52] Lack of HIV virologic control among methamphetamine-using MSM living with HIV, combined with increased HIV/STI prevalence within their sexual networks, contributes to ongoing HIV/STI transmission among within these subpopulations.

These contexts govern the contribution of stimulant use to the ongoing HIV/STI epidemic among MSM, yet prior research consists predominantly of association studies that have either linked stimulant use with risk behaviors or have been cross-sectional in design.[37, 53-58] Given that stimulant use is associated with increased HIV/STI prevalence among MSM, it is importantly pressing to study the impacts of stimulant use on the biological and behavioral factors that drive HIV/STI transmission among MSM. This dissertation seeks to build upon this knowledge by evaluating the effects of stimulant use on HIV/STI transmission dynamics among a cohort of predominantly MSM of color in Los Angeles, California.

Dissertation Aims

Despite significant advances in the fields of antiretroviral therapy and biomedical HIV prevention, disparities in relation to HIV prevention and treatment remain. These disparities are

particularly relevant in the Western U.S., where the drug linked most with HIV/STI transmission is methamphetamine, and the population impacted the most by HIV/STIs is MSM.[29, 59] Given these contexts, it is important to understand the influence of stimulant and substance use on HIV/STI transmission dynamics, which can be used to inform targeted HIV prevention interventions and effective public health programming tailored for MSM subpopulations that are most affected by the epidemic. This dissertation seeks to develop this knowledge through three distinct yet related projects 1) Examining the relative contributions of methamphetamine use, depression, and sexual risk behavior on rectal gonorrhea/chlamydia; 2) Evaluating risk behaviors associated with patterns of sexualized stimulant and alcohol use; and 3) Comparing factors associated with increased stimulant use in relation to HIV status using a machine learning and prediction modelling approach.

The first aim of this dissertation examined the relative contributions of methamphetamine use, depression, and sexual risk behavior on rectal gonorrhea/chlamydia. Many studies have demonstrated that methamphetamine use, mental health, and sexual risk behaviors are associated with an STI diagnosis. However, the relative contributions of these different factors on STI diagnosis are less well understood, particularly when evaluated together. As mental health, methamphetamine use, and sexual risk behaviors are all significant drivers of STI transmission, it is important to understand the relative contributions of these factors to better contextualize the HIV/STI epidemic among MSM. This study used path analysis to evaluate the relative contributions of depression, methamphetamine use, and sexual risk behaviors on STI diagnosis, while also taking secondary contributors into account, such as HIV status, and sociodemographics. Findings from this analysis could be used to understand which factors contributing to HIV/STI transmission need to be prioritized in public health programming efforts.

The second aim of this dissertation evaluated risk behaviors associated with patterns of sexualized stimulant and alcohol use. Substance use surrounding sexual encounters or during sexual

activity is common among MSM and linked with HIV/STI transmission. However, patterns of substance use have regional variation and change with time. Furthermore, there is a paucity of data examining discrete substance use patterns, particularly in the context of sexual acts. This study seeks to bridge this gap by evaluating patterns of stimulant and alcohol use during specific sexual acts as well as characteristics associated with these discrete patterns. This goal was accomplished by using latent class analysis to identify latent classes of individuals based on their patterns of sexualized stimulant and alcohol use. As risk for HIV/STI acquisition differs according sexual practice (i.e., receptive oral intercourse does not confer the same HIV/STI risk as receptive anal intercourse), it is increasingly important to understand patterns sexual activities that occur within the context of sexualized drug use in order to appropriately conceptualize the impact substance use has on sexual risk and, consequently, HIV/STI transmission among MSM.

The third aim of this dissertation compared factors associated with increased stimulant use in relation to HIV status using a machine learning and prediction modelling approach. Stimulant use is substantially higher among MSM compared to the U.S. general population, with stimulant use, particularly methamphetamine, representing one of the predominant factors contributing to the ongoing HIV epidemic. While stimulant use is linked to risky sexual behaviors, evidence suggests that the stimulant and HIV epidemics among MSM are likely to be complex, nuanced and that contexts surrounding stimulant use may differ according to HIV status. However, data explicitly evaluating factors contributing to increased stimulant use according to HIV status is limited. This study seeks to bridge this gap by evaluating differences in factors associated with reported increases in stimulant use frequency and risk behaviors according to HIV status. This analysis utilized machine learning techniques, specifically least absolute shrinkage operator (lasso) and elastic net, for variable selection and prediction modelling to evaluate factors associated with interval increases in self-

reported stimulant use among a longitudinal cohort of MSM. Additionally, a sub-analysis was conducted to evaluate differences in factors associated with increased stimulant use by HIV status.

Motivations and Contributions to the Field

This dissertation has two primary goals. The first goal of the dissertation is to utilize methods, specifically path analysis, latent class analysis, and machine learning techniques, to examine the influence of stimulant use on HIV transmission dynamics within a longitudinal cohort of MSM and to evaluate the extent to which these methods can be used to examine these constructs. The second goal of this dissertation is to provide a more nuanced understanding of the contributions that stimulant use has on HIV/STI transmission dynamics among MSM. This research will make significant contributions to the literature in multiple ways. The analyses contained within this dissertation focuses on subpopulations of MSM that face the largest disparities regarding HIV/STI transmission, and that should be prioritized in public health programming efforts. This dissertation is particularly relevant in the context of the Western U.S., where the substance linked most with HIV/STI transmission is methamphetamine and the population impacted the most by HIV/STIs is MSM, both of which are the focus of this PhD dissertation.[29, 59] This dissertation will utilize a dataset that comprises a longitudinal cohort of racially/ethnically diverse MSM in Los Angeles, California, which represents a subpopulation of MSM that faces substantial disparities involving HIV/STIs. These analyses will utilize longitudinal data, which will greatly add to the literature, as the current body of knowledge evaluating these constructs have substantially been cross-sectional in design. Furthermore, this dissertation will take a more nuanced approach to the contributions of stimulant use on the HIV/STI epidemic by evaluating the direct and indirect effects of theoretical constructs on HIV/STI transmission, such as substance use, mental health, risk behaviors, and sociodemographics. These findings will add to the current body of knowledge, as research has predominantly consisted of association studies that have either linked stimulant use with risk

behaviors or have been cross-sectional in design.[37, 53-58] Collectively, findings from this dissertation can provide useful knowledge that can be used to inform HIV prevention and HIV/STI programming efforts.

Chapter 2.

Data Source

The analyses contained in this dissertation utilized data from the Men Who Have Sex with Men and Substance Use Cohort at UCLA Linking Infections, Noting Effects (mSTUDY). The mSTUDY is a NIDA-funded (U01 DA036267; MPIs: Gorbach and Shoptaw) longitudinal cohort of predominantly Black/African American and Latinx/Hispanic MSM. Half of participants were selected for HIV-positive status and half were selected for active substance use. Secondary data from study visits that occurred between August 2014 (study inception) until December 2020 were used for this dissertation.

The mSTUDY Cohort

The mSTUDY is an ongoing longitudinal cohort study that is designed to evaluate the immunological and epidemiological impacts of substance use on HIV transmission dynamics among minority MSM in Los Angeles. The cohort consists predominantly of Black/African American and Latinx/Hispanic MSM. Participants were selected to include half MSM living with HIV and half HIV-negative MSM in the cohort. Additionally, half of the participants were selected for active substance use. Participants living with HIV were recruited from HIV and sexual health clinics associated with the Los Angeles LGBT Center, which provides a broad spectrum of clinical and community resources for the lesbian, gay, and transgender community in Los Angeles. HIV-negative MSM were recruited from the UCLA Vine Street Clinic (a community-based university research clinic) through community flyers and online advertisements. Inclusion criteria for the mSTUDY includes: 18-45 years of age at study enrollment, born male, reporting unprotected anal intercourse with a man in the past 6 months (if HIV-negative), capable of providing informed consent, and willing/able to return to the study every 6 months to complete study-related activities including questionnaires, clinical assessments, and biological specimen collection. The cohort began

enrollment in August 2014 and is ongoing. There are approximately 577 participants enrolled in the mSTUDY and recruitment is ongoing to replace participants that are lost to follow-up.

Study visits in this dataset occurred every 6 months. At each study visit, participants underwent physical examination, laboratory testing, and completion of a computer-assisted self-interview survey that collected sociodemographic data, information surrounding sexual behaviors and practices, and self-reported substance use. Urine samples as well as rectal and pharyngeal swabs were collected and tested for GC/CT infection with nucleic acid amplification testing (NAAT) technology (Aptima Combo 2, GenProbe, San Diego, CA). Urine samples were collected for toxicology screening for recent substance use. Blood samples were collected for HIV and syphilis testing. Syphilis testing was conducted using the rapid plasma reagin test (RPR) with confirmatory testing performed with the *Treponema pallidum* particle agglutination test (TPPA). HIV testing among HIV-negative participants was conducted with antibody testing (ELISA) with Western blot confirmation. Primary and secondary syphilis was defined following the Centers for Disease Control determination following positive test results and confirmation from the local health department. The study questionnaire, physical examination, and laboratory testing were completed at all follow-up visits. Participants were compensated for their time ($75 per completed visit) and STI testing results were made available to participants. Study personnel assisted with notifying participants of their test results and facilitated linkages to care for positive test results. All participants provided written informed consent before enrollment in the study. The mSTUDY has received IRB approval from the Office of the Human Research Protection Program (OHRPP) at UCLA for primary data collection (#18-000876). All secondary data analyses contained in this dissertation were approved by the UCLA OHRPP (#20-002026).

Study Population Descriptive Statistics

The study population for these aims will contain all participants and study visits included in the mSTUDY cohort to date. However, analyses that involve STI screening results involved study visits from 8/2014-3/2020, as study visits were converted to remote visits due to the COVID-19 pandemic, limiting the study's ability to collect specimens for STI screening. Data used in the analyses for this dissertation involved demographic and behavioral data as well as HIV/STI screening data that were collected at study visits. Table 2.1 demonstrates baseline descriptive statistics for the 557 participants that have been enrolled in the cohort to date who had completed 2,961 study visits between 8/2014-3/2020. Median range of completed follow-up visits was 5 per participant (range 1-12). Median age of participants was 30 years old (interquartile range [IQR] 26-37). Most participants identified as Latinx/Hispanic 49.0%; n=273) or Black/African American (40.6%; n=226) while 7.0% of participants identified as White/Caucasian (n=39) and 3.4% identified with other racial/ethnic groups (n=31). Many participants had either completed high school (36.7%; n=202) or had attended college (45.2%; n=249). Most participants (67.7%) had an income less than $10,000 annually.

Table 2.2 shows visit-level STI screening results and sexual risk behaviors for study visits completed prior to March 2020. Participants tested positive for any site (rectal, pharyngeal, genital) gonorrhea and/or chlamydia at 14.3% (n=423) visits and tested positive for syphilis at 4.1 (n=120) visits. Participants reported having a concurrent sexual partner at 39.7% (n=1,056) visits and reported having participated in transactional sex at 16.7% (n=473) of visits. Figure 2.1 demonstrates frequency of last 6-month substance use that was reported across all study visits. Overall, alcohol was the most frequently reported substance, followed by cannabis, methamphetamine, then poppers (e.g., amyl nitrite, butyl nitrite). Any methamphetamine use was reported at 37.3% (n=1,103) and any cocaine use was reported at 20.1% (n=593) of study visits. Approximately 68.2% of participants (n=375) reported any stimulant use (methamphetamine or cocaine) use at a minimum of one study

visit. Among the 375 participants who reported stimulant use at a minimum of one study visit, 56.3% were living with HIV and 43.7% were HIV-negative.

Tables and Figures

Table 2.1 Baseline characteristics of participants in the mSTUDY cohort stratified by HIV status, August 2014-March 2020 (n=557)

	HIV-Negative (n=280) n (%)	Living with HIV (n=277) n (%)	Total n (%)
Study visits completed[a]	5 (2-7; 1-12)	6 (3-8; 1-11)	5 (3-8; 1-12)
Age[b]	27.5 (24-33)	34 (29-39)	30 (26-37)
Race/Ethnicity			
White/Caucasian	16 (5.7%)	23 (8.3%)	39 (7.0%)
Black/African American	115 (41.1%)	111 (40.1%)	226 (40.6%)
Latinx/Hispanic	136 (48.6%)	137 (49.5%)	273 (49.0%)
Other	13 (4.6%)	6 (2.2%)	19 (3.4%)
Education			
Less than High School	27 (9.6%)	42 (15.5%)	69 (12.5%)
High School	100 (35.7%)	102 (37.6%)	202 (36.7%)
Undergraduate/Some college	136 (48.6%)	113 (41.7%)	249 (45.2%)
Graduate	17 (6.1%)	14 (5.2%)	31 (5.6%)
Income			
Less than $10k annually	154 (61.6%)	185 (73.7%)	339 (67.7%)
$10k-$30k annually	62 (24.8%)	49 (19.5%)	111 (22.2%)
Over $30k annually	34 (13.6%)	17 (6.8%)	51 (10.2%)

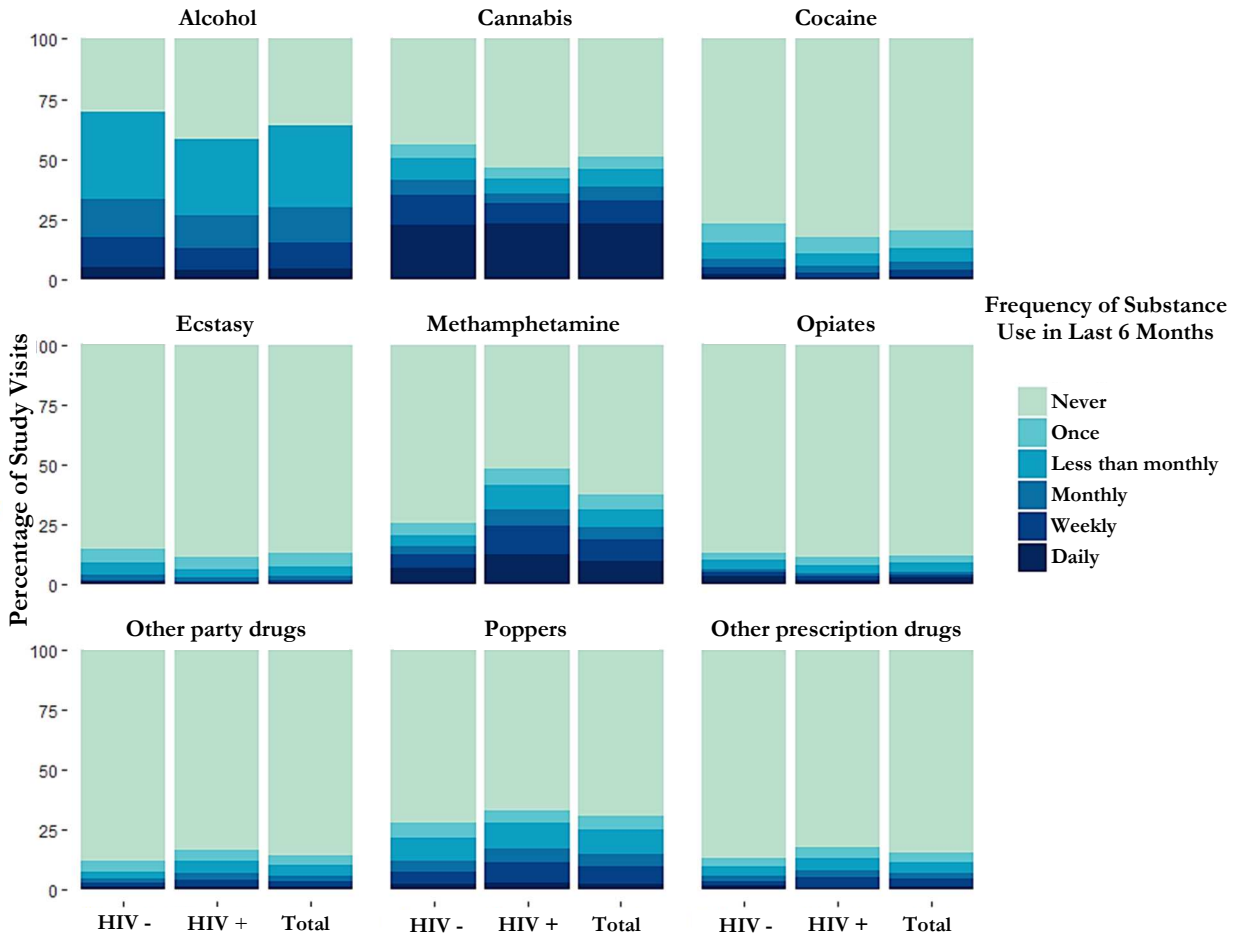
[a]Median (IQR; range); [b]Median (IQR)

Table 2.2 Visit-level STI screening results and self-reported sexual risk behaviors among participants in the mSTUDY cohort stratified by HIV status August 2014-March 2020 (n=2,961 study visits)

	HIV-Negative n=1,396 n (%)	Living with HIV n=1,572 n (%)	Total n (%)
STI Screening Results			
Gonorrhea/Chlamydia[a]			
Negative	1,216 (87.2%)	1,322 (84.4%)	2,538 (85.7%)
Positive	179 (12.8%)	244 (15.6%)	423 (14.3%)
Syphilis			
Negative	1,366 (98.2%)	1,475 (93.9%)	2,841 (96.0%)
Positive	25 (1.8%)	95 (6.1%)	120 (4.1%)
Sexual Risk Behaviors			
Number male partners[b,c]	3 (1-6; 0-500)	2 (1-6; 0-1,200)	2 (1-6; 0-1,200)
Number RAI partners[b,c]	1 (0-3; 0-400)	2 (1-5; 0-1,100)	1 (1-4; 0-1,100)
Sexual concurrency[b]			
No	709 (56.2%)	892 (63.9%)	1,601 (60.3%)
Yes	553 (43.8%)	503 (36.1%)	1,056 (39.7%)
Transactional sex (last 3 months)			
No	1,112 (83.7%)	1,244 (82.9%)	2,356 (83.3%)
Yes	216 (16.3%)	257 (17.1%)	473 (16.7%)

[a]Any site (urethral, pharyngeal, rectal); [b]Last 6 months; [c]Median (IQR; range); RAI = receptive anal intercourse

Figure 2.1 Self-reported last 6-month substance use frequency stratified by HIV status, mSTUDY August 2014-March 2020 (n=2,961 study visits)



Cocaine = cocaine powder, crack cocaine; Opiates = heroin, prescription opiates, fentanyl; Other party drugs = GHB, special K, mushrooms, LSD; Poppers = amyl nitrite, butyl nitrite; Other prescription drugs = erectile dysfunction medications, benzodiazepines

Chapter 3.

Examining the relative contributions of methamphetamine use, depression, and sexual risk behavior on rectal gonorrhea/chlamydia among a cohort of men who have sex with men in Los Angeles, California

Abstract

Background: Methamphetamine use, sexual risk behaviors, and depression are thought to contribute to ongoing HIV and sexually transmitted infection (STI) disparities among men who have sex with men (MSM). However, the relative contributions of these effects longitudinally are not as well understood. This analysis aimed to identify the longitudinal effects of methamphetamine use, depression, and sexual risk behaviors on rectal STIs.

Methods: This analysis used visit-level data from a longitudinal cohort of MSM, half with HIV and half with substance use, in Los Angeles, California. From 8/2014-3/2020, participants completed follow-up visits every 6 months and underwent screening for rectal gonorrhea/chlamydia (GC/CT) and completed surveys on depressive symptoms, number of receptive anal intercourse (RAI) partners, and methamphetamine use frequency. Structural equation modelling was used to conduct a path analysis with a cross-lagged panel design to identify the relative contributions of methamphetamine use and depression on number of RAI partners and number of RAI partners on rectal GC/CT across time. Separate path models were created stratified based on HIV status to evaluate differences in paths based on HIV status.

Results: 557 MSM across 6 study visits (3 years) were included for a total of 2,437 observations. Methamphetamine use and depressive symptoms were positively associated with number of RAI partners which was positively associated with rectal GC/CT. Past depressive symptoms,

methamphetamine use, and number of RAI partners were associated with future depressive symptoms, methamphetamine use, and RAI partners, respectively. When stratified by HIV status, depressive symptoms were positively associated with RAI partners for HIV-negative MSM but was not associated for MSM living with HIV.

Conclusions: Factors and patterns which contribute to risk behaviors may differ according to HIV status. Our findings demonstrate the potential utility of combined treatment and prevention efforts that link screening and treatment of stimulant use and depression with HIV/STI prevention and treatment.

Introduction

Sexual risk behavior, sexually transmitted infections (STIs), and substance use are considered to be key factors that contribute to ongoing HIV transmission among men who have sex with men (MSM).[4-7] This observation is particularly true in the context of methamphetamine use, which has been independently associated with HIV/STI transmission among MSM and is driven by risky sexual behaviors occurring within high-risk sexual networks.[6, 42, 43] Prevalence of methamphetamine use is highest in the Western U.S. with past year methamphetamine use reported among 1.2% of individuals over 18 years old, compared to 0.7% prevalence reported nationally.[60] In the Western U.S., methamphetamine is linked to more HIV/STI transmission than any other substance.[29, 59] Among MSM, methamphetamine is often used in sexual contexts and socially, leading to increased sexual risk behaviors and risk for HIV/STI transmission.[35, 42] Methamphetamine use among MSM is further compounded by the high prevalence of mental health comorbidities that are experienced by this population, with MSM experiencing 17% higher rates of depression compared to heterosexual men, thought to be due in part to minority stress.[24-26, 61] Higher levels of depression symptomatology have been associated with poor linkages to healthcare, comorbid substance use disorders, antiretroviral therapy non-adherence, and increased sexual risk behaviors (such as condomless anal intercourse).[24, 27, 28]

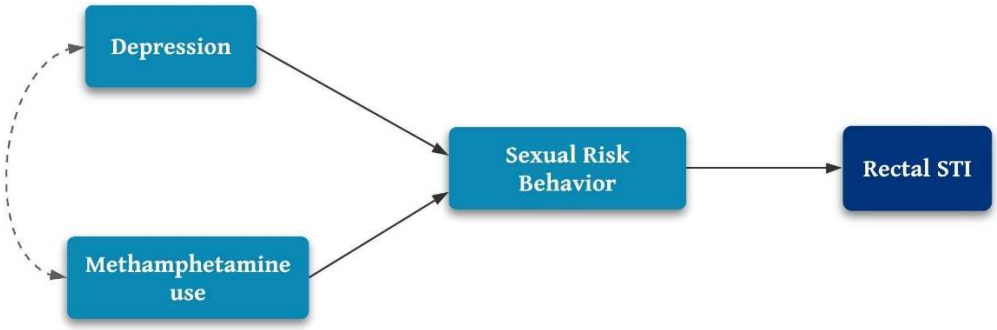
While the associations of methamphetamine use, sexual risk behaviors, and mental health comorbidities with increased HIV/STI transmission have been well-established in the literature, the relative contributions of these factors are less well understood, particularly when considered together. Furthermore, prior research evaluating these constructs has predominantly been cross-sectional in nature.[62-64] As mental health comorbidities (especially depression) and methamphetamine use disorder are often chronic conditions that contribute to sexual risk behavior and thus HIV/STI transmission among MSM, it is important to understand the relative contributions of these factors

longitudinally in order to better contextualize the HIV/STI epidemic and to develop targeted, efficacious HIV/STI prevention interventions. To address this gap, this study will utilize path analysis with a cross-lagged panel design to understand the relative contributions of methamphetamine use, depression, and sexual risk behaviors on rectal gonorrhea/chlamydia (GC/CT) infection among a high-risk cohort of MSM. A strength of this analysis is that it will utilize data from a relatively young cohort of MSM, representing a population that is at highest risk for HIV/STI transmission, with individuals living with and without HIV – allowing for consideration of contributions to both transmission and acquisition of HIV. Findings from this analysis will help contextualize which contributors to HIV/STI transmission need to be prioritized in public health programming efforts.

Conceptual Model

Figure 3.1 demonstrates the conceptual model, which demonstrates our cross-sectional framework that was incorporated into the cross-lagged panel model. Theoretical relationships between constructs are described below.

Figure 3.1 Conceptual model demonstrating relationships between depression, methamphetamine use, and sexual risk behavior on rectal STIs



Depression and methamphetamine use. While the link between depression and methamphetamine use within the literature is well-established, the directionality of this relationship is unclear.[65-67] The uncertainty of directionality between depression and methamphetamine use is

reflected in the conceptual model by allowing depression and methamphetamine use to covary. Chronic methamphetamine use is linked with depression, possibly due to reductions in dopamine stores and damage to serotonin and dopamine nerve terminals that result from chronic use.[68, 69] Methamphetamine has also been demonstrated to induce depressive symptoms, which tend to be more severe with methamphetamine compared to other substances.[70-72] Conversely, pre-existing depression may predispose individuals to use methamphetamine. In a large survey of adult methamphetamine users, 41.6% of participants endorsed a history of depression.[73] Studies have demonstrated that increased severity of depressive symptoms is associated with higher frequency of methamphetamine use and greater risk of relapse.[74, 75] Furthermore, treatment of concomitant depression has been shown to prevent relapse among methamphetamine using individuals.[76]

Depression and sexual risk behavior. Multiple studies have demonstrated that depression is associated with increased sexual risk behavior among MSM, though results have been mixed.[77-81] It has been hypothesized that MSM may utilize sexual intercourse and sensation-seeking (i.e., risky sexual behavior) as a method to mitigate the negative symptoms associated with depression.[27, 82] Furthermore, MSM with depressive symptoms may utilize avoidant coping to manage their symptoms, which has been associated with condomless intercourse with serodiscordant partners.[83, 84] Depressive symptoms may also result in distortions in perceived social norms as well as lower self-efficacy with regard to HIV preventative behaviors, resulting in increased sexual risk behaviors.[85, 86]

Methamphetamine and sexual risk behavior. Methamphetamine use is associated with increased risk behaviors for HIV/STI acquisition, including group sex, sexual concurrency, condomless intercourse with non-primary partners and partners of unknown HIV status, and increased number of sexual partners.[35, 38, 42, 53, 87] Furthermore, methamphetamine use has been temporally related to increased sexual risk-taking, with a recent longitudinal study demonstrating that sexual risk behavior increased following initiation of methamphetamine use.[37] The associations

between methamphetamine use and sexual risk behaviors are thought to be due, in part, to the collective psychological and physiological effects of methamphetamine, which results in increased libido, impulsivity, and sexual stamina as well as decreased inhibitions.[88] While these effects often result in the frequent consumption of methamphetamine in sexualized settings among MSM,[34, 88] acute intoxication with methamphetamine can also impair negotiations with sexual partners such as the ability to provide consent as well as condom use.[89, 90]

Sexual risk behavior and STIs. Sexual risk behaviors, particularly condomless receptive anal intercourse (RAI) confers an increased risk of HIV/STI transmission.[11, 91] With the advent of HIV pre-exposure prophylaxis (PrEP) and treatment as HIV prevention (TasP), condom use among MSM has declined, which has contributed to increased STI incidence within this population.[92-94] Rectal STIs are of particular public health importance as they result in increased risk of HIV transmission.[7, 16]

Methods

Data Source

We analyzed data collected as part of the Men Who Have Sex with Men and Substance Use Cohort at UCLA Linking Infections, Noting Effects (mSTUDY; U01 DA036267; MPIs Gorbach and Shoptaw). The mSTUDY is a longitudinal cohort of predominantly Black/African American and Latinx/Hispanic MSM that is designed to evaluate the impact of substance use on HIV transmission dynamics among minority MSM in Los Angeles. The cohort consists of half MSM living with HIV and half with active substance use at enrollment. HIV-negative MSM were recruited from the UCLA Vine Street Clinic (a community-based university research clinic) through community flyers and online advertisements. Participants living with HIV were recruited from sexual health and HIV clinics associated with the Los Angeles LGBT Center, which provides a broad spectrum of clinical and community resources for the lesbian, gay, and transgender

community in Los Angeles. Inclusion criteria for the mSTUDY cohort were: 1) 18-45 years old at study enrollment, 2) born male, 3) condomless anal intercourse with a man in past 6 months (if HIV-negative). Participant enrollment for the mSTUDY started in August 2014 with participants having follow-up every six months. At the time of this analysis, 557 MSM have been enrolled in the mSTUDY cohort. This analysis consists of study visits that occurred between August 2014 and March 2020 from all 557 MSM across 6 study visits (3 years) for a total of 2,437 observations. Not all participants were followed across all 6 study visits as some participants were enrolled within the past 3 years (recruitment is ongoing to replace participant dropout) or due to participant dropout.

Study Procedures

Following written informed consent, participants underwent clinician interview, specimen collection (rectal and pharyngeal swabs and urine) for STI testing, substance use testing (data not reported here), and completion of a computer-assisted self-interview survey at each study visit that collected sociodemographic data as well as information regarding sexual risk behaviors, depression symptoms, and substance use. STI screening was conducted at each visit using rectal swabs that were tested for GC/CT infection with nucleic acid amplification testing (NAAT) (Aptima Combo 2, GenProbe, San Diego, CA). HIV screening used antibody testing (ELISA) with Western blot confirmation. STI/HIV testing results were made available to participants, and study personnel assisted with notifying participants of their test results and facilitated linkages to care for positive test results.

Measures

Sociodemographics. Age at baseline visit was reported in years and is continuous. Participants self-reported their race/ethnicity, and options included American Indian or Alaskan Native, Asian, Asian Indian, Black or African American, Native Hawaiian or Pacific Islander, White, Hispanic or Latinx or Spanish, or other race. As this cohort consisted predominantly of

Black/African American and Latinx/Hispanic MSM, this variable was trichotomized to Black, Latinx, and non-Black/non-Latinx.

HIV status. At enrollment, participants underwent HIV screening. HIV status is a dichotomous variable (living with HIV or HIV-negative).

Depression. Depressive symptoms were measured using the Center for Epidemiological Studies – Depression (CESD) scale. The CESD is a validated 20-item measure that asks participants to rank how often they have experienced depressive symptoms, such as feelings of loneliness, sadness, or hopelessness as well as having restless sleep or poor appetite.[95] Response options ranged from 0 to 3 for each item (0 = "rarely or none of the time," 1 = "some or little of the time," 2 = "moderately or much of the time," 3 = "most or almost all the time"). Scores ranged from 0-60 with higher scores indicative of more severe depressive symptoms. Cutoff scores of 16 or greater are used to identify individuals who are at risk for clinical depression and the measure has been demonstrated to have good sensitivity and high internal consistency with a Cronbach's alpha of 0.85-0.90.[95, 96] This variable was dichotomized with a variable cutoff of 23, as a cutoff of 23 was determined to be more optimal to evaluate clinical depression risk among individuals living with HIV.[97] Depressive symptoms were dichotomized to positive and negative CESD score (< 23 or ≥ 23).

Methamphetamine use. Methamphetamine use in past six months was adapted from the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST).[98] Participants were asked the question "In the past 6 months, how often have you used methamphetamine (speed, crystal meth, ice, etc.)?". Response options were on an ordinal scale (0 = "None," 1 = "Once," 2 = "Less often," 3 = "Monthly," 4 = "Weekly," and 5 = "Daily"). As using an ordinal scale assumes equal, one-point differences between response options (e.g., differences between daily and weekly use are treated as a one-point difference when daily methamphetamine use may actually be 7 times higher than weekly methamphetamine use), a sensitivity analysis was conducted where the number of

receptive anal intercourse (RAI) partners was regressed on methamphetamine use separately as a ordinal variable and as a categorical variable with 5 levels (data not shown). When methamphetamine use was evaluated categorically, it revealed a monotonic increase with the different levels of methamphetamine use. However, there was not a standard difference between the different levels of categorical methamphetamine use, suggesting that weighting different levels of methamphetamine use would not add much improvement. Additionally, when comparing the regression models with categorical and continuous methamphetamine use, the R^2 between the models were similar, suggesting that treating methamphetamine as categorical variable would not provide much improvement in precision. As such, an ordinal scale was ultimately selected 1) to maintain fidelity with how the question was worded in the original survey and 2) because structural equation modelling, which does not allow for categorical data, was used to create the path models.

Sexual risk behavior. As our outcome variable was rectal GC/CT infection, sexual risk behavior was measured by self-reported number of receptive anal intercourse (RAI) partners in past 6 months (continuous). As this variable was highly right skewed (median 1; interquartile range [IQR] 0-3; range 0-1,100 partners), this variable was transformed using Winsorization to a maximum value of 15 (95^{th} percentile of reported RAI partners).

Rectal GC/CT. Participants underwent screening for rectal GC/CT at each study visit. Positive rectal GC/CT was defined as positive screening for rectal gonorrhea and/or chlamydia based on NAAT testing. Rectal GC/CT is a dichotomous variable (positive versus negative screen).

Statistical Analysis

The purpose of this analysis was to evaluate how methamphetamine use, sexual risk behaviors, and depressive symptoms contribute to positive rectal GC/CT longitudinally. Descriptive statistics including median, range, and frequency distributions were utilized to characterize the study sample and predictors of interest. As the relationship between depressive symptoms and

methamphetamine use on rectal GC/CT is mediated by sexual risk behavior, we created a cross-lagged panel mediation model adapted from Selig & Preacher using a structural equation modeling (SEM) approach, given the longitudinal nature of the data.[99] A strength of the cross-lagged panel mediation model is that it can be used to evaluate both interindividual changes in predictors and their downstream effects over time, such as the effect of past methamphetamine use on future methamphetamine use or past depressive symptoms on future sexual risk behaviors.[99, 100] Furthermore, the use of a cross-lagged panel mediation model using longitudinal data allows us to test the relationships and mediation paths between variables in a more rigorous manner and to control for time-varying confounding compared to if the path model was created using a cross-sectional design.

The cross-lagged panel mediation model (Figure 3.2) was developed from our cross-sectional conceptual model. Lagged paths across timepoints were used to evaluate each construct as a function of the same construct at a previous timepoint (e.g., a path from methamphetamine use at Time 1 (T1) to methamphetamine use at Time 2 (T2) or depressive symptoms at T1 to number of RAI partners at T2). These lagged paths were used to evaluate the interindividual changes in predictors and to evaluate the effect of past behaviors on future behaviors (e.g., the effect of past methamphetamine use on future methamphetamine use). Contemporaneous paths (e.g., at the same timepoint) according to our cross-sectional conceptual model were created to evaluate the paths between methamphetamine use and sexual risk behavior, depressive symptoms and sexual risk behavior, and sexual risk behavior and rectal GC/CT at each timepoint.

Of note, our cross-lagged panel model contains a contemporaneous (i.e., at the same timepoint) path in addition to a lagged path from sexual risk behavior to rectal GC/CT, where published examples of cross-lagged panel models typically have a lagged path from the mediator variable (sexual risk behavior) to the outcome variable (rectal GC/CT) only.[99, 100] The rationale for

this was that rectal GC/CT infection was a downstream result of the preceding risk behaviors that were reported at the same visit where the GC/CT testing occurred. As such, the presence or absence of rectal GC/CT infection was already lagged from the number of RAI partners in last 6 months that were reported at the same visit. An additional deviation from published cross-lagged panel models was that direct paths from methamphetamine use and depression to rectal GC/CT were not included in our model, as the relationship between methamphetamine use and depression with rectal GC/CT is fully mediated by sexual risk behavior (i.e., depressive symptoms cannot cause rectal GC/CT without sexual risk behavior).

Models were fit using SEM with maximum likelihood with missing values (mlmv), which retains as much information as possible by using equation-wise instead of list-wise deletion of missing values.[101] This method relies on the assumption of joint normality of all variables. Given the repeated measures in this dataset, all paths that were repeated across timepoints were constrained to provide one aggregate value across timepoints to reduce the number of coefficients reported and to aid in the interpretability of our results. After models were created, we iteratively calculated modification indices to select correlated error terms to improve model fit.[101, 102] Only error terms that made sense conceptually were allowed to be correlated, therefore correlated error terms were limited to repeated measures of the same variable (e.g., depressive symptoms at T1 with depressive symptoms at T2) and methamphetamine use with depressive symptoms at the same timepoint, as the literature demonstrates that there is a relationship between methamphetamine and depression but the directionality is unclear.[71, 73, 75]

Goodness of fit was evaluated using the following goodness of fit indices: the chi-square test, root mean square error of approximation (RMSEA), the comparative fit index (CFI), and the Tucker Lewis index (TLI).[103, 104] Non-significant chi-square goodness of fit tests ($p > 0.05$) are supportive of a better fitting model, but are dependent on sample size, and were therefore assessed

in the context of other goodness of fit indices.[104] The RMSEA was used to evaluate the degree to which data deviate from the model with a cutoff of < 0.05 indicating a good fit.[104] The CFI compared the specified model with the null model assuming zero covariances within the observed variables and is based on non-centrality, and a CFI cutoff of > 0.90 was used.[103] The TLI compared the lack of a fit of the specified model to the lack of fit of the null model and penalized for model complexity, and a TLI cutoff of > 0.90 was used.[103] Sample size recommendations in the literature are to have a minimum of 20 observations per variable included in the model.[105] As our models include 96 variables across all timepoints, this would suggest that a sample of 1,920 would be required to achieve adequate power. As our analysis utilized data from 2,437 observations, our sample size was adequate. Unstandardized β coefficients were reported, as reporting of unstandardized β have been recommended to allow for researchers to compare effect sizes across studies.[105]

After models were fit, we compared models with contemporaneous paths only, lagged paths only, and both contemporaneous and lagged paths to 1) determine the impact that lagged paths had on our models, 2) evaluate whether certain lagged paths should be eliminated from the model, and 3) examine the stability of our coefficients with/without lagged paths. We found that the overall magnitude and stability of our coefficients were stable across paths. We selected the model with contemporaneous paths (no lags) as our final model, due to multicollinearity in the model that resulted from including both contemporaneous and lagged paths (see Figure 3.3 for final model, see Results for rationale in selecting final model).

We also stratified our final model by HIV status to evaluate whether there were any differences in the relationships between depressive symptoms, methamphetamine use, sexual risk behavior, and rectal GC/CT according to HIV status. To understand how predictors differed between those living with and without HIV, descriptive statistics of baseline predictors stratified by

HIV status were obtained prior to fitting the stratified path model. Differences between participant demographic factors, methamphetamine use, depressive symptoms, RAI partners, and rectal GC/CT according to HIV status were assessed with bivariate analyses using chi-square analysis for categorical predictors and Kruskal-Wallis tests for continuous variables. All analyses were conducted using Stata 15.1 (StataCorp, College Town, TX).

Results

This sample consisted of 557 participants across 2,437 observations, with 48.7% (n=271/557) having follow-up through their sixth visit. At baseline, median age was 30 years (IQR 26-37) and 278 (49.9%) of participants were living with HIV (Table 3.1). Most participants were either Black (40.6%) or Latinx (49.0%). Median CESD baseline score was 18 (IQR 10-28), with 37.5 of participants reporting symptoms concerning for depression (CESD ≥ 23). Median number of last 6-month RAI partners was 2 (IQR 0-5) and 11.1% of participants had rectal GC/CT at baseline (n=62). Almost half (44.2%) of participants reported methamphetamine use in last 6 months. When stratified by HIV status, participants living with HIV were older (median age 34, IQR 28-39) compared to HIV-negative MSM (28; 34-33). Participants living with HIV also had higher prevalence of methamphetamine use at baseline (57.6%) compared to those who were HIV-negative (30.9%). Distribution of participant characteristics and variables of interest remained stable across all six timepoints (Appendix - Supplemental Table 3.1).

Selection of Final Path Model

A sensitivity analysis was conducted that compared path coefficients between the model without lags (contemporaneous paths only), the model with lags only, and the full model (Table 3.2 and Figure 3.4). The magnitude of β coefficients evaluating the same variable across timepoints (e.g., past methamphetamine use on future methamphetamine use) were similar across all models for depression, methamphetamine use, RAI partners, and rectal GC/CT. In the model with lags only,

lagged methamphetamine use was not associated with number of RAI partners with the β coefficient having a small magnitude with wide confidence interval (β=0.027; 95% CI -0.052-0.106). These findings suggest that the relationship between lagged methamphetamine use and RAI partners is unstably estimated when evaluating lagged paths only, which may be due to these variables being separated by a long period of time.[106, 107] Similarly, lagged depression was not associated with number of RAI partners (β=0.068; 95% CI -0.210-0.345).

In the model with both contemporaneous and lagged paths, including a contemporaneous path estimating methamphetamine use on RAI partners substantially reduced the lagged effect of methamphetamine use and resulted in a negative association between lagged methamphetamine use and future RAI partners (β= -0.233; 95% CI -0.331- -0.136). Additionally, the magnitude of the β coefficient of contemporaneous methamphetamine use increased in the model with lagged and contemporaneous paths (β= 0.417; 95% CI 0.320-0.513) compared to the model with contemporaneous paths only (0.284; 0.205-0.364). Collectively, these findings suggest that when the effects of both lagged and contemporaneous methamphetamine use on RAI partners are included in the same model, these variables compete for variance and result in unstable and biased estimates. These findings are likely due to multicollinearity, as methamphetamine use and RAI partners are highly correlated across timepoints (Appendix – Supplemental Table 3.2). Multicollinearity resulting in biased estimates is similarly observed with lagged depression on RAI partners, which also has a negative β coefficient, though this relationship was not associated. However, unlike methamphetamine use and depression, rectal GC/CT does not appear have the same collinearity issues across timepoints. As such, in our model with contemporaneous and lagged paths, the number of lagged and contemporaneous RAI partners were both associated with rectal GC/CT (β= 0.006; 95% CI 0.002-0.009 and 0.013; 0.009-0.016, respectively) and their coefficients had similar magnitude as the models that evaluated the lagged and contemporaneous effects separately. This

finding further supports the concern that the estimates for methamphetamine use and depression may be biased when lagged and contemporaneous paths are included in the same model. As such, we selected the model with contemporaneous paths only as our final model, which still accounts for upstream impacts and potential time-varying confounding.

Path Models

Table 3.3 presents the unstandardized path coefficients constrained across timepoints for our final model. Both methamphetamine use (β=0.284; 95% CI 0.205-0.364) and depression (0.334; 0.058-0.610) were positively associated with number of RAI partners reported at the same visit. Number of RAI partners in last 6 months was associated with rectal GC/CT infection (β=0.015; 95% CI 0.012-0.018). Past depressive symptoms, methamphetamine use, and number of RAI partners were associated with future depressive symptoms, methamphetamine use, and RAI partners, respectively. Similarly, past rectal GC/CT infection was associated with future rectal GC/CT (β=0.101; 95% CI 0.049-0.153).

When stratified by HIV status, depressive symptoms were positively associated with number of RAI partners in last 6 months for HIV-negative MSM (β=0.495; 95% CI 0.137-0.854) but was not associated among MSM living with HIV (0.121; -0.293-0.535) (Table 3.4). Methamphetamine use was positively associated with number of RAI partners for both groups, though a slightly higher magnitude of association was observed among MSM living with HIV (β=0.379; 95% CI 0.263-0.495) compared to those who were HIV-negative (0.252; 0.131-0.372). Past depressive symptoms and methamphetamine use were associated with future depressive symptoms and methamphetamine use for both groups, respectively. The positive association of past number of RAI partners on number of future RAI partners had a higher magnitude of association among MSM living with HIV (β= 0.436; 95% CI 0.375-0.496) compared to their HIV-negative counterparts (0.196; 0.051-0.342). However, the positive association between number of RAI partners in last 6 months and rectal

GC/CT were similar in magnitude between both groups (β=0.015; 95% CI 0.012-0.019 for MSM living with HIV and 0.013; 0.009-0.018 for HIV-negative MSM). While past rectal GC/CT infection was associated with future rectal GC/CT among MSM living with HIV (β=0.142; 95% CI 0.077-0.207), past and future rectal GC/CT were not associated among HIV-negative MSM.

Discussion

Our findings demonstrate that depression and methamphetamine use were positively associated with number of RAI partners which, in turn, was associated with rectal GC/CT. While associations between depression and methamphetamine use with risky sexual behaviors and HIV/STI transmission have been well-documented in the literature,[36, 37, 108, 109] our analysis extends the current body of knowledge by using a path analysis on longitudinal data that utilizes a laboratory diagnosis (not self-report) of rectal GC/CT. The design of our panel model enables us to evaluate contemporaneous effects as well as the effects of past behaviors on future outcomes.

Methamphetamine use was positively associated with number of RAI partners which was not unexpected as methamphetamine use has been associated with increased sexual risk behaviors.[35, 38] Past methamphetamine use was strongly associated with future methamphetamine use, with the highest magnitude of association of all paths included in our model. These findings are consistent with previous research demonstrating high rates of sustained methamphetamine use among younger MSM subpopulations.[110, 111] Given the association of methamphetamine use with sexual risk behaviors and the persistence of methamphetamine use over time, these findings demonstrate the importance of prioritizing screening and treatment of substance use disorders in STI screening and HIV prevention programs.

In addition to methamphetamine use, depressive symptoms were positively associated with number of RAI partners. Depressive symptoms may lead to sexual risk behaviors as a means to mitigate negative symptoms through sensation-seeking, reliance on avoidant coping mechanisms, or

lower self-efficacy surrounding HIV preventative behaviors.[27, 84, 86] Our results suggest that methamphetamine use and depressive symptoms may persist over time. As higher levels of methamphetamine use have been shown to worsen depressive symptoms, it is possible that depressive symptoms may contribute to co-morbid methamphetamine use and vice versa.[112-114] Furthermore, severe depressive symptoms occurring in the context of co-morbid methamphetamine use may act synergistically to increase sexual risk-taking and ongoing HIV/STI transmission within the sexual networks of methamphetamine-using MSM.[115] These findings demonstrate the importance of aggressive screening for depressive symptoms and methamphetamine use disorders among MSM at risk for HIV, particularly given the elevated prevalence of methamphetamine and depression that is observed within this population.[29, 30, 116, 117] An additional benefit of prioritizing methamphetamine treatment among methamphetamine-using MSM with depressive symptoms is that treatment for methamphetamine use disorder has been demonstrated to reduce depressive symptoms.[112]

While the path between number of RAI partners and rectal GC/CT was strongly associated, the magnitude of this path was relatively low (β=0.015) - the reasons for this observation are likely multifactorial. First, the number of RAI partners in last 6 months variable was on a continuous scale (0-15), while depression was dichotomous and methamphetamine use was ordinal with 6 levels (0-5). As RAI partners had more levels compared to methamphetamine use and depression, the magnitude of change with each unit increase in RAI partners was comparatively lower. Additionally, the lower magnitude of RAI partners may have been due to omitted variables bias. While number of RAI partners is a risk factor for HIV/STI transmission, the factors that contribute to sexual risk and HIV/STI transmission are numerous, complex, and may not have been completely captured in our analysis. For example, it is possible that a participant may have had a main partner who engaged in high-risk sexual behavior and had concurrent partnerships. As such, while the participant may have

reported their main partner as their only RAI partner, it is possible that this partner may have been high-risk in terms of HIV/STI transmission. Finally, the path between RAI partners and rectal GC/CT may have been influenced by the overall sexual network prevalence of rectal GC/CT in our sample, given the relatively high prevalence of rectal GC/CT in this cohort.

Stratification by HIV status

When stratifying by HIV status, methamphetamine use was positively associated with number of RAI partners for both groups. The magnitude of association for RAI partners over time was higher for MSM who were living with HIV compared to HIV-negative MSM. Similarly, MSM living with HIV had a slightly higher magnitude of association between methamphetamine use and RAI partners compared to MSM who were HIV-negative, though their confidence intervals overlapped. While it is clear that methamphetamine use is linked with risky sexual behaviors regardless of HIV status, these findings demonstrate that the epidemic of methamphetamine use among MSM is likely complex and multifaceted.[118, 119] The higher magnitudes of association between methamphetamine use and RAI partners as well as RAI partners over time that were observed among MSM living with HIV may be related to increased stimulant-associated sexual risk behaviors. These stimulant-associated risk behaviors may have led to HIV acquisition and may have also persisted following HIV seroconversion.[120]

In addition, motivations and settings associated with methamphetamine use may differ according to status. For example, qualitative evidence demonstrated that MSM living with HIV tended to use methamphetamine for sexual reasons while HIV-negative MSM used methamphetamine socially, which may be demonstrated by the higher magnitude of RAI partners over time that was observed among MSM living with HIV.[119] Furthermore, in a study evaluating methamphetamine use patterns between MSM living with and without HIV, MSM living with HIV were more likely to report methamphetamine use in sexualized settings, such as bath houses or sex

parties, and to avoid unpleasant emotions or social pressures compared to their HIV-negative counterparts.[121] The higher use of methamphetamine in sexual contexts among MSM living with HIV suggests that methamphetamine may be used as an avoidant coping strategy to deal with an HIV diagnosis or to dismiss potential fears or anxieties associated with sexual activity.[119, 122] Collectively, these motivations and contexts of methamphetamine use among MSM living with HIV may result in comparatively riskier sexual behaviors compared to HIV-negative MSM. This is further supported by the finding that rectal GC/CT was associated across timepoints among MSM living with HIV, yet not among their HIV-negative counterparts. These results suggest that MSM living with HIV may have more persistent sexual risk behaviors within networks of high HIV/STI prevalence and demonstrate the need for aggressive STI screening as well as efforts to achieve and maintain virologic control within this population.

Interestingly, depression was positively associated with RAI partners among HIV-negative MSM, yet this path was not associated among participants living with HIV. One possibility for this observation could be that participants living with HIV may be more likely to receive treatment for their depressive symptoms through their HIV-related care. An additional consideration may be related to our use of RAI partners as a count variable. Previous studies investigating the relationship between depression and sexual risk have been mixed.[81, 123] These discrepant findings may be due to how sexual risk was operationalized, as it has been demonstrated that using sexual risk behavior as a count variable (e.g., number of RAI partners) may be more sensitive than using a dichotomous variable when evaluating the relationship between sexual risk and depression.[62] For example, Houston et al. used a count variable to evaluate episodes of condomless anal intercourse and found that depression was associated with condomless anal intercourse among HIV-negative MSM but was not associated among MSM living with HIV.[124] In a study evaluating day-level behavioral risk associated with affective states, increased sexual risk behavior occurred during days where

participants reported diminished positive affect, suggesting that the effect of depressive symptoms on risk behaviors may be event-driven and that aggregate measures of risk may be insensitive.[82] Consequently, our analytic approach may have been sensitive enough to capture the differential impacts of depression according to HIV status.

Certain factors that are distinct to HIV-negative MSM may also contribute the relationship between depressive symptoms and sexual risk among HIV-negative participants. In a qualitative study involving MSM who were predominantly HIV-negative, participants who reported depressive symptoms were more likely to have increased sexual interest and to utilize sexual contact as a means of validation or to improve negative symptoms.[125] Depression may also lead to increased sexual risk-taking due to diminished concern about negative consequences and HIV risk.[126, 127] This finding is particularly relevant in the context of our findings as RAI poses a greater health risk for HIV-negative MSM compared to those living with HIV. It is also possible that sexual risk-taking among HIV-negative MSM with depressive symptoms may be related to the desire for intimacy or fatalistic beliefs with staying HIV-negative.[128, 129] Conversely, anxiety related to acquiring HIV from sexual risk behaviors may result in increased anxiety or depressive symptoms among HIV-negative participants.[130] These findings demonstrate the importance of improved efforts toward depression screening and treatment among HIV-negative MSM, particularly those with a history of stimulant use.

Limitations

Our findings must be considered in the context of limitations. As this analysis comprises a cohort of MSM who are predominantly of color and with high prevalence of substance use, generalizations of our findings to other populations of MSM may be limited. While the longitudinal design is a strength in our analysis, causal inferences cannot be drawn from our results. Given the numerous paths across timepoints, the use of constraints aids in the interpretability of our models,

yet the use of constraints relies on the assumption that associations are consistent across time and may lead to misspecification. However, as the goal of this analysis was to evaluate aggregate relationships between variables across time, rather than individual associations at each timepoint, we feel that the use of constraints was justified. While the longitudinal design of our analysis allows us to test relationships between variables in a more rigorous manner, a drawback is the number of paths that are generated by this approach which prevented us from being able to measure standardized β coefficients or total, indirect, and direct effects across paths. As path models are extremely sensitive to model specification, there is the concern that path coefficients could be significantly affected if extraneous variables are included or relevant predictors are excluded from the model. However, we were careful to ensure that conceptually relevant predictors were included in the model and extraneous variables were excluded.

Since the constructs that contribute to an STI diagnosis are multifaceted and complex, it is difficult to comprehensively assess all factors that may contribute to STIs through surveys alone, potentially resulting in omitted variable bias. While the number of RAI partners is an important risk factor for HIV/STI acquisition/transmission, it is not the only risk factor. For example, it is possible that a participant may have reported RAI with their main partner who engaged in risky behavior. As such, the participant may be at higher HIV/STI transmission risk through their main partner, despite having few RAI partners. We would like to note that we conducted a sensitivity analysis evaluating rectal GC/CT with an interaction term of reporting a main partner and number of RAI partners, which did not reveal any association. However, the possibility of omitted variables bias does remain, particularly as this is a secondary data analysis. As genital and pharyngeal GC/CT was not included in our path models, it is possible that rectal GC/CT may have been due to reinfection from past genital or pharyngeal infection. However, we feel that the exclusion of genital and pharyngeal GC/CT is justified as inclusion of other site GC/CT at T_{n-1} on rectal GC/CT at T_n in

path models would imply a causal association, potentially introducing bias into our models. Furthermore, in exploratory analysis, genital and/or pharyngeal GC/CT at the study visit immediately preceding rectal GC/CT was relatively small and noted at less than 10% of visits - of the 187 visits with rectal GC/CT, 9 had positive pharyngeal GC and 5 had positive genital GC/CT testing at the visit immediately preceding positive rectal GC/CT testing. Additionally, as all data is self-reported, there is the risk of recall and social desirability bias, though surveys were administered through computer-assisted self-interview to minimize such bias.

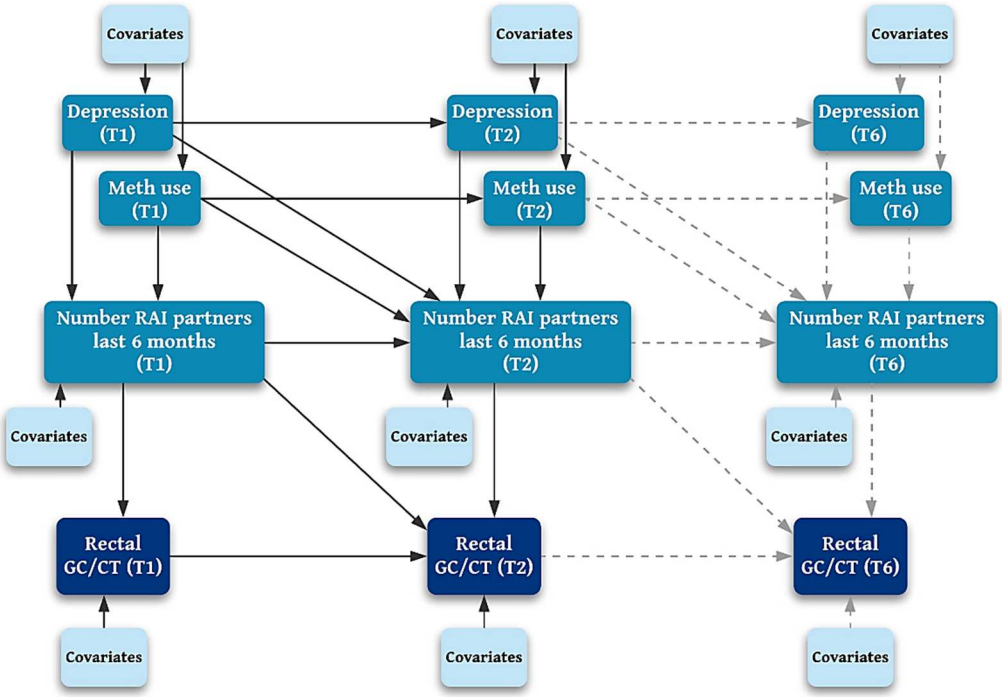
It is possible that participants living with HIV may have received treatment for depression as part of their HIV-related care. As we did not account for depression treatment in our path models, this may have introduced bias into the study, particularly as depressive symptoms and number of RAI partners were not associated among participants living with HIV. However, we believe that this potential bias is mitigated somewhat as we used depressive symptoms (and not treated depression) as a measure in our path models and models were stratified based on HIV status (i.e., participants living with HIV were only compared to other participants living with HIV in stratified models – all of whom should theoretically have some access to HIV-related care). As the CESD utilizes symptoms experienced in last 7 days, it is possible that the timing of substance use or risk behaviors may not have coincided with depressive symptoms. Additionally, while the association between depressive symptoms and methamphetamine use has been well-documented in the literature, the directionality of this relationship is unclear. This consideration caused us to not place a path between methamphetamine use and depression as it would require assumptions regarding the direction of this relationship. However, we attempted to account for the potential relationship between depression and methamphetamine use by correlating their error terms.

Conclusions

To the best of our knowledge, this analysis is one of the first to explicitly evaluate the relative contributions of methamphetamine use, depression, and sexual risk behavior on rectal GC/CT longitudinally, which is an important step in disentangling the relationship between depression and methamphetamine use with HIV/STI transmission. Our findings demonstrate that depression and methamphetamine use contribute to increased sexual risk behaviors which, in turn, are associated with rectal GC/CT. Additionally, our findings suggest that the factors and patterns which contribute to risk behaviors may differ according to HIV status. Specifically, depression may have a stronger influence on sexual risk behaviors among HIV-negative MSM while methamphetamine use may have a more substantial impact for MSM living with HIV. Collectively, our findings demonstrate the importance of screening for stimulant use and making linkages to substance use treatment among MSM living with HIV, while HIV-negative MSM would benefit from HIV prevention interventions that screen for depressive symptoms and facilitating linkages to mental health treatment. These findings also demonstrate the potential utility of combined treatment and prevention efforts that link screening and treatment of stimulant use and depression with HIV/STI prevention and treatment.

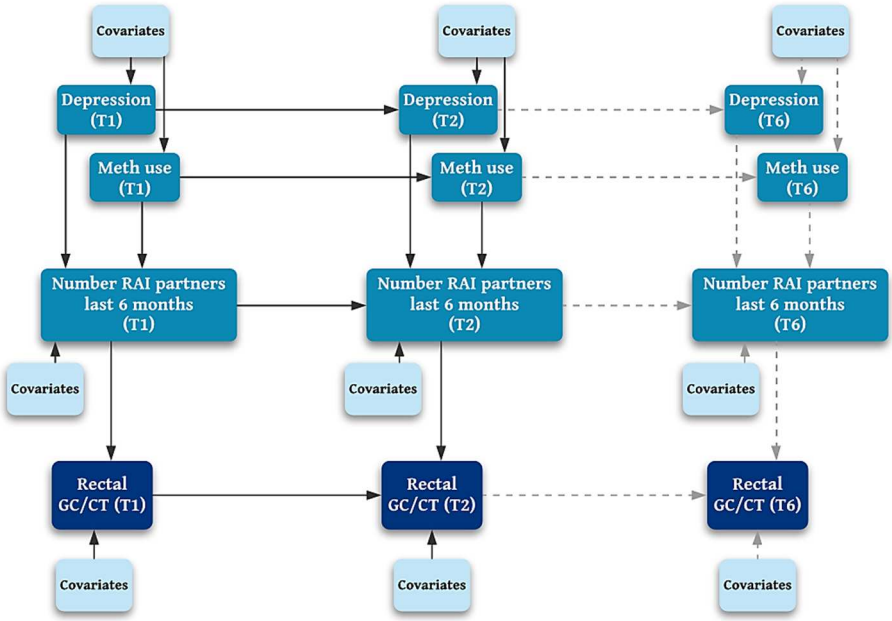
Tables and Figures

Figure 3.2 Cross-lagged panel mediation model evaluating the association of depression, methamphetamine use, and sexual risk behavior on rectal gonorrhea/chlamydia



Meth = methamphetamine; GC/CT = gonorrhea/chlamydia, RAI = receptive anal intercourse
Covariates = HIV status, race/ethnicity, age

Figure 3.3 Final panel model evaluating the association of depression, methamphetamine use, and sexual risk behavior on rectal gonorrhea/chlamydia



Meth = methamphetamine; GC/CT = gonorrhea/chlamydia, RAI = receptive anal intercourse
Covariates = HIV status, race/ethnicity, age

Table 3.1 Descriptive statistics and baseline characteristics of mSTUDY cohort stratified by HIV status (N=557)

	Total (n=557)	HIV-negative (n=279)	Living with HIV (n=278)	p-value
Age (median, IQR)	30 (26-37)	28 (24-33)	34 (28-39)	<0.001
Race/Ethnicity				
Black	226 (40.6%)	114 (40.9%)	112 (40.3%)	0.99
Latinx	273 (49.0%)	136 (48.8%)	137 (49.3%)	
Non-Black/Non-Latinx	58 (10.4%)	29 (10.4%)	29 (10.4%)	
Rectal GC/CT				
Negative	495 (88.9%)	251 (90.0%)	244 (87.8%)	0.41
Positive	62 (11.1%)	28 (10.0%)	34 (12.2%)	
CESD				
Negative	347 (62.3%)	187 (67.0%)	160 (57.6%)	0.021
Positive	210 (37.7%)	92 (33.0%)	118 (42.5%)	
RAI partners last 6 months (median, IQR)	2 (0-5)	1 (0-4)	2 (0-5)	0.014
Methamphetamine use last 6 months				
Never	309 (55.8%)	192 (69.1%)	117 (42.4%)	<0.001
Once	39 (7.0%)	19 (6.8%)	20 (7.3%)	
Less than monthly	49 (8.8%)	23 (8.3%)	26 (9.4%)	
Monthly	31 (5.6%)	8 (2.9%)	23 (8.3%)	
Weekly	67 (12.1%)	18 (6.5%)	49 (17.8%)	
Daily	59 (10.7%)	18 (6.5%)	41 (14.9%)	

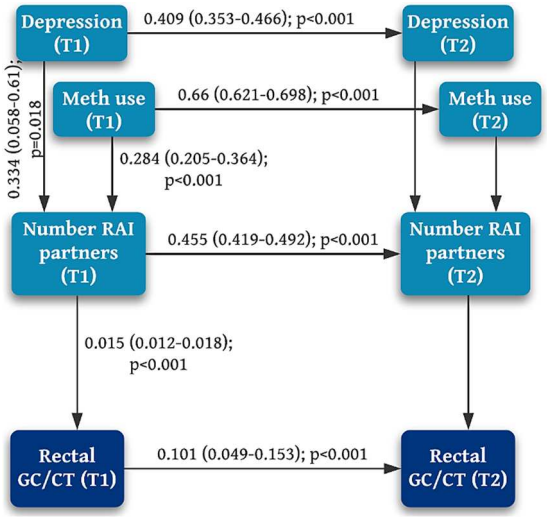
IQR = interquartile range; GC/CT = gonorrhea/chlamydia; CESD = Center for Epidemiological Studies Depression scale; RAI = receptive anal intercourse
Note: p-values calculated from chi-square or Kruskal-Wallis tests comparing MSM living with HIV to HIV-negative MSM

Table 3.2 Unstandardized path coefficients of final model, model with both lags and contemporaneous paths (cross-lagged panel mediation model), and model with lags only

	Final model (contemporaneous only)[1]		Contemporaneous and lagged paths[2]		Lags only[3]	
Outcome and predictor variables	**β (95% CI)**	**p**	**β (95% CI)**	**p**	**β (95% CI)**	**p**
Depression						
RAI partners*	0.334 (0.058-0.610)	0.018	0.386 (0.095-0.678)	0.009	--	--
RAI partners (T_n to T_{n+1})	--	--	-0.119 (-0.411-0.174)	0.43	0.068 (-0.210-0.345)	0.63
Depression (T_n to T_{n+1})	0.409 (0.353-0.466)	<0.001	0.361 (0.314-0.408)	<0.001	0.361 (0.314-0.408)	<0.001
Methamphetamine use						
RAI partners*	0.284 (0.205-0.364)	<0.001	0.417 (0.320-0.513)	<0.001	--	--
RAI partners (T_n to T_{n+1})	--	--	-0.233 (-0.331--0.136)	<0.001	0.027 (-0.052-0.106)	0.51
Meth use (T_n to T_{n+1})	0.660 (0.621-0.698)	<0.001	0.660 (0.621-0.698)	<0.001	0.659 (0.621-0.697)	<0.001
RAI partners						
Rectal GC/CT*	0.015 (0.012-0.018)	<0.001	0.013 (0.009-0.016)	<0.001	--	--
Rectal GC/CT (T_n to T_{n+1})	--	--	0.006 (0.002-0.009)	0.004	0.013 (0.009-0.016)	<0.001
RAI partners (T_n to T_{n+1})	0.455 (0.419-0.492)	<0.001	0.490 (0.449-0.531)	<0.001	0.490 (0.448-0.532)	<0.001
Rectal GC/CT						
Rectal GC/CT (T_n to T_{n+1})	0.101 (0.049-0.153)	<0.001	0.106 (0.059-0.153)	<0.001	0.090 (0.037-0.142)	0.001

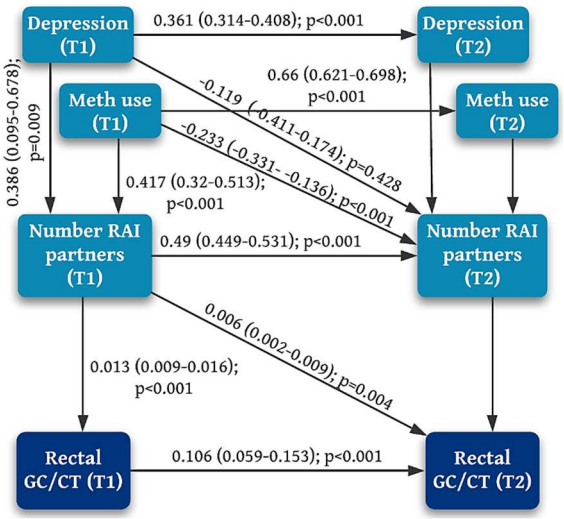
[1] χ^2 (287) = 535.42, RMSEA 0.039, CFI 0.937, TLI 0.924
[2] χ^2 (285) = 508.81, RMSEA 0.038, CFI 0.944, TLI 0.931
[3] χ^2 (285) = 633.95, RMSEA 0.047, CFI 0.912, TLI 0.893
Note: estimates are adjusting for HIV status, age, and race/ethnicity
*Contemporaneous path

Figure 3.4 Unstandardized path coefficients of final model, model with both lags and contemporaneous paths (cross-lagged panel mediation model), and model with lags only



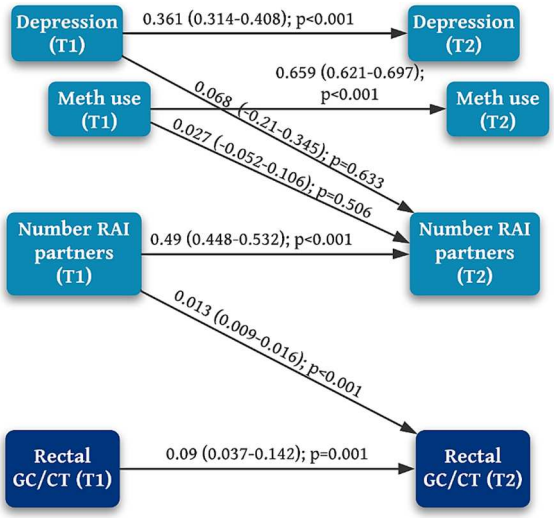
Final model (contemporaneous only)

χ^2 (287) = 535.42, RMSEA 0.039, CFI 0.937, TLI 0.924



Contemporaneous and lagged paths

χ^2 (285) = 508.81, RMSEA 0.038, CFI 0.944, TLI 0.931



Lags only

χ^2 (285) = 633.95, RMSEA 0.047, CFI 0.912, TLI 0.893

Note: Results are presented as β (95% CI); p-value. Estimates are adjusting for HIV status, age, and race/ethnicity.

Table 3.3 Unstandardized path coefficients of path model evaluating the association of depression, methamphetamine use, and sexual risk behavior on rectal gonorrhea/chlamydia

Outcome and predictor variables	Unstandardized β (95% CI)	p
Depression		
RAI partners last 6 months	0.334 (0.058-0.610)	0.018
Depression*	0.409 (0.353-0.466)	<0.001
Methamphetamine use		
RAI partners last 6 months	0.284 (0.205-0.364)	<0.001
Methamphetamine use*	0.660 (0.621-0.698)	<0.001
RAI partners last 6 months		
Rectal GC/CT	0.015 (0.012-0.018)	<0.001
RAI partners last 6 months*	0.455 (0.419-0.492)	<0.001
Rectal GC/CT		
Rectal GC/CT*	0.101 (0.049-0.153)	<0.001

χ^2 (287) = 535.42, RMSEA 0.039, CFI 0.937, TLI 0.924
Note: estimates are adjusting for HIV status, age, and race/ethnicity
*Path from T_n to T_{n+1}

Table 3.4 Unstandardized path coefficients of lagged panel model evaluating the association of depression, methamphetamine use, and sexual risk behavior on rectal gonorrhea/chlamydia stratified by HIV status

Outcome and predictor variables	HIV-negative β (95% CI)	p	Living with HIV β (95% CI)	p
Depression				
RAI partners last 6 months	0.495 (0.137-0.854)	0.007	0.121 (-0.293-0.535)	0.57
Depression*	0.358 (0.294-0.421)	<0.001	0.375 (0.319-0.431)	<0.001
Methamphetamine use				
RAI partners last 6 months	0.252 (0.131-0.372)	<0.001	0.379 (0.263-0.495)	<0.001
Methamphetamine use*	0.700 (0.652-0.748)	<0.001	0.655 (0.607-0.702)	<0.001
RAI partners last 6 months				
Rectal GC/CT	0.013 (0.009-0.018)	<0.001	0.015 (0.012-0.019)	<0.001
RAI partners last 6 months*	0.196 (0.051-0.342)	0.008	0.436 (0.375-0.496)	<0.001
Rectal GC/CT				
Rectal GC/CT*	0.033 (-0.032-0.098)	0.32	0.142 (0.077-0.207)	<0.001

χ^2 (554) = 876.10, RMSEA 0.046, CFI 0.918, TLI 0.904
Note: estimates are adjusting for age and race/ethnicity
*Path from T_n to T_{n+1}

Appendix

Supplemental Table 3.1 Descriptive statistics and baseline characteristics of mSTUDY cohort across timepoints

	T1 (n=557)	T2 (n=479)	T3 (n=423)	T4 (n=380)	T5 (n=327)	T6 (n=271)
Age[a,b]	30 (26-37)	31 (26-37)	31 (26-37)	31 (26-37)	32 (26-38)	32 (26-38)
HIV[b]						
HIV-negative	279 (50.1%)	239 (49.9%)	209 (49.4%)	183 (48.2%)	151 (46.2%)	126 (46.5%)
Living with HIV	278 (49.9%)	240 (50.1%)	214 (50.6%)	197 (51.8%)	176 (53.8%)	145 (53.5%)
Race/Ethnicity[b]						
Black	226 (40.6%)	193 (40.3%)	171 (40.4%)	154 (40.5%)	134 (41.0%)	114 (42.1%)
Latinx	273 (49.0%)	238 (49.7%)	211 (49.9%)	188 (49.5%)	163 (49.9%)	134 (49.5%)
Non-Black/Non-Latinx	58 (10.4%)	48 (10.0%)	41 (9.7%)	38 (10.0%)	30 (9.2%)	23 (8.5%)
Rectal GC/CT						
Negative	495 (88.9%)	426 (88.9%)	377 (89.1%)	345 (90.8%)	299 (91.4%)	246 (90.8%)
Positive	62 (11.1%)	53 (11.1%)	46 (10.9%)	35 (9.2%)	28 (8.6%)	25 (9.2%)
CESD						
Negative	347 (62.3%)	310 (64.7%)	276 (65.3%)	253 (66.8%)	213 (65.1%)	191 (70.5%)
Positive	210 (37.7%)	169 (35.3%)	147 (34.8%)	126 (33.3%)	114 (34.9%)	80 (29.5%)
RAI partners[a,c]	2 (0-5)	1 (0-3)	1 (0-3)	1 (0-4)	1 (0-3)	1 (0-2)
Methamphetamine use[c]						
Never	309 (55.8%)	293 (61.4%)	269 (64.2%)	239 (63.1%)	210 (64.2%)	173 (64.1%)
Once	39 (7.0%)	31 (6.5%)	20 (4.8%)	26 (6.9%)	16 (4.9%)	16 (5.9%)
Less than monthly	49 (8.8%)	40 (8.4%)	33 (7.9%)	26 (6.9%)	22 (6.7%)	23 (8.5%)
Monthly	31 (5.6%)	28 (5.9%)	22 (5.3%)	18 (4.8%)	16 (4.9%)	10 (3.7%)
Weekly	67 (12.1%)	43 (9.0%)	42 (10.0%)	30 (7.9%)	25 (7.7%)	18 (6.7%)
Daily	59 (10.7%)	42 (8.8%)	33 (7.9%)	40 (10.6%)	38 (11.6%)	30 (11.1%)

IQR = interquartile range; GC/CT = gonorrhea/chlamydia; CESD = Center for Epidemiological Studies Depression scale; RAI = receptive anal intercourse

[a]Median (IQR); [b]At baseline; [c]Last 6 months

Supplemental Table 3.2 Pairwise correlation of variables across timepoints

	T1 (n=557)	T2 (n=479)	T3 (n=423)	T4 (n=380)	T5 (n=327)	T6 (n=271)
CESD						
T1	1					
T2	0.47***	1				
T3	0.39***	0.43***	1			
T4	0.37***	0.44***	0.36***	1		
T5	0.42***	0.42***	0.46***	0.42***	1	
T6	0.44***	0.38***	0.50***	0.37***	0.53***	1
Methamphetamine use						
T1	1					
T2	0.75***	1				
T3	0.65***	0.73***	1			
T4	0.60***	0.68***	0.76***	1		
T5	0.56***	0.61***	0.68***	0.69***	1	
T6	0.52***	0.53***	0.66***	0.67***	0.79***	1
RAI partners last 6 months						
T1	1					
T2	0.58***	1				
T3	0.62***	0.70***	1			
T4	0.56***	0.63***	0.61***	1		
T5	0.55***	0.45***	0.54***	0.62***	1	
T6	0.52***	0.53***	0.49***	0.61***	0.65***	1
Rectal GC/CT						
T1	1					
T2	0.15***	1				
T3	0.11*	0.13**	1			
T4	0.09	0.09	0.14**	1		
T5	0.11*	0.14*	0.20***	0.05	1	
T6	0.17**	0.13*	0.19**	0.29***	0.27***	1

GC/CT = gonorrhea/chlamydia; CESD = Center for Epidemiological Studies Depression scale; RAI = receptive anal intercourse

Note: Correlations represent pairwise correlations of the same variable across different timepoints

*p<0.05; **p<0.01; ***p<0.001

Chapter 4.

Risk behaviors associated with patterns of sexualized stimulant and alcohol use among MSM: a latent class analysis

Abstract

Background: Substance use during sexual encounters (sexualized substance use) is an important driver of HIV and sexually transmitted infection (STI) disparities that are experienced by men who have sex with men (MSM). This analysis aimed to identify patterns of sexualized substance use and their associations with HIV risk behaviors.

Methods: We utilized visit-level data from a longitudinal cohort of predominantly Black/Latinx MSM, half with HIV and half with substance use in Los Angeles, California. Every 6 months from 8/2014-3/2020, participants underwent STI screening and completed surveys on the following: demographics, sexualized substance use (stimulant and/or alcohol intoxication during oral sex, receptive anal intercourse [RAI] and/or insertive anal intercourse [IAI]), transactional sex, biomedical HIV prevention (pre-/post-exposure prophylaxis use or undetectable viral load), and depression. Latent class analysis was used to identify patterns of sexualized substance use. Multinomial logit models evaluated risk behaviors associated with latent classes.

Results: Among 2,395 study visits from 540 participants, 5 classes were identified: no substance use, sexualized stimulant use, sexualized alcohol use, sexualized stimulant and alcohol use, and stimulant/alcohol use during oral sex and RAI. Compared to the no substance-using class, sexualized stimulant use was associated with transactional sex, STIs, not using biomedical prevention, and depression. Sexualized alcohol use had fewer associations with HIV risk behaviors.

Conclusions: Patterns of sexual activities, and the substances that occur during those activities, confer different risk behavior profiles for HIV/STI transmission and demonstrate the potential utility of interventions that combine substance use treatment with HIV prevention.

Introduction

Men who have sex with men (MSM) are disproportionately impacted by the HIV and substance use epidemics, with MSM having higher prevalence of substance use and HIV compared to the general U.S. population.[29, 30] Previous research has revealed that MSM have unique patterns of substance use, with substance use commonly occurring within sexual encounters or during sexual activity (sexualized substance use).[34] Two substances that are highly prevalent among MSM and are often used in sexual contexts are alcohol and stimulants (e.g., crystal methamphetamine and cocaine).[57, 131, 132] Motivations for sexualized stimulant use include to increase libido, facilitate partner acquisition, enhance sexual stamina, and for disinhibition.[88, 133] As stimulant use frequently occurs within sexual contexts, these drugs are independently associated with sexual risk behaviors, HIV, sexually transmitted infections (STIs), and mental health comorbidities among MSM.[89, 134-136] In addition to stimulants, alcohol use is common among MSM and is often used in both social and sexual settings.[137, 138] Alcohol consumption has been associated with increased prevalence of sexual risk behaviors as well as reduced health preventative behaviors, such as condom use.[139, 140]

Despite evidence that sexualized substance use is associated with increased HIV/STI transmission, the concept of evaluating the impact of discrete substance use patterns on HIV transmission dynamics among MSM has only emerged rather recently.[141-144] There is mounting evidence that distinct substance use patterns confer separate behavioral risk profiles for HIV/STI transmission – yet, most studies examining these constructs have occurred in Western Europe and Australia.[141, 145-147] Sexualized substance use is associated with higher prevalence of sexual risk behaviors for HIV/STI transmission, including group sex, sexual concurrency, condomless intercourse with non-primary partners and partners of unknown HIV status, and increased number of sexual partners.[35, 38, 42, 53, 87, 148] However, risk for HIV/STI transmission differs based on sex act as well as sexual positioning.[149-151] This differential risk for HIV/STI transmission is especially true for

MSM, with condomless receptive anal intercourse (RAI) conferring higher risk for HIV/STI acquisition than condomless insertive anal intercourse (IAI).[8-11] Furthermore, unlike heterosexual networks, MSM can engage in both insertive (high risk for transmission) and receptive (high risk for acquisition) anal intercourse, which contributes to the rapid and efficient spread of HIV and STIs within sexual networks that comprise MSM.[9, 13] This consideration is particularly relevant in the context of sexualized substance use, as certain substance use patterns are associated with sexual positioning. For example, MSM who use stimulants may experience erectile dysfunction resulting in a preference for RAI.[152]

Despite sexualized substance use and sexual risk behavior representing dominant drivers of ongoing HIV/STI transmission among MSM, there is a paucity of data evaluating the joint patterns of sexual activities that occur in the context of sexualized stimulant and alcohol use. To date, most studies have either focused on specific substances used in conjunction with aggregate risk behaviors – such as condomless anal intercourse or number of partners, rather than patterns of sexual acts.[42, 141, 142, 148] As risk for HIV/STI acquisition differs according sexual practice (i.e., oral intercourse does not confer the same HIV/STI risk as RAI), it is increasingly important to understand the patterns of specific sexual activities that occur within the setting of sexualized substance use in order to appropriately contextualize the impact substance use has on sexual risk and, consequently, HIV/STI transmission among MSM.

The purpose of this analysis will be to differentiate patterns of stimulant and alcohol use that occur during specific sexual activities among a cohort of racially/ethnically diverse MSM, most of which have a history of substance use, in Los Angeles, California. Latent class analysis (LCA) will be used to determine patterns of sexual activities (e.g., oral sex, RAI, IAI) that occur with stimulant and/or alcohol consumption and to evaluate whether certain characteristics or distal outcomes are associated with each latent class. Collectively, these analyses seek to determine nuanced

heterogeneities in sexualized stimulant and alcohol use within a cohort of MSM that are high-risk overall for HIV/STI transmission. Given the complex relationship of substance use and sexual risk behavior among MSM, further understanding of sexualized substance use patterns and how they relate to HIV/STI transmission is increasingly important for the development of novel and efficacious HIV prevention interventions.

Methods

Data Source

We analyzed data collected as part of an ongoing longitudinal cohort study that is designed to evaluate the impact of substance use on HIV transmission dynamics among MSM of color in Los Angeles, California. The Men Who Have Sex with Men and Substance Use Cohort at UCLA Linking Infections, Noting Effects (mSTUDY; U01 DA036267; MPIs Gorbach and Shoptaw) is a longitudinal cohort of racially/ethnically diverse MSM living with or at high-risk for HIV. Methods have been previously described.[153, 154] Briefly, participants were recruited from a community-based university research clinic and a community-based organization that provides clinical and community resources for the lesbian, gay, bisexual, and transgender community in Los Angeles, California. Follow-up visits occur every 6 months, and the cohort consists of half MSM living with HIV and half with active substance use at enrollment. Inclusion criteria for the cohort include: 1) 18-45 years old at study enrollment, 2) born male, 3) condomless anal intercourse with a man in past 6 months (if HIV-negative). Recruitment is ongoing to replace participant dropout and 577 MSM have been enrolled to date. This analysis consists of study visits that took place from August 2014 (study inception) to March 2020 where participants reported participating in either oral and/or anal intercourse in the past 3 months.

Study Procedures

At each study visit, participants underwent clinician interview, STI testing, and completion of a computer-assisted self-interview survey that collected sociodemographic data as well as information surrounding substance use, depression symptoms, HIV pre-exposure or post-exposure prophylaxis (PrEP/PEP) use, and sexual risk behaviors. At each visit, urine samples as well as rectal and pharyngeal swabs were collected for gonorrhea/chlamydia (GC/CT) screening with nucleic acid amplification testing (NAAT) (Aptima Combo 2, GenProbe, San Diego, CA) and for toxicology screening for recent substance use. Blood samples were also collected at each study visit and were screened for syphilis as well as HIV (if HIV-negative) and/or measurement of HIV-1 RNA levels (if living with HIV). Syphilis testing used rapid plasma reagin (RPR) with confirmatory testing via the *Treponema pallidum* particle agglutination test (TPPA). Infectious syphilis (i.e., primary, secondary, or early latent) was defined using the Centers for Disease Control determination following positive test results and confirmation from the local health department.[155] STI testing results were made available to participants and study personnel assisted with notifying participants of their test results and facilitated linkages to care for positive test results. The study was reviewed and approved by the Office of Human Research Participant Protection (OHRPP) at the University of California, Los Angeles.

Measures

Sociodemographics. Participants self-reported their race/ethnicity, and options included Black or African American, Hispanic or Latinx or Spanish, White, American Indian or Alaskan Native, Asian, Asian Indian, Native Hawaiian or Pacific Islander, or other race. As 89.6% of the cohort self-identified as either Latinx/Hispanic or Black/African American, this variable was trichotomized to Black, Latinx, and non-Black/non-Latinx.

Substance use during sexual activity. Participants were asked the question "Which drugs and/or alcohol did you use during this sexual activity in the last 3 months?" Possible sexual activities

included: oral sex, RAI, and IAI. Possible substances used included alcohol, methamphetamine, cocaine powder, and crack cocaine. Participants were asked to respond "yes" or "no" for whether they used each substance during each sexual activity. Methamphetamine, cocaine powder, and crack cocaine were combined into one "stimulants" variable for each sexual activity. These variables were combined into six possible substance/sexual activity combinations: alcohol use during oral sex (yes/no), stimulant use during oral sex (yes/no), alcohol use during IAI (yes/no), stimulant use during IAI (yes/no), alcohol use during RAI (yes/no), and stimulant use during RAI (yes/no).

STI screening and HIV status. Positive STI screening was a dichotomous variable and was defined as having a positive screening test for GC and/or CT at any site (pharyngeal, urethral, and/or rectal) and/or infectious syphilis. HIV status was defined as positive or negative HIV test.

Biomedical prevention. As this cohort consisted of half HIV-negative MSM and half MSM who were living with HIV, a variable evaluating PrEP and/or PEP use (for HIV-negative participants) or undetectable HIV viral load (for participants living with HIV) was created to evaluate use of biomedical prevention as a strategy to prevent HIV acquisition/transmission. HIV-negative participants were asked if they had a current prescription for PrEP or PEP. Blood samples from participants who were living with HIV were evaluated for whether they had an undetectable HIV-1 viral load (detectable or undetectable viral load). These variables were combined to create a biomedical prevention variable with two levels "Yes" (i.e., current prescription for PrEP/PEP or had an undetectable HIV viral load) or "No" (i.e., no current prescription for PrEP/PEP or had a detectable HIV viral load).

Sexual risk behaviors. Participants were asked whether they had participated in oral sex, IAI, or RAI in the last 3 months (yes/no). To better understand patterns of sexual behaviors irrespective of whether substances were used during those behaviors, these variables were coded in multiple ways to understand visit-level sexual practices reported in the cohort. First, three dichotomous

dummy variables were created to evaluate self-reported prevalence of any oral sex (either receptive and/or insertive oral sex - yes/no), IAI (yes/no), and RAI (yes/no) in last 3 months. Second, a composite variable was created to describe whether respondents participated in oral sex and/or any anal intercourse (AI) in last 3 months, which consisted of 3 levels: oral sex only, AI only, and oral sex and AI. As frequency of AI only was very low (n=38 [1.6%] of visits), a third composite variable was created that 1) did not contain an AI only group and 2) stratified AI based on whether the participant reported being the receptive or insertive partner. This variable consisted of 4 levels: oral sex only, IAI and oral sex, RAI and oral sex, and RAI, IAI, and oral sex. Finally, a fourth composite variable was created stratifying participants based on RAI and/or IAI during the last 3 months, which consisted of 4 levels: no AI, IAI only, RAI only, and both RAI and IAI.

Participants were asked whether they had attended a circuit party, hook up, or sex party in the last 6 months. This variable was coded as a dichotomous variable indicating whether the participant attended a circuit, hook up, or sex party in the last 6 months (yes/no). Participants were asked whether they had engaged in transactional sex in the past 3 months (i.e., whether they had exchanged drugs, money, shelter, or other goods for sex), which was coded as a dichotomous variable (yes/no).

Substance use. Participants were asked the question "In the last 6 months, how often did you use [drug name]?". Possible drugs included methamphetamine, cocaine powder, and crack cocaine. Potential response options included: "Daily", "Weekly", "Monthly", "Less often", "Once", and "Never". Methamphetamine, cocaine powder, and crack cocaine were combined into one composite "stimulants" variable which was dichotomized to regular/heavy use (daily, weekly) and not regular use (monthly, less often, once, and never). Participants were asked the question "During the past 6 months, how often did you have 6 or more drinks on one occasion?". Potential response options included "Never", "Less than monthly", "Monthly", "Weekly", and "Daily or almost daily".

Responses were trichotomized to a binge drinking variable with three levels: none (never), monthly or less (monthly, less than monthly), and weekly/daily (weekly, daily).

Depression. Depressive symptoms were measured using the Center for Epidemiological Studies – Depression (CESD) Scale, which is a validated 20-item measure that assesses depressive symptoms. Participants are asked to rank how often they have experienced symptoms, such as feelings of hopelessness, sadness, or loneliness as well as poor appetite or restless sleep in the past 2 weeks.[95] Response options ranged from 0 to 3 for each item based on frequency of the symptom (0 = "rarely or none of the time," 1 = "some or little of the time," 2 = "moderately or much of the time," 3 = "most or almost all of the time"). Possible scores range from 0-60 with higher scores indicating more intense depressive symptoms. In the general population, a score cutoff of 16 or greater has been used to identify individuals at risk for clinical depression with good sensitivity and high internal consistency with a Cronbach's alpha of 0.85-0.90.[95, 96] For our analysis, we utilized a score cutoff of 23, as this has been demonstrated to be more optimal to evaluate clinical depression among individuals living with HIV.[97] Depression was a dichotomous variable indicating positive or negative CESD score (< 23 or ≥ 23).

Statistical Analysis

The purpose of this analysis was to describe patterns of sexualized stimulant and alcohol use among MSM in the mSTUDY cohort and to evaluate characteristics associated with different sexualized substance use patterns. Latent class analysis (LCA) was used to determine and evaluate distinct patterns of substance use during intercourse. LCA is a type of mixture-modelling to determine unobserved (latent) heterogeneity within a sample population based on respondent response patterns to observed variables within the data.[156] Individuals are grouped based on similar patterns of responses to observed variables within the data, with the assumption that individuals within groups have similarities on unobserved, latent constructs.[156, 157] LCA is a non-parametric test

and does not rely on any assumptions with regard to homogeneity, linearity, or distribution of the data.[158] However, LCA relies on the assumption of conditional independence - that observations should be independent in each class.[156] While longitudinal data was used for this study, data was analyzed at the visit-level as LCA is designed for cross-sectional data. While cluster analysis is a statistical method that can also be used to classify individuals into groups,[156] LCA was selected over cluster analysis because it allows for uncertainty in class membership and for greater flexibility to include predictor variables to improve class distinctions.[159, 160]

An exploratory analysis was conducted to evaluate the distribution of responses across variables, missingness, and skip patterns. The exploratory analysis was additionally used to select which substance use during sexual activity predictors should be considered for inclusion in the latent classes. Conceptually relevant combinations of substance use during sexual activity variables were iteratively fit into latent classes to evaluate which combinations provided sufficient class separation and item response probabilities that should be considered for inclusion into the final latent class model. It was determined that the combination of two possible substances used (e.g., alcohol and stimulants) during three possible sexual activities (e.g., oral sex, RAI, IAI), provided the most parsimonious fit to the data for creating the latent classes. Descriptive statistics (frequency, percentage, median, interquartile range [IQR]) of the study population and predictors of interest were calculated for the entire cohort and the cohort stratified by type of AI (i.e., no AI, IAI only, RAI only, and RAI and IAI). Differences between demographic factors, substance use during sexual activity, and predictors of interest according to type of AI reported were assessed using chi-square analysis for categorical predictors and Kruskal-Wallis tests for continuous variables.

The expectation maximization algorithm was used to develop the appropriate number of latent classes. Models with successively larger number of latent classes were created based upon the maximum likelihood estimation, and goodness of fit tests were calculated to determine the most

parsimonious number of classes.[157] Model fit statistics included the Likelihood Ratio statistic (G^2), the Akaike Information Criterion (AIC), the Consistent AIC (CAIC), the Bayesian Information Criterion (BIC), Sample Size Adjusted BIC (ABIC), and the Bootstrapped Likelihood Ratio Test (BLRT).[161, 162] Of all the methods, the BIC and BLRT are considered to be the most reliable fit statistics.[157, 163] These model fit statistics were used to determine the most parsimonious number of classes (k) to include in the final LCA model.[164]

The G^2 measures the degree of agreement between predicted and observed response pattern frequencies in the contingency table formed during LCA, with a non-significant G^2 ($p > 0.05$) supporting a better fitting model. The G^2 is preferred over the chi-squared, as it allows for sparseness in the contingency table, but it was assessed in the context of other goodness of fit statistics as the G^2 is dependent on sample size.[165] The AIC, CAIC, BIC, and ABIC evaluated models with successive number of classes, and the number of classes where there was diminishing decrement in the information criteria for each class added to the model was selected. The BLRT with 1,000 bootstrapped samples compared models with k classes to k+1 classes, with a p-value < 0.05 suggesting that adding an additional class does not give a significant improvement in fit and that the k-1 class model should be selected.[164-166]

After the model with the appropriate number of classes was determined, entropy values were calculated to evaluate class differentiation, with a threshold of > 0.8 suggesting that the model performed well with classifying individuals into classes.[167] Item response probabilities were calculated to determine class homogeneity in terms of item responses. Class membership probabilities were also calculated to evaluate the proportion of the sample that comprised each latent class.[164, 168] It is important to note the development of conceptually meaningful classes was evaluated in the context of goodness of fit statistics, entropy values, item response probabilities, and class membership probabilities when selecting the final number of classes for the model.

After a model with the appropriate number of classes was determined, the proportion of participants comprising each latent class was assessed at each timepoint to assess stability of latent class membership across time. Multinomial logistic regression models were used to evaluate differences in predictors associated with class membership. Predictors of interest included sexual risk behaviors (e.g., attendance at a circuit/hookup/sex party,[169] transactional sex[170]), health protective behaviors (i.e., use of PrEP/PEP or undetectable viral load),[171, 172] STI diagnosis,[7] and depression,[25] given their known associations with HIV transmission in the literature. To evaluate differences in class membership according to self-reported race/ethnicity, multinomial logistic regression models stratified by race/ethnicity were created. It is important to note that, due to sparseness of the contingency table related to the relatively small n of participants comprising the "Non-Black/Non-Latinx" group, transactional sex was not included in the stratified multinomial logistic model. Measurement invariance was imposed across all racial/ethnic groups to ensure item response probabilities were equal across groups.[166] Equation-wise deletion for missing variables was used to develop the latent classes and list-wise deletion (complete case analysis) was used for all regression analyses. As such, the sum of variables used for the latent classes may not equal the sum of the observations that were used in the regression analyses. Of the 548 participants that reported engaging in oral and/or anal intercourse in the last 3 months and that comprised the 2,580 visits during the study period, 185 observations were excluded due to missing data, resulting in a final sample size of 2,395 observations across 540 participants in regression models, which was above the sample size minimum threshold of 300-1000 that has been suggested in the literature.[159, 163, 164, 173, 174] All analyses were conducted using Stata 16.1 (StataCorp, College Town, TX).

Results

The sample consisted of 2,395 study visits among 540 participants. Of the study visits included in the analysis, 50.2% (n=1,201) were completed by HIV-negative participants and 49.9%

(n=1,194) were completed by participants living with HIV (Table 4.1). Median age of the sample was 32 (range 18-50) and 49.8% (n=1,193) of visits were completed by Latinx participants, 39.4% (n=943) by Black participants, and 10.8% (n=259) by non-Black/non-Latinx participants. A positive screen for GC/CT and/or infectious syphilis occurred at 18.0% of visits, and participants endorsed using biomedical prevention (i.e., used PrEP/PEP or had an undetectable viral load) at 34.4% of visits. Positive depression screen occurred at 33.4% of visits. Regular stimulant use was reported at 22.3% of visits and weekly/daily binge drinking was reported at 11.2% of visits. Among sexual activities reported (Table 4.2), oral sex was reported at 98.4%, IAI at 75.3%, and RAI at 69.4% of visits. Most participants reported participating in both AI and oral sex (89.5%), while very few participants reported AI only (n=38, 1.6%). Over half of participants reported both RAI and IAI in the last 3 months (53.6%, n=1,278), while 15.7% reported RAI only and 21.7% reported IAI only. Participants reported using alcohol or stimulants during oral sex at 39.1% and 35.4% of visits, respectively. Participating in IAI while using alcohol or stimulants was reported at 29.0% and 24.1% of visits, respectively.

When stratifying by type of AI (Table 4.3), participants who did not report any AI in last 3 months (n=214 study visits) tended to be older (median age 35; IQR 29-42), had negative STI testing (91.1%), were not using biomedical prevention (72.9%), and had lower frequency of sexual risk behaviors such as transactional sex and attending a circuit/hookup/sex party, compared to participants who had engaged in AI. Participants who reported IAI only in last 3 months more frequently reported stimulant use during oral sex (80.2%; n=414/516 of visits) compared to visits where no AI (69.8%; 148/214), RAI only (63.5%; 238/375), and RAI and IAI (58.1%; 742/1,278) were reported. Those who did not report AI in last 3 months more frequently reported alcohol use during oral sex (74.5%; n=158/214) compared to visits where IAI only (63%; 325/516), RAI only (68.3%; 256/375), and RAI and IAI (55.6%; 711/1,278) were reported. Participants who reported

both RAI and IAI in last 3 months tended to report higher frequencies of transactional sex, attending a circuit/hookup/sex party, and depressive symptoms compared to other groups.

Class Selection for Final Model

Goodness of fit indices are in Table 4.4 and are graphically presented in Figure 4.1. Overall, the entire range of classes (1-9 classes) were above the entropy threshold of > 0.8, with most entropy values falling within the 0.93-0.96 range. Graphically, it appeared that the relative improvement in fit indices markedly declined at 5 and 6 classes, particularly with the BIC and CAIC which demonstrated very little change in value among models with greater than 5 classes. Fit indices were the lowest at 7 classes and started to increase at 8 and 9 classes. While the BLRT is considered to be one of the more reliable fit statistics, the BLRT favored an 8-class model, which would have resulted in an uninterpretable number of classes consisting of small sample size, limiting the inferences that could be drawn. As such, we relied on the fit indices (G^2, AIC, CAIC, BIC, and ABIC) to determine the optimal number of classes. As the relative decrement in fit indices occurred at 5-6 classes and plateaued after 6 classes, we compared the 5- and 6-class models (Table 4.5 and Table 4.6). Compared to the 5-class model, the 6-class model had inferior discrimination between responses (e.g., for Class 2, oral sex with stimulants and RAI with alcohol had response probabilities of 0.400 and 0.258 respectively), which obfuscated relative response patterns between classes. Additionally, the 6-class model comprised two classes that had small sample sizes (Classes 2 and 6 with 5.4% and 2.2% membership probabilities, respectively), which would have limited the interpretability of our results. As such, we decided to include 5-classes in our final model.

Final LCA Model and Predictions of Class Membership

Response patterns for the 5-class model are in Table 4.5. Class labels were determined by identifying the more highly self-reported (proportion ≥ 0.6) substances used during sexual activity. The stimulants/alcohol class (11.2% of visits) endorsed both stimulant and alcohol use during oral

sex, IAI, and RAI. The no substance use class (44.8% of visits) did not report any alcohol or stimulant use during the sexual activities surveyed. The stimulants only class (17.4%) reported stimulant use during oral sex, IAI, and RAI but did not report alcohol use during these activities. The stimulants/alcohol use during oral sex and RAI class (3.9%) reported both stimulants and alcohol use during oral sex and RAI but did not report using these substances during IAI. The alcohol only class (22.6%) reported alcohol use during oral sex, IAI, and RAI but did not report stimulant use during these activities. Figure 4.2 demonstrates the percentage of participants who maintained latent class membership at each time point. Overall, the no substance use class had the most consistent class membership, with 70.3-83.3% of participants maintaining class membership across timepoints, followed by alcohol only (51.1-71.4%) and stimulants only (42.9-79.4%). The two classes that had the least consistent class membership across timepoints were the stimulants/alcohol use class (38.6-69.2%, though no participants maintained class membership at timepoint 10) and the stimulants/alcohol use during oral sex and RAI class (19.1-83.3%, though no participants maintained class membership at timepoint 9).

Adjusted odds ratios (aORs) for factors associated with predicted class membership are in Table 4.7. In all multivariable adjusted models, the no substance use class was the referent group. Compared to the no substance use class, participants among all classes where substances were used had higher odds of attending a circuit/hookup/sex party in the last 6 months. The stimulants/alcohol, stimulants only, and stimulants/alcohol during oral sex and RAI classes all had higher odds of having an STI and reporting transactional sex. The stimulants/alcohol and stimulants only classes had higher odds of a positive depression screen. Additionally, the stimulants only and stimulants/alcohol use during oral sex and RAI groups both had lower odds of using biomedical HIV prevention strategies.

Predicted Class Membership Stratified by Race/Ethnicity

Factors associated with predicted class membership stratified by race/ethnicity are in Table 4.8 and Figure 4.3. Class membership probabilities remained similar overall across race/ethnicity. However, a slightly lower percentage of Black participants comprised the stimulants only class (13.5%) compared to Latinx (19.1%) and non-Black/non-Latinx participants (22.4%). Additionally, higher proportions of Black and Latinx participants comprised the alcohol only class (23.0% and 22.3%, respectively) compared to non-Black/non-Latinx participants (15.7%). Living with HIV was positively associated with belonging to the stimulants only class across all racial/ethnic groups and negatively associated with the alcohol only class among Latinx and non-Black/non-Latinx participants. Among both Black and Latinx participants, stimulants only class had higher odds of a positive STI screen, compared to the no substance use class.

Among Black participants, any substance use was positively associated with attending a circuit/hookup/sex party. Belonging to the stimulants only or stimulants/alcohol use during oral sex and RAI classes were associated with lower odds of biomedical prevention among Black participants. No associations were observed between any of the substance use classes and biomedical prevention for Latinx and non-Black/non-Latinx participants. Among Latinx participants, the stimulants/alcohol and stimulants only classes had higher odds of having a positive depression screen.

Discussion

Among this diverse cohort of MSM, we utilized LCA to 1) determine patterns of stimulant and alcohol use during specific sexual activities, 2) evaluate whether risk behaviors and syndemic conditions served as predictors for class membership, and 3) examine if predictors of class membership differed by race/ethnicity. To the best of our knowledge, this analysis is among the first to utilize LCA to evaluate patterns of substances used during specific sexual activities. In our analysis, five classes of sexualized stimulant and alcohol use were identified: stimulant/alcohol use

during all sex, no substance use, stimulants only, alcohol only, and stimulants/alcohol use during oral sex and RAI. Collectively, our findings revealed that patterns of sexual activities, and the specific substances that were used during those activities, conferred different risk behavior profiles for HIV/STI acquisition/transmission. Our results suggest that all classes involving stimulant use were associated with increased sexual risk behaviors and depressive symptoms, compared to the class that did not have sexualized stimulant or alcohol use. Conversely, the sexualized alcohol use only class had the fewest associations with sexual risk behaviors. When stratifying by race/ethnicity, Black and Latinx MSM who participated in sexualized substance use were more likely to experience syndemic (i.e., co-occurring) health conditions, potentially leading to increased risk for HIV/STI transmission/acquisition. Given the substantial contribution of substance use to the ongoing HIV/STI epidemic among MSM, findings from this analysis highlight the importance of incorporating substance use screening and treatment into HIV/STI prevention and treatment efforts.

All classes with sexualized substance use had higher odds of participating in a circuit/sex party compared to those belonging to the class that did not engage in sexualized substance use. These findings are not surprising, as substance use, particularly stimulants, poppers, and gamma-hydroxybutyrate (GHB), has been ingrained into the MSM party scene and is frequently used during sexualized settings.[89, 175] Interestingly, those who only consumed alcohol in sexualized settings were more than twice as likely to attend a circuit or sex party compared to those who did not endorse sexualized substance use, supporting the concept that any substance use (not just stimulants or club drugs) may result in increased sexual risk behaviors. Individuals who engage in sexualized substance use may also be more likely to be sensation seeking, which may result in a greater desire to participate in circuit or sex parties and has been positively associated with condomless sex.[176] As many MSM participate in circuit and sex parties for the purposes of sex, sexualized substance use

may be used as a method to overcome inhibitions, physical limitations (such as fatigue or hunger), or to form connections with others without restrictions or limitations.[177, 178] Use of substances within these party settings have also been shown to be used intentionally as a means to engage in condomless sex and sexual risk behaviors as well as a method to justify those behaviors after they have occurred.[179] Given the increased prevalence of condomless sex, sexual concurrency, and risk behaviors associated with participating in circuit/sex parties, these risks are likely amplified by sexualized substance use, resulting in sexual networks that have elevated prevalence of HIV/STIs and which should be prioritized in HIV/STI prevention and treatment efforts.[169, 180]

Our findings demonstrated that membership to any stimulant-using class was associated with almost 2-3 times higher odds of having an STI and 7-8 times higher odds of engaging in transactional sex compared to the no sexualized substance use class. The observation of higher-risk sexual behaviors among stimulant-using classes is not surprising, as stimulant use has been independently associated with increased sexual risk-taking as well as higher prevalence of HIV/STIs.[6, 35, 42] Stimulants often result in increased energy, libido, impulsivity and sexual stamina - conferring a higher risk for HIV/STI transmission particularly as stimulants are often used in sexualized settings.[34, 88] Prevalence of recent transactional sex in this cohort was 18.6%, which is higher than the 5-13% that has been estimated in other studies evaluating transactional sex among MSM.[181-184] The higher prevalence observed in our cohort is likely multifactorial and partially due to this cohort representing a group of relatively young MSM who were selected based on history of substance use and risk for HIV/STI transmission. Substance use, particularly stimulants, has been independently associated with transactional sex, with one study demonstrating that 21% of substance-dependent MSM had participated in transactional sex in the past 3 months.[185, 186] The markedly high association of transactional sex with sexualized stimulant use is likely due, in part, to our wide definition of transactional sex to encompass exchanging goods and services (such as shelter

and drugs), rather than solely monetary compensation. This distinction is important as engaging in transactional sex may not be related to sex work, per se, but may occur due to certain settings/opportunities, to obtain drugs, or related to social norms within certain gay subpopulations.[187-190] In fact, a previous analysis from our group demonstrated that most transactional sex within this cohort occurred for the purposes of obtaining drugs.[191] Transactional sex may also be related to involvement in sexually adventurous gay party subcultures, particularly as classes that used stimulants were more likely to both participate in transactional sex as well as attend a circuit/sex party.[184]

MSM who engage in transactional sex are at elevated risk for HIV/STI transmission due to a multitude of factors, which include individual-level risk factors (e.g., substance use, higher prevalence of psychosocial problems, poverty, unstable housing) that predispose to transactional sex, as well as factors associated with the nature of sex occurring as an economic transaction.[170, 185, 192] Power differentials that occur during transactional sex may limit abilities for health protective behaviors, such as condom negotiation.[188, 193] These power differentials may be augmented when drugs are exchanged for sex, with the drug seeking of the individual who is receiving drugs for sex adding to the power of the individual who is offering drugs in exchange for sex.[188] This unequal power differential may be particularly relevant to our findings, as the two classes who associated most highly with transactional sex were the classes that either endorsed sexualized stimulant use only or had co-substance use during RAI but not IAI. As these two classes were also negatively associated with utilization of biomedical prevention, members of these classes may be at increased risk for HIV transmission or acquisition. Individuals who engage in transactional sex may be less likely to use PrEP/PEP due to anticipated stigma from partners finding out about either sex work or risk behaviors.[185, 194] This stigma may also be compounded by co-occurring vulnerabilities that pose barriers to engagement in HIV prevention/treatment services, such as economic instability, unstable

housing, lack of health insurance, or distrust in the health system.[170, 195-197] Additionally, lack of a current PrEP/PEP prescription or having a detectable viral load may be related to substance use itself, as stimulant use has been associated with PrEP and antiretroviral therapy nonadherence.[118, 198-201] Furthermore, previous studies have suggested that patterns of sexualized substance use, such as frequency of drug use and ability to plan for sex, may affect acceptability and adherence to PrEP.[202] As MSM who engage in sexualized substance use and transactional sex are particularly vulnerable to HIV/STIs, these findings demonstrate the importance of improving outreach efforts and reducing barriers to PrEP/PEP and HIV care among stimulant-using MSM.

In addition to the aforementioned sexual risk behaviors, depression was positively associated with sexualized stimulant use - consistent with previous research linking stimulants with depression.[65-67] While stimulant use in general has been associated with depression, recent studies have demonstrated that sexualized substance use has also been linked with depressive symptoms.[133, 203] As MSM have been shown to utilize both stimulants and sexual intercourse as avoidant coping mechanisms for depression, it is possible that MSM in this cohort may have utilized sexualized stimulant use as a means of sensation seeking in order to mitigate negative depressive symptoms.[27, 84, 204] Collectively, these findings further support a syndemic of substance use, transactional sex, depression, sexual risk behavior, and HIV risk among MSM, which has been previously described in the literature, and is likely contributing to ongoing HIV/STI disparities that are observed among MSM.[205, 206] These results further affirm the need for continued development of comprehensive HIV prevention/treatment programs that address these intersecting burdens which are contributing to the ongoing HIV/STI epidemic.

When stratified by race/ethnicity, our findings demonstrated that HIV risk behaviors, depression, and STIs were highly associated with membership in a sexualized substance-using class among Black and Latinx MSM, compared to non-sexualized substance-using Black/Latinx MSM

and non-Black/non-Latinx MSM. These findings were consistent with prior research demonstrating that Black and Latinx MSM are disproportionately affected by syndemic conditions, such as substance use, transactional sex, depression, and barriers to HIV prevention/treatment, which contribute to ongoing HIV/STI disparities that are experienced by these subpopulations.[193, 197, 207, 208] However, our research extends the literature by suggesting that Black/Latinx MSM who participate in certain patterns of sexualized substance use may be disproportionately affected by syndemic conditions than their Black/Latinx counterparts who do not engage in sexualized substance use. These disparities were particularly notable for Black MSM, who represented the only racial/ethnic group where sexualized substance was negatively associated with using biomedical prevention.

MSM of color face numerous barriers to engagement in HIV prevention/treatment services, including socioeconomic factors, stigma, difficulties navigating the health system, discrimination from healthcare providers, and medical distrust, all of which contribute to disparities in PrEP utilization and viral load suppression.[209-213] Further complicating these barriers to HIV treatment/prevention are high rates of social marginalization and minority stress experienced by MSM of color, which have been shown to contribute to increased rates of depression, substance use, transactional sex, and condomless sex.[214-217] In fact, a recent study demonstrated that Black MSM who reported more syndemic conditions, such as sexual orientation stigma, substance use, depression, and transactional sex, were less likely to use PrEP, despite having high rates of PrEP knowledge.[218] These factors are additionally complicated by higher prevalence of HIV/STIs within sexual networks that comprise Black and Latinx MSM, further reinforcing the disproportionate impact of HIV/STIs experienced by this subpopulation.[219, 220] Consequently, future research and interventions are needed to understand and address these intersecting vulnerabilities that are contributing to ongoing HIV/STI disparities experienced by MSM of color.

Limitations

Our findings must be considered in the context of limitations. Given that this analysis comprises a diverse cohort of MSM with high prevalence of substance use and sexual risk behaviors, generalization of our findings to other populations of MSM may be limited. While LCA provided us with the ability to group individuals based on latent constructs and to evaluate characteristics based on class membership, this method does come with limitations. As LCA assigns individuals to classes based on response patterns to select variables, assignment of individuals to the correct class may not occur.[156, 221] Additionally, we were unable to determine the exact number of participants who comprised specific classes, as class membership is based on probabilities.[156] As the number of classes were derived from model fit statistics and investigator decisions, it is possible that model classes may be biased. Furthermore, as latent class models are constrained to measures contained within the data, there is the potential for omitted variables bias or poor specification of the latent classes. This limitation is particularly relevant as this was a secondary data analysis and certain constructs regarding sexual risk behaviors were not captured within the dataset, such as sexual partnership dynamics within specific dyadic relationships and contexts/settings in which the substance use and sexual activities took place. While this is a longitudinal dataset, LCA analyzes data cross-sectionally, which may lead to bias. For example, when we evaluated class membership across timepoints, we observed variation in the proportion of participants who maintained the same class membership across visits, suggesting that class membership by individual participants likely changed over time. As such, this analysis may benefit from a LCA with a longitudinal framework, such as a latent transition analysis, which would be an important future direction. While more complex analytic approaches, such as latent transition analysis, were outside the scope of the dissertation, we feel that our LCA findings are useful given visit-level data. As all data was self-reported, there is the possibility of social desirability and recall bias, though surveys were administered through computer-assisted self-interview to minimize such bias. An additional limitation was that cannabis use was not

included in our analysis which may have biased our results, given the high prevalence of cannabis use in the sample. Finally, as we combined insertive and receptive oral sex into one composite oral sex variable, this may have introduced bias into our sample. However, as reported insertive and receptive oral sex were highly concordant (over 83% of the sample reported participating in both receptive and insertive oral sex or no oral sex), we believe the risk of bias is low.

Conclusions

As sexualized substance use is an important contributor to ongoing HIV/STI disparities that are experienced by MSM, research evaluating risk behaviors and contexts surrounding sexualized substance use are critical to inform public health efforts designed to reduce disparities that are experienced by this population. To the best of our knowledge, this analysis is among the first to utilize LCA to evaluate patterns of sexualized stimulant and alcohol use at the level of specific sex acts that occurred. In addition to increasing the body of knowledge, findings from this study provide critical information regarding sexual risk behaviors and syndemic conditions that surround sexualized stimulant and alcohol use which can be used to develop tailored HIV prevention interventions for substance-using MSM, a subpopulation of MSM at high risk for HIV/STI transmission. For example, these findings highlight the importance of combining screening and treatment of substance use disorders into HIV prevention interventions and the HIV care continuum.

Collectively, our findings revealed that patterns of sexual activities, and the specific substances that are used during those activities, confer different risk behavior profiles for HIV/STI acquisition/transmission among this cohort of MSM. For example, sexualized stimulant use was positively associated with risk factors for HIV/STI transmission such as having an STI, engaging in transactional sex, attending a circuit/hookup/sex party, depressive symptoms, and was negatively associated with health protective behaviors, such as using biomedical prevention to prevent HIV

transmission. These findings demonstrate the potential utility of interventions that link substance use treatment with HIV/STI treatment/prevention as well as importance of future research to better understand the contexts during which sexualized stimulant use occurs. Additionally, our findings demonstrated that Black/Latinx MSM who engaged in sexualized stimulant use were more likely to experience syndemic health conditions, such as having an STI and depressive symptoms, than their Black/Latinx counterparts who did not engage in sexualized stimulant use. These disparities were particularly notable among Black MSM, where stimulant use only or stimulant/alcohol use during oral sex and RAI were negatively associated with the use of biomedical prevention. Together, these results highlight the disproportionate impact that sexualized substance use has on HIV/STI transmission dynamics among MSM of color. Our findings underscore the importance of future research and interventions that are designed to both understand and address these intersecting vulnerabilities which contribute to ongoing HIV/STI disparities experienced by subpopulations of substance using MSM.

Tables and Figures

Table 4.1 Participant characteristics, sexual risk behaviors, mental health, and sexualized substance use reported at mSTUDY visits 8/2014-3/2020 (N=2,395)

Variable	n (%)	Sexualized substance use**	n (%)
Age (median, IQR)	32 (27-38)	Oral sex stimulants	
HIV		No	1,545 (64.6%)
Negative	1,201 (50.2%)	Yes	847 (35.4%)
Living with HIV	1,194 (49.9%)	Oral sex alcohol	
Race/Ethnicity		No	1,456 (60.9%)
Non-Black/Non-Latinx	259 (10.8%)	Yes	936 (39.1%)
Black	943 (39.4%)	IAI stimulants	
Latinx	1,193 (49.8%)	No	1,813 (75.9%)
Sexually transmitted infection		Yes	577 (24.1%)
Negative	1,963 (82.0%)	IAI alcohol	
Positive	432 (18.0%)	No	1,696 (71.0%)
Biomedical prevention		Yes	694 (29.0%)
No	1,572 (65.6%)	RAI stimulants	
Yes	823 (34.4%)	No	1,741 (72.9%)
Regular stimulant use		Yes	646 (27.1%)
No	1,860 (77.7%)	RAI alcohol	
Yes	533 (22.3%)	No	1,747 (73.2%)
Binge drinking frequency		Yes	640 (26.8%)
None	1,215 (50.8%)		
Monthly or less	909 (38.0%)		
Weekly/daily	269 (11.2%)		
Transactional Sex			
No	1,950 (81.4%)		
Yes	445 (18.6%)		
Circuit/hookup/sex party			
No	1,919 (80.1%)		
Yes	476 (19.9%)		
Depression			
No	1,594 (66.6%)		
Yes	801 (33.4%)		

IAI = insertive anal intercourse; RAI = receptive anal intercourse

**May not equal 2,395 as equation-wise deletion was used for development of latent classes

Table 4.2 Sexual activities occurring in last 3 months reported at mSTUDY visits 8/2014-3/2020 (N=2,395)

Sexual activity	n (%)
Oral sex	
No	38 (1.6%)
Yes	2,354 (98.4%)
Receptive oral sex	
No	278 (11.6%)
Yes	2,111 (88.4%)
Insertive oral sex	
No	196 (8.2%)
Yes	2,195 (91.8%)
Insertive anal intercourse (IAI)	
No	590 (24.7%)
Yes	1,800 (75.3%)
Receptive anal intercourse (RAI)	
No	731 (30.6%)
Yes	1,656 (69.4%)
Oral sex and/or any anal intercourse (AI)	
Oral sex only	214 (9.0%)
AI only	38 (1.6%)
Oral sex and AI	2,139 (89.5%)
Oral sex, RAI, and/or IAI	
Oral sex only	214 (9.1%)
IAI and oral sex	506 (21.6%)
RAI and oral sex	354 (15.1%)
RAI, IAI, and oral sex	1,272 (54.2%)
RAI and/or IAI	
No AI	214 (9.0%)
IAI only	516 (21.7%)
RAI only	375 (15.7%)
Both RAI and IAI	1,278 (53.6%)

Table 4.3 Participant characteristics stratified by type of anal intercourse in last 3 months (N=2,395 study visits)

	No AI (n=214)	IAI only (n=516)	RAI only (n=375)	RAI and IAI (n=1,278)	
	n (%)	n (%)	n (%)	n (%)	p-value
Number participants	128	220	164	418	--
Study visits*	1 (1-2; 1-9)	2 (1-3; 1-9)	1 (1-3; 1-10)	2 (1-4; 1-10)	--
Age (median, IQR)	35 (29-42)	34 (29-38)	31 (27-39)	31 (27-38)	**<0.001**
Race/Ethnicity					
Non-Black/Non-Latinx	27 (12.6%)	54 (10.5%)	36 (9.6%)	141 (11.0%)	**<0.001**
Black	108 (50.5%)	250 (48.4%)	142 (37.9%)	438 (34.3%)	
Latinx	79 (36.9%)	212 (41.1%)	197 (52.5%)	699 (54.7%)	
HIV					
Negative	109 (50.9%)	330 (64.0%)	163 (43.5%)	593 (46.4%)	**<0.001**
Living with HIV	105 (49.1%)	186 (36.0%)	212 (56.5%)	685 (53.6%)	
Sexually transmitted infection					
Negative	195 (91.1%)	450 (87.2%)	306 (81.6%)	1,001 (78.3%)	**<0.001**
Positive	19 (8.9%)	66 (12.8%)	69 (18.4%)	277 (21.7%)	
Biomedical prevention					
No	156 (72.9%)	332 (64.3%)	256 (68.3%)	818 (64.0%)	**0.046**
Yes	58 (27.1%)	184 (35.7%)	119 (31.7%)	460 (36.0%)	
Regular stimulant use					
No	164 (76.6%)	445 (86.2%)	291 (77.6%)	954 (74.8%)	**<0.001**
Yes	50 (23.4%)	71 (13.8%)	84 (22.4%)	322 (25.2%)	
Binge drinking frequency					
None	128 (59.8%)	253 (49.0%)	193 (51.5%)	637 (49.9%)	**0.020**
Monthly or less	62 (29.0%)	199 (38.6%)	131 (34.9%)	511 (40.0%)	
Weekly/daily	24 (11.2%)	64 (12.4%)	51 (13.6%)	128 (10.0%)	
Transactional Sex					
No	202 (94.4%)	465 (90.1%)	308 (82.1%)	965 (75.5%)	**<0.001**
Yes	12 (5.6%)	51 (9.9%)	67 (17.9%)	313 (24.5%)	
Circuit/hookup/sex party					
No	192 (89.7%)	446 (86.4%)	328 (87.5%)	943 (73.8%)	**<0.001**
Yes	22 (10.3%)	70 (13.6%)	47 (12.5%)	335 (26.2%)	
Depression					
No	154 (72.0%)	372 (72.1%)	247 (65.9%)	818 (64.0%)	**0.003**
Yes	60 (28.0%)	144 (27.9%)	128 (34.1%)	460 (36.0%)	
Oral sex stimulants**					
No	64 (30.2%)	102 (19.8%)	137 (36.5%)	536 (41.9%)	**<0.001**
Yes	148 (69.8%)	414 (80.2%)	238 (63.5%)	742 (58.1%)	
Oral sex alcohol**					
No	54 (25.5%)	191 (37.0%)	119 (31.7%)	567 (44.4%)	**<0.001**
Yes	158 (74.5%)	325 (63.0%)	256 (68.3%)	711 (55.6%)	

*median (interquartile range [IQR]; range)

IAI = insertive anal intercourse; RAI = receptive anal intercourse

**May not equal 2,395 as equation-wise deletion was used for development of latent classes

Table 4.4 LCA goodness of fit indices according to number of classes

Classes	G^2	DF	AIC	CAIC	BIC	ABIC	Entropy	BLRT
1	7435.2	57	7447.2	7488.7	7482.7	7463.7	1	0.001
2	3905.7	50	3931.7	4021.8	4008.8	3967.5	0.95	0.001
3	1628.8	43	1668.8	1807.4	1787.4	1723.8	0.94	0.001
4	482.4	36	536.4	723.4	696.4	610.6	0.95	0.001
5	254.9	29	322.9	558.4	524.4	416.3	0.95	0.001
6	99.7	22	181.7	465.7	424.7	294.4	0.96	0.034
7	35.6	15	131.6	464.1	416.1	263.6	0.93	0.002
8	15.9	8	125.9	506.8	451.8	277.1	0.93	0.255
9	15.4	1	139.4	568.8	506.8	309.8	0.81	--

G^2 = Likelihood Ratio statistic; DF = degrees of freedom; AIC = Akaike Information Criterion; CAIC = Consistent AIC; BIC = Bayesian Information Criterion; ABIC = Sample Size Adjusted BIC; BLRT = Bootstrapped Likelihood Ratio Test (p-value for 1,000 bootstrap samples)
Note: the BLRT compared models of k to k+1 classes with 1,000 bootstrap samples

Figure 4.1 LCA goodness of fit indices according to number of classes

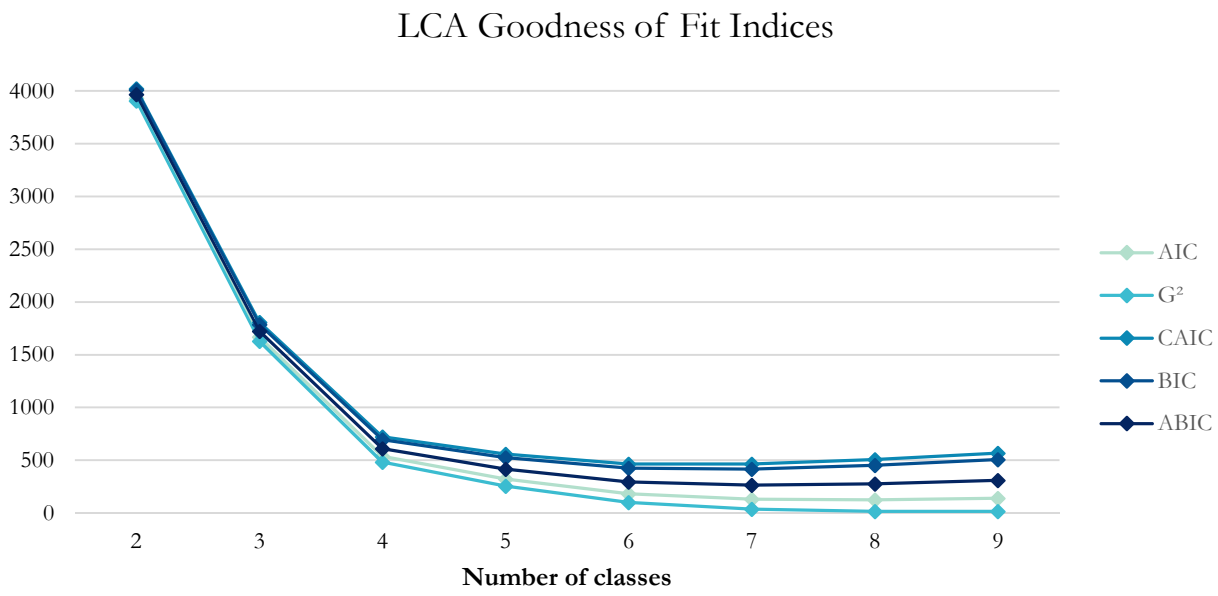


Table 4.5 Item response and membership probabilities of each latent class (5-class model)

	Stimulants/ Alcohol	No Substance Use	Stimulants Only	Stimulants/Alcohol Oral Sex and RAI	Alcohol Only
Membership probability	11.2%	44.8%	17.4%	3.9%	22.6%
Sex type/Substance used					
Oral sex stimulants	**0.999**	0.049	**0.983**	**0.942**	0.044
Oral sex alcohol	**0.993**	0.047	0.007	**0.956**	**0.974**
IAI stimulants	**0.963**	0.003	**0.739**	0.008	0.010
IAI alcohol	**0.976**	0.002	0.003	0.021	**0.789**
RAI stimulants	**0.810**	0.013	**0.843**	**0.652**	0.004
RAI alcohol	**0.808**	0.017	0.012	**0.696**	**0.622**

Note: item response probabilities > 0.6 are in bold
IAI = insertive anal intercourse; RAI = receptive anal intercourse

Table 4.6 Item response and membership probabilities of the 6-class model

	Class 1	Class 2	Class 3	Class 4	Class 5	Class 6
Membership probability	11.6%	5.4%	17.5%	42.3%	21.0%	2.2%
Sex type/Substance used						
Oral sex stimulants	**0.999**	0.400	**0.984**	0.039	0.027	**0.918**
Oral sex alcohol	**0.995**	**0.882**	0.008	0.002	**0.979**	**0.921**
IAI stimulants	**0.782**	0.009	**0.730**	0.003	0.000	**0.918**
IAI alcohol	**0.800**	0.005	0.000	0.002	**0.831**	**0.985**
RAI stimulants	**0.961**	0.071	**0.843**	0.013	0.004	0.007
RAI alcohol	**0.959**	0.258	0.014	0.016	**0.635**	0.006

Note: item response probabilities > 0.6 are in bold
IAI = insertive anal intercourse; RAI = receptive anal intercourse

Figure 4.2 Percentage of participants who maintained latent class membership at each timepoint

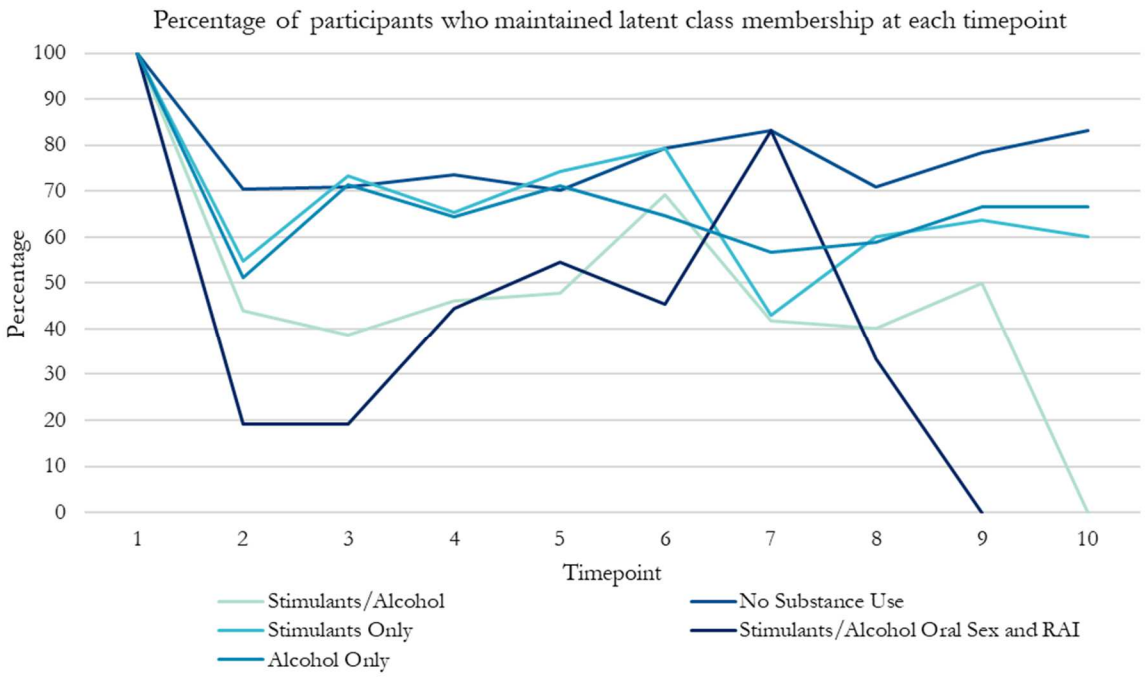


Table 4.7 Multivariable adjusted associations of predicted LCA class membership

	Stimulants/ Alcohol	No Substance Use	Stimulants Only	Stimulants/Alcohol Oral Sex and RAI	Alcohol Only
Variable	aOR (95% CI)	Ref	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
HIV	**1.43 (1.07-1.91)**	Ref	**3.68 (2.77-4.90)**	1.25 (0.74-2.09)	**0.41 (0.33-0.51)**
Positive STI	**1.81 (1.29-2.56)**	Ref	**2.71 (2.03-3.63)**	**1.97 (1.14-3.39)**	1.12 (0.83-1.52)
Biomedical prevention	0.92 (0.68-1.22)	Ref	**0.75 (0.57-0.98)**	**0.50 (0.29-0.84)**	1.15 (0.92-1.44)
Transactional sex	**7.04 (5.01-9.89)**	Ref	**8.11 (5.88-11.17)**	**8.19 (4.95-13.55)**	1.07 (0.73-1.59)
Circuit/hookup/sex party	**3.25 (2.34-4.53)**	Ref	**2.87 (2.10-3.91)**	**1.93 (1.12-3.33)**	**2.16 (1.63-2.87)**
Depression	**1.75 (1.31-2.33)**	Ref	**1.95 (1.51-2.52)**	1.14 (0.72-1.80)	0.99 (0.78-1.26)

Note: Bold indicates aOR does not cross 1
IAI = insertive anal intercourse; RAI = receptive anal intercourse

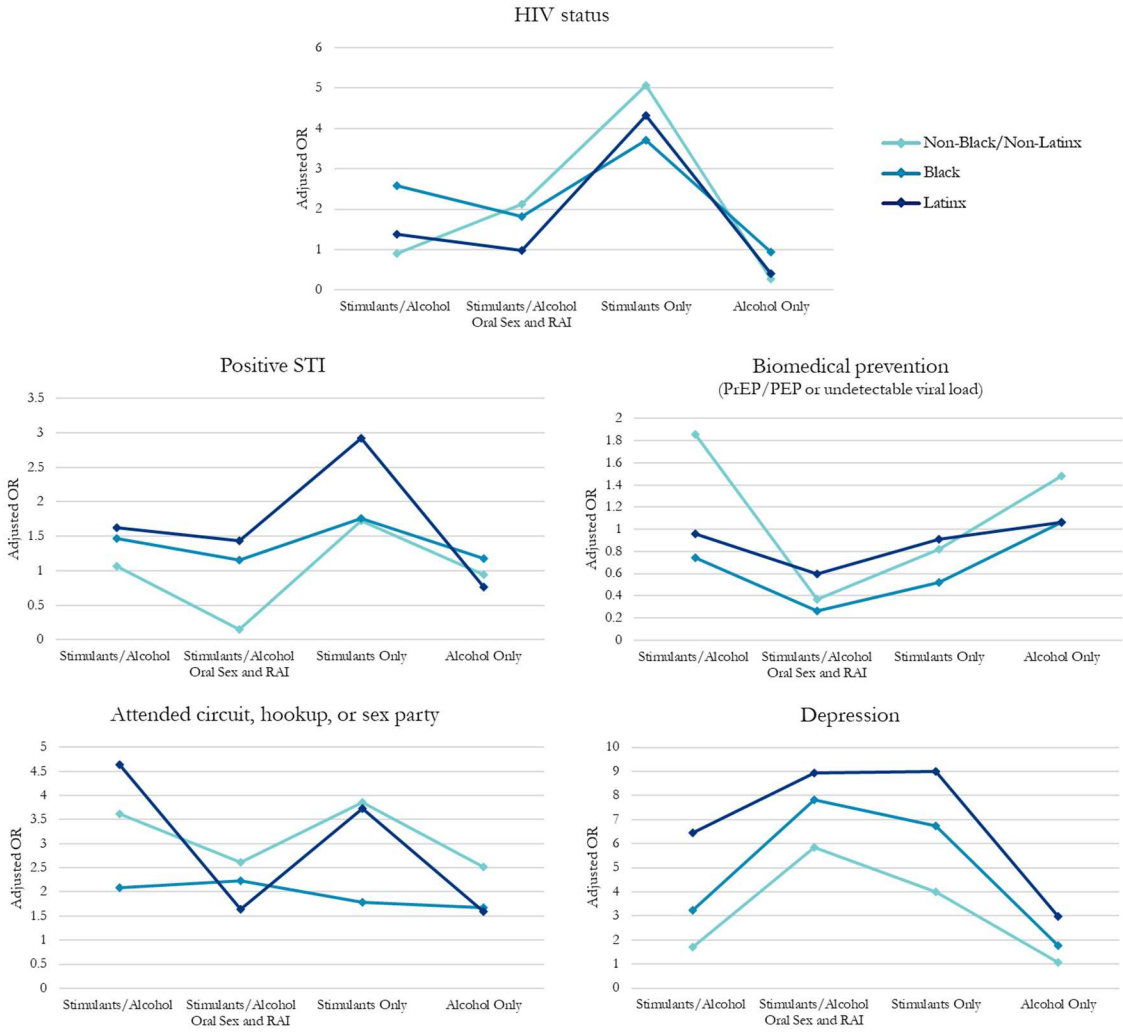
Table 4.8 Multivariable adjusted associations of predicted LCA class membership stratified by race/ethnicity

	Stimulants/ Alcohol	No Substance Use	Stimulants Only	Stimulants/Alcohol Oral Sex and RAI	Alcohol Only
Non-Black/Non-Latinx					
Membership probability	10.8%	48.7%	22.4%	2.5%	15.7%
Variable	aOR (95% CI)	Ref	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
HIV	0.90 (0.39-2.06)	Ref	**5.06 (2.32-11.02)**	2.13 (0.27-16.55)	**0.27 (0.12-0.60)**
Positive STI	1.07 (0.41-2.75)	Ref	1.73 (0.80-3.70)	0.15 (0.00-62.55)	0.94 (0.38-2.28)
Biomedical prevention	1.86 (0.81-4.23)	Ref	0.82 (0.42-1.62)	0.37 (0.03-4.02)	1.48 (0.70-3.12)
Circuit/hookup/sex party	**3.62 (1.51-8.70)**	Ref	**3.86 (1.86-8.03)**	2.62 (0.34-20.04)	**2.52 (1.05-6.02)**
Depression	1.71 (0.73-3.99)	Ref	**3.99 (2.03-7.81)**	5.85 (0.86-39.76)	1.08 (0.49-2.37)
Black					
Membership probability	10.1%	48.7%	13.5%	4.7%	23.0%
Variable	aOR (95% CI)	Ref	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
HIV	**2.58 (1.62-4.08)**	Ref	**3.70 (2.35-5.81)**	1.81 (0.87-3.74)	0.94 (0.67-1.33)
Positive STI	1.47 (0.85-2.54)	Ref	**1.76 (1.06-2.93)**	1.16 (0.49-2.71)	1.18 (0.75-1.87)
Biomedical prevention	0.74 (0.46-1.19)	Ref	**0.52 (0.32-0.85)**	**0.26 (0.09-0.72)**	1.06 (0.75-1.51)
Circuit/hookup/sex party	**2.09 (1.23-3.57)**	Ref	**1.78 (1.05-3.02)**	**2.23 (1.00-4.95)**	**1.67 (1.09-2.56)**
Depression	1.53 (0.96-2.41)	Ref	**2.75 (1.79-4.23)**	1.97 (0.99-3.94)	0.70 (0.47-1.05)
Latinx					
Membership probability	11.7%	42.8%	19.1%	4.2%	22.3%
Variable	aOR (95% CI)	Ref	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
HIV	1.38 (0.92-2.05)	Ref	**4.32 (2.93-6.37)**	0.98 (0.51-1.86)	**0.40 (0.29-0.56)**
Positive STI	**1.63 (1.00-2.64)**	Ref	**2.92 (1.96-4.34)**	1.43 (0.59-3.48)	0.77 (0.48-1.22)
Biomedical prevention	0.96 (0.64-1.44)	Ref	0.91 (0.64-1.31)	0.60 (0.29-1.26)	1.06 (0.76-1.48)
Circuit/hookup/sex party	**4.63 (2.95-7.25)**	Ref	**3.73 (2.46-5.65)**	1.64 (0.71-3.80)	**1.59 (1.04-2.42)**
Depression	**3.21 (2.16-4.77)**	Ref	**2.27 (1.59-3.23)**	1.11 (0.54-2.28)	1.20 (0.84-1.70)

Note: Bold indicates aOR does not cross 1

IAI = insertive anal intercourse; RAI = receptive anal intercourse

Figure 4.3 Adjusted odds ratios of predicted class membership stratified by race/ethnicity



Reference group: no substance use
RAI = receptive anal intercourse; PrEP = pre-exposure prophylaxis; PEP = post-exposure prophylaxis

Chapter 5.

Comparing factors associated with increased stimulant use in relation to HIV status using a machine learning and prediction modelling approach

Abstract

Background: Stimulant use is an important driver of HIV/STI transmission among MSM. Evaluating factors associated with increased stimulant use is critical to inform HIV prevention programming efforts. This study seeks to use machine learning techniques for variable selection to determine characteristics associated with increased stimulant use and whether these factors differ by HIV status.

Methods: This analysis utilized data from a longitudinal cohort of predominantly Black/Latinx MSM in Los Angeles, California, half with substance use and half living with HIV. Every 6 months from 8/2014-12/2020, participants underwent STI screening and completed surveys evaluating the following: demographics, substance use, sexual risk behaviors, and last partnership characteristics. Least absolute shrinkage and selection operator (lasso) and elastic net models were used for variable selection and creation of predictive models to determine factors associated with an interval increase in self-reported stimulant use from prior visit. Mixed-effects logistic regression models were used to evaluate associations between predictors selected from lasso and elastic net models and increased stimulant use. Sub-analyses stratifying participants based on HIV status were conducted to evaluate differences in predictors associated with increased stimulant use by HIV status.

Results: Among 2,095 study visits from 467 participants, an interval increase in stimulant use was reported at 20.9% (n=438) study visits. Increased stimulant use was positively associated with unstable housing, co-substance use, STI diagnosis, anal intercourse while intoxicated, transactional

sex, and last partner stimulant use. Among participants living with HIV, increased stimulant use was associated with binge drinking, vaping/cigarette use, use of poppers, and transactional sex. Among HIV-negative participants, increased stimulant use was associated with sexual partner concurrency, anal intercourse while intoxicated, group sex while intoxicated, transactional sex, and last partner alcohol use.

Conclusions: Machine learning techniques can be a useful tool for variable selection and creation of predictive models. Our findings demonstrated that risk behaviors associated with increased stimulant use may differ based on HIV status and suggest that co-substance use and partnership contexts should be considered in the development of HIV prevention/treatment interventions.

Introduction

Stimulant use is substantially higher among MSM compared to the U.S. general population.[29, 30] Consumption of stimulants among MSM frequently occurs within social and sexual contexts, such as night clubs, bath houses, circuit parties, and sex clubs.[32-34] Additionally, stimulant use, particularly methamphetamine, is a significant driver of HIV transmission among MSM - thought to be driven by risky sexual behaviors with serodiscordant partners.[6, 39, 40, 42, 43] Despite significant advances in the field of biomedical HIV prevention, HIV transmission among stimulant-using MSM remains one of the predominant factors contributing to the ongoing HIV epidemic.[33, 133] As such, understanding factors that are related to stimulant use and HIV risk behavior is important to develop effective, targeted interventions for this key population.

Factors contributing to HIV transmission among MSM differs by HIV status. For HIV-negative individuals, HIV acquisition is predominantly through condomless receptive anal intercourse with sexual partners living with HIV.[9, 11, 13] For individuals living with HIV, risk for transmitting HIV to sexual partners is driven by condomless anal intercourse (particularly insertive) and HIV viral load, with higher levels of HIV viremia associated with increased risk of HIV transmission.[222-225] Furthermore, prevalence of stimulant use differs based on HIV status, with MSM living with HIV having higher prevalence of stimulant use (12.3%) compared to HIV-negative MSM (5.9%).[29, 30] Given the differences that exist with regard to mechanisms of HIV transmission and prevalence of stimulant use, it is important to understand stimulant use and risk behavior within the context of HIV status, given the impact that these distinctions may have on HIV transmission dynamics.

While it is clear that stimulant use is linked to risky sexual behaviors, evidence suggests that the epidemic of stimulant use among MSM is likely complex and multifaceted.[118, 119] For example, in a qualitative study by Halaktis et al., motivations for stimulant use differed by HIV status, with MSM

living with HIV tending to report that they used stimulants for sexual reasons while HIV-negative MSM used stimulants socially.[119] Furthermore, MSM living with HIV have a higher likelihood of using stimulants to avoid unpleasant emotions, social pressures, and conflict, compared to their HIV-negative counterparts.[121] The higher use of stimulants in sexual contexts among MSM living with HIV suggests that stimulants may be used as an avoidance coping strategy to deal with an HIV diagnosis or as a means to dispel potential anxieties or fears associated with sexual activity.[119, 122] Furthermore, evidence suggests that the contribution of stimulants on sexual risk behavior may also differ. Specifically, stimulants may have a greater impact on frequency of condomless intercourse among individuals living with HIV compared those who are HIV-negative.[122] Longitudinal analysis of a cohort of MSM in the U.S. revealed that MSM who used stimulants and underwent HIV seroconversion had higher frequency of risky sexual behaviors and stimulant use than those who remained HIV-negative.[120]

The heterogeneities in stimulant use patterns that are observed among MSM highlight that the factors which are driving the ongoing stimulant and HIV epidemics are nuanced and complex. Determining whether the contexts that surround stimulant use patterns differ based on HIV status represents an important next step in understanding how stimulant use contributes to HIV transmission dynamics within the sexual networks of MSM and the development of effective interventions. However, data explicitly evaluating these differential factors contributing to ongoing stimulant use is limited, with most studies either including HIV status as a covariate or evaluating stimulant use within the context of a cohort comprised exclusively of MSM living with HIV or their HIV-negative counterparts.[42, 111, 115, 226] This study seeks to bridge this gap by evaluating differences in factors associated with increased stimulant use among a diverse cohort of MSM and how these factors may differ according to HIV status. This analysis will utilize machine learning techniques, specifically least absolute shrinkage and selection operator (lasso) and elastic net regression, for

variable selection and to create predictive models to evaluate factors associated with increased stimulant use. Sub-analyses stratifying participants based on HIV status will be conducted to evaluate differences in predictors associated with increased stimulant use by HIV status. To the best of our knowledge, this will be one of the first studies to use machine learning techniques for variable selection to select predictors associated with increased stimulant use and to compare potential differences according to HIV status. Findings from this analysis will provide important information on whether contexts surrounding stimulant use differ according to HIV status, which can be used to inform future HIV programming efforts.

Methods

Data Source and Study Procedures

Data for this analysis came from the Men Who Have Sex with Man and Substance Use Cohort at UCLA Linking Infections, Noting Effects (mSTUDY; U01 DA036267) – a NIDA-funded, ongoing longitudinal cohort designed to evaluate the impact of substance use on HIV transmission. The cohort consists of a group of racially/ethnically diverse MSM who are living with or are at high-risk for HIV. Methods have been previously described.[153, 154] Briefly, the cohort consists of predominantly Black and Latinx MSM, half with active substance use at enrollment, and participants were recruited to include half MSM living with HIV and half HIV-negative MSM by design. HIV-negative MSM were recruited from the UCLA Vine Street Clinic, a community-based university research clinic through online advertisements and community flyers. Participants living with HIV were recruited from the Los Angeles LGBT Center, which provides clinical and community resources for the lesbian, gay, and transgender community in Los Angeles. Inclusion criteria for the cohort were: 1) 18-45 years old, 2) born male, 3) condomless anal intercourse with a man in past 6 months (if HIV-negative). Study enrollment began in August 2014, and recruitment is ongoing to replace loss to follow-up. As of the date of this study, 577 MSM have been enrolled. This

analysis consists of study visits that occurred from August 2014 (study inception) to December 2020.

Study visits occurred every 6 months. At each visit, participants underwent STI screening, clinician interview, and completed a computer-assisted self-interview survey that collected sociodemographic data as well as information surrounding substance use, mental health, and sexual behaviors. Rectal and pharyngeal swabs as well as urine samples were collected at each visit and screened for gonorrhea/chlamydia (GC/CT) with nucleic acid amplification testing (Aptima Combo 2, GenProbe, San Diego, CA). Blood samples were collected at each study visit for syphilis screening that used rapid plasma reagin (RPR) with confirmatory testing via the *Treponema pallidum* particle agglutination test (TPPA). Infectious syphilis (i.e., primary, secondary, or early latent) was defined following positive test results through confirmation from the local health department and using the Centers for Disease Control determination.[155] Study personnel assisted with notifying participants of their STI testing results and facilitated linkages to care for positive test results. The study was reviewed and approved by the Office of Human Research Participant Protection (OHRPP) at the University of California, Los Angeles.

Statistical Analysis

Measures and Exploratory Analysis

The purpose of this analysis was to utilize machine learning for variable selection and prediction to determine which factors were associated with increased stimulant use. We additionally sought to evaluate if predictors associated with increased stimulant use differed by HIV status. Our increased stimulant use outcome variable was constructed from the question "In the last 6 months, how often did you use [drug name]?". Possible drugs included methamphetamine, cocaine powder, and crack cocaine. Potential response options included: "Daily", "Weekly", "Monthly", "Less often", "Once", and "Never". Methamphetamine, cocaine powder, and crack cocaine were

combined into one composite "stimulants" variable. A lag variable was then created that indicated whether there was an increase in reported stimulant use compared to the immediately preceding visit (e.g., reporting using stimulants once at T_n followed by weekly use at T_{n+1} or never at T_n followed by once at T_{n+1}). The increase in stimulant use outcome variable was coded as a dichotomous variable (no increase in reported stimulant use vs increased reported stimulant use). An exploratory analysis was conducted to evaluate the stability of reported stimulant use across timepoints, changes in reported stimulant use across time, missing data, skip patterns, and to determine if multiple imputation would be appropriate.[227-229]

Variables for inclusion in machine learning models were selected based on two criteria 1) if the variable was retained in the dataset for the duration of the study and 2) if the variable had a conceptually relevant relationship with stimulant use based on the literature. First, all variables were screened to determine whether the variable was retained in participant questionnaires across the duration of the study. As this is a longitudinal cohort that serves as a research platform for multiple investigators, questions are added and removed from the dataset due the addition of sub-projects as well as to maintain a questionnaire that is not too long and cumbersome for participants to complete. After variables that were consistently asked for the duration of the dataset were identified, variables were then selected based on their relationships with stimulant use based on the literature. These variables are listed in Table 5.1 and included participant demographics as well as the following constructs: housing instability,[230] history of incarceration,[231] intimate partner violence,[232] depression,[114] substance use,[233] sexual behaviors,[234, 235] and reported characteristics of the participant's last sexual partner.[236]

Lasso and Elastic Net

Two statistical methods were used for variable selection and creation of predictive models: least absolute shrinkage and selection operator (lasso) and elastic net. Both methods are used for

regularization of variables that facilitate model selection and can be used for creation of prediction models.[237, 238] Lasso and elastic net were selected over ordinary least squares (OLS) regression as they provide more sparse models (i.e., models with fewer parameters) that allow for prediction and improve interpretability of the final model. As OLS regression maintains all variables within the model (even if irrelevant or redundant), OLS models are prone to overfitting, resulting in models with low bias but high variance, which may perform well on a training dataset but make inaccurate predictions on testing data. Furthermore, standard goodness of fit tests tend to perform poorly on evaluating the validity of OLS models until non-linearity becomes severe.[239, 240] As lasso and elastic net prevent overfitting of models, both methods were selected as they outperform OLS with variable selection and creation of predictive models.

Lasso regression facilitates sparse models by using L1 regularization, adding a penalty to the model that is equal to the absolute value of the magnitude of the coefficients. The sum of the absolute value of the coefficients is constrained, which reduces some coefficient magnitudes to 0, resulting in the elimination of those predictors from the model.[241, 242] A regularization parameter (λ) controls the strength of the L1 penalty, creating a larger penalty for more complex models. Increases in λ cause increased bias in the model, while decreases in λ cause increased variance. These features make lasso a useful method in creating models that initially have large numbers of predictors and can assist with incorporating only relevant predictors into the model.[237] A limitation of lasso is that if variables are similar or correlated, lasso will arbitrarily retain only one variable and set the remaining correlated variables to zero, potentially resulting in biased models.[243] Due to the potential limitation of lasso eliminating correlated variables from the model, lasso models were compared to models where variables were selected with elastic net regression.

Elastic net is an extension of lasso regression that combines L1 and L2 regularization. L2 regularization, commonly known as ridge regression, is similar to lasso regression with the difference

being that the penalty added to the model is equal to the square of the magnitude of the coefficients. The λ in ridge regression regularizes the coefficients so that large magnitudes of coefficients are more heavily penalized, reducing complexity and multicollinearity. As such, ridge regression shrinks the magnitude of spurious coefficients.[237, 243] However, an important distinction between ridge and lasso is that ridge regression does not eliminate variables from the models. While the risk of overfitting is reduced by shrinking the magnitude of coefficients, models that arise from ridge regression can still be extremely complex as all variables are retained in the model.[241]

Elastic net is a hybrid of ridge and lasso regression in that it includes L1 and L2 regularization. By doing this, elastic net can maintain correlated predictors within the model if at least one of the predictors has a strong relationship with the outcome variable. Unlike lasso regression, correlated variables are not dropped from the model, which prevents loss of information and improves model performance.[244] Similar to lasso, elastic net does come with limitations. First, elastic net can be computationally expensive, as the relative weight of the L1 and L2 penalties require cross-validation. An additional limitation of elastic net comes with its flexibility of combining both L1 and L2 regularization. As elastic net is more flexible in terms of its parameters, it can be vulnerable to overfitting. As such, the model that elastic net chooses could perform well with the training/testing data for that specific dataset but may result in overfitting if the same prediction model were to be used with different datasets.[237, 243] Given the advantages and drawbacks of each regularization method, both approaches were utilized and models from each method were compared based on goodness of fit, interpretability, and reliability.

The dataset was split into two subsamples to create a testing and training dataset.[244] Predictors of interest that were selected based on the exploratory analysis and that were conceptually relevant based on the literature (Table 5.1) were included in initial models. All models controlled for age, race/ethnicity, and HIV status. Models were fit on the testing dataset using ten-fold cross-

validation and ordered based on the magnitude of the tuning parameter (λ).[245] The model with the value of λ that minimized the out-of-sample prediction error was identified and cross-validation plots were created to ensure that that λ was minimized. To prevent overfitting with lasso models, cross-validation plots were used to select the largest λ within one standard error of the λ that minimized out-of-sample prediction error.[246] For lasso models, a table of knot points (value of λ's where variables were added or dropped) was created to compare the model where λ was minimized to models with progressively larger values of λ within one standard error.[244, 245, 247] Goodness of fit and model performance was compared for lasso knots within one standard error of the minimal value of λ based on the parameters below. The one standard error rule was only used for lasso and not elastic net models, since elastic net utilizes both L1 and L2 regularization (not just L1 regularization as lasso) and utilization of the one standard error rule would ignore the relative weights of the L1 and L2 penalties. As such, only one elastic net model was selected, which was the model with the value of α (the relative weight of L1 and L2 regularization) and λ that minimized out-of-sample prediction error via cross-validation.[244]

Following model selection based on cross-validation for both lasso and elastic net, goodness of fit (GOF) and model performance was assessed. Models were evaluated by 1) deviance and deviance ratios (GOF), 2) area under the receiver operating curve (AUC; performance), and 3) Matthews Correlation Coefficient (MCC; performance). Deviance and deviance ratios were calculated for both the training and testing datasets using lasso and elastic net models, with lower deviance suggestive of a better fitting model.[237] Given the longitudinal structure of the data, mixed-effects logistic regression models were created using participant ID as the random intercept. Using the mixed-effects logistic regression models, receiver operating curves were created, with the model with the highest AUC indicating better predictive performance.[248, 249] A confusion matrix was created

for each model to calculate the MCC, which evaluated each model's performance in correctly identifying positive and negative cases, with the following formula:[250]

$$MCC = \frac{(TP*TN)-(FP*FN)}{\sqrt{(TP+FP)(TP+FN)(TN+FP)(TN+FN)}}$$

The MCC takes a value of -1 to 1, where values close to the absolute value of 1 indicating that the model performs well in predicting both positive and negative cases.[251, 252] MCC was used over other commonly used scalar metrics, such as accuracy, precision, recall, and F1 score, to predict model performance as these other metrics can be subject to class imbalance and asymmetry.[251] Unlike other scalar metrics, MCC is perfectly symmetric and values both positive and negative classification equally.[252] The lasso model that had the lowest deviance ratio, highest AUC, MCC closest to an absolute value of 1, and had the most consistent indices between the training and testing datasets was selected as the lasso model that would be compared to elastic net. The selected lasso model was then compared to elastic net. The model that had the lowest deviance ratio, highest AUC, MCC closest to an absolute value of 1, most consistent indices between the training and testing datasets, and had the least amount of spurious predictors (suggestive of overfitting) was selected as the final model.

We also conducted a series of sensitivity analyses. Given the limitation of correlated variables potentially being eliminated from lasso models, we conducted several sensitivity tests to ensure that our results were not biased by the elimination of correlated predictors from lasso models. First, we conducted pair-wise correlations between all potential variables outlined in Table 5.1, identified pairs of variables that had a correlation > 0.5, and then ran the lasso models with each correlated predictor separately to ensure that inclusion/exclusion of one or both of the correlated predictors would not alter the variables that were selected by the models. We calculated variance inflation factors (VIF) and tolerance across variables to ensure no predictors had a tolerance < 0.1 or VIF >

10, which would be suggestive of multicollinearity. Additionally, we changed how variables were coded to evaluate how variable coding may affect selection of predictors. We also created a lasso model that used reported stimulant use (instead of increased stimulant use) to evaluate whether predictors selected by the models changed. As stimulant use was reported on 5-levels ("Daily", "Weekly", "Monthly", "Less often", "Once", and "Never") this lasso model was creased using lasso with linear regression, rather than logistic regression. We selected linear regression as lasso only supports linear, logit, probit, and poisson models in Stata. Finally, we also created a model using decreased stimulant use as our outcome variable to evaluate differences in selected predictors.

Stratification by HIV Status

To evaluate how predictors of increased stimulant use may differ by HIV status, the dataset was stratified according to HIV status – with one dataset containing only MSM living with HIV and one dataset containing HIV-negative cases only. Training and testing datasets were created, and lasso and elastic net models were fit as above. However, when we attempted to control for age and race/ethnicity while fitting the lasso and elastic net models, the models performed poorly with some models only selecting the control variables. As such, lasso and elastic net models were fit without the control variables. Age and race/ethnicity were then added to the mixed-effects logistic regression models using the predictors that were selected by lasso and elastic net. Additionally, as lasso models tended to select fewer predictors when the dataset was stratified by HIV status, we also evaluated lasso models up to one standard error above, in addition to one standard error below, where λ was minimized. GOF and model performance were evaluated as above, and the same criteria were used to select the final models.

For the final models selected, descriptive statistics (frequency, percentage, median, interquartile range [IQR]) of the selected predictors were calculated. Chi-square and Kruskal-Wallis tests were used to evaluate whether the distribution of predictors differed based on whether there

was an increase in reported stimulant use. Mixed-effects logistic regression analyses were used to calculate unadjusted and adjusted odds ratios using the variables that were selected from the final lasso model, using increased stimulant use as our outcome variable and participant ID as the random intercept. Complete case analysis was used for all regression analyses, and all analyses were conducted using Stata 16.1 (StataCorp, College Town, TX).

Results

Goodness of Fit and Selection of Final Models

Entire Cohort

The cross-validation plot for lasso models using the training dataset for the entire cohort is in Figure 5.1. The value of λ that minimized out of sample prediction error was 0.016. Based on the cross-validation plot, the maximum value of λ within 1 standard error (SE) was 0.030. Table 5.2 demonstrates GOF indices for three potential lasso models (largest λ within 1SE, λ between the largest λ within 1 SE and minimal λ, and the minimal λ based on cross-validation) and the elastic net model. As expected, the number of variables included in lasso models increased as the λ penalty declined. Interestingly, the elastic net model selected similar predictors as the lasso models and selected the same predictors as the model with the minimal λ plus 5 additional variables (knowing last partner HIV status, last partner used poppers, had a one-time partner in last 6 months, group sex while intoxicated, and had a partner who was an unknown person in last 6 months). As the number of predictors included in models increased, the sample size decreased slightly across models due to observations that were removed due to missing data, as complete case analysis was used. Comparing GOF indices for all 4 models, the elastic net model did appear to slightly outperform the lasso models. However, GOF between all 4 models were very similar overall. For example, the range of deviance values were 0.91-0.95 and AUC was 0.73-0.81 across all 4 models. We then evaluated

the GOF indices, in the context of bias-variance tradeoff, when selecting the final lasso model to be compared to elastic net.

We selected the lasso model with the largest λ within 1SE as our final lasso model because 1) the improvement in GOF offered by including additional predictors across lasso models was minimal, 2) it allowed for the sparsest model, and 3) while inclusion of additional predictors improved GOF statistically, the real-world utility of including these variables was unlikely to provide substantial benefit. A table demonstrating descriptive statistics as well as a table showing unadjusted and adjusted odds ratios are in Tables 5.3 and 5.4 for the selected lasso model and Tables 5.5 and 5.6 for the selected elastic net model, respectively. When comparing the mixed-effects logistic regression models, it appeared that, while the elastic net model selected more predictors than the lasso model, most of these additional predictors were not associated with increased stimulant use. This finding suggested that, while elastic net did provide improved GOF indices compared to the lasso model with including additional variables, these additional variables were unlikely to provide meaningful inferences from which we would be able to draw conclusions. Additionally, while elastic net did reduce variance by including these additional predictors (as evidenced by the improved GOF indices) this likely came at the expense of adding potential bias to our models. As such, we chose to use the lasso model as our final model.

Cohort Stratified by HIV Status

The cross-validation plot for lasso models that included only participants living with HIV are in Figure 5.2. Compared to the cross-validation plot of the entire cohort, the slope of the line leading to the minimal value of λ was steeper with a less smooth descent and the potential values of λ that minimized out of sample error were much more narrow when the sample was limited to only participants living with HIV. Table 5.7 demonstrates GOF indices for potential lasso models and the elastic net model. Similar to the models created for the entire cohort, GOF statistics did not vary

much across the different models. However, there were bigger discrepancies in fit indices between testing and training datasets when the dataset was restricted to only participants living with HIV, compared to the models that were fit on the entire cohort. As the amount of predictors that minimized λ were rather sparse, we opted to evaluate models 2 knots above the minimal λ value (e.g., the models with smaller λ than the minimal λ value) to observe if GOF indices improved when the number of predictors in the model were increased, suggesting that the minimal λ may be underfit. When comparing the lasso models, the model with the best fit statistics overall had a λ smaller than the λ that was selected by the lasso algorithm, suggesting that the λ that was selected by the lasso algorithm may have been too sparse and underfit the data. As such, we selected the model where λ=0.030, as this model had the highest AUC and MCC of the lasso models selected. A table demonstrating descriptive statistics as well as a table showing unadjusted and adjusted odds ratios are in Tables 5.8 and 5.9 for the selected lasso model and Tables 5.10 and 5.11 for the selected elastic net model, respectively. We ultimately selected the lasso model as the final model for participants living with HIV, as the elastic net model suggested that the additional variables selected were unlikely to provide meaningful inferences from which we would be able to draw conclusions, similar to the elastic net model which included the entire cohort.

Finally, we fit lasso and elastic net models for the participants who were HIV negative, with the lasso cross-validation plot in Figure 5.3. Similar to findings we had encountered when the models were fit with the cohort living with HIV, the slope of the line leading to the minimal value of λ was much steeper and the potential values of λ that minimized out of sample error were much more narrow than the models fit on the whole cohort. Table 5.12 demonstrates GOF indices for the potential lasso models and the elastic net model. Given the sparsity of predictors selected in the model selected by the lasso algorithm, we also evaluated models that were up to 3 lasso knots higher than the minimal λ, due to concern that the values selected by the lasso algorithm may be underfit.

We ultimately selected the lasso model where $\lambda = 0.040$, as this lasso model had the best GOF indices, further supporting our concern that the model selected by the lasso algorithm may be underfit. A table demonstrating descriptive statistics as well as a table demonstrating the unadjusted and adjusted odds ratios are in Tables 5.13 and 5.14 for the selected lasso model and Tables 5.15 and 5.16 for elastic net. We ultimately selected the lasso model as our final model, as the additional variables included in the elastic net model did not appear to provide meaningful inferences from which we would be able to draw conclusions – similar to the findings we encountered when evaluating models that involved the entire cohort and when restricting to only participants living with HIV. Additionally, the lasso model outperformed the elastic net model in terms of GOF indices, particularly with regard to the MCC, suggesting that the elastic net was not only overfit, but that the model was so overfit that it interfered with the performance of the model.

Findings

Entire Cohort

The sample consisted of 2,095 visits across 467 participants. Participants reported an interval increase in stimulant use at 20.9% (n=438) of study visits (Table 5.3). Participant-level stimulant use patterns across timepoints that were plotted for 60 randomly selected participants are in Figure 5.4. Median age at study visits was 33 years (IQR 28-40; range 18-50) and 53.8% (n=1,126) of study visits were completed by participants who were living with HIV. Almost half of study visits were completed by Latinx participants (50.1% of study visits; n=1,049), followed by Black participants (38.9%; n=814), then White participants (6.5%; n=136), with the smallest group comprising participants who identified in other racial/ethnic groups (4.6%; n=96). Most participants had not used stimulants in the past 6 months (56.7% of visits, n=1,187), whereas daily use was reported at 10% (n=209) of visits, weekly use at 9.6% (n=62) of visits, and monthly use reported at 6.1% (n=43) of visits. Participants who reported an interval increase in stimulant use tended to more

frequently report unstable housing, unemployment, higher levels of cannabis use and binge drinking, regular opiate use, and having a last partner who used substances (specifically, stimulants and ecstasy). Screening positive for an STI occurred more frequently during visits where there was an interval increase in stimulant use (23.7%; n=104/334) compared to visits where there was no increase in stimulant use (13.8%; n=228/1,429).

Lasso models tended to select predictors that were associated with constructs surrounding financial insecurity (e.g., unstable housing, employment status, transactional sex), substance use (e.g., binge drinking, cannabis use, and regular opiate use), sexual risk behaviors (e.g., anal intercourse while intoxicated, transactional sex, screening positive for an STI), and last partnership characteristics (e.g., last partner used stimulants, last partner used ecstasy, last partner was an unknown person). In unadjusted analysis, all predictors that were selected by lasso were associated with increased stimulant use, except for the control variables that were forced into models (Table 5.4). While HIV status, employment status, having a last partner who used ecstasy, and regular opiate use were associated with increased stimulant use in unadjusted analyses, these variables were no longer associated with increased stimulant use when controlling for all predictors in the adjusted model. Participating in transactional sex associated the most highly with increased stimulant use, with MSM who participated in transactional sex having 2.30 times higher odds of reporting increased stimulant use (95% CI 1.60-3.30) compared to those who did not participate in transactional sex. Any cannabis use was associated with an increase in stimulant use, with participants reporting daily cannabis use having 2.24 times higher odds (95% CI 1.55-3.25) and weekly or less frequent cannabis use having 1.82 times higher odds (1.31-2.54) of reporting increased stimulant use compared to participants who did not report any cannabis use. Participants who reported that their last partner used stimulants had higher odds of reporting increased stimulant use (aOR 2.21; 95% CI 1.62-3.00) than those who's last partner did not use stimulants. Having a positive

STI screen was associated with 1.59 times higher odds (95% CI 1.14-2.21) of reporting increased stimulant use, compared to participants who had a negative STI screen. Increased stimulant use was also positively associated with unstable housing, binge drinking, vaping/cigarette use, regular opiate use, participating in anal intercourse while intoxicated, and having a last partner who was an unknown person, compared to participants who did not report those behaviors.

We also conducted a sensitivity analysis using decreased stimulant use as our outcome. Decreased stimulant use was reported at 23.1% (n=521/2,251) of visits (Table 5.17). In adjusted analysis, decreased stimulant use was positively associated with unemployment, living with HIV, binge drinking, substance use treatment, and anal intercourse while intoxicated, compared to participants who did not report those characteristics/behaviors. While many of these predictors overlap with increased stimulant use, we believe that this overlap is likely due to the high prevalence of substance use and sexual risk behaviors in this cohort as a whole - particularly as this cohort was designed to comprise a high-risk sample of MSM. Table 5.18 shows the unadjusted and adjusted β coefficients of the lasso model that used the native, 5-level self-reported stimulant use variable. Overall, stimulant use was positively associated with living with HIV, unstable housing, incarceration, intimate partner violence, cannabis use, cigarette/vaping, regular other prescription drug use, regular opiate use, anal intercourse while intoxicated, group sex while intoxicated, transactional sex, and having a last partner that used stimulants.

Stratified by HIV Status

Among participants living with HIV, the sample consisted of 1,199 study visits across 242 participants. An interval increase in stimulant use was reported at 22.9% (n=274) of visits completed by participants living with HIV. Median age was 36 (IQR 31-41) and at 50.5% (n=606) of visits participants reported never using stimulants in last 6 months, 12.1% (n=145) reported daily use, 11.6% (n=139) reported weekly use, and 11.7% (n=140) reported less than monthly use (Table 5.8).

Participants who reported increased stimulant use tended to report higher frequency of unstable housing, binge drinking, vaping/cigarette use, using poppers regularly, having a regular sexual partner in last 6 months, participating in transactional sex, and having their last sexual partner use ecstasy compared to those who did not report increased stimulant use. When limiting the sample to only participants living with HIV, many of the predictors that lasso models selected were the same as the lasso models that were fit on the entire cohort, including unstable housing, binge drinking, vaping/cigarette use, regular opiate use, participating in transactional sex, and reporting that their last sexual partner used ecstasy. Predictors that were correlated with increased stimulant use among participants living with HIV but that lasso did not select for the entire cohort included reporting regular poppers use, having a regular partner in the last 6 months, and reporting that one's last partner was a regular/main partner. In adjusted analyses (Table 5.9), increased stimulant use was positively associated with unstable housing, binge drinking, vaping/cigarette use, using poppers regularly, and transactional sex and was negatively associated with reporting that one's last partner was a regular/main partner, compared to participants who were living with HIV that did not report those characteristics/behaviors.

Among HIV-negative participants, the sample consisted of 912 study visits across 228 participants. Increased stimulant use was reported at 18.2% (n=166) of study visits completed by the HIV-negative cohort. Median age was 30 (IQR 26-36). Compared to participants living with HIV, HIV-negative participants tended to report stimulant use less frequently, with HIV-negative participants reporting never using stimulants in last 6 months at 64.7% (n=590) of visits, daily stimulant use at 7.1% (n=65) of visits, weekly use at 6.8% (n=62) of visits, and less than monthly use at 7.5% (n=68) of visits. HIV-negative participants who reported increased stimulant use tended to report lower income and education levels as well as higher frequency of unemployment, unstable housing, cannabis use, sexual risk behaviors (anal intercourse while intoxicated, group sex while

intoxicated, transactional sex, concurrent partners), and last partner substance use (alcohol, poppers, and injection drug use) compared to those who did not report increased stimulant use (Table 5.13). In adjusted analysis (Table 5.14), increased stimulant use was positively associated with unstable housing, cannabis use, transactional sex, group sex while intoxicated, and having a last sexual partner who injected drugs and was negatively associated with higher levels of education, compared to HIV-negative participants who did not endorse those characteristics/behaviors.

When limiting the sample to HIV-negative participants, the predictors selected by lasso did not have as much overlap with the entire cohort as the lasso models that only included participants living with HIV. However, lasso models for the HIV-negative participants and the entire cohort both contained employment status, unstable housing, cannabis use, transactional sex, and anal sex while intoxicated. However, the lasso models that included the HIV-negative participants tended to include more sexual risk behaviors (e.g., group sex while intoxicated and concurrent partners) and last partner substance use (last partner used alcohol, poppers, or injected drugs) that were not included in the lasso models for entire cohort. When comparing lasso models between those living with HIV and HIV-negative participants, unstable housing and transactional sex were correlated with increased stimulant use for both groups, yet additional selected predictors between the two groups appeared to differ. Among HIV-negative MSM, constructs pertaining to socioeconomic status, sexual risk behaviors, and last partner substance use appeared to correlate highly with increased stimulant use and were selected by lasso models. Conversely, among participants living with HIV, polysubstance use (i.e., reported use of other drugs and binge drinking) correlated highly with increased stimulant use and was selected by lasso models.

Discussion

In this analysis of a diverse cohort of MSM in Los Angeles, California, increased stimulant use was positively associated with unstable housing, transactional sex, polysubstance use, STI

diagnosis, and sexual risk behavior. However, when stratified by HIV status, polysubstance use was highly correlated with increased stimulant use among participants living with HIV, whereas last partnership characteristics and sexual risk behaviors were correlated with increased stimulant use for HIV-negative participants. This analysis is among the first to utilize lasso for variable selection and creation of predictive models to evaluate factors that are associated with increased stimulant use. Our approach demonstrates that machine learning techniques can be a useful and efficient tool to assist with selecting relevant predictors from datasets with large amounts of potential variables to create conceptually relevant models. By using lasso for variable selection, this approach allowed us to evaluate differences in predictors that were associated with increased stimulant use according to HIV status. These findings provide an important next step in understanding the disproportionate effect that the complicated stimulant use epidemic has on certain MSM subpopulations and could potentially be used to inform future HIV prevention interventions.

Our findings demonstrate that increased stimulant use was positively associated with unstable housing and transactional sex, which is concordant with prior studies.[253-255] Unstable housing and transactional sex were consistently selected across all models, suggesting that these variables were highly correlated with increased stimulant use, which may be attributed to minority stress and bias experienced by MSM. Compared to the general population, sexual minorities disproportionately experience unstable housing, often due to homophobia, rejection, and abuse that forces them from their homes.[256, 257] Stimulants may be used to cope with distressing emotions associated with stigmatization, victimization, and bias associated with being a sexual minority.[258, 259] Furthermore, stimulants are often used as form of coping with stressful feelings associated with being unstably housed as well as a means of survival.[260, 261] For example, stimulants may be utilized to stay awake to protect belongings, facilitate social interaction with others, and as an alternative to psychiatric medications.[262] Unstably housed MSM may also use stimulants to obtain a sense of

belonging, to bond with others, or due to perceived social norms, given the higher prevalence and social acceptance of substance use among unstably housed individuals.[261, 263] Transactional sex has a strong association with unstable housing, as transactional sex can be used as a mechanism to obtain financial support or shelter among unstably housed individuals.[264, 265] Transactional sex may also occur for the purpose of obtaining drugs, which may also explain its association with increased stimulant use.[266] Collectively, these findings underscore the importance of addressing the underlying factors that often drive the interdependent relationship between unstable housing, stimulant use, and transactional sex. Specifically, these findings suggest the potential utility of interventions, such as contingency management, that are designed to reduce these barriers through linkages to financial or community resources in exchange for not using substances.[267, 268]

In addition to variables associated with socioeconomic disadvantage (e.g., unstable housing and transactional sex), having a last partner who used stimulants and engaging in anal intercourse while intoxicated were positively associated with increased stimulant use. These findings highlight the social and sexual contexts during which stimulants are used by MSM and the prominence of stimulant use within certain gay subcultures, where stimulants are frequently used in sex clubs, circuit parties, and bath houses.[32-34] Stimulants are often used by MSM in sexual settings to obtain sexual partners, increase libido, augment sexual stamina, and for disinhibition.[88, 133] However, sexualized stimulant use can impair decision making and lead to sexual risk behaviors, such as increased number of casual partners and impaired condom negotiation.[37, 269] Due to these contexts, sexualized stimulant use is independently associated with HIV/STIs and is an important driver of HIV/STI transmission within the sexual networks of stimulant-using MSM.[39, 44] For example, recent stimulant use was attributed to 32.7% of HIV seroconversions among MSM enrolled in a multi-institutional cohort.[40] As increased stimulant use was also positively associated with having an STI, which is a known risk factor for HIV transmission, these findings underscore the importance of

coordinated public health efforts that incorporate treatment of comorbid stimulant use into HIV/STI treatment and prevention interventions.

Among individuals living with HIV, polysubstance use both correlated highly and was associated with increased stimulant use. Polysubstance use among MSM living with HIV may be used as a means to cope with an HIV diagnosis, HIV-related stigma, or depressive symptoms.[270, 271] Substance use may be used as an avoidant coping strategy to mitigate stress associated with being a sexual minority.[272, 273] This minority stress may be exacerbated with the stigma of living with HIV, potentially resulting in increased substance use. This consideration is highlighted in a study by Jerome et. al., where MSM living with HIV who used substances tended to report higher levels of distressing emotions related to an undesirable self-image and daily stressors than their HIV-negative counterparts.[274] The need for external validation due to a negative self-image may cause MSM living with HIV to engage in substance use to feel more desirable and to form connections with others in both social and sexual contexts.[275] MSM living with HIV may use substances for social inclusion among groups where substance use is socially accepted and due to fear that they may be excluded from these groups if they do not engage in substance use.[178] Furthermore, the normalization of substance use within social circles may perpetuate continued substance use and serve as a potential barrier to reductions in substance use, particularly if the individual perceives that their social network would not be supportive of their desire to stop using substances.[275, 276] Understanding these contexts and drivers of substance use among MSM living with HIV is particularly important from a public health standpoint given the well-established connection between substance use and sexual risk behavior,[53, 277] which was further supported by our findings demonstrating that increased stimulant use was associated with transactional sex and having a last partner that was a non-primary partner. In addition to increased sexual risk behavior, substance use is also associated with antiretroviral therapy nonadherence, further reinforcing the contribution of substance use to ongoing HIV

transmission within certain MSM subpopulations.[278] Collectively, these findings highlight the importance of interventions designed to improve peer support, reduce HIV-related stigma, and the potential value of integrating substance use treatment into the HIV care continuum.

In contrast to participants living with HIV where polysubstance use was associated with increased stimulant use, among HIV-negative participants, socioeconomic status, sexual risk behaviors (e.g., having group sex or anal intercourse while intoxicated), and last partner substance use correlated highly with increased stimulant use. These findings are consistent with data demonstrating that stimulant use is highly prevalent within sexual contexts and associated with increased individual-level sexual risk behaviors among stimulant-using MSM.[38, 279] However, these findings suggest that partnership dynamics may influence stimulant use patterns or vice versa. It is possible that stimulant-using MSM may seek out partners with similar patterns of substance use or that their partners' substance use may influence their own behaviors.[280-282] Alternatively, HIV-negative MSM may have a tendency to use stimulants within sexualized contexts where substance use is more common and where they are more likely to encounter partners who also engage in sexualized substance use, such as circuit parties, bath houses or sex clubs.[89, 283] Beyond individual-level risk behavior, substance use within sexual partnerships has been associated with increased sexual risk behaviors, such as condomless anal intercourse with serodiscordant partners.[284, 285] Furthermore, within stable partnerships, partnership-level substance use may influence couples' sexual behavior as well as decision-making surrounding risk mitigation strategies, such as sexual agreements and whether those agreements are broken.[286] These findings highlight the sexual contexts in which substances are used among HIV-negative MSM and further support the extant literature indicating that stimulant use likely plays a substantial role in HIV seroconversion and STI transmission within these stimulant-using subpopulations.[37, 287] As partnership dynamics likely influence sexualized substance use and subsequent sexual risk behaviors, these results suggest that

partnership dynamics should be considered when creating HIV prevention interventions and demonstrate the potential utility of sexual partnership-based interventions that combine substance use treatment with HIV prevention.

Limitations

Our findings must be considered within the context of limitations. While machine learning techniques can be a useful tool for variable selection, the variables that are selected by these models are prone to misspecification, which may have resulted in variables associated with increased stimulant use being excluded from models. This limitation is particularly relevant in the context of lasso, which has the tendency to exclude correlated variables from models. However, we attempted to account for this in our approach by conducting a series of sensitivity analyses to ensure that correlated variables were not spuriously deleted. It is also important to note that, while lasso and elastic net selected variables that were highly correlated with our outcome, we are unable to make causal inferences from our models. While our outcome variable measured self-reported increased stimulant use in last 6-months, other measures that were included in our models varied in terms of timeline (i.e., sexual risk behaviors were assessed at 6 months, 3 months, and with last partner). As such, it is possible that spurious associations may have occurred due to the multiple timeframes that were assessed, such as associations with risk behaviors that did not overlap in time with each other or when the stimulant use occurred. However, we felt that inclusion of these multiple timepoints were justified in our analysis so that we could limit omitted variables bias as much as possible by including numerous potential measures that may be associated with increased stimulant use in our models.

As this was a secondary data analysis, our study was constrained to measures that were contained in the dataset, resulting in potential omitted variables bias. This consideration is particularly relevant as constructs surrounding stimulant use are multifaceted and complex and may

not have been adequately captured in the surveys that were administered as part of the parent study. Furthermore, certain constructs regarding sexual risk behaviors and substance use were not captured within the dataset, such as partnership dyadic characteristics and contexts/settings in which the substance use and sexual activities took place, which need to be considered in the interpretation of our results and represent an important area of future research, given the association of last partnership characteristics with increased stimulant use. Finally, as this cohort comprises a diverse sample of MSM with high rates of substance use, this limits the generalizability of our findings to other subpopulations of MSM.

Conclusions

As stimulant use is an important driver of sexual risk behavior and HIV/STI transmission among certain MSM subpopulations, research evaluating factors that contribute to increased stimulant use is critical to improve the health of this population and to inform targeted, effective HIV prevention interventions. This study is among the first to utilize lasso for variable selection to evaluate factors associated with increased stimulant use among a diverse cohort of MSM. Our analysis adds to the literature by demonstrating that variables commonly collected in HIV and substance use research can be used to build models which predict stimulant use with a reasonable degree of accuracy. Our findings demonstrate that increased stimulant use was positively associated with unstable housing and transactional sex across all models. These results underscore the importance of designing HIV prevention interventions that address the underlying factors that often drive the interdependent relationship between unstable housing, stimulant use, and transactional sex which contribute to ongoing HIV/STI transmission among vulnerable MSM subpopulations. Specifically, these findings suggest the potential utility of interventions that incorporate strategies such as contingency management, which provides linkages to community or financial resources in exchange for not using substances.[267, 268]

Our analysis revealed that polysubstance use was associated with increased stimulant use among participants living with HIV. These findings suggest that MSM living with HIV may use stimulants in conjunction with other substances as a coping strategy to mitigate negative feelings associated with an HIV diagnosis, HIV-related stigma, or depressive symptoms.[270, 274] In contrast, our analysis demonstrated that increased stimulant use among HIV-negative participants was associated with sexual risk behaviors, sexualized substance use, and last partner substance use. As increased stimulant use was also associated with having a last partner who used stimulants for the entire cohort, these findings highlight that sexual contexts and partnership dynamics likely drive stimulant use within certain MSM subpopulations. Collectively, these findings indicate that the underlying motivations and factors which contribute to stimulant use patterns among MSM likely differ based on HIV status and suggest that these differences should be accounted for in the design of HIV prevention and treatment interventions. Our results demonstrate the potential role of interventions that reduce HIV-related stigma and integrate substance use treatment into the HIV care continuum for stimulant-using MSM living with HIV. Conversely, stimulant-using HIV-negative MSM may benefit from HIV prevention interventions that address sexualized substance use as well as sexual partnership-based interventions.

Tables and Figures

Table 5.1 Predictors included in lasso and elastic net models

Variable	Levels	Variable	Levels
Outcome Variable		Circuit party*	Yes, No
Increased stimulant use	Yes, No	New male partners*	Yes, No
Control Variables		Transgender partner*	Yes, No
Age	Continuous	Main partner*	Yes, No
Race/ethnicity	White, Black, Latinx, Other	Regular partner*	Yes, No
HIV	Yes, No	Unknown partner*	Yes, No
Demographics/Mental Health		One-time partner*	Yes, No
Education	< HS, HS, > HS	Number male partners*	0, 1-2, 3-9, 10+
Income	< 10k, 10-30k, > 30k	Group sex while intoxicated**	Yes, No
Sexual orientation	Gay, Bisexual/Other	AI while intoxicated**	Yes, No
Gender identity	Male, Not Male	***Last Partner***	
Employment	Employed, Unemployed	Main/Regular partner	Yes, No
Unstable housing*	Yes, No	Length of relationship	Days, Months, Years
Incarcerated*	Yes, No	Used alcohol	Yes, No
Intimate partner violence	Yes, No	Used cannabis	Yes, No
Depression	CESD ≤ 23, CESD > 23	Used poppers	Yes, No
Substance Use*		Used ecstasy	Yes, No
Vaping or cigarette use	Yes, No	Used ED meds	Yes, No
Binge drinking	Never, ≤ Monthly, Weekly/Daily	Used stimulants	Yes, No
Receiving substance use tx	Yes, No	Used opiates	Yes, No
Cannabis use	Never, < Daily, Daily	Injected drugs	Yes, No
Regular opiate use	Yes, No	Concurrency with last partner	Yes, No
Regular poppers use	Yes, No	Transactional sex with	Yes, No
Regular other rx drug use	Yes, No	Partied with	Yes, No
Sexual Risk		Met in public setting for sex	Yes, No
PrEP/PEP or Undetect VL	Yes, No	Was a one-time partner	Yes, No
STI	Yes, No	Was an unknown person	Yes, No
Exchange sex last 3 months	Yes, No	Never saw again after sex	Yes, No
Concurrent partners*	Yes, No	Knew HIV status	Yes, No

HS = High School; CESD = Center of Epidemiological Studies Depression Scale; tx = treatment; rx = prescription; PrEP = Pre-Exposure Prophylaxis; PEP = Post-Exposure Prophylaxis; Undetect VL = Undetectable Viral Load; STI = Sexually Transmitted Infection (any site gonorrhea/chlamydia and/or syphilis); AI = Anal Intercourse; ED = Erectile Dysfunction

*last 6 months; **last 3 months

Figure 5.1 Lasso cross-validation plot for entire cohort

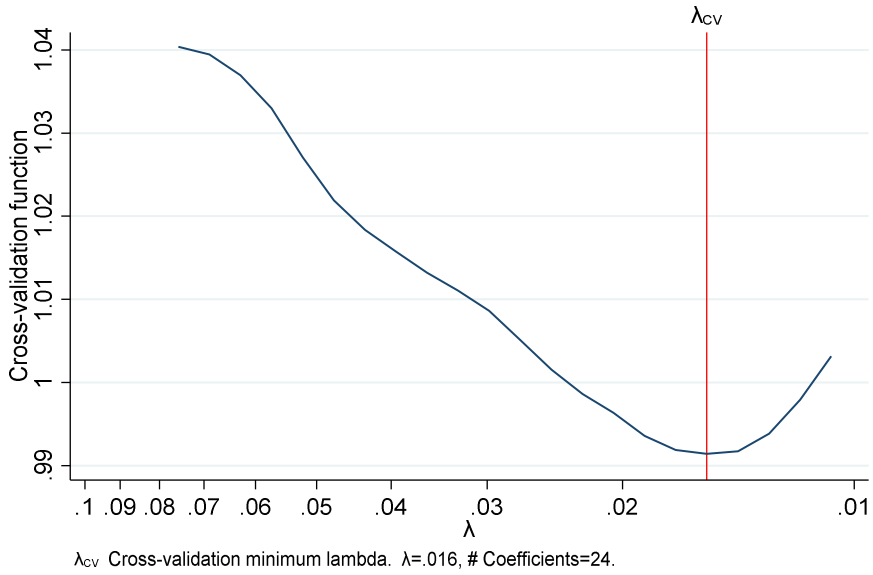


Table 5.2 Goodness of fit indices for lasso and elastic net models for entire cohort

		Lasso Models				Elastic Net	
λ	λ=0.030*		λ=0.021		λ=0.016**		--	
Variables added			Regular poppers use		Regular poppers use		Regular poppers use	
			Last partnership length		Last partnership length		Last partnership length	
			Regular use other rx drugs		Regular use other rx drugs		Regular use other rx drugs	
					Education		Education	
					Income		Income	
							Know last partner serostatus	
							Last partner used poppers	
							One-time partner last 6 mos	
							Group sex while intoxicated	
							Unknown partner last 6 mos	
	Training	**Testing**	**Training**	**Testing**	**Training**	**Testing**	**Training**	**Testing**
n	1,028	1,059	985	1,021	949	986	917	947
Deviance	0.95	0.93	0.94	0.91	0.92	0.92	0.93	0.91
Deviance Ratio	0.08	0.09	0.09	0.10	0.10	0.10	0.10	0.10
AUC	0.73	0.79	0.74	0.79	0.75	0.79	0.76	0.81
MCC	0.23	0.30	0.27	0.30	0.26	0.30	0.27	0.34

AUC = Area Under the Receiving Operating Curve; MCC = Matthew's Correlation Coefficient; rx = prescription
*Largest λ within 1 standard error; **Minimal λ based on cross-validation

Note all models contain the following variables: age, race/ethnicity, HIV status, cannabis use last 6 months, unstable housing, vaping/cigarette use, transactional sex, anal intercourse while intoxicated, last partner used stimulants, employment status, binge drinking, last partner was unknown person, STI diagnosis, last partner used ecstasy, regular opiate use

Table 5.3 Visit-level participant characteristics stratified by increased stimulant use for final lasso model of the entire cohort (N=2,095 study visits)

	No Change (n=1,657)	Increased Use (n=438)	p-value
Control Variables	**n (%)**	**n (%)**	
Age (median, IQR)	33 (28-40)	33 (28-39)	0.76
Race/Ethnicity			
White	104 (6.3%)	32 (7.3%)	0.13
Black	665 (40.1%)	149 (34.0%)	
Latinx	812 (49.0%)	237 (54.1%)	
Other	76 (4.6%)	20 (4.6%)	
HIV			
Negative	791 (47.7%)	178 (40.6%)	**0.008**
Living with HIV	866 (52.3%)	260 (59.4%)	
Demographics			
Employment status			
Employed	1,327 (80.1%)	311 (71.0%)	**<0.001**
Unemployed	330 (19.9%)	127 (29.0%)	
Unstable housing			
No	1,454 (87.7%)	326 (74.4%)	**<0.001**
Yes	203 (12.3%)	112 (25.6%)	
Substance Use			
Binge drinking last 6 months			
Never	965 (58.2%)	207 (47.3%)	**<0.001**
Monthly or less	540 (32.6%)	166 (37.9%)	
Weekly/daily	152 (9.2%)	65 (14.8%)	
Vaping/Cigarette			
No	1,226 (74.0%)	247 (56.4%)	**<0.001**
Yes	431 (26.0%)	191 (43.6%)	
Cannabis Use			
No	890 (53.7%)	157 (35.8%)	**<0.001**
Weekly or less frequent	434 (26.2%)	144 (32.9%)	
Daily	333 (20.1%)	137 (31.3%)	
Regular opiate use			
No	1,606 (96.9%)	416 (95.0%)	**0.048**
Yes	51 (3.1%)	22 (5.0%)	
Stimulant use			
Never	590 (79.1%)	0 (0%)	**<0.001**
Once	38 (5.1%)	46 (27.7%)	
Less than monthly	35 (4.7%)	33 (19.9%)	
Monthly	23 (3.1%)	20 (12.1%)	
Weekly	27 (3.6%)	35 (21.1%)	
Daily	33 (4.4%)	32 (19.3%)	
Sexual Risk Behavior			
Sexually transmitted infection			
No	1,429 (86.2%)	334 (76.3%)	**<0.001**
Yes	228 (13.8%)	104 (23.7%)	
Anal intercourse while intoxicated			
No	915 (55.2%)	132 (30.1%)	**<0.001**
Yes	742 (44.8%)	306 (69.9%)	
Transactional sex			
No	1,484 (89.6%)	311 (71.0%)	**<0.001**
Yes	173 (10.4%)	127 (29.0%)	
Last partner			
Last partner was unknown person			
No	1,502 (90.6%)	376 (85.8%)	**0.003**
Yes	155 (9.4%)	62 (14.2%)	
Last partner used stimulants			
No	1,292 (78.0%)	225 (51.4%)	**<0.001**
Yes	365 (22.0%)	213 (48.6%)	
Last partner used ecstasy			
No	1,591 (96.0%)	398 (90.9%)	**<0.001**
Yes	66 (4.0%)	40 (9.1%)	

Table 5.4 Unadjusted and adjusted odds ratios of factors associated with increased stimulant use for final lasso model of the entire cohort (N=2,095 study visits)

	OR (95% CI)	p-value	aOR (95% CI)	p-value
Control Variables				
Age	1.00 (0.98-1.02)	0.97	1.01 (0.98-1.03)	0.68
Race/Ethnicity				
White	Ref	--	Ref	--
Black	0.77 (0.40-1.50)	0.44	1.08 (0.57-2.06)	0.80
Latinx	1.11 (0.58-2.12)	0.76	1.55 (0.82-2.91)	0.17
Other	0.87 (0.35-2.11)	0.75	1.30 (0.55-3.05)	0.55
HIV				
Negative	Ref	--	Ref	--
Living with HIV	1.44 (1.03-2.02)	**0.035**	1.30 (0.93-1.81)	0.12
Demographics				
Employment status				
Employed	Ref	--	Ref	--
Unemployed	1.49 (1.09-2.02)	**0.011**	1.13 (0.82-1.55)	0.45
Unstable housing				
No	Ref	--	Ref	--
Yes	2.74 (1.94-3.86)	**<0.001**	1.81 (1.27-2.57)	**0.001**
Substance Use				
Binge drinking				
Never	Ref	--	Ref	--
Monthly or less	1.55 (1.15-2.08)	**0.004**	1.59 (1.17-2.15)	**0.003**
Weekly/daily	2.04 (1.30-3.22)	**0.002**	1.76 (1.13-2.75)	**0.013**
Vaping/Cigarette				
No	Ref	--	Ref	--
Yes	2.29 (1.69-3.10)	**<0.001**	1.69 (1.24-2.31)	**0.001**
Cannabis Use				
No	Ref	--	Ref	--
Weekly or less frequent	2.22 (1.59-3.08)	**<0.001**	1.82 (1.31-2.54)	**<0.001**
Daily	2.87 (1.98-4.16)	**<0.001**	2.24 (1.55-3.25)	**<0.001**
Regular opiate use				
No	Ref	--	Ref	--
Yes	2.07 (1.06-4.04)	**0.032**	1.00 (0.50-2.01)	1.00
Sexual Risk Behavior				
Sexually transmitted infection				
No	Ref	--	Ref	--
Yes	2.09 (1.51-2.88)	**<0.001**	1.59 (1.14-2.21)	**0.006**
Anal intercourse while intoxicated				
No	Ref	--	Ref	--
Yes	3.01 (2.27-3.98)	**<0.001**	1.64 (1.21-2.20)	**0.001**
Transactional sex				
No	Ref	--	Ref	--
Yes	4.17 (2.97-5.85)	**<0.001**	2.30 (1.60-3.30)	**<0.001**
Last Partner				
Last partner was unknown person				
No	Ref	--	Ref	--
Yes	1.89 (1.27-2.83)	**0.002**	1.54 (1.03-2.32)	**0.037**
Last partner used stimulants				
No	Ref	--	Ref	--
Yes	3.55 (2.69-4.69)	**<0.001**	2.21 (1.62-3.00)	**<0.001**
Last partner used ecstasy				
No	Ref	--	Ref	--
Yes	2.45 (1.43-4.20)	**0.001**	1.25 (0.71-2.18)	0.44

Table 5.5 Visit-level participant characteristics stratified by increased stimulant use for final elastic net model of the entire cohort (N=1,864 study visits)

	No Change (n=1,474)	Increased Use (n=390)	p-value
Control Variables	**n (%)**	**n (%)**	
Age (median, IQR)	33 (28-40)	34 (28-39)	0.94
Race/Ethnicity			
White	90 (6.1%)	25 (6.4%)	0.06
Black	585 (39.7%)	126 (32.3%)	
Latinx	733 (49.7%)	221 (56.7%)	
Other	66 (4.5%)	18 (4.6%)	
HIV			
Negative	703 (47.7%)	153 (39.2%)	**0.003**
Living with HIV	771 (52.3%)	237 (60.8%)	
Demographics			
Employment status			
Employed	1,174 (79.6%)	282 (72.3%)	**0.002**
Unemployed	300 (20.4%)	108 (27.7%)	
Unstable housing			
No	1,286 (87.2%)	291 (74.6%)	**<0.001**
Yes	188 (12.8%)	99 (25.4%)	
Income			
Less than 10k	579 (39.3%)	184 (47.2%)	**0.002**
10-30k	536 (36.4%)	140 (35.9%)	
More than 30k	359 (24.4%)	66 (16.9%)	
Education			
Less than high school	146 (9.9%)	51 (13.1%)	0.18
High school	470 (31.9%)	124 (31.8%)	
More than high school	858 (58.2%)	215 (55.1%)	
Substance Use			
Binge drinking last 6 months			
Never	853 (57.9%)	185 (47.4%)	**<0.001**
Monthly or less	486 (33.0%)	150 (38.5%)	
Weekly/daily	135 (9.2%)	55 (14.1%)	
Vaping/Cigarette			
No	1,098 (74.5%)	220 (56.4%)	**<0.001**
Yes	376 (25.5%)	170 (43.6%)	
Cannabis Use			
No	781 (53.0%)	138 (35.4%)	**<0.001**
Weekly or less frequent	395 (26.8%)	128 (32.8%)	
Daily	298 (20.2%)	124 (31.8%)	
Regular opiate use			
No	1,427 (96.8%)	372 (95.4%)	0.17
Yes	47 (3.2%)	18 (4.6%)	
Regular poppers use			
No	1,360 (92.3%)	318 (81.5%)	**<0.001**
Yes	114 (7.7%)	72 (18.5%)	
Regular use of other prescription drugs			
No	1,413 (95.9%)	359 (92.1%)	**0.002**
Yes	61 (4.1%)	31 (7.9%)	
Stimulant use			
Never	1,050 (71.2%)	0 (0%)	**<0.001**
Once	67 (4.6%)	81 (20.8%)	
Less than monthly	112 (7.6%)	68 (17.4%)	
Monthly	52 (3.5%)	65 (16.7%)	
Weekly	99 (6.7%)	81 (20.8%)	
Daily	94 (6.4%)	95 (24.4%)	
Sexual Risk Behavior			
Sexually transmitted infection			
No	1,271 (86.2%)	297 (76.2%)	**<0.001**
Yes	203 (13.8%)	93 (23.8%)	
Anal intercourse while intoxicated			
No	788 (53.5%)	107 (27.4%)	**<0.001**
Yes	686 (46.5%)	283 (72.6%)	

Transactional sex			
No	1,322 (89.7%)	277 (71.0%)	**<0.001**
Yes	152 (10.3%)	113 (29.0%)	
Unknown partner last 6 months			
No	1,124 (76.3%)	256 (65.6%)	**<0.001**
Yes	350 (23.7%)	134 (34.4%)	
One-time partner last 6 months			
No	885 (60.0%)	199 (51.0%)	**0.001**
Yes	589 (40.0%)	191 (49.0%)	
Trade partner last 6 months			
No	1,231 (83.5%)	255 (65.4%)	**<0.001**
Yes	243 (16.5%)	135 (34.6%)	
Last Partner			
Last partner length of relationship			
Days	856 (58.1%)	236 (60.5%)	0.62
Months	405 (27.5%)	104 (26.7%)	
Years	213 (14.5%)	50 (12.8%)	
Knew last partner's HIV status			
No	394 (26.7%)	125 (32.1%)	**0.037**
Yes	1,080 (73.3%)	265 (67.9%)	
Last partner was unknown person			
No	1,336 (90.6%)	336 (86.2%)	**0.01**
Yes	138 (9.4%)	54 (13.8%)	
Last partner used stimulants			
No	1,137 (77.1%)	198 (50.8%)	**<0.001**
Yes	337 (22.9%)	192 (49.2%)	
Last partner used ecstasy			
No	1,417 (96.1%)	355 (91.0%)	**<0.001**
Yes	57 (3.9%)	35 (9.0%)	
Last partner used poppers			
No	1,167 (79.2%)	276 (70.8%)	**<0.001**
Yes	307 (20.8%)	114 (29.2%)	

Table 5.6 Unadjusted and adjusted odds ratios of factors associated with increased stimulant use for final elastic net model of the entire cohort (N=1,864 study visits)

	OR (95% CI)	p-value	aOR (95% CI)	p-value
Control Variables				
Age	1.00 (0.98-1.03)	0.92	1.01 (0.98-1.03)	0.53
Race/Ethnicity				
White	Ref	--	Ref	--
Black	0.86 (0.42-1.79)	0.69	1.25 (0.61-2.52)	0.54
Latinx	1.33 (0.66-2.71)	0.43	1.91 (0.95-3.83)	0.07
Other	1.01 (0.38-2.65)	0.99	1.57 (0.62-3.99)	0.34
HIV				
Negative	Ref	--	Ref	--
Living with HIV	1.56 (1.09-2.22)	**0.014**	1.32 (0.93-1.88)	0.12
Demographics				
Employment status				
Employed	Ref	--	Ref	--
Unemployed	1.34 (0.97-1.86)	0.08	1.00 (0.71-1.42)	0.99
Unstable housing				
No	Ref	--	Ref	--
Yes	2.67 (1.86-3.85)	**<0.001**	1.70 (1.17-2.48)	**0.006**
Income				
Less than 10k	Ref	--	Ref	--
10-30k	0.85 (0.62-1.16)	0.31	1.07 (0.77-1.48)	0.69
More than 30k	0.62 (0.41-0.93)	**0.02**	0.86 (0.56-1.32)	0.48
Education				
Less than high school	Ref	--	Ref	--
High school	0.71 (0.42-1.21)	0.20	0.82 (0.49-1.35)	0.43
More than high school	0.69 (0.41-1.15)	0.15	0.76 (0.46-1.24)	0.27
Substance Use				
Binge drinking last 6 months				
Never	Ref	--	Ref	--
Monthly or less	1.55 (1.13-2.12)	**0.006**	1.61 (1.16-2.22)	**0.004**
Weekly/daily	2.01 (1.24-3.27)	**0.005**	1.74 (1.08-2.79)	**0.022**
Vaping/Cigarette				
No	Ref	--	Ref	--
Yes	2.37 (1.72-3.27)	**<0.001**	1.74 (1.25-2.42)	**0.001**
Cannabis Use				
No	Ref	--	Ref	--
Weekly or less frequent	2.05 (1.44-2.90)	**<0.001**	1.71 (1.20-2.44)	**0.003**
Daily	2.85 (1.93-4.20)	**<0.001**	2.17 (1.47-3.22)	**<0.001**
Regular opiate use				
No	Ref	--	Ref	--
Yes	1.70 (0.83-3.49)	0.15	0.82 (0.37-1.79)	0.62
Regular poppers use				
No	Ref	--	Ref	--
Yes	3.19 (2.07-4.92)	**<0.001**	1.74 (1.10-2.77)	**0.019**
Regular use of other prescription drugs				
No	Ref	--	Ref	--
Yes	2.51 (1.36-4.62)	**0.003**	0.66 (0.33-1.30)	0.23
Sexual Risk Behavior				
Sexually transmitted infection				
No	Ref	--	Ref	--
Yes	2.07 (1.47-2.92)	**<0.001**	1.51 (1.05-2.15)	**0.025**
Anal intercourse while intoxicated				
No	Ref	--	Ref	--
Yes	3.17 (2.35-4.28)	**<0.001**	1.70 (1.21-2.38)	**0.002**
Transactional sex				
No	Ref	--	Ref	--
Yes	4.07 (2.85-5.82)	**<0.001**	2.20 (1.47-3.28)	**<0.001**
Unknown partner last 6 months				
No	Ref	--	Ref	--
Yes	1.64 (1.22-2.22)	**0.001**	0.93 (0.66-1.31)	0.67
One-time partner last 6 months				
No	Ref	--	Ref	--

Yes	1.49 (1.13-1.97)	**0.005**	1.09 (0.80-1.48)	0.58
Trade partner last 6 months				
No	Ref	--	Ref	--
Yes	3.10 (2.24-4.30)	**<0.001**	1.20 (0.82-1.75)	0.36
Last Partner				
Last partner length of relationship				
Days	Ref	--	Ref	--
Months	0.89 (0.66-1.20)	0.45	1.05 (0.76-1.44)	0.77
Years	0.84 (0.57-1.26)	0.41	1.03 (0.68-1.56)	0.88
Knew last partner's HIV status				
No	Ref	--	Ref	--
Yes	0.75 (0.55-1.01)	0.06	0.92 (0.67-1.27)	0.62
Last partner was unknown person				
No	Ref	--	Ref	--
Yes	1.79 (1.17-2.75)	**0.008**	1.43 (0.90-2.27)	0.13
Last partner used stimulants				
No	Ref	--	Ref	--
Yes	3.44 (2.57-4.61)	**<0.001**	2.03 (1.46-2.83)	**<0.001**
Last partner used ecstasy				
No	Ref	--	Ref	--
Yes	2.58 (1.45-4.61)	**0.001**	1.61 (0.88-2.93)	0.12
Last partner used poppers				
No	Ref	--	Ref	--
Yes	1.50 (1.09-2.05)	**0.013**	0.83 (0.59-1.19)	0.31

Figure 5.2 Lasso cross-validation plot for participants living with HIV

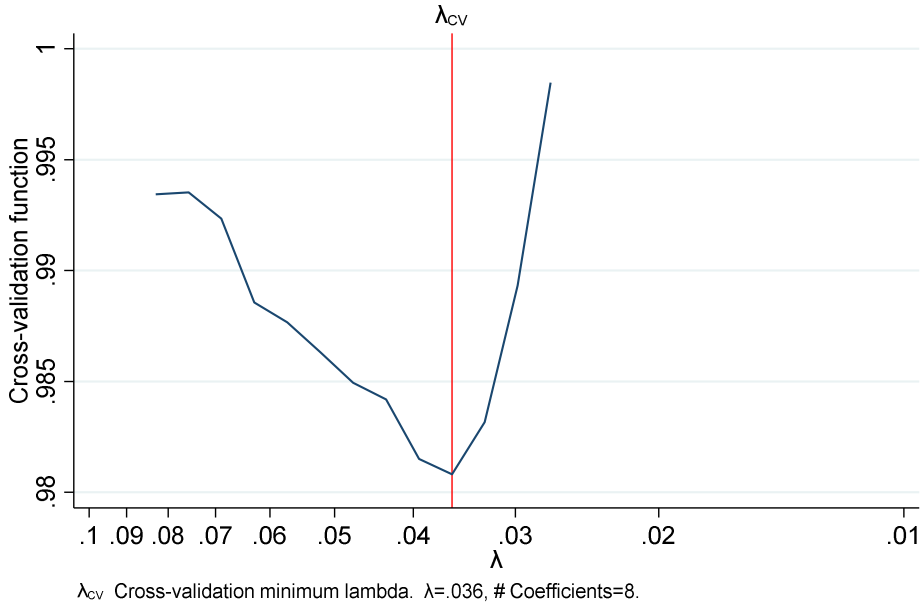


Table 5.7 Goodness of fit indices for lasso and elastic net models for participants living with HIV

	Lasso Models						Elastic Net	
λ	λ=0.047*		λ=0.036**		λ=0.030		--	
Variables added			Regular partner last 6 mos		Regular partner last 6 mos Race/ethnicity Unstable housing Regular opiate use		Regular partner last 6 mos Race/ethnicity Unstable housing Regular opiate use Group sex while intoxicated AI while intoxicated Male partners last 6 mos One-time partner last 6 mos	
	Training	**Testing**	**Training**	**Testing**	**Training**	**Testing**	**Training**	**Testing**
n	594	609	591	609	590	609	557	565
Deviance	1.03	1.06	1.01	1.05	0.99	1.05	1.01	1.07
Deviance Ratio	0.04	0.02	0.05	0.03	0.07	0.04	0.05	0.03
AUC	0.71	0.71	0.71	0.71	0.73	0.72	0.74	0.75
MCC	0.21	0.20	0.19	0.19	0.20	0.23	0.19	0.29

AUC = Area Under the Receiving Operating Curve; MCC = Matthew's Correlation Coefficient; AI = Anal Intercourse
*Largest λ within 1 standard error; **Minimal λ based on cross-validation

Note all models contain the following variables: binge drinking frequency, vaping/cigarette use, regular poppers use, transactional sex, last partnership type, last partner used ecstasy

Table 5.8 Visit-level participant characteristics stratified by increased stimulant use for final lasso model for participants living with HIV (N=1,199 study visits)

	No Change (n=925)	Increased Use (n=274)	p-value
Control Variables	**n (%)**	**n (%)**	
Age (median, IQR)	37 (31-42)	35 (30-40)	**0.014**
Race/Ethnicity			
White	55 (5.9%)	22 (8.0%)	0.25
Black	334 (36.1%)	89 (32.5%)	
Latinx	466 (50.4%)	148 (54.0%)	
Other	70 (7.6%)	15 (5.5%)	
Demographics			
Unstable housing			
No	809 (87.5%)	202 (73.7%)	**<0.001**
Yes	116 (12.5%)	72 (26.3%)	
Substance Use			
Binge drinking			
Never	623 (67.4%)	153 (55.8%)	**0.002**
Monthly or less	240 (25.9%)	95 (34.7%)	
Weekly/daily	62 (6.7%)	26 (9.5%)	
Vaping/Cigarette			
No	660 (71.4%)	146 (53.3%)	**<0.001**
Yes	265 (28.6%)	128 (46.7%)	
Regular poppers use			
No	845 (91.4%)	216 (78.8%)	**<0.001**
Yes	80 (8.6%)	58 (21.2%)	
Regular opiate use			
No	902 (97.5%)	265 (96.7%)	0.47
Yes	23 (2.5%)	9 (3.3%)	
Stimulant use			
Never	606 (65.5%)	0 (0%)	**<0.001**
Once	36 (3.9%)	46 (16.8%)	
Less than monthly	95 (10.3%)	45 (16.4%)	
Monthly	34 (3.7%)	53 (19.3%)	
Weekly	81 (8.8%)	58 (21.2%)	
Daily	73 (7.9%)	72 (26.3%)	
Sexual Risk Behavior			
Regular partner last 6 months			
No	688 (74.4%)	177 (64.6%)	**0.002**
Yes	237 (25.6%)	97 (35.4%)	
Transactional sex			
No	828 (89.5%)	201 (73.4%)	**<0.001**
Yes	97 (10.5%)	73 (26.6%)	
Last Partner			
Last partner was regular/main partner			
No	497 (53.7%)	165 (60.2%)	0.06
Yes	428 (46.3%)	109 (39.8%)	
Last partner used ecstasy			
No	889 (96.1%)	255 (93.1%)	**0.034**
Yes	36 (3.9%)	19 (6.9%)	

Table 5.9 Unadjusted and adjusted odds ratios of factors associated with increased stimulant use for final lasso model for participants living with HIV (N=1,199 study visits)

	OR (95% CI)	p-value	aOR (95% CI)	p-value
Control Variables				
Age	0.97 (0.94-1.00)	0.07	0.99 (0.96-1.02)	0.34
Race/Ethnicity				
White	Ref	--	Ref	--
Black	0.78 (0.33-1.82)	0.56	1.28 (0.56-2.91)	0.56
Latinx	1.02 (0.45-2.32)	0.96	1.54 (0.69-3.43)	0.29
Other	0.54 (0.19-1.50)	0.23	0.96 (0.35-2.63)	0.93
Demographics				
Unstable housing				
No	Ref	--	Ref	--
Yes	2.91 (1.88-4.48)	**<0.001**	2.25 (1.45-3.51)	**<0.001**
Substance Use				
Binge drinking last 6 months				
Never	Ref	--	Ref	--
Monthly or less	1.70 (1.16-2.48)	**0.006**	1.63 (1.12-2.38)	**0.011**
Weekly/daily	2.02 (1.05-3.88)	**0.035**	1.87 (1.00-3.51)	0.05
Vaping/Cigarette				
No	Ref	--	Ref	--
Yes	2.06 (1.41-3.00)	**<0.001**	1.99 (1.36-2.92)	**<0.001**
Regular poppers use				
No	Ref	--	Ref	--
Yes	3.29 (2.01-5.40)	**<0.001**	2.28 (1.38-3.76)	**0.001**
Regular opiate use				
No	Ref	--	Ref	--
Yes	1.40 (0.55-3.59)	0.48	0.80 (0.29-2.20)	0.67
Sexual Risk Behavior				
Regular partner last 6 months				
No	Ref	--	Ref	--
Yes	1.74 (1.20-2.51)	**0.003**	1.38 (0.95-2.02)	0.09
Transactional sex				
No	Ref	--	Ref	--
Yes	3.28 (2.13-5.05)	**<0.001**	2.33 (1.48-3.65)	**<0.001**
Last Partner				
Last partner was regular/main partner				
No	Ref	--	Ref	--
Yes	0.71 (0.50-1.00)	**0.05**	0.70 (0.49-0.99)	**0.043**
Last partner used ecstasy				
No	Ref	--	Ref	--
Yes	1.52 (0.73-3.19)	0.27	1.28 (0.60-2.75)	0.52

Table 5.10 Visit-level participant characteristics stratified by increased stimulant use for final elastic net model for participants living with HIV (N=1,122 study visits)

	No Change (n=862)	Increased Use (n=260)	p-value
Control Variables	**n (%)**	**n (%)**	
Age (median, IQR)	37 (31-42)	35 (30-40)	**0.019**
Race/Ethnicity			
White	53 (6.1%)	21 (8.1%)	0.53
Black	320 (37.1%)	86 (33.1%)	
Latinx	447 (51.9%)	140 (53.8%)	
Other	42 (4.9%)	13 (5.0%)	
Demographics			
Unstable housing			
No	750 (87.0%)	192 (73.8%)	**<0.001**
Yes	112 (13.0%)	68 (26.2%)	
Substance Use			
Binge drinking frequency			
Never	571 (66.2%)	150 (57.7%)	**0.041**
Monthly or less	232 (26.9%)	87 (33.5%)	
Weekly/daily	59 (6.8%)	23 (8.8%)	
Vaping/Cigarette			
No	615 (71.3%)	136 (52.3%)	**<0.001**
Yes	247 (28.7%)	124 (47.7%)	
Regular poppers use			
No	782 (90.7%)	205 (78.8%)	**<0.001**
Yes	80 (9.3%)	55 (21.2%)	
Regular opiate use			
No	841 (97.6%)	252 (96.9%)	0.57
Yes	21 (2.4%)	8 (3.1%)	
Sexual Risk Behavior			
Regular partner last 6 months			
No	626 (72.6%)	163 (62.7%)	**0.002**
Yes	236 (27.4%)	97 (37.3%)	
One-time partner last 6 months			
No	572 (66.4%)	139 (53.5%)	**<0.001**
Yes	290 (33.6%)	121 (46.5%)	
Transactional sex			
No	765 (88.7%)	188 (72.3%)	**<0.001**
Yes	97 (11.3%)	72 (27.7%)	
Number male partners last 6 months			
0	226 (26.2%)	46 (17.7%)	**<0.001**
1-2	278 (32.3%)	80 (30.8%)	
3-9	225 (26.1%)	65 (25.0%)	
10+	133 (15.4%)	69 (26.5%)	
Group sex while intoxicated			
No	714 (82.8%)	170 (65.4%)	**<0.001**
Yes	148 (17.2%)	90 (34.6%)	
Anal intercourse while intoxicated			
No	495 (57.4%)	74 (28.5%)	**<0.001**
Yes	367 (42.6%)	186 (71.5%)	
Last Partner			
Last partner was regular/main partner			
No	463 (53.7%)	156 (60.0%)	0.07
Yes	399 (46.3%)	104 (40.0%)	
Last partner used ecstasy			
No	828 (96.1%)	241 (92.7%)	**0.025**
Yes	34 (3.9%)	19 (7.3%)	

Table 5.11 Unadjusted and adjusted odds ratios of factors associated with increased stimulant use for final elastic net model for participants living with HIV (N=1,122 study visits)

	OR (95% CI)	p-value	aOR (95% CI)	p-value
Control Variables				
Age	0.97 (0.94-1.00)	0.08	0.99 (0.96-1.02)	0.40
Race/Ethnicity				
White	Ref	--	Ref	--
Black	0.75 (0.32-1.76)	0.50	1.24 (0.54-2.87)	0.62
Latinx	0.98 (0.43-2.25)	0.96	1.59 (0.70-3.60)	0.27
Other	0.80 (0.26-2.48)	0.70	1.19 (0.40-3.58)	0.76
Demographics				
Unstable housing				
No	Ref	--	Ref	--
Yes	2.84 (1.81-4.46)	**<0.001**	2.12 (1.34-3.36)	**0.001**
Substance Use				
Binge drinking frequency				
Never	Ref	--	Ref	--
Monthly or less	1.46 (0.99-2.15)	0.06	1.26 (0.85-1.86)	0.25
Weekly/daily	1.66 (0.85-3.26)	0.14	1.29 (0.67-2.49)	0.45
Vaping/Cigarette use				
No	Ref	--	Ref	--
Yes	2.17 (1.48-3.19)	**<0.001**	2.00 (1.35-2.96)	**0.001**
Regular poppers use				
No	Ref	--	Ref	--
Yes	3.01 (1.81-4.98)	**<0.001**	1.66 (0.99-2.77)	0.05
Regular opiate use				
No	Ref	--	Ref	--
Yes	1.30 (0.47-3.53)	0.61	0.78 (0.27-2.27)	0.65
Sexual Risk Behavior				
Regular partner last 6 months				
No	Ref	--	Ref	--
Yes	1.72 (1.18-2.50)	**0.005**	1.24 (0.82-1.89)	0.31
One-time partner last 6 months				
No	Ref	--	Ref	--
Yes	1.81 (1.28-2.56)	**0.001**	1.26 (0.84-1.90)	0.27
Transactional sex				
No	Ref	--	Ref	--
Yes	3.28 (2.11-5.08)	**<0.001**	1.71 (1.06-2.77)	**0.029**
Number male partners last 6 months				
0	Ref	--	Ref	--
1-2	1.49 (0.92-2.42)	0.10	0.75 (0.43-1.30)	0.31
3-9	1.56 (0.92-2.64)	0.10	0.51 (0.27-0.96)	**0.036**
10+	2.96 (1.68-5.19)	**<0.001**	0.63 (0.31-1.28)	0.20
Group sex while intoxicated				
No	Ref	--	Ref	--
Yes	2.96 (1.98-4.44)	**<0.001**	1.16 (0.71-1.88)	0.55
Anal intercourse while intoxicated				
No	Ref	--	Ref	--
Yes	3.75 (2.58-5.43)	**<0.001**	2.93 (1.82-4.71)	**<0.001**
Last Partner				
Last partner was regular/main partner				
No	Ref	--	Ref	--
Yes	0.70 (0.49-0.99)	**0.046**	0.69 (0.47-1.01)	0.06
Last partner used ecstasy				
No	Ref	--	Ref	--
Yes	1.61 (0.77-3.39)	0.21	1.28 (0.60-2.74)	0.52

Figure 5.3 Lasso cross-validation plot for HIV-negative participants

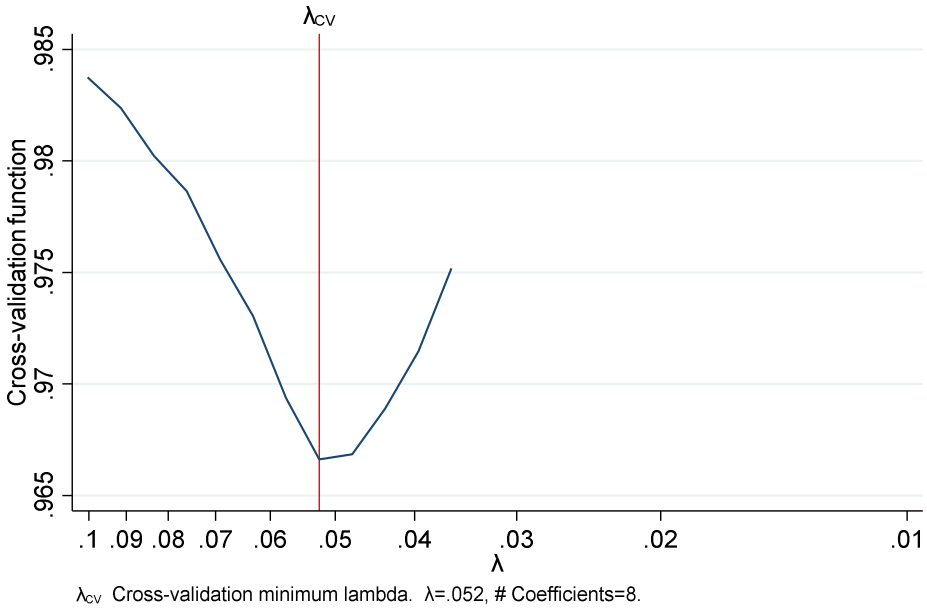


Table 5.12 Goodness of fit indices for lasso and elastic net models for HIV-negative participants

	Lasso Models						Elastic Net	
λ	λ=0.063*		λ=0.052**		λ=0.040		--	
Variables added			Last partner used alcohol		Last partner used alcohol Education Last partner used poppers Cannabis use Unemployment		Last partner used alcohol Education Last partner used poppers Cannabis use Unemployment Race/ethnicity Intimate partner violence Sexually transmitted infection Sexual orientation Regular partner last 6 mos Never saw LP again after sex Last partner exchanged drugs Depression Last partner used poppers LP was one-time partner	
	Training	**Testing**	**Training**	**Testing**	**Training**	**Testing**	**Training**	**Testing**
n	460	478	453	473	444	468	304	348
Deviance	0.94	0.87	0.93	0.84	0.90	0.82	0.91	0.78
Deviance Ratio	0.06	0.05	0.08	0.07	0.10	0.08	0.11	0.07
AUC	0.72	0.71	0.72	0.73	0.74	0.76	0.91	0.78
MCC	0.23	0.21	0.22	0.20	0.29	0.21	0.11	0.07

AUC = Area Under the Receiving Operating Curve; MCC = Matthew's Correlation Coefficient; LP = Last Partner
*Largest λ within 1 standard error; **Minimal λ based on cross-validation

Note all models contain the following variables: income, unstable housing, anal intercourse while intoxicated, exchange sex, group sex while intoxicated, sexual partner concurrency, last partner injected drugs

Table 5.13 Visit-level participant characteristics stratified by increased stimulant use for final lasso model for HIV-negative participants (N=912 study visits)

	No Change (n=746)	Increased Use (n=166)	p-value
Control Variables	**n (%)**	**n (%)**	
Age (median, IQR)	30 (26-36)	29.5 (26-36)	0.63
Race/Ethnicity			
White	49 (6.6%)	10 (6.0%)	0.06
Black	322 (43.2%)	54 (32.5%)	
Latinx	341 (45.7%)	95 (57.2%)	
Other	34 (4.6%)	7 (4.2%)	
Demographics			
Education			
Less than high school	41 (5.5%)	24 (14.5%)	**<0.001**
High school	222 (29.8%)	45 (27.1%)	
More than high school	483 (64.7%)	97 (58.4%)	
Income			
Less than 10k	253 (33.9%)	77 (46.4%)	**0.006**
10-30k	286 (38.3%)	57 (34.3%)	
More than 30k	207 (27.7%)	32 (19.3%)	
Employment status			
Employed	609 (81.6%)	114 (68.7%)	**<0.001**
Unemployed	137 (18.4%)	52 (31.3%)	
Unstable housing			
No	656 (87.9%)	119 (71.7%)	**<0.001**
Yes	90 (12.1%)	47 (28.3%)	
Substance Use			
Cannabis Use			
No	352 (47.2%)	49 (29.5%)	**<0.001**
Weekly or less frequent	237 (31.8%)	63 (38.0%)	
Daily	157 (21.0%)	54 (32.5%)	
Stimulant use			
Never	590 (79.1%)	0 (0%)	**<0.001**
Once	38 (5.1%)	46 (27.7%)	
Less than monthly	35 (4.7%)	33 (19.9%)	
Monthly	23 (3.1%)	20 (12.1%)	
Weekly	27 (3.6%)	35 (21.1%)	
Daily	33 (4.4%)	32 (19.3%)	
Sexual Risk Behavior			
Sexual partner concurrency last 6 months			
No	473 (63.4%)	84 (50.6%)	**0.002**
Yes	273 (36.6%)	82 (49.4%)	
Anal intercourse while intoxicated			
No	383 (51.3%)	47 (28.3%)	**<0.001**
Yes	363 (48.7%)	119 (71.7%)	
Group sex while intoxicated			
No	635 (85.1%)	107 (64.5%)	**<0.001**
Yes	111 (14.9%)	59 (35.5%)	
Transactional sex			
No	676 (90.6%)	116 (69.9%)	**<0.001**
Yes	70 (9.4%)	50 (30.1%)	
Last Partner			
Last partner used alcohol			
No	579 (77.6%)	108 (65.1%)	**0.001**
Yes	167 (22.4%)	58 (34.9%)	
Last partner used poppers			
No	617 (82.7%)	128 (77.1%)	0.09
Yes	129 (17.3%)	38 (22.9%)	
Last partner injected drugs			
No	689 (92.4%)	134 (80.7%)	**<0.001**
Yes	57 (7.6%)	32 (19.3%)	

Table 5.14 Unadjusted and adjusted odds ratios of factors associated with increased stimulant use for final lasso model for HIV-negative participants (N=912 study visits)

	OR (95% CI)	p-value	aOR (95% CI)	p-value
Control Variables				
Age	1.00 (0.96-1.04)	0.93	1.01 (0.97-1.05)	0.73
Race/Ethnicity				
White	Ref	--	Ref	--
Black	0.98 (0.30-3.20)	0.97	1.01 (0.34-3.00)	0.99
Latinx	1.86 (0.58-5.94)	0.29	1.54 (0.53-4.49)	0.43
Other	1.11 (0.23-5.37)	0.90	1.05 (0.24-4.56)	0.94
Demographics				
Education				
Less than high school	Ref	--	Ref	--
High school	0.30 (0.13-0.71)	**0.006**	0.40 (0.17-0.91)	**0.03**
More than high school	0.33 (0.15-0.75)	**0.008**	0.41 (0.19-0.92)	**0.03**
Income				
Less than 10k	Ref	--	Ref	--
10-30k	0.71 (0.43-1.16)	0.17	0.90 (0.54-1.50)	0.68
More than 30k	0.53 (0.29-0.99)	**0.047**	0.64 (0.33-1.23)	0.18
Employment status				
Employed	Ref	--	Ref	--
Unemployed	1.78 (1.08-2.94)	**0.024**	1.40 (0.81-2.42)	0.23
Unstable housing				
No	Ref	--	Ref	--
Yes	3.06 (1.78-5.27)	**<0.001**	1.94 (1.09-3.45)	**0.025**
Substance Use				
Cannabis Use				
No	Ref	--	Ref	--
Weekly or less frequent	2.25 (1.32-3.82)	**0.003**	2.15 (1.26-3.66)	**0.005**
Daily	2.73 (1.51-4.96)	**0.001**	2.00 (1.11-3.59)	**0.02**
Sexual Risk Behavior				
Sexual partner concurrency last 6 months				
No	Ref	--	Ref	--
Yes	1.70 (1.11-2.62)	**0.016**	1.18 (0.75-1.87)	0.47
Anal intercourse while intoxicated				
No	Ref	--	Ref	--
Yes	2.54 (1.60-4.02)	**<0.001**	1.59 (0.96-2.62)	0.07
Group sex while intoxicated				
No	Ref	--	Ref	--
Yes	3.73 (2.26-6.15)	**<0.001**	1.81 (1.04-3.18)	**0.037**
Transactional sex				
No	Ref	--	Ref	--
Yes	5.02 (2.88-8.76)	**<0.001**	2.53 (1.40-4.55)	**0.002**
Last Partner				
Last partner used alcohol				
No	Ref	--	Ref	--
Yes	1.77 (1.09-2.88)	**0.021**	1.31 (0.81-2.13)	0.28
Last partner used poppers				
No	Ref	--	Ref	--
Yes	1.70 (1.00-2.91)	0.05	1.31 (0.77-2.23)	0.33
Last partner injected drugs				
No	Ref	--	Ref	--
Yes	2.90 (1.54-5.47)	**0.001**	1.96 (1.02-3.74)	**0.043**

Table 5.15 Visit-level participant characteristics stratified by increased stimulant use for final elastic net model for HIV-negative participants (N=652 study visits)

	No Change (n=537)	Increased Use (n= 115)	p-value
Control Variables	**n (%)**	**n (%)**	
Age (median, IQR)	30 (26-35)	30 (26-35)	0.83
Race/Ethnicity			
White	36 (6.7%)	8 (7.0%)	0.08
Black	237 (44.1%)	36 (31.3%)	
Latinx	241 (44.9%)	66 (57.4%)	
Other	23 (4.3%)	5 (4.3%)	
Demographics			
Education			
Less than high school	28 (5.2%)	17 (14.8%)	**0.001**
High school	159 (29.6%)	33 (28.7%)	
More than high school	350 (65.2%)	65 (56.5%)	
Income			
Less than 10k	201 (37.4%)	62 (53.9%)	**0.004**
10-30k	199 (37.1%)	34 (29.6%)	
More than 30k	137 (25.5%)	19 (16.5%)	
Employment status			
Employed	431 (80.3%)	73 (63.5%)	**<0.001**
Unemployed	106 (19.7%)	42 (36.5%)	
Unstable housing			
No	466 (86.8%)	84 (73.0%)	**<0.001**
Yes	71 (13.2%)	31 (27.0%)	
Intimate partner violence			
No	487 (90.7%)	91 (79.1%)	**<0.001**
Yes	50 (9.3%)	24 (20.9%)	
Sexual orientation			
Gay	373 (69.5%)	75 (65.2%)	0.37
Bisexual/Other	164 (30.5%)	40 (34.8%)	
Depression			
No	405 (75.4%)	68 (59.1%)	**<0.001**
Yes	132 (24.6%)	47 (40.9%)	
Substance Use			
Cannabis Use			
No	253 (47.1%)	35 (30.4%)	**0.004**
Weekly or less frequent	175 (32.6%)	46 (40.0%)	
Daily	109 (20.3%)	34 (29.6%)	
Sexual Risk Behavior			
Sexual partner concurrency last 6 months			
No	330 (61.5%)	59 (51.3%)	**0.044**
Yes	207 (38.5%)	56 (48.7%)	
Anal intercourse while intoxicated			
No	289 (53.8%)	35 (30.4%)	**<0.001**
Yes	248 (46.2%)	80 (69.6%)	
Group sex while intoxicated			
No	466 (86.8%)	74 (64.3%)	**<0.001**
Yes	71 (13.2%)	41 (35.7%)	
Transactional sex			
No	482 (89.8%)	77 (67.0%)	**<0.001**
Yes	55 (10.2%)	38 (33.0%)	
Sexually transmitted infection			
No	472 (87.9%)	92 (80.0%)	**0.025**
Yes	65 (12.1%)	23 (20.0%)	
Regular partner last 6 months			
No	337 (62.8%)	56 (48.7%)	**0.005**
Yes	200 (37.2%)	59 (51.3%)	
Sexual partner concurrency last 6 months			
No	330 (61.5%)	59 (51.3%)	**0.044**
Yes	207 (38.5%)	56 (48.7%)	
Last Partner			
Last partner used alcohol			

No	418 (77.8%)	76 (66.1%)	**0.008**
Yes	119 (22.2%)	39 (33.9%)	
Last partner used poppers			
No	452 (84.2%)	89 (77.4%)	0.08
Yes	85 (15.8%)	26 (22.6%)	
Last partner injected drugs			
No	494 (92.0%)	93 (80.9%)	**<0.001**
Yes	43 (8.0%)	22 (19.1%)	
Never saw last partner again after sex			
No	412 (76.7%)	81 (70.4%)	0.15
Yes	125 (23.3%)	34 (29.6%)	
Transactional sex with last partner			
No	502 (93.5%)	92 (80.0%)	**<0.001**
Yes	35 (6.5%)	23 (20.0%)	
Last partner used stimulants			
No	461 (85.8%)	67 (58.3%)	**<0.001**
Yes	76 (14.2%)	48 (41.7%)	
Last partner was a one-time partner			
No	432 (80.4%)	100 (87.0%)	0.10
Yes	105 (19.6%)	15 (13.0%)	

Table 5.16 Unadjusted and adjusted odds ratios of factors associated with increased stimulant use for final elastic net model for HIV-negative participants (N=652 study visits)

	OR (95% CI)	p-value	aOR (95% CI)	p-value
Control Variables				
Age	1.00 (0.96-1.05)	0.87	1.01 (0.97-1.06)	0.59
Race/Ethnicity				
White	Ref	--	Ref	--
Black	0.80 (0.24-2.65)	0.71	0.76 (0.23-2.50)	0.65
Latinx	1.53 (0.48-4.93)	0.47	1.17 (0.37-3.72)	0.79
Other	1.06 (0.20-5.56)	0.95	1.22 (0.24-6.16)	0.81
Demographics				
Education				
Less than high school	Ref	--	Ref	--
High school	0.31 (0.12-0.81)	**0.016**	0.49 (0.18-1.32)	0.16
More than high school	0.31 (0.13-0.75)	**0.009**	0.42 (0.16-1.12)	0.08
Income				
Less than 10k	Ref	--	Ref	--
10-30k	0.60 (0.34-1.06)	0.08	0.81 (0.44-1.51)	0.51
More than 30k	0.41 (0.20-0.84)	**0.015**	0.67 (0.30-1.48)	0.32
Employment status				
Employed	Ref	--	Ref	--
Unemployed	2.36 (1.36-4.10)	**0.002**	1.83 (0.99-3.40)	0.06
Unstable housing				
No	Ref	--	Ref	--
Yes	2.64 (1.42-4.91)	**0.002**	1.14 (0.55-2.35)	0.72
Intimate partner violence				
No	Ref	--	Ref	--
Yes	3.33 (1.62-6.87)	**0.001**	1.49 (0.66-3.34)	0.33
Sexual orientation				
Gay	Ref	--	Ref	--
Bisexual/Other	1.29 (0.72-2.31)	0.40	0.80 (0.44-1.46)	0.47
Depression				
No	Ref	--	Ref	--
Yes	2.52 (1.45-4.36)	**0.001**	1.43 (0.79-2.59)	0.23
Substance Use				
Cannabis Use				
No	Ref	--	Ref	--
Weekly or less frequent	2.46 (1.30-4.63)	**0.005**	2.60 (1.36-4.98)	**0.004**
Daily	2.86 (1.41-5.78)	**0.003**	2.07 (1.01-4.26)	**0.048**
Sexual Risk Behavior				
Sexual partner concurrency last 6 months				
No	Ref	--	Ref	--
Yes	1.48 (0.90-2.44)	0.12	0.97 (0.53-1.77)	0.93
Anal intercourse while intoxicated				
No	Ref	--	Ref	--
Yes	2.64 (1.58-4.41)	**<0.001**	1.48 (0.81-2.70)	0.20
Group sex while intoxicated				
No	Ref	--	Ref	--
Yes	4.60 (2.54-8.33)	**<0.001**	1.77 (0.86-3.63)	0.12
Transactional sex				
No	Ref	--	Ref	--
Yes	5.50 (2.93-10.33)	**<0.001**	2.75 (1.25-6.06)	**0.012**
Sexually transmitted infection				
No	Ref	--	Ref	--
Yes	2.07 (1.08-3.97)	**0.029**	1.99 (1.00-3.93)	**0.049**
Regular partner last 6 months				
No	Ref	--	Ref	--
Yes	1.85 (1.14-3.01)	**0.013**	1.09 (0.62-1.90)	0.78
Sexual partner concurrency last 6 months				
No	Ref	--	Ref	--

Yes	1.48 (0.90-2.44)	0.12	0.97 (0.53-1.77)	0.93
Last Partner				
Last partner used alcohol				
No	Ref	--	Ref	--
Yes	1.65 (0.95-2.86)	0.08	0.94 (0.51-1.75)	0.85
Last partner used poppers				
No	Ref	--	Ref	--
Yes	1.78 (0.96-3.31)	0.07	1.38 (0.71-2.68)	0.34
Last partner injected drugs				
No	Ref	--	Ref	--
Yes	2.46 (1.19-5.11)	**0.015**	1.00 (0.41-2.45)	1.00
Never saw last partner again after sex				
No	Ref	--	Ref	--
Yes	1.39 (0.80-2.40)	0.24	1.15 (0.61-2.16)	0.67
Transactional sex with last partner				
No	Ref	--	Ref	--
Yes	3.47 (1.69-7.11)	**0.001**	0.74 (0.29-1.86)	0.52
Last partner used stimulants				
No	Ref	--	Ref	--
Yes	4.62 (2.70-7.92)	**<0.001**	2.52 (1.29-4.94)	**0.007**
Last partner was a one-time partner				
No	Ref	--	Ref	--
Yes	0.62 (0.31-1.23)	0.17	0.62 (0.29-1.34)	0.22

Figure 5.4 Frequency of self-reported stimulant use in last 6 months across study visits for 60 randomly selected participants

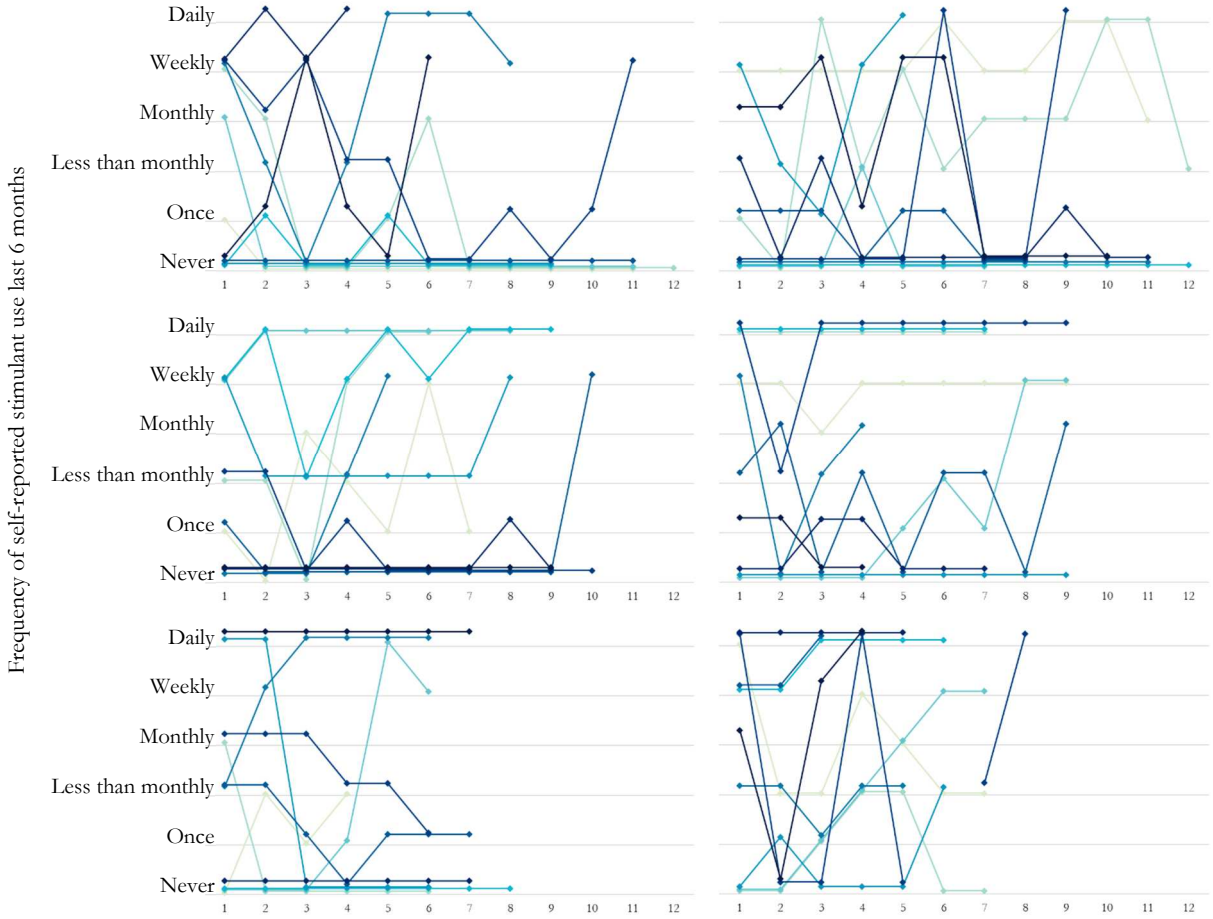


Table 5.17 Visit-level participant characteristics stratified by decreased stimulant use for final lasso model for the entire cohort (N=2,251 study visits)

	No Change (n=1,730)	Decreased Use (n=521)	p-value
Control Variables	**n (%)**	**n (%)**	
Age (median, IQR)	34 (28-40)	33 (28-40)	0.79
Race/Ethnicity			
White	106 (6.1%)	35 (6.7%)	0.24
Black	674 (39.0%)	178 (34.2%)	
Latinx	829 (47.9%)	265 (50.9%)	
Other	121 (7.0%)	43 (8.3%)	
HIV			
Negative	830 (48.0%)	215 (41.3%)	**0.007**
Living with HIV	900 (52.0%)	306 (58.7%)	
Demographics			
Education			
Less than high school	190 (11.0%)	76 (14.6%)	**0.02**
High school	555 (32.1%)	180 (34.5%)	
More than high school	985 (56.9%)	265 (50.9%)	
Employment status			
Employed	1,387 (80.2%)	367 (70.4%)	**<0.001**
Unemployed	343 (19.8%)	154 (29.6%)	
Substance Use			
Binge drinking			
Never	1,011 (58.4%)	262 (50.3%)	**<0.001**
Monthly or less	568 (32.8%)	183 (35.1%)	
Weekly/daily	151 (8.7%)	76 (14.6%)	
Cannabis Use			
No	917 (53.0%)	236 (45.3%)	**0.004**
Weekly or less frequent	463 (26.8%)	150 (28.8%)	
Daily	350 (20.2%)	135 (25.9%)	
Current substance use treatment			
No	1,600 (92.5%)	464 (89.1%)	**0.013**
Yes	130 (7.5%)	57 (10.9%)	
Stimulant use			
Never	1,088 (62.9%)	226 (43.4%)	**<0.001**
Once	109 (6.3%)	72 (13.8%)	
Less than monthly	123 (7.1%)	91 (17.5%)	
Monthly	94 (5.4%)	43 (8.3%)	
Weekly	154 (8.9%)	57 (10.9%)	
Daily	162 (9.4%)	32 (6.1%)	
Sexual Risk Behavior			
Anal intercourse while intoxicated			
No	958 (55.4%)	227 (43.6%)	**<0.001**
Yes	772 (44.6%)	294 (56.4%)	
Circuit party last 6 months			
No	1471 (85.0%)	444 (85.2%)	0.91
Yes	259 (15.0%)	77 (14.8%)	

Table 5.18 Unadjusted and adjusted odds ratios of factors associated with decreased stimulant use for final lasso model for the entire cohort (N=2,251 study visits)

	OR (95% CI)	p-value	aOR (95% CI)	p-value
Control Variables				
Age (median, IQR)	0.99 (0.97-1.01)	0.30	0.99 (0.97-1.01)	0.21
Race/Ethnicity				
White	Ref	--	Ref	--
Black	0.86 (0.46-1.59)	0.63	0.83 (0.47-1.47)	0.53
Latinx	1.04 (0.57-1.90)	0.89	1.02 (0.58-1.77)	0.96
Other	1.14 (0.56-2.33)	0.72	1.27 (0.65-2.49)	0.48
HIV				
Negative	Ref	--	Ref	--
Living with HIV	1.41 (1.04-1.91)	**0.027**	1.47 (1.09-1.98)	**0.012**
Demographics				
Education				
Less than high school	Ref	--	Ref	--
High school	0.82 (0.53-1.27)	0.37	0.83 (0.55-1.25)	0.37
More than high school	0.63 (0.41-0.97)	**0.036**	0.69 (0.46-1.04)	0.08
Employment status				
Employed	Ref	--	Ref	--
Unemployed	1.59 (1.21-2.10)	**0.001**	1.53 (1.17-2.01)	**0.002**
Substance Use				
Binge drinking last 6 months				
Never	Ref	--	Ref	--
Monthly or less	1.21 (0.93-1.58)	0.16	1.22 (0.93-1.59)	0.15
Weekly/daily	1.62 (1.07-2.46)	**0.023**	1.70 (1.13-2.55)	**0.011**
Cannabis Use				
No	Ref	--	Ref	--
Weekly or less frequent	1.15 (0.86-1.54)	0.35	1.12 (0.84-1.51)	0.44
Daily	1.31 (0.94-1.82)	0.11	1.28 (0.92-1.77)	0.14
Current substance use treatment				
No	Ref	--	Ref	--
Yes	1.58 (1.04-2.40)	**0.03**	1.52 (1.02-2.28)	**0.041**
Sexual Risk Behavior				
Anal intercourse while intoxicated				
No	Ref	--	Ref	--
Yes	1.38 (1.07-1.77)	**0.011**	1.36 (1.05-1.76)	**0.018**
Circuit party last 6 months				
No	Ref	--	Ref	--
Yes	0.88 (0.62-1.23)	0.45	0.85 (0.61-1.19)	0.34

Table 5.18 Unadjusted and adjusted regression coefficients of factors associated with last 6 month reported stimulant use frequency for final lasso model for the entire cohort (N=2,720 study visits)

	β (95% CI)	p-value	adj β (95% CI)	p-value
Control Variables				
Age	1.01 (0.99-1.03)	0.20	1.02 (1.00-1.03)	**0.012**
Race/Ethnicity				
White	Ref	--	Ref	--
Black	0.97 (0.67-1.43)	0.89	1.31 (0.98-1.75)	0.07
Latinx	1.12 (0.78-1.60)	0.53	1.33 (1.00-1.75)	**0.048**
Other	1.00 (0.65-1.54)	1.00	1.26 (0.88-1.80)	0.21
HIV				
Negative	Ref	--	Ref	--
Living with HIV	1.97 (1.54-2.51)	**<0.001**	1.49 (1.25-1.79)	**<0.001**
Demographics				
Unstable housing				
No	Ref	--	Ref	--
Yes	1.59 (1.38-1.83)	**<0.001**	1.30 (1.14-1.47)	**<0.001**
Incarcerated last 6 months				
No	Ref	--	Ref	--
Yes	1.51 (1.33-1.71)	**<0.001**	1.26 (1.13-1.41)	**<0.001**
Intimate partner violence				
No	Ref	--	Ref	--
Yes	1.44 (1.23-1.68)	**<0.001**	1.19 (1.04-1.36)	**0.013**
Substance Use				
Cannabis Use				
No	Ref	--	Ref	--
Weekly or less frequent	1.68 (1.48-1.91)	**<0.001**	1.34 (1.19-1.51)	**<0.001**
Daily	1.69 (1.44-1.98)	**<0.001**	1.29 (1.12-1.49)	**<0.001**
Regular other prescription drug use				
No	Ref	--	Ref	--
Yes	4.31 (3.36-5.53)	**<0.001**	2.49 (1.97-3.14)	**<0.001**
Cigarette/Vaping				
No	Ref	--	Ref	--
Yes	1.55 (1.33-1.80)	**<0.001**	1.34 (1.17-1.52)	**<0.001**
Regular opiate use				
No	Ref	--	Ref	--
Yes	3.02 (2.32-3.94)	**<0.001**	1.67 (1.31-2.14)	**<0.001**
Sexual Risk Behavior				
Anal intercourse while intoxicated				
No	Ref	--	Ref	--
Yes	2.28 (2.04-2.53)	**<0.001**	1.59 (1.43-1.77)	**<0.001**
Group sex while intoxicated				
No	Ref	--	Ref	--
Yes	2.23 (1.96-2.53)	**<0.001**	1.40 (1.23-1.59)	**<0.001**
Transactional sex				
No	Ref	--	Ref	--
Yes	2.44 (2.11-2.81)	**<0.001**	1.52 (1.33-1.75)	**<0.001**
Last Partner				
Used stimulants				
No	Ref	--	Ref	--
Yes	3.45 (3.06-3.90)	**<0.001**	2.65 (2.36-2.98)	**<0.001**

Chapter 6.

Conclusions

In summary, this dissertation reports three distinct but related projects designed to understand the influence of stimulant use on HIV/STI transmission dynamics among a cohort of MSM in Los Angeles, California. The analyses detailed in this dissertation had two primary goals. The first goal of the dissertation was to utilize methods, specifically path analysis, latent class analysis, and machine learning techniques, to examine the influence of stimulant use on HIV transmission dynamics within a longitudinal cohort of MSM and to evaluate the extent to which these methods can be used to examine these constructs. The second goal of this dissertation was to provide a more nuanced understanding of the contributions that stimulant use has on HIV/STI transmission dynamics among MSM.

The first analysis examined the relative contributions of methamphetamine use, depression, and sexual risk behavior on rectal gonorrhea/chlamydia (GC/CT) using path analysis. Findings from this analysis demonstrated that depression and methamphetamine use contribute to increased sexual risk behaviors which, in turn, are associated with rectal GC/CT. Our results also demonstrated that the factors and patterns which contribute to risk behaviors may differ according to HIV status. Specifically, depression may have a stronger influence on sexual risk behaviors among HIV-negative MSM while methamphetamine may have a more substantial impact on risk behaviors for MSM living with HIV. Collectively, these findings demonstrate the potential utility of combined treatment and prevention efforts that link screening and treatment of stimulant use and depression with HIV/STI prevention and treatment.

The second analysis evaluated risk behaviors associated with patterns of sexualized stimulant and alcohol use utilizing latent class analysis. Findings from this analysis revealed that patterns of sexual activities, and the specific substances that are used during those activities, confer different risk

behavior profiles for HIV/STI transmission among this cohort of MSM. Sexualized stimulant use was positively associated with risk factors for HIV/STI transmission such as having an STI, engaging in transactional sex, attending a circuit/hookup/sex party, depressive symptoms, and was negatively associated with health protective behaviors, such as using biomedical prevention to prevent HIV transmission. Our findings additionally demonstrated that Black/Latinx MSM who engaged in sexualized stimulant use were more likely to experience syndemic health conditions, such as having an STI and depressive symptoms, than their Black/Latinx counterparts who did not engage in sexualized stimulant use. These disparities were particularly notable among Black MSM, where stimulant use only or stimulant/alcohol use during oral sex and receptive anal intercourse were negatively associated with the use of biomedical prevention. Findings from this analysis highlight the disproportionate impact that sexualized substance use has on HIV/STI transmission dynamics among MSM of color. These results demonstrate the potential utility of interventions that link substance use treatment with HIV/STI prevention and treatment. Findings from this study also provide critical information regarding sexual risk behaviors and syndemic conditions that surround sexualized stimulant and alcohol use which can be used to develop tailored HIV prevention interventions for stimulant-using MSM, a subpopulation of MSM at high-risk for HIV/STI transmission.

The third analysis in this dissertation compared factors associated with increased stimulant use in relation to HIV status using a machine learning and prediction modelling approach. Findings from this analysis demonstrated that increased stimulant use was positively associated with unstable housing and transactional sex across all models. These results underscore the importance of designing HIV prevention interventions that address the underlying factors that often drive the interdependent relationship between unstable housing, stimulant use, and transactional sex which contribute to ongoing HIV/STI transmission among vulnerable MSM subpopulations. These

findings also suggest the potential utility of HIV prevention interventions that incorporate strategies such as contingency management, which provides linkages to financial or community resources in exchange for not using substances. This analysis highlighted differences in factors correlated with increased stimulant use based on HIV status. Specifically, among MSM living with HIV, polysubstance use was associated with increased stimulant use, suggesting that stimulants may be used in conjunction with other substances as a coping strategy to mitigate negative feelings associated with an HIV diagnosis, HIV-related stigma, or depressive symptoms. In contrast, increased stimulant use among HIV-negative MSM correlated with increased sexual risk behaviors, sexualized substance use, and last partner substance use, suggesting that sexual contexts and partnership dynamics may drive stimulant use among HIV-negative MSM. Findings from this analysis indicate that underlying motivations and factors which contribute to stimulant use patterns among MSM likely differ based on HIV status and suggest that these differences should be accounted for in the design of HIV prevention and treatment interventions.

To the best of our knowledge, these analyses were among the first to utilize these statistical methods to examine the impacts of stimulant use on HIV/STI transmission dynamics among a longitudinal cohort of MSM, which represents an important contribution to the literature. Specifically, our first project was one of the first to explicitly evaluate the relative contributions of methamphetamine use, depression, and sexual risk behavior on rectal GC/CT longitudinally using path analysis with a cross-lag panel design, which is an important step in disentangling the relationship between depression and methamphetamine use with HIV/STI transmission. This analysis demonstrated that conducting a path analysis using a cross-lag panel design can be a useful tool to account for time-varying confounding with longitudinal data. A limitation of this approach is the numerous paths across timepoints, necessitating the use of constraints to aid in the interpretation of the results. However, the use of constraints relies on the assumption that estimates

are stable across time and prevents the ability to provide standardized beta coefficients and direct/indirect effects. Our second project was among the first to utilize latent class analysis to evaluate patterns of sexualized stimulant and alcohol use at the level of specific sex acts that occurred. This analysis demonstrated that the use of latent class analysis can be a useful tool to classify individuals based on latent constructs and to evaluate characteristics based on class membership. Given that this cohort was a relatively high-risk cohort of MSM with high prevalence of substance use and sexual risk behaviors, our analysis demonstrated that latent class analysis can be a useful method to identify and analyze heterogeneities within data that may otherwise appear homogeneous. However, latent class analysis relies on the assumption that data is cross-sectional, not serial cross-sectional or longitudinal. While we feel that the use of latent class analysis was justified for this analysis as we utilized visit-level predictors and more complex analyses were outside the scope of this dissertation, our results suggest the potential utility of latent class analysis methods specifically designed for longitudinal data, such as latent transition analysis, for future research. The third project in this dissertation was among the first to utilize lasso for variable selection to evaluate factors associated with increased stimulant use among a diverse cohort of MSM. This project demonstrated that machine learning techniques can be a useful tool to select conceptually relevant predictors that are associated with increased stimulant use and to evaluate how those determinants may differ by HIV status.

The overarching purpose of this dissertation was to take a more nuanced approach toward understanding the contributions of stimulant use on HIV/STI transmission dynamics by utilizing the different statistical approaches we outlined above. Our results underscore the importance of future research and interventions to better understand the contexts in which sexualized stimulant use occurs, specifically those that are designed to understand and address the intersecting vulnerabilities which contribute to ongoing HIV/STI disparities experienced by subpopulations of

stimulant-using MSM. Furthermore, while the links between stimulant use and HIV/STIs have been well established, these analyses demonstrate that factors contributing to stimulant use and its impact on HIV/STI transmission dynamics are complex and likely dependent on the individual contexts in which stimulant use occurs, highlighting the importance of integrating improved substance use screening and treatment paradigms into clinical care and HIV treatment/prevention interventions. Current HIV prevention and treatment services often do not systematically screen for mental health comorbidities or substance use disorders and are often siloed from substance use treatment and mental health services.[288, 289] Consequently, many substance use disorders and mental health conditions among MSM at risk for or living with HIV remain undetected and untreated, possibly contributing to low adherence to antiretroviral therapy and biomedical prevention, destabilization of financial resources, and poorer perceived quality of life.[290] Collectively, findings from this dissertation highlight the importance of incorporating substance use treatment with HIV prevention and treatment efforts for stimulant-using MSM.

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