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Sexual Risk Behaviors among Men Who Have Sex with Men: Implications for the Delivery of New HIV Prevention Interventions

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Sexual Risk Behaviors among Men Who Have Sex with Men: Implications for the Delivery of New HIV Prevention Interventions

A dissertation submitted in partial satisfaction of the

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by

Heather Alisa Pines

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ABSTRACT OF THE DISSERTATION

Sexual Risk Behaviors among Men Who Have Sex with Men:
Implications for the Delivery of New HIV Prevention Interventions

by

Heather Alisa Pines
Doctor of Philosophy in Epidemiology
University of California, Los Angeles 2013
Professor Pamina M. Gorbach, Chair

Recent clinical trial results suggest that new HIV prevention interventions, such as pre-exposure prophylaxis and treatment as prevention, protect against HIV infection. However, several barriers to widespread implementation of these interventions have been identified. In response to some of these challenges, many argue that new HIV prevention interventions should only be delivered to high-risk populations within integrated HIV prevention programs that consist of biomedical, behavioral, and structural interventions. In the United States, men who have sex with men (MSM) remain the most heavily HIV affected population, and thus will likely be the target of such programs. This dissertation aims to inform the development of MSM-specific HIV prevention programs by providing a better understanding of the situations in which new prevention strategies could have the greatest impact within this population.

More specifically, this dissertation examines longitudinal patterns of sexual risk behavior, socio-demographic and behavioral factors associated with partnership type and serostatus, and individual-level and sexual event-level predictors of condom use during receptive anal

intercourse among MSM. Chapter 2 is based on data from the Multicenter AIDS Cohort Study (MACS) and demonstrates that HIV-negative MSM exhibit distinct sexual risk trajectories and that those following a high risk trajectory exhibit “seasons of risk” over time. Chapter 3 also uses data from the MACS to show that the reported number of male sexual partners is associated with partnership type and serostatus and that the magnitude and direction of this relationship differs by HIV status. Chapter 4 is based on longitudinal data from a cohort of racially/ethnically diverse HIV-negative MSM followed for one year in Los Angeles, and demonstrates that the effect of methamphetamine use on condom use during receptive anal intercourse at the sexual event-level is greatest in the context of non-main partnerships. Findings from this dissertation expand the current understanding of risk behaviors among MSM, and have implications for the development of integrated HIV prevention programs for MSM in the United States.

The dissertation of Heather Alisa Pines is approved.

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2013

To my family. Thank you for your endless love, support, and encouragement.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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Chapter 1. Introduction and Background

1.1 Introduction

Recent clinical trial results suggest that new HIV prevention interventions, such as pre-exposure prophylaxis (PrEP) and treatment as prevention (TasP), protect against HIV infection.[1-5] However, several barriers to widespread implementation of these interventions have been identified.[6-9] In response to some of these challenges, many argue that new HIV prevention interventions should only be delivered to high-risk populations within comprehensive HIV prevention programs.[10-11] In the United States (US), men who have sex with men (MSM) remain the most heavily HIV affected population,[12] and thus will likely be the target of such programs. Recognizing that MSM exhibit varying levels of sexual risk behavior, interim guidelines from the Centers for Disease Control and Prevention (CDC) state that PrEP should be offered to MSM "at substantial, ongoing, high risk for acquiring HIV infection."[13] However, a better understanding of what characterizes "ongoing, high risk" among MSM and the situations (e.g., partnerships characteristics) in which they engage in high risk behaviors is needed to inform the implementation of these guidelines. Moreover, the World Health Organization (WHO) recommends early initiation of antiretroviral therapy (ART) for HIV-positive individuals in heterosexual serodiscordant couples for the purpose of utilizing TasP.[14] However, the potential impact of TasP among MSM in serodiscordant main partnerships may be diluted by the frequency of casual partnerships within this population.[15] Thus, additional research on partnership type and serostatus is needed to inform TasP guidelines for MSM.

To address these gaps in knowledge, this dissertation project used longitudinal data from the Multicenter AIDS Cohort Study (MACS) to examine patterns in sexual risk behaviors among HIV-negative MSM over time in order to characterize sexual risk trajectories, determine the duration of high risk periods, and identify factors associated with following a high risk

trajectory within this population. MACS data were also used to investigate socio-demographic and behavioral factors associated with partnership type and serostatus over time among MSM. Finally, longitudinal data from a cohort of racially/ethnically diverse HIV-negative MSM that was followed for one year in Los Angeles were used to examine the effect of individual-level and sexual event-level characteristics on condom use during receptive anal intercourse (RAI) at the last sexual event within partnerships reported over time.

Findings from this dissertation expand the current understanding of sexual risk behaviors and partnerships among MSM, and have implications for the development of comprehensive HIV prevention programs for MSM in the US.

1.2 Epidemiology of HIV/AIDS

Worldwide and in the United States

In 2012, an estimated 35.3 (95% CI: 32.2-38.8) million individuals were living with HIV/AIDS worldwide and 2.3 (95% CI: 1.9-2.7) million individuals were newly infected with HIV.[16] In the US, an estimated 49,273 individuals were diagnosed with HIV infection in 2011.[12] However, MSM are disproportionately affected by HIV/AIDS in the US. In 2011, 92% of all newly diagnosed HIV infections among adults and adolescents were attributed to sexual contact, of which 70% were due to male-to-male sexual contact.[12] The HIV epidemic among MSM in the US is also defined by age and racial disparities. Between 2008 and 2011, the largest percentage increase (26%) in the number of new HIV diagnoses among MSM was seen for those 13 to 24 years of age.[17] In 2011, 58% of all new HIV diagnoses among MSM 13 to 24 years of age occurred among Black MSM - nearly 3 times the percentage of new diagnoses observed among White MSM (20%) and Hispanic/Latino MSM (18%) within the same age group.[17]

Los Angeles County

By the end of 2009, 76,383 cumulative cases of HIV/AIDS had been reported in Los Angeles County (LAC) since the beginning of the epidemic, which accounts for 5.3% of the cumulative cases reported in the US.[18] In LAC, HIV/AIDS disproportionately affects MSM and Latinos, who accounted for 72% and 39% (larger than any other racial/ethnic group in LAC), respectively, of the estimated 42,000 individuals living with HIV/AIDS in LAC in 2009.[18] However, preliminary calculations suggest that in 2007 there were between 2,000 and 2,500 incident cases of HIV in LAC, with the highest estimated incidence rate among African-American MSM.[18]

1.3 New HIV prevention interventions

Despite the efficacy of condoms in preventing sexual transmission of HIV, many individuals are unwilling to consistently use condoms during sexual intercourse.[10] In a nationally representative survey conducted among 5,865 males and females living in the US, 21.5% of males and 18.4% of females reported using condoms during their last 10 vaginal intercourse (VI) events, while 25.8% of males and 13.2% of females reported using condoms during their last 10 anal intercourse (AI) events.[19] Further, it is estimated that as many as 60 million individuals worldwide could become infected with HIV before an effective preventive vaccine is developed.[20] Thus, there is a great need for alternative biomedical HIV prevention interventions.

Pre-exposure prophylaxis

Pre-exposure prophylaxis (PrEP) refers to the use of antiretroviral medications by HIV-negative individuals to reduce their risk of HIV infection. The multi-site Pre-exposure

Prophylaxis Initiative (iPrex) trial conducted among MSM around the world observed a 44% reduction in the risk of HIV acquisition in those randomized to a daily dose of oral tenofovir and emtricitabine (TDF/FTC).[1] However, higher efficacy (73%) was observed among participants with ≥90% adherence,[1] and more recent analyses of iPrex data suggest that adherence was higher among MSM participating in the US compared to those in other countries.[21] In addition, efficacy trials of the same PrEP regimen conducted in Sub-Saharan Africa reported a 62.2% reduction in risk associated with PrEP use among HIV-negative heterosexual males and females[2] and a 75% reduction in risk among HIV-negative individuals in serodiscordant, heterosexual couples (Partners PrEP Study).[3] More recently, a trial conducted among injection drug users in Thailand reported a 48.9% reduction in risk associated with a daily dose of oral tenofovir. [5]

Several trials and demonstration projects are currently underway to evaluate the efficacy, safety, and/or acceptability of oral and topical PrEP based on both daily and intermittent dosing schedules.[22] However, numerous barriers to widespread PrEP implementation have been identified and include: adherence, acceptability, behavioral disinhibition/risk compensation, cost, the lack of existing infrastructure for monitoring side effects, and viral resistance among PrEP users who become HIV infected.[6-9] Given the plethora of potential challenges, many argue that PrEP should be targeted to high-risk populations, such as serodiscordant couples, sex workers, and MSM, within comprehensive HIV prevention packages that consist of biomedical, behavioral, and structural interventions.[10-11]

Treatment as prevention

Treatment as prevention (TasP) refers to the initiation of ART by HIV-positive individuals to prevent HIV transmission to their uninfected sexual partners. In a recent clinical trial conducted by the HIV Prevention Trials Network (HPTN 052), early initiation of ART in the

context of stable serodiscordant couples reduced HIV transmission risk by 96%.[4] However, given current barriers to HIV testing and the detection of acute infections, linkage and access to care, adherence to ART, and achieving viral suppression, many question the feasibility of widespread implementation of TasP as an HIV control measure.[23-24] Nevertheless, upon the release of findings from HPTN 052, the WHO recommended treatment of all HIV-positive individuals in heterosexual serodiscordant partnerships regardless of their CD4 cell count.[14] MSM were excluded from these recommendations because only 2% of the serodiscordant couples included in HPTN 052 were between MSM, thus it was unclear whether the study's findings could be generalized to other high-risk populations.[14, 25]

1.4 Patterns in sexual risk behaviors among MSM over time

Few nationally representative studies have been conducted among MSM in the US, thus the prevalence of specific sexual behaviors within this population remains unknown. However, it is unlikely that all MSM engage in high-risk behaviors. In an online survey conducted among 24,787 MSM in the United States, 75% reported giving oral sex at their last sexual encounter, while only 36% and 34% reported having RAI and insertive anal intercourse (IAI), respectively, at their last sexual encounter.[26] Further, among those who reported having AI, only 46% reported using condoms.[26] Similarly, 56% of MSM enrolled in the LA Men's Survey reported having unprotected anal intercourse (UAI) in the past year.[18]

However, several factors in addition to condom use must be considered prior to classifying UAI as a risky sexual behavior. First, because unprotected receptive anal intercourse (URAI) confers a greater risk of HIV infection per sex act compared to unprotected IAI (UIAI),[27-29] knowing the type of UAI an individual engages in is critical to assigning risk. Although, URAI in the context of a seroconcordant partnership is not necessarily a risky sexual

behavior.[30] Thus, the partner's serostatus and whether either partner has concurrent partners of an unknown or discordant serostatus must also be considered.[30]

Recognizing the importance of each of these factors and that it is unlikely that all MSM exhibit the same levels or patterns of sexual risk behavior over time, current CDC guidelines state that PrEP should be offered to MSM "at substantial, ongoing, high risk for acquiring HIV infection."[13] Previous serial cross-sectional studies conducted among MSM have examined population trends in sexual risk behaviors over time.[31-33] However, little data exists on the duration or patterns of sexual risk behavior within individuals over time, which would be needed to facilitate the implementation of these guidelines.

Several longitudinal studies have examined individual patterns or trajectories of sexual risk behavior among adolescents as they transition into adulthood, and suggest that distinct patterns do exist within populations; however, none of these studies were conducted among MSM.[34-36] One longitudinal study of sexual risk behaviors conducted among MSM in Vancouver, British Columbia found that the proportion of MSM within various risk categories remained relatively constant over time; however, no information on how individuals moved between categories over time was presented.[37] Thus, additional research is needed to identify longitudinal patterns in sexual risk behaviors and the duration of risk among HIV-negative MSM.

1.5 Partnership-level characteristics and HIV infection risk among MSM

In addition to individual-level characteristics, various partnership-level characteristics (i.e., partnership type, age discordance, and partnership serostatus) affect HIV infection risk among MSM, and should be considered in the design of HIV prevention strategies for this population.[38]

Partnership Type

Among MSM a greater proportion of HIV transmission events occur during sex with main partners than with casual partners,[39-40] which is likely due to the high rate of UAI with main partners within this population.[40-42] This phenomenon has been explained by the belief that UAI is a symbol of trust within partnerships[43] and that UAI offers an increased sense of intimacy, which condoms are perceived to interfere with.[44] Further, the establishment of "negotiated safety" agreements (i.e., agreements to engage in UAI with each other, but to always use condoms with other sex partners)[45-46] between partners also contributes to the high rates of UAI within main partnerships.

Age Discordance

Previous research suggests that having older sexual partners is associated with HIV infection among MSM,[47-50] which may be due to some young MSM's preference for older partners[51] and the higher prevalence of HIV among older MSM.[12] In the context of heterosexual couples, females with older male sexual partners are also at increased risk of sexually transmitted infections (STI), including HIV.[52-54] In addition to the higher prevalence of STI/HIV among older male partners, this increased risk has been attributed to power differentials within these partnerships, such that young females may be forced to have unprotected sex.[50, 52] Few studies have examined power dynamics or issues of coercion within MSM partnerships. One study found that the odds of having UAI were higher for MSM in age concordant partnerships, which suggests that power differentials within age discordant partnerships may not be driving the observed increase in HIV risk among MSM with older partners.[50] However, the measures of UAI used in that study were not partner-specific. Another study did not report an association between UAI and having a partner greater than 40 years of age at the last sexual encounter among HIV-negative MSM; however, the participant's age relative to their partner's was not accounted for in that study.[55] Thus, additional partner-specific

data on the relationship between age discordance and condom use during AI is needed, and may elucidate the mechanism by which having older partners confers a greater risk of acquiring HIV.

Partnership Serostatus

Some MSM decide to engage in risky sexual behaviors based on the perceived HIV status of their sexual partners,[56-57] and thus practice seroadaptation in the form of serosorting or seropositioning. Serosorting refers to the practice of AI or UAI with partners of the same serostatus (i.e., seroconcordant).[56-58] Seropositioning, on the other hand, refers to the practice of less risky sexual acts with serodiscordant partners.[56-58] That is, HIV-negative MSM may choose to engage in RAI or URAI with seroconcordant (i.e., HIV-negative) partners, but only engage in IAI or UIAI with their serodiscordant (i.e., HIV-positive or HIV status unknown) partners to reduce their risk of HIV infection. Data from the 2008 National HIV Behavioral Surveillance (NHBS) survey conducted among MSM in San Francisco suggest that 40.5% of HIV-negative MSM and 51.1% of HIV-positive MSM engaged in seroadaptive behaviors in the past six months.[59] Further, findings from a meta-analysis suggest that among HIV-positive MSM in the US the prevalence of URAI (20%, 95% CI: 15-25) with HIV-negative or serostatus unknown partners is higher than the prevalence of UIAI (13%, 95% CI: 9-18) with these partners.[60] Yet, despite the widespread practice of seroadaptation among MSM, its effectiveness as a risk reduction strategy is controversial because its success is dependent on accurate knowledge of each partners' true HIV status, and thus, routine HIV testing for both partners.[61-64]

1.6 Impact of partnership characteristics on UAI among MSM

Previous research suggests that sexual risk behaviors vary within individuals depending on multiple situational factors (or partnerships characteristics),[65-68] which may interact with one another to influence risk behaviors. Further, Zea et al.[65] argue that within-person variation in sexual risk behaviors can be explained by Ewart's Social Action Theory, which suggests that self-protective behavior, such as condom use, is a function of individual-level factors as well as social-contextual factors, such as partnership characteristics, surrounding the particular occasion in which the behavior is to be practiced.[65, 69] Zea et al. applied the Social Action Theory by examining the effect of personal and situational characteristics on UAI at last sex in a cross-sectional sample of Latino MSM in the US.[65] Mustanski et al. extended the approach used by Zea et al. to a longitudinal sample of young MSM in the Midwest, by examining the effect of partnership characteristics on the frequency of UAI across multiple partnerships reported by the same individual over time.[68] However, additional longitudinal research on condom use during RAI at the sexual event-level is needed among racially/ethnically diverse MSM. This information could be used to plan for the use of new HIV prevention interventions in the context of in high-risk sexual partnerships among MSM.

1.7 Potential impact of treatment as prevention among MSM in serodiscordant main partnerships

Previous research has examined the relationship between partner type (i.e., main vs. casual) and the practice of sexual risk behaviors[41, 68, 70] and HIV seroconversion,[39-40] as well as factors associated with engaging in UAI with serodiscordant partners (main or casual) among MSM.[55, 71] However, little research has been done to characterize MSM who have serodiscordant main partners. Given the frequency of casual partnerships among MSM,

potential exposure to HIV during intercourse with such partners could dilute the population-level impact of TasP in the context serodiscordant couples.[15] Although data collected from MSM by the NHBS system suggest that having a main partner in the past year is associated with having fewer casual partners,[72] additional information on this association by main partnership serostatus is needed to evaluate the potential impact of TasP within this population

1.8 Conceptual Model

The conceptual model shown in Figure 1.1 was adapted from a model developed by Gorbach and Holmes[38] to explain how individual-level and partnership-level characteristics affect sexual risk behaviors and the incidence of HIV/STIs. Further, this model reflects key elements of the Social Action Theory[69] as both personal and situational factors (i.e., partnership characteristics) interact to affect the self-protective behavior of condom use within partnerships. Thus, this model guided all analyses undertaken as part of this dissertation project.

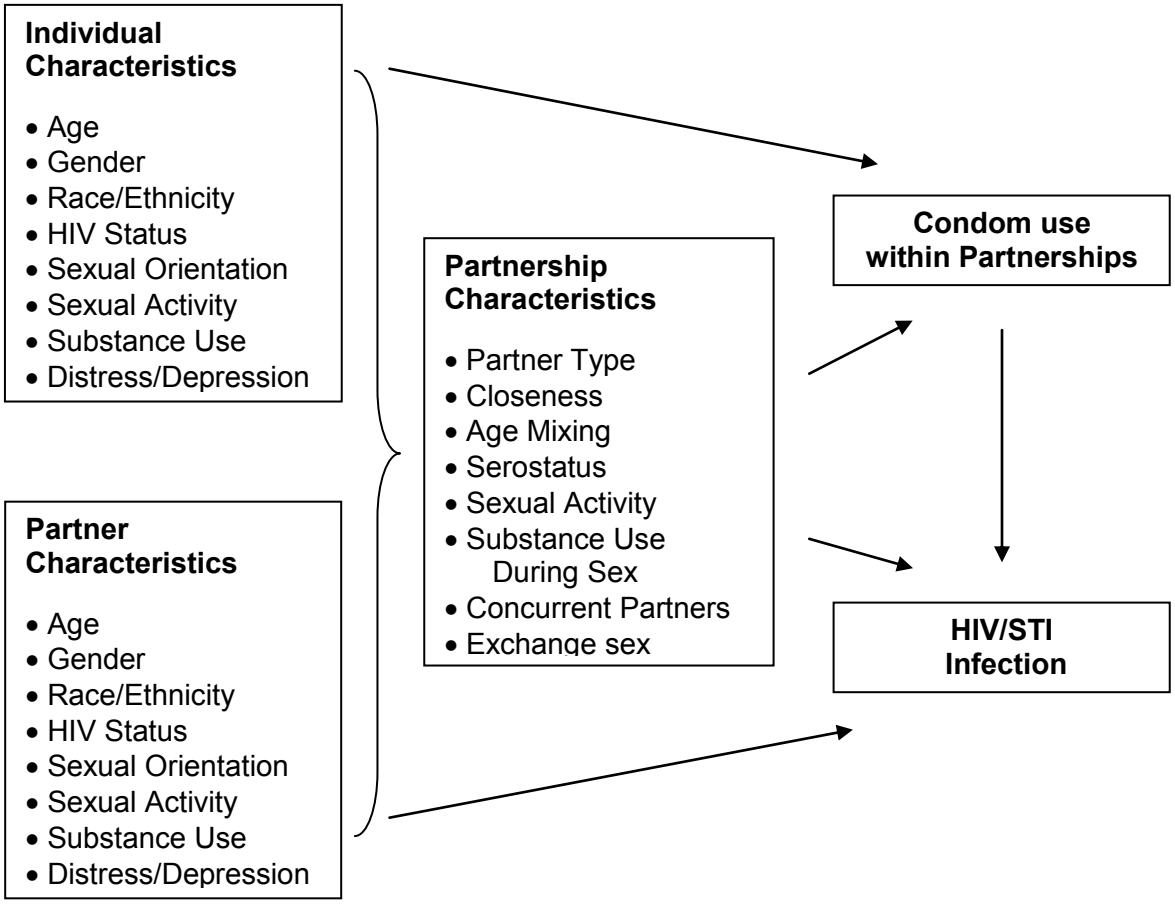

Figure 1.1. Conceptual model of partnership characteristics, condom use, and HIV/STI risk.

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Chapter 2. Sexual risk trajectories among MSM in the United States: implications for pre-exposure prophylaxis delivery

2.1 Abstract

Background: Despite evidence supporting pre-exposure prophylaxis (PrEP) efficacy, there are concerns regarding the feasibility of widespread use among men who have sex with men (MSM). To inform the development of targeted PrEP delivery guidelines, we characterized sexual risk trajectories among HIV-negative MSM.

Methods: At semiannual visits from 2003-2011, HIV-negative MSM (N=419) participating in the Multicenter AIDS Cohort Study provided data on sexual risk behaviors since their last visit. Based on reported behaviors, participants were assigned a sexual risk behavior (SRB) score at each visit as follows: (0) no insertive or receptive anal intercourse (IAI/RAI), (1) no unprotected IAI/RAI (UIAI/URAI), (2) only UIAI, (3) URAI with 1 HIV-negative partner, (4) condom-serosorting, (5) condom-seropositioning, and (6) no seroadaptive behaviors. Group-based trajectory modeling was used to examine SRB scores (<4 vs. ≥4) and identify groups with distinct sexual risk trajectories.

Results: Three sexual risk trajectory groups were identified: low risk (N=264; 63.0%), moderate risk (N=96; 22.9%; mean duration of consecutive high risk intervals~1 year), and high risk (N=59; 14.1%; mean duration of consecutive high risk intervals~2 years). Compared to low risk group membership, high risk group membership was associated with younger age (in years) (adjusted odds ratio [AOR]=0.93, 95% confidence interval [CI]: 0.89-0.96), being White (AOR=2.29, 95% CI: 1.08-4.85), earning an income ≥$20,000 (AOR=4.65, 95% CI: 2.03-10.67),

distress/depression symptoms (CESD≥16) (AOR=2.15, 95% CI: 1.04-4.43), and substance use (AOR=2.07, 95% CI: 1.04-4.09).

Conclusion: Screening for the socio-demographic and behavioral factors described above may facilitate targeted PrEP delivery during high risk periods among MSM.

2.2 Introduction

Daily oral pre-exposure prophylaxis (PrEP), a biomedical intervention for HIV prevention, reduces the risk of HIV acquisition between 44 and 75% depending on the population.[1-3] Although demonstration projects to assess the acceptability and feasibility of PrEP use are underway,[4-6] potential barriers to widespread PrEP implementation have been identified and include: adherence, acceptability, behavioral disinhibition/risk compensation, cost, the lack of existing infrastructure for monitoring side effects, and viral resistance among PrEP users who become HIV infected.[7-10] Thus, many argue PrEP should only be delivered to high risk populations within comprehensive HIV prevention programs that consist of behavioral, biomedical, and structural interventions.[11-12]

Given the robust data suggesting PrEP's efficacy among men who have sex with men (MSM)[1] and the high rate of HIV infection within segments of this population,[13-14] MSM will likely be a group prioritized for PrEP delivery in the United States (US). Interim recommendations from the Centers for Disease Control and Prevention (CDC) state that PrEP should be offered to MSM "at substantial, ongoing, high risk for acquiring HIV infection."[15] Modeling studies also suggest that a targeted approach to PrEP implementation among MSM at greatest risk of HIV infection should be employed to control costs and maximize effectiveness.[16-18] While risk prediction models have informed the development of tools to screen and identify high risk MSM,[19-20] little is known about the duration of risk among MSM or how MSM at ongoing high risk should be identified for PrEP use.

Several repeated cross-sectional studies conducted among MSM have examined population trends in sexual risk behavior over time.[21-23] To our knowledge, no studies have specifically investigated patterns of sexual risk behavior within individual HIV-negative MSM over sustained periods of time. One study conducted among older, HIV-positive and HIV-negative MSM identified sexual risk trajectories based on the number of sexual partners

reported over time.[24] However, the measure of risk used in that study did not consider sexual practices associated with the greatest risk of HIV acquisition, such as unprotected receptive anal intercourse (URAI),[25-27] or the HIV status of reported partners. Given the different levels of risk associated with specific sexual practices, some MSM base their decision to engage in high risk behaviors on the perceived HIV status of their sexual partners.[28-29] This phenomenon is known as seroadaptation and often results in serosorting or seropositioning.[30] Serosorting refers to the practice of anal intercourse (AI), regardless of condom use, with seroconcordant partners only, whereas seropositioning refers to the practice of risky sexual acts (i.e., URAI if HIV-negative) with seroconcordant partners only and less risky sexual acts (i.e., oral sex) with serodiscordant partners.[28-30] Yet, whether seroadaption is an effective risk reduction strategy remains controversial because its success depends on accurate knowledge of each partners' true HIV status.[31-34] To better classify and understand longitudinal patterns of risk among MSM, a comprehensive measure of risk that accounts for the practice of specific sexual acts and the HIV status of sexual partners over time, in addition to the number of sexual partners, should be employed.

We created a comprehensive sexual risk behavior score that incorporates multiple factors affecting the risk of HIV acquisition and used data from the Multicenter AIDS Cohort Study (MACS) to characterize distinct sexual risk trajectories among HIV-negative MSM and identify socio-demographic and behavioral factors associated with longitudinal patterns of risk.

2.3 Methods

The MACS is an ongoing prospective study of the natural and treated histories of HIV infection among MSM living in Baltimore, MD; Chicago, IL; Los Angeles, CA; and Pittsburgh, PA. MSM were enrolled in the MACS at three time points between 1984 and 1985 (1,814 HIV-positive and 3,140 HIV-negative), 1987 and 1990 (382 HIV-positive and 286 HIV-negative), and

2001 and 2003 (688 HIV-positive and 662 HIV-negative). MACS participants complete study visits every six months during which they are tested for HIV (if HIV-negative), provide a blood sample to be stored in a repository for future research, undergo a physical exam, and complete study questionnaires, which collect demographic, psychosocial, behavioral, medical history, and health services data. Audio computer-assisted self-interviewing (ACASI) is used at most MACS sites to collect data on sensitive information, such as sexual behaviors and substance use. More detailed descriptions of the methods used to conduct the MACS have been described elsewhere.[35-36] Study protocols were approved by institutional review boards at each of the study centers and all participants provided informed consent.

Study Population

The following criteria were used to select HIV-negative MACS participants for inclusion in the current study: (1) enrolled in the MACS during the third recruitment wave between 2001 and 2003, (2) completed visit 40 (between October 1, 2003 and March 31, 2004) or visit 41 (between April 1, 2004 and September 30, 2004) as an HIV-negative participant, and (3) completed ≥1 additional visit by visit 55 (between April 1, 2011 and September 30, 2011). Because HIV infection rates in the US are highest among young (<30 years-old), minority MSM,[14] the study population was restricted to participants enrolled during the third recruitment wave as they are younger and more racially/ethnically diverse than participants enrolled at earlier time points. Visit 40 was selected as the "index visit" for this study because MACS behavioral questionnaires did not begin collecting the HIV status of participants' insertive anal intercourse (IAI) or receptive anal intercourse (RAI) partners with whom they did not use condoms during IAI/RAI until visit 40. Restricting to this time period (2003-2011) also allowed for an examination of risk within a contemporary population of MSM during the highly active antiretroviral therapy (HAART) era. Participants were followed from their index visit (visit 40/41)

to their last study visit, death, or the end of the follow-up period (visit 55), whichever came first. Those who seroconverted over the course of follow-up were censored after their first HIV-positive visit.

Of the 662 HIV-negative MACS participants enrolled between 2001 and 2003, 419 were still active and provided covariate and outcome data at the index visit and ≥1 additional visit during the study period. Although there was no statistically significant difference in the number of male sexual partners reported, MACS participants who were inactive (i.e., lost to follow-up or deceased) at the index visit were slightly younger, less likely to be White, less educated, and earned a lower annual income than those who were still active members of the cohort.

Outcome of Interest: Sexual Risk Behavior

We created a comprehensive sexual risk behavior (SRB) score based on findings from a pooled analysis conducted by Vallabhaneni *et al.*, which examined the association between the practice of seroadaptive behaviors and HIV acquisition among MSM.[37] At semiannual study visits, participants included in Vallabhaneni *et al.*'s analysis were tested for HIV and reported on their sexual behaviors since their last visit. Based on their reported behaviors, Vallabhaneni *et al.* sequentially assigned participants to one of the following risk categories at each visit: no unprotected anal intercourse (UAI), UAI with a single HIV-negative partner, unprotected top (only UIAI), condom serosorting (UAI with HIV-negative partners only), condom seropositioning (URAI with HIV-negative partners only), and high risk sex (URAI with HIV-positive/HIV status unknown partners or no seroadaptive behaviors).

At each MACS study visit, participants reported their number of IAI/RAI partners since their last visit, the number of partners with whom they used condoms every time during IAI/RAI, and the HIV status of partners with whom they did not use condoms every time during IAI/RAI. We assigned participants SRB scores (0 to 6) at each visit based on their reported behaviors

during the six month interval since their last visit as described in Table 2.1. Although we based our SRB score on the risk categories defined by Vallabhaneni *et al.*, there are a few slight differences between their risk categories and the levels of our score. First, our SRB score contains a separate level for those who did not engage in any AI since their last visit (SRB score=0) and those who engaged in AI, but always used condoms (SRB score=1). Second, we only assigned participants to our single HIV-negative partner category (SRB score=3) if they engaged in *URAI* with a single HIV-negative partner. Those who engaged in *only UIAI* with a single HIV-negative partner were assigned to our only UIAI category (SRB score=2). Because only three of the risk categories defined by Vallabhaneni *et al.* (condom seropositioning, condom serosorting, and high risk sex/no seroadaptive behaviors) were associated with HIV acquisition,[37] we assigned intervals with an SRB score≥4 a value of 1 and intervals with an SRB score<4 a value of 0 and used this binary variable as the outcome in our analysis.

Covariates of Interest

We examined the following characteristics measured at the index visit as predictors of interest in our analysis: age, race/ethnicity (White vs. non-White), education (<college education vs. ≥college education), annual income (<$20,000 vs. ≥$20,000), distress or depression symptoms (Center for Epidemiologic Studies Depression Scale [CESD] score ≥16),[38] and reported substance use (ecstasy, methamphetamine, poppers, crack, or other cocaine) since the last study visit. These covariates were chosen because they represent risk factors for HIV seroconversion and can be easily ascertained at the time of HIV counseling and testing by clinicians considering a PrEP prescription for their MSM patients. Missing values for education (N=10) and income (N=17) at the index visit were imputed with values provided at the subsequent visit.

Statistical Methods

To examine crude patterns of risk, we investigated trends in SRB scores over time within our study population. To identify sub-groups of participants that follow different sexual risk trajectories, we modeled SRB scores (<4 vs. ≥4) over time using Nagin's group-based trajectory modeling.[39] Group-based trajectory models are semi-parametric, finite mixture models fit using maximum likelihood estimation.[39] In contrast to traditional growth curve modeling, which identifies a single mean trajectory for an entire population, group-based trajectory modeling identifies clusters or sub-groups of individuals within populations that follow distinct trajectories over time.[39]

To determine the number of trajectory groups present within our study population, we fit a series of group-based trajectory models with 2 to 5 groups. In selecting the appropriate number of trajectory groups, we considered the following criteria: (1) the Bayesian Information Criterion (BIC), (2) average posterior probabilities of group membership, as a measure of classification quality, (3) group size, and (4) the usefulness of the number of groups in terms of the similarities/differences in their trajectory shapes.[39-40] Once the number of groups was decided upon, we varied the shape of the trajectory curves (i.e., zero-order, linear, quadratic, and cubic) and selected the trajectory model with the highest BIC value. Next, we added the covariates of interest to the trajectory model. This allowed for joint estimation of (1) the parameters that describe the shape of trajectory group curves and (2) adjusted odds ratios (AOR) for the relationship between the covariates of interest and trajectory group membership. An advantage of employing this joint estimation process is that it yields standard errors that account for the uncertainty of group assignments.[39] All group-based trajectory modeling was conducted using Proc Traj[41] in SAS 9.2 (SAS Institute, Inc.; Cary, NC).

To describe the frequency and duration of risk for each trajectory group, we calculated the mean length of consecutive high risk intervals, where intervals were defined as the time

between study visits (~6 months) and high risk intervals were defined as intervals with an SRB score≥4. Intervals with no data due to missed visits were assumed to be no or low risk intervals (i.e., SRB score<4) so as not to overestimate the duration of risk.

2.4 Results

A total of 419 participants, providing 4,366 visits or intervals of data, were included in this study and the mean number of visits was 11.5 (SD=4.3; median=13.0; IQR=8.0-15.0). At the index visit, study participants were racially/ethnically diverse (38.4% White; 42.2% Black; 15.0% Hispanic) and had a mean age of 38.3 years (SD=9.8); ~20% were under 30 years of age (Table 2.2). Since their last study visit, 42.5% of participants reported having RAI, of which 25.8% reported having URAI with ≥1serodiscordant (HIV-positive/HIV status unknown) partner. The proportion of participants with an SRB score≥4 remained below 20% over time, while the proportion of participants who did not have IAI or RAI (SRB score=0) since their last study visit rose from 43 to 56% (Figure 2.1).

Our final model identified three sexual risk trajectory groups, which we labeled the low risk (N=264, 63.0%), moderate risk (N=96, 22.9%), and high risk groups (N=59, 14.1%). The average posterior probabilities of group membership for each group ranged from 0.89 to 0.95, which indicates good classification quality of our model.[39] Over the course of follow-up, 3.0% (8/264), 11.5% (11/96), 30.5% (18/59) of participants seroconverted from the low risk, moderate risk, and high risk groups, respectively.

While the mean number of intervals did not differ across the trajectory groups (low risk: 11.6, SD=4.4; moderate risk: 11.7, SD=3.7; high risk: 11.1, SD=4.7; p-value=0.44), the frequency of high risk intervals and the length of consecutive high risk intervals were greater for the high risk group relative to both the moderate and low risk groups (Figure 2.2). No consecutive high risk intervals were observed among participants in the low risk group;

however, 47.9% of participants in the moderate risk group and 93.2% of participants in the high risk group had consecutive high risk intervals (data not shown). Among participants with consecutive high risk intervals, the mean length was 2.3 intervals (~1 year; SD=0.7) and 3.7 intervals (~2 years; SD=2.7) for the moderate and high risk groups, respectively.

To model the probability of engaging in high risk behaviors (SRB score≥4) over time we selected zero-order trajectories for the low risk and high risk groups and a linear trajectory for the moderate risk group (Figure 2.3). The predicted probability of engaging in high risk behaviors (SRB score≥4) over time for the low risk group was approximately 0.009 (95% CI: 0.004-0.014), while it started at 0.30 (95% CI: 0.23-0.37) and declined to 0.17 (95% CI: 0.12-0.23) for the moderate risk group and remained constant at 0.71 (95% CI: 0.66-0.77) for the high risk group.

Several covariates of interest were associated with sexual risk trajectory group membership (Table 2.3). Compared to low risk group membership, moderate risk group membership was associated with younger age (in years) (AOR=0.93, 95% CI: 0.90-0.96), being White (AOR=2.60, 95% CI: 1.36-4.98), and earning an annual income ≥$20,000 (AOR=2.52, 95% CI: 1.22-5.20) at the index visit. Similarly, being in the high risk group, as compared to the low risk group, was associated with younger age (in years) (AOR=0.93, 95% CI: 0.89-0.96), being White (AOR=2.29, 95% CI: 1.08-4.85) and earning an annual income ≥$20,000 (AOR=4.65, 95% CI: 2.03-10.67) at the index visit. Compared to membership in the low risk group, reporting symptoms of distress or depression (AOR=2.15, 95% CI: 1.04-4.43) and reporting substance use (AOR=2.07, 95% CI: 1.04-4.09) at the index visit were associated with membership in the high risk group, but not the moderate risk group.

2.5 Discussion

Our analysis of longitudinal data from the MACS demonstrates that HIV-negative MSM exhibit distinct patterns of sexual risk behavior over time. More than half of our sample rarely engaged in high risk behaviors (low risk group: 63.0%) over the eight year study period. However, 22.9% of participants (moderate risk group) occasionally practiced high risk behaviors, while 14.1% of participants (high risk group) engaged in such behaviors with greater frequency and duration.

Given the high probability of engaging in sexual risk behaviors among members of the high risk group and that 30.5% of participants in this group seroconverted during the study period, HIV-negative MSM similar to those following a high risk trajectory in our sample would likely benefit most from PrEP use. While most members of the high risk group were not at constant risk throughout the course of follow-up, over 90% of participants following a high risk trajectory exhibited continuous risk periods with an average duration of ~2 years. These findings suggest that high risk MSM transition between low risk periods and high risk periods or "seasons of risk" over time. Thus, a targeted approach to PrEP delivery among MSM during "seasons of risk" may be more feasible and beneficial than continuous or prolonged PrEP use among all high risk MSM.

Our findings also indicate that MSM following distinct sexual risk trajectories can be distinguished by certain individual-level characteristics. Many of the characteristics associated with following a high risk trajectory within our sample (i.e., young age, distress or depression and substance use) have previously been associated with the practice of sexual risk behaviors among MSM,[42-48] suggesting that MSM traditionally recognized as high risk may also follow sexual risk trajectories characterized by multiple high risk periods. Younger age, being White, and earning an annual income ≥$20,000 at the index visit were associated with membership in both the moderate risk and high risk trajectory groups. Young MSM (<30 years of age) are at

greatest risk of HIV infection in the US[14] and engage in UAI more frequently than older MSM,[42-43] thus young MSM are often the focus of HIV prevention efforts. However, given that 61.0% of participants in the high risk group were at least 30 years of age at the index visit, our findings suggest that high risk periods occur well beyond 30 years of age among MSM. Incorporating and retaining young MSM in HIV prevention programs that include targeted PrEP delivery could potentially reduce their risk of HIV acquisition over a number of years.

Despite the fact that Black MSM are disproportionately affected by HIV/AIDS and are at greatest risk of HIV infection in the US,[14, 49-50] we found that being non-White was associated with membership in the low risk group. Previous studies have shown that high risk behaviors are practiced with the same or lower frequency among Black MSM compared to other MSM, and suggest that sexual network characteristics among Black MSM may explain racial disparities in the risk of HIV infection.[51-54] Although we used a comprehensive sexual risk behavior score to identify trajectory groups, our score does not account for sexual network characteristics, such as age or race mixing, which may be needed to accurately describe the risk of HIV infection among non-White MSM.

Both distress or depression symptoms and reported substance use at the index visit were associated with following a high risk trajectory, but not a moderate risk trajectory. This is not surprising given that mental health and substance use problems are associated with the practice of URAI among MSM.[44-48] While distress or depression symptoms and reported substance use may be ongoing for individuals who follow high risk trajectories, our findings suggest that reports of these factors even at a single point in time are predictive of long-term patterns of risk. Assessing recent or current distress or depression and substance use may aid clinicians in the identification of MSM who exhibit “seasons of risk” for potential PrEP use. However, given that mental health and substance use disorders are associated with poor adherence to HAART among HIV-positive MSM,[55-56] HIV-negative MSM with similar conditions

may have difficulty adhering sufficiently to PrEP regimens, which may dilute the protective benefits of PrEP use. To maximize PrEP's effectiveness, evidence is needed to guide whether and how treatment and counseling for mental health and substance use disorders can be incorporated into targeted PrEP delivery programs for MSM.

Our study has several limitations. First, MACS participants represent a highly motivated group of MSM who have been retained in a cohort study for a number of years, and thus may differ from MSM in general. Further, although we restricted our sample to younger and more racially/ethnically diverse MACS participants, these MSM are still older and less diverse than those at greatest risk of HIV infection in the US. Second, there is some suggestion that group-based trajectory modeling has a tendency to over-extract trajectory groups within populations.[57] However, Nagin argues that trajectory groups should be thought of as an approximation to a continuous distribution of individual-level trajectories within populations and cautions against the interpretation of identified groups as truly distinct entities.[58] Thus, as was seen in our sample where both the frequency and duration of risk increased across the identified trajectory groups, group-based trajectory modeling is useful for describing individuals with similar trajectories along a continuum. Third, despite the fact that participants were assigned to the group for which they had the highest posterior probability of membership, trajectory group assignments are not certain. However, the majority of HIV seroconversions occurred among members of the high risk group suggesting that participants were appropriately assigned according to risk. Fourth, because data were not complete for all study participants and we assumed that intervals with missing data were no or low risk intervals, we may have underestimated the true frequency and duration of risk within our sample. Fifth, we cannot be certain of the accuracy of the reported HIV status of partners with whom participants did not use condoms every time during IAI/RAI as partners were not interviewed directly in the MACS. Finally, despite the fact that ACASI was implemented at most MACS sites, social desirability bias may have led to under-

reporting of sexual risk behaviors, and hence an underestimation of the associated risks particularly in the high-risk group.

Despite these limitations, the large sample of HIV-negative MSM from across the US, long duration of follow-up, and use of a comprehensive sexual risk behavior score are some of the many strengths our study. Our findings expand the current understanding of sexual risk behaviors among MSM and should be considered in the development of targeted PrEP delivery guidelines for similar MSM populations. Such guidelines could potentially enable clinicians to efficiently screen and identify MSM who exhibit “seasons of risk” for potential PrEP use.

Table 2.1. Sexual risk behavior (SRB) score.

Score	Label	Description
0	No IAI or RAI	No IAI or RAI since the last visit
1	No UIAI or URAI	Only protected IAI or RAI since the last visit, regardless of the number of reported IAI or RAI partners or the HIV status of those partners
2	Only UIAI	Only unprotected IAI since the last visit, regardless of the number of reported IAI or RAI partners or the HIV status of those partners
3	URAI with one HIV- partner	Only 1 partner since the last visit and condoms were not used every time during RAI with that partner (regardless of condom use during IAI), but the partner was HIV-
4	Condom Serosorting	RAI only or IAI and RAI since the last visit (multiple partners) • Condoms not used every time with ≥1 RAI partner, but RAI partners with whom condoms were not used were all HIV- AND • Condoms not used every time with ≥1 IAI partner, but IAI partners with whom condoms were not used were all HIV- OR • Condoms used every time with all IAI partners OR • No IAI partners
5	Condom Seropositioning	IAI and RAI since the last visit (multiple partners) • Condoms not used every time with ≥1RAI partner, but RAI partners with whom condoms were not used were all HIV- • Condoms not used every time with ≥1 IAI partner and ≥ 1 partner was HIV+/HIV status unknown
6	No Seroadaptive Behaviors	RAI only or RAI and IAI since the last visit (1 partner or multiple partners) • Condoms not used every time with ≥1 RAI partner and ≥ 1 partner was HIV+/HIV status unknown, regardless of the number of IAI partners, condom use during IAI or the HIV status of IAI partners

HIV - = HIV-negative; HIV+ = HIV-positive; IAI = insertive anal intercourse; UIAI = unprotected insertive anal intercourse; RAI = receptive anal intercourse; URAI = unprotected receptive anal intercourse.

Table 2.2. Characteristics of HIV-negative Multicenter AIDS Cohort Study (MACS) participants at the index visit, October 1, 2003 - September 30, 2004.

	Sexual Risk Trajectory Group							
	Low Risk (N=264)		Moderate Risk (N=96)		High Risk (N=59)		Total (N=419)	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Study Site								
Baltimore	81	30.7	17	17.7	18	30.5	116	27.7
Chicago	46	17.4	14	14.6	9	15.3	69	16.5
Pittsburgh	68	25.8	41	42.7	18	30.5	127	30.3
Los Angeles	69	26.1	24	25.0	14	23.7	107	25.5
Mean age in years (SD)	40.6	8.9	34.1	9.7	34.7	10.7	38.3	9.8
Race/Ethnicity								
White, non-Hispanic	74	28.0	54	56.3	33	55.9	161	38.4
Black, non-Hispanic	147	55.7	19	19.8	11	18.6	177	42.2
Hispanic	32	12.1	18	18.7	13	22.0	63	15.0
Other	11	4.2	5	5.2	2	3.4	18	4.3
Education								
≤ High school graduate	100	37.9	15	15.6	9	15.3	124	29.6
Some College	65	24.6	29	30.2	19	32.2	113	27.0
≥ College graduate	99	37.5	52	54.2	31	52.5	182	43.4
Annual income ≥ $20,000	93	35.2	58	60.4	41	69.5	192	45.8
Distress/depression (CESD ≥16)	136	51.5	55	57.3	39	66.1	230	54.9
Male sex partner since last visit	132	50.0	93	96.9	59	100.0	284	67.8
Mean # of male sex partners (SD)	4.4	7.1	9.4	23.1	14.6	22.1	8.1	17.7
RAI since last visit	52	19.7	69	71.9	57	96.6	178	42.5
Mean # of RAI partners (SD)	1.5	1.7	3.5	6.7	7.5	14.1	4.2	9.3
URAI	20	38.5	40	58.0	46	80.7	106	59.6
URAI with ≥1 serodiscordant partner	3	5.8	13	18.8	30	52.6	46	25.8
IAI since last visit	86	32.6	71	74.0	49	83.1	206	49.2
Mean # of IAI partners (SD)	2.3	2.8	5.9	11.6	7.2	14.3	4.7	10.1
UIAI	42	48.8	45	63.4	38	77.6	125	60.7
UIAI with ≥1 serodiscordant partner	17	19.8	22	31.0	24	49.0	63	30.6
Substance use since last visit								
Any substance use^	87	32.9	39	40.6	31	52.5	157	37.5
≥5 alcohol beverages per day	36	13.6	18	18.8	11	18.6	65	15.5
Marijuana	86	32.6	39	40.6	28	47.5	153	36.5
Amyl nitrates (poppers)	20	7.6	25	26.0	21	35.6	66	15.8
Crack	53	20.1	13	13.5	4	6.8	70	16.7
Other Cocaine	25	9.5	12	12.5	4	6.8	41	9.8
Uppers (crystal, methamphetamines)	8	3.0	13	13.5	8	13.6	29	6.9

Numbers may not sum to column totals due to missing data; Percents may not sum to 100 due to rounding or omission of one category for binary variables.

^ Excludes alcohol and marijuana, but includes amyl nitrates, ecstasy, crack, other cocaine, and uppers.

SD = standard deviation; CESD = Center for Epidemiologic Studies Depression Scale; IAI = insertive anal intercourse;

UIAI = unprotected insertive anal intercourse; RAI = receptive anal intercourse; URAI = unprotected receptive anal intercourse.

Table 2.3. Adjusted odds ratios for the association between covariates of interest and sexual risk trajectory group membership among 419 HIV-negative Multicenter AIDS Cohort Study (MACS) participants.

	Sexual Risk Trajectory Group			
	Moderate Risk		High Risk	
Covariate	**AOR**	**95% CI**	**AOR**	**95% CI**
Age (in years)	0.93	0.90, 0.96	0.93	0.89, 0.96
White, non-Hispanic	2.60	1.36, 4.98	2.29	1.08, 4.85
≥ College graduate	1.00	0.47, 2.11	0.86	0.38, 1.98
Annual income ≥$20,000	2.52	1.22, 5.20	4.65	2.03, 10.67
Distress/depression (CESD ≥16)	1.40	0.76, 2.58	2.15	1.04, 4.43
Substance use^	1.32	0.71, 2.45	2.07	1.04, 4.09

Reference group = low risk group.

^ Substance use: amyl nitrates, ecstasy, crack, other cocaine, or uppers.

AOR = adjusted odds ratio; CI = confidence interval; CESD = Center for Epidemiologic Studies Depression Scale.

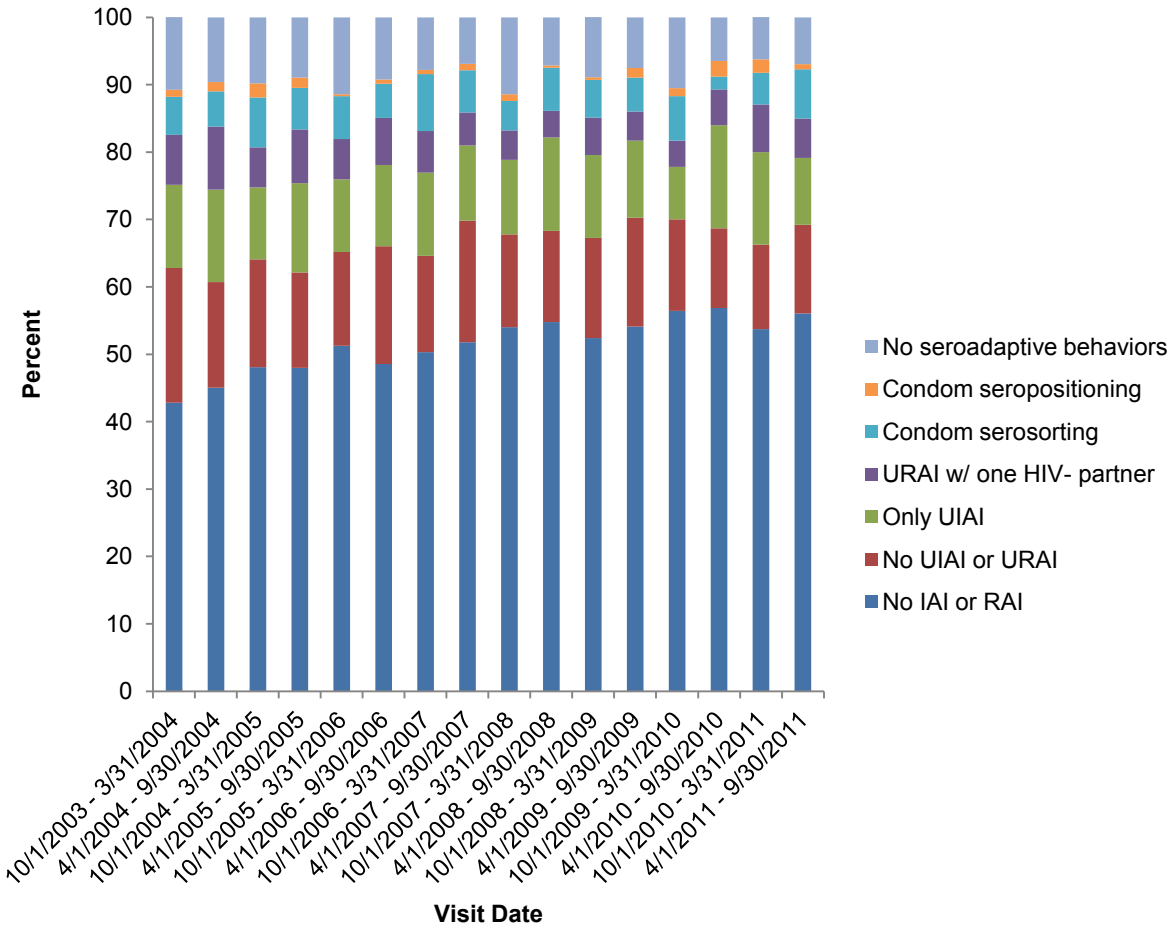

Figure 2.1. Trends in sexual risk behaviors among 419 HIV-negative Multicenter AIDS Cohort Study (MACS) participants (2003 – 2011).

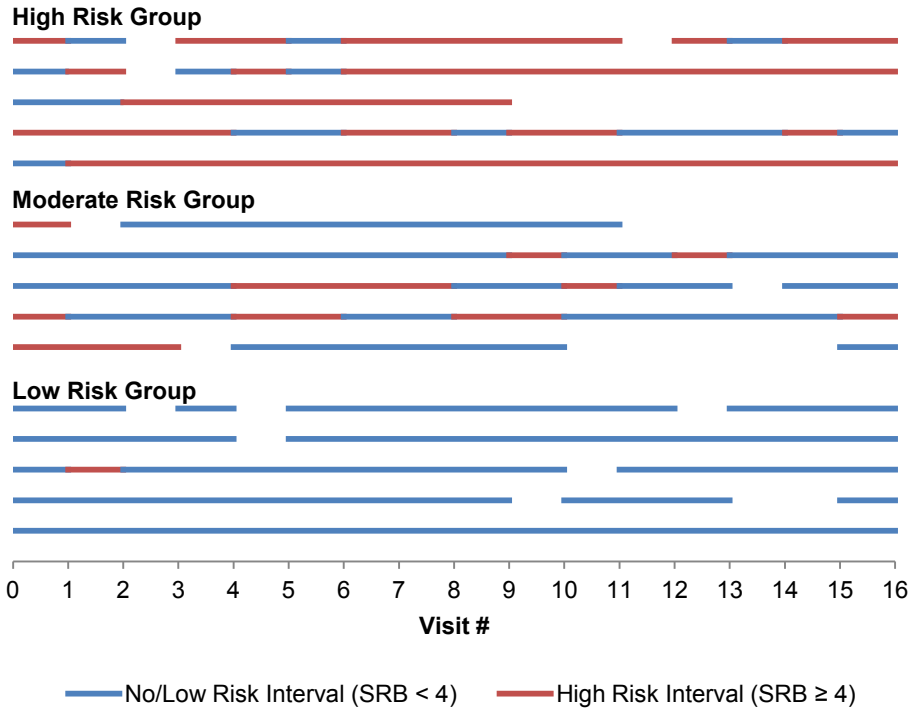

Figure 2.2. Individual risk patterns for a random sample of 5 HIV-negative Multicenter AIDS Cohort Study (MACS) participants with ≥8 study visits from each of the identified sexual risk trajectory groups: low risk, moderate risk, and high risk. Blue lines indicate no or low risk intervals between study visits with an SRB score<4. Red lines indicate high risk intervals between study visits with an SRB score≥4. Blank intervals indicate a missed visit at the end of the interval, thus data on the risk behaviors practiced during the interval were not obtained.

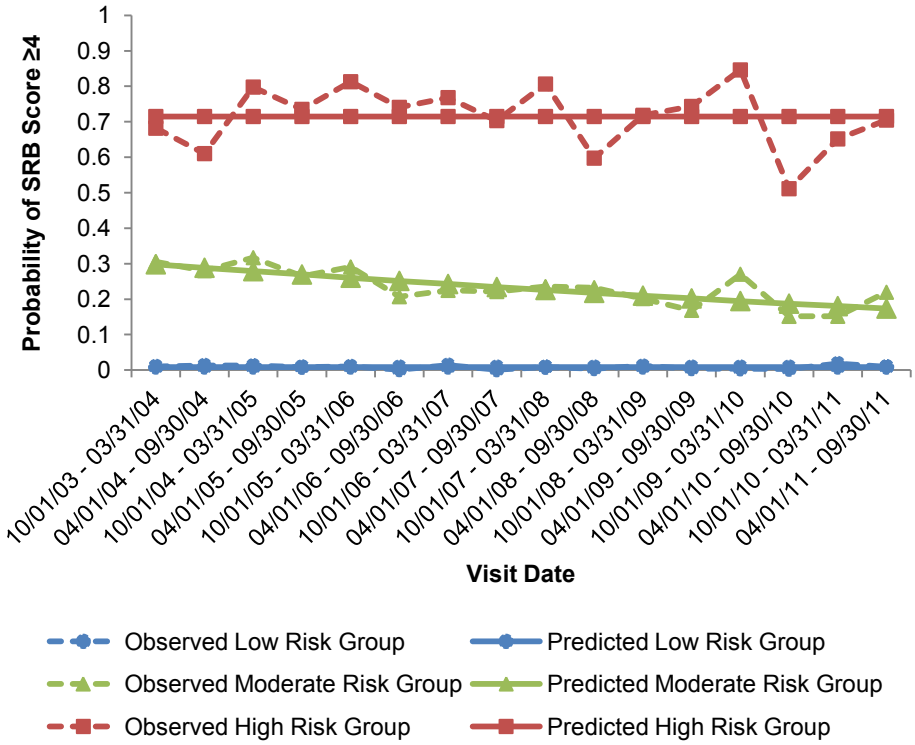

Figure 2.3. Sexual risk trajectories among 419 HIV-negative Multicenter AIDS Cohort Study (MACS) participants (2003 – 2011). Sexual risk behavior (SRB) scores ≥4 indicate condom serosorting, condom seropositioning, and practicing no seroadaptive behaviors. The identified groups represent individuals who exhibited low risk (N=264, 63.0%), moderate risk (N=96, 22.9%) and high risk (N=59, 14.1%) trajectories over time.

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Chapter 3. Partnership type and serostatus among MSM: implications for the implementation of treatment as prevention

3.1 Abstract

Background: The potential impact of treatment as prevention (TasP) among men who have sex with men (MSM) in serodiscordant main partnerships may be diluted by the frequency of casual partners within this population. To inform MSM-specific guidelines on TasP, we examined whether the reported number of male sexual partners is associated with partnership type and serostatus among MSM.

Methods: At semiannual visits between 2006 and 2011, 606 MSM participating in the Multicenter AIDS Cohort Study reported on their male sexual partners and the HIV status of their main partners. Using stabilized inverse probability weighted (SIPW) multinomial logistic random effects models, we examined the effect of time-fixed and time-varying exposures on partnership type and serostatus, defined as: (1) no partners since the last study visit, (2) ≥1 casual partner (CP) only, (3) seroconcordant main partner (SCMP), and (4) serodiscordant main partner (SDMP).

Results: In our SIPW model, the effect of the number of male sexual partners on partnership type and serostatus differed by HIV status (product term p-value<0.0001). Among HIV-negative participants, compared to reporting ≥1 CP only, reporting 1 partner at the prior visit was positively associated with reporting an SCMP (odds ration [OR]=10.07, 95% confidence interval [CI]: 2.96-34.31), while reporting >1 partner at the prior visit was negatively associated with reporting an SDMP (OR=0.15, 95% CI: 0.04-0.54). Among HIV-positive participants, compared

to reporting ≥1 CP only, reporting >1 partner at the prior visit was negatively associated with reporting an SCMP (OR=0.51, 95% CI: 0.24-1.10) or an SDMP (OR=0.22, 95% CI: 0.12-0.44).

Conclusions: The inverse relationship between having multiple partners and SDMPs among HIV-negative participants suggests TasP may provide adequate protection against HIV infection for HIV-negative MSM with SDMPs. However, given that having multiple partners was inversely associated with having main partners among HIV-positive participants, TasP may have a greater population-level impact if offered to all HIV-positive MSM regardless of whether they have SDMPs.

3.2 Introduction

Men who have sex with men (MSM) remain disproportionately affected by HIV/AIDS in the United States (US).[1-2] Despite the efficacy of condoms in preventing HIV acquisition, HIV infection rates remain stable among MSM and in 2009 sexual contact between MSM accounted for 61% of all incident HIV infections in the US.[1] Thus, new HIV prevention strategies are needed within this high risk population.

Treatment as prevention (TasP) represents a promising new biomedical HIV prevention intervention in which HIV-positive individuals initiate antiretroviral therapy (ART) to prevent HIV transmission to their HIV-negative sexual partners. A recent trial conducted by the HIV Prevention Trials Network (HPTN 052) demonstrated that early initiation of ART reduces the risk of HIV transmission by 96% in the context of serodiscordant couples.[3] Since TasP in combination with behavioral and structural interventions could dramatically reduce HIV infection rates at the population-level,[4-5] the effectiveness of such combination HIV prevention programs is currently being evaluated.[6]

However, soon after the results from HPTN 052 were announced, the World Health Organization released guidelines recommending ART for all HIV-positive individuals in heterosexual serodiscordant couples given its benefits at the individual-level.[7] MSM were excluded from these recommendations because only 2% of the couples included in HPTN 052 were between MSM and it was unclear whether the study's findings could be generalized beyond heterosexual couples.[7-8] While previous studies have examined the relationship between partner type (i.e., main vs. casual) and the practice of sexual risk behaviors[9-11] and HIV seroconversion,[12-13] as well as factors associated with engaging in unprotected anal intercourse with serodiscordant partners (main or casual) among MSM,[14-15] little research has been done to characterize MSM who have serodiscordant main partners.

Of the seroconversions observed in HPTN 052, only 71.8% of incident infections were linked to the HIV-positive participant in study-partner pairs, suggesting that HIV-negative participants were exposed to HIV outside of their stable partnerships.[3] It has been estimated that 68% of HIV transmission events among MSM occur in the context of main partnerships, which has been attributed to the frequency of anal intercourse and decreased condom use during anal intercourse with main partners.[13] However, given the frequency of casual partnerships among MSM, potential exposure to HIV during intercourse with such partners could dilute the protective effect of TasP in the context of serodiscordant main partnerships within this population.[16] Data collected from MSM between 2003 and 2005 by the National HIV Behavioral Surveillance (NHBS) system suggest that having a main partner in the past year is associated with having fewer casual partners,[17] suggesting that exposure to HIV with casual partners may be limited among MSM in main partnerships. However, additional information on this association by the serostatus of main partnerships is needed to evaluate the potential impact of TasP within this population.

To fill this gap in knowledge and aid the development of guidelines on TasP for MSM, the present study was designed to identify socio-demographic and behavioral factors associated with partnership type and serostatus among MSM. More specifically, we used longitudinal data collected as part of the Multicenter AIDS Cohort Study (MACS) to examine the effect of time-fixed and time-varying exposures on partnership type and serostatus among MSM over time. Exposures of interest included factors known to be associated with HIV seroconversion among MSM, including the number of male sexual partners.

3.3 Methods

Sample Selection

The MACS is an ongoing prospective study of the natural and treated histories of HIV infection among MSM. HIV-positive and HIV-negative men enrolled in the MACS at study sites located in four US cities (Baltimore, MD; Chicago, IL; Los Angeles, CA; and Pittsburgh, PA) during three recruitment waves from 1984 to 1985 (1,814 HIV-positive and 3,140 HIV-negative), 1987 to 1990 (382 HIV-positive and 286 HIV-negative), and 2001 to 2003 (688 HIV-positive and 662 HIV-negative). Detailed information on the study design and procedures have previously been described.[18-19] Briefly, at semiannual study visits, MACS participants provide a blood sample for laboratory testing and storage in a repository for future research, undergo a physical exam, and complete study questionnaires, which collect demographic, psychosocial, behavioral, medical history, and health services data. MACS study questionnaires are administered via face-to-face interviews and audio computer-assisted self-interviews (ACASI). However, at most MACS sites, ACASI is used to collect data on sensitive information, such as sexual behaviors and substance use, which has been shown to reduce the potential for social desirability bias and result in greater accuracy and completeness of reporting on such information.[20-21] Study protocols were approved by institutional review boards at each of the study sites and all participants provided informed consent.

MACS participants enrolled during the third recruitment wave (between 2001 and 2003) who provided outcome data at each of the first three eligible study visits between visit 46 (between October 1, 2006 and March 31, 2007) and visit 55 (between April 1, 2011 and September 30, 2011) were selected for inclusion in our analysis. Given that the goal of this study was to characterize partnerships among MSM and that older MSM report fewer sexual partners per year than younger MSM,[22] we restricted our sample to MACS participants enrolled during the third recruitment wave as they are younger than those enrolled at earlier time points. Visit 46 was selected as the “index visit” for this analysis because MACS behavioral questionnaires did not consistently collect the HIV status of reported main partners prior to visit

46. Follow-up ended at visit 55, the first missed visit, or the first failure to provide covariate or outcome data, whichever came first.

Of the 1,350 participants who enrolled in the MACS between 2001 and 2003, 826 (61.2%) were still active members of the cohort at the index visit (visit 46). Those who were inactive (i.e., lost to follow-up or deceased) at the index visit were younger, less educated, earned a lower annual income, and were more likely to be non-White than those who remained active; however, there was no significant difference between the two groups in the reported number of male sexual partners since the last study visit. Of the participants who were still active at the index visit, 621 (75.2%) also completed visits 47 and 48. However, only 604 (97.3%) of those also provided complete covariate and outcome data at visits 46 and 47, and thus were eligible for inclusion in our study sample.

Outcome of Interest

The outcome of interest was partnership type and serostatus. At each study visit, participants reported the number of male partners with whom they engaged in oral or anal intercourse since their last visit. Those who reported ≥1 partner were then asked whether one of their partners was a main partner (someone they have a longstanding relationship with) or whether all their partners were casual partners (one time partners or partners they have not developed a longstanding relationship with). Those who reported having a main partner were then asked the HIV status of that partner (HIV-positive, HIV-negative, or HIV status unknown). Based on participants' responses to these questions, for this analysis they were assigned to one of the following four categories of partnership type and serostatus at each visit: (1) no partners since the last study visit, (2) ≥1 casual partner only, (3) seroconcordant main partner, and (4) serodiscordant main partner. To minimize the potential for outcome categories with zero participants, we combined those who reported a main partner only or a main partner plus ≥1

casual partner into one category. Main partners reported by participants of the same HIV status were considered seroconcordant. HIV-positive or HIV status unknown main partners reported by HIV-negative participants were considered serodiscordant, while HIV-negative or HIV status unknown main partners reported by HIV-positive participants were considered serodiscordant.

Exposures of Interest

Time-fixed exposures of interest were measured at the index visit and included: age (in years), race (white vs. non-white), education (≥college education vs. <college education), annual income (≥$20,000 vs. <$20,000), and HIV status. Because only 10 of the 257 HIV-negative participants included in our sample seroconverted over the course of follow-up, HIV status was considered a time-fixed covariate in the analysis. However, those who seroconverted were censored after their first HIV-positive visit so as not to misclassify their outcome status following seroconversion. Missing values for education (N=10) and income (N=9) at the index visit were imputed with values provided at the subsequent visit. Time-varying exposures of interest were measured at each study visit and included: number of male sexual partners (no partners, 1 partner, or >1 partner), distress or depression (Center for Epidemiologic Studies Depression [CESD] Scale score ≥16),[23] and illicit drug use (ecstasy, methamphetamine, amyl nitrates, crack, or other cocaine) since the last study visit.

Statistical Analysis

Standard methods used to model repeated measures as a function of time-varying exposures and confounders can be biased when time-varying confounders are also intermediates in the causal pathway between the exposure and outcome of interest.[24-25] However, assuming there is no unmeasured confounding or misclassification, inverse probability of exposure weights can be used to obtain unbiased estimates of the causal effect of

time-varying exposures in the presence of time-varying confounders.[26-27] As is shown in Figure 3.1, our time-varying exposures of interest measured at a particular visit are likely affected by time-varying covariates measured at the prior visit, which may simultaneously predict one's outcome status at the subsequent visit and be affected by exposures reported at previous visits. Thus, we estimated the effect of our time-fixed and time-varying exposures of interest on partnership type and serostatus using multinomial logistic random effects models fit with stabilized inverse probability of exposure and censoring weights to account for time-varying confounding and selection bias due to incomplete follow-up (see Appendix for more details on weight estimation).[26-27] Participants were censored at their last study visit, first missed study visit, first failure to provide covariate or outcome data, or after their first HIV-positive visit if they seroconverted during the study period. Because the temporal sequence of events must be maintained when estimating the effect of time-varying exposures on time-varying outcomes in the presence of time-varying confounders, we lagged exposures by one study visit and confounders by two study visits in our analysis. Separate weighted multinomial logistic random effects models for the time-fixed exposures of interest and each of the time-varying exposures of interest were fit using Proc Glimmix and the "weight" statement in SAS 9.2 (SAS Institute, Inc.; Cary, NC). Finally, a product term between HIV status and the reported number of male sexual partners was included in our model for the association between the reported number of partners and partnership type and serostatus because differences in the magnitude and direction of this relationship by HIV status could have implications for the delivery of TasP and may indicate a need for alternative prevention strategies. Although effect modification may be more appropriately estimated using other g-methods, such as g-estimation of structural nested models, the present approach is valid given that HIV status is a time-fixed covariate in our analysis.[26]

3.4 Results

Our final sample consisted of 604 MACS participants who contributed data from 4,756 study visits (mean=7.9, SD=2.7; median=10.0, IQR=5.5-10.0) to the analysis. By the end of the study period (visit 55), 45.1% of the sample was censored. However, there were no significant differences between those who were censored due to loss to follow-up and those who were censored due to a missed visit or missing covariate or outcome data (Table 3.1). The mean age of our sample was 43.2 years (SD=8.7; min=20.7; max=71.9) at the index visit and 47.5 years (SD=8.3; min=25.5; max=71.2) at visit 55 (Table 3.2). Participants included in our sample were racially and ethnically diverse: 34.6% White non-Hispanic, 46.9% Black non-Hispanic, and 12.1% Hispanic. At the index visit, 57.5% of our sample was HIV-positive and 39.6% had at least a college education. Since the last study visit at the index visit, 37.3% of our sample did not report any male partners. Among HIV-negative participants, 27.2% reported ≥1 casual partner only, 2.3% reported a serodiscordant main partner only, and 3.5% reported a serodiscordant main partner plus ≥1 casual partner at the index visit (Figure 3.2). Among HIV-positive participants, 29.1% reported ≥1 casual partner only, 8.7% reported a serodiscordant main partner only, and 9.2% reported a serodiscordant main partner plus ≥1 casual partner at the index visit. About a quarter of the serodiscordant partners reported by HIV-negative (23/93) and HIV-positive (135/524) participants over time were of an unknown HIV status.

Table 3.3 presents weighted odds ratios from our multinomial logistic random effects models for the associations between partnership type and serostatus and time-fixed and time-varying exposures. Our stabilized inverse probability weights had a mean of 1.0 across all time points for all exposures except the reported number of male sexual partners, which had a mean of 1.01 (SD=0.54) (data not shown). Compared to reporting ≥1 casual partner only, being older (OR=1.14, 95% CI: 1.07, 1.22) was positively associated with reporting no partners, while being White non-Hispanic (OR=0.05, 95% CI: 0.01, 0.23), reporting at least a college education

(OR=0.06, 95% CI: 0.02, 0.24), earning an annual income ≥$20,000 (OR=0.04, 95% CI: 0.01, 0.17), and reporting illicit drug use at the prior visit (OR=0.48, 95% CI: 0.29, 0.80) were negatively associated with reporting no partners. Compared to reporting ≥1 casual partner only, being older (OR=0.89, 95% CI: 0.84, 0.95) was negatively associated with reporting a seroconcordant main partner, while being White non-Hispanic (OR=6.56, 95% CI: 1.81, 23.80) was positively associated with reporting a seroconcordant main partner. Compared to reporting ≥1 casual partner only, reporting illicit drug use at the prior visit (OR=0.39, 95% CI: 0.23, 0.66) was negatively associated with reporting a serodiscordant main partner.

The effect of the reported number of male sexual partners on partnership type and serostatus differed by the participant's HIV status (product term p-value<0.0001). Among HIV-negative participants, compared to reporting ≥1 casual partner only, reporting 1 partner at the prior visit (OR=10.07, 95% CI: 2.96, 34.31) was positively associated with reporting a main seroconcordant partner, while reporting >1 partner at the prior visit (OR=0.15, 95% CI: 0.04, 0.54) was negatively associated with reporting a serodiscordant main partner. Among HIV-positive participants, compared to reporting ≥1 casual partner only, reporting >1 partner at the prior visit was negatively associated with reporting a seroconcordant main partner (OR=0.51, 95% CI: 0.24, 1.10) or a serodiscordant main partner (OR=0.22, 95% CI: 0.12, 0.44), although only the latter was statistically significant.

3.5 Discussion

We used longitudinal data collected from 604 MSM participating in the MACS between 2006 and 2011 to identify time-fixed and time-varying exposures associated with partnership type and serostatus. After accounting for time-varying confounding and selection bias due to incomplete follow-up, we found an association between the reported number of male sexual partners and partnership type and serostatus within our sample. Overall, participants who

reported multiple partners were less likely to report main partners at the subsequent visit, which is consistent with NHBS data suggesting that MSM with main partners have fewer casual partners.[17] However, to our knowledge, our study is the first to investigate this relationship by main partnership serostatus and identify a difference in the magnitude and direction of the effect by the participant's HIV status. Thus, while the exact mechanisms underlying our findings are unknown, our analysis expands the current understanding of sexual partner frequency among MSM in seroconcordant or serodiscordant main partnerships and has implications for the development of MSM-specific guidelines on TasP.

More specifically, HIV-negative participants who reported multiple partners were less likely to report a serodiscordant main partner at the subsequent visit. Despite the fact that 24.7% of serodiscordant main partners reported by HIV-negative participants over time were of an unknown serostatus, the majority were HIV-positive. HIV-negative MSM with HIV-positive main partners often experience distress over the possibility of acquiring HIV,[28] and thus HIV-negative MSM may be more cautious about entering main partnerships with serodiscordant partners than seroconcordant partners. Although data on the stability of or dynamics within serodiscordant partnerships among MSM are limited, one study found that serodiscordant couples and HIV-negative seroconcordant couples are characterized by more trust, higher levels of intimacy, and a greater sense of commitment than HIV-positive seroconcordant couples.[29] Another study found that the average duration of serodiscordant couples among MSM (6.8 years) was 2 years longer than HIV-negative seroconcordant couples and 2.5 years longer than HIV-positive seroconcordant couples.[30] Thus, given the potential for HIV acquisition, it is possible that HIV-negative MSM only establish main partnerships with HIV-positive partners with whom they share an emotional connection or to whom they feel strongly committed. This enhanced sense of commitment may at least partially explain the inverse association between having multiple partners and having a serodiscordant main partner among

HIV-negative MSM within our sample. Nevertheless, this finding suggests that potential exposure to HIV during intercourse with casual partners may be less likely among HIV-negative MSM with serodiscordant main partners. Thus, if their main partners are taking ART, many HIV-negative MSM in serodiscordant main partnerships may be adequately protected from HIV infection via TasP.

We also found that HIV-negative participants who reported only one partner were more likely to report a seroconcordant main partner at the subsequent visit. Given that having multiple sexual partners is a well known risk factor for HIV infection among MSM,[31] HIV-negative participants reporting only a single partner since their last study visit may have actively chosen to have fewer partners in order to reduce their risk of HIV acquisition. Despite controversy over its effectiveness as a risk reduction strategy,[32-34] some MSM also only choose sexual partners perceived to be of the same HIV status (i.e., serosorting) to minimize their risk of acquiring or transmitting HIV.[35] Thus, the adoption of multiple risk reduction strategies among HIV-negative MSM concerned about their risk of HIV acquisition may possibly be one explanation for the strength of the association observed between reporting only one partner and reporting an HIV-negative seroconcordant main partner at the subsequent visit within our sample. This finding also suggests that there may be less potential for exposure to HIV during intercourse with casual partners among HIV-negative MSM who report seroconcordant main partners.

Among HIV-positive participants, those who reported multiple partners were less likely to report a main partner (seroconcordant or serodiscordant) at the subsequent visit. Although data on HIV disclosure are not collected in the MACS, these findings may at least partially be explained by the anxiety HIV-positive MSM experience when deciding whether to disclose their HIV status to their sexual partners. Given the potential for experiencing stigma or rejection after disclosing their serostatus, HIV-positive MSM are more likely to disclose to main partners with

whom they share a stronger "emotional bond" and to whom they feel a greater sense of responsibility to disclose their serostatus.[36-40] One study found that some HIV-positive MSM avoid having to disclose their serostatus by maintaining less intimate, casual relationships with their sexual partners,[40] while other studies have shown that having multiple sexual partners is associated with a decreased likelihood of HIV disclosure among HIV-positive MSM.[36, 38] Taken together these findings suggest that the inverse association observed between reporting multiple partners and main partners among HIV-positive participants in our sample may be due to their desire to avoid the potentially negative consequences associated with disclosing their serostatus. However, given that HIV-positive participants who reported multiple partners were more likely to report casual partners at the subsequent visit, with whom HIV disclosure may not have occurred, early ART initiation for HIV-positive MSM might be beneficial from a public health perspective, regardless of whether they report serodiscordant main partners.

Several other exposures of interest were also associated with partnership type and serostatus within our sample. Older participants were less likely to report any sexual partners since their last study visit over time, which is consistent with findings from previous studies conducted among older MSM in the US and males in the general population that showed a decrease with age in the reported number of sexual partners in the past year.[22, 41] While race/ethnicity was not associated with reporting serodiscordant main partners over time, being non-White was associated with reporting no partners and being White was associated with reporting seroconcordant main partners. Previous research suggests that Black MSM report fewer sexual partners than other MSM,[42] thus it is not surprising non-White participants more frequently reported having no partners than only casual partners in our sample. However, these findings suggest that TasP in the context of serodiscordant main partnerships may have little impact on HIV transmission among Black MSM, which is of concern given the high rates of HIV infection among Black MSM in the US.[1, 43]

Finally, participants reporting illicit drug use were less likely to report no sexual partners or a serodiscordant main partner at the subsequent visit. Substance use is a well established risk factor for HIV infection among MSM[31, 44-46] and has been associated with sexual risk behaviors, such as having multiple partners and engaging in unprotected receptive anal intercourse.[17, 47-50] Given that participants who reported multiple partners were also less likely to report no partners or serodiscordant main partners within our sample, the inverse association between substance use and reporting no partners or reporting a serodiscordant main partner within our sample may be mediated by the observed effect of the reported number of partners on partner type and serostatus. Although additional data on the association between substance use and partnership development or partnership dynamics within established partnerships among MSM are needed, our findings suggest TasP in the context of serodiscordant main partnerships may not be an adequate prevention strategy for substance using MSM at risk of transmitting or acquiring HIV infection.

Our study has several limitations. First, given that the MSM in our sample have been participating in a cohort study for a number of years, which may have indirectly affected their risk behaviors and sexual partnering, our findings may not be representative of MSM in the general population. Further, the mean age of our sample was nearly 50 years at the end of the study period, and the frequency of casual partnerships and partnership dynamics likely differ between younger and older MSM. Thus, our findings may not be generalizable to young MSM (<30 years of age) at greatest risk of HIV infection in the US. However, in 2009, 20.5% of the estimated number of incident HIV infections among MSM in the US occurred among those between 40 and 49 years of age.[1] Therefore, HIV incidence rates among older MSM in the US are not trivial and even older MSM could potentially benefit from the introduction of new HIV prevention interventions, such as TasP. Second, the serostatus of reported casual partners was not collected in the MACS making it impossible to examine whether the serostatus of

casual partners differed according to the serostatus of main partners, which would have implications for the implementation of HIV prevention strategies. Third, the HIV status of main partners was reported by study participants, thus because we cannot be certain of the accuracy of this information some values for partnership type and serostatus may have been misclassified. Fourth, MACS behavioral questionnaires collect limited data on the characteristics of reported main partners, thus our findings may be biased due to confounding from unmeasured partnership characteristics. For example, some of the reported main partnerships were likely longstanding and may have had different dynamics than more recently established main partnerships. Although we used inverse probability weighting to account for as many potential confounders as possible, this approach does not account for bias due to unmeasured confounding or misclassification.

Despite these limitations, this is one of the first studies to use longitudinal data to identify differences between MSM who report casual partners only and those who report no partners, seroconcordant main partners, or serodiscordant main partners. Although additional quantitative and qualitative research are needed to elucidate the mechanisms underlying our observations, our findings broaden the current understanding of MSM in main partnerships and the potential impact of delivering TasP in the context of serodiscordant main partnerships within this population. More specifically, our findings suggest that TasP may provide adequate protection against HIV infection for HIV-negative MSM with serodiscordant main partners. However, given the possibility for HIV transmission from HIV-positive MSM with multiple partners to their potentially HIV-negative casual partners, TasP may have a greater population-level impact if recommended for all HIV-positive MSM.

Table 3.1. Characteristics of 604 Multicenter AIDS Cohort Study (MACS) participants at the index visit by follow-up status.

		Censored due to:				
	Complete follow-up (N=331)	Lost to follow-up (N=54)	Missed visit or no covariate/ outcome data (N=210)	Sero-converted (N=9)	p ‡	p^
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Age (in years)	43.1 (8.3)	43.6 (10.1)	43.4 (8.9)	39.4 (8.9)	0.70	0.93
	n (%)	n (%)	n (%)	n (%)		
Study Site					0.22	0.23
Baltimore	68 (20.5)	14 (25.9)	51 (24.3)	3 (33.3)		
Chicago	101 (30.5)	12 (22.2)	51 (24.3)	3 (33.3)		
Pittsburgh	93 (28.1)	20 (37.0)	54 (25.7)	3 (33.3)		
Los Angeles	69 (20.9)	8 (14.8)	54 (25.7)	0 (0.0)		
White non-Hispanic	124 (37.5)	16 (29.6)	66 (31.4)	3 (33.3)	0.26	0.8
≥College education	139 (42.0)	21 (39.0)	78 (37.1)	1 (11.1)	0.52	0.81
Annual income ≥ $20,000	159 (48.0)	18 (33.3)	95 (45.2)	5 (55.6)	0.13	0.11
HIV-positive	213 (64.4)	32 (59.3)	102 (48.6)	0 (0.0)	0.001	0.16
Distressed/depressed§	174 (52.6)	32 (59.3)	106 (50.5)	5 (55.6)	0.51	0.25
Substance use						
Binge drinking*	139 (42.0)	17 (31.5)	91 (43.3)	4 (44.4)	0.28	0.11
Illicit drug use~	103 (31.1)	21 (38.9)	67 (31.9)	3 (33.3)	0.52	0.33
Male sexual partner					0.69	0.35
No partners	121 (36.6)	25 (46.3)	76 (36.2)	3 (33.3)		
≥1 CP only	92 (27.8)	14 (25.9)	58 (27.6)	4 (44.4)		
≥1 MP	118 (35.7)	15 (27.8)	76 (36.2)	2 (22.2)		
Seroconcordant MP	72 (61.0)	9 (60.0)	48 (63.2)	0 (0.0)		
Serodiscordant MP	46 (39.0)	6 (40.0)	28 (36.8)	2 (100.0)		

Numbers may not sum to column total due to missing data; Percents may not sum to 100 due to rounding or omission of one category for binary variables.

CP=casual partner; MP=main partner; SD=standard deviation.

§ Center for Epidemiologic Studies Depression (CESD) scale score ≥16.

* Binge drinking = ≥6 alcoholic drinks on 1 occasion.

~ Includes amyl nitrates (poppers), crack, other cocaine, uppers, and ecstasy.

‡ Comparison of those who had complete follow-up versus those who were censored due to loss to follow-up or a missed visit or missing covariate/outcome data.

^ Comparison of those who were censored due to loss to follow-up versus those who missed a visit or had missing covariate/outcome data.

Table 3.2. Characteristics of Multicenter AIDS Cohort Study (MACS) participants over time.

	Visit 46 10/1/06 - 3/31/07 (N=604)		Visit 50 10/1/08 - 3/31/09 (N=480)		Visit 55 4/1/11 - 9/30/11 (N=331)	
Time-fixed covariates^	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (in years)‡	43.2	8.7	45.5	8.6	47.5	8.3
	n	**%**	**n**	**%**	**n**	**%**
Study Site						
Baltimore	136	22.5	103	21.5	68	20.5
Chicago	167	27.7	137	28.5	101	30.5
Pittsburgh	170	28.2	143	29.8	93	28.1
Los Angeles	131	21.7	97	20.2	69	20.9
Race/Ethnicity						
White non-Hispanic	209	34.6	169	35.2	124	37.5
Black non-Hispanic	283	46.9	225	46.9	147	44.4
Hispanic	73	12.1	56	11.7	39	11.8
Other	39	6.5	30	6.3	21	6.3
≥College education	239	39.6	193	40.2	139	42.0
Annual income ≥ $20,000	277	45.9	225	46.9	159	48.0
HIV-positive	347	57.5	288	60.0	213	64.4
Time-varying covariates†	**n**	**%**	**n**	**%**	**n**	**%**
Distressed/depressed since last visit§	317	52.5	213	44.9	155	46.8
Substance use since last visit						
Binge drinking*	251	41.6	197	41	123	37.2
Illicit drug use~	194	32.1	159	33.1	105	31.7
Marijuana	166	27.5	138	28.8	95	28.7
Amyl nitrates (poppers)	91	15.1	89	18.5	56	16.9
Crack	93	15.4	64	13.4	40	12.1
Other Cocaine	30	5.0	20	4.2	20	6.0
Uppers (crystal, methamphetamines)	29	4.8	16	3.3	14	4.2
Ecstasy	10	1.7	13	2.7	6	1.8
Sexual performance enhancers	38	6.3	26	5.4	17	5.1
Male sexual partners since last visit						
No partners	225	37.3	185	38.5	132	39.9
1 partner	127	21.0	101	21.0	73	22.0
>1 partner	252	41.7	194	40.4	126	38.1

Numbers may not sum to column total due to missing data; Percents may not sum to 100 due to rounding or omission of one category for binary variables.

SD=standard deviation.

^ Measured at the index visit (visit 46).

‡ Mean age at each study visit, index visit (visit 46) values not presented for visit 50 or visit 55.

† Measured at each study visit.

§ Center for Epidemiologic Studies Depression (CESD) scale score ≥16.

* Binge drinking = ≥6 alcoholic drinks on 1 occasion.

~Excludes marijuana and sexual performance enhancers.

Table 3.3. Stabilized inverse probability weighted odds ratios from multinomial logistic random effects models for the association between partnership type and serostatus (time=*k+1*) and time-fixed (time=0) and time-varying (time=*k*) exposures in the Multicenter AIDS Cohort Study (MACS) (N=604).

	No Partners OR (95% CI)	Seroconcordant Main Partner OR (95% CI)	Serodiscordant Main Partner OR (95% CI)
Time-fixed exposures[a]			
Age (years)	1.14 (1.07, 1.22)	0.89 (0.84, 0.95)	0.96 (0.91, 1.01)
White, non-Hispanic	0.05 (0.01, 0.23)	6.56 (1.81, 23.80)	1.54 (0.53, 4.50)
≥ College education	0.06 (0.02, 0.24)	0.54 (0.17, 1.73)	0.51 (0.19, 1.36)
Annual income ≥ $20,000	0.04 (0.01, 0.17)	0.89 (0.29, 2.75)	1.67 (0.63, 4.46)
Time-varying exposures[b]			
Distress/depression (CESD≥16)	0.87 (0.60, 1.25)	0.80 (0.52, 1.21)	0.88 (0.59, 1.32)
Illicit drug use[c]	0.48 (0.29, 0.80)	1.14 (0.66, 1.97)	0.39 (0.23, 0.66)
HIV-negative[d]			
# Males sex partners			
No partners	Ref	Ref	Ref
1 partner	0.26 (0.11, 0.59)	10.07 (2.96, 34.31)	0.52 (0.14, 1.93)
>1 partner	0.02 (0.01, 0.03)	1.30 (0.40, 4.20)	0.15 (0.04, 0.54)
HIV-positive[d]			
# Males sex partners			
No partners	Ref	Ref	Ref
1 partner	0.30 (0.17, 0.51)	0.68 (0.32, 1.44)	0.71 (0.37, 1.37)
>1 partner	0.06 (0.03, 0.12)	0.51 (0.24, 1.10)	0.22 (0.12, 0.44)

Abbreviations: OR=odds ratio; CI=confidence interval; CESD=Center for Epidemiologic Studies Depression Scale.

Reference group = participants who reported ≥1 casual partner only at time *k+1*.

[a] Measured at time=0; Estimates from a model adjusted for time-fixed covariates (site, age, race, education, income, and HIV status) and stabilized inverse probability of censoring weighted for time-fixed and time-varying covariates measured at time k-1: (# males sexual partners, distress/depression, illicit drug use, and partnership type and serostatus).

[b] Measured at time=k; Estimates from a model adjusted for time-fixed covariates (site, age, race, education, income, and HIV status) and stabilized inverse probability of exposure and censoring weighted for time-fixed and time-varying covariates measured at time k-1: (# males sex partners, distress/depression, illicit drug use, and partnership type and serostatus).

[c] Illicit drugs include: amyl nitrates, crack, other cocaine, uppers, and ecstasy.

[d] HIV status= time-fixed covariate measured at the index visit, time=0.

p-value for product term between HIV status and # of male partners < 0.0001.

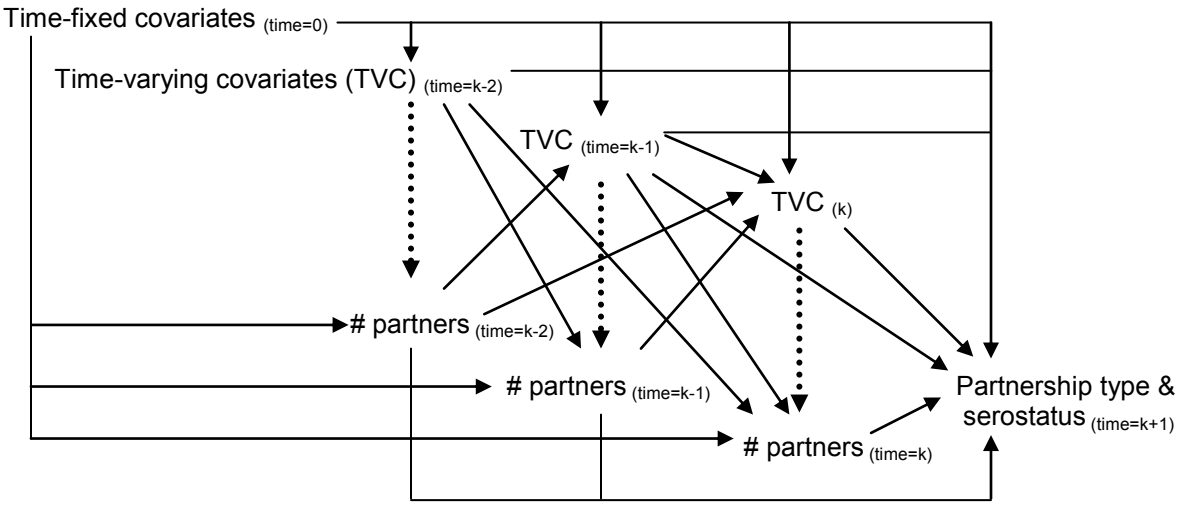

Figure 3.1. Causal diagram for the effect of the reported number of male sexual partners (a time-varying exposure of interest) measured at each study visit on partnership type and serostatus measured at the subsequent study visit. Time-fixed covariates include site, age, race, education, income, and HIV status. Time-varying covariates represent time-varying confounders and intermediates in the casual pathway and include distress/depression, illicit drug use, and partnership type and serostatus. The direction of the arrows on dotted lines are uncertain as the time ordering of events measured at the same study visit is unknown.

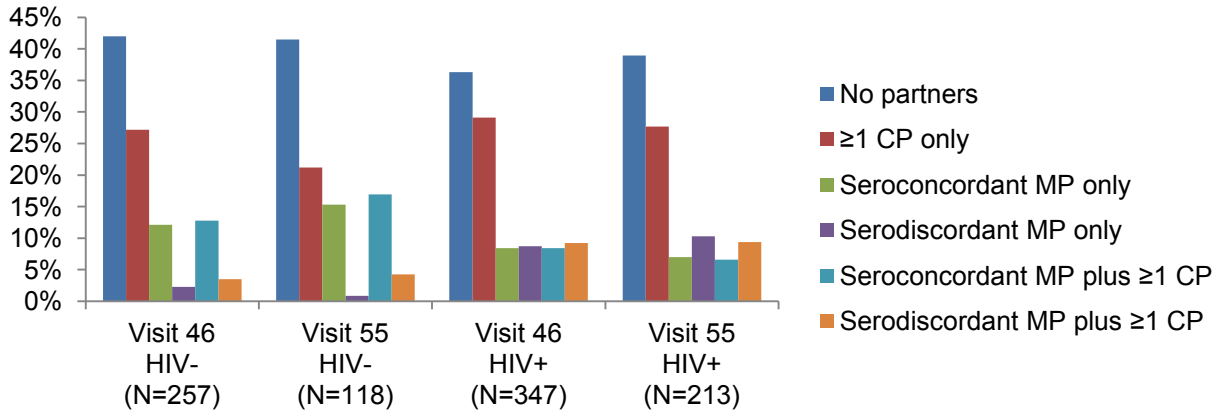

Figure 3.2. Partnership type and serostatus at the index visit (visit 46) and the end of the study period (visit 55) by participants' HIV status. Abbreviations: CP=casual partner; MP=main partner.

3.6 Appendix

Stabilized inverse probability weights [$sw_i(t)$] used in our analysis were the product of the stabilized inverse probability of exposure, $sw_i^A(t) = \prod_{k=0}^{t} \frac{\Pr(A_i(k)|\overline{C_1}(k-1)=0,\overline{A}_i(k-1),V_i)}{\Pr(A_i(k)|\overline{C_1}(k-1)=0,\overline{A}_i(k-1),\overline{L_1}(k-1),\overline{Y}_i(k-1))}$, and the stabilized inverse probability of censoring, $sw_i^C(t) = \prod_{k=0}^{t} \frac{\Pr(C_i(k+1)=0|\overline{C_1}(k)=0,\overline{A}_i(k),V_i))}{\Pr(C_i(k+1)=0|\overline{C_1}(k)=0,\overline{A}_i(k),\overline{L_1}(k),\overline{Y}_i(k))}$, where $A_i(k)$ is subject *i*'s exposure status at time *k*, V_i is a vector of time-fixed covariates measured at the index visit, $L_i(k-1)$ is a vector of time-varying covariates measured at time *k-1* and includes V_i, and $Y_i(k-1)$ is subject *i*'s outcome status (i.e., partnership type and serostatus) at time *k-1*. $C_i(k)$ is a censoring indicator for subject *i* at time *k,* which is coded as 1 if subject *i* seroconverted at time *k* or did not provide covariate data at time *k* or outcome data beyond time *k* (i.e., if the subject is censored) and 0 if subject *i* remained uncensored beyond time *k*. Time-varying covariates measured at the same study visit as exposures were not treated as confounders (i.e., they were not considered during the estimation of stabilized weights) because we could not be certain of the time-ordering of events for covariates measured at the same study visit. The numerator and denominator of $sw_i^A(t)$ were estimated separately using pooled logistic regression for binary exposures or multinomial logistic regression for categorical exposures, and then their ratio was calculated to obtain stabilized weights, while $sw_i^C(t)$ was similarly estimated using pooled logistic regression. The product of these stabilized weights [$sw_i(t)$] was then applied to the study population creating a pseudopopulation with sw_i copies of each subject *i* at each study visit or time *k*. This effectively balances the levels of time-varying confounders measured at time *k-1* across levels of the exposure measured at time *k* within the pseudopopulation.[26] Thus, we were able to obtain estimates of the associations of interest without having to adjust for time-varying confounders in our multinomial logistic random effects models.

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Chapter 4. Individual-level and sexual event-level predictors of condom use during receptive anal intercourse among HIV-negative men who have sex with men

4.1 Abstract

Background: Given the risk of HIV infection associated with unprotected receptive anal intercourse (URAI), additional research on factors associated with condom use during receptive anal intercourse (RAI) among HIV-negative men who have sex with men (MSM) at the sexual event-level is needed to inform the development of MSM-specific HIV prevention programs.

Methods: From 2007-2010, HIV-negative MSM reporting RAI in the past year were followed for one year in Los Angeles. At baseline, 3 month, and one year study visits, computer-assisted self-interviews collected partner-specific data for up to three recent male sexual partners. Logistic random effects models were used to identify individual-level and sexual event-level characteristics associated with condom use during RAI at the last sexual event within reported partnerships.

Results: Our sample (N=165) was racially/ethnically diverse (37.7% White; 26.7% Hispanic; 23.9% African American) and had a mean age of 35.7 years (range=18.0-72.0). Of the 409 partnerships reported over time, 23.8% were with main partners and 58.6% were HIV seroconcordant. After adjusting for individual-level and sexual event-level characteristics, partner type (main vs. non-main) (adjusted odds ratio [AOR]=0.52, 95% confidence interval [CI]: 0.27, 1.00) and methamphetamine use (AOR=0.46, 95% CI: 0.21, 0.97) were negatively associated with condom use during RAI at the last sexual event within reported partnerships. In a model including an interaction between partner type and methamphetamine use (p-value=0.05), methamphetamine use was negatively associated with condom use during RAI at

the last sexual event within non-main partnerships (AOR=0.34, 95% CI: 0.15, 0.77), but no association was observed within main partnerships (AOR=1.58, 95% CI: 0.36, 6.95).

Conclusions: Our findings suggest that partner type and methamphetamine use are inversely associated with condom use during RAI at the sexual event-level. Our finding that methamphetamine use is strongly associated with condom use during RAI in non-main partnerships should be considered in the design of HIV-prevention strategies for MSM.

4.2 Introduction

Men who have sex with men (MSM) remain disproportionately affected by HIV/AIDS in the United States (US).[1-2] In 2011, 92% of all newly diagnosed HIV infections among adults and adolescents in the US were attributed to sexual contact, and of those nearly three quarters were due to male-to-male sexual contact.[2] Given the observed efficacy of new biomedical HIV prevention interventions, such as pre-exposure prophylaxis and treatment as prevention,[3-7] demonstration projects are currently underway to evaluate their use within high risk populations, such as MSM.[8-9] However, a better understanding of sexual risk behaviors and factors that drive such behaviors among MSM is still needed to inform the development of MSM-specific HIV prevention programs and ultimately reduce HIV incidence in the US.

Previous research suggests that sexual risk behaviors vary within individuals depending on multiple situational or contextual factors, which may interact with one another to influence risk.[10-13] Numerous studies have examined the relationship between sexual risk behaviors and various individual-level and sexual event-level characteristics (e.g., substance use and partnership type).[14-16] However, most studies have investigated the effect of substance use and partnership characteristics on global measures of risk, such as the practice of unprotected anal intercourse (UAI) during a defined period of time, making it difficult to assess the potential impact of these characteristics on the practice of specific sexual behaviors.

Zea et al. argue that within-person variation in sexual risk behaviors can be explained by Ewart's Social Action Theory, which suggests that self-protective behavior, such as condom use, is a function of individual-level factors as well as social-contextual factors, such as partnership characteristics, surrounding the particular occasion in which the behavior is practiced.[11, 17] Zea et al. applied the Social Action Theory in a cross-sectional study of Latino MSM in New York and New Jersey to examine the effect of personal and situational characteristics on UAI at their last sexual encounter.[11] The authors found that closeness of the

partnership and HIV seroconcordance were positively associated with UAI at the last sexual encounter, while concern about STIs was negatively associated with UAI.[11]

Building on Zea et al.'s research, Mustanski et al. used data from a longitudinal study young, Midwestern MSM to examine the effect of partnership characteristics on the frequency of unprotected intercourse (vaginal or anal) across multiple partnerships reported by the same individual over time.[13] The authors found that having serious partners, having older partners, drug use before sex with partners, physical violence within partnerships, forced sex within partnerships, and being in a partnership for longer than six months were associated with unprotected sex.[13] However, because their analysis was not restricted to partnerships between males, the authors were unable to focus on condom use in the context of receptive anal intercourse (RAI), which confers the greatest risk of HIV infection.[18-20] Thus, additional sexual event-level analyses of condom use during RAI are needed to inform targeted HIV prevention strategies.

Using longitudinal data from In the Pipeline, we examined the effect of individual-level and sexual event-level characteristics on condom use during RAI at the last sexual event with recent male sexual partners reported by a cohort of high risk, racially/ethnically diverse, and mostly low-income HIV-negative MSM.

4.3 Methods

Study Design

In the Pipeline – Enrollment in a Research Registry for Microbicide Clinical Trials – was conducted in Los Angeles between 2007 and 2010 among 422 MSM who practice RAI by the Network for AIDS Research in Los Angeles (NARLA), a consortium of infectious disease doctors, epidemiologists, psychologists, and behavioral scientists from the University of

California, Los Angeles (UCLA), Friends Research Institute, Inc. (FRI), and AIDS Project Los Angeles (APLA). In the Pipeline was designed to examine barriers to microbicide trial participation among MSM and identify the best format for the delivery of educational materials on rectal microbicides within this population. A racially/ethnically diverse sample of MSM was recruited to participate in the study via flyers and advertisements posted online and at three community-based service organizations in Los Angeles: the UCLA Clinical AIDS Research and Education (CARE) Center, the Friends Community Center, and APLA. Most HIV-negative participants (65.5%) were recruited at the Friends Community Center, which primarily serves low-income substance using MSM and transgender women. To be eligible for participation, interested individuals had to be at least 18 years of age, anatomically male, willing to test for sexually transmitted infections (STIs), including HIV, self-report RAI within the past 12 months, and provide informed consent. By design, approximately 50% of In the Pipeline study participants were HIV-positive. At enrollment, all participants who reported being HIV-negative were tested for HIV using rapid tests and confirmatory Western Blots, while those who reported being HIV-positive either (1) had their HIV status confirmed via medical records maintained at the UCLA CARE Center or APLA or (2) were tested for HIV using rapid tests and confirmatory Western Blots.

Study Procedures

In the Pipeline study participants were followed for one year and completed study visits at baseline, three months, and one year. Study visits were conducted by trained study staff at the UCLA CARE Center, the Friends Community Center, and APLA. During each study visit, participants completed computer-assisted self-interviews (CASI), which collected information on demographics, substance use, and sexual behaviors. At the one year visit, all HIV-negative participants were re-tested for HIV. Participants were compensated up to $105 for completing

all three study visits. All study procedures were approved by the Human Subjects Protection Committees at UCLA, FRI, and APLA.

Measures

Individual-level characteristics. CASI collected data on the following individual-level characteristics at the baseline visit: age, gender, race/ethnicity, sexual identity, education, employment, annual income, homelessness in the past year, and substance use in the past 6 months. Global data on sexual activity in the past month were also collected at each study visit.

Sexual event-level characteristics. Sexual event-level characteristics refer to partner characteristics as well the specific behaviors engaged in during the sexual event (e.g., substance use). At each study visit, CASI collected partner-specific data on up to three recent sexual partners (i.e., last partner [P1], second to last partner [P2], and third to last partner [P3]). Age, race/ethnicity, HIV status (HIV-negative, HIV-positive or HIV status unknown), and partner type were collected for each reported partner. In our analysis, HIV-positive and HIV status unknown partners were considered serodiscordant and older partners were defined as >5 years older than the participant. Main partners were defined as the participant's primary or most important sexual partner, while regular partners (someone the participant had sex with on a regular basis, but did not consider a main partner), friends, acquaintances, one-time partners, unknown individuals, or trade partners were considered non-main partners. For the last sexual event with each of their reported partners participants reported the date, whether any substances (methamphetamine, ecstasy, amyl nitrates, and cocaine) were used, whether they had RAI, and if they reported having RAI, whether condoms were used during RAI. Given that the goal of In the Pipeline was to inform future research on rectal microbicides, which will most likely be applied by the receptive partner prior to or during anal intercourse, data on insertive anal intercourse at the last sexual event were not collected.

Additional information was collected for P1 only on the following: whether the participant believed P1 ever had other partners concurrent to their partnership, whether drugs, money or other goods were ever exchanged for sex within the partnership, and the level of intimacy within the partnership. The level of intimacy was measured using the Partnership Assessment Scale (PAS),[21] which was developed based on findings from a qualitative study of sexual partnerships among MSM[22] and consists of 27 items designed to ascertain the amount of information known about and activities engaged in with sexual partners.

CASI also included a unique partner tracking system to identify partnerships continuing at subsequent study visits. Identifying information was collected for partners reported at each study visit, and included: nickname, age, race/ethnicity, height, and meeting place. As participants reported each recent partner at the three month and one year study visits, they were prompted with the identifying information collected for partners reported at previous visits. Participants were then asked if the current recent partner had also been reported on at an earlier visit, and if so, to identify the previous partner. If a partner reported at baseline or three months was selected at a subsequent visit, that partnership was considered a continuing partnership.

Statistical Analysis

To describe the study population, we calculated means (standard deviations [SD]) for continuous measures (for example, number of RAI partners in the past month) and marginal distributions for categorical measures (for example, race/ethnicity) at the baseline visit. To determine the effect of individual-level and sexual event-level characteristics on condom use during RAI at the last sexual event within reported partnerships, condom use during RAI was modeled with a logistic generalized linear mixed model (GLMM) with a participant or individual random effect. Although some of the reported partnerships were continuing throughout the

course of the study, there was not enough information in the data to fit a model with partnership-level random effects. Thus, our final model only included individual-level random effects and our analysis was restricted to the first observation for continuing partnerships. Unadjusted and adjusted odds ratios (OR) and corresponding 95% confidence intervals (CI) were examined for each of the individual-level and sexual event-level characteristics of interest; however, our final model was selected based on *a priori* knowledge of factors associated with sexual risk behaviors and HIV seroconversion among MSM. Because several partnership characteristics (listed above in the sexual event-level characteristics section) were only collected for participants' most recent sexual partners [P1], analyses considering these sexual event-level characteristics were limited to the partnerships for which they were collected. For consistency, adjusted estimates of the effects of these characteristics were adjusted only for sexual event-level characteristics collected for all reported partners [P1, P2, and P3]. Finally, we examined whether the relationship between condom use during RAI and any of the sexual event-level characteristics collected for all reported partners differed by partner type (main vs. non-main) through the inclusion of interaction terms in our model. All statistical analyses were conducted using SAS 9.2 (SAS Institute, Inc.; Cary, NC).

Sample Selection

Given that the goal of the present study is to inform the development of HIV prevention strategies for MSM, we restricted our analysis to HIV-negative In the Pipeline study participants. Of the 210 HIV-negative participants, 209 reported partner-specific data for ≥1 recent sexual partner at ≥1 study visit. Of those participants, only 165 reported having RAI at their last sexual event with reported partners and whether condoms were used during RAI at those events. Thus, our sample consists of 165 HIV-negative MSM who reported on condom use during RAI at their last sexual event with 409 non-continuing recent sexual partners during the study period.

4.4 Results

The mean age of participants included in our analysis was 35.7 years (SD=11.0; min=18.0; max=72.0) and 35% were under 30 years of age (Table 4.1). Participants were racially/ethnically diverse (37.7% White; 26.7% Hispanic; 23.9% African American) and 58.1% identified as gay or homosexual. While 86.8% of participants reported at least a high school education, 37.3% reported being unemployed and almost half reported an annual income less than $9,800 or being homeless in the past year at the baseline visit. Substance use was common with 59.9% of participants reporting any substance use (cocaine, methamphetamine, inhalants, sedatives, hallucinogens or opioids), 40.1% reporting cocaine use, and 35.0% reporting methamphetamine use in the past six months at the baseline visit.

Over the course of follow-up, participants reported having 409 partnerships within which they reported RAI at their last sexual event and whether condoms were used during RAI at those events (Table 4.2). Of these partnerships, 23.8% were with main partners and 27.9% were with partners >5 years older than the participant. Slightly more than half of the reported partnerships were HIV seroconcordant (58.6%); however, few partnerships were with known HIV-positive partners (3.0%). Participants reported methamphetamine use at the last sexual event within 18.4% of reported partnerships. Of partnerships reported with most recent partners (P1) (N=243), participants believed their partner ever had concurrent partners within 50.9% of partnerships and participants reported ever exchanging of drugs, money or other goods for sex within 22.5 % of partnerships.

Table 4.3 displays the results from our GLMM model for condom use during RAI as a function of individual-level and sexual event-level characteristics. None of the individual-level characteristics were significantly associated with condom use during RAI at the last sexual event in unadjusted or adjusted analyses. After adjusting for age, race/ethnicity, education,

homelessness in the past year, number of RAI partners in the past month, having an older partner, and partnership serostatus, partner type and methamphetamine use were negatively associated with condom use during RAI at the last sexual event. Compared to partnerships with non-main partners, those with main partners had lower odds of condom use during RAI (adjusted odds ratio [AOR]=0.52, 95% confidence interval [CI]: 0.27, 1.00). Similarly, higher PAS scores were negatively associated with condom use during RAI (AOR=0.97, 95% CI: 0.93, 1.01), although not significantly. Compared to partnerships within which the participant did not report methamphetamine use at the last sexual event, those in which the participant did report methamphetamine use also had lower odds of condom use during RAI (AOR=0.46, 95% CI: 0.21, 0.97).

Although there was no difference in the proportion of participants reporting methamphetamine use at their last sexual event by partner type (main=17.4% [16/92] and non-main=18.5% [56/303]; p-value=0.62), the effect of methamphetamine use on condom use during RAI was modified by partner type (partner type by methamphetamine use interaction p-value=0.05). Among main partnerships, methamphetamine use at the last sexual event was not associated with condom use during at those events (OR=1.58, 95% CI: 0.36, 6.95). Among non-main partnerships, methamphetamine use at the last sexual was negatively associated with condom use during RAI at those events (OR=0.34, 95% CI: 0.15, 0.77).

4.5 Discussion

To inform the targeted delivery of new HIV prevention interventions among MSM at greatest risk of HIV infection, we applied the approach used by Zea et al.[11] and Mustanski et al.[13] to a sample of relatively low-income, heavily substance using, and racially/ethnically diverse HIV-negative MSM who practice RAI in Los Angeles. More specifically, we used longitudinal data from In the Pipeline to examine the effect of individual-level and sexual event-

level characteristics on condom use during RAI at the last sexual event within recent partnerships reported over time.

We did not observe an association between any of the individual-level characteristics of interest and condom use during RAI at the last sexual event within reported partnerships. Individual-level characteristics, such as younger age and lower levels of education and income, have previously been associated with global measures of sexual risk.[23-27] However, our findings are consistent with those reported by Zea et al. as none of the demographic characteristics measured at the individual-level (i.e., age, education, income and nationality) were associated with UAI in their event-level analysis after accounting for sexual event-level characteristics.[11] Thus, our findings add further support to Zea et al.'s conclusion that sexual event-level characteristics, which can change within individuals across sexual events, have a greater influence on the practice of sexual risk behaviors within a particular sexual event than those that remain constant.[11]

Main partnerships were less likely to use condoms during RAI at the last sexual event. This finding is consistent with those from previous studies that measured the effect of partner type on condom use during anal intercourse at both the global and event levels, [11, 13-14, 16] and likely explains evidence suggesting that 68% of HIV transmission events within this population occur in the context of main partnerships.[28] Previous research indicates that decreased condom use with main partners may be explained by the beliefs not using condoms is a symbol of trust and that condom use interferes with intimacy, and is further supported by the negative association between higher PAS scores and condom use during RAI within our sample.[29-31]

Partnerships in which the participant reported methamphetamine use at the last sexual event were also less likely to use condoms during RAI at those events. Numerous studies have identified a relationship between substance use, particularly methamphetamine use, and the practice of risky sexual behaviors[14, 32-33] as well as HIV seroconversion.[34-36] Although Zea et

al.[11] did not observe an association between substance use and UAI at the last sexual event and Mustanski et al.[13] observed a more modest association between substance use prior to sex and the frequency of unprotected sex in their analysis,[13] the presence and strength of the association in our analysis may be due to the high rate of methamphetamine use within our sample – 35.0% reported methamphetamine use in the past six months at the baseline visit and 18.4% reported methamphetamine use at their last sexual event within reported partnerships.

However, we also found that the relationship between methamphetamine use and condom use during RAI at the last sexual event differed by partner type. While methamphetamine use was not associated with condom use in the context of main partnerships, we did observe a strong inverse association between methamphetamine use and condom use during RAI at the last sexual event within non-main partnerships. Given the frequency of non-condom use at the last sexual event within main partnerships, non-main partnerships may be more susceptible to the dis-inhibitory effects of methamphetamine use. Further, MSM in main partnerships may establish "negotiated safety" agreements (e.g., agreements to engage in UAI with each other, but to always use condoms with other sex partners) as a form of risk reduction.[37-38] Thus, without such agreements or a routine surrounding condom use to rely on, methamphetamine use in the context of RAI with non-main partners may reduce concern surrounding HIV acquisition and result in the practice of higher risk behaviors.

Although the serostatus of one's sexual partner is a major determinant of risk, and previous research suggests that some MSM decide to engage in risky sexual behaviors based on the perceived HIV status of their sexual partners,[39-40] condom use during RAI at the last sexual event within partnerships with serodiscordant (HIV-positive or HIV status unknown) partners was not more common than in those with seroconcordant partners within our sample. However, only 7.3% of serodiscordant partnerships were with known HIV-positive partners and

may explain the absence of an association between partnership serostatus and condom use during RAI. Nevertheless, the fact that condom use during RAI was not higher within serodiscordant partnerships than in seroconcordant partnerships is concerning as participants could have been exposed to HIV during sexual events with their HIV status unknown partners.

Our study has several limitations. First, HIV-negative In the Pipeline study participants do not represent a random selection of RAI practicing MSM in Los Angeles as they were largely recruited from the Friends Community Center, which primarily serves low-income, substance using MSM and transgender women. Additionally, partnerships included in our analysis do not represent a random selection of partnerships as partner-specific data were only collected for up to three recent sexual partners at each study visit. Moreover, we further restricted our analysis to partnerships in which the participant reported having RAI at the last sexual event. Thus, while our findings may not be generalizable to all RAI practicing partnerships, our findings may be most applicable to partnerships among high risk MSM in greatest need of new HIV prevention interventions. Second, due to the sensitive nature of information on substance use and sexual risk behaviors, participants may have under-reported such behaviors. However, given that In the Pipeline utilized CASI, it is likely that such under-reporting was minimized relative to data collection via face-to-face interviews.[41-42] Third, we cannot be certain of the accuracy of reported partner characteristics as partners were not directly interviewed as part of the study. Finally, because of our limited sample size, we were unable to fit a model with partnership-level random effects.

Despite these limitations, some major strengths of our study are its focus on RAI practicing partnerships reported by high risk, racially/ethnically diverse MSM and use of detailed data at the sexual event-level. In our analysis, we were able to demonstrate that URAI is associated with both partner type and methamphetamine use at the sexual event-level. Given the frequency of methamphetamine use among MSM,[43-44] the strength of the inverse

association between methamphetamine use and condom use during RAI in non-main partnerships may be contributing to the stable HIV infection rates observed among MSM in the US and should be considered in the design of MSM-specific HIV-prevention strategies.

Table 4.1. Baseline characteristics of HIV-negative In the Pipeline study participants who reported RAI at their last sexual event with recent sexual partners at ≥1 study visit and whether condoms were used during RAI at those events.

	(N=165)	
	n	**%**
Age group (years)		
18-29	56	35.0
30-39	47	29.4
40-49	38	23.8
≥50	19	11.9
Gender		
Male	157	98.7
Transgender	2	1.3
Race/Ethnicity		
African American	38	23.9
White	60	37.7
Hispanic	44	26.7
Other	17	10.7
Single	112	68.3
Sexual identity		
Gay/homosexual	90	58.1
Bisexual	58	37.4
Straight/heterosexual	7	4.5
≥ High school education	138	86.8
Work Situation		
Unemployed	59	37.3
Full-time employment	33	20.9
Part-time employment	30	19.0
Other	36	22.8
Annual income < $9,800	76	48.7
Homeless (past year)	72	46.2
Substance use (past 6 months)*	94	59.9
Alcohol	121	78.1
Marijuana	82	52.9
Cocaine	63	40.1
Methamphetamine	56	35.0
Inhalants	11	7.1
Sedatives	39	25.2
Hallucinogens	19	12.3
Opioids	19	12.6
	Mean	**SD**
Age (in years)	35.7	11.0
# RAI partners (past month)	2.4	4.1

Numbers may not sum to column total due to missing data; percents may not sum to 100 due to rounding or omission of one category for binary variables.

Abbreviations: RAI=receptive anal intercourse; SD=standard deviation.

* Excludes alcohol and marijuana.

Table 4.2. Participant-level and sexual event-level characteristics by condom use during RAI at the last sexual event with recent sexual partners reported by HIV-negative In the Pipeline study participants.

Characteristic	Last sexual event with partner: No condom used during RAI		Last sexual event with partner: Condom used during RAI		Total	
	(N=177)		(N=232)		(N=409)	
Participant-level	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (in years)	35.8	10.4	35.5	11.1	35.6	10.8
# RAI partners (past month)	3.0	4.2	3.6	7.3	3.3	6.1
	n	**%**	**n**	**%**	**n**	**%**
White	68	40.0	99	43.6	167	42.1
≥ High school education	152	90.5	195	85.2	347	87.4
Annual income < $9,800	69	41.3	88	39.8	157	40.5
Homeless (past year)	71	43.0	79	35.1	150	38.5
Sexual event-level						
Collected P1, P2 & P3						
Partner Type						
Main partner	51	30.0	44	19.2	95	23.8
Regular partner	17	10.0	24	10.5	41	10.3
Friend/acquaintance	49	28.8	81	35.4	130	32.6
One-time partner/unknown person	36	21.2	70	30.6	106	26.6
Trade partner	17	10.0	10	4.4	27	6.8
Partner >5 years older than participant	43	26.1	64	29.4	107	27.9
Partner's HIV status						
HIV-negative	96	55.8	136	60.7	232	58.6
HIV-positive	6	3.5	6	2.7	12	3.0
Unknown	70	40.7	82	36.6	152	38.4
Substance use at last sexual event[a]	70	41.4	78	33.8	148	37.0
Marijuana	42	24.1	54	23.4	96	23.7
Methamphetamine	43	25.0	31	13.4	74	18.4
Ecstasy	2	1.2	9	3.9	11	2.7
Amyl Nitrates (poppers)	19	10.9	23	10.0	42	10.4
Cocaine	16	9.3	33	14.4	49	12.2
Ketamine	0	0.0	2	0.9	2	0.5
Gamma-Hydroxybutyric acid	5	2.9	5	2.2	10	2.5
Heroin	6	3.5	5	2.2	11	2.7
Acid	1	0.6	4	1.7	5	1.2
Mushrooms	3	1.7	4	1.7	7	1.7
Oxycontin	0	0.0	5	2.2	5	1.2
Vicodin	1	0.6	5	2.2	6	1.5
Valium	0	0.0	4	1.7	4	1.0
Viagra	9	5.2	18	7.8	27	6.7
Collected for P1 only	(N=113)		(N=130)		(N=243)	
Partner had concurrent partners[b]	50	45.9	70	55.1	120	50.9
Exchanged sex[c]	30	27.3	24	18.5	54	22.5
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Partnership assessment scale	14.7	8.5	12.9	8.0	13.8	8.3

Numbers may not sum to column total due to missing data; percents may not sum to 100 due to rounding or omission of one category for binary variables.

Abbreviations: RAI=receptive anal intercourse; SD=standard deviation; P1=last sexual partner; P2=second to last sexual partner; P3=third to last sexual partner.

[a] Excludes marijuana.

[b] Participant believed partner ever had other partners concurrent to their partnership.

[c] The participant ever gave his partner drugs, money, or other good in exchange for sex or the partner ever gave the participant drugs, money, or other goods in exchange for sex.

Table 4.3. Participant-level and sexual event-level characteristics associated with condom use during RAI at the last sexual event with recent sexual partners reported by HIV-negative In the Pipeline study participants.

	Unadjusted	Adjusted[a]	
		Model 1[b] (N=344)	Model 2[c] (N=344)
Characteristic	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Visit			
Baseline	Ref	Ref	Ref
3 months	0.98 (0.55, 1.74)	0.89 (0.43, 1.86)	0.90 (0.43, 1.89)
1 year	0.78 (0.49, 1.25)	0.76 (0.44, 1.29)	0.77 (0.45, 1.32)
Participant-level			
Age (units=5 years)	0.98 (0.87, 1.10)	1.05 (0.90, 1.22)	1.05 (0.90, 1.23)
White	1.08 (0.63, 1.83)	1.00 (0.54, 1.87)	0.94 (0.50, 1.78)
≥ High school education	0.61 (0.28, 1.34)	0.43 (0.16, 1.15)	0.44 (0.17, 1.19)
Homeless (past year)	0.73 (0.42, 1.24)	0.59 (0.30, 1.18)	0.58 (0.29, 1.17)
# RAI partners (past month)	1.03 (0.98, 1.08)	1.02 (0.97, 1.07)	1.02 (0.97, 1.07)
Sexual event-level			
Collected for P1, P2 & P3			
Main partner	0.55 (0.33, 0.94)	0.52 (0.27, 1.00)	-
Partner >5 years older than participant	1.28 (0.77, 2.12)	1.40 (0.77, 2.53)	1.38 (0.76, 2.50)
Serodiscordant partner	1.00 (0.63, 1.57)	0.89 (0.52, 1.50)	0.86 (0.51, 1.46)
Methamphetamine use	0.52 (0.28, 0.94)	0.46 (0.21, 0.97)	-
Amyl Nitrates (poppers)	1.09 (0.53, 2.25)	1.23 (0.51, 2.96)	1.30 (0.53, 3.16)
Cocaine	1.59 (0.78, 3.25)	1.79 (0.75, 4.32)	1.72 (0.71, 4.16)
Partner type by methamphetamine use[d]			
Main partner			
Methamphetamine use	-	-	1.58 (0.36, 6.95)
Non-main partner			
Methamphetamine use	-	-	0.34 (0.15, 0.77)
Collected for P1 only			
Partner had concurrent partners[e]	1.39 (0.79, 2.43)	1.30 (0.68, 2.48)	-
Exchanged sex[f]	0.63 (0.33, 1.23)	0.65 (0.29, 1.47)	-
Partnership assessment scale[g]	0.98 (0.94, 1.01)	0.97 (0.93, 1.01)	-

Abbreviations: RAI=receptive anal intercourse; OR=odds ratio; CI=confidence interval; P1=last sexual partner; P2=second to last sexual; P3=third to last sexual partner.

[a] Adjusted for visit, age, race/ethnicity, education, homelessness (past year) # RAI partners (past month), partner type, older partner, partnership serostatus, & substance use (methamphetamine, ecstasy, amyl nitrates, cocaine & viagra) at last sexual event.

[b] Model 1 - no interaction between partner type and methamphetamine use at last sexual event with partner.

[c] Model 2 - interaction between partner type and methamphetamine use at last sexual event with partner.

[d] Partner type by methamphetamine use product term = 0.05 (model 2).

[e] Participant believed partner ever had partners concurrent to their partnership.

[f] The participant ever gave his partner drugs, money, or other good in exchange for sex or the partner ever gave the participant drugs, money, or other goods in exchange for sex.

[g] Highly correlated with partner type, therefore the adjusted odds ratio is not adjusted for partner type.

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Chapter 5. Concluding Remarks

Given that nearly three quarters of all sexually transmitted HIV infections in the US occur in the context of male-to-male sexual contact,[1] new HIV prevention interventions that account for the current sexual practices of men who have sex with men (MSM) are needed to reduce the incidence of HIV infection in the US. While new biomedical HIV prevention interventions, such as pre-exposure prophylaxis (PrEP) and treatment as prevention (TasP), could dramatically reduce HIV transmission via sexual contact, numerous barriers to widespread implementation of these new interventions have been identified.[2-5] Thus, many argue for their delivery to those at greatest risk in the context of integrated HIV prevention programs that include biomedical, behavioral, and structural interventions.[6-7] Yet, identifying those at greatest risk and the situations in which new prevention strategies could have the greatest impact among MSM remains a challenge. The goal of this dissertation was to address these gaps in knowledge and inform the delivery of new HIV prevention interventions among MSM in the US.

Chapter 2 aimed to characterize longitudinal patterns of risk among HIV-negative MSM and determine the length of their high risk periods during which they would need to be covered by new HIV prevention interventions, such as PrEP. This study demonstrates that HIV-negative MSM exhibit distinct sexual risk trajectories, which we defined as low risk, moderate risk, and high risk. Over the eight year study period, the estimated probability of engaging in high risk behaviors among participants in the high risk group was 0.71 compared to only 0.30 to 0.17 for the moderate risk group and 0.009 for the low risk group. While members of the high risk group were not at constant risk, over 90% exhibited continuous periods of risk with an average duration of ~2 years, suggesting that high risk MSM exhibit “seasons of risk” over time and that targeted PrEP use may provide sufficient protection against HIV infection among high risk MSM. We also found that following a high risk trajectory was associated distress or depression and substance use, both of which have previously been identified as predictors of sexual risk

behaviors among MSM.[8-12] However, to our knowledge, this is the first study to associate these factors with longitudinal patterns of risk as opposed to concurrent or cross-sectional patterns of risk. Thus, screening for mental health and substance use disorders may facilitate the identification of MSM who exhibit ”seasons of risk” for potential PrEP use.

The purpose of Chapter 3 was to assess the feasibility of TasP in the context of serodiscordant main partnerships among MSM by identifying socio-demographic and behavioral factors associated with partnership type and serostatus over time. The results show that participants reporting substance use were less likely to report a serodiscordant main partner at the subsequent visit, suggesting that TasP in the context of serodiscordant main partnerships may offer little protection against HIV acquisition or transmission among substance using MSM. This study also shows that the reported number of male sexual partners is associated with partnership type and serostatus and that the magnitude and direction of this relationship differs by HIV status. Among HIV-negative participants, those reporting >1 male sexual partner were less likely to report a serodiscordant main partner at the subsequent visit, suggesting that potential exposure to HIV during intercourse with casual partners may not dilute the protective effect of TasP for HIV-negative MSM in serodiscordant main partnerships. Among HIV-positive participants, those reporting >1 male sexual partner were less likely to report seroconcordant or serodiscordant main partners, suggesting that TasP may have a greater population-level impact if offered to all HIV-positive MSM regardless of whether they have serodiscordant main partners.

To identify the situations in which new HIV prevention interventions may have the greatest impact among MSM and inform their targeted delivery within this population, Chapter 4 aimed to examine the effect of individual-level and sexual event-level characteristics on condom use during receptive anal intercourse (RAI) at the last sexual event within partnerships reported over time. This analysis demonstrates that partner type and methamphetamine use are

negatively associated with condom use during RAI at the sexual event-level among racially/ethnically diverse, mostly low-income, substance using MSM. Moreover, this study shows that the dis-inhibitory effects of methamphetamine use may be strongest in the context of non-main partnerships, which may be contributing to the continued burden of HIV among MSM given the frequency of casual partnerships and substance use within this population.[13-14]

Although the individual studies included in this dissertation are not without their limitations, one of their many strengths is their focus on specific barriers to the implementation of new HIV prevention strategies among MSM at greatest risk of HIV infection in the US. Thus, findings from this dissertation should be considered in the development of targeted guidelines on the use of these new interventions within this population.

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