ALCOHOL AND HIV SEROCONVERSION IN MEN WHO HAVE SEX WITH MEN

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ABSTRACT
PETRA MICHELLE SANDER: Alcohol and HIV Seroconversion in Men Who Have Sex with Men
(Under the direction of Stephen R. Cole)

Previous findings linking alcohol consumption and HIV seroconversion among men who have sex with men (MSM) have been inconsistent. This study argues those findings may be limited by inadequate control for confounding due to time-updated factors affected by prior alcohol consumption. We examined prospective data from 3,725 HIV-seronegative MSM enrolled in the Multicenter AIDS Cohort Study (MACS). Participants made semiannual study visits from 1984-2007, self-reported alcohol consumption, and underwent HIV testing. Potential predictors of alcohol consumption were explored. Demographic and time-updated factors including smoking, self-reported depression symptoms, illicit drug use and sexual practices were considered. Associations were modeled using logistic and lognormal multivariable regression. We next examined the joint effects of alcohol consumption and unprotected receptive anal intercourse (URAI) on HIV seroconversion. At baseline, median alcohol consumption by seronegative MACS men was 5 drinks/week (interquartile range (IQR): 1-12) and 18% were nondrinkers. Over 47,261 follow-up visits, median alcohol consumption was 2 drinks/week (IQR: 0-8) and 26% of participants were nondrinkers. Comparing users of marijuana, poppers and cocaine to non-users, the odds ratio (OR) for any current drinking among drinkers at the prior visit was 2.90 (95% CL: 2.21, 3.80). For this group, the median number of drinks consumed per week was 1.14 (95% CL: 1.11, 1.18) times the median consumed by non-users. Over follow-up, 529 HIV

seroconversions occurred. After accounting for several measured confounders using a joint marginal structural Cox proportional model, the hazard ratio (HR) of HIV seroconversion for moderate drinking (1-14 drinks/week) compared to nondrinking was 1.10 (95% CL: 0.78, 1.54) and for heavy drinking (>14 drinks/week) was 1.61 (95% CL: 1.12, 2.29) compared to nondrinking. The HRs for heavy drinking compared to nondrinking for participants with 0-1 or >1 URAI partner were 1.37 (95% CL: 0.88, 2.16) and 1.96 (95% CL: 1.03, 3.72), respectively (robust joint Wald P for interaction = 0.42). These findings suggest first, that illicit drug use may identify MSM whose alcohol puts them at risk for adverse alcohol-related health outcomes, and second, that alcohol interventions to reduce heavy drinking among MSM should be integrated into existing HIV prevention activities.

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ACASI	audio computer-assisted self-interview
ADH	alcohol dehydrogenase
AIDS	acquired immune deficiency syndrome
AUDIT	Alcohol Use Disorders Identification Test
BAC	Blood Alcohol Content
CES-D	Center of Epidemiologic Studies – Depression scale
CL	confidence limit
dL	deciliter
g	gram
HIV	human immunodeficiency virus
HR	hazard ratio
IQR	interquartile range
IL	interleukin
IPW	inverse probability weighting
MACS	Multicenter AIDS Cohort Study
MSM	men who have sex with men
OR	odds ratio
PBMC	peripheral blood monocytes
RR	relative risk
URAI	unprotected receptive anal intercourse
US	United States

CHAPTER I

SPECIFIC AIMS

Introduction

Alcohol consumption is believed to be an upstream determinant of drug use and sexual risk behavior and therefore an indirect determinant of human immunodeficiency virus (HIV) risk; however, little empirical evidence exists to support the latter claim and the possible (immune-modulated) direct effects of alcohol on HIV have not been considered. Findings related to alcohol exposure have been inconsistent [1-14] and therefore insufficient to support increased HIV prevention activities targeted at drinking behavior. The overall goal of this study is to estimate the impact of alcohol consumption on HIV acquisition using quantitative methods that permit the unbiased estimation of causal effects under stated assumptions.

The aims have been undertaken with data from the Multicenter AIDS Cohort Study (MACS), which is based in four United States (US) metropolitan areas: Baltimore, Maryland/Washington, DC; Pittsburgh, Pennsylvania; Chicago, Illinois; and Los Angeles, California. Since 1984, this cohort of men who have sex with men (MSM), has collected data on 3,725 men at risk of contracting HIV, of whom 562 had seroconverted by 1 January 2008. MACS participants are monitored through semiannual study visits, at which they provide blood samples for HIV testing and repository and complete interviewer-administered and

computer-assisted interviews concerning demographic, medical and behavioral data. This observational cohort represents perhaps the best available domestic data source to consider long-term alcohol consumption, which is impossible to assess using a randomized design.

An unbiased and precise estimate of the effect of alcohol consumption on HIV seroconversion is essential to the development of targeted HIV interventions for men who have sex with men and other groups at risk for HIV in which alcohol consumption is common.

Specific aim 1. Estimate the association of measured behavioral and demographic factors with subsequent alcohol consumption.

Hypothesis 1: Baseline demographic factors (e.g., younger age, white race, non-Hispanic ethnicity), prior time-varying high risk health behaviors (e.g., higher number of past sexual partners, higher number of acts of unprotected receptive anal intercourse, illicit drug use), and prior time-varying biomedical factors (e.g., serious health concerns in the medical history, body-mass index, weakened immune function) will be associated with heavier subsequent alcohol consumption.

Specific aim 2. Estimate the effect of alcohol consumption on the risk of HIV seroconversion.

Hypothesis 2.1: High levels of alcohol consumption will be related to an increased risk of HIV seroconversion independent of prior behavioral and demographic factors. We will observe a threshold effect wherein the highest quartile of drinkers shows an increased risk of HIV seroconversion when compared to the lowest three quartiles of drinkers.

Hypothesis 2.2: Alcohol consumption within the 12 months prior to HIV seroconversion will show a stronger association with HIV seroconversion than alcohol consumption in the 36 months prior to HIV seroconversion.

Hypothesis 2.3: The joint effects of high levels of alcohol consumption and multiple unprotected receptive anal intercourse partners will be greater than those expected under multiplicative combination.

CHAPTER II

BACKGROUND AND SIGNIFICANCE

The HIV epidemic among MSM in the US

According to 2006 estimates there were 56,300 [15] new HIV infections in the US with MSM transmission accounting for 72% of male seroconverters including 81% of new infections among whites, 63% among Blacks, and 72% among Hispanics [16]. Among MSM, unprotected anal intercourse, particularly unprotected receptive anal intercourse, is the major mode of HIV transmission [17-25] with an estimated *per contact* infectivity of 0.82% (95% CL: 0. 24, 2.76) [17]. The friction of anal-penile sexual contact is thought to compromise innate immunity at the mucosal surface by producing micro-tears in the epithelial linings of the rectum and colon, allowing cell-free HIV to be transcytosed into the underlying *lamina propria*. There it may locally infect HIV target cells, including submucosal dendritic cells, Langerhans cells and CD4+ T cells before ultimately spread via the lymph nodes and producing systemic infection [26, 27].

In the absence of an HIV vaccine to protect high-risk populations, behavioral interventions to modify high-risk behaviors or their prerequisites are primary intervention strategies [28]. Problem alcohol use is common among MSM at risk for HIV [29] and a frequent co-diagnosis among those who test positive for HIV or are receiving treatment [30]. Therefore, substance abuse in general and alcohol abuse in particular are gaining attention in

the field of HIV treatment adherence research [31, 32], particularly as these activities may lead to physiologic changes that lead to poor prognosis [33] and hasten progression to AIDS [34].

Alcohol consumption in the US

Two-thirds of the US adult population identify as alcohol consumers [35], making alcohol along with caffeine and nicotine, one of the most widely used addictive substances nationally. Moderate to heavy drinkers make up 20% of the drinking population (Figure 2.1), with a smaller proportion of the population reporting heavy (>14 drinks/week for men) or binge (>5 drinks per sitting for men) than in Europe [36]. Among adult males in the general population, alcohol use (i.e., choosing to drink alcohol rather than abstaining) is associated with white race, higher levels of education, younger ages, and being married. Higher levels of alcohol consumption, the number of drinks consumed in a typical day, among those who drink are associated with more recent birth cohort, younger age, periods of higher per capita drinking, being unmarried, non-white race, higher levels of education, non-suburban residence, smoking, and psychological comorbidities, particularly depression [37, 38].

MSM were historically thought to consume alcohol at rates that exceed the general population. As reviewed extensively by others [39, 40], early studies of alcohol consumption and alcohol-related disorders among MSM observed low abstention rates, high alcohol consumption and smaller age-related declines in alcohol consumption when compared to the general population [41, 42]. However, these studies suffered from bias due to recruitment of homosexuals from alcohol-saturated settings (e.g., gay bars, urban settings) and differential recruitment of MSM and general population participants. Early findings were not corroborated by population-based studies of alcohol consumption that employed random-

digit dialing of homosexuals and heterosexuals [40, 43]. Additionally, knowledge of the ongoing HIV epidemic among MSM has corresponded to overall declines in alcohol abuse [44].

Literature review

Three types of studies characterize the existing literature linking alcohol consumption to HIV and sexual risk behavior: general association studies, which consider average measures of alcohol consumption and resulting outcomes; situational covariation studies that consider the use of alcohol in specific (e.g., sexual) contexts; and event-level analyses that consider risk behavior around the time of an index sexual act [45-50]. When HIV infection is the outcome, the latter study types are subject to differential recall bias, because the precise timing of infection is usually unknown to the study participant and he may preferentially assign the index act to a time at which he engaged in high risk activities. By contrast, seroconversion, the development of an antibody response by the immune system to HIV, can be detected independent of the participant self-report and is more frequently the outcome in general association studies.

A review of twenty African studies of alcohol consumption which focused primarily on heterosexual HIV transmission and included three prospective studies, reported an unadjusted pooled odds ratio of 1.70 (95% CL: 1.42, 1.72). While the drinking status of HIV-positive individuals is certainly of interest to the study of predictors of care seeking and treatment adherence, cross-sectional associations are insufficient to support causal conclusions linking alcohol consumption to HIV seroconversion. There is no assurance that alcohol consumption prior to HIV seroconversion resembles use after diagnosis at the time of

interview, indeed high risk behaviors are likely to change following notification [51]. Therefore, subsequent discussion will be limited to studies that gather information on alcohol consumption or use during at least one period prior to HIV diagnosis. This approach assures the temporal order role of alcohol consumption *vis-à-vis* HIV seroconversion.

To our knowledge, 14 previous studies [1-14] have considered alcohol use prospectively with HIV seroconversion as an outcome in a variety of populations (Table 2.1). These studies report relative unadjusted effect measures between 1.21 (comparing light to nondrinkers [11]) and 4.82 (comparing individuals drinking more than 30 standard alcoholic drinks per week to nondrinkers [10]). Adjustment for a variety of baseline covariates including: sociodemiographic factors such as race [2, 5, 9, 11], ethnicity [9, 11], religion [4, 6], age [1, 4-6, 9, 10], and education level [2, 5, 6, 9]; and variables considered to be time-dependent confounders or intermediates including: illicit drug use [2, 3, 5, 9, 11, 13] or injections [10], number of sexual partners [4, 6, 9, 11, 12], mental health [2, 9, 11], immunological health [2], risky sexual behavior [1, 3, 6, 9, 10, 13, 14] and history of other sexually transmitted infections [4, 10, 11, 13] attenuates the relationship been alcohol consumption and HIV seroconversion substantially at all but the most extreme levels of consumption. An inverse-variance-weighted estimate of the eight studies that provide adjusted results and sufficient details on confidence limits [2, 4-6, 9-14], gives an average effect of 1.57 (95% CL: 1.45, 1.69). However, this measure is likely biased away from the null due to the exclusion of negative studies that do not report sufficient data for averaging [1, 3, 7]. When we attempt to recapture the influence of these studies by assuming their standard error is a function of the number of observed events and that these events were distributed equally across the exposure levels, the average effect is 1.42 (95% CL: 1.32,

1.53). Thus, the previous studies on this subject collectively support an association between alcohol consumption HIV risk; however, the causal link between alcohol and HIV acquisition is an open question due in part to shortcomings as well as the differences observed between studies [52].

At the time this research was proposed no previous study that included time-varying exposure or covariate levels has appropriately estimated the effect of alcohol on HIV seroconversion as there is confounding by time-dependent covariates (e.g., sexual risk behaviors, immunological health, drug use, etc.), which are determined in part by prior alcohol consumption and both predict HIV seroconversion and subsequent alcohol consumption (Figure 2.2) [53]. Under these conditions traditional adjustment approaches (e.g., regression methods), even those which adjust for time-dependent confounders, may produce biased estimates of the effect estimate of interest [54]. Therefore, the opportunity exists to apply novel techniques [54], which allow for the unbiased estimation of time-dependent alcohol consumption on HIV seroconversion, adjusting for both baseline and time-dependent confounding.

Measurements of alcohol consumption in the HIV seroconversion literature

Self-report of alcohol consumption is notoriously unreliable [55-59] and is highly dependent on the context in which it is reported. When excessive alcohol consumption is socially undesirable or suggestive of pathology it may be underreported by participants; when it gives the appearance of being more worldly or when the drinkers have previously self-identified as heavy alcohol consumers, it may be over-reported [59]. The failure of participants to respond truthfully as has been seen in epidemiologic and substance abuse

literature [58] is also apparent in studies of alcohol consumption and HIV acquisition. Here, Woolf and Maisto warn that "Continuing to take a unitary approach to research design could impede the advancement of knowledge regarding alcohol use and risky sex among MSM. Unfortunately it appears that researchers in this area have done little to obtain empirical evidence on the reliability or accuracy of the self-report data that they do collect" [60].

In the previously cited meta-analyses of alcohol consumption and HIV infection [46, 60], the authors have considered alcohol use as a dichotomous (yes or no) variable, regardless of the time period covered or if the study queried using a diagnostic instrument such as the Alcohol Use Disorders Identification Test (AUDIT) or its abridged form, the AUDIT-C (Table 2.2), another quantity-frequency questionnaire, or a contextual marker of alcohol consumption, such as living in a home from which alcohol is sold. Similarly, alcohol consumption measurement in prospective studies has relied exclusively on non-validated self-report, and has generally been dichotomized by the authors into categories of ever vs. never or heavy drinker vs. non-heavy drinker using various cut points (Table 2.1). Only the study by Watson-Jones et al. presents adjusted *and* unadjusted effect measure estimates across exposure levels of alcohol, reporting adjusted hazards ratios of HIV seroconversion of 1.73, 3.00 and 4.39 for drinking levels of 1-9, 10-29 and ≥30 drinks per week reported at a baseline screening interview relative to nondrinkers [10]. However, even this exposure metric is not indicative of consumption history as it relies on a single self-report drinking obtained at baseline. Alcohol exposure is dynamic, with variation due to day of the week, age and even employment status [61], therefore a more appropriate metric would consider how duration, frequency and intensity of alcohol use as it changes over time. The measures used by Kippax *et al.* [1] and Zablotska *et al.* [6] define the timing of alcohol use with respect to

sexual contact and reflect an "event level" analytic approach. In the study by Kippax *et al.* [1], respondents report on the sex act at which they believe they were infected with HIV, a possibly misleading approach due to differential recall. Zablotska *et al.* [6] consider alcohol consumption by one or both partners as a risk factor; however, the reported findings do not distinguish which partner was drinking. The drinking status of the HIV negative partner may influence the risk of HIV transmission through behavioral and immunological pathways; Zablotska *et al.*'s approach, however, would muddy the indirect effects due to biological changes.

Biomarkers have been applied to assess the validity of self-reported alcohol consumption by insurance agencies [62], in dependence research [63] and law enforcement, all settings where confidence in accurate self-report is low. No gold standard for measuring moderate to long term alcohol intake exists across all levels of consumption, however personal monitoring of the transdermal or exhaled ethanol to measure a Blood Alcohol Content (BAC) around the time alcohol is imbibed (within 8 hours) is likely the best measure currently available of acute drinking [64]. Both these methods are used, for example, when legal or health concerns warrant heightened vigilance [65]. However, they are costly, intrusive, and measure only short-term consumption.

Alcohol and sexual risk behavior

The acute influence of alcohol consumption on human behavior is biphasic [66]. Beginning soon after drinking onset, at a BAC of 0.02-0.05 g/dL, the response to alcohol is stimulatory and includes the experience of mild euphoria and a reduction in anxiety. As the number of drinks imbibed increases, alcohol acts as a depressant: at BAC levels of 0.06-0.10

(3-5 drinks), judgment and motor coordination are impaired; at a BAC of 0.20-0.25 (~10 drinks) there are signs of sedation; and at higher levels, loss of consciousness, asphyxiation, coma and death are more likely [67, 68]. Alcohol levels of as low as 0.1 may interfere with maintaining an erection [68]; however, the precise impact of alcohol on sexual function is highly dependent on context [69]. The median lethal dose of ethanol corresponds to a BAC of approximately 0.4-0.5 [67].

In popular opinion, alcohol consumption is a social lubricant associated with an attitude of disinhibition and risk taking, particularly sexual risk taking [70]. This intuitive understanding is borne out by some [71-78], but not all [79-83] epidemiologic investigations of the subject among MSM. Alcohol consumption was associated with higher numbers of sexual partners [84, 85], higher numbers of unprotected anal sex acts, and condom failure [86]. The influence of alcohol was modified by partner type [72, 87, 88] and sexual behavior [74, 89] with casual partners and receptive anal intercourse with individual of unknown HIV status correlating to alcohol consumption prior to sex.

Behavioral scientists have studied this association and posited three theoretical models [23, 90] through which to understand increased individual sexual risk behavior following alcohol use.

Alcoholic myopia, or the ability of alcohol to cloud short-term decision making processes, may predict sexual risk behavior [91]. Specifically, alcohol limits the attention capacity of the intoxicated person and causes them to overlook both internal and external inhibiting cues (e.g., a prior knowledge that unprotected sex is risky, no available condom). In laboratory settings, young men who were sexually aroused were more likely to report the intention of having unprotected sex if they were intoxicated than if they were sober [92]. Yet

several population-based cross-sectional studies [81, 93] and an event-level analysis [94] failed to show reduction in condom use when alcohol consumption preceded sex. Indeed, the results suggest that pre-existing behavior patterns were unaltered by drinking [94], and that observed unsafe sex practices under the influence were common to participants who were also inconsistent condom users while sober.

Alcohol expectancy theory posits that individuals drink in anticipation of a heightened sexual experience [95]. This is supported by research in adolescents that shows alcohol use is associated with earlier initiation of sexual activity and more sexual partners [96-98]. Among MSM, the consumption of alcohol accompanies a desire to cognitively escape from fears of HIV risk [99, 100].

A third behavioral theory suggests that risky sexual behavior and alcohol use may both be expressions of an underlying risk-prone personality type [23, 94, 101]. The presence of a *sensation-seeking personality type* assessed through survey inquiry into dimensions of thrill and adventure-seeking, experience-seeking, disinhibition, and susceptibility to boredom [102]. Zuckerman [102] found that individuals who scored high on a questionnaire assessing sensation-seeking had more sexual partners compared to participants who scored low. Sensation-seeking is also implicated in initiation and addiction to illicit substances and is believed to wane with increasing age [103]. Kalichman and his colleagues have conducted numerous studies of sensation-seeking in relation to alcohol consumption and sexual risk behavior, concluding that risk-prone personality types are influential in both behaviors [98, 104-106].

Physiologic responses to alcohol

A healthy occasional drinker can metabolize one standard drink (Table 2.3) in one hour. When a person ingests an alcoholic beverage, the ethanol it contains passes into the stomach and intestinal tract, where it may be immediately metabolized by alcohol dehydrogenase (ADH) isoenzymes. The extent of this first pass metabolism is influenced by the amount of time alcohol remains in the stomach. Unmetabolized ethanol passes from the stomach and intestines into the circulatory system and on to the liver for metabolism. There, ethanol is converted into acetaldehyde by ADH and then from acetaldehyde into acetic acid by aldehyde dehyrodgenase (ALDH). Depending on the needs of the body, acetic acid is further metabolized into carbon dioxide and water or transported to cells outside of the liver. Oxidized nicotinamide adenine dinucleotide molecules act as coenzymes required for the activity of both alcohol metabolizing enzymes. Once reduced, this coenzyme may shuttle the energy from the breakdown of alcohol to other parts of the cell.

Polymorphic variants of the genes that encode alcohol metabolism enzymes are associated with altered kinetic properties. These have been linked to differences in alcohol consumption patterns and may explain some of the disparities observed in alcohol dependence across races and ethnicities [107, 108]. For example, homozygosity for the *ALDH2*2* allele is associated with low-dose alcohol hypersensitivity (e.g., flushing and general discomfort) and with a reduced likelihood of heavy drinking and alcoholism in Asians [109, 110]. Similarly *ADH* variants *ADH1B*2* and *ADH1B*3*, most common among those of Asian and African descent, also appear to confer a greater sensitivity to alcohol consumption [111, 112].

Alcohol consumption has consequences for virtually every part of the body, including the immune system. For example, it is well established that chronic alcohol consumption is associated with increased susceptibility to bacterial infection, including tuberculosis [113]. No confirmed biologic mechanism has been established linking acute or chronic alcohol consumption to HIV infection. Nevertheless, two general hypotheses are currently under exploration in the laboratory: first, that alcohol increases host cell susceptibility to initial HIV infection and second, that once cells are infected, HIV proliferation is enhanced in the presence of alcohol and may hasten an individual's progression to AIDS [101].

A study in humans collected peripheral blood monocytes (PBMCs) from six healthy adult volunteers before and after a weekend of social drinking (700 to 3100 ml of beer or an equivalent amount of alcohol in another beverage) and measured the ability of HIV-1 to replicate in the PBMC *in vitro* [114]. Alcohol consumption was correlated with an increase in HIV-1 replication in the PBMCs and a decreased ability of these cells to produce cytokines, such as interleukin-2 (IL-2), which regulate the responses of other immune components to the virus-infected cell. A second study applied the same hypothesis as above, this time with 60 healthy volunteers who were asked to engage in "social drinking" over a weekend. In this case, moderate alcohol consumption (53.50g alcohol ± 15.00) greatly increased HIV replication in PBMCs and was associated with decreases in both T-helper and T-suppressor cell function. A reduction in CD8+ T cells in turn leads to an increase in HIV replication *in vitro* [115].

Alcohol acts directly on HIV target cells. Exposure of human and mouse T cells to alcohol treated dendritic cells led to T cell anergy and impaired proliferation to subsequent stimulation [116, 117]. In the oral cavity, alcohol-exposure increased cell-surface expression

of the CXCR4 receptor [118]. Secondary effects of alcohol exposure include modulation of cytokines released from immune cells: dendritic cell function appears to decline in response to alcohol exposure, leading to a decrease in IL-12 circulation and an increase in IL-10 [119]. Under binge drinking conditions, an increase in pro-inflammatory cytokines was observed [120] alongside an increase in the proportion of HIV-susceptible cells in the circulatory system [121]. Chronic alcohol consumption reduces delayed-type hypersensitivity response [122, 123], decreases the absolute lymphocyte count, reduces macrophage functions [116, 124], increases natural killer cell activity, and increases tumor necrosis factor α production which may in turn increase HIV-1 replication. Among immunized macaques, exposure to simian immune deficiency virus was associated with a hastened SIV-related decrease in CD4+ T cells in alcohol-consuming versus control animals [125].

Significance

Our study of alcohol consumption in the nation's largest cohort of MSM at risk for HIV infection addresses deficiencies in the current literature and aims to improve upon existing methodological approaches for handling confounding. Our work specifically builds on the contributions of Penkower, *et al.* [2] who were to our knowledge the first to investigate alcohol and HIV seroconversion with prospective data drawn from the early waves of MACS. The inability of the field to reach consensus since 1991 speaks to the necessity of this research.

Alcohol dependency is a behavior that often requires intense intervention to realize long-lasting behavior change. Pre-treatment and post-treatment comparisons of heterosexuals receiving individualized alcohol treatment showed decreased HIV risk behaviors, including

unprotected intercourse, a year after entry into alcohol treatment; however, the numbers of observed seroconversions was too small to draw conclusions about that endpoint [126]. Compared to their peers, MSM may be less likely to seek individual treatment for alcohol use disorders [127] and if they do enter, may leave due to limited MSM-specific training of treatment providers or overt homophobia [128]. Community-based HIV prevention interventions targeted specifically at MSM that include modules about negotiating intercourse under the influence of alcohol but do not directly promote reduced consumption of alcohol have been tested [129, 130]. However, the long-term impact of these interventions is unclear. Community-based interventions in South Africa based on the World Health Organizations' model of alcohol intervention, which includes motivational and behavioral skills training, have been associated with promising short-term declines in risky sexual practices [131, 132].

A first step in this effort to design appropriate alcohol interventions for MSM in the US is to provide convincing findings using the most rigorous analytic approaches available to present to policymakers and primary care providers who remain unconvinced that alcohol intervention is an HIV prevention activity.

Table 2.1. Prospective studies of alcohol and HIV seroconversion.

First Author, Year, and Reference	Location	Exposure Metric	Exposure Assessment Timing/Frequency	HIV seroconversions (Study Population)	Unadjusted Estimate (95% CL)	Adjusted Estimate (95% CL)
Penkower, 1991 [2][a]	Pittsburgh, Los Angeles, Baltimore, Chicago	At least weekly drinking of 3 -4 drinks	Baseline	181 (644)	2.28 (1.55, 3.36)	1.39 (1.12, 1.72)
Celentano, 1996 [13]	Northern Thailand	Use/nonuse for the previous 6 months	Baseline + semiannually	85 (1932)	2.92 (1.05, 8.08)	1.72 (0.61, 4.85)
Page-Shafer, 1997 [12][a]	Amsterdam, the Netherlands; San Francisco; Vancouver, Canada; Sydney, Australia	Use/nonuse for the 6-month interval before the visit	Once (Pre-seroconversion period)	345 (690)	1.67 (0.88, 3.16)	1.73 (0.90, 3.45)
Chesney, 1998 [3][a]	San Francisco	5+ drinks at a time on at least a weekly basis	Baseline+ semiannually	39 (337)	2.74 (1.26, 5.92)	NS
Kippax, 1998 [1][a]	Sydney, Australia	5-point Likert-like alcohol usage scale	Baseline	23 (392)	NS	NS
Kapiga, 1998 [4]	Dar es Salaam, Tanzania	Any drinking during follow-up period	Baseline + semiannually	75 (2471)	2.43 (1.54, 3.82)	1.85 (1.14, 3.00)
Nopkesorn, 1998 [14]	Northern Thailand	8+ drinks at a time	Baseline + month 6, 17 and 23	14 (1036)	3.8 (1.1, 12.8)	3.1 (1.0, 10.9)
Wang, 2005 [5]	Baltimore	Daily alcohol use	Baseline + semiannually	308 (1927)	--	1.15 (0.82, 1.62)
Zablotska, 2006 [6]	Rakai, Uganda	Both partners drank before most recent sexual encounter	Baseline + every 10-12 months	287 (14875)	2.12 (1.60, 2.81)	1.58 (1.13, 2.21)
Mehta, 2006 [7]	Baltimore	Not defined	Baseline + semiannually	304 (1984)	Significant	NS
Koblin, 2006 [11][a]	Boston, Chicago, Denver, New York, San Francisco, Seattle	Light (≤3 drinks/day on no more than 1–2 days/week), Moderate (4-5 drinks/day on no	Baseline + semiannually	259 (4295)	Light vs. None 1.21(0.79, 1.87) Moderate vs. None 1.45 (0.92, 2.28) Heavy vs. None	Heavy vs. <Heavy 1.97 (1.32, 2.96)

First Author, Year, and Reference	Location	Exposure Metric	Exposure Assessment Timing/Frequency	HIV seroconversions (Study Population)	Unadjusted Estimate (95% CL)	Adjusted Estimate (95% CL)
		more than 1–2 days/week, or 1-5 drinks/day on 3–6 days/ week, or 1-3 drinks/day on a daily basis) Heavy (≥4 drinks every day or ≥6 drinks on a typical drinking day)			2.75 (1.62, 4.66)	
Read, 2007 [8][a]	Victoria, Australia	Alcohol use (>60 g/sitting) at least weekly in the year before test	At time of test	26 (644)	3.6 (1.1, 11.4)	----
Plankey, 2007 [9][a]	Baltimore-Washington, DC; Chicago; Los Angeles; and Pittsburgh	Binge: 5 + drinks per occasion at least monthly.	Baseline + semiannually	436 (4003)	2.05 (1.53 , 2.74)	1.13 (0.81 , 1.56)
Watson-Jones, 2008 [10]	Northwestern Tanzania	Number of drinks per week reported at baseline	Baseline	63 (821)	1-9 vs. 0 1.85 (0.99, 3.46) 10-29 vs. 0 3.41 (1.76, 6.62) ≥30 vs. 0 4.82 (1.91, 12.13)	1-9 vs. 0 1.73 (0.92, 3.27) 10-29 vs. 0 3.00 (1.51, 5.98) ≥30 vs. 0 4.39 (1.70,11.33)

Abbreviations: CL, confidence limit; NS, not significant.
[a]This study was restricted to men who have sex with men

Table 2.2. The Alcohol Use Disorders Identification Test – Consumption questions [133].

For men, a score >4 is considered positive (i.e., optimal for identifying hazardous drinking or active alcohol use disorders).

1. How often do you have a drink containing alcohol? SCORE

Never (0)
Monthly or less (1)
Two to four times a month (2)
Two to three times per week (3)
Four or more times a week (4)

_____

2. How many drinks containing alcohol do you have on a typical day when you are drinking?

1 or 2 (0)
3 or 4 (1)
5 or 6 (2)
7 to 9 (3)
10 or more (4)

_____

3. How often do you have six or more drinks on one occasion?

Never (0)
Less than Monthly (1)
Monthly (2)
Two to three times per week (3)
Four or more times a week (4)

_____

TOTAL SCORE
Add the number for each question to get your total score. _____

Table 2.3. US standard drink [133]

Equivalents of 13.7 grams ethanol	
12 oz. of beer or cooler	5% ethanol
8–9 oz. of malt liquor	7% ethanol
5 oz. of table wine	12% ethanol
3–4 oz. of fortified wine (such as sherry or port)	17% ethanol
2–3 oz. of cordial, liqueur, or aperitif	24% ethanol
1.5 oz. of brandy (a single jigger)	40% ethanol
1.5 oz. of spirits (a single jigger of 80-proof gin, vodka, whiskey, etc.)	40% ethanol

Figure 2.1. Distribution of drinking levels, for men 18 years of age and older: United Status, National Health Interview Survey, 1997-2008 [134]. Drinking levels: abstainer, fewer than 12 drinks in lifetime or no drinks in the past year; light drinker, on average, 3 or fewer drinks per week in the past year; moderate drinker, on average, no more than 14 drinks per week for men in the past year; and heavy drinker, on average, more than two drinks per day for men in the past year.

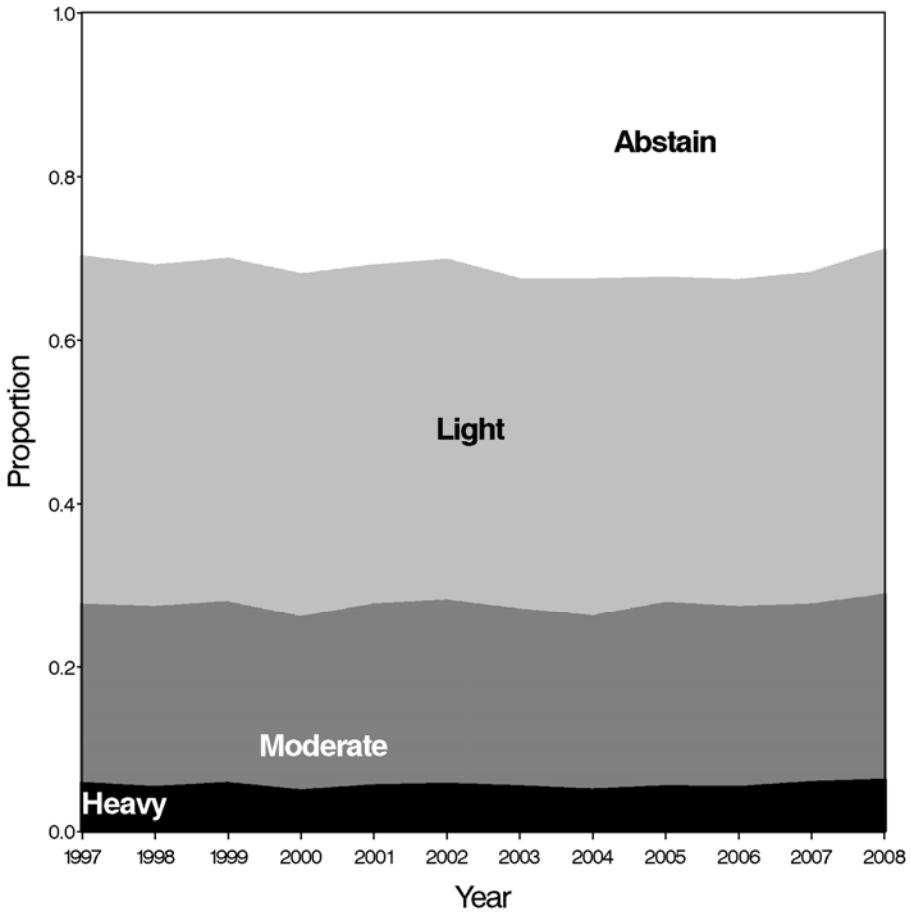
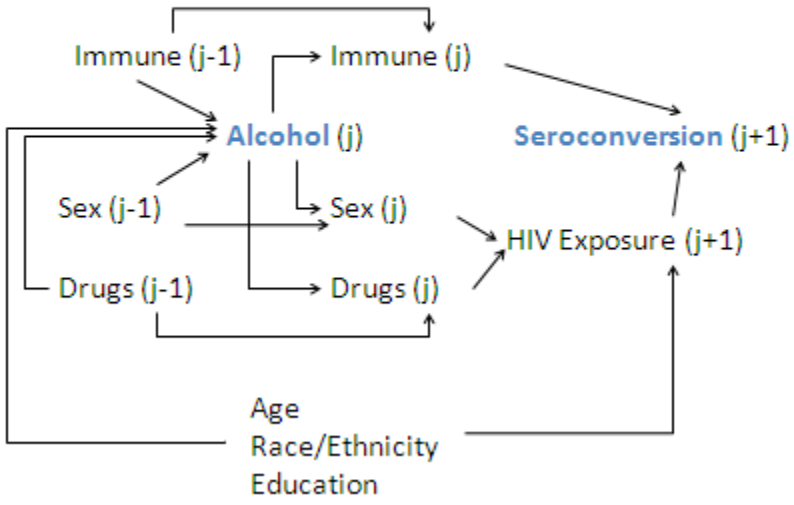


Figure 2.2. Overview of the association between alcohol consumption and HIV seroconversion



CHAPTER III

METHODS

Study population

The Multicenter AIDS Cohort Study (MACS), an ongoing prospective study of the natural and treated history of HIV infection in MSM, was initiated in 1983 by sites located in the metropolitan areas of Baltimore, Maryland/Washington DC; Chicago, Illinois; Pittsburgh, Pennsylvania, and Los Angeles, California [135]. From April 1984 through March 1985, 4,954 HIV negative and positive men were recruited into the MACS. To increase minority enrollment, an additional 668 men were recruited from 1987-91, of whom 433 (65%) were non-Caucasian. In 1993, 1,710 seronegative participants (approximately half those still being followed) were administratively censored by the study [136]. In 2001, the four clinical sites enrolled an additional 1,350 participants including 662 HIV seronegative men. Thus, a total of 6,972 men have been enrolled in the MACS of whom 3,725 are HIV negative men with 38,220 person-years of follow-up observed through 1 January 2008.

MACS participants were recruited through publicity (e.g., newspaper articles, advertisements); political groups, community centers and medical facilities catering to MSM; health care provider referral; and in some cities, active recruitment at gay bath houses and bars [135]. At enrollment, participants completed surveys in which they detailed their behaviors over the previous two years. At subsequent semiannual visits they were asked to

report only on behaviors in the 6 months since their last study visit. These visits could last over 3 hours in duration. Study personnel maximized retention by collecting identifying information on participants including social security and driver's license numbers and by collecting information on close contacts or personal physicians [137]. When participants failed to arrive for scheduled follow-up visits, the MACS attempted to resurrect contact through phone calls, mail, contacts and available databases. When participants could not come to the study site, they were allowed to complete portions of the survey at home and provide blood samples through the mail.

Data collection and measures

Standardized interviewer-administered and/or audio computer-assisted structured interview (ACASI) questionnaires at each semiannual study visit collected information on demographics, risk behaviors, psychosocial characteristics (e.g., depression), illnesses, utilization of health services, and an extensive medication use inventory using medication photographs for select medications for prophylaxis or treatment. The demographic and risk behavior portions of the questionnaire were interviewer-administered initially and were converted to ACASI for newly enrolled participants beginning in October 2001 and at follow-up visits for all participants in October 2002. The four clinical sites are experienced in maintaining the cohort and core laboratories, conducting data collection and optimizing the use of resources.

Self-reported Alcohol Consumption

The MACS assesses participant alcohol consumption using a self-administered quantity-frequency questionnaire at semi-annual study visits. As part of the questionnaire, a drink of alcohol is defined for the participant as equivalent to any of the following: 12 ounces of beer, 4 ounces of wine, 1.5 ounces of liquor or a mixed drink with that amount of liquor. Instructions in the MACS were modified to define a 5 oz glass of wine as standard beginning at visit 40 (October 1, 2003 - March 31, 2004). The latter definition mirrors the current standard drink measures applied by the U.S. Food and Drug Administration [138] (Table 3.1). We treated the definitions at different visits as interchangeable.

Participants are asked to estimate their drinking frequency over the period since the last visit: at least 1/day, nearly every day, 3-4/week, 1-2/week, 2-3/month, 1/month, 6-11/year, 1-5/year, or never (Table 3.1). From this response, we calculate the corresponding weekly drinking frequency multiplier for each participant of 7, 5.5, 3.5, 1.2, 0.625, 0.25, 0.106, and 0.058. The usual quantity of drinks consumed on a drinking day is elicited with options of: 1-2, 3-4, 5-6, or 7-9, 10 or more drinks/day, which we transform into average drinking day counts of 1.5, 2.5, 5.5, 8 and 11 (Table 3.1). From these, we defined self-reported average weekly alcohol consumption (A) for the prior six-month period as the product of the weekly probability of drinking and drinking intensity (i.e., quantity-frequency). We chose weekly alcohol consumption for analysis, as it is a measure easily communicated to clinicians and applied to other research.

Human subjects

Data and specimen collection in the MACS have been approved by institutional review boards at all participating institutions. During the consent for this study, participants

were informed that both their responses to questionnaires and the biological samples they provided would be used to answer research questions related to HIV risk factors and etiology; they were also informed that they could withdraw participation and refuse the use of their data at anytime.

A data use agreement was put into place between the University of North Carolina and the MACS, which limited potential breaches of confidential information to persons outside of the study by using only de-identified participant information, limiting covariate data to variables pre-specified in the aims of this research, and restricting data access to authorized individuals at the University of North Carolina, at Chapel Hill. The aims of this dissertation were deemed "not human subjects research" by the University of North Carolina Public Health-Nursing Institutional Review Board.

Statistical methods for aim 1

The aim of the first dissertation manuscript was to identify time-independent and time-dependent predictors of alcohol consumption in HIV-seronegative men enrolled in the MACS. The structure and general practices of the MACS have been described previously. Here we focus on the variables and statistical methods specific to this analysis.

Descriptive methods

We examined the distribution of alcohol consumption (drinks/week) and all other continuous covariates (Table 3.2) graphically and by examining their means and standard deviations or medians and interquartile ranges at each visit and across visits. As appropriate, we considered categorization or restricted cubic splines for continuous variables. The latter

approach creates a smoothly-joined piecewise polynomial that allow for a flexible non-linear relation between continuous exposures and an outcome [139]. For dichotomous and categorical potential predictors we characterized the percentage of the population for each level of the predictor.

Outcome assessment

At each semi-annual study visit, participants were asked about their consumption of alcohol as part of a behavioral questionnaire that also asked about illicit drug use and sexual activity in the past six months. The few (< 1%) reports of 10 or more drinks per drinking-day were classified as 12 drinks. Participants were censored at the first visit at which they failed to answer questions about their alcohol consumption or at their last study visit when they were not observed subsequently for a period of more than two years regardless of whether they ultimately returned for visits thereafter.

Predictors of alcohol consumption

The predictors of alcohol consumption considered in this aim and how each was categorization for modeling are presented in Table 3.2. Predictors were selected from variables associated with alcohol consumption in previous cross-sectional analyses, and the results of a longitudinal study of alcohol consumption among injection drug users at risk for HIV [140]. Where restricted cubic splines were chosen, these were implemented with the Harrell's %DASPLINE SAS macro available at: http://biostat.mc.vanderbilt.edu/wiki/pub/Main/SasMacros/survrisk.txt. With respect to illicit drug use, we explored several different categorizations. We first considered the use of each

of three most common illicit drugs (marijuana/hash, poppers and cocaine/crack cocaine) individually and categorized them by frequency: each drug category alone, each pair of these drug categories and all three drug categories used in combination as had been done in previous work in this cohort [141]. In ancillary analyses we also considered there use of any versus no illicit drugs. We anticipated that prior alcohol consumption would strongly predict subsequent consumption, and treated this predictor as an effect modifier.

Models

Multivariable logistic regression was used to model the log-odds of reporting any drinking at the current visit as a function of baseline predictors and time-dependent predictors, lagged one visit. All logistic regression models were stratified by drinking status at the prior visit. Multivariable lognormal regression models were used to model alcohol consumption among current drinkers. These models produce effect measure estimates referred to as the median ratio [142]. For categorical predictors, the median ratio represents the expected median number of drinks per week consumed by one group divided by the median number of drinks per week consumed by those in the reference group. The use of multiple observations per participant results in correlated measurements of alcohol within participants. To account for this, we used robust variance estimates [143], which are equivalent to generalized estimating equations [144] with a diagonal/independent working covariance matrix [145]. This approach provides estimation of the coefficients for intercepts and predictors using a maximum likelihood approach while the variance estimates for each parameter are allowed to inflate in the presence of the positive dependence between alcohol consumption. Precision was assessed with 95% CLs.

Statistical methods for aim 2

The aim of the second dissertation manuscript was to use marginal structural models to characterize the association between alcohol consumption and HIV seroconversion for MACS participants. As part of this aim, we characterized the joint effects of alcohol consumption and high risk sexual behavior (specifically unprotected receptive anal intercourse). Here we first describe how both exposures are implemented in this aim. Next, we give an overview of marginal structural models as they are implemented for a single exposure. We conclude with a description of the joint marginal structural model used in the analysis of this paper.

Exposure definitions

The primary exposure of interest for this aim was alcohol consumption reported and collected as describe previously. We initially intended to define quantiles of alcohol consumption based on the distribution of consumption of alcohol across person time in the study population. However, after considering the large proportion of moderate and nondrinking observed in Aim 1 and experimenting with tertiles, quartiles and quintiles of the alcohol consumption of cases and non-cases, we ultimately decided to use previously defined levels of drinking [138]. Specifically, we considered three levels of drinking: nondrinkers, moderate drinkers (1-14 drinks/week), and heavy drinkers (>14 drinks/week) based on reports averaged over the prior two visits (approximately one year).

The secondary exposure was the number of unprotected receptive anal intercourse partners reported, hereafter referred to as partners. Participants self-reported the number of

partners they have had at each semiannual visit. The few (<1%) reports of more than six partners since the previous visit were reset to the median of those with more than six partners (10 partners). In joint models, we considered two levels of receptive anal intercourse: one or fewer partners and multiple partners. Similar to alcohol measures, we averaged the number of partners over the previous two visits.

Outcome assessment

HIV status was determined from blood specimens tested by enzyme-linked immunosorbent assay and was confirmed by Western blot at each semiannual visit. Participants are classified as being seronegative if they had a negative or equivocal enzyme immunoassay result or a negative or indeterminate confirmatory Western Blot result. Individuals with positive HIV test results received outside of the study have these results confirmed through the same algorithm. All laboratories have been certified by the standards of the Clinical Laboratory Improvement Amendment regulations and by the National Institute of Allergy and Infectious Diseases.

Participants were followed from their baseline visit until HIV seroconversion, death, loss to follow-up, or administrative censoring. The midpoint between dates of the last seronegative and the first seropositive test was taken as the estimated date of HIV seroconversion; when this date was more than one year after the last seronegative test date (n = 33), participants were classified as lost to follow-up at one year post-last seronegative test date. Follow-up practices in the MACS cohort have been described previously [137]. Briefly, death information was obtained from death certificates, the Social Security Death Index, the National Death Index, autopsy records, and other notification sources. We censored follow-up for participants who failed to attend study visits for more than one year at the minimum

of: their date of death (if applicable), one year after their last visit, or 1 January 2008 (date of administrative censoring). All remaining seronegative participants seen after 1 January 2007 were administratively censored on 1 January 2008.

Marginal structural models

Overview

It has been established that standard statistical approaches (i.e., stratification, regression) used to adjust for time-varying confounding in observational longitudinal data may produce biased effect estimates in situations where there are time-updated confounders that are also causal intermediates even under the null hypothesis of no effect [54]. Figure 3.1, a directed acyclic graph depicting the association between alcohol consumption and HIV seroconversion, is simplified to illustrate how this might occur when only a single time-updated confounder is concerned. In this case, drug use is a time-updated covariate that is a risk factor for both HIV seroconversion and subsequent alcohol consumption, and alcohol consumption predicts subsequent drug use. Standard approaches would adjust for drug use because it is a confounder of the relationship of interest. However, as is clear from the figure, adjusting for drug use would block part of the indirect effects of alcohol consumption mediated through illicit drug use [54]. Additionally, adjustment might induce a selection bias when confounders are affected by prior levels of the main exposure [146].

Several approaches, known collectively as "g-methods" are available for the estimation of effects of time-varying exposures in the presence of time-dependent confounding from observational data: g-computation algorithm formula, g-estimation of structural nested models, and inverse probability weighted (IPW) estimation of marginal

structural models [147]. We select the last approach, which is easily implemented in standard statistical software and suitable when the null hypothesis (i.e., no effect of alcohol on HIV seroconversion) has not been excluded. Like the other g-methods, the marginal structural model estimates contrasts in potential (counterfactual) outcomes.

Notation

Failure time is denoted by T and was measured continuously in days since the participant enrolled in the MACS. Study visits are indexed by j and ranged from study entry j =0 to visit j =47. In the methods that follow, capital letters represent random variables and lowercase letters represent possible values of random variables. A_{ij} is a time-updated variable indicating alcohol consumption by participant i reported at visit j. Similarly, the time-updated number of partners is given by R_{ij}. The vector $\mathbf{L}_{ij}$ indicates values of the time-updated predictors of HIV seroconversion, alcohol consumption and unprotected receptive anal intercourse partners, which include depressive symptoms, illicit drug use, current smoking status and sexually transmitted infections. Time-independent covariates whose values do not vary after measurement at baseline (i.e., race, ethnicity, enrollment age, city, and educational attainment) are denoted by $\mathbf{V}_i$. The subscripted i is generally suppressed in the following formulae for simplicity. Potential outcomes are represented as $T_{a_j=0}$, $T_{a_j=1}$, $T_{a_j=2}$ or the time to HIV seroconversion that would have been observed had the level of alcohol consumption been set to 0, 1-14 or >14 drinks/week, respectively. C_{ij} is a dichotomous variable indicating if the participant was censored due to loss to follow-up by that visit or not.

Model assumptions

Assuming no unmeasured confounding, no informative censoring, no model misspecification, consistency, and positivity, marginal structural models yield asymptotically consistent estimates of the true causal effect [54, 148, 149].

The assumption of no unmeasured confounding is well appreciated in epidemiology; it is reviewed here in the language of potential outcomes and referred to as conditional exchangeability, defined as $T_{a_j} \coprod A|\mathbf{V},\mathbf{L}$. Here the potential failure time is independent of observed exposure within levels of measured covariates. Analogously, potential failure times are assumed to be independent of censoring within levels of measured covariates.

Under consistency, we understand that for every subject with observed exposure $A_{ij} = a_j$, the potential outcome T_{a_j} is equal to that subject's observed outcome, T_{ij}. While in experimental studies consistency is generally taken for granted because the intervention is assigned and often administered by the researcher; in observational studies such as this one, this assumption requires careful consideration and assessment of the exposure of interest. Stated differently, there should not be multiple versions the exposure. For example, in this case it means that we must able to assume that it is of consequence with respect to his HIV outcome if a subject consumes 7 drinks/week at a single sitting or one drink per day; or if the alcohol consumed came from distilled spirits instead of beer; or if the alcohol was consumed shortly prior to sexual activity instead of afterwards.

The positivity assumption states that $\Pr[A = a_j \,|\mathbf{V} = \mathbf{v},\mathbf{L} = \mathbf{l}_j] > 0$ for all $\Pr[\mathbf{V} = \mathbf{v},\mathbf{L} = \mathbf{l}_j] \neq 0$ in the target population or said differently that there are both exposed and unexposed individual at all levels of the observed confounders [148, 150]. In

observational data, positivity may be violated by chance or deterministically [151]. We address this assumption further in our description of the weight construction below.

Model

In the Cox proportional hazards marginal structural model the potential failure time, T_{a_j}, represents a subject's time to event with (possibly contrary to fact) exposure equal to a_j [152, 153].

$$\lambda_{T_{a_j}}\left(t\middle|\mathbf{V}\right)=\lambda_0\left(t\right)\exp(\beta_j a_j+\gamma\mathbf{V})$$

Here, $\lambda_{T_{a_j}}\left(t\middle|\mathbf{V}\right)$ is the hazard rate of T_{a_j} at *t*, conditioned on the vector of baseline covariates $\boldsymbol{V}$; $\lambda_0\left(t\right)$ is an unspecified baseline hazard function; and $\exp\left(\beta\right)$ is the so-called causal hazard ratio (HR) for the effect of an increase of one level of alcohol consumption averaged across follow-up [54]. For example, one might be interested in contrasting the time to HIV seroconversion in a population in which everyone was a heavy drinker compared to the time to HIV seroconversion in the same population if no one drank alcohol. By the consistency assumption, only the outcome in a given individual under the exposure he truly experienced is observed by the researcher. The time to HIV seroconversion for a heavy drinker had he been a nondrinker is therefore a missing value.

We fit the above model using stabilized IPW to address confounding and selection biases due to measured variables. IPW is an extension of the Horvitz-Thompson estimator used to handle nonresponse in survey sampling [154]. Continuing the example from above, other men contributing data to the cohort at that time and with identical covariate and alcohol consumption histories, but different levels of current alcohol consumption, are weighted to

represent the outcome of the heavy drinker, had he not consumed alcohol heavily. If no unmeasured confounding is present, alcohol consumption will be unassociated with past history of measured covariates in the weighted pseudopopulation, but the HR of interest will remain the same as in the original population.

The general form of our stabilized exposure weights is given below, where alcohol consumption A_j may take on discrete values from the range of observed drinks/week consumed (e.g., 5 drinks/week). Overbars refer to the history of a variable ($\bar{A}_j = \{A_1, A_2 \ldots A_j\}$).

$$SW^A(t) = \prod_{k=0}^{j \le t} \frac{\Pr[A_k \mid \bar{A}_{k-1}, \mathbf{V}, \bar{C}_{k-1} = 0, T \ge k]}{\Pr[A_k \mid \bar{A}_{k-1}, \mathbf{V}, \bar{\mathbf{L}}_{k-1}, \bar{C}_{k-1} = 0, T \ge k]}$$

The denominator of these weights has been described informally as the probability that a subject had his own observed exposure, given his covariate history [152]. We mitigated the impact of highly variable weights by stabilizing our weights by the numerator [54, 148]. As part of this stabilization, baseline covariates, **V**, were included in the numerator and denominator of these weights and must therefore be adjusted for in the final Cox model in order to account for confounding by time these time fixed covariates. Practically, these weights were calculated from the observed data using pooled cumulative logistic regression [155] in SAS PROC LOGISTIC using a cumulative logistic link.

Censoring weights were similarly fit for both the censoring due to lost to follow-up and censoring due to death. Weights for censoring due to loss to follow-up are given by:

$$SW^{C}(t) = \prod_{k=0}^{j \le t} \frac{\Pr[C_k = 0 \mid C_{k-1} = 0, \bar{A}_{k-1}, \mathbf{V}, T \ge k]}{\Pr[C_k = 0 \mid C_{k-1} = 0, \bar{A}_{k-1}, \bar{\mathbf{L}}_{k-1}, T \ge k]}$$

Note that we did not consider participants who were administratively censored by the study to be drop outs as we assumed that the procedures implemented in the MACS for this process excluded individuals at random.

Joint marginal structural Cox models

The previous exposition of methods used for this analysis considered only a single exposure. While the effect of alcohol consumption was of primary interest in this work, we hypothesized there was an interaction with high risk sexual behavior, another time-updated behavior. An approach to interaction in marginal structural models was first detailed by Hernan, *et al.* [156], but to our knowledge has seen limited application [157-159]. Whereas the results from marginal structural model described previously will, under the stated assumptions, approximate the results of a randomized trial in which a single treatment was randomized; the results of the joint marginal structural model will give the results one would have seen had two treatments been randomized and correspond to an intervention in which we could imagine manipulating both exposures. A joint model requires that the previously stated assumptions hold for both exposures.

This final joint marginal structural Cox proportional hazards model for HIV seroconversion included as regressors alcohol consumption averaged over the prior year (categorized as none, moderate (1-14 drinks/week), or heavy(>14 drinks/week), number of receptive anal intercourse partners averaged over the prior year (categorized as ≤ 1 or >1),

and their product terms. Additionally, the final model includes baseline covariates used to stabilize the IPW.

$$\lambda_{T_{a_j,r_j,c=0}}\left(t\middle|\mathbf{V}\right)=\lambda_0\left(t\right)\exp(\beta_j a_j+\delta_j r_j+\eta_j a_j r_j+\gamma\mathbf{V})$$

We presented HRs and 95% CLs using robust variances based on this model. Departure from proportional hazards for the alcohol and partner effects were assessed through models that included exposure by time and exposure by log-time product terms and by visual inspection of log(-log)-survival plots. The contribution of the interaction term was assessed using a joint robust Wald χ^2 test. We did not find this interaction to be meaningful on the multiplicative scale and therefore also include results from models that exclude that term. We went on to consider departure from additivity using the relative excess risk due to interaction (RERI) using methods for the proportional hazards model developed by Li and Chambless [160]. This RERI is interpreted as the increased risk due to additive interaction after accounting for confounders. SAS code from the authors [161] was adapted to calculate RERIs from the marginal structural model. Wald χ^2 trend tests were used across levels of alcohol consumption with the median (0, 5, and 22 drinks/week, respectively) assigned for each of the three levels of alcohol consumption considered.

Exposure weights were calculated from a pair of cumulative pooled logistic regression models as described previously [155]: each accounted for the following dichotomous time-updated confounders, lagged one visit: elevated depression symptoms, smoking status, use of illicit drugs and self-reported sexually transmitted infection. In addition, the weight model for partner number also included concurrent alcohol consumption. Note, we needed to include concurrent alcohol consumption in the partner number weights because of the multiplication rule of conditional probability, which states that when two

events are dependent, the probability of both occurring is given by:

$\Pr[A,R] = \Pr[A]\Pr[R|A]$. Therefore, to produce joint weights, one of the two exposure weights needed to include the concurrent level of the other exposure.

These weights were stabilized to improve precision by alcohol consumption history (product terms between alcohol consumption at 6, 12, and 18 months prior and restricted cubic splines with knots at the 5th, 27.5th, 50th, 72.5th and 95th percentiles for consumption at those times), partner history (product terms between partner number at 6, 12 and 18 months prior), and time-independent covariates measured at baseline [148].

The final weights were calculated as the product of exposure, censoring, and death weights. These weights have an expected mean of 1 and reduced variance compared to unstabilized weights [54, 148]. We graphically examined the distribution of our weights and calculated the mean and variance. Based on the distribution of the weights, additional truncation [148] was not deemed necessary. Furthermore, the behavior of the weights, suggests that nonpositivity is not a major concern.

We compared our results to those from a standard Cox proportional hazards model [162] that includes main effects of alcohol consumption and unprotected receptive anal intercourse partners and their interaction.

$$\lambda(t) = \lambda_0(t)\exp(\beta' A_j + \delta' R_j + \eta' A_j R_j)$$

We additionally compared these results to those from a model that adjusted for both baseline and time-updated confounders, lagged one visit.

$$\lambda(t|\mathbf{L},\mathbf{V}) = \lambda_0(t)\exp(\beta_j'' a_j + \delta_j'' r_j + \eta_j'' a_j r_j + \mu_j \mathbf{L}_{j-1} + \gamma'\mathbf{V})$$

We also considered as a comparison models that adjusted for concurrent values of time-updated values, but found that these gave similar results.

Finally, we described the public health impact of our findings by calculating the excess fraction [163] of HIV seroconversion associated with heavy drinking:

$$\text{Excess risk} = (p)\frac{HR_{\text{heavy v. <heavy}} - 1}{HR_{\text{heavy v. <heavy}}}$$

Where p is the proportion of heavy drinkers who reduced their alcohol consumption to at least moderate levels and could vary between 0 and 1. This excess risk was interpreted as the percentage of HIV seroconversions that could be avoided if a given percentage of heavy drinkers reduced their alcohol consumption.

Table 3.1. MACS follow-up visit questionnaire, semiannual visit

41. The next set of questions are about alcoholic beverages. They may seem similar, but they are asked in a slightly different way.
Please answer each of the following questions for the past 6 months.

A. How often have you had drinks containing alcohol?
   - o Never →STOP- SKIP TO Q41K
   - o Less than monthly
   - o Monthly
   - o Weekly
   - o Daily or almost daily

B. During the past 6 months, how many drinks containing alcohol have you had on a typical day when you are drinking? (A "drink" is defined as one 12-ounce beer, one 5-ounce glass of wine, or one mixed drink with 1 and ½ ounces of 80 proof hard liquor.)
   - o 1 or 2
   - o 3 or 4
   - o 5 or 6
   - o 7 to 9
   - o 10 or more
   - o None

C. During the past 6 months, how often have you had six or more drinks on one occasion? (A "drink" is defined as one 12-ounce beer, one 5-ounce glass of wine, or one mixed drink with 1 and ½ ounces of 80 proof hard liquor.)
   - o Never
   - o Less than monthly
   - o Monthly
   - o Weekly
   - o Daily or almost daily

Table 3.2. Covariables

Variables	Classification	Type
Demographic		
Race/ethnicity	Categorical: Black White Hispanic White non-Hispanic	Time-independent
Age at enrollment	Restricted cubic spline	Time-independent
Education level	Dichotomous: Less than College College Graduate	Time-independent
Behavioral		
Number of receptive anal sex partners	Categorical: 0 1 >1	Time-dependent
Center for Epidemiologic Studies Depression Scale Score (Table 3.3)	Dichotomous >16 ≤16	Time-dependent
Drug Use		
Current smoking (tobacco)	Dichotomous (Yes/No)	Time-dependent
Marijuana/Hashish use	Dichtomous (Yes/No)	Time-dependent
Cocaine/crack cocaine use	Dichtomous (Yes/No)	Time-dependent
Poppers/amyl, butyl or isopropyl nitrite use	Dichtomous (Yes/No)	Time-dependent
Other		
Enrollment (time)	Restricted cubic spline	Time-independent
Enrollment city	Categorical	Time-independent

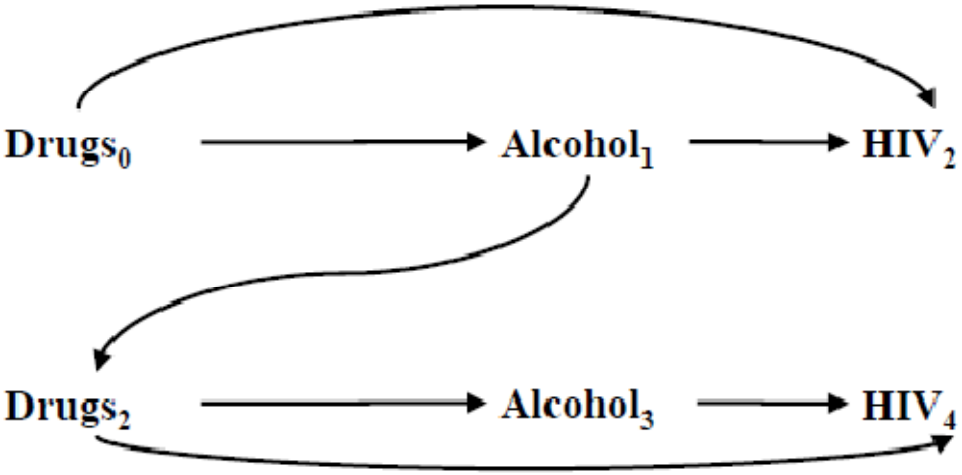
Table 3.3. Center for Epidemiologic Studies- Depression scale [164]

CENTER FOR EPIDEMIOLOGIC STUDIES—DEPRESSION SCALE

Circle the number of each statement which best describes how often you felt or behaved this way – DURING THE PAST WEEK.

	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of the time (3-4 days)	Most or all of the time (5-7 days)
During the past week:	0	1	2	3
1) I was bothered by things that usually don't bother me	0	1	2	3
2) I did not feel like eating; my appetite was poor	0	1	2	3
3) I felt that I could not shake off the blues even with help from my family and friends	0	1	2	3
4) I felt that I was just as good as other people	0	1	2	3
5) I had trouble keeping my mind on what I was doing	0	1	2	3
6) I felt depressed	0	1	2	3
7) I felt that everything I did was an effort	0	1	2	3
8) I felt hopeful about the future	0	1	2	3
9) I thought my life had been a failure	0	1	2	3
10) I felt fearful	0	1	2	3
11) My sleep was restless	0	1	2	3
12) I was happy	0	1	2	3
13) I talked less than usual	0	1	2	3
14) I felt lonely	0	1	2	3
15) People were unfriendly	0	1	2	3
16) I enjoyed life	0	1	2	3
17) I had crying spells	0	1	2	3
18) I felt sad	0	1	2	3
19) I felt that people disliked me	0	1	2	3
20) I could not get "going"	0	1	2	3

Figure 3.1. Directed acyclic graph illustrating time-varying confounding



CHAPTER IV

A LONGITUDINAL STUDY OF ALCOHOL CONSUMPTION AMONG US MEN WHO HAVE SEX WITH MEN, 1984-2007

Introduction

Alcohol is a popular recreational drug in the United States (US). Consumption produces both stimulatory and anxiolytic physiologic effects, which may be enhanced when its use is coupled with the expectation of positive social, emotional or physical effects [165]. Greater than moderate alcohol consumption is linked to adverse health consequences including cancer, psychiatric illness, cardiovascular disease, liver cirrhosis, and injury [166]. Alcohol consumption is indirectly linked to the acquisition of sexually transmitted infections, including HIV, in large part as a result of increased sexual risk-taking by intoxicated persons [2, 3, 11, 60]. Moreover, use of illicit drugs while under the influence of alcohol may increase high risk drug use behaviors (e.g., needle sharing) [167]. Understanding the longitudinal predictors of alcohol consumption may assist in the development of timely, targeted interventions to reduce harmful alcohol consumption and its adverse consequences. This knowledge would also provide insight into potential confounders when studying the health effects of alcohol consumption.

Studies in the general population suggest that alcohol consumption decreases with age; whereas higher consumption is associated with male gender, white race, being

unmarried, having a higher educational level, and smoking [168, 169]. Few longitudinal studies of alcohol consumption have focused on adult men who have sex with men (MSM). Alcohol consumption among MSM should be considered separately from men in the general population, because MSM are thought to consume alcohol at higher levels [39, 40] and their substance use behaviors may have changed in response to the US HIV epidemic [44].

Repeated assessments of potential predictors and alcohol consumption are necessary to explore the association between time-updated variables and alcohol consumption because many of the factors that may predict subsequent alcohol consumption (e.g., drug use, depression) may also be affected by prior alcohol consumption. Therefore, assuring the correct temporal ordering is essential to making inferences. In this study, we use self-reported data on alcohol consumption from MSM in the prospective Multicenter AIDS Cohort Study (MACS). The current study is restricted to men at risk for HIV acquisition, because the symptoms of HIV, the receipt of HIV primary care, and the side effects of antiretroviral medication may all modify drinking behavior and suggest that MSM with HIV should be considered separately [30, 170, 171]. We investigate the association of time-fixed and time-updated factors with subsequent alcohol consumption between 1984 and 2007.

Materials and methods

Study sample

The study sample consisted of a subset of participants enrolled in the MACS, an ongoing study of the natural history of HIV infection among MSM in the US metropolitan areas of Baltimore, Maryland/Washington, DC; Chicago ,Illinois; Los Angeles, California and Pittsburgh, Pennsylvania [135]. The MACS enrolled 6,972 men: 5,622 between 1984 and

1992 and 1,350 in 2001. Of these 6,972 men, 4,029 were HIV-seronegative at their baseline visit.

Participants are followed semiannually at study visits that include physical examinations, blood draws and standardized questionnaires (including the Center for Epidemiologic Studies Depression (CES-D) scale [164]). The demographic and risk behavior portions of the questionnaire were interviewer-administered initially and were converted to audio computer-assisted self-interview for newly enrolled participants beginning in October 2001 and at follow-up visits for all participants in October 2002 because audio computer-assisted self-interview was found to yield higher reports of sensitive and high risk behaviors [172]. Informed consent was obtained from all participants in compliance with the appropriate ethical committee at each study site. Study design details and questionnaires are available at http://www.statepi.jhsph.edu/macs/macs.html.

We restricted the study sample to the 3,651 of 4,029 HIV-seronegative men who attended a first follow-up visit within two years of their initial study visit. Participants were followed through their last planned study visit before 1 January 2008 (administrative censoring), death or HIV seroconversion. Dates of HIV seroconversion were determined from blood specimens tested by enzyme-linked immunosorbent assay and confirmed by Western blot. Participants were classified as lost to follow up at their last study visit when they were not observed subsequently for a period of more than two years regardless of whether they ultimately returned for visits thereafter. Participants were censored at the first visit at which they failed to answer questions about their alcohol consumption.

Measurements

We defined alcohol consumption as the typical number of drinks per week in the last 6 months, calculated as the product of the reported average number of drinking-days per week and the average number of drinks per drinking-day. Participants reported drinking at least daily, nearly every day, 3-4 times per week, 1-2 times per week, 2-3 times per month, monthly, 6-11 times per year, 1-5 times per year or never. A drink was defined as one 12-ounce beer, one 4 or 5-ounce glass of wine, or one mixed drink with 1.5 ounces of 80 proof hard liquor. Participants reported the category that best corresponded to the number of drinks they consumed per drinking-day: 0, 1-2, 3-5, 6-9, or >10. The few (<1%) reports of 10 or more drinks per drinking-day were classified as 12 drinks. For graphical presentation of overall alcohol consumption, heavy drinking was defined as greater than 14 drinks per week [138]; all other consumption was considered moderate.

Potential predictors of alcohol consumption were identified *a priori* by a review of the literature and included the following covariates measured at the baseline study visit: age, race, and whether the participant graduated from college. Time-updated potential predictors reflected behavior in the 6-12 months temporally prior to alcohol consumption. They included illicit drug use, elevated depression symptoms (CESD >16), current smoking status, and the number of partners with whom the participant practiced unprotected receptive anal intercourse (none, 1 or ≥ 2). We considered three classes of illicit drugs: marijuana or hash, poppers (i.e., inhaled alkyl nitrites), and cocaine, including crack cocaine. Time-updated predictors were lagged one visit to ensure values were temporally prior to reported alcohol consumption (i.e., 6-12 months prior). We anticipated that prior alcohol consumption would strongly predict subsequent consumption, and treated this predictor as an effect modifier; we examined whether predictors of alcohol consumption varied by prior drinking status.

Missing data were rare. Specifically, data were missing for 7% and 5% of variables at baseline for the number of unprotected receptive anal intercourse partners and CES-D, respectively and was missing for <2% of all other variables. For values missing at baseline we imputed the mode. For missing values over follow-up, the value from the previous visit was carried forward (number of unprotected receptive anal intercourse partners, 6%; CES-D, 4%; and all others, <2%).

Statistical Analysis

We calculated adjusted odds ratios (OR) to estimate the association between potential predictors and drinking status, modeled as any versus no drinking at each visit. We stratified results by whether the participant had reported any alcohol consumption at the prior visit and modeled the probability of any drinking at the current visit. Because the distribution of alcohol consumption was expected to be right-skewed, we modeled the logarithm of alcohol consumption among current drinkers. Lognormal regression models produce effect measure estimates referred to as the median ratio [142]. For categorical predictors, the median ratio represents the expected median number of drinks per week consumed by one group divided by the median number of drinks per week consumed by those in the reference group. In the lognormal model, the number of drinks consumed per week reported at the prior visit was included as a restricted cubic spline with knots at the 5^{th}, 27.5^{th}, 50^{th}, 72.5^{th} and 95^{th} percentiles [173]. Splines create a smoothly-joined piecewise polynomial that allow for a flexible non-linear relation between prior alcohol consumption and current alcohol consumption [139]. For all models, 95% confidence limits (CL) with robust variances were used to account for the dependence incurred by multiple visits by each participant [143]. We included the following variables in all models: time-on-study, modeled as a cubic spline with

knots at the same locations as given above; baseline visit date, modeled as a cubic spline with knots at the same locations as given above; and indicators for study site. Analyses were conducted using SAS version 9.2 (SAS Institute, Inc.; Cary, North Carolina).

Results

At baseline, the 3,651 men were a median of 33 years of age (interquartile range (IQR): 28-39), 12% of black race, 6% Hispanic and 59% had completed college (Table 4.1). As of 1 January 2008, they had been followed for a median of 5.7 years (IQR: 2.5-10.3). Thirty-seven (1%) participants died during follow up, 433 (12%) acquired HIV infection, 524 (14%) were lost to follow-up, 342 (9%) were censored when they failed to report alcohol consumption, and 2,315 (63%) were administratively censored. Among all participants, the median alcohol consumption reported was 5 drinks per week (IQR: 1-12) at baseline. Among self-reported drinkers, median alcohol consumption was 5 drinks per week (IQR: 2-12).

Alcohol consumption decreased over follow-up: abstention from alcohol consumption was reported at 26% of follow-up visits versus 18% of baseline visits ($p < 0.0001$). Median alcohol consumption was 2 drinks per week (IQR: 0-8) over 47,261 visits (Appendix 2.4.1). Self-reported drinkers maintained a median alcohol consumption of 5 drinks per week (IQR: 1-12). As participants aged, the proportion abstaining from alcohol appeared to increase; however the proportion reporting heavy drinking did not appear to decrease (Figure 4.1, Panel A). A similar trend was apparent over calendar time: in 1984, 16% of participants were nondrinkers and 17% were heavy drinkers; in 2003, 29% were nondrinkers and 11% were heavy drinkers (Figure 4.1, Panel B).

Use of marijuana/hash, poppers and cocaine/crack cocaine was common (67%, 52%, and 26% of participants used each drug in the two years prior to their baseline visit, Table

4.1). Injection drug use was uncommon (<1%) as was methamphetamine use (4%), which furthermore was not captured consistently over follow-up. Just 7% of the cohort reported use of any other drugs, including heroin. We therefore considered these three most common illicit drugs categories as potential predictors and model the use of each drug category alone, each pair of these drug categories and all three drug categories used in combination (Appendix 2.3.2) [141]. In ancillary analyses we consider the use of any versus none of these three drug categories.

Table 4.2 presents results from the 75% of study visits preceded by a visit at which any alcohol consumption was reported. Among drinkers at the prior visit, the number and type of illicit drugs used were associated with any current drinking: current drinking was reported at 97% of visits by users of marijuana/hash, poppers and cocaine/crack and 91% of visits by non-users of these three drug categories (Table 4.2). In the ancillary multivariable-adjusted model that included any illicit drug use versus none, the OR was 2.78 (95% CL: 2.58, 3.01). In our main analysis, the multivariable-adjusted OR for any current drinking comparing users of marijuana, poppers and cocaine to non-users was 2.90 (95% CL: 2.21, 3.80). Among drinkers at the prior visit, college graduates were more likely to report any current drinking (94%) than non-graduates (92%); whites were more likely to report any current drinking (94%) than blacks (87%); and men without elevated depression symptoms were more likely to report any current drinking (94%) than those with elevated depression symptoms (91%). All these observed associations persisted after multivariable adjustment (Table 4.2).

Table 4.3 presents results from the 25% of study visits that were preceded by a visit at which no alcohol consumption was reported. Among nondrinkers at the prior visit, illicit

drug use was associated with current drinking: current drinking was reported at 32% of visits by users of marijuana/hash, poppers and cocaine/crack and 14% of visits by non-users. The multivariable-adjusted OR for any current drinking by men who used marijuana/hash, poppers and cocaine/crack cocaine compared to men who used no drugs was 2.93 (95% CL: 1.79, 4.78). Among nondrinkers at the prior visit, the use of individual drug categories or pairs of drug categories was also associated with reports of any current drinking. After multivariable adjustment, use of cocaine/crack cocaine was the strongest predictor of any current drinking among prior nondrinkers (OR: 3.52; 95% CL: 2.19, 5.64). Among nondrinkers at the prior visit, no other measured predictors were strongly associated with any current drinking in the main analysis; black race was marginally associated with any current drinking (OR: 1.37; 95% CL: 1.00, 1.88). In the ancillary analysis, the OR for any illicit drug use versus no illicit drug use was 2.07 (95% CL: 1.76, 2.45).

Table 4.4 presents how the median number of drinks consumed by current drinkers differed by time-fixed and time-updated predictors. Over follow-up, current drinkers who used marijuana/hash, poppers and cocaine/crack cocaine consumed a median of 8 drinks/week (IQR: 5-12) whereas non-users consumed a median of 5 drinks/week (IQR: 2-8); users of all three categories of drugs consumed alcohol at a level consistent with highest quartile of non-users (crude median ratio: 1.60 = 8/5). The multivariable-adjusted ratio of median alcohol consumption was 1.14 (95% CL: 1.11, 1.18) comparing users of marijuana, poppers and cocaine to non-drug users. Users of marijuana alone, poppers alone or cocaine alone consumed a median of 5 drinks per week (IQR: 2-11, 2-11, and 2-13, respectively). After multivariable adjustment, the median alcohol consumption ratio of marijuana or poppers users compared to non-users was 1.06 (95% CL: 1.03, 1.09); for cocaine users the

median ratio was 1.16 (95% CL: 1.09, 1.25). In an ancillary model which considered use of any of the three illicit drug categories, the median ratio of alcohol consumed comparing illicit drug user to non-users was 1.04 (95% CL: 1.02, 1.07). In the main analysis, current drinkers who smoked cigarettes consumed a median of 5 drinks/week (IQR: 2-8) as did non-smokers (IQR: 2-12). After multivariable adjustment the median alcohol consumption ratio of smokers compared to non-smokers was similar to that of marijuana or poppers users (1.07; 95% CL: 1.04, 1.09).

Discussion

This paper presents self-reported alcohol use and consumption patterns over 24 years in a cohort of 3,651 urban, predominantly white MSM at risk for HIV infection. We show that the proportion of the population that consumed alcohol varied from 82% at baseline to 64% at its nadir over follow-up. In this cohort, we found that marijuana/hash, poppers and cocaine/crack cocaine use predicts higher levels of subsequent alcohol consumption. In particular, illicit drug use increased the likelihood of reporting current drinking among prior drinkers and prior nondrinkers and was associated with a higher median number of drinks per week consumed.

The proportion of MSM who consume alcohol in our cohort over time is consistent with the point prevalence reported in prior cross-sectional and serial cross-sectional studies conducted within the same study period. Prior studies that asked HIV seronegative MSM participants to recall alcohol consumption from the prior month or longer reported overall drinking prevalence between 68% and 97% [3, 170, 174-180]. These rates and ours are higher than the 57% of males (age >12 years) of all sexual orientations who reported

consuming alcohol as part of the 2006 National Survey on Drug Use and Health [181]. However, direct comparisons across these studies should be treated with caution, as the sampling methods differed by study: convenience samples of MSM were sometimes recruited from venues that serve alcohol [3, 175-177] and predictably differ from national samples and surveys of MSM which randomly sampled from the population [170, 174, 178-180, 182].

Our findings expand upon the results of two previous studies examining alcohol consumption among MACS participants. In 1991, Penkower et al. reported a heavy drinking prevalence of 19% among a sample of 463 members who were HIV-seronegative between 1984 and 1987 [2]. In 1993, Ostrow et al. examined drinking patterns between 1984 and 1990 among members of the Chicago MACS/Coping and Change Study cohort, a sub-cohort of 384 Chicago MACS participants [79]. Participants reported a near universal history of alcohol consumption (90-95%) and a decline in heavy drinking (defined as >59 drinks/month) from 28% at baseline to 12-15% 5 years later. Our analysis differs from these studies of heavy drinking by observing trends over longer time periods and modeling alcohol consumption at the level of drinks per week rather than categorizing drinking practices into light, moderate or heavy. Our findings confirm that following declines in alcohol consumption within the earliest years, the proportion of the cohort who drank ultimately stabilized. However, we cannot rule out that men limited alcohol consumption in response to the risk reduction messages they received as a result of participating in a long-term study of HIV infection, therefore these findings may not be representative of alcohol consumption changes in the general population of MSM over this time period.

The longitudinal nature of our data allowed us to examine the association between potential predictors and alcohol consumption in a way that respected temporality. We report that lower education, elevated depression symptoms and black race decreased the likelihood of reporting any current drinking among men who reported any drinking at the prior visit. Illicit drug was associated with current drinking among prior drinkers and prior nondrinkers, and with increased alcohol consumption among current drinkers. Similar to the cross-sectional findings of Greenwood and colleagues [84], who considered heavy drinking in a sample of young MSM (mean age 26 years), age and unprotected receptive anal intercourse practices were not predictive of alcohol consumption in our study. However, we did not replicate the association they observed with lower education level and we could not examine how alcohol consumption differed by profession. Our inability to observe an association between education and the number of drinks/week consumed may be due to the relatively homogenous high educational attainment of initial MACS participants. MACS participants enrolled in the earliest waves of the study are predominantly white, of high socioeconomic population status and are likely not representative of the US MSM population overall. We anticipate that additional follow-up data from men enrolled into the MACS between 2001 and 2003 will be able to provide more information on education effects over follow-up, because these later recruits are more educationally and racially diverse. Additionally, data on other illicit drugs which may be associated with alcohol consumption, such as methamphetamine, has been collected consistently for this group. Other large cohorts that represent younger, non-urban and minority MSM should be queried to see if the associations we report can be replicated in these populations.

Examining the association between alcohol consumption and time-updated behaviors measured at a previous semiannual visit may obscure the effects of factors whose influence is short-lived. For example, cocaine/crack cocaine use may be a strong determinant of alcohol consumption over subsequent hours or days, whereas in our analysis the effect of cocaine/crack cocaine use in the prior 6-12 months is associated with only a moderate increase in alcohol consumption over the subsequent 6-month interval (Table 4.4). A more nuanced understanding of the short-term predictors of alcohol consumption requires study designs that allow for the collection of study data over shorter intervals or event-level data capture.

Self-reported alcohol consumption over the preceding 6 months is subject to several sources of measurement error. First, participants may struggle to recall consumption following intoxication or to express the quantity consumed in the same units as the questionnaire [58]. Second, retrospectively asking about the quantity and frequency of alcohol consumed has been shown to elicit modal rather than median consumption levels [183], likely underestimating true self-reported alcohol consumption. Third, social desirability bias may lead to the underreporting of stigmatizing behaviors including alcohol and other drug use [184]. We believe this latter bias to be minimized in later waves of the MACS due to the use of computer-assisted self-administered survey tools [185, 186]. Nevertheless, the collection of information on both the study outcome and other sensitive risk factors (e.g., illicit drug use) through questionnaires with possible dependent measurement errors may bias the observed associations even if misclassification is non-differential [187, 188]. If participants tend to misreport alcohol consumption in a manner similar to that in which they misreport drug use, observed associations may be inflated.

Our findings suggest future methodological and health research directions. Longitudinal investigations of the association between use of illicit drugs and adverse health outcomes among MSM are confounded by alcohol consumption. Future studies should consider our finding that prior illicit drug use also affects alcohol consumption. In cases such as this, statistical adjustment for alcohol consumption as a time-updated confounder may provide biased estimates of the effect of illicit drug use [189]. Therefore, methods that account for feedback of confounding covariates on exposures, such as marginal structural models [54, 159, 190] are needed to accurately assess the effect of behaviors on downstream health events, such as unprotected sexual intercourse that may lead to sexually transmitted infection or HIV acquisition.

Although the median alcohol consumption we observed over follow-up was moderate suggesting that most MSM consume alcohol at reasonable levels, the prevalence of heavy drinking even among older MSM, should encourage healthcare providers to engage MSM patients in discussions of drinking. Barriers to health care and substance abuse treatment exist for this vulnerable population [191]. Standards for culturally-competent alcohol treatment of MSM are needed that explicitly address the contributions of common recreational drugs to the level of alcohol consumption.

Tables

Table 4.1. Characteristics of 3,651 men who have sex with men, 3,651 baseline visits and 47,261 follow-up visits between1984 and 2007.

Characteristic	Baseline (*n* = 3,651) No.	Baseline (*n* = 3,651) %, IQR	Follow-up (visits = 47,261) No.	Follow-up (visits = 47,261) %, IQR
Age, median in years	33.0	28.0, 39.0	34.4	28.0, 39.0
Race/ethnicity:				
White non-Hispanic	3,003	82.3	41,863	88.6
White Hispanic	200	5.5	1,711	3.6
Black non-Hispanic	435	11.9	3,618	7.7
Black Hispanic	13	0.4	69	0.2
College graduate	2,158	59.1	31,363	66.4
City:				
Baltimore	1,000	27.4	13,769	29.1
Chicago	796	21.8	9,913	21.0
Los Angeles	888	24.3	11,707	24.8
Pittsburgh	967	26.5	11,872	25.1
Smoker, current[b]	1,528	41.9	13,361	28.3
Elevated depression symptoms[a,b]	664	18.2	8,091	17.1
Illicit drug use[b]:				
None	851	23.3	22,517	47.6
Marijuana/hash only	622	17.0	7,077	15.0
Poppers only	280	7.7	5,900	12.5
Cocaine/crack only	51	1.4	549	1.2
Marijuana/hash and poppers	948	26.0	6,008	12.7
Marijuana/hash and cocaine/crack	231	6.3	2,067	4.4
Poppers and cocaine/crack	18	0.5	290	0.6
All	650	17.8	2,853	6.0
Number of URAI partners [b]:				
0	1,636	44.81	36,406	77.0
1	917	25.12	7,801	16.5
≥ 2	1,098	30.07	3,054	6.5

Abbreviations: IQR, interquartile range; URAI, unprotected receptive anal intercourse.
[a]Center for Epidemiologic Studies Depression Scale (CES-D) >16
[b]At baseline visit, in the prior two years; at follow-up visits, in the prior 6-12 months.

Table 4.2. Report of any current drinking among 3,102 men who reported any drinking at the prior visit, 35,520 visits between 1984 and 2007.

	Drinking Reported	Visits	OR[a]	95% CL
Time-fixed				
Race:				
White	31,068	33,099	1.	
Black	2,114	2,421	0.49	0.37, 0.63
Education:				
Less than college graduate	10,672	11,564	1.	
College graduate	22,510	23,956	1.30	1.12, 1.51
Time-updated				
Smoking, current[b]				
No	23,164	24,825	1.	
Yes	10,018	10,695	1.03	0.89, 1.18
Elevated depression symptoms[b,c]				
No	27,995	29,849	1.	
Yes	5,187	5,671	0.75	0.66, 0.86
Illicit drug use[c]:				
None	12,852	14,078	1.	
Marijuana/hash only	5,681	6,035	1.67	1.43, 1.95
Poppers only	4,399	4682	1.39	1.15, 1.68
Cocaine/crack only	406	448	1.34	0.93, 1.92
Marijuana/hash and poppers	5,174	5404	2.16	1.77, 2.63
Marijuana/hash and cocaine/crack	1,812	1,906	2.27	1.75, 2.96
Poppers and cocaine/crack	240	259	1.27	0.70, 2.32
All	2,618	2,708	2.90	2.21, 3.80
Number of URAI partners[c]:				
0	24,768	26,637	1.	
1	5,983	6,320	1.18	1.02, 1.36
≥ 2	2,431	2,563	1.05	0.84, 1.30

Abbreviations: CL, confidence limits; OR, odds ratio; URAI, unprotected receptive anal intercourse.

[a]Adjusting for other variables in the table, study site, time since baseline (cubic spline), age at baseline (cubic spline) and date of baseline visit (cubic spline).

[b]Center for Epidemiologic Studies Depression Scale (CES-D) >16.

[c]In the prior 6-12 months.

Table 4.3. Report of any current drinking among 1,554 men who reported no drinking at the prior visit, 11,741 visits between 1984 and 2007.

	Drinking Reported	Visits	OR[a]	95% CL
Time-fixed				
Race:				
White	1,754	10,475	1.	
Black	248	1,266	1.37	1.00, 1.88
Education:				
Less than college graduate	749	4,334	1.	
College graduate	1,253	7,407	1.05	0.87, 1.26
Time-updated				
Smoking, current[c]				
No	1,484	9,075	1.	
Yes	518	2,666	1.03	0.85, 1.25
Elevated depression symptoms[b,c]				
No	1,609	9,321	1.	
Yes	393	2,420	0.88	0.75, 1.04
Illicit drug use[c]:				
None	1,173	8,439	1.	
Marijuana/hash only	280	1,042	2.27	1.84, 2.80
Poppers only	234	1,218	1.50	1.15, 1.97
Cocaine/crack only	35	101	3.52	2.19, 5.64
Marijuana/hash and poppers	167	604	2.37	1.77, 3.18
Marijuana/hash and cocaine/crack	57	161	3.30	2.24, 4.88
Poppers and cocaine/crack	9	31	2.75	1.17, 6.49
All	47	145	2.93	1.79, 4.78
Number of URAI partners[c]:				
0	1,632	9,769	1.	
1	276	1,481	1.06	0.88, 1.28
≥ 2	94	491	0.94	0.70, 1.27

Abbreviations: CL, confidence limits; OR, odds ratio; URAI, unprotected receptive anal intercourse.

[a]Adjusting for other variables in the table, study site, time since baseline (cubic spline), age at baseline (cubic spline) and date of baseline visit (cubic spline).

[b]Center for Epidemiologic Studies Depression Scale (CES-D) >16.

[c]In the prior 6-12 months.

Table 4.4. Number of drinks per week consumed by 2,644 current drinkers, 35,184 visits between 1984 and 2007.

	Visits	Median drinks/ week	IQR	Median Ratio [a]	95% CL
Time-fixed					
Race:					
White	32,822	5	2, 11	1.	
Black	2,362	5	2, 11	0.98	0.93, 1.02
Education:					
Less than college graduate	11,421	5	2, 11	1.	
College graduate	23,763	5	2, 11	0.98	0.96, 1.01
Time-updated					
Smoking, current [c]					
No	24,648	5	2, 8	1.	
Yes	10,536	5	2, 12	1.07	1.04, 1.09
Elevated depression symptoms[b,c]					
No	29,604	5	2, 11		
Yes	5,580	5	2, 11	1.01	0.98, 1.03
Illicit drug use[c]:					
None	14,025	5	2, 8	1.	
Marijuana/hash only	5,961	5	2, 11	1.06	1.03, 1.09
Poppers only	4,633	5	2, 11	1.06	1.03, 1.09
Cocaine/crack only	441	5	2, 13	1.16	1.09, 1.25
Marijuana/hash and poppers	5,341	5	2, 12	1.09	1.06, 1.12
Marijuana/hash and cocaine/crack	1,869	5	2, 12	1.10	1.06, 1.15
Poppers and cocaine/crack	249	8	5, 12	1.13	1.03, 1.23
All	2,665	8	5, 12	1.14	1.11, 1.18
Number of URAI partners[c]:					
0	26,400	5	2, 11	1.	
1	6,259	5	2, 11	0.99	0.98, 1.01
≥ 2	2,525	5	2, 12	0.99	0.95, 1.02

Abbreviations: CL, confidence limits; IQR, interquartile range; URAI, unprotected receptive anal intercourse.

[a]Adjusting for other variables in the table, study site, time since baseline (cubic spline), age at baseline (cubic spline), date of baseline visit (cubic spline), and alcohol consumption reported at the prior visit (cubic spline).

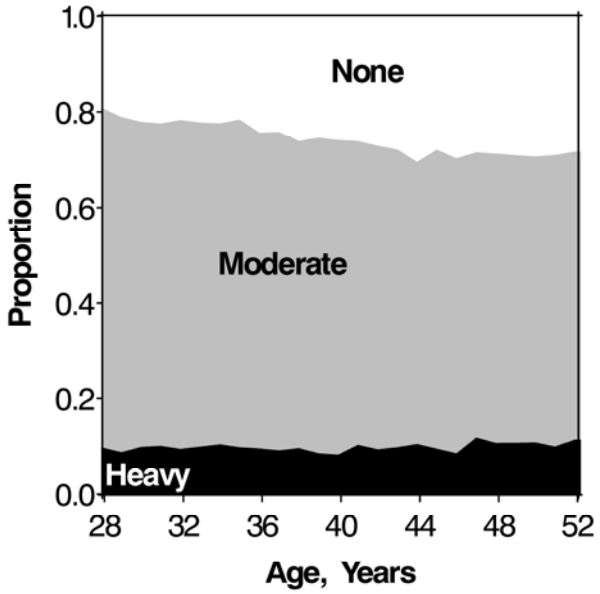
[b]Center for Epidemiologic Studies Depression Scale (CES-D) >16.

[c]In the prior 6-12 months.

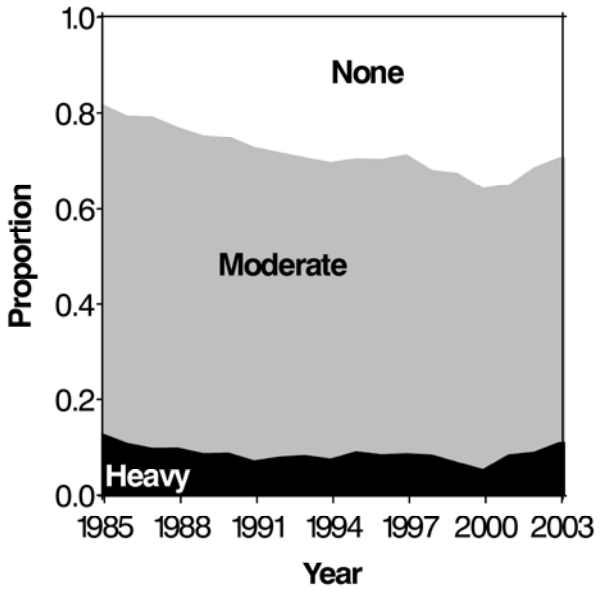
Figures

Figure 4.1. Plots showing the proportion of participants abstaining from alcohol, consuming alcohol at moderate levels (0-14 drinks/week) or at heavy levels (>14 drinks/week) by (A) participant age and (B) calendar time at baseline and over 47,261 follow-up visits by 3,651 men between 1984 and 2007.

A.



B.


1.0
0.8
0.6
0.4
0.2
0.0
Proportion
None
Moderate
Heavy
1985
1988
1991
1994
1997
2000
2003
Year

CHAPTER V

JOINT EFFECTS OF ALCOHOL CONSUMPTION AND HIGH-RISK SEXUAL BEHAVIOR ON HIV SEROCONVERSION AMONG MEN WHO HAVE SEX WITH MEN

Introduction

Men who have sex with men (MSM) remain disproportionately burdened by the HIV epidemic. In the United States, an estimated 25,000 to 37,000 MSM were newly infected with HIV in 2006 [15], primarily through receptive anal intercourse [12, 24, 192]. Alcohol consumption is common among MSM [170] and has been implicated as a risk factor for HIV infection [60]. However, existing epidemiologic evidence of an effect of alcohol consumption on HIV seroconversion has been mixed [53, 193] and therefore inconclusive for supporting population-level alcohol interventions as a strategy for HIV prevention [194].

In particular, recent studies using multiple time-updated measures of alcohol consumption and adjusting for potential time-updated confounders also provide mixed results with one [11] supporting an earlier finding of a harmful association [2] and two not supporting a harmful association [3, 9]. However, the standard statistical methods (e.g., regression, stratification) used in these recent studies may have failed to provide consistent estimates of the hypothesized detrimental effect of alcohol consumption because of inadequate control of time-updated confounders [54, 152]. Recent work among injection drug users suggests that adjustment for time-updated confounders (e.g., illicit drug use) may

block indirect effects of alcohol consumption mediated through such confounders and lead to biased effect estimates [195].

Here we applied marginal structural models to estimate the association between alcohol consumption and HIV seroconversion. Using this approach, we can account for measured time-updated confounders affected by prior alcohol consumption. We analyzed data from MSM at risk of HIV seroconversion using prospective data from the Multicenter AIDS Cohort Study (MACS) collected between 1984 and 2007. Specifically, we examined the joint effects of alcohol consumption and unprotected receptive anal intercourse on the risk of HIV seroconversion. We hypothesized that both high levels of alcohol consumption and unprotected receptive anal intercourse increase the hazard of HIV seroconversion, and that this joint effect is greater than multiplicative.

Materials and methods

Study Sample

The study sample consisted of a subset of participants enrolled in the MACS, an ongoing study of the natural history of HIV infection among MSM in the US metropolitan areas of Baltimore, Maryland/Washington DC; Chicago, Illinois; Los Angeles, California; and Pittsburgh, Pennsylvania [135]. Enrolled were 6,972 men: 5,622 in 1984-1992 and 1,350 in 2001. Of these 6,972 men, 4,029 were HIV-seronegative at their baseline visit and were therefore eligible for this study. We analyzed data on the 3,725 HIV-seronegative men who completed at least one follow-up visit.

Participants are followed semiannually at study visits that involve a physical examination, blood draws, and standardized questionnaires including the Center for

Epidemiologic Studies Depression (CES-D) scale [164]. The demographic and risk behavior portions of the questionnaire were interviewer administered initially and were converted to audio computer-assisted self-interview for newly enrolled participants beginning in October 2001 and at follow-up visits for all participants in October 2002. Institutional review boards approved protocols and written informed consent forms completed by all study participants. MACS design details and questionnaires are available at http://www.statepi.jhsph.edu/macs/macs.html.

Ascertainment of HIV seroconversion

Participants were followed from their baseline visit until HIV seroconversion, death, loss to follow-up, or administrative censoring. HIV status was determined from blood specimens tested by enzyme-linked immunosorbent assay and was confirmed by Western blot at each semiannual visit. The midpoint between dates of the last seronegative and the first seropositive test was taken as the estimated date of HIV seroconversion; when this date was more than one year after the last seronegative test date ($n = 33$), participants were classified as lost to follow-up. Follow-up practices in the MACS cohort have been described previously [137]. Briefly, death information was obtained from death certificates, the Social Security Death Index, the National Death Index, autopsy records, and other notification sources. We censored follow-up for participants who failed to attend study visits for more than one year at the minimum of: their date of death (if applicable), one year after their last visit, or 1 January 2008 (date of administrative censoring). All remaining seronegative participants seen after 1 January 2007 were administratively censored on 1 January 2008.

Assessment of alcohol consumption

The typical number of drinks per week consumed by each participant was calculated as the product of participant-reported average number of drinking-days per week and average number of drinks per drinking-day (range: 0-84 drinks/week). A drink was defined explicitly as one 12-ounce beer, one 4-5-ounce glass of wine, or one mixed drink with 1.5 ounces of 80-proof hard liquor. The few (<1%) reports of 10 or more drinks per drinking-day were classified as 12 drinks. In joint models, we considered three levels of drinking: nondrinkers, moderate drinkers (1-14 drinks/week), and heavy drinkers (>14 drinks/week) based on reports averaged over the prior two visits (approximately one year). This exposure window was chosen to maximize stability of the alcohol measurement. We considered the impact of this choice of exposure window on our results by considering a range of empirical induction periods (≥2 years prior) shown in Appendix 1.5.1. Trends were generally insensitive to the exposure window chosen although, as expected, the magnitude of the observed effect decreased as length of the exposure window increased.

Assessment of sexual risk behavior

The number of unprotected receptive anal intercourse partners (hereafter, partners) a participant reported was previously identified as a strong predictor of HIV seroconversion in the MACS [24, 192] and other cohorts [12]; we therefore consider this exposure a marker of overall sexual risk behavior. Participants self-report the number of partners they have had at each semiannual visit. The few (<1%) reports of more than six partners since the previous visit were reset to the median of those with more than six partners (10 partners). In joint models, we considered two levels of receptive anal intercourse: one or fewer partners and

multiple partners. Similar to alcohol measures, we averaged the number of partners over the previous two visits. The overall joint distribution of alcohol consumption and partner number is presented in Appendix 2.5.1 and by time in Appendix 1.5.2.

Assessment of covariates

Based on previously identified determinants of alcohol consumption [140, 196] and HIV risk factors [9], we considered several time-fixed and time-updated covariates as confounders. The following variables were assessed at baseline: participant's race and ethnicity (white non-Hispanic, white Hispanic, or black), age, enrollment city, and education (college graduate or not). Data on time-updated confounders were recorded at each semiannual visit and included depressive symptoms indicated by a CES-D score >16; self-report of either gonorrhea or Chlamydial infection; cigarette smoking (current or not); and use of any of the following illicit drugs: cocaine, crack cocaine, marijuana/hash, or nitrite inhalants (i.e., poppers). Injection drug use was uncommon (<1%) as was methamphetamine use (4%), which furthermore was not captured consistently over follow-up. Just 7% of the cohort reported use of any other drugs, including heroin. We therefore considered these three most common illicit drugs categories as confounders.

Baseline data on smoking, CES-D score and number of partners were missing for 6%, 6%, and 7% of participants, respectively. Data on all other variables were missing for <2% of participants. For values missing at baseline, we imputed the mode. For missing values over follow-up, the value from the previous visit was carried forward (smoking, 6%; CES-D score, 8%; number of partners, 9%; all others, <4%).

Statistical Analysis

We used a marginal structural Cox proportional hazards model to estimate the joint effects of alcohol consumption and partner number on HIV seroconversion [156]. The joint marginal structural model provides asymptotically consistent estimates of contrasts in potential outcomes under the assumptions of consistency, exchangeability, positivity, and correct model specification for each exposure and censoring.

Inverse probability of exposure weights for all models were constructed to account for confounding as the product of the inverse probability of each participant's observed alcohol consumption and the inverse probability of his observed number of partners estimated as a function of his history of measured time-updated predictors. Exposure weights were calculated from a pair of cumulative pooled logistic regression models [155]: each accounted for the following time-updated confounders, lagged one visit: elevated depression symptoms, smoking status, use of illicit drugs and self-reported sexually transmitted infection. In addition, the weight model for partner number also included concurrent alcohol consumption. These weights were stabilized to improve precision by alcohol consumption history (product terms between alcohol consumption at 6, 12, and 18 months prior and restricted cubic splines with knots at the 5^{th}, 27.5^{th}, 50^{th}, 72.5^{th} and 95^{th} percentiles for consumption at those time points), partner history (product terms between partner number at 6, 12 and 18 months prior), and time-fixed covariates measured at baseline [148]. To reduce the potential impact of informative censoring, inverse probability of dropout and death weights were calculated similarly using separate pooled logistic models and those weights were combined with the exposure weights by multiplication. The final weights had a mean of 1.00 (standard deviation, 0.26) with a range of 0.10-7.56 (Appendix 2.5.2).

This final joint marginal structural Cox proportional hazards model for HIV seroconversion included as regressors alcohol consumption averaged over the prior year (categorized as none, moderate, or heavy), number of receptive anal intercourse partners averaged over the prior year (categorized as ≤ 1 or >1), and their product terms. All models also included a restricted cubic spline representing time since baseline, with knots at the percentiles described above, as well as baseline variables race, ethnicity, college graduation, study site and age (modeled as a restricted cubic spline; described above). Cumulative incidence of HIV seroconversion curves are presented in the weighted population [197]. Effects were quantified using hazard ratios (HRs), and precision was assessed through 95% confidence limits (CL) based on robust variances. Departure from additivity was assessed using the relative excess risk due to interaction (RERI) [160]. We evaluated the contribution of the product term using a joint robust Wald χ^2 test. No evidence of departure from proportional hazards for the joint effect was observed in models that included exposure by time ($P = 0.86$) or exposure by log-time ($P = 0.70$) product terms.

Alongside our weighted results, we present observed counts of HIV seroconversions and corresponding incidence rates calculated as number of HIV seroconversions divided by the number of person years of observation. We also present results from standard analyses, which adjust for time-updated confounders by including lagged values of time-updated covariates in a standard Cox model [162]. All analyses were conducted with SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina).

Results

Between 1984 and 2007, 3,725 men were followed for a median of 10.5 years (interquartile range (IQR): 4.7-11.7), during which 529 HIV seroconversions were observed. Eighty-three (2%) participants died during follow-up, 311 (8%) were lost to follow-up, and 2,802 (75%) were administratively censored.

Participants were mostly white non-Hispanic (82%) and college educated (59%) (Table 5.1). At baseline, members of this sexually active population reported a median of 1 (IQR: 0-2) partner in the prior two years. Illicit drug use was common (77%), as was smoking (51%) and most participants consumed alcohol (9% nondrinkers) but at a generally moderate level: median 8 drinks/week (IQR: 2-16). Over follow-up, HIV risk behaviors were less prevalent: 78% of participants reported no partners; illicit drug use was reported by 48% of participants, and median alcohol consumption was 4 drinks/week (IQR: 2-12), each measured in the prior six months (Appendix 1.5.3).

Reports of heavy drinking were most common from white non-Hispanics (92%), illicit drug users (73%), and men reporting multiple partners (13%) (Appendix 1.5.4). Men reporting 0-1 or >1 partner on average over the prior year experienced crude HIV incidence rates of 9 (95% CL: 8, 10) and 76 (95% CL: 66, 86) cases per 1,000 person-years, respectively. Figure 5.1A depicts this cumulative incidence for these two groups in the weighted population. For nondrinkers, moderate drinkers and heavy drinkers over the prior year the crude incidence of HIV seroconversion were 10 (95% CL: 7, 13), 13 (95% CL: 12, 15), and 26 (95% CL: 22, 31) cases per 1,000 person-years, respectively (Table 5.2). Heavy drinkers were most likely to HIV seroconvert over follow-up in the weighted population (χ^2 Wald trend test P = 0.0057) (Figure 5.1B).

Table 5.2 presents the effects of alcohol consumption on HIV seroconversion from models that average over partner effects. In unadjusted, adjusted, and weighted models, the hazard for moderate drinkers was similar to that for nondrinkers, whereas the hazard for heavy drinkers was elevated. Compared to the unadjusted HR for heavy drinkers of 1.52 (95% CL: 1.07, 2.16), adjustment for age, race, ethnicity, study site, depression symptoms, college graduation, smoking, illicit drug use, number of partners, and sexually transmitted infection using standard methods produced an attenuated HR of 1.19 (95% CL: 0.83, 1.70). After accounting for the same variables using marginal structural models, the hazard of HIV seroconversion for heavy drinkers in the past year was 1.61 (95% CL: 1.12, 2.29) times that of nondrinkers.

Table 5.4 presents the joint effects of alcohol consumption and partners in the prior year from models that include a product term. We represent these joint effects in two ways: (1) by examining the effect of alcohol consumption within strata of partners; and (2) by presenting HRs relative to a common referent: nondrinkers without multiple partners. In the weighted model, the association between heavy drinking and HIV seroconversion appeared stronger among men with multiple partners (HR = 1.96; 95% CL: 1.03, 3.72) versus without (HR = 1.37; 95% CL: 0.88, 2.16), although this difference was imprecise (P = 0.42) (Table 5.4). The observed HR for moderate drinkers with multiple partners compared to nondrinkers without multiple partners (HR = 4.48) was similar to those expected under a multiplicative model ($HR_{expected} = 4.04$). The observed HR for heavy drinkers with multiple partners compared to nondrinkers without multiple partners was larger than expected under a multiplicative model: HR = 7.40 and $HR_{expected} = 5.18$, although this departure was imprecise (Table 5.4). With respect to interaction on the additive scale, the RERI suggests departure

from additivity for heavy drinkers with multiple partners (RERI = 3.25; 95% CL: 0.32, 6.17) but not moderate drinkers with multiple partners (RERI = 0.63; 95% CL: -1.81, 3.07).

Again, compared to results from the standard Cox model, results from the weighted model suggested a stronger effect. For example, when heavy drinkers with multiple partners were compared to nondrinkers without multiple partners, the HR from the marginal structural model was 7.40 (95% CL: 4.74, 11.54) and the analogous HR from the standard adjusted model was 4.97 (95% CL: 3.18, 7.77) (Table 5.4). Similar to the weighted analysis, no statistically significant evidence was found for greater-than-multiplicative interaction in the standard analysis (P = 0.28) (Table 5.4).

Discussion

We reported the effect of alcohol consumption and risky sexual behavior on HIV seroconversion in prospective data on 3,725 MSM followed in 1984-2007. Heavy alcohol consumption was associated with 1.61 times the hazard of HIV seroconversion compared to no consumption. We furthermore presented results from models that use traditional adjustment approaches alongside results from weighted models showing that traditional approaches appeared to produce attenuated estimates. Without results from the weighted models, we might have erroneously concluded that there was no independent association between alcohol consumption and HIV seroconversion.

The unadjusted HR of 1.52 we reported for heavy alcohol consumption versus nondrinking is similar to unadjusted HRs reported in previous studies of MSM populations [1-3, 9, 11, 12]. We reported an attenuated HR of 1.19 when adjusted for time-updated confounders using traditional adjustment. This attenuation mirrors that reported by the San

Francisco Men's Health Study [3] and in an earlier report of MACS data [9]. The latter study reported an unadjusted HR of 2.05 (95% CL: 1.53, 2.74) for heavy versus less-than-heavy drinking but an HR of 1.13 (95% CL: 0.81, 1.56) after adjustment for time-updated confounders. A statistically significant adjusted association between heavy alcohol consumption and HIV seroconversion persisted in only the EXPLORE cohort (HR= 1.97; 95% CL: 1.32, 2.96) [11]. Our findings and the majority of previous studies suggest that standard adjustment removes part of the indirect effect of alcohol consumption mediated through other time-updated HIV risk factors for which authors have previously adjusted (e.g., illicit drug use).

Changes in behaviors and expectancy that accompany alcohol consumption may be responsible for increased sexual risk behaviors and for subsequent HIV seroconversion observed among heavy drinkers [91, 101]. Alcohol consumption is associated with higher numbers of sexual partners, higher numbers of unprotected anal sex acts, and condom failure [84, 86]. Acute alcohol consumption has also been linked to suppression of both the innate and adaptive immune response and increased susceptibility to numerous infections, including HIV [101, 115, 198, 199].

A limitation of the present data is collection of alcohol consumption measures that require recall over a 6-month period. As researchers have stated previously, global measures of alcohol consumption do not allow investigation of specific contextual modifiers of the relationships between alcohol consumption and sexual risk behaviors such as partner type and partner's alcohol consumption [47, 60, 200]. These contextual factors in turn may explain why we did not see a dramatic departure from multiplicative combination between the effects of alcohol consumption and sexual risk behavior. For example, researchers have

found that MSM are more likely to use condoms with casual partners while drinking but less likely to use condoms with steady partners in the same setting [72, 87, 88].

Self-reported alcohol consumption may also be an inadequate proxy for alcohol-induced responses. The behavioral and physiologic effects of alcohol are person-specific, dependent on genetic background, body mass composition and diet. Future research applying biomarkers of alcohol consumption to evaluate the reliability or accuracy of self-report data is needed in studies of sexual health.

As with any analysis, the validity of our inferences is limited by the degree to which we met our assumptions. First, we assumed no unmeasured confounding and no informative censoring due to unmeasured factors. However, there are likely unmeasured behavioral factors confounding the observed association. Moreover, we acknowledge that measurement of the confounders we included is imperfect (e.g., self-reported as opposed to directly assessed sexually transmitted infections). Second, we assumed that heavy drinkers who seroconverted during the study period are representative of those who seroconverted prior to study entry. Men who seroconverted prior to study entry may have engaged in more concomitant high-risk behaviors than those whose seroconversion was observed, leading us to observe a weaker association between alcohol consumption and HIV seroconversion. Third, we assumed that mode of exposure is irrelevant to the observed outcome [149]. However, the behavioral mechanisms described above suggest that ignoring type of alcohol consumed and timing of its consumption with respect to HIV exposure may not be reasonable and may limit our ability to prescribe generalizable interventions based on our findings. Nevertheless, the demonstrable effect of alcohol consumption, measured broadly, is

valuable in that it supports research to identify the particular means of exposure relevant for interventions.

This study has several important strengths. First, it used information from a large prospective cohort of sexually active MSM followed for over 2 decades. Second, a large number of HIV seroconversions were observed, including a sizable portion among men previously reporting heavy drinking. Finally, using state-of-the-art quantitative methods, this study more fully captures the direct and indirect effects of alcohol consumption on HIV seroconversion-- specifically, both the direct effect of alcohol on HIV susceptibility and the indirect effects mediated through HIV risk behaviors, such as illicit drug use that are also affected by prior alcohol consumption.

The potential for linking alcohol interventions with HIV prevention activities was described more than a decade ago [201], and randomized interventions that explicitly address alcohol's contribution to HIV have been tested in Africa [131, 132, 202]. However, such interventions have lagged behind for US adult MSM [200]. We have reported an effect of alcohol consumption on HIV seroconversion among MSM of similar magnitude to illicit drugs such as methamphetamine, cocaine, and ecstasy [9]. Under the above-stated assumptions, our results support the conclusion that 16% of HIV seroconversions among heavy drinkers could be prevented if half of these drinkers reduced their drinking to moderate levels; 21% could be prevented if two-thirds reduced their drinking to moderate levels [163]. If replicated, our findings renew the call for population-level HIV interventions among US MSM that explicitly address heavy alcohol consumption.

Tables

Table 5.1. Enrollment characteristics of 529 Multicenter AIDS Cohort Study HIV seroconverters and 3,196 HIV-seronegative participants

Characteristic	Seroconverters (*n* = 529)		Seronegative Participants (*n* = 3,196)		Total (*n* = 3,725)	
	n	%	n	%	n	%
Median age at baseline in years (IQR)	30.8 (26.3, 36.4)		33.7 (28.4, 40.0)		33.4 (28.0, 39.6)	
Race/ethnicity:						
White non-Hispanic	440	83.2	2,623	82.1	3,063	82.2
White Hispanic	38	7.2	166	5.2	204	5.5
Black	51	9.6	407	12.7	458	12.3
College graduate	274	51.8	1921	60.1	2195	58.9
US city:						
Baltimore, Maryland	134	25.3	882	27.6	1,016	27.3
Chicago, Illinois	123	23.3	687	21.5	810	21.7
Los Angeles, California	118	22.3	874	27.3	992	26.6
Pittsburgh, Pennsylvania	154	29.1	753	23.6	907	24.3
Median alcohol consumption[a] in drinks/week (IQR)	8 (4, 16)		8 (2, 14)		8 (2, 16)	
0	29	5.5	286	8.9	315	8.5
1-14	327	61.8	2,119	66.3	2,446	65.7
>14	173	32.7	791	24.7	964	25.9
Smoker[a]	292	55.2	1591	49.8	1883	50.6
Depressive symptoms[a,b]	88	16.6	588	18.4	676	18.1
Illicit drug use[a,c]	466	88.1	2,387	74.7	2,853	76.6
Number of URAI partners[a]						
0 -1	225	42.5	2,380	74.5	2,605	69.9
>1	304	57.5	816	25.5	1,120	30.1
Sexually transmitted infections[a,d]	63	11.9	215	6.7	278	7.5

Abbreviations: IQR, interquartile range; URAI, unprotected receptive anal intercourse.
[a] Prior two years.
[b] Center for Epidemiologic Studies Depressions (CES-D) >16.
[c] Marijuana/hash, cocaine/crack cocaine, or poppers.
[d] Chlamydia or gonorrhea.

Table 5.2. Effect of alcohol consumption[a] on HIV seroconversion among 3,725 men in the Multicenter AIDS Cohort Study between 1984 and 2007.

			Unadjusted		Adjusted[b]		Weighted[c]	
	Number of Seroconversions	PY	HR	95% CL	HR	95% CL	HR	95% CL
Nondrinker	40	4,062.98	1.		1.		1.	
Moderate Drinker	340	26,084.75	1.11	0.80, 1.54	0.91	0.65, 1.27	1.10	0.78, 1.54
Heavy Drinker	149	5,722.04	1.52	1.07, 2.16	1.19	0.83, 1.70	1.61	1.12, 2.29

Abbreviations: CL, confidence limits; HR, hazard ratio; PY, person-years.

[a] Alcohol consumption in the prior year: nondrinker (0 drinks/week), moderate drinker (0-14 drinks/week), heavy drinker (>14 drinks/week).

[b] Cox proportional hazards model adjusted for baseline (age (spline), race, ethnicity, education) covariates and time-updated (illicit drug use, cigarette smoking, depression, sexually transmitted infection, and multiple unprotected receptive anal intercourse partners) covariates lagged one visit.

[c] Cox proportional hazards model weighted to account for confounding and selection bias by time-updated covariates lagged one visit and adjusted for baseline covariates

Table 5.3. Effects of alcohol consumption[a] and risky sexual behavior in the prior year on HIV seroconversion among 3,725 men in the Multicenter AIDS Cohort Study between 1984 and 2007.

	≤ 1 URAI Partner		>1 URAI Partner				
	HR[b]	95% CL	HR[b]	95% CL	HR[c]	95% CL	P-value[d]
Unadjusted							0.50
Nondrinker	1.		4.12	2.04, 8.32	1.		
Moderate drinker	1.07	0.73, 1.58	5.04	3.33, 7.63	1.22	0.66, 2.27	
Heavy drinker	1.31	0.84, 2.05	7.62	4.97, 11.70	1.85	0.99, 3.46	
Adjusted[e]							0.28
Nondrinker	1.		3.21	1.57, 6.60	1.		
Moderate drinker	0.86	0.58, 1.28	3.31	2.15, 5.10	1.03	0.55, 1.94	
Heavy drinker	0.97	0.61, 1.52	4.97	3.18, 7.77	1.55	0.81, 2.94	
Weighted[f]							0.42
Nondrinker	1.		3.78	1.82, 7.82	1.		
Moderate drinker	1.07	0.72, 1.59	4.48	2.91, 6.88	1.19	0.63, 2.24	
Heavy drinker	1.37	0.88, 2.16	7.40	4.74, 11.54	1.96	1.03, 3.72	

Abbreviations: CL, confidence limits; HR, hazard ratio; URAI, unprotected receptive anal intercourse.

[a] Alcohol consumption in the prior year: nondrinker (0 drinks/week), moderate drinker (0-14 drinks/week), heavy drinker (>14 drinks/week).

[b] Nondrinkers with ≤ 1 URAI partner as referent.

[c] Nondrinkers with >1 URAI partner as referent.

[d] Joint robust Wald χ^2 test.

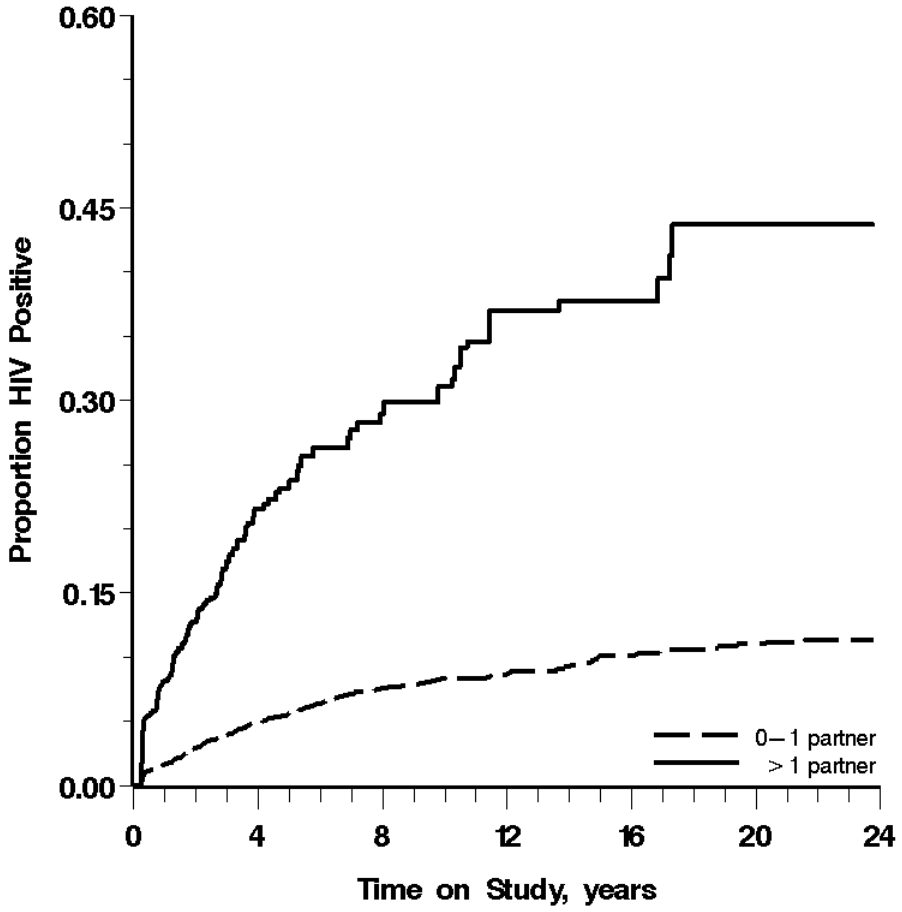
[e] Adjusted for baseline (age (spline), race, ethnicity, education) covariates and time-updated (illicit drug use, cigarette smoking, depression, sexually transmitted infection) covariates lagged one visit.

[f] Weighted to account for time-updated covariates lagged one visit and adjusted for baseline covariates.

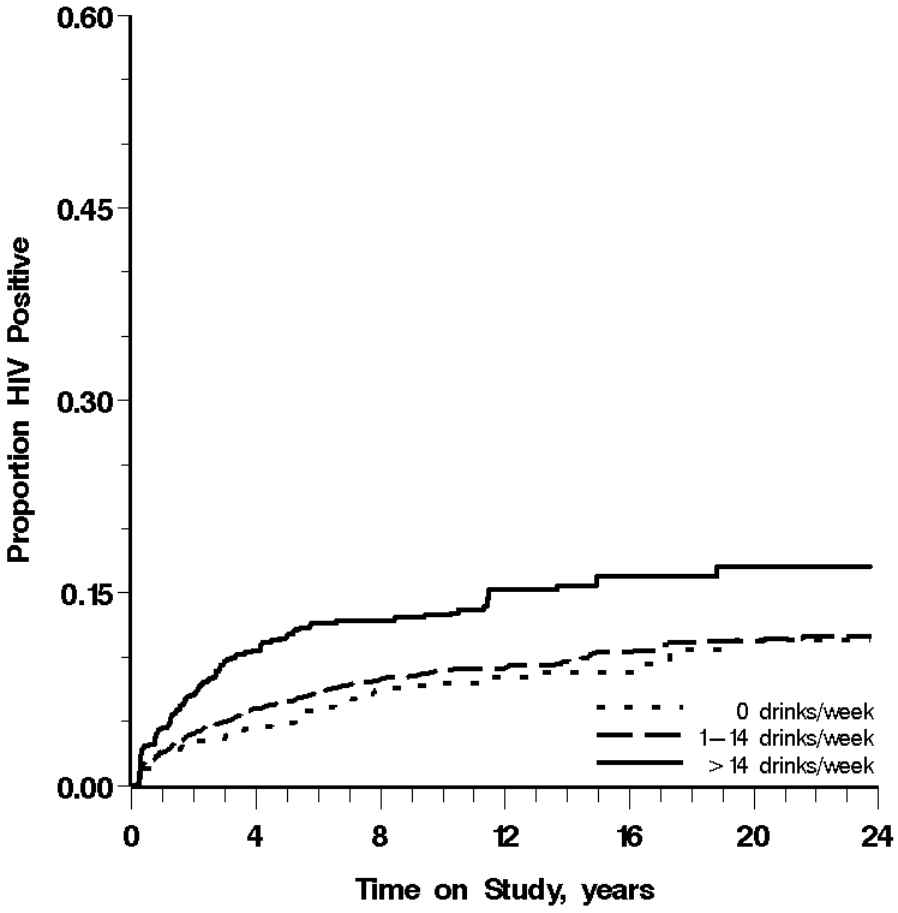
Figures

Figure 5.1. Cumulative incidence of HIV seroconversion between 1984 and 2007 among 3,725 men who have sex with men, stratified by (A) the number of sexual partners with whom the participant was the receptive anal intercourse partner and (B) alcohol consumption, in the prior year.

A.



B.


0.60
0.45
0.30
0.15
0.00
Proportion HIV Positive
0
4
8
12
16
20
24
Time on Study, years
0 drinks/week
1–14 drinks/week
> 14 drinks/week

CHAPTER VI

CONCLUSIONS

Summary

In this dissertation, we have implemented methods to obtain estimates of the effect of alcohol consumption on HIV seroconversion among MSM. Alcohol consumption patterns in the MACS were detailed, showing that the proportion of the population that consumed alcohol varied from 82% at enrollment to 64% at its nadir over follow-up. Illicit drug use predicted higher levels of subsequent alcohol consumption. We applied an understanding of the time-varying predictors of alcohol consumption to an inverse probability of exposure weighted marginal structural model to estimate the effect of alcohol consumption on HIV seroconversion and found that heavy alcohol consumption (>14 drinks/week) was associated with 1.61 (95% CL: 1.12, 2.29) times the hazard of HIV seroconversion compared to no consumption after accounting for measured confounders. This effect is similar to the pooled relative risk of 1.77 (95% CL l: 1.43, 2.19) observed in a recent meta-analysis of alcohol consumption and HIV seroconversion that did not account for time-varying confounding [193].

The MACS is the largest and longest-running prospective cohort of adult MSM in the US. We observed a large number of HIV seroconversions including a sizable portion among men previously reporting heavy drinking. A strength of this study that it is the first work to

present longitudinal predictors of alcohol consumption among adult MSM over multiple visits. We improve upon previous methodologies by intentionally lagging time-updated predictor variables and alcohol outcomes. Our examination of alcohol consumption, unprotected receptive anal intercourse and HIV seroconversion is also novel in that it applied state-of-the-art quantitative methods that explicitly address the potential interaction between alcohol consumption and high risk sexual behavior.

Limitations

The MACS was not intended to be a nationally representative sample of MSM by design, nor was it fully representative of MSM in the metropolitan areas from which participants were recruited [135]. Compared to the general population, men in the MACS are disproportionately well-educated, financially secure and of white non-Hispanic. We have speculated that younger, non-urban, and economically disadvantaged MSM may not have decreased risk behaviors as a result of the HIV epidemic in the same ways MACS enrollees in the mid-1980s appear to have done. While white men continue to make up the majority of new HIV infections among MSM in the US, they are rapidly being outnumbered by men of color [16]. Lack of representation in the MACS may have implications for the results of our second aim if the circumstances of alcohol consumption or the susceptibility to the alcohol-induced effects on HIV seroconversion are different for members of underrepresented subgroups. Additionally, we can only generalize with caution to populations with vastly different alcohol consumption profiles or where the underlying distribution of unmeasured confounders differs. Therefore ongoing study of alcohol consumption by minority and younger MSM is needed to inform interventions for these groups; cohorts that represent

younger, non-urban and minority MSM should be queried to see if the associations we report can be replicated in these populations.

As in prior studies, the alcohol consumption reported by study participants was not verified. The potential impact of this measurement error has been discussed in the preceding chapters. More work is needed in developing and applying biomarkers of alcohol consumption useful for research as opposed to clinical purposes. We viewed with optimism the recent application of carbohydrate-deficient transferrin to validate sustained heavy drinking among HIV seroconverters in Uganda [203] and anticipate more HIV cohorts will include alcohol biomarker as part of routine testing.

No examination of how participant-specific genetic, neurocognitive, and metabolic factors may influence alcohol expectancies, consumption or subsequent risk behaviors could be addressed in the current work. These will certainly have implication for future alcohol interventions and must be considered.

Implications

Improving the health, safety, and well-being of lesbian, gay, bisexual, and transgender individuals is among the US government's health goals of the current decade [204]. Priority areas for MSM include curbing HIV transmission and addressing disparities in alcohol consumption in this subpopulation, both points addressed by this dissertation. Our findings support alcohol intervention for MSM who use illicit substances and, along with previous findings, suggest that interventions which explicitly address alcohol consumption should be developed as HIV primary prevention methods.

Challenges exist to moving alcohol interventions forward. Alcohol consumption is socially accepted and central to the identities of many MSM. With the exceptions of driving penalties and alcohol taxes, top-down population-level approaches to reducing alcohol consumption are also limited. Nevertheless, the magnitude of the reported findings support primary prevention approaches focused at reducing heavy alcohol consumption of the same scale as those directed against illicit drugs. Approaches to reducing alcohol consumptions should include developing, piloting, and promoting culturally-competent alcohol treatment programs for heavy drinkers, particularly those with comorbid substance abuse, who require medical support. Furthermore, improvements to existing community-based alcohol interventions should also be considered, so that they incorporate messages that encourage MSM to moderate their drinking.

Future studies

When we applied marginal structural models to examine the independent association between alcohol consumption and HIV seroconversion, we found an effect that was not apparent under standard adjustment. Therefore such analysis should be replicated in other HIV risk groups including longitudinal cohorts in sub-Saharan Africa, where alcohol interventions are already underway and HIV is more prevalent. Our results also suggest that other associations for which there have been limited or contradictory results so far and where time-varying confounders affected by prior exposure are a concern should be re-examined using this methodology. Future studies should reconsider the associations between alcohol consumption and unprotected receptive anal intercourse and non-HIV sexually transmitted infections [45, 49].

Next steps for characterizing the effect of alcohol consumption on HIV seroconversion include effect decomposition approaches using marginal structural models [205]. Under specific conditions, the effect of alcohol consumption mediated through identifiable pathways can be estimated. These approaches may support the existence of immune-modulated pathways suggested by laboratory studies.

Finally, more research is needed on the effect of alcohol on the natural history of HIV infection following seroconversion. In particular, research on the extent to which alcohol consumption influences adherence to antiretroviral medication and secondary prevention (i.e., long-term immunologic and virologic outcomes). Recent findings that early treatment of HIV provides protection to HIV seronegative partners [206], suggests that research into factors that impede early treatment-seeking and long-term adherence are needed.

APPENDICES

Appendix 1. Additional tables

Appendix 1.5.1. Comparison of empirical induction periods.

Length of Exposure Window, Years	1		1.5		2	
	HR	95% CL	HR	95% CL	HR	95% CL
Overall						
Nondrinker	1.		1.		1.	
Moderate drinker	1.10	0.78, 1.54	1.06	0.75, 1.49	1.02	0.72, 1.44
Heavy drinker	1.61	1.12, 2.29	1.56	1.08, 2.23	1.44	1.00, 2.08
>1 URAI partner						
Nondrinker	1.		1.		1.	
Moderate drinker	1.19	0.63, 2.24	1.23	0.63, 2.39	1.12	0.60, 2.10
Heavy drinker	1.96	1.03, 3.72	1.90	0.97, 3.70	1.67	0.88, 3.16
0-1 URAI partner						
Nondrinker	1.		1.		1.	
Moderate drinker	1.07	0.72, 1.59	0.99	0.66, 1.49	0.97	0.64, 1.49
Heavy drinker	1.37	0.88, 2.16	1.39	0.89, 2.18	1.30	0.82, 2.07

Abbreviations: CL, confidence limits; HR, hazard ratio; URAI, unprotected receptive anal intercourse.

Appendix 1.5.2. Distribution of alcohol consumption and risky sexual behavior by time-on-study over 57,651 follow-up visits by 3,725 men between 1984 and 2007.

		>1 URAI Partner, %			0-1 URAI Partner, %		
Year	n	None	Moderate	Heavy	None	Moderate	Heavy
0	3,725	7.95	15.47	1.97	51.66	7.04	15.92
1	3,210	2.22	5.18	0.81	65.69	10.74	15.38
2	2,934	1.13	2.7	0.23	69.82	11.62	14.49
3	2,725	0.77	1.84	0.21	70.35	12.95	13.88
4	2,530	0.49	1.43	0.31	70.17	12.93	14.67
5	2,177	0.51	0.99	0.3	69.79	13.59	14.83
6	2,032	0.72	1.35	0.24	68.8	15.84	13.06
7	1,965	0.33	1.14	0.28	69.24	15.06	13.95
8	1,903	0.35	1.03	0.15	68.03	16.24	14.2
9	1,836	0.3	0.7	0.33	70.56	15.51	12.61
10	2,235	0.36	1.16	0.04	68.05	17.41	12.98
11	1,494	0.62	1.33	0	66.67	18.66	12.72
12	624	0.89	1.58	0	69.33	16.96	11.24
13	417	0.53	3.48	0.67	65.37	17.38	12.57
14	390	0.14	3.01	1	68.05	15.76	12.03
15	362	0.3	3.35	0.91	67.99	16.16	11.28
16	367	0.45	3.33	0.91	64.75	18.31	12.25
17	439	0	4.76	0.54	68.3	15.92	10.48
18	418	0.82	4.12	1.23	64.06	15.23	14.54
19	378	0.94	3.94	1.57	63.94	16.38	13.23
20	320	0.9	4.32	1.08	67.63	16.37	9.71
21	260	0.64	5.75	0.64	64.89	18.51	9.57
22	200	1.75	5.26	1.17	65.79	13.74	12.28
23	37	0	8.11	0	64.87	13.51	13.51

Abbreviation: URAI, unprotected receptive anal intercourse.

Appendix 1.5.3. Characteristics of 529 Multicenter AIDS Cohort Study HIV seroconverters and 3,196 HIV-seronegative participants studied over 57,651 follow-up visits.

	Seroconverter (3,192 visits)		Seronegative (54,459 visits)		Total (57,651 visits)	
Characteristic:	n	%	n	%	n	%
Median age at baseline, in years (IQR)	30.2 (26.3, 36.4)		33.8 (28.8, 39.7)		33.6 (28.7, 39.5)	
Race/ethnicity						
White non-Hispanic	2,715	85.1	48,304	88.7	51,019	88.5
White Hispanic	249	7.8	4,179	7.5	4,428	7.7
Black	228	7.1	1,976	3.6	2,204	3.8
College graduate	1,804	56.5	35,698	65.6	37,502	65.1
US City						
Baltimore, Maryland	750	23.5	14,934	27.4	15,684	27.2
Chicago, Illinois	708	22.2	10,976	20.2	11,684	20.3
Los Angeles, California	1,052	33.0	14,702	27.0	15,754	27.3
Pittsburgh, Pennsylvania	682	21.4	13,847	25.4	14,529	25.2
Median alcohol consumption[a], in drinks/week	8 (2, 14)		4 (2, 12)		4 (2, 12)	
0	352	11.0	7,638	14.0	7,990	13.9
1-14	2,144	67.2	38,402	70.5	40,546	70.3
>14	696	21.8	8,419	15.5	9,115	15.8
Smoker, ever	1,845	57.8	26,466	48.6	28,311	49.1
Depressive symptoms[a]	397	12.4	9,393	17.2	9,790	17.0
Illicit drug use[a,c]	1,990	62.3	25,714	47.2	27,704	48.1

	Seroconverter (3,192 visits)		Seronegative (54,459 visits)		Total (57,651 visits)	
Characteristic:	n	%	n	%	n	%
Number of URAI partners[a]:						
0	1,978	62.0	42,761	78.5	44,739	77.6
1	640	20.1	8,939	16.4	9,579	16.6
>1	574	18.0	2,759	5.1	3,333	5.8
Sexually transmitted infections[a,d]	201	6.3	1,533	2.8	1,733	3.0

Abbreviations: IQR, interquartile range; URAI, unprotected receptive anal intercourse.

[a] Prior six months.

[b] Center for Epidemiologic Studies Depression scale (CES-D) >16.

[c] Marijuana/hash, cocaine/crack cocaine or poppers.

[d] Chlamydia or gonorrhea.

Appendix 1.5.4. Characteristics of Multicenter AIDS Cohort Study participants stratified by alcohol consumption reported over 57,651 follow-up visits.

	0 drinks/week (7,990 visits)		1-14 drinks/week (40,546 visits)		>14 drinks/week (9,115 visits)	
Characteristic:	n	%	n	%	n	%
Median age at baseline, in years (IQR)	35.6 (30.1, 40.8)		33.4 (28.4, 39.1)		33.9 (28.5, 39.7)	
Race/ethnicity:						
White non-Hispanic	6,783	84.9	35,921	88.6	8,315	91.2
White Hispanic	324	4.1	1,647	4.1	233	2.6
Black	883	11.1	2,978	7.3	567	6.2
College graduate	4,662	58.3	27,407	67.6	5,433	59.6
Smoker, ever	4,751	59.5	17,931	44.2	5,629	61.8
Depressive symptoms[a]	1,863	23.3	6,966	17.2	1,637	18.0
Illicit drug use[a,c]	2,094	26.2	21,817	53.8	6,646	72.9
Number of URAI partners[a]:						
0	6,552	82.0	29,932	73.8	6,202	68.0
1	1,012	12.7	7,733	19.1	1,767	19.4
>1	426	5.3	2,881	7.1	1,146	12.6
Sexually transmitted infections[a,d]	203	2.5	1,216	3.0	315	3.5

Abbreviations: IQR, interquartile range; URAI, unprotected receptive anal intercourse.

[a] Prior six months

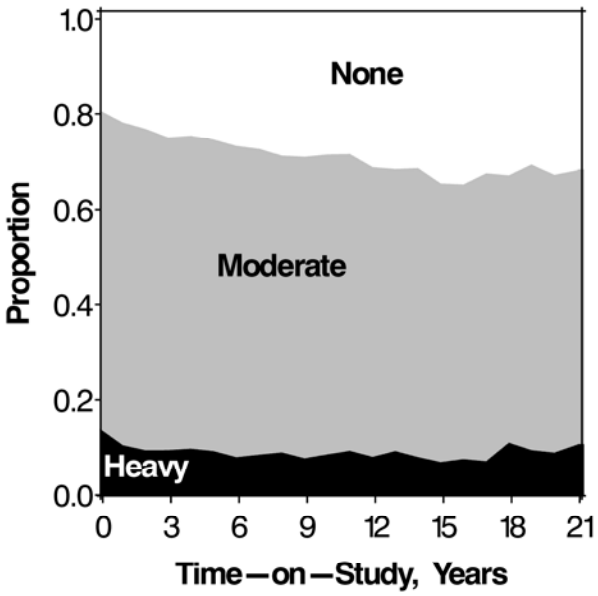
[b] Center for Epidemiologic Studies Depression Scale (CES-D) >16

[c] Marijuana/hash, cocaine/crack cocaine or poppers

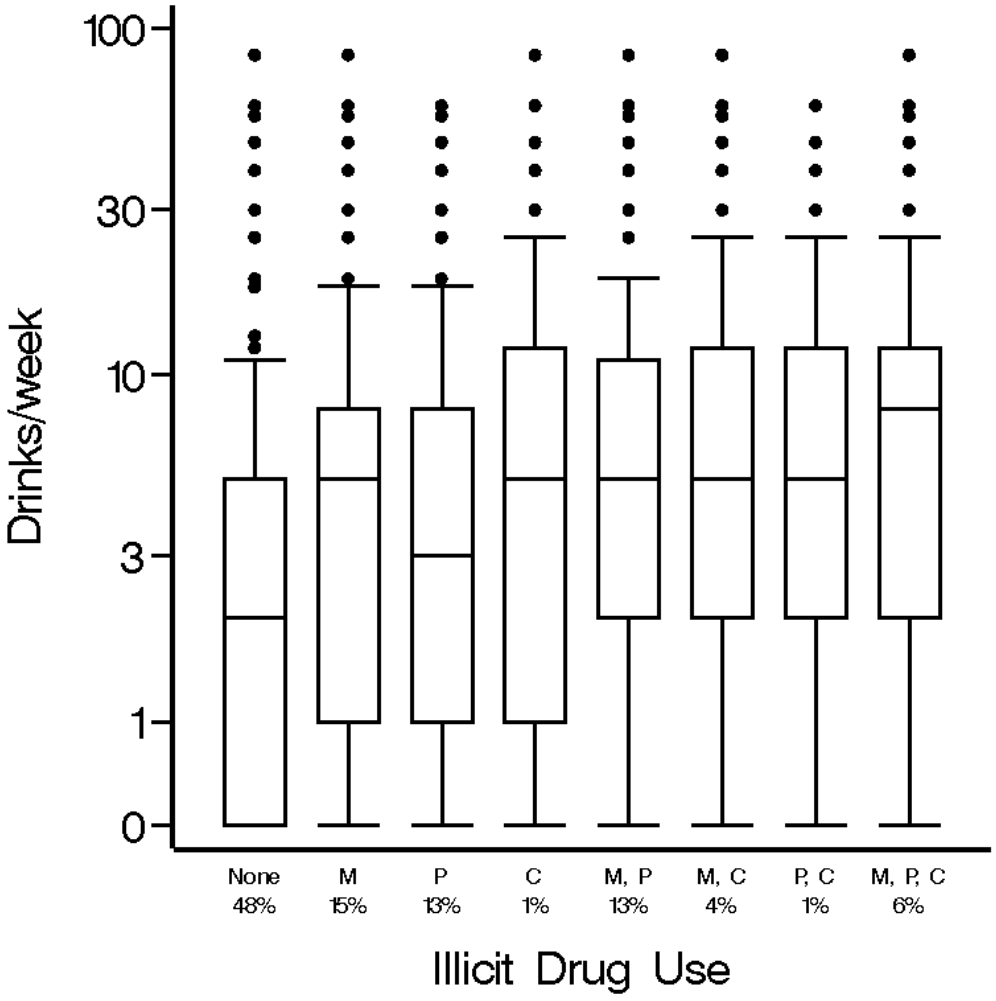
[d] Chlamydia or Gonorrhea

Appendix 2. Additional figures

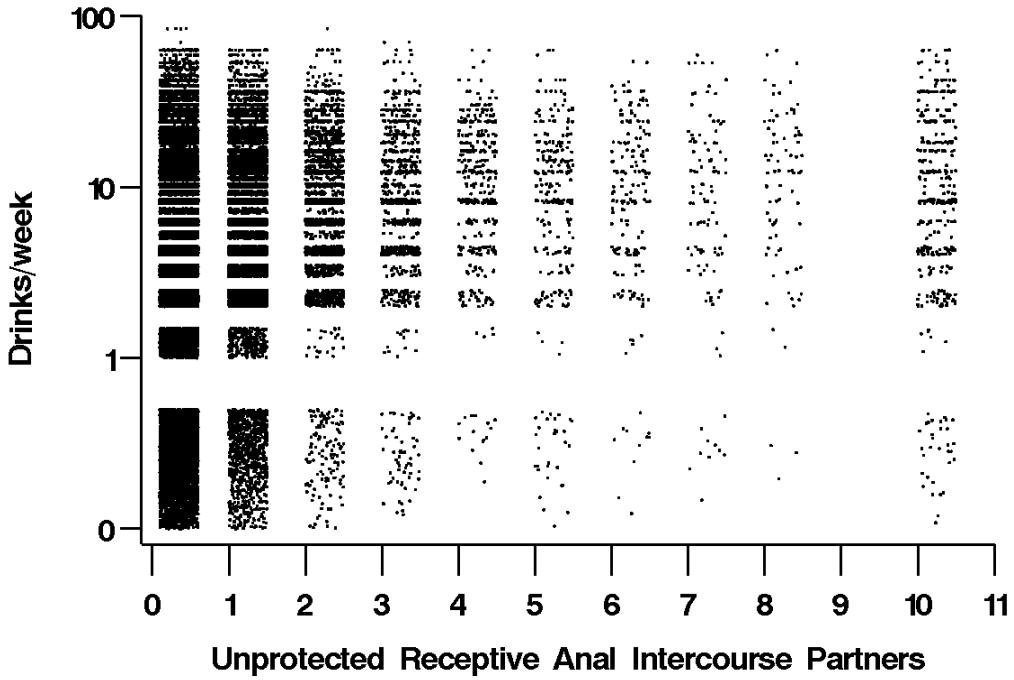
Appendix 2.4.1. Plot of alcohol consumption by time-on-study at baseline and over 47,261 follow-up visits by 3,651 men between 1984 and 2007.



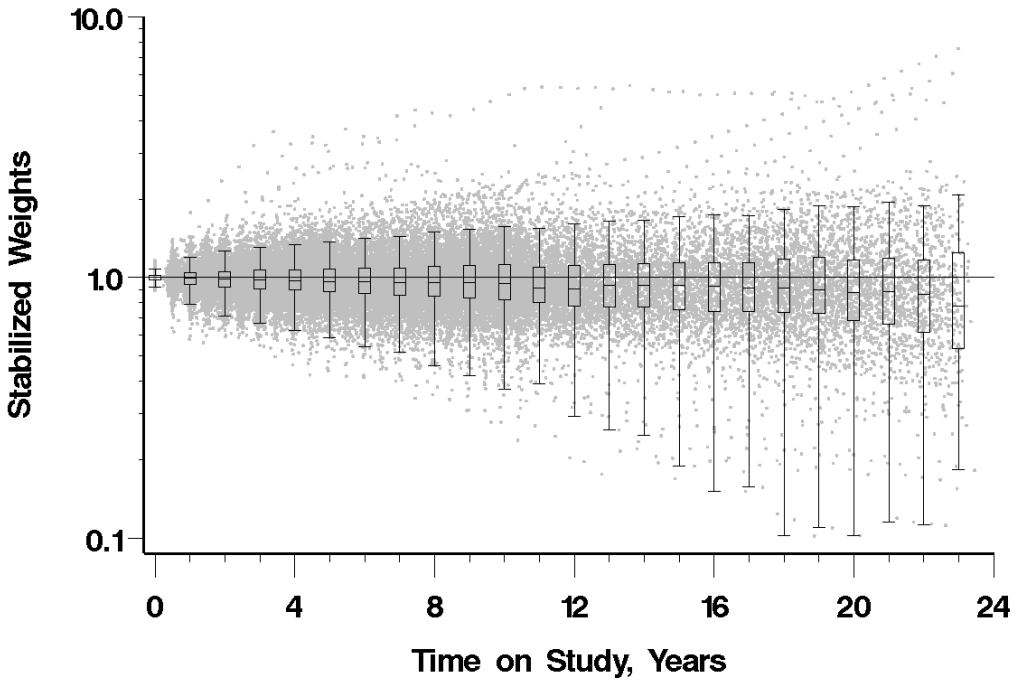
Appendix 2.4.2. Box plots of alcohol consumption by illicit drug use (marijuana/hash (M), poppers (P) or cocaine/crack cocaine (C)) for 3,651 men seen at baseline and at 47,261 follow-up visits (percentages are of visits) between 1984 and 2007.



Appendix 2.5.1. Scatterplot of alcohol consumption (drinks/week) by number of unprotected receptive anal intercourse partners reported over 57,651 follow-up visits, between 1984 and 2007.



Appendix 2.5.2. Distribution of stabilized weights (mean, 1.00; standard deviation, 0.26) over time and as box plots by study visit year.



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