Alcohol Use and HIV Risk in the iPrEx Study

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A thesis
submitted in partial fulfillment of the
requirements for the degree of

Master of Science

University of Washington
2015

Committee:
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Program Authorized to Offer Degree:
Health Services
Abstract

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Chair of the Supervisory Committee:
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Introduction: HIV acquisition continues to be a critical global health concern even with existing effective prevention strategies. Men who have sex with men (MSM) are disproportionately affected by the epidemic. Unhealthy alcohol consumption is prevalent in certain MSM populations and has been shown to be a risk factor for HIV infection. The objective of this study is to describe the association between unhealthy alcohol use over time and HIV acquisition in the iPrEx (Pre-exposure Prophylaxis Initiative) study, which was an HIV pre-exposure prophylaxis (PrEP) trial in MSM enrolled in 6 countries.

Methods: Data for this study were obtained from the iPrEx study, which was a phase III, randomized placebo-controlled trial that evaluated the safety and efficacy of daily, oral FTC/TDF for HIV PrEP in initially HIV-uninfected MSM. Alcohol use and sex behavior data were collected quarterly throughout follow-up and HIV laboratory assays were performed
monthly. Cox proportional hazards models were used to assess the association between time-varying average volume of alcohol consumed and HIV acquisition. The Cox models were sequentially adjusted in order to ensure adequate control for measured confounders.

**Results:** The analytical sample included 2,361 participants of whom 139 became HIV infected during the study. The mean age of the sample was 27 years old, and the range of follow-up time was between 3 months and 3.3 years (median = 1.8). At baseline, the majority of the cohort reported drinking (87%), and over half reported typically drinking 1-4 drinks or 5 or more drinks (52%). There was a positive, but not statistically significant association between HIV acquisition and reporting an average of 1-4 drinks or 5 or more drinks, relative to no drinking, in all of the models. There was a significant association between sharing large bottles/pitchers of beer and HIV acquisition compared to not drinking alcohol in the model adjusting for site and treatment assignment, (adjusted hazard ratio [AHR] 2.01, 95% CI: 1.03, 3.90); however, this finding was no longer significant after further adjustment for demographic characteristics and sex behavior (AHR 1.83, 95% CI: 0.94, 3.56).

**Conclusions:** In this diverse but select cohort of MSM, we did not observe a statistically significant association between average volume of drinking and HIV acquisition. In the model only adjusted for site and treatment assignment we did find a significant association between reporting sharing of bottles/pitchers of beer. While this association was attenuated after adjustment for additional demographic and behavioral characteristics, findings related to shared bottles/pitchers are hypothesis-generating and may warrant further investigation.
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ACKNOWLEDGEMENTS

I would like to thank my thesis committee members, Emily Williams and Patrick Heagerty, for their expert guidance, support, and helpful critiques. I would also like to thank the iPrEx study team, especially the Principal Investigator, Robert Grant, and statistician, David Glidden, for their study leadership, and the data analyst, Megha Mehrotra, for her analytical advice. I am grateful for the dedication of the iPrEx study participants, without whom this study would not have been possible.
Introduction

HIV acquisition continues to be a critical global health concern even with existing effective prevention strategies; in 2013 there were 2.1 million new HIV infections worldwide.\(^1\) Certain communities bear the brunt of the HIV burden, including men who have sex with men (MSM), who are disproportionately affected by the epidemic.\(^2\) Identifying behaviors that place MSM at risk for HIV infection is of paramount importance for the uptake and success of prevention interventions. Unhealthy alcohol consumption is prevalent in certain MSM populations\(^3,4,5,6\) and has been shown to be a risk factor for HIV infection.\(^7\)

Several previous studies have assessed the association between alcohol use and HIV risk and acquisition among MSM. Most of these studies have employed a cross-sectional design\(^8\) and used a variety of outcome measurements, including self-reported HIV risk behavior, \(^4,6,9,10,11,12,13\) sexually transmitted infection (STI) diagnosis,\(^14\) and HIV antibody assays.\(^15,16,17\) The majority of the studies that have evaluated alcohol use and self-reported HIV risk behavior have found positive associations, with the exception of two studies.\(^4,13\) While these two studies did not find an association between alcohol and HIV-related risk behaviors, one found a positive association when alcohol and drugs were used together.\(^4\) In a study that evaluated alcohol use and recent diagnosis of an STI, a potential indicator of HIV risk behaviors, alcohol use was not associated with reporting recent STI diagnosis.\(^14\) Three studies using cross-sectional HIV antibody testing, did not find an association between alcohol use and HIV prevalence, but did find associations between alcohol use and known risk factors (i.e., having sex with a casual partner and unprotected anal sex).\(^15,16,17\)

While the majority of these findings suggest a strong relationship between unhealthy alcohol use and HIV risk behavior, cross-sectional designs have certain limitations, including the
inability to measure patterns of alcohol use over time. Alcohol use patterns may vary within individuals over time, and some dimensions of alcohol use may be more risky than others (e.g., heavy episodic, or “binge,” drinking may be riskier than occasional use within recommended limits). Analyses seeking to understand whether unhealthy alcohol use is associated with HIV infection should carefully select the pattern of alcohol use of interest, including longitudinal time-varying measures for characterizing alcohol use over time. Furthermore, in longitudinal studies incident HIV infections can be measured and reverse causality can be ruled out.

To evaluate time-varying alcohol use and incident HIV infections, three longitudinal studies have been performed. All three were nested in larger HIV prevention cohort studies in the United States, and results were mixed. One of these studies identified strong positive associations between heavy drinking and HIV acquisition in their unadjusted and adjusted models. This study defined “heavy” drinking as 4 or more drinks every day or 6 or more drinks on a typical drinking day in the past 6 months. The second study found a strong positive association during the first year in their unadjusted model, but not during subsequent years and not after adjusting for sex behavior. This study defined “heavy” drinking as 5 or more drinks on at least a weekly basis. The third study also found a significant association between binge drinking and HIV acquisition in their unadjusted analysis, but not after adjusting for demographic characteristics, site, and sex behavior. This last study defined “binge” drinking as 5 or more drinks per occasion at least monthly. In order to further elucidate the relationship between unhealthy drinking and HIV acquisition, additional investigation of associations between time-varying unhealthy alcohol use and HIV acquisition in prospective cohort studies is warranted.

Moreover, because these longitudinal studies were conducted in United States-based cohorts of MSM, the association between time-varying alcohol use and HIV incidence in MSM
from other countries has not been explored. Studies of alcohol-associated risk factors for HIV acquisition in additional countries is needed, because the contexts and consequences of unhealthy drinking may vary based on cultural context, and both the prevalence of unhealthy alcohol use and the burden of HIV may be higher in low- and middle-income countries than in the United States.

The present study aims to begin to fill needed research gaps describing the association between unhealthy alcohol use over time and HIV acquisition in the iPrEx (Pre-exposure Prophylaxis Initiative) study, which was a randomized HIV pre-exposure prophylaxis (PrEP) trial in MSM enrolled in 6 countries, including the United States and 5 middle-income countries. The iPrEx study provides the unique opportunity to assess if there is an association between time-varying unhealthy alcohol use and HIV acquisition in a cohort of MSM largely based in middle-income countries outside of the United States.

**Conceptual Model**

Figure 1 shows the hypothesized associations between unhealthy alcohol use over time and HIV acquisition. It is postulated that unhealthy alcohol use may act as a risk factor for HIV acquisition via two mechanisms: 1) increasing HIV risk behavior (e.g., condomless receptive anal sex) and 2) negative impacts on immune function, which can increase one’s susceptibility for infection. Associations between unhealthy alcohol use and HIV acquisition may vary by demographic and social factors. Younger age, less educational background, and lower socioeconomic status have been associated with unhealthy alcohol use over time in MSM. Differences in alcohol use have also been described across racial/ethnic groups in previous studies of MSM. The risk of HIV infection has also been shown to be associated with younger age, less education, and lower socioeconomic status and to vary across racial identity in populations of MSM.
In addition to these demographic characteristics, it has been postulated that an individual’s increased proclivity for risk-taking behaviors may be associated with both unhealthy alcohol use and HIV risk behaviors.\textsuperscript{28,29} Drug use has been shown to be associated to both unhealthy alcohol use\textsuperscript{29} and HIV risk;\textsuperscript{4,12,16,19,20} however, the temporal relationship (e.g., if drug use precedes alcohol use or occurs after alcohol use) is often unclear.

In addition to personal characteristics and behaviors, one’s social context may be associated with unhealthy alcohol use and HIV acquisition. It has been seen that MSM who experience stigma and social exclusion and have less access to HIV prevention resources are at higher risk of HIV infection.\textsuperscript{1} These same social factors may impact patterns of alcohol use in

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**Figure 1.** Conceptual model of how unhealthy alcohol use is hypothesized to affect HIV acquisition.
MSM. Furthermore, these individual characteristics and social factors may be related to one or both of the proposed mediators of unhealthy alcohol use and HIV acquisition.

Methods

Study Setting

Data for this study were obtained from the iPrEx study, which was a phase III, randomized placebo-controlled trial that evaluated the safety and efficacy of daily, oral FTC/TDF for HIV PrEP in MSM. The study was implemented at 11 sites, which were located in Lima (INMENSA and Impacta) and Iquitos (ACSA), Peru; Guayaquil (Equidad), Ecuador; San Francisco and Boston (SFDPH and Fenway), the United States; Rio de Janeiro and São Paulo (FIOCRUZ, Praca Onze, and USP), Brazil; Cape Town (DTHF), South Africa; and Chiang Mai (RIHES), Thailand. The iPrEx study enrolled 2,499 MSM between July 2007 and December 2009. Inclusion criteria included being male at birth, 18 years of age or older, HIV-uninfected, reporting high risk for HIV acquisition, and meeting laboratory and clinical criteria indicative of good health. All study visits concluded in February 2011. Additional details of the study visits and primary outcomes are described elsewhere.30

Sample Selection

The present study includes 2,361 iPrEx study participants who were HIV uninfected at baseline and had follow-up data on both HIV status and alcohol use. Specifically, of the 2,499 participants who were enrolled in the parent study, 138 were not included in the present study because they left the iPrEx study before their first quarterly visit (n=49), had no follow-up HIV test (n=47), did not complete any follow-up questionnaires (n=23), were found to be HIV infected at baseline via retrospective laboratory testing (n=10), or did not provide baseline alcohol use data (n=9). For participants who remained HIV negative throughout the study, all visits between
enrollment and their final HIV antibody test were included in this analysis. For participants who became HIV-positive during the study, all visits between enrollment and the first date of laboratory evidence of HIV infection were included.

**Assessments**

Clinical, laboratory, and face-to-face interview data were recorded on paper case report forms (CRFs) at baseline and all follow-up visits. Behavioral data was collected using a computer-assisted behavioral interview (CASI) administered at baseline, every 12 weeks after enrollment, and 8 weeks after stopping the study drug.

Demographic characteristics were collected at the screening visit. Participants were asked to report their age and self-identified race during an in-person interview. Racial categories were tailored to the country of enrollment. For instance, at the DTHF site in South Africa, “black African” “white,” “Indian,” and “colored” were used. Education level was obtained via the baseline CASI and was recorded as “no schooling;” “some primary school, but not complete;” “completed primary school;” “some secondary school, but not complete;” “completed secondary school;” “vocational/trade school;” “attended college or university;” and “graduate/professional school.”

Alcohol and drug use data were collected via CASI questionnaires. The CASI had two questions that assessed alcohol use: “How many alcoholic beverages did you drink (beer, wine, mixed drink, shot liquor or any kind of alcoholic beverage) in the last month?” and “Last month, how many did you usually drink? (Beer, wine, mixed drink, shot liquor or any kind of alcoholic beverage).” The response options for the first alcohol use question were “I never drink,” “less than once in the last month,” “2 or 3 times in the last month,” “once or twice a week in the last month,” “2 or 3 times a week in the last month,” and “every day.” For the question about the typical volume of alcohol consumed on a drinking day the response options were “1-2 drinks per day,” “3-4 drinks
Drug use over the prior 30 days was also assessed using CASI, which asked participants to select all of the illicit drugs that they had consumed from a list. The list of drugs included marijuana, inhalants, cocaine, crack, amphetamines, tranquilizers, ecstasy, hallucinogens, mushrooms, and Viagra. There was an “other, specify” option for drugs that were used in the prior 30 days but not included in the list of responses. Participants could reply to either the alcohol or drug use CASI questions as “don’t know” or “decline to answer.”

Participants were asked about their sexual behavior over the previous 3 months at baseline and quarterly visits in a face-to-face interview. The sex of their partners was ascertained and, if they reported male sex partners, the number of insertive and receptive anal sex partners and the number of partners with whom a condom was not used was recorded.

Rapid HIV antibody testing was performed at all monthly visits. Participants who had a positive antibody test were reviewed by the study Endpoint Committee, which adjudicated each event. In order to determine the earliest date of laboratory evidence of HIV infection blood specimens that had been previously collected and stored were used for retrospective viral testing.

**Analytic Measures**

**Primary Exposure: Alcohol Use**

The two alcohol questions in the baseline and quarterly CASI questionnaires were used to derive one primary exposure measure: average volume of alcohol consumed in the past month. Average volume was measured categorically with the following categories: “None,” “1-4 drinks,” “5-6 drinks per day,” “7-8 drinks per day,” “9-11 drinks per day,” “more than 12 drinks per day,” and “I share large bottles/pitchers of beer with my friends so I do not know how many glasses of beer I drink.” Each response option had the conversion into beer and wine, for example “or 1-2 personal bottles of beer a day, or 1-2 glasses of wine.” Response options differed slightly between the baseline and follow-up CASI.
“≥ 5 drinks,” “Shared large bottles/pitchers of beer,” and “Don’t know/Decline.” These categories were derived to meaningfully differentiate between no, low-level, and unhealthy drinking, as well as to reflect cultural drinking norms across study sites. Participants that replied that they did not drink in the past month or never drank to the question asking about frequency of drinking in the past month, and also did not report a volume were categorized as “none.” Categories of “1-4 drinks” and “≥ 5 drinks” were selected to differentiate between low-level and unhealthy drinking consistent with the National Institute of Alcohol Abuse and Alcoholism’s recommended limits, and, in particular, their definition of binge-drinking (5 or more drinks on an occasion).31

The category of sharing beer was derived from the “I shared large bottles of beer/pitchers with my friends so I do not know how many glasses of beer I drank” answer option, which was included in the questionnaire to reflect cultural norms at study sites, especially in the Andes, where at baseline 17.7% who reported alcohol use in the past month reported sharing large bottles/pitchers of beer. Finally, because a large number of participants who reported alcohol use in the past month declined to report the volume that they had consumed in the previous month, by either replying “I Don’t Know” or “Decline to Answer” (23.4% at baseline), an independent category of “Don’t know/Decline” was included.

For participants with missing baseline alcohol data, imputation was used. Specifically, of the 54 participants who did not indicate whether they drank in the last month on the baseline CASI, 45 responses were imputed using data collected at their first quarterly CASI and 9 participants were excluded from the analysis due to not providing alcohol data on either the baseline or first quarter questionnaire. Of the 14 participants who reported drinking alcohol in the past month but did not provide data regarding the volume consumed, responses were imputed from answers to the participant’s first follow-up CASI at their first quarterly visit.
Primary Outcome: HIV Acquisition

HIV infection was based on the adjudication of the Endpoint Committee and the date of infection was the date of earliest evidence of laboratory infection, as determined by the Committee.

Baseline Covariates

The available demographic variables included in this analysis were site of enrollment, age, race, and education. These covariates were chosen based on known associations between each variable and both unhealthy alcohol use and HIV (see Figure 1), and based on data availability. Two measures for age were derived: a four-category ordinal variable using 18-24, 25-29, 30-39, and $\geq 40$ years old as interval ranges, and a continuous age variable. Education was categorized as “less than secondary,” “completed secondary,” or “post-secondary.” There were 22 instances of missing education at baseline; these values were imputed using the site-specific modal value. A measure for race was derived from the site-specific categories of race, using the following categories: “Black,” “White,” “Asian,” and “Mixed/Other.” The majority of participants reporting that their race was “Mixed/Other” which mostly reflects the mestizo race that is prevalent in the Andes. Finally, a binary measure for treatment assignment represented the assignment of each participant at enrollment to either placebo or FTC/TDF.

Time-varying Covariates

Binary measures were derived for drug use and condomless receptive anal sex for each quarter of follow-up. Drug use was considered as occurring in the past 30 days if the participant reported that they had consumed any of the drugs on the list or reported an “other” drug and entered a known illicit substance in the “other, specify” field. Reports of Viagra were not considered as drug use for this analysis. Condomless receptive anal sex was considered as occurring if the
participant reported receptive anal sex in the past 3 months and not using a condom with 1 or more partners.

**Statistical Analyses**

Participant demographic and behavioral characteristics at baseline were described across average volume of alcohol consumed at baseline, and site was compared across average volume using a Chi square test. Because all remaining characteristics (age, race, education, sex behavior, and drug use) vary by site, these characteristics were compared across baseline volume of alcohol use with multinomial regression models adjusted for site. Post-estimation Chi square tests were performed to assess statistical significance.

We used Cox proportional hazards models to assess the risk of HIV incidence associated with average volumes of alcohol consumption reported over time and used as a time-varying predictor. CASI questionnaires and associated measurements were assigned to their closest quarterly visit for this analysis. In situations where participants took two CASIs in a given quarter, the CASI taken closer to the scheduled quarterly visit was used in the analysis and the other one was excluded. If a quarterly visit occurred, but did not have CASI data, the reported alcohol data from the immediate prior CASI was lagged one quarter.

Quarterly reports of alcohol use were used to impute data during the following two monthly visits, at which alcohol use data was not collected. Reported volume of alcohol consumption was modeled as a time-varying behavior and the reference category was defined as “no alcohol consumption”. Sex behavior and drug use were also modeled as time-varying covariates that were updated quarterly over time in the analysis.

The Cox models were sequentially adjusted in order to ensure adequate control for measured confounders, and Models 1 and 2 did not adjust for any factors in the pathway through which alcohol use may influence HIV acquisition. The initial model (Model 1) was adjusted only
for site and treatment assignment; Model 2 was adjusted for site, treatment assignment, and demographics. We also considered adjusting for drug use, but due to the sparseness of the drug data and the strong collinearity between drug and alcohol use, we do not present analyses that attempt to adjust for drug use.

We conducted some exploratory, hypothesis-generating analyses to begin to assess potential mediation by condomless anal receptive sex. Specifically, Model 3 included site, treatment assignment, demographics, and both time-varying alcohol use and condomless receptive anal sex. The goal of analysis using Model 3 is to determine whether the alcohol association is attenuated when controlling for the potential mediator (condomless receptive anal sex), and to report on the association between this sexual risk variable and HIV acquisition.

Results

The final analytical sample included 2,361 participants, among whom 139 became HIV infected during the study. The mean age of the sample was 27 years old, and the range of follow-up time was between 3 months and 3.3 years (median = 1.8). The exclusion of participants who were HIV positive at baseline and those who did not provide sufficient alcohol use data did not impact the balanced assignment to treatment group (1,188 placebo vs. 1,173 FTC/TDF).

Table 1 describes the baseline demographic and behavioral characteristics overall and by average volume of alcohol at baseline. At baseline, the majority of the cohort reported drinking (87%), and over half reported typically drinking 1-4 drinks or 5 or more drinks (52%). The Impacta site in Lima and the two United States sites had the lowest reports of don’t know/decline to answer (12% at Impacta, 3% at SFDPH, and 11% at Fenway). Sharing bottles/pitchers of beer was reported mostly at the sites in Peru and Ecuador (94%). The Peru sites reported the highest rates
of drinking 5 or more drinks at baseline (26% at Impacta, 27% at INMENSA, 31% at ACSA). The sites reporting the lowest prevalence of drinking 5 or more drinks at baseline were FIOCRUZ in Rio de Janeiro (6%) and SFDPH in San Francisco (7%). Average volume of alcohol consumed at baseline was significantly different across study site, and baseline age, education, condomless anal sex and drug use (all p-values <0.05). Racial identity categories did not vary across baseline reported average volume of alcohol (p=0.35).

Half of the analytical sample was between 18 and 24 years old (50%) and the majority reported mixed race (70%), likely reflecting the majority of the cohort participating in Peru (57%). There were few Asian-identified participants (5%) or black-identified participants (8%). The majority of the analytical sample reported condomless receptive anal sex in the past 3 months (60%), of which most reported drinking in the past month (87%). The minority of the sample reported drug use in the past 30 days (16%) and among those who reported drug use, the vast majority also reported drinking alcohol (94%).
Table 1. Baseline Participant Characteristics by Reported Baseline Alcohol Use

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<th>Baseline Characteristics</th>
<th>Typical Number of Drinks on Drinking Days in the Past 30 Days</th>
<th>Total</th>
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<th>1-4 Drinks</th>
<th>≥5 Drinks</th>
<th>Sharing Bottles/Pitch</th>
<th>Don’t Know/Decline</th>
<th>P-value</th>
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<td></td>
<td>N  %</td>
<td>N  %</td>
<td>N  %</td>
<td>N  %</td>
<td>N  %</td>
<td>N  %</td>
<td>N  %</td>
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<td>24  28</td>
<td>12  14</td>
<td>1   1</td>
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<td>Less than secondary</td>
<td>484 20</td>
<td>66 14</td>
<td>111 23</td>
<td>103 21</td>
<td>61  13</td>
<td>143 30</td>
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<tr>
<td>Completed secondary</td>
<td>857 36</td>
<td>108 13</td>
<td>217 25</td>
<td>199 23</td>
<td>108 13</td>
<td>225 26</td>
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<td>Post-secondary</td>
<td>1,020 43</td>
<td>135 13</td>
<td>387 38</td>
<td>210 21</td>
<td>103 10</td>
<td>185 18</td>
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<tr>
<td>Behaviors</td>
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<tr>
<td>Receptive anal sex without a condom in past 3 months</td>
<td>1,408 60</td>
<td>177 13</td>
<td>424 30</td>
<td>330 23</td>
<td>186 13</td>
<td>291 21</td>
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<tr>
<td>Drug use in past month</td>
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<td></td>
<td>374 16</td>
<td>21 6</td>
<td>154 41</td>
<td>56 15</td>
<td>11  3</td>
<td>132 37</td>
<td></td>
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</tbody>
</table>

† Adjusted for site.

Figure 2 shows the percent of participants reporting each of the five categories of average alcohol consumed (none, 1-4 drinks, ≥ 5 drinks, sharing bottles/pitchers, or don’t know/decline) by site and quarter for the first 6 quarters of follow-up. Six months was chosen as the cut-off since all sites had data representing at least a moderate number of participants through 6 months. All sites had participant reports of volumes in each of the four categories and there was variation over the first 6 quarters of follow-up in the percent of participants reporting each category.
Figure 2. Percent of Participants Reporting 1-4 Drinks, ≥ 5 Drinks, Sharing Bottles/Pitchers, or Don’t Know for the Average Volume of Alcohol Consumed Each of the First 6 Quarters of Follow-up by Site
Primary Analyses: Association between Average Volume of Alcohol Consumed and HIV Acquisition

The hazard ratios and 95% confidence intervals for HIV acquisition associated with average volume of alcohol consumed are presented in Table 2. There was a positive, but not statistically significant association between HIV acquisition and reporting an average of 1-4 drinks or 5 or more drinks, relative to no drinking, in all of the models. Reporting “don’t know/decline” for alcohol use in the past month had a positive, but not statistically significant association with HIV acquisition in the model adjusted for site and treatment assignment, but not in the further-adjusted models.

Participants who reported sharing large bottles/pitchers of beer were 2.01 as likely to become HIV infected compared to participants who did not drink alcohol (95% CI: 1.03, 3.90) in the model adjusted for site and treatment assignment. However, after further adjustment for demographic characteristics and condomless receptive anal sex, sharing bottles/pitchers of beer was found to not be significantly associated with HIV acquisition.

Secondary Analyses: Exploration of Potential Mediation by Condomless Anal Sex

In the model adjusting for condomless anal sex we did not find a significant association between any category of average volume of alcohol consumed and HIV acquisition. The hazard ratios associated with each category of average volume of alcohol consumed are attenuated compared to the models in the primary analyses. Participants reporting condomless receptive anal sex were 1.73 times more likely to become HIV infected compared to participants that did not report this sex behavior (95% CI: 1.22, 2.47) when controlling for reported volume of alcohol consumed in the prior month.
Table 2. Sequentially-Adjusted Hazard Ratios (HR) for HIV Infection Associated with Average Volume of Alcohol Used Compared to Not Drinking Over Time Among HIV-Uninfected MSM in the iPrEx Study with Complete Alcohol and HIV Data (n=2,361)

<table>
<thead>
<tr>
<th></th>
<th>Primary Analyses</th>
<th>Secondary Analyses</th>
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<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td>Adjusted for site and treatment assignment</td>
<td>Adjusted for site, treatment assignment, and demographics</td>
<td>Adjusted for site, treatment assignment, demographics, and condomless receptive anal sex</td>
</tr>
<tr>
<td>Average Volume of Alcohol Consumed in Past Month</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>None</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>1-4 drinks</td>
<td>1.47 (0.79, 2.72)</td>
<td>1.42 (0.77, 2.63)</td>
</tr>
<tr>
<td>≥ 5 drinks</td>
<td>1.16 (0.63, 2.14)</td>
<td>1.12 (0.61, 2.07)</td>
</tr>
<tr>
<td>Shared large bottles/pitchers of beer</td>
<td>2.01 (1.03, 3.90)</td>
<td>1.90 (0.98, 3.69)</td>
</tr>
<tr>
<td>Don’t know/decline</td>
<td>1.01 (0.47, 2.15)</td>
<td>0.94 (0.44, 2.01)</td>
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<tr>
<td></td>
<td></td>
<td>HR for condomless receptive anal sex, adjusting for average volume of alcohol</td>
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<td></td>
<td></td>
<td>1.71 (1.20, 2.43)</td>
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</table>

**Discussion**

This study investigated whether average volume of alcohol used over time was a risk factor for HIV acquisition among a cohort of initially-uninfected MSM from 6 countries who enrolled in a randomized, controlled trial testing the safety and efficacy of HIV PrEP. In this diverse but select
cohort of MSM, we did not observe a statistically significant association between average volume of drinking and HIV acquisition.

In the model only adjusted for site and treatment assignment we did find a significant association between reporting sharing of bottles/pitchers of beer. While this association was attenuated after adjustment for additional demographic and behavioral characteristics, findings related to shared bottles/pitchers are hypothesis-generating and may warrant further investigation. Specifically, although sharing bottles/pitchers appeared to be common in this sample of MSM, it is unclear what volume of alcohol (e.g., heavy drinking that would lead to intoxication or low-level drinking) is represented by sharing bottles/pitchers of beer. If shared pitchers represents heavy drinking, it could be that sharing bottles/pitchers of beer leads to intoxication and, thus, resultant risk behaviors or immune processes that could increase risk for HIV infection. However, if the latter, it could be that the shared social context of drinking may spread HIV risk via a social networking mechanism.\textsuperscript{32} Future research should seek to more clearly define volume of drinking associated with sharing bottles/pitchers in these settings, and to understand whether and via what mechanisms sharing bottles/pitchers may be associated with HIV acquisition.

Considering prior results in longitudinal studies assessing time-varying unhealthy alcohol use and HIV acquisition in MSM, it is surprising to see no significant association of drinking 5 or more drinks on a typical drinking day and HIV acquisition in any of the models. In all three other longitudinal studies previously described, there were significant associations with heavy drinking in at least one univariate model, as well as in the adjusted multivariate model in one study.

It is possible that the lack of an association in our sample is due to our study being underpowered. Varying measures of alcohol use may be another reason for differing results among
studies evaluating unhealthy drinking behavior and HIV; two of the other longitudinal studies used cut-offs for “heavy drinking” indicative of drinking larger quantities or more frequent alcohol consumption. Inconsistent measures of alcohol use limit the comparability of findings across these studies. It is also possible that associations between unhealthy alcohol use and HIV acquisition differ across populations of MSM, and further investigation of the impact of unhealthy alcohol use on HIV risk in international cohorts of MSM is warranted.

Since the sample used in the present study was derived from participants in an HIV pre-exposure prophylaxis trial, half of the sample had access to an effective HIV prevention method. It is possible that an association between alcohol use and HIV risk could be obviated by PrEP use. Since a large portion of those assigned to PrEP did not adhere to the medications in the iPrEx study its efficacy to inhibit HIV acquisition may not have impacted this analysis; however, a more detailed analysis of unhealthy alcohol use and HIV acquisition in the context of PrEP adherence is merited. Furthermore, since the sample in this study were enrolled in an HIV prevention trial, it is possible that the motivation of the participants to prevent HIV impacts our ability to see an association between unhealthy alcohol use and HIV.

Time-varying condomless receptive anal sex had a significant association with HIV acquisition in this study, controlling for average volume of alcohol consumed, demonstrating that an association between unhealthy alcohol use and HIV acquisition may be working through a different mechanism than this sex behavior. Similarly, two of the longitudinal studies previously described also found an attenuation of the association between unhealthy alcohol use and HIV acquisition once they adjusted for sex behavior.
It is possible that immune deficiency resulting from unhealthy drinking may be related to HIV acquisition or that a personal characteristic, such as the proclivity for risk, which was not measured in this study, is associated with unhealthy alcohol use, condomless receptive anal sex, and HIV acquisition. Future research should aim to measure these participant characteristics more rigorously in order to elucidate the associations among them and how they may impact the risk of HIV acquisition in MSM.

**Limitations and Strengths**

The study has several limitations. Fewer MSM-friendly resources, stigma, less social support, and a proclivity for risk-taking are likely to be associated with unhealthy alcohol use and HIV acquisition (Figure 1), which we were unable to measure directly. The potential importance of the social context of drinking is emphasized by our finding that sharing pitchers or bottles, which had a significant association with HIV acquisition in one model, is a social act. While study site was used in this analysis as a proxy for social, economic, and structural differences, better measures of social context may provide a more accurate understanding of how alcohol use and HIV acquisition are related. Furthermore, definitions of unhealthy drinking that have been validated in the United States may not be appropriate in international settings.

The sample for this study was comprised of participants in an HIV prevention clinical trial, which may have impacted the results and limits generalizability. Study participants complied with study inclusion criteria, including reported risk behavior for HIV acquisition and overall good health, which may not characterize other populations of MSM. Additionally, the study enrolled participants in the United States and 5 middle-income countries, and MSM in lower-income countries were not represented.
There was missing alcohol use data in this sample. We tried to account for missing data that occurred intermittently throughout participation by using data from the prior quarter if it was available, but it may have not appropriately reflected participant behavior at each specific time point. Furthermore, it is possible that risk behaviors occurring when participants are not in sustained follow-up place them at a greater risk for HIV, and missing questionnaires should have been considered as a separate analytical category. Many participants replied that they “didn’t know” or “declined to reply” the volume of alcohol they consumed and this may have masked a true association of unhealthy alcohol drinking and HIV acquisition.

The baseline and follow-up CASI questionnaires had slightly different answer options for the alcohol assessments, which could have resulted in a misclassification of average volume of alcohol consumed; however, we addressed this by deriving a measure of average volume of alcohol consumed that collapse these different responses into the same categories. Both our alcohol and sex behavior assessments were self-reported by trial participants and are prone to recall and social desirability bias, which could mask an association between high levels of drinking and HIV acquisition.

Despite these limitations, this study is the first study to our knowledge to assess time-varying alcohol use and HIV acquisition in a large international cohort of MSM. The size and diversity of the cohort are strengths of this study. The high frequency of the CASI assessments employed in the iPrEx study improve the accuracy of measuring alcohol use patterns over time and retrospective viral testing better approximates the timing of HIV acquisition.

The literature on the association between time-varying unhealthy alcohol use and HIV acquisition in MSM is limited. To date the results have been mixed and the measurements have
had limited comparability. This study adds to the extant literature by assessing the association between time-varying unhealthy alcohol use and HIV incidence in an international cohort of MSM. Contrary to our hypothesis, the present study identified no significant association between unhealthy alcohol use, relative to none, although estimates went in the expected direction. However, sharing bottles/pitchers of beer was significantly associated with HIV incidence in one model, adjusted for site and treatment assignment, but not after further adjustment for other factors. Given mixed findings and a strong theoretical basis for alcohol use as a risk factor for HIV, further investigation of alcohol use patterns and potential associations with certain dimensions of alcohol use in MSM living in middle-income countries, where MSM bear a disproportionate burden of the HIV epidemic and alcohol use is prevalent, is warranted. In particular, sharing bottles/pitchers of beer should be evaluated further, namely if any association with HIV due to high levels of drinking or the social act of sharing alcohol with others. Finally, more work should be done to conceptualize and test the mechanisms via which unhealthy alcohol use may induce HIV infection in samples of MSM in various settings.
References


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