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The Longitudinal Patterns of Stimulant and Amyl Nitrite Use and Sexual Behavior Pre- and Post-HIV Seroconversion among MSM --Manuscript Draft--

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Abstract:	<p>Background and Aims. The use of stimulant drugs alone or in combination with amyl nitrites (stimulant/nitrites) has been associated with higher rates of risky sexual behavior and predictive of HIV infection among men who have sex with men. However, the temporal pattern of stimulant/nitrite use pre- and post-seroconversion has not been well established. This study assessed changes in stimulant/nitrite use and risky sexual behavior among seroconverting MSM over time.</p> <p>Setting. Data were collected in the Baltimore-Washington, DC; Pittsburgh; Chicago; and Los Angeles sites of the Multicenter AIDS Cohort Study (MACS), a longitudinal study of the natural history of HIV infection among MSM.</p> <p>Participants. We used propensity scores to select 1,044 MSM from 7,087 MACS participants composed of 348 seroconverting, 348 seronegative, and 348 seroprevalent participants matched on demographics, recruitment cohort, and study visits.</p> <p>Design. We centered up to four-years of semi-annual data around the seroconversion visit of the seroconverting case within each matched group of participants. Mixed effects regressions estimated the effects of serostatus, recruitment cohort, and time on self-reported stimulant/nitrite use, numbers of male intercourse partners, and numbers of unprotected receptive anal intercourse (URAI) partners. Covariates included demographics, binge drinking, and marijuana use.</p> <p>Findings. Seroconverters had the highest odds of stimulant/inhaled nitrite use (AOR=10.3, CI=4.8-22.0), incident rates of intercourse (IRR = 1.6, CI=1.3-2.1), and URAI partners (IRR = 5.1, CI=3.5-7.3). All participants decreased drug use and sexual risk behavior over time. However, the decreases were largest for seroconverters who nevertheless maintained the highest rates of stimulant/nitrite use and sexual risk. Cohort-related effects were associated with sharp reductions in stimulant/nitrite use</p>	

	<p>and URAI in the early 1990s that rebounded considerably within the first decade of the 2000s.</p> <p>Conclusions. Although all participants decreased risky sexual behavior and stimulant and/or nitrite use over time, seroconverters had the largest decreases. There was no evidence for abrupt or substantial increases in drug use or risky sex post-seroconversion. However, there was substantial variation at the individual level, with the factors underlying this variation not well understood and worth further study. Moreover, stimulant/nitrite use and risky sexual behavior appear to have been strongly influenced by contextual historical and socio-cultural effects. The manner in which contextual factors influence individual behavior is also not well understood and also warrants further study.</p>
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STIMULANTS, AMYL NITRITES AND HIV

**The Longitudinal Patterns of Stimulant and Amyl Nitrite Use
and Sexual Behavior Pre- and Post-HIV Seroconversion among MSM**

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ABSTRACT

Background and Aims. The use of stimulant drugs alone or in combination with amyl nitrites (stimulant/nitrites) has been associated with higher rates of risky sexual behavior and predictive of HIV infection among men who have sex with men. However, the temporal pattern of stimulant/nitrite use pre- and post-seroconversion has not been well established. This study assessed changes in stimulant/nitrite use and risky sexual behavior among seroconverting MSM over time.

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Participants. We used propensity scores to select 1,044 MSM from 7,087 MACS participants composed of 348 seroconverting, 348 seronegative, and 348 seroprevalent participants matched on demographics, recruitment cohort, and study visits.

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Findings. Seroconverters had the highest odds of stimulant/inhaled nitrite use (AOR=10.3, CI=4.8-22.0), incident rates of intercourse (IRR = 1.6, CI=1.3-2.1), and URAI partners (IRR = 5.1, CI=3.5-7.3). All participants decreased drug use and sexual risk behavior over time. However, the decreases were largest for seroconverters who nevertheless maintained the highest rates of stimulant/nitrite use and sexual risk. Cohort-related effects were associated with sharp reductions in stimulant/nitrite use and URAI in the early 1990s that rebounded considerably within the first decade of the 2000s.

Conclusions. Although all participants decreased risky sexual behavior and stimulant and/or nitrite use over time, seroconverters had the largest decreases. There was no evidence for abrupt or substantial increases in drug use or risky sex post-seroconversion. However, there was substantial variation at the individual level, with the factors underlying this variation not well understood and worth further study. Moreover, stimulant/nitrite use and risky sexual behavior appear to have been strongly influenced by contextual historical and socio-cultural effects. The manner in which contextual factors influence individual behavior is also not well understood and also warrants further study.

Keywords: Stimulant Use, Amyl Nitrites, Poppers, MSM, HIV, Multi-Site AIDS Cohort Study, MACS, Longitudinal Study

A Study of the Longitudinal Patterns of Stimulant and Amyl Nitrite Use and Sexual Behavior Pre- and Post-HIV Seroconversion among MSM

Numerous studies have shown that, relative to the general population, men who have sex with men (MSM) disproportionately use an array of drugs; in particular, drugs in the stimulant class (e.g., cocaine, methamphetamine) and inhaled amyl nitrites (“poppers,” referred to hereafter as nitrites).(1-8) The reasons for elevated rates of substance use, including alcohol use, among MSM are thought to be related to a confluence of factors including stigma, higher rates of depression, and social isolation.(9) Use of stimulants and amyl nitrites, often in combination with other drugs such as club drugs or drugs for treating erectile dysfunction, has been strongly associated with increased risk for HIV infection as use often occurs in the context of riskier and more frequent sex with higher numbers of partners.(10-13) These drugs are used to heighten sexual desire, enhance sexual experience, prolong sexual activity, and facilitate meeting partners for sex.(14, 15) An additional problematic aspect of the drug-sex link among MSM is evidenced by the fact that stimulant and nitrite use are prevalent among a subset of HIV+ MSM who continue to engage in relatively high-rates of unprotected sex with multiple partners and who, in association with their substance use, are less likely to adhere to their HIV medication regimens.(7, 12, 16-19)

Although the connections between stimulants, nitrites, sexual behavior, and risk for HIV infection are well established, the temporal patterns pre- and post- HIV seroconversion are less clear.(20) A good deal of the ambiguity is owing to methodological limitations in studies conducted to date: reliance on cross-sectional data; samples that include only substance users; lack of comparison groups composed of long-term HIV- and HIV+ seroprevalent MSM; and assessing substance use and sexual risk behaviors either prior to or following but not across HIV seroconversion.(7, 17, 21-25) Consequently, the extent to which the use of stimulants, nitrites, and risky sexual behaviors that precedes and contributes to the risk for HIV infection increases, decreases, or is maintained post-infection has not been determined.

Using data obtained for the Multicenter AIDS Cohort Study (MACS), we examined the patterns of stimulant and nitrite use as well as sexual behavior pre-and post- HIV seroconversion and comparatively analyzed temporal changes by HIV serostatus for MSM who seroconverted during the study, were seroprevalent (HIV+) at enrollment, or who remained seronegative (HIV-). These three groups were selected to allow for comparative assessment of substance use and sexual behavior among participants shortly before and after seroconversion with participants whose HIV status was unchanged over the same time. Secondly, we examined whether recruitment cohort affected substance use and sexual behavior given research that indicates different patterns of these behaviors for more recent (post 2000) compared with cohorts of MSM coming of age in the 1980s and 1990s.(3, 24, 26)

Method

This secondary analysis used the P24 release of the MACS public data set (<https://statepi.jhsph.edu/macspdt.html>). MACS is an ongoing longitudinal study of the course of HIV infection and treatment among MSM. Participating MACS centers are in Baltimore-Washington, DC; Chicago; Los Angeles; and Pittsburgh. MACS began in 1984 and has enrolled over 7,000 MSM to date, most of whom were recruited in 1 of 3 cohorts: 1984-1985 (n=4,954); 1987-1990 (n=668), and 2001-2003 (n=1,350). The last recruitment in 2001-2003 focused on enrolling younger racial/ethnic minority individuals. Data are collected semi-annually and include self-reported information on past six-month sexual behavior and substance use. Eligibility criteria include: being male, ages 18 to 70, having had sex with another man in the prior five years, and not having been diagnosed with AIDS.(27) Further detail on MACS rationale, eligibility criteria, data collection and instrumentation, and current status are available at <http://www.statepi.jhsph.edu/macspdt.html>.

All MACS participants provided informed consent and the study protocol was reviewed and approved by each participating site's respective IRBs. As this study used the de-identified public use data

set, we applied for and received determinations of exemption from the University of Illinois at Chicago and California State University at Northridge IRBs.

Participants

We selected the analytic sample from 7,087 study participants across multiple steps using multiple selection criteria at each step (Figure 1). Our goal was to retrospectively create matched “triads” with each composed of one seroconverting participant matched to one HIV+ and one HIV- participant. We first selected participants with available demographic and HIV status information (n=6,988) who were recruited in cohorts 1 to 3 (n=6,969) and had completed at least 4 interviews. Seroconverting participants had the additional selection criteria of having at least 1 interview within two years prior to seroconversion. The resulting subsample (n=5,773) was composed of: 464 of the 712 participants that seroconverted after study enrollment; 2,372 that were HIV+ at enrollment; and 2,937 that remained HIV- over the follow-up period.

Insert Figure 1 about here

We stratified this subsample by cohort and applied propensity score matching with calipers set at .25 s.d. of the propensity score to select the closest matching HIV+ and HIV- comparison cases for each seroconverting case.(28) Multiple iterations of the matching algorithm for each cohort were used to identify the best-matching HIV+ and HIV- cases after taking into account available interviews for matched cases.(29) Stratifying the propensity scoring by cohort allowed us to match seroconverting participants with HIV+ and HIV- participants in the same cohort, thereby maximizing the possibility matched participants would have corresponding visits and interview data. Participant attributes used to calculate propensity scores were: age at study entry, race/ethnicity, education level, first and last study visits, and total number of visits completed. Propensity scoring using these attributes resulted in matches for 391 (84.3%) of the 464 seroconverters who met study inclusion criteria, representing 54.9% of the 712 seroconverters in the data set.

In the final selection step, we removed seroconverters and their matched controls if any of the selected controls had fewer than two visits within the two years prior and two years following the indexed seroconversion study visit for the matched seroconverting case or if we could not match a seroconverter with both an HIV- and HIV+ control. This step was complicated by the fact that between April 1992 and April 1996 (visits 16-25), questions about amphetamine and MDA use were dropped from the MACS questionnaire and later re-added. However, for the affected study visits, preliminary analyses showed substantially suppressed estimates of stimulant/nitrite use. To minimize loss of cases, we set the variable for stimulant/nitrite use to missing where questions on stimulants and MDA use were not asked (143 of 7,189 total visits or 2.0%) and re-estimated the number of available visits excluding those with missing substance use data. Participants were retained only if they continued to meet inclusion criteria (e.g., 2+ interviews, matching HIV+ and HIV- cases for each seroconverting case) resulting in the deletion of 129 additional cases. Bivariate analyses comparing the deleted with retained cases found no significant differences for any of the modeled independent or dependent variables except cohort where a significantly (chi-square (2) LR = 34.4, $p < .001$) higher proportion of deleted cases (21.1%, $n = 27$) were from the second recruitment cohort compared with retained cases (4.4% $n = 45$). The final analytic sample was composed of 1,044 participants: 348 seroconverters individually matched to 348 HIV+ and 348 HIV- participants.

Measures

Demographics. Because the de-identified MACS data set contains only birth year, we approximated age at each visit by subtracting birth year from visit year, accounting for semi-annual visits by adding .5 years to every other visit. Race/ethnicity was dummy coded into four dichotomous variables: White, Black/AA, Hispanic/Latino, and Other. Highest year of education reported at baseline was also dummy coded into four dichotomous variables: less than high school, high school graduate, some college, or college graduate.

Study Visit. Study visit data were selected based on the first HIV-positive visit of the seroconverting case within each triad, centered between (up to) 4 visits immediately preceding and (up to) four immediately following seroconversion. Thus, each participant contributed up to nine interviews spanning two years (4 visits) prior and two years (4 visits) post the indexed seroconversion visit. All available study visits within the time-frame established by the seroconverting case were selected for the matched HIV+ and HIV- cases. For instance, if a participant seroconverted at MACS study visit 10, the preceding (6 through 9) and subsequent (11 through 14) visits were selected for analysis for this participant as well as for the matched seronegative and seroprevalent participants. All available study visits within waves 6 to 14 were selected for the three matched cases and then centered around the seroconversion visit, which was set as time 5. The 4 pre-seroconversion visits were set as times 1 through 4, and the 4 post-seroconversion visits set as times 6 through 9. If a visit within the time frame was unavailable, it was set to missing. Participants within each triad could contribute a minimum of two and a maximum of nine data points for the analyses. In the multivariable regression models, because we were interested in how a positive HIV test changed stimulant use and sexual risk behavior, time was represented by a series of dichotomous indicators. The 1,044 matched cases averaged 6.4 interviews (s.d. = 1.8, range = 2 to 9). The interquartile range of visit year for the indexed seroconversion visit was: cohort 1 – 1985-1988; cohort 2 – 1989-1991; and cohort 3 – 2005-2008.

Serostatus. For the MACS, HIV serostatus is assessed biannually at each study visit for all HIV- participants.(30) Participants were classified as a seroconverter if they tested negative for HIV at enrollment but tested positive at a later visit ; the seroconversion visit was indicated by the first visit with a positive test. Participants were classified as seroprevalent HIV+ if they were HIV+ at enrollment or seroprevalent HIV- if they were HIV- at enrollment with no subsequent positive HIV test. Serostatus was the primary independent variable.

Cohort. To capture potential contextual/historical effects, we included MACS recruitment cohort as a predictor variable. Cohort was represented by dummy-coded variables representing the first, second, and third recruitment cohorts.

Binge drinking. MACS participants are asked: “On days when you drank any alcoholic beverages, how many drinks do you usually have altogether?” and “How often you had a drink containing alcohol?” Binge drinking was defined as reporting having 5 or more drinks on a weekly or more frequent basis in the past 6 months. Binge drinking was included as a dichotomous model predictor as research has found it is associated with both riskier sexual behavior and HIV infection. (31-35)

Marijuana use. MACs participants are asked if they have used any of a series of drugs even once in the past six months. We included marijuana use in our models to assess its association with stimulant and nitrite use and sexual behavior. Excepting alcohol, marijuana was the most commonly used drug by participants (Table 1). Marijuana use was categorized dichotomously as any use in the past six months (no/yes) and included as predictor in the multivariable models.

Stimulants and nitrites. Use of stimulants and/or inhaled nitrites were measured in a single dichotomous variable (no/yes) based on any self-reported use of two or more of four drugs at any frequency of use in the past six months: amphetamine/methamphetamine/speed, any form of cocaine, MDA (i.e., “Ecstasy,” “X,” “Molly”), and inhaled nitrites. We selected these drugs based on studies that have found concurrent use of two or more of these drugs associated with more frequent sexual risk behaviors and predictive of HIV seroconversion. (7, 12, 24, 25, 36-38) The dichotomous variable stimulant/nitrite use was assessed as a binary outcome in the multivariable models.

Number of male sex and URAI partners. Number of male sex partners was defined as the number of men with whom a participant reported having sexual intercourse of any kind (i.e., oral or anal, receptive or Insertive) in the past six months. Variables representing each measure were assessed as outcomes on a count level in separate negative binomial models.

Analyses

Analyses were conducted using Stata 14.1 (39). Descriptive bivariate analyses used data from the enrollment visit. We used likelihood ratio chi-square tests or F-tests to compare participants by serostatus on demographics, stimulants, nitrites, and other substance use, number of available interviews, and number of male intercourse and URAI partners. Multivariable analyses were conducted using two-level, mixed effects regressions with interview occasions (level 1) nested within participant (level 2). Models included random intercepts representing subject-specific effects for each dependent variable. Each model assessed changes in the dependent variable with respect to time referenced to the first HIV+ interview of the seroconverting participants (time 5). Additionally, to examine the associations between sexual behavior and stimulant use over time, the regression models with number of male sex partners and number of male URAI partners as the dependent variables, stimulant and/or nitrite use in the prior six months became a predictor. Stimulant and nitrite use was modeled using the logit-link function and binomial distribution whereas, the models regressing number of male and URAI sex partners used the log-link function and negative binomial distribution.

Modeling proceeded sequentially by first estimating a main-effects only model. Interaction terms for time by cohort and time by serostatus were then added one at a time to the main-effects model and assessed for significance using post-estimation, likelihood ratio chi-square tests and the BIC statistic to compare each interaction-term model with the main-effects model. We estimated the preliminary models using maximum likelihood estimation whereas final models used restricted maximum likelihood estimation. All models were estimated assuming unstructured covariances, adaptive quadrature with 30 integration points, and robust standard errors to provide less biased (i.e., more conservative) estimates of the standard errors and associated p-values and to control for residual heteroscedasticity. (40, 41)

Results

Sample Characteristics

Table 1 presents bivariate results by serostatus. Reflecting that the large majority of MACS participants were recruited for the initial cohort (1984 – 1985), there were 921 (88.2%) participants from the first cohort; 45 (4.3%) from the second; and 78 (7.5%) from the third. Participants were predominantly white (83.5%), averaged 33.0 years of age at enrollment, and had an education level of some college or higher (87.3%). Participants averaged 24 visits (s.d. = 15.3) across study participation and 6.4 (s.d. = 1.8) visits over the sampled range. None of these covariates were significantly different by serostatus indicating the propensity score matching produced demographically balanced groups.

Insert Table 1 about here

Consistent with prior study findings, however, there were large and statistically significant differences by HIV serostatus on most of the substance use measures as well as numbers of sex partners.(10, 17, 42) Except for binge drinking, substance use was more prevalent for participants who seroconverted or were HIV+ compared with HIV- participants. For instance, 22.4% of MACS participants who seroconverted and 20.7% of HIV+ participants reported using amphetamine/methamphetamine in the past six months at time 5 (the indexed seroconversion interview) compared with 12.6% of HIV- participants (LR chi-square $(df=2) = 13.1$, $p = .001$). Participants who seroconverted or were HIV+ also had significantly higher rates than HIV- participants on all three dependent variables: use of any 2+ stimulants in the past 6 months (LR chi-square $(df=2) = 40.9$, $p < .001$); mean number of male sexual intercourse partners ($F_{(df=2, 1040)}=7.58$, $p < .001$) and mean number of URAI partners ($F_{(df=2, 1040)} = 7.18$, $p < .001$).

Multivariable Models

Table 2 shows the results for the multivariable mixed-effects regressions. Likelihood ratio tests of the comparisons of the fixed effects only models to the mixed effects models that included the random intercept terms were all significant, indicating the models with random intercepts fit the data better than the fixed-effects only models (stimulant/nitrite use: LR chi-square_(df= 1) = 2,051.63, $p < .001$; number of male sex partners: LR chi-square_(df= 1) = 4,587.38, $p < .001$; number of URAI partners: LR chi-square_(df= 1) = 1,612.54, $p < .001$). Consequently, we used the mixed effects models when testing the addition of interaction terms representing cohort and serostatus by time to the main-effects only models.

Insert Table 2 about here

Stimulant/Nitrite Use. Parameter estimates represented as odds ratios, confidence intervals, and significance levels are shown in Table 2. The residual intraclass correlation of .75 (95% CI = .72 - .78) indicated a large amount of the variation in stimulant/nitrite use is accounted for at the individual level, providing further evidence that using a multilevel framework was warranted. Comparisons of the models that included interaction terms for cohort by time (LR chi-square_(df=16) = 49.13, $p < .001$) and serostatus by time (LR chi-square_(df=16) = 117.20, $p < .001$) to the main-effects only model yielded significant results. Consequently, as shown in the second half of Table 2, we retained these interactions in the final model. Figure 2 depicts estimations of the predicted marginal mean probability of stimulant/nitrite use by serostatus, time and cohort based on final model results.

Demographics related to lower odds of 2+ stimulant use were: age (AOR = .96, $p < .01$) and being African=American (AOR = .26, $p < .01$; White = reference category). Recruitment cohorts 2 (AOR = .13, $p < .001$) and 3 (AOR = .15, $p < .01$) also had significantly lower odds of 6-month stimulants/nitrite use relative to the initial MACS cohort. The main effect of time indicated that stimulant/nitrite use declined in the subsequent two years, reaching the lowest point at the two-years following the midpoint (AOR = 0.29, $p < .001$).

.001). Factors related to increased odds of using 2+ stimulants included: binge drinking (AOR = 2.21, $p < .001$), and any use of marijuana (AOR = 8.89, $p < .001$). Participants who seroconverted (AOR = 10.24, $p < .001$) or were HIV+ throughout the study (AOR = 3.42, $p < .01$) were more likely to use stimulants/nitrites than participants who remained HIV-.

The significant interaction effects obtained indicated that across serostatus and cohort, stimulant/nitrite use was relatively constant in the first two years assessed and not significantly different from the mid-point interview. However, in contrast to the reference group participants in the first cohort, third cohort participants did not show consistent declines in stimulant/nitrite use with statistically significant increased odds of use at the 6-month (AOR = 4.00, $p < .05$), 18-month (AOR = 5.05, $p < .01$), and two-year interviews (AOR = 5.73, $p < .01$) relative to the indexed seroconversion interview. The significant serostatus by time interaction was also due to post-seroconversion differences. Relative to HIV- participants, seroconverting MACS participants had larger reductions at 1-year (AOR = .41, $p < .05$), 18-months (AOR = .30, $p < .01$), and 2-years post-seroconversion (AOR = .30, $p < .05$). Hence, seroconverting participants had the highest rates of stimulant/nitrite use across time, their use declined more sharply following the seroconversion visit than HIV+ participants relative to the reference group of HIV- participants

Insert Figure 2 about here

Number of Male Sex Partners. Model estimates for number of male sex partners are reported as incident rate ratios (IRR) reflecting that this dependent variable was assessed using counts of partners per unit time (six months). MACS participants who seroconverted had a higher number of male intercourse partners relative to HIV- participants (IRR = 1.62, $p < .001$). Binge drinking (IRR = 1.24, $p < .001$), any marijuana use (IRR = 1.28, $p < .001$), and stimulant/nitrite use (IRR = 1.56, $p < .001$) were all significantly associated with having higher numbers of male sex partners. Conversely, significantly lower numbers of male sex partners were reported by participants who were Black/African-American (IRR = .57, $p < .001$).

Whereas the number of male sex partners increased by 17% prior to the mid-point visit (IRR = 1.17, $p < .05$), the IRRs trended lower at subsequent visits (e.g., 2 years IRR = 0.78, $p < .01$).

The interactions between cohort (LR chi-square_(df=16) = 49.13, $p = .001$) and serostatus (LR chi-square_(df=16) = 117.20, $p < .001$) by time were again statistically significant and retained in the final model (Table 2 and Figure 3). The significant cohort by time interaction effects were exclusively due to participants in the third cohort who, relative to the first cohort, had lower numbers of male sex partners at two-years (IRR = .55, $p < .01$) and 18 months (IRR = .61, $p < .05$) prior to the index visit but higher numbers (IRR = 1.61, $p < .01$) at 6 months index visit. The significant serostatus by time interaction effects were due primarily to seroconverting participants having the largest decreases in the number of male sex partners relative to HIV- participants over the two years post-seroconversion: (6-months, IRR = .69, $p < .001$; 1-year, IRR = .61, $p < .001$; 18-months, IRR = .62, $p < .001$; 2-years, IRR = .53, $p < .001$).

Insert Figure 3 about here

Number of URAI Partners. Results for number of URAI partners are also reported as IRRs. Main effects associated with an increased number of URAI partners were: marijuana use (IRR = 1.39, $p < .001$), stimulant/nitrite use (IRR = 2.20, $p < .001$), seroconverting (IRR = 5.07, $p < .001$) or being HIV+ (IRR = 3.00, $p < .001$) or being in the third cohort (IRR = 1.41, $p < .01$). Conversely, age (IRR = .95, $p < .001$), being black/African American (IRR = .58, $p < .05$) or in the other racial/ethnic category (IRR = .20, $p < .01$), and having a HS/GED or lower education level (IRR = .62, $p < .05$) were all associated with a lower number of URAI partners.

Insert Figure 4 about here

As with the prior two models, interaction terms for both cohort (LR chi-square_(df=14) = 136.43, $p < .001$) and serostatus (LR chi-square_(df=14) = 47.99, $p < .001$) by time were also statistically significant and retained in the model. The cohort by time interaction effect (Figure 4) was due to three very different temporal patterns for each cohort: participants in the first cohort showed very large drops in the rates of URAI partners regardless of serostatus whereas cohort 2 had persistently low (near zero) URAI partners over nine interview periods assessed. Cohort 3, however, showed a striking and increasing rebound in the number of URAI partners, reversing the trends seen with cohorts 1 and 2. The serostatus by time interaction effect is attributable to seroconverters reporting larger relative decreases in the number of URAI partners at every interview following the indexed seroconversion interview (6-months, IRR = .52, $p < .01$; 1-year, IRR = .50, $p < .01$; 18-months, IRR = .30, $p < .001$; 2-years, IRR = .29, $p < .001$).

Discussion

This study of MACS participants examined the temporal pattern of stimulant/nitrite use among MSM over four-and-a-half-year periods centered around the time of seroconversion. Results indicate that study participants, including those who seroconverted, decreased their use of stimulants and nitrites over time. MSM who seroconverted had the highest rates of use compared with other participants, but their decrease in use over time was more pronounced. Still, even after these sharper declines, seroconverting participants continued to have the highest rate of stimulant/nitrite use relative to other participants.

These results are consistent with more circumscribed longitudinal as well as cross-sectional studies that have examined stimulant use either prior to or following seroconversion and found stimulant use to be elevated both leading up to and following seroconversion among recently HIV+ MSM. (3, 20, 24, 42, 43) Our study adds to these findings by showing that although stimulant/nitrite use among seroconverters is elevated compared with seronegative MSM as well as MSM with longer-standing HIV infections, their (seroconverters) higher rates of stimulant/nitrite use post-seroconversion reflects a decrease from even

higher pre-seroconversion rates. Their relatively high rate of stimulant/nitrite use does not represent sustained or increased use as might be concluded if only post-seroconversion data are examined.

Therefore, whereas the findings don't support a general pattern of increased stimulant/nitrite use as an immediate response to HIV seroconversion, MSM who seroconvert continue to evidence relatively higher rates of stimulant/nitrite use and riskier sex than MSM who remain seronegative or whose seroconversion was a more distal event. Moreover, despite declining use, substance use among recently seroconverted MSM remains an issue immediately post-seroconversion and should be assessed and, as needed treated particularly given it's known negative association with medication adherence. Similarly, the rates of male sexual and URAI partners also decreased over time. As with stimulant/nitrite use, seroconverters had the highest rates of male sexual intercourse and URAI partners over time and across cohorts but sharply decreased their rates of sexual partners. They maintained or continued lowering these rates across the two-years of post-conversion interviews.

Cohort-related effects. However, these just-noted changes over time in stimulant/nitrite use and numbers of male sexual partners, particularly number of URAI partners, were subject to cohort-related effects. MACS recruitment of MSM in three temporally distinct cohorts provided the opportunity to examine the effects of changing and unique historical contexts such as medical advancements in HIV treatment as well as changing cultural norms that have accompanied and framed the HIV epidemic in the United States.(44) We believe the significant cohort and cohort-by-time effects reflect these macro-level changes and show how broader, contextual factors influence individual behavior. These effects are most evident for the third (2001-2003) MACS recruitment cohort. Averaging across time and serostatus, participants in the third cohort, which includes higher proportions of African American (42.3%) and Latino participants (32.1%) with lower education levels (34.6% with ≤ 12 years) and a higher mean age at seroconversion(45), had the highest rates of stimulant use even though, as shown in Figure 2, the rates of the first cohort appear higher overall. This apparent discrepancy is because unlike participants in the first two MACS cohorts, participants in the third cohort maintained their stimulant/nitrite use over time

regardless of serostatus. The unique temporal pattern for the third cohort is consistent with the findings of other studies that show an increase in stimulant use among MSM that began approximately in the late 1990s and continuing through the present. (6, 10, 19, 46)

Cohort differences appear to be most pronounced for number of URAI partners. Whereas participants in the first MACS cohort showed steep and continued declines in URAI partners over time, second cohort participants maintained an extremely low rate. Conversely, cohort 3 participants had a sharp increase in number of URAI partners over time. We believe this finding captures several important contextual and historical influences: For members of the second cohort, who enrolled in 1987 – 1991 when contracting HIV was most likely to result in death and who had likely witnessed first-hand the death of many partners and friends, stimulant/nitrite use and sexual risk behaviors were at their lowest levels. Third cohort MACS participants were recruited ten years later following the advent and increasing use of much more effective treatments for HIV circa the mid 1990s (i.e., highly active anti-retroviral treatment or HAART).(47) The resultant “treatment optimism” as well as “safe-sex fatigue” along with the emerging availability of the Internet for readily finding sexual partners were all likely contributors to the rebound in stimulant/nitrite use as well as to higher rates of URAI partners reflected in the cohort and cohort by time effects.(48, 49) It is important to note, however, that despite these cohort effects, seroconverting MSM had the most elevated rates of stimulant/nitrite use and highest numbers of URAI partners over time and cohort. These findings suggest that whereas cultural context plays an important role in shaping behavior, it does not completely over-ride individual-level propensities for using drugs and engaging in risky sexual behavior.

Poly-drug use. While the research is clear that stimulant/nitrite use is strongly associated with risky sexual behavior among MSM regardless of HIV serostatus, binge drinking and marijuana use also appear to contribute to and are indicative of an overall risky lifestyle that involves poly-drug use. MSM who binge drink and/or use marijuana in addition to using stimulants/nitrites appear to be at highest risk for HIV infection.(16, 37) Hence, tailored prevention and intervention efforts need to take what is likely

opportunistic and “wide-ranging” use of multiple drugs into account for this highest risk group of MSM regardless of HIV serostatus. Binge drinking and marijuana use could, in effect, be indicators for poly-drug use that involves stimulants/nitrites. As alcohol and marijuana are less socially-sanctioned drugs than stimulants like cocaine or methamphetamine, individuals could be more likely to admit use at screening, warranting further assessment for poly-drug use and risky sex.

Limitations. Matching participants by visit and demographics across serostatus and selecting only those participants with more than two interviews reduced the pool of eligible participants and could have limited study generalizability as could the limited geographical coverage of MACS generally. Substance use and sexual behaviors over the prior six months were collected via self-report and can be subject to over- or, more likely, under-reporting particularly for sanctioned drugs like cocaine and methamphetamine.(50, 51) We used single item measures of substance use with unknown psychometric properties and we did not have measures of the motivation for substance use. Most of the MSM in this study were long-term MACS participants and were interviewed and tested repeatedly every six months over many years. Participation in the study could have increased participants’ awareness of HIV-risk factors on a regular basis thereby affecting their rates of substance use as well as sexual behavior contributing to the decreases over time that we found for both. The relatively small numbers of participants in cohorts two and three means that cohort effects for these participants, especially for URAI partners where the rates of having any partners were relatively low, should be interpreted with caution. Recent studies suggest different trends in stimulant use among young MSM, meaning that the findings for the MACS recruitment cohorts might no longer apply to the current generation of MSM.(46) The finding of distinct temporal patterns of stimulant use and URAI partners by cohort underscores the importance of macro-level and historical factors and the need to obtain comparable data from more recent cohorts of MSM.

Conclusions and recommendations. This study contributes to the literature on stimulant use and sexual behavior of MSM by taking advantage of the unique opportunity afforded by the MACS to compare changes over time prior to and following HIV seroconversion. Our findings suggest that among MSM, both

risky sexual behavior and stimulant/nitrite use tend to decrease following an HIV diagnosis. These findings are encouraging as they suggest HIV+ MSM, in general, do act to reduce their chances of spreading HIV. However, the findings also show sexual behavior and drug use are based on individual factors such as age and race/ethnicity as well as macro-level, social norms and historical events which can act to increase an individual's level of behavior. This finding means that community-level interventions aimed at changing social and cultural norms could be at least as important as individual-level interventions in reducing the still high HIV infection rate among MSM; both are clearly needed.

Relatedly, it is interesting to note that research has found some individuals maintain or even increase stimulant use after being diagnosed with HIV and that the intra-individual pattern of stimulant use can vary episodically over time including substitution of one stimulant (cocaine) for another (methamphetamine). (52, 53) We also found substantial inter- and intra-individual variation in stimulant/nitrite use as evidenced by the variation in intercepts and residuals in the statistical models. The motivations behind, or causes of increased or sustained use remain unclear as we focused on average behaviors in this study and did not try to further determine or characterize variation at the individual level.(54) Yet because of the individual as well as public health concerns represented, we believe further researching the small subgroup of MSM who might maintain or increase substance use and high rates of risky sexual behaviors post-seroconversion is warranted. Such study will help us better understand the reasons why this minority's high-risk behavior runs contrary to the majority, and how to more effectively engage them in health promotion and HIV prevention/risk-reduction interventions. At the same time, we should also note that MSM whose substance use puts them at high risk are indeed in the minority; identifying the resiliencies of most MSM who are NOT high-risk substance users might also provide important information for shaping more successful individual and community-based interventions.(25)

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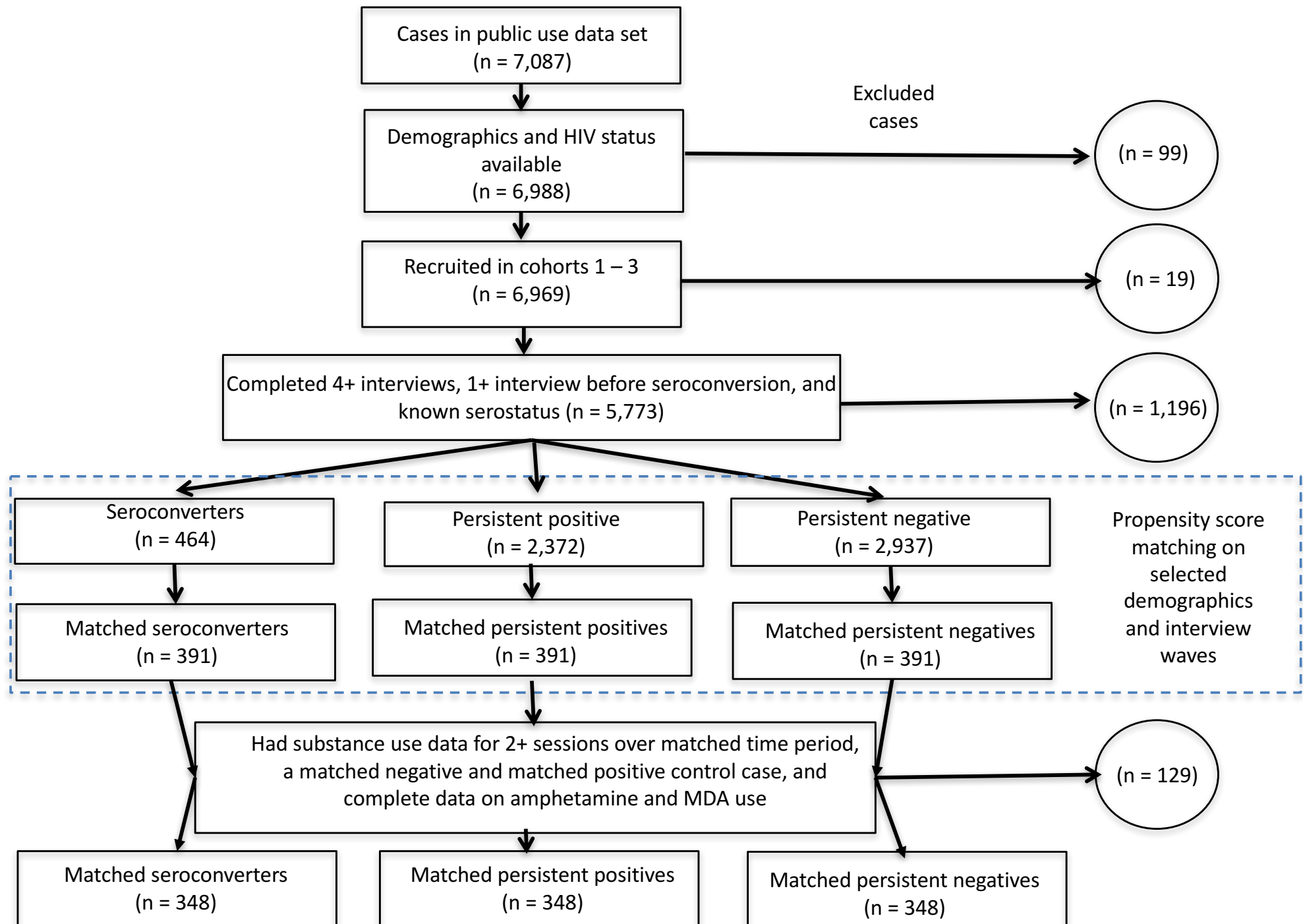
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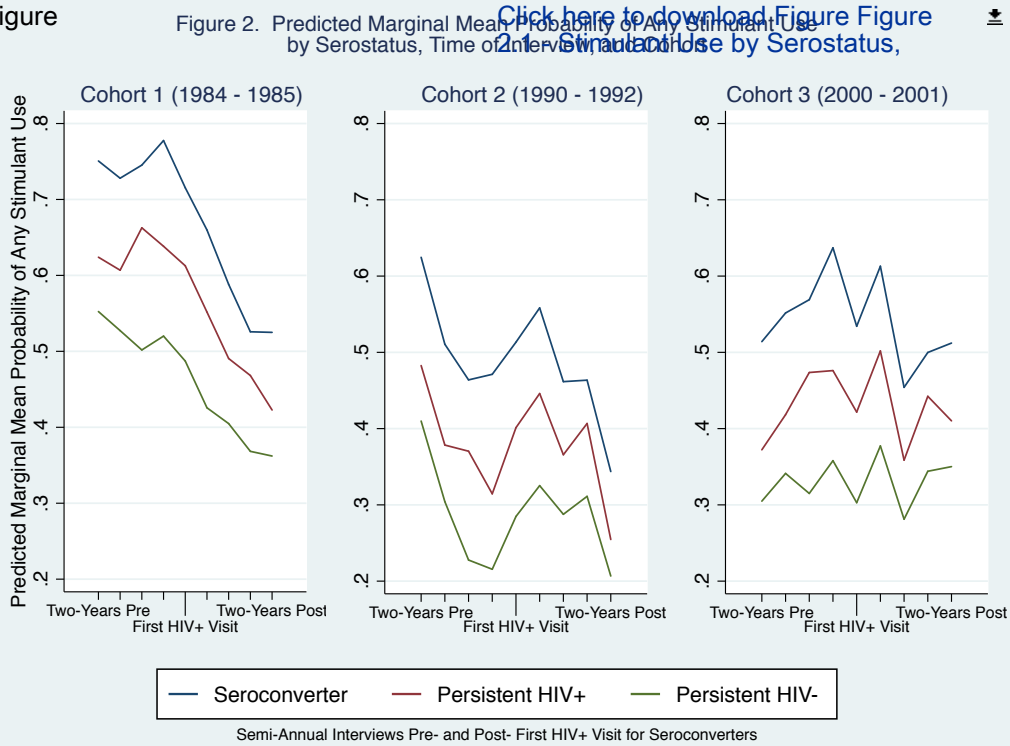
Figure 1. Participant selection process by exposure status and corresponding sample sizes.





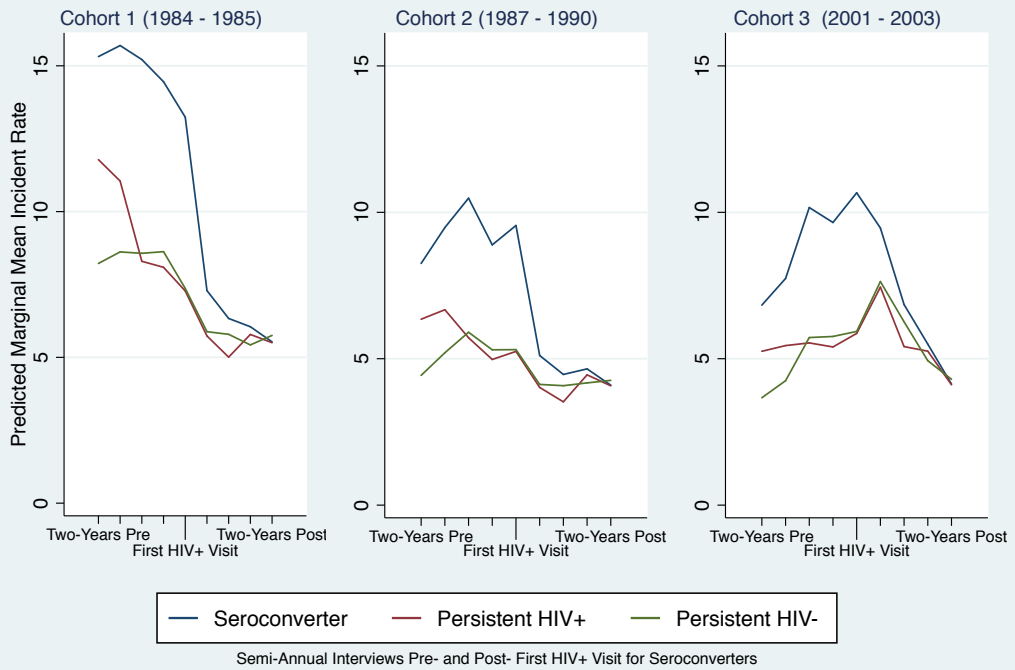
Figure

Figure 2. Predicted Marginal Mean Probability of Any Stimulant Use by Serostatus, Time of Interview, and Cohort



Figure

Figure 3. Predicted Marginal Mean Incident Rate of Male Sex Partners by Serostatus, Time of Interview, and Cohort



Figure

Figure 4. Predicted Marginal Mean Incident Rate of URAI by Serostatus, Time of Interview, and Cohort

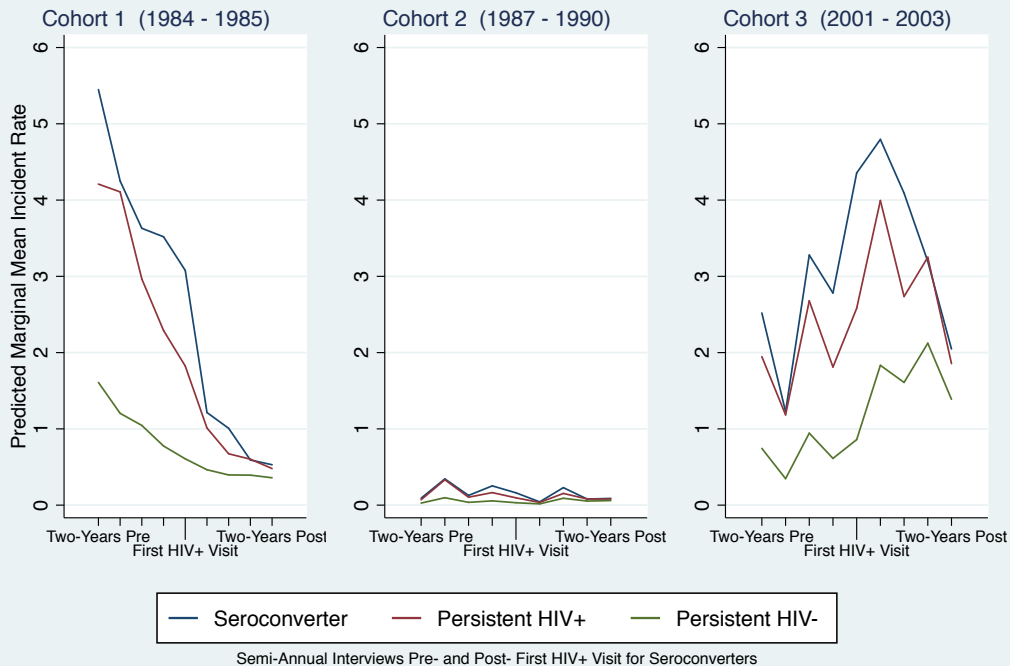


Table 1.

Demographics, Substance Use, and Number of Male Sexual Partners by HIV Serostatus

	HIV Serostatus	Seroconversion (N = 348)		HIV+ (N = 348)		HIV- (N = 348)		Totals (N = 1,044)		
		N	%(SD)	N	%(SD)	N	%(SD)	N	%(SD)	
Cohort (recruitment years)										
	1 (1984 - 1985)	307	88.2%	307	88.2%	307	88.2%	921	88.2%	NS
	2 (1987 - 1991)	15	4.3%	15	4.3%	15	4.3%	45	4.3%	
	3 (2001 - 2003)	26	7.5%	26	7.5%	26	7.5%	78	7.5%	
Mean number of interviews		22.7 (15.2)		23.4 (16.0)		25.3 (14.5)		23.8 (15.2)		NS
Race/Ethnicity										
	White	295	84.8%	290	83.3%	287	82.5%	872	83.5%	NS
	Black/African American	24	6.9%	31	8.9%	26	7.5%	81	7.8%	
	Latino	29	8.3%	27	7.8%	35	10.1%	91	8.7%	
Education (highest grade)										
	< High school	9	2.6%	9	2.6%	15	4.3%	33	3.2%	NS
	High school	35	10.1%	30	8.6%	35	10.1%	100	9.6%	
	Some college	118	33.9%	112	32.2%	110	31.6%	340	32.6%	
	College degree	77	22.1%	86	24.7%	84	24.1%	247	23.7%	
	Post-graduate	109	31.3%	111	31.9%	104	29.9%	324	31.0%	
Mean age at study admission (in years)		32.6 (7.9)		33.0 (6.7)		33.3 (8.0)		33.0 (7.6)		NS
Mean number of interviews MACS study ^a		22.8 (15.2)		23.6 (16.1)		25.5 (14.6)		24.0 (15.3)		NS
Mean number of interviews in sampled time frame ^a		6.3 (1.8)		6.4 (1.8)		6.3 (1.9)		6.4 (1.8)		NS
Alcohol/other substance use (past 6 months)										
	Weekly or more frequent binge drinking	137	39.4%	121	34.8%	124	35.6%	382	36.6%	NS
	Marijuana/Hashish	222	63.8%	252	72.4%	187	53.7%	661	63.3%	**
	Cocaine (any form)	121	34.8%	136	39.1%	86	24.7%	343	32.9%	***
	Amphetamine/Methamphetamine	78	22.4%	72	20.7%	44	12.6%	194	18.6%	***
	MDA ("Ecstasy")	28	8.0%	46	13.2%	14	4.0%	88	8.4%	***
	Amyl nitrites ("Poppers")	238	68.4%	208	59.8%	161	46.3%	607	58.1%	***
	Any use of 2+ stimulants ^b	267	76.7%	242	69.5%	189	54.3%	698	66.9%	***
	Any stimulants + binge drinking ^c	51	14.7%	37	10.6%	42	12.1%	130	12.5%	NS
Mean number of male sex partners (past 6 months)		18.4 (38.6)		11.0 (17.6)		10.5 (28.5)		13.3 (30.1)		***
Mean number of men had URAI (past 6 months) ^d		1.6 (7.9)		0.9 (2.6)		0.2 (1.0)		0.9 (4.9)		***

Note. Except for mean number of interviews, statistics are based on the first non-missing value for each variable across all available selected interview waves for each participant. Statistical significance for categorical variables is based on likelihood-ratio chi-square tests and oneway ANOVA F-tests for interval level variables. Figures reflect N's and percentages unless otherwise indicated.

^a Mean number of interviews was measured as the total number of MACS interviews for which a participant had data on past-six month substance use and sexual behavior. Sampled time frame refers solely to the interviews done in the two years prior and two years post the first HIV+ visit of the seroconverting case in each matched triad. This period of time covered nine possible interviews, including the seroconversion interview.

^b Any use of stimulant drugs is defined as the use of 2 or more of the following drugs in the previous 6 months: cocaine, amphetamine/methamphetamine, MDA, and amyl nitrites.

^c Any stimulants + binge drinking is defined as the use of 2 or more stimulant drugs plus binge drinking (i.e., 5 or more drinks on a weekly or more frequent basis) during the previous six months.

^d URAI is defined as unprotected receptive anal intercourse.

NS = non-significant; * p < .05; ** p < .01; *** p < .001

Table 2.

Mixed Effects Regression Results for Past Six Month Stimulant Use, Male Sex Partners, and Unprotected Receptive Anal Intercourse Partners

		Stimulant Use		Number of Male Sex Partners		Number of Unprotected Receptive Anal Intercourse Partners	
		OR	(95% CI)	IRR	(95% CI)	IRR	(95% CI)
Main Effects							
	Age	0.96	(0.93 - 0.98) **	1.00	(0.99 - 1.00)	0.95	(0.94 - 0.96) ***
	Race/ethnicity						
	Black/African American	0.26	(0.11 - 0.71) **	0.57	(0.42 - 0.77) ***	0.58	(0.36 - 0.92) *
	Hispanic	0.88	(0.36 - 2.17)	1.20	(0.90 - 1.59)	1.18	(0.77 - 1.78)
	Other race/ethnicity (White = reference)	0.71	(0.37 - 1.75)	0.50	(0.28 - 0.89) *	0.20	(0.07 - 0.54) **
	Education level						
	High school or GED	0.81	(0.37 - 1.75)	0.80	(0.63 - 1.03)	0.62	(0.43 - 0.90) *
	Some college or college graduate ($<$ High school = reference)	0.75	(0.45 - 1.24)	0.97	(0.83 - 1.13)	0.81	(0.64 - 1.03)
	Past 6 month substance use						
	Binge drinking	2.21	(1.64 - 2.98) ***	1.24	(1.15 - 1.32) ***	1.42	(1.26 - 1.61) ***
	Marijuana/hashish	8.89	(6.73- 11.74) ***	1.28	(1.20 - 1.38) ***	1.39	(1.21 - 1.59) ***
	Stimulants (No use = reference)	NE		1.56	(1.10 - 1.54) ***	2.20	(1.91 - 2.54) ***
	Serostatus						
	Seroconversion	10.24	(4.77 - 22.02) ***	1.62	(1.28 - 2.05) ***	5.07	(3.51 - 7.31) ***
	Persistent HIV positive (Persistent HIV negative = reference)	3.42	(1.62 - 7.22) **	0.82	(0.54 - 1.19)	3.00	(2.06 - 4.38) ***
	Cohort						
	Second (recruited 1987 - 1990)	0.13	(0.02 - 0.73) ***	0.72	(0.43 - 1.21)	0.05	(0.88 - 5.20)
	Third (recruited 2001 - 2003) (Cohort recruited 1984-1955 = reference)	0.15	(0.04 - 0.59) **	0.81	(0.36 - 1.12)	1.41	(1.69 - 6.56) **
	Time						
Pre-Seroconversion Interview	2 years	1.88	(0.88 - 3.99)	1.12	(0.92 - 1.35)	2.65	(1.74 - 4.01) ***
	18 months	1.47	(0.76 - 2.87)	1.17	(0.99 - 1.38)	1.98	(1.35 - 2.91) ***
	1 year	1.15	(0.61 - 2.17)	1.16	(0.99 - 1.36)	1.72	(1.20 - 2.48) **
	6 months (Seroconversion interview = reference)	1.37	(0.61 - 2.17)	1.17	(1.02 - 1.34) *	1.28	(0.93 - 1.74)
Post-Seroconversion Interview	6 months	0.55	(0.31 - 0.96) *	0.80	(0.69 - 0.92) **	0.76	(0.54 - 1.09)
	1 year	0.45	(0.25- 0.79) **	0.79	(0.67 - 0.91) **	0.65	(0.45 - 0.95) *
	18 months	0.31	(0.17 - 0.55) ***	0.74	(0.63 - 0.86) ***	0.65	(0.44 - 0.94) *
	2 years	0.29	(0.16 - 0.53) ***	0.78	(0.67 - 0.91) **	0.59	(0.40 - 0.88) *

Note. All analyses are based on the sample of 1,044 MACS participants composed of equal numbers (N = 348) of participants who seroconverted and matched controls that were persistently HIV positive or persistently HIV negative over the course of study participation. These participants provided a total of 6,641 interviews for the analyses although owing to a small amount of missing data on model covariates, the actual number of interviews analyzed ranged from 6,605 for stimulant use to 6,554 for number of unprotected receptive anal intercourse partners.

Stimulant use was defined as any use of two of more of the following drugs in the six months prior to the interview: amphetamine/methamphetamine, cocaine, MDA, and amyl nitrites. Interview times for all participants were defined relative to the first HIV positive interview of the seroconverting case in each matched group. Number of male sex partners was defined as the number of men with whom the participant had oral or anal intercourse in the prior six months. Binge drinking was defined as having five or more drinks on a single occasion on at least a weekly basis in the past six months.

All models included a random intercept for each participant with fixed effects coefficients for model covariates estimated using mixed effects binary logistic or negative binomial regression with unstructured residual covariance matrices. Initial models were estimated using maximum likelihood estimation with likelihood ratio tests were used to compare the addition of interaction terms to the main effects only model. Final models were estimated using restricted maximum likelihood, robust standard errors, and adaptive quadrature with 30 integration points.

OR = Odds Ratio; IRR = Incidence Rate Ratio; NE = Not Estimated

* = $p < .05$; ** = $p < .01$; *** = $p < .001$

Table 2. (continued)

Mixed Effects Regression Results for Past Six Month Stimulant Use, Male Sex Partners, and Unprotected Receptive Anal Intercourse Partners

			Stimulant Use		Number of Male Sex Partners		Number of Unprotected Receptive Anal Intercourse Partners	
			OR	(95% CI)	IRR	(95% CI)	IRR	(95% CI)
Interaction Effects								
Cohort by Time								
Second Cohort Pre-Seroconversion Interview	2 years	1.98	(0.22 - 17.91)	0.75	(0.43 - 1.03)	0.32	(0.01 - 6.90)	
	18 months	0.84	(0.12 - 5.91)	0.84	(0.50 - 1.40)	1.54	(0.14 - 17.60)	
	1 year	0.44	(0.06 - 3.17)	0.96	(0.57 - 1.59)	0.67	(0.03 - 13.19)	
	6 months	0.31	(0.05 - 1.90)	0.85	(0.52 - 1.39)	1.37	(0.12 - 16.21)	
Second Cohort Post-Seroconversion Interview	6 months	2.85	(0.45 - 18.18)	0.97	(0.58 - 1.63)	0.67	(0.29 - 15.82)	
	1 year	2.31	(0.39 - 13.80)	0.98	(0.58 - 1.64)	4.34	(0.37 - 50.90)	
	18 months	4.35	(0.71 - 26.59)	1.07	(0.63 - 1.80)	2.59	(0.16 - 40.76)	
	2 years	1.32	(0.17 - 10.27)	1.03	(0.57 - 1.84)	3.17	(0.16 - 64.13)	
Third Cohort Pre-Seroconversion Interview	2 years	0.54	(0.13 - 2.32)	0.55	(0.38 - 0.81) **	0.33	(0.17 - 0.64) **	
	18 months	1.02	(0.25 - 4.22)	0.61	(0.42 - 0.89) *	0.20	(0.10 - 0.43) ***	
	1 year	0.99	(0.27 - 3.67)	0.83	(0.59 - 1.16)	0.64	(0.34 - 1.19)	
	6 months	1.31	(0.35 - 4.90)	0.83	(0.59 - 1.16)	0.56	(0.30 - 1.05)	
Third Cohort Post-Seroconversion Interview	6 months	4.00	(1.12 - 14.34) *	1.61	(1.16 - 2.24) **	2.79	(1.57 - 4.96) ***	
	1 year	1.76	(0.46 - 6.65)	1.34	(0.96 - 1.87)	2.87	(1.58 - 5.20) **	
	18 months	5.05	(1.41 - 18.08) *	1.12	(0.80 - 1.58)	3.81	(2.08 - 7.00) ***	
	2 years	5.73	(1.55 - 21.27) **	0.93	(0.64 - 1.32)	2.73	(1.40 - 5.32) **	
(First Cohort/Seroconversion Interview = reference categories)								
Serostatus by Time								
Seroconverters Pre-Seroconversion Interview	2 years	0.47	(0.16 - 1.46)	1.04	(0.81 - 1.33)	0.67	(0.40 - 1.10)	
	18 months	0.72	(0.26 - 2.00)	1.01	(0.81 - 1.27)	0.70	(0.44 - 1.10)	
	1 year	0.66	(0.28 - 1.55)	0.99	(0.80 - 1.22)	0.69	(0.44 - 1.06)	
	6 months	1.89	(0.86 - 4.16)	0.93	(0.78 - 1.15)	0.90	(0.62 - 1.30)	
Seroconverters Post-Seroconversion Interview	6 months	0.76	(0.34 - 1.69)	0.69	(0.57 - 0.83) ***	0.52	(0.34 - 0.78) **	
	1 year	0.41	(0.18 - 0.95) *	0.61	(0.50 - 0.74) ***	0.50	(0.32 - 0.78) **	
	18 months	0.30	(0.13 - 0.70) **	0.62	(0.51 - 0.76) ***	0.30	(0.39 - 1.02) ***	
	2 years	0.30	(0.12 - 0.77) *	0.53	(0.43 - 0.66) ***	0.29	(0.19 - 0.47) ***	
HIV Positive Pre-Seroconversion Interview	2 years	1.55	(0.55 - 4.35)	1.45	(1.12 - 1.88) **	0.87	(0.52 - 1.46)	
	18 months	0.89	(0.36 - 2.18)	1.30	(1.03 - 1.63) *	1.13	(0.71 - 1.82)	
	1 year	0.80	(0.34 - 1.88)	0.98	(0.79 - 1.22)	0.94	(0.61 - 1.47)	
	6 months	1.48	(0.69 - 3.21)	0.95	(0.79 - 1.14)	0.98	(0.67 - 1.44)	
HIV Positive Post-Seroconversion Interview	6 months	0.92	(0.43 - 1.99)	0.99	(0.81 - 1.20)	0.73	(0.47 - 1.11)	
	1 year	0.56	(0.24 - 1.28)	0.88	(0.76 - 1.18)	0.57	(0.35 - 0.90) *	
	18 months	0.48	(0.21 - 1.09)	1.08	(0.88 - 1.33)	0.51	(0.32 - 0.82) **	
	2 years	0.57	(0.24 - 1.35)	0.97	(0.78 - 1.20)	0.44	(0.26 - 0.75) **	
(HIV negative /Seroconversion Interview = reference categories)								
Random Intercept Variance			9.93	(8.33 - 11.85)	1.19	(1.08 - 1.32)	2.14	(1.86 - 2.46)
Model Statistics								
Participants (N)			1,044		1,043		1,043	
Interviews (N)			6,605		6,570		6,554	
ICC			0.75	(0.72 - 0.78)	NE		NE	
Wald Chi-Square (df)			615.20(52) ***		1710.41 (55) ***		1586.95 (53) ***	

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