Published in final edited form as:
J Acquir Immune Defic Syndr. 2014 December 15; 67(5): 508–513. doi:10.1097/QAI.0000000000000364.

Stimulant Use and Progression to AIDS or Mortality After The Initiation of Highly Active Anti-Retroviral Therapy

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Abstract

Background—HIV-positive persons who use stimulants (e.g., methamphetamine) experience profound health disparities, but it remains unclear if these persist after highly active anti-retroviral therapy (HAART) initiation. Conducted within the Multicenter AIDS Cohort Study, this investigation examined if stimulant use is associated with progression to AIDS or all-cause mortality after the initiation of HAART.

Methods—Using marginal structural modeling, the cumulative proportion of visits where any stimulant use was reported (i.e., 0%, 1 – 49%, 50 – 99%, and 100%) was examined as a time-varying predictor of: 1) all-cause mortality; and 2) AIDS or all-cause mortality.

Results—Among the 1,313 men who have sex with men (MSM) who initiated HAART, findings showed no significant association of any level of stimulant use with all-cause mortality. A competing risks analysis indicated that no level of stimulant use was associated with increased AIDS-related or non-AIDS mortality separately. Among the 648 participants without AIDS at HAART initiation, a secondary analysis indicated that stimulant use at 50% or more of study visits was associated with a 1.5-fold increase in the odds of progression to AIDS or all-cause mortality (Adjusted OR = 1.54; 95% CI = 1.02 – 2.33, $p < .05$).

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Conclusions—HIV-positive, stimulant-using MSM receiving HAART appear to face no greater overall risks for all-cause, AIDS-related, or non-AIDS mortality compared to non-users. However, men without AIDS at HAART initiation who more frequently reported stimulant use demonstrated modestly increased odds of progression to AIDS or all-cause mortality. Comprehensive approaches are needed to optimize the effectiveness of HAART with stimulant-using MSM.

Keywords

Cocaine; HIV/AIDS; Methamphetamine; Mortality; Treatment as Prevention

Introduction

HIV-positive persons who use stimulants (e.g., methamphetamine, cocaine, and crack-cocaine) are at elevated risk for more rapid HIV disease progression,[1–4] though the underlying biological or behavioral mechanisms for this disturbance have not been clearly elucidated.[5–10] There is evidence that substance users are less likely to access highly active anti-retroviral therapy (HAART),[11,12] and stimulant users initiate HAART at lower T-helper (CD4+) cell counts than their peers who do not use substances.[3,5] HIV-positive persons who engage in more regular stimulant use are also at greater risk for poorer adherence to HAART, which contributes to elevated viral load,[6–8] greater risk of onward HIV transmission,[13–15] and potentially faster HIV disease progression.[5]

Studies conducted to date have not consistently observed that stimulant users on HAART experience more negative health outcomes. One recent investigation with a cohort of substance users found that crack-cocaine use predicted a greater rate of CD4+ cell count decline to less than 200 cells/μl, an effect that was most pronounced among those who were not prescribed HAART at baseline.[2] Kapadia and colleagues[3] also reported that stimulant-using women experienced a two-fold faster rate of progression to AIDS and concurrently lower rates of HAART initiation. Consistent with these results, another study conducted with this cohort of women observed that persistent and intermittent crack-cocaine users were more likely to develop an AIDS-defining illness (ADI), but only persistent crack-cocaine users displayed a 3-fold greater AIDS-related mortality rate after controlling for adherence to HAART.[4] In contrast, a study with a cohort of homeless and marginally housed persons with high rates HAART utilization did not observe a significant association of current crack-cocaine use with all-cause mortality.[16] Because many studies have examined the effects of stimulant use irrespective of when or if HAART was started, it is difficult to determine the extent to which negative health outcomes among stimulant users are attributable to delayed initiation of HAART or poorer adherence to HAART.

In order to inform evidence-based practice, this study examined if time-varying stimulant use independently predicted increased risk of HIV disease progression outcomes after the initiation of HAART in the Multicenter AIDS Cohort Study (MACS). We hypothesized that stimulant use would be independently associated with increased all-cause mortality as well as progression to AIDS or all-cause mortality after accounting for HAART adherence.

Methods

Study Design and Procedures

Participants were enrolled in the MACS, an ongoing prospective study of HIV infection among gay and bisexual men as well as other men who have sex with men (MSM) in the United States.[17,18] Enzyme-linked immunosorbent assays with confirmatory Western Blot tests were performed on all participants at enrollment and every semiannual visit thereafter for initially HIV-negative participants. T-lymphocyte subsets were quantified using standardized flow cytometry and HIV viral load was measured using standardized polymerase chain reaction methods.[19,20] MACS protocols were approved by the institutional review boards of each of the participating centers. Informed consent was obtained from all participants.

The present study included all MACS participants who initiated HAART, had at least one follow-up visit with assessment of stimulant use after initiation, and had data for covariates available within two years before stimulant use was assessed. This study utilized data collected prospectively from MACS visits 26 to 57 (October 1996 – September 2012). Baseline was defined as the first visit after initiating HAART. The characterization of HAART regimens was guided by the DHHS/Kaiser Panel guidelines and defined as three or more antiretroviral drugs consisting of: 1) one or more protease inhibitors; or 2) one non-nucleoside reverse transcriptase inhibitor; or 3) the nucleoside reverse transcriptase inhibitors - Abacavir or Tenofovir; or 4) an integrase or an entry inhibitor.[21]

Outcomes: AIDS and All-Cause Mortality

Using the 1993 Centers for Disease Control classification system,[22] participants were assessed for an ADI during MACS visits. Participants met the criteria for AIDS if they were diagnosed with an ADI or had a CD4+ cell count less than 200 cells/μl or CD4+ cell percentage of less than fourteen. The date of AIDS diagnosis was confirmed through medical chart abstraction and interviews with medical providers. Using the National Death Index – Plus, final mortality information (including date and cause) was obtained for enrolled participants over the follow-up period.

Primary Predictor: Stimulant Use

Participants reported whether they had used methamphetamine, cocaine, crack-cocaine, or ecstasy since their last MACS visit. Participants were categorized as reporting any stimulant use (1) or no stimulant use (0) at each visit. The time-varying, cumulative proportion of MACS visits with any self-reported stimulant use was calculated. Compared to a reference group that reported no stimulant use (0%), patterns of intermittent (i.e., 1 – 49%, 50 – 99%) and persistent (i.e., 100%) stimulant use were characterized to investigate an expected dose-response association.

Covariates

Demographics and HIV disease markers were included to adjust for possible confounding. Age at each MACS study visit was calculated using self-reported date of birth and was treated as a time-varying continuous covariate (centered at 50 years). Self-reported race/

ethnicity was categorized as Caucasian (reference group), African American/Black, and Hispanic/Latino or other ethnic minority. Self-reported highest level of education completed at enrollment was categorized as high school or less (reference group), some college (grades 13 – 15), and college graduate or greater (grade 16 or more). CD4+ cell count prior to HAART initiation was measured using peripheral venous blood samples for the MACS visit before starting HAART. For those who began HAART prior to enrolling in the MACS, pre-HAART CD4+ cell count was measured using medical chart abstraction. Participants with a pre-HAART CD4+ cell count of 500 or more cells/μl (reference group) were compared to those with 499-350, 349-200, and less than 200 cells/μl. Time-varying CD4+ cell count, $\log_{10}$ HIV viral load, and self-reported HAART adherence were lagged (approximately six months) to adjust for time-dependent confounding with stimulant use. Self-reported HAART adherence was measured using a single item where participants indicated how often they took HAART medications as prescribed by selecting one of the following options: 100%, 95 – 99%, 75 – 94%, and < 75%.

Health status indicators and behavioral factors were measured as possible confounders. Hepatitis C virus (HCV) co-infection was defined as antibody or RNA positive at baseline. Other lagged, time-varying health status indicators measured at each visit included: body mass index (BMI; weight in kg/height in meters^2), high blood pressure (i.e., systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or diagnosed with hypertension and use of antihypertensive medications), and dyslipidemia (i.e., fasting total cholesterol ≥ 200 mg/dl or LDL ≥ 130 mg/dl or HDL < 40 mg/dl or triglycerides ≥ 150 mg/dl or use of lipid lowering medications with self-report of clinical diagnosis in the past). Lagged, time-varying self-reported physical health and mental health were assessed using the SF-36 Physical Component Summary and Mental Component Summary scores.[23] Participants with scores of 16 or greater on Centers for the Epidemiologic Study of Depression (CES-D) scale were categorized as reporting clinically significant distress,[24,25] which was examined as a lagged, time-varying covariate. Finally, binge drinking (i.e., ≥ 5 alcoholic drinks per day for at least once a month) and cigarette smoking in the last 6 months were included as time-varying covariates.

Marginal Structural Model Analyses

Because we were concerned that declining health might lead to a subsequent reduction in the use of stimulants (i.e., a “sick quitter” effect), marginal structural modeling was utilized to address time-dependent confounding.[26,27] This requires an initial longitudinal unordered multinomial logistic model with time-varying stimulant use [4 categories: 0% (reference), 1 – 49%, 50 – 99%, 100%] as the outcome to obtain stabilized weights for the final weighed models. The logistic model for determining the numerator of the weights for stimulant use included all time-fixed covariates (i.e., site, race/ethnicity, education, baseline HCV status, and pre-HAART CD4+ cell count), number of visits from baseline, and cumulative percent of the prior three visits where any stimulant use was reported. To obtain the denominator of the weights for stimulant use, all time-varying covariates were also included (i.e., age, CD4+ cell count, HIV viral load, self-reported HAART adherence, BMI, high blood pressure, dyslipidemia, self-reported physical health, self-reported mental health, CES-D, binge drinking, and cigarette smoking). Similarly, a second logistic model determined the weights

of remaining uncensored to control for informative dropout. The final stabilized weights were calculated by multiplying the weights of stimulant use and weights of remaining uncensored. If the weights were greater than four, they were set to four.

The primary analyses consisted of separate weighted, pooled logistic regression models for time to all-cause mortality and time to AIDS or all-cause mortality. Pooled logistic regression is a standard method for the analysis of discrete-time survival data, involving expansion of the binary outcome data to reflect a time-to-event outcome.[28] A weighted competing risks analysis was also performed with a pooled multinomial logistic model (i.e., alive, AIDS-related mortality, and non-AIDS mortality) to examine the association of stimulant use with AIDS-related and non-AIDS mortality separately. This was a discrete version of a competing risks analysis based on cumulative incidence functions.[28]

Results

The sample included 1,313 HIV-positive MSM contributing 19,270 person-visits. The median number of observations per participant was 15 (IQR = 7 – 20). There were 190 deaths (50% AIDS-related; 38% non-AIDS related, and 12% indeterminate) during the 8.5-year median follow-up period (IQR = 4.2 – 11.5 years). The crude mortality rate was 14.5% (95% CI = 12.6% – 16.5%). Among the 648 participants (8,657 person-visits) without AIDS at the initiation of HAART, 15% (N = 97; 95% CI = 12% – 18%) developed AIDS over the course of follow-up. Table 1 provides detailed information regarding the demographic and clinical characteristics of participants.

Before performing the marginal structural modeling analyses, the distribution of the final stabilized weights was examined. Prior to trimming, the averages in the four stimulant groups were very close to one. The minimum values in each group were greater than 0.15 and the number exceeding four was very small, less than 1% and only in one group. This provided support for the validity of the marginal structural pooled logistic regression model.

As shown in Table 2, results of marginal structural model analyses demonstrated that HCV co-infection at baseline (Adjusted OR (AOR) = 2.11; 95% CI = 1.40-3.17) as well as pre-HAART CD4+ cell counts from 200 – 349 cells/ μl (AOR = 1.84; 95% CI = 1.07-3.16) and less than 200 cells/μl (AOR = 4.37; 95% CI = 2.68 – 7.12) were associated with increased odds of all-cause mortality over follow-up. No level of stimulant use was significantly associated with increased odds of all-cause mortality. Results of a competing risks analysis also indicated that stimulant use was not significantly associated with increased odds of AIDS-related or non-AIDS mortality separately.

HCV co-infected participants (AOR = 2.28; 95% CI = 1.29-4.02) had increased odds of progression to AIDS or all-cause mortality over follow-up. However, no level of stimulant use was significantly associated with increased odds of progression to AIDS or all-cause mortality. Where participants reported stimulant use at 50 – 99% and 100% of visits there were comparable associations with progression to AIDS or all-cause mortality. Consequently, a secondary analysis was conducted to combine these categories of time-varying stimulant use. Findings suggested that where participants reported using stimulants

at 50% or more of study visits, there was a 1.5-fold increase in the odds of progression to AIDS or all-cause mortality over follow-up (AOR= 1.54; 95% CI = 1.02 – 2.33, $p < .05$) compared to those who reported no stimulant use.

Discussion

This study of HIV-positive MSM observed that stimulant use over time was not significantly associated with greater odds of all-cause mortality. This absence of a statistically significant association of stimulant use with mortality was unchanged in competing risk analysis that examined AIDS-related and non-AIDS mortality separately. In secondary analyses with a subset of participants without AIDS at HAART initiation, any self-reported stimulant use at 50% or more of study visits was associated with a 1.5-fold increase in the odds of progression to AIDS or all-cause mortality. Although stimulant use was not linked to overall mortality, more frequent stimulant use was modestly associated with HIV disease progression (i.e.., AIDS or all-cause mortality) in men without AIDS at HAART initiation.

The present study indicated that men with a pre-HAART CD4+ cell count below 350 cells/μl had increased odds of all-cause mortality. This underscores the expected benefits of early HAART initiation to optimize health outcomes.[13,29] Although HIV-positive stimulant users are more likely to experience difficulties with adherence,[6,7] ensuring that these patients have access to HAART at higher CD4+ cell counts could optimize health outcomes and potentially decrease onward HIV transmission rates similar to non-stimulant-using individuals.[13] In the context of HIV care, implementing evidence-based interventions to enhance adherence as well as promoting linkages to formal substance abuse treatment would enhance the quality of care that stimulant-using MSM receive and could maximize the benefits that this population derives from HAART.[30–32]

Findings from this study must be interpreted in context of some important limitations. First and foremost, the overall mortality rate in the MACS was relatively low after the initiation of HAART and this may have limited statistical power to detect an association of stimulant use with mortality outcomes. It is also noteworthy that stimulant use was assessed using self-report measures that did not adequately characterize patterns of use, route(s) of administration, or screen for the presence of a stimulant use disorder. Different stimulants or modes of stimulant administration could increase risk for specific illnesses, including those that are indicative of clinical AIDS. For example, there is some evidence that smoking stimulants such as crack-cocaine increases risk for pulmonary illnesses like tuberculosis and bacterial pneumonia.[33,34] Finally, only 26% of cohort members reported any stimulant use at baseline; cohort studies that systematically enroll larger samples of active and former stimulant users would measure with greater precision any associations between stimulant use and specific negative health outcomes. Future cohort studies should also include biomarkers of recent stimulant use, diagnostic interviews for stimulant use disorders, and multi-method assessment of HAART adherence.

There is emerging evidence that even HIV-positive persons who achieve sustained viral suppression are at elevated risk for developing HIV-associated non-AIDS conditions.[35] However, the present study did not examine relationships between stimulant use and specific

illnesses that are not AIDS-defining. Stimulants such as cocaine also have well characterized deleterious effects on cardiovascular functioning,[36],[37] and future research should examine whether stimulant use increases risk of cardiovascular events or cardiovascular-related death among HIV-positive persons. Bearing in mind the HCV co-infection was independently associated with more than a 2-fold increase in the odds of progression to AIDS or all-cause mortality, the effects of stimulant use on hepatoxicity could accelerate the onset or course of hepatic diseases.[38] Although further research is needed to examine stimulant-induced end-organ damage in HIV-positive persons, findings from the present study have important clinical implications. Stimulant-using MSM should have access to HAART because they derive life saving benefits that are comparable to non-users, and comprehensive approaches to HIV care could optimize the effectiveness of HAART with this population.[32]

Acknowledgments

Data in this manuscript were collected by the Multicenter AIDS Cohort Study (MACS) with centers (Principal Investigators) at: Johns Hopkins University Bloomberg School of Public Health (Joseph Margolick), U01-AI35042; Northwestern University (Steven Wolinsky), U01-AI35039; University of California, Los Angeles (Roger Detels), U01-AI35040; University of Pittsburgh (Charles Rinaldo), U01-AI35041; the Center for Analysis and Management of MACS, Johns Hopkins University Bloomberg School of Public Health (Lisa Jacobson), UM1-AI35043. The MACS is funded primarily by the National Institute of Allergy and Infectious Diseases (NIAID), with additional co-funding from the National Cancer Institute (NCI). Targeted supplemental funding for specific projects was also provided by the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute on Deafness and Communication Disorders (NIDCD). MACS data collection is also supported by UL1-TR000424 (JHU CTSA). Website located at http://www.statepi.jhsph.edu/macs/macs.html. The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health (NIH).

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Table 1

Demographic and clinical characteristics at the visit after HAART initiation (N = 1,313)

Site	
Baltimore	314(23.9)
Chicago	311(23.7)
Pittsburgh	295(22.5)
Los Angeles	393(29.9)
Age, median (IQR), yrs	42.9(37.9–48.3)
Ethnicity, n (%)	
Caucasian	758(57.7)
Hispanic/Latino	187(14.3)
African American	348(26.5)
Other Ethnic Minority	20(1.5)
Education, n (%)	
High School or Less	319(24.3)
Some College	417(31.8)
College Degree or Higher	577(43.9)
Ever Clinical AIDS Diagnosis, n (%)	175(13.3)
Pre-HAART CD4+ Cell Count (μl), median (IQR)	306(174–464)
< 200	397(30.2)
200 – 349	375(28.6)
350 – 499	259(19.7)
≥ 500	282(21.5)
Log_{10}HIV Viral Load, median (IQR)	3.5(1.6–4.6)
HCV-Positive, n (%)	137(10.4)
Body Mass Index, median (IQR)	24.4(22.5–27)
High Blood Pressure, n (%)	338(25.7)
Dyslipidemia, n (%)	566(43.1)
SF-36 Physical Component Summary, median (IQR)	52.3(42.9–56.1)
SF-36 Mental Component Summary, median (IQR)	51.0 (38.6–57.1)
CES-D ≥ 16, n (%)	408(31.1)
Binge Drinking, n (%)	120(9.1)
Smoking, n (%)	
Current	503(38.3)
Past	470(35.8)
Never	340(25.9)
Any Stimulant Use, n (%)	341(26)

HAART: highly active antiretroviral therapy. High Blood Pressure was defined if systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or diagnosed with hypertension and use of antihypertensive medications.

Dyslipidemia was defined if fasting total cholesterol ≥ 200 mg/dl or LDL ≥ 130 mg/dl or HDL < 40 mg/dl or triglycerides ≥ 150 mg/dl or use of lipid lowering medications with self-report of clinical diagnosis in the past.

Table 2

Marginal structural models examining stimulant use and disease progression

	All-Cause Mortality (N = 19,270 person-visits)		AIDS or All-Cause Mortality (N = 8,657 person-visits)	
	AOR (95% CI)	***p*-value**	**AOR (95% CI)**	***p*-value**
Site				
Baltimore (Reference)	1	-	1	-
Chicago	0.68 (0.45,1.01)	0.058	1.91 (1.08,3.39)	0.026
Pittsburgh	0.62 (0.40,0.96)	0.030	1.13 (0.60,2.12)	0.700
Los Angeles	0.81 (0.54,1.22)	0.313	2.14 (1.22,3.75)	0.008
Ethnicity				
Caucasian (Reference)	1	-	1	-
African American	0.67 (0.45,1.01)	0.056	0.87 (0.54,1.39)	0.558
Hispanic/Latino or Other Minority	0.60 (0.35,1.03)	0.065	0.49 (0.25,0.97)	0.040
Education				
High School or Less (Reference)	1	-	1	-
Some College	0.80 (0.53,1.21)	0.300	0.66 (0.40,1.09)	0.107
College Degree or Higher	0.74 (0.49,1.12)	0.157	0.68 (0.41,1.12)	0.131
HCV-Positive	2.11 (1.40,3.17)	< 0.001	2.28 (1.29,4.02)	0.005
Pre-HAART CD4+ Cell Count (cells/μl)				
≥ 500 (Reference)	1	-	1	-
350 – 499	1.41 (0.75,2.64)	0.284	1.22 (0.79,1.88)	0.376
200 – 349	1.84 (1.07,3.16)	0.026	1.18 (0.76,1.83)	0.459
< 200	4.37 (2.68,7.12)	< 0.001	-	-
Stimulant Use (% of Visits)				
0	1	-	1	-
1–49	0.66 (0.41,1.05)	0.079	0.90 (0.53,1.52)	0.695
50–99	1.27 (0.82,1.95)	0.283	1.55 (0.93,2.61)	0.096
100	0.69 (0.36,1.31)	0.254	1.52 (0.88,2.64)	0.134

HAART: highly active antiretroviral therapy.