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Association of Ongoing Drug and Alcohol Use with Non-Adherence to Antiretroviral Therapy and Higher Risk of AIDS and Death: Results from ACTG 362

Susan E. COHN, M.D., M.P.H.[1],[2], **Hongyu JIANG, M.S.**[3], **J. Allen MCCUTCHAN, M.D., M.Sc.**[4], **Susan L. KOLETAR, M.D.**[5], **Robert L. MURPHY, M.D.**[2], **Kevin R. ROBERTSON, Ph.D.**[6], **Annabelle DESTMAURICE, M.D.**[7], **Judith S. CURRIER, M.D., M.Sc.**[8], and **Paige L. WILLIAMS, Ph.D.**[3]

[1] University of Rochester Medical Center, Rochester, NY, United States [UO1 AI27658 and U01 A1069511]

[2] Northwestern University, Chicago, IL, United States [U01 AI069471]

[3] Harvard School of Public Health, Boston, MA, United States [U01 A1068634]

[4] University of California San Diego, San Diego, CA, United States [5 UO1 AI069432-035, P30 MH62512-08]

[5] Ohio State University, Columbus, OH, United States [5U 01 AI069474]

[6] University of North Carolina at Chapel Hill, Chapel Hill, NC, United States [U01 A125868 and AI50410, GCRC Grant #RR00046]

[7] University of Pittsburgh School of Medicine, Pittsburgh, PA, United States

[8] UCLA Medical Center, Los Angeles, CA, United States [Supported by U01 AI06924 and K24AI056933]

Abstract

Drug and alcohol use have been associated with a worse prognosis in short-term and cross-sectional analyses of HIV-infected populations, but longitudinal effects on adherence to antiretroviral therapy (ART) and clinical outcomes in advanced AIDS are less well characterized. We assessed self-reported drug and alcohol use in AIDS patients, and examined their association with non-adherence and death or disease progression in a multicenter observational study. We defined non-adherence as reporting missed ART doses in the 48 hours before study visits. The association between drug use and ART non-adherence was evaluated using repeated measures generalized estimating equation (GEE) models. The association between drug and alcohol use and time to new AIDS diagnosis or death was evaluated via Cox regression models, controlling for covariates including ART adherence. Of 643 participants enrolled between 1997–1999 and followed through 2007, at entry 39% reported ever using cocaine, 24% amphetamines, and 10% heroin. Ongoing drug use during study follow-up was reported by 9% using cocaine, 4% amphetamines, and 1% heroin. Hard drug (cocaine, amphetamines, or heroin) users had 2.1 times higher odds (p=0.001) of ART non-adherence in GEE models and 2.5 times higher risk (p=0.04)

Address for Correspondence and reprint requests: Susan E. Cohn, MD, MPH, Professor of Medicine, Infectious Diseases Division, Northwestern University, Feinberg School of Medicine, 645 N. Michigan Avenue, Suite 900, Chicago, IL 60611, 312-926-3693 (0ffice), 312-695-5088 (fax), Susan-Cohn@northwestern.edu.

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of AIDS progression or death in Cox models. Use of hard drugs was attenuated as a risk factor for AIDS progression or death after controlling for non-adherence during follow-up (HR=2.11, p=0.08), but was still suggestive of a possible adherence-independent mechanism of harm. This study highlights the need to continuously screen and treat patients for drug use as a part of ongoing HIV care.

Keywords

Substance use; drug use; alcohol use; HIV/AIDS; Outcomes; Adherence; Antiretroviral Therapy; Mortality

INTRODUCTION

Adherence to antiretroviral therapy (ART) is crucial to optimize treatment efficacy and prolong survival in patients with HIV disease [1–3]. The longitudinal effect of alcohol and illicit substance use (hereafter, “drug use”) on adherence to highly active antiretroviral therapy (HAART) and on clinical outcomes in patients with advanced AIDS has been less well characterized.

Drug and alcohol use are highly prevalent among HIV-infected populations in the United States [4]; but the long-term impact of these substances among patients on HAART is unclear [5–9]. Drug and alcohol use have been associated with decreased use of HAART [10–15], non-adherence to HAART [14–20], decreased viral suppression [14,21–24], and HIV disease progression in cross-sectional and short-term analyses of HIV-infected populations [6,15,16,19,22,23,25,26]. Active drug use was linked to disease progression in a university-based HIV-infected population, followed for up to 21/2 years from a single clinic [24]. Even intermittent use of intravenous drugs was associated with diminished virologic response to HAART in a population with lower HIV severity [14]. Recent heroin or cocaine use and homelessness were associated with increased short-term mortality in HIV-infected patients with alcohol problems [27]. Little is known about the prevalence of drug and alcohol use and its impact on morbidity and mortality over longer periods or after prolonged immune reconstitution.

The objective of this study is to describe the prevalence and impact of self-reported alcohol and drug use in patients enrolled in a decade-long clinical trial of AIDS patients who experienced immune reconstitution on therapy. We assessed the impact of reported drug and alcohol use on self-reported adherence to antiretroviral medications and on HIV disease progression and death within the context of an observational extension of a multicenter, randomized clinical study.

METHODS

Study Population

In the clinical trial, we enrolled 643 HIV-infected subjects without prior *Mycobacterium avium* complex (MAC) and with documented immune reconstitution (CD4 cell counts <50 followed by CD4 >100 cells/mm^3 on two separate occasions before study entry) from October 1997 through April 1999. AIDS Clinical Trials Group (ACTG) 362, a prospective, placebo-controlled multicenter trial of discontinuing MAC prophylaxis, was stopped in October 1999 after failing to show a treatment difference for azithromycin versus placebo. We enrolled 433 of the participants still on study in an observational cohort to evaluate cardiovascular, metabolic, and neurological outcomes of HAART therapy [28]. Self-administered questionnaires were used to assess alcohol and drug use at entry and during

follow-up visits among participants [26]. The protocol and its successive amendments were approved by institutional review boards at 29 participating U.S. ACTG sites; all participants provided written informed consent.

Data Collection and Event Definitions

Subjects were assessed at baseline, weeks 4 and 8, and then at 8–32 week intervals through the end of the study at week 512. They were evaluated for alcohol and drug use, medication adherence, new opportunistic infections or cardiovascular events, interval medical histories, CD4 counts, plasma HIV-1 RNA measurements, and any changes in ART or other medications. HIV-1 RNA measurements were obtained using the Roche Amplicor standard assay (Roche Diagnostics, Branchburg, NJ), with a lower limit of quantification of 500 copies/mL.

Data was collected from October 1997 to April 2007 on ART use before and at study entry and throughout the follow-up period. Individual clinical events and specific diagnoses were reviewed and corroborated using the Adult ACTG Criteria for Clinical Events by study clinicians (SEC, SLK, JSC) [29].

Adherence Assessment

At each follow-up visit, subjects were asked whether they were prescribed and adhering to ART. Non-adherence to ART was defined as missing any doses during the prior 48 hours. In addition, we defined “ever non-adherent” to ART if the subject reported ever missing ART in the past week at baseline or in the prior 48 hours at any follow-up visit throughout the study.

At baseline, participants completed a self-report questionnaire to assess potential factors affecting adherence [30]. Baseline adherence was assessed based on this question: “When was the last time you skipped any of your medications?” with the options “within the past week,” ”within the past 2 weeks,” “2–4 weeks ago,” “1–3 months ago,” “more than 3 months ago,” and “never skip medications or not applicable.” The responses to this question were grouped as “within the past week” versus “more than a week ago” (i.e., any of last 5 options) to be most similar to the 2-day adherence assessment.

Assessment of Drug and Alcohol Use

At each visit, subjects completed a self-reported questionnaire describing their current use of alcohol, cocaine (or crack), heroin, and amphetamines, and whether they were in methadone treatment. Patients reported their quantity and frequency of their alcohol consumption during the past 30 days. Drinking was dichotomized in 2 ways, as heavy drinkers (regularly drinking >4 drinks per day on average when they drank over the past 30 days) or not; and as binge drinkers (5 or more drinks *within a couple of hours* at least once in the last 30 days) or not [16,31]. Ongoing use of cocaine, heroin, and/or amphetamines within 30 days prior to a study visit was referred to as “ongoing hard drug use.” Participants were also asked whether or not they injected cocaine, amphetamines or heroin in the past 30 days, and frequency of use per day. They reported whether they had ever used cocaine, amphetamines and heroin at baseline and throughout the study, and alcohol use in the 30 days prior to each visit.

Statistical Analysis

Non-adherence to ART over the prior two days and recent substance use over the prior 30 days were assigned to the nearest scheduled study visit, at weeks 0 and 4, at 8 week intervals from weeks 8 to 224,, and at 16–32 week intervals from week 224 to 512. The association between drug use and non-adherence to ART was evaluated using repeated measures generalized estimating equation (GEE) models, with an assumption of equal correlation

between any pair of visits within each participant. The repeated measures models considered the indicator of recent hard drug use and non-adherence for each study visit. Other possible predictors of non-adherence included demographic factors (e.g. age, sex, race/ethnicity), HIV disease severity (baseline viral load, baseline CD4 count, Karnofsky score<80, prior AIDS defining condition), and treatment indicators (years of combination ART at entry, randomization to azithromycin or placebo). We performed backward selection of candidate predictors for multivariable models, retaining covariates with $p<0.10$.

The association between drug and alcohol use and time to new AIDS diagnosis or death was evaluated via Cox regression models, controlling for the potential confounders described above along with ART non-adherence. Two approaches for controlling for non-adherence were considered: one which controlled only for recent non-adherence to ART in the week prior to study entry (i.e., baseline non-adherence), and a second approach using time-updated indicators of ART non-adherence during study follow-up (time-dependent non-adherence). The association between ART non-adherence and virologic treatment failure (HIV-1 RNA ≥ 500 copies/mL) was evaluated in two ways. First, non-adherence was evaluated as a time-dependent covariate in a Cox model for time to first viral load failure. Second, non-adherence immediately prior to each visit was evaluated as a correlate of virologic failure at that visit in a GEE repeated measures analysis. All analyses were performed using Statistical Analysis System 9.1 (SAS Institute, Cary, NC). P-values less than 0.05 were considered statistically significant.

RESULTS

Subject characteristics

The demographic and clinical characteristics of the 643 participants are presented in Table 1. All subjects were on ART at baseline. Subjects had an average of 11 visits (IQR=5–16) at which adherence and drug and alcohol use were assessed. Maximum time on study was 9.4 years and median time on study was 6.0 years (IQR=1.9–8.6). The rate of loss to follow up was approximately 6% per year during the first two years of the clinical trial and less than 3% per year during the last 7 years of the observational study. Of the 643 subjects, 434 completed the clinical trial, 53 died during study follow-up, 17 were at sites that lost funding to continue the study, and 144 were lost to follow-up (81 refused contact, 51 were unable to be contacted, 4 moved, 1 was incarcerated, and 7 discontinued due to other reasons). The 144 lost to follow-up were more likely to be younger and black or Hispanic rather than white non-Hispanic, but were similar in other baseline characteristics (gender, CD4 count, HIV-1 RNA, adherence, ART use, and lifetime drug use or alcohol use reported in the 30 days prior to entry).

Of the 53 deaths during the study, 28 were determined to be non-HIV associated, 10 were HIV-associated, 4 were other disease processes, and 11 were of unknown causes. Seventy AIDS-related events occurred over the course of the study, half of which were microscopically or histologically confirmed. The vast majority were opportunistic infections including 15 with esophageal candidiasis, 14 with *Pneumocystis jiroveci* pneumonia, 7 with cytomegalovirus disease and 6 with cryptosporidiosis. There were 4 confirmed cases of MAC disease and 7 with HIV wasting syndrome. Only 5 developed HIV-associated malignancies, 3 with Kaposi's sarcoma and 2 with lymphoma.

Incidence and prevalence of drug and alcohol use

At baseline, 253 (39%) reported ever having used cocaine, 154 (24%) amphetamines and 65 (10%) heroin. Only 28 (2%) reported ever having used methadone treatment at baseline. Ninety-nine patients (15%) reported ever having injected drugs at baseline. While on study,

6 patients (0.9%) reported having injected cocaine, 4 (0.6%) amphetamines, and 3 (0.5%) heroin, with 1 (0.2%) having recently injected more than one drug within 30 days of a study visit. Baseline drug use in the participants who enrolled in the observational study was similar to those who did not continue (data not shown).

During the study, 9% reported having used cocaine, 4% amphetamines, 1% heroin, and 4% methadone treatment in the past 30 days prior to study entry or any subsequent study visit (See Table 1). Of the 77 patients who used hard drugs in the 30 days prior to study entry or any study visit, only 8 (11%) were new users who had not reported using hard drugs prior to entry.

At baseline, of the 373 patients who reported use of alcohol in the prior 30 days (58%), 31 (8%) were heavy drinkers and 119 (32%) were binge drinkers. During the study, 102 (16%) patients were classified as heavy drinkers and 276 (43%) were classified as binge drinkers. Most of the patients classified as heavy drinkers were also binge drinkers (97%) but only a third of binge drinkers were also classified as heavy drinkers (36%). Of those who reported being heavy or binge drinkers during the study, 69 (68%) had reported not being heavy drinkers, and 151 (55%) were not binge drinkers in the 30 days prior to their baseline visit (See Table 1).

Current or prior IV drug use, heavy or binge drinking, and non-adherence to ART were significantly associated with hard drug use during the study (Table 1). At any visit, the maximum prevalence of reporting binge drinking was 19% and hard drug use was<5% (See Figure 1). Figure 1 depicts the percentage of heavy and binge alcohol use and drug use through the study with reported non-adherence to ART by week.

ART non-adherence

At baseline, 15% of participants reported ART non-adherence during the prior week (Figure 1). While on study, reported ART non-adherence at any one visit ranged from 5 to 12%. Overall, the percentage of patients who reported ART non-adherence at least once between baseline and the end of study follow-up, e.g., “ever non-adherent,” was 49% (316). We found each additional decade of age was associated with a 25% decrease in odds of non-adherence (adjusted OR=0.75, p<0.001), using repeated measures GEE models. The odds of non-adherence increased slightly over the study follow-up (OR=1.02 per 24 weeks, p=0.03).

Association of drug and alcohol use with ART non-adherence

In multivariable GEE analyses adjusting for age, sex, and correlation among visits for each subject, hard drugs users had 2.14 times higher odds (95% CI: 1.36, 3.38, p<0.001) of ART non-adherence compared to non-users (see Table 2). In addition, those who recently used cocaine had 2.60 times higher odds (95% CI: 1.63, 4.13, p<0.001) and those who recently used methadone had 2.33 times higher odds than non-users (95% CI: 1.16, 4.69, p=0.02). Heavy drinking was not associated with non-adherence, but binge drinking was associated with a 1.53 times higher odds (95% CI: 1.21, 1.95, p<0.01) of ART non-adherence.

Association of non-adherence with AIDS progression or death

Of the 55 subjects with new AIDS diagnoses during the study, 15 subsequently died. In multivariate Cox proportional hazards models adjusting for potential confounders, there was no association of baseline ART non-adherence with risk of AIDS or death (adjusted HR=0.78, 95% CI=0.50,1.21, p=0.26) (See Table 3). However, time-updated measures of non-adherence during the study were associated with an almost two-fold increase in the odds of developing an AIDS condition or death (adjusted HR=1.84, 95% CI=1.15,2.94, p=0.01).

Association of drug and alcohol use with AIDS progression or death

The association between drug and alcohol use and a new AIDS diagnosis or death was evaluated via Cox regression models, controlling for covariates with and without adjustment for non-adherence (See Table 3). After controlling for baseline VL and Karnofsky Score, hard drug users had 2.46 times higher risk (p=0.04) of a new AIDS outcome or death. When we controlled for baseline adherence in addition, use of hard drugs was associated with a significant increase in risk of an AIDS outcome or death (adjusted HR=2.58, p=0.03). However, when we controlled for adherence as a time-dependent covariate throughout study follow-up, risk from hard drug use was attenuated (adjusted HR=2.11, p=0.08). Neither binge drinking nor heavy drinking was found to increase the risk of an AIDS outcome or death when controlling for baseline VL and Karnofsky score.

In Cox regression models for time to death, the effect of hard drug use was associated with a 3-fold higher risk after adjusting for age, baseline RNA>500 copies/mL, and Karnofsky score ≤80 (adjusted HR=3.09, p=0.03), but no association was found for alcohol use.

Association of non-adherence with virologic treatment failure (VTF)

Non-adherence was associated with VTF (e.g. HIV-1 RNA ≥500 copies/ml) when evaluated as time-dependent non-adherence in a Cox regression model controlled for baseline hard drug use (adjusted HR=1.42, p=0.004). Likewise, non-adherence at each visit correlated with VTF at that visit in a GEE repeated measured analysis adjusted for recent hard drug use, visit week, age, sex, and correlation among visits for a given participant (adjusted OR=1.41, p<0.001). In this GEE model, we found that recent hard drug use was also significantly associated with VTF (adjusted OR=1.63, p=0.002).

DISCUSSION

Our study patients with advanced AIDS who had responded to HAART had a high prevalence of drug and alcohol use. Almost 40% of participants reported a history of hard drug use and 12% reported some ongoing use during the study. Similarly, over half reported recent use of alcohol, with 43% reporting binge drinking during the study. These data are in keeping with statistics on alcohol and drug use in HIV-infected persons in care for HIV in the United States [10,16], and are significantly higher than those found in the general population [32].

Our findings are consistent with previous studies that have found that active drug use is associated with non-adherence to HAART and incomplete viral suppression when actively using drugs [14,16,17]. Adherence to ART is essential to decrease the incidence of opportunistic infections and improve the overall outcomes of patients with HIV. Our study used a self-reported measure of adherence that has been used successfully throughout the ACTG and many other HIV clinical trials. This adherence measure predicted AIDS progression and death in the first year of follow-up of this study [26]. In the current analysis, hard drug users had higher odds of developing a new AIDS-related condition or dying, even after controlling for adherence. Similar to findings from a four year observational study of illicit drug users in Baltimore by Lucas et al., we found that drug users, had a two-fold higher risk of developing new opportunistic conditions or death after adjusting for HAART use and time-dependent adherence [17].

Although drug users may have been excluded from clinical trials in the past, more recent ACTG studies exclude subjects only if, in the opinion of the investigator, active drug or alcohol use would interfere with adherence to study requirements. Thus, compared with AIDS patients in care, patients on this trial were probably less likely to use drugs and alcohol. Those who used alcohol may also have been more likely to admit to drinking >4

drinks on one occasional despite drinking more than that, leading to underreporting of "heavy drinking" in this study. Reporting binge drinking has previously been shown to be associated with ART nonadherence [20,33], although its impact on clinical outcomes warrants further investigation.

Drug and alcohol use may increase the risk of AIDS progression and death through direct biological effects and/or indirect behavioral effects [17]. In vitro, opioids impair lymphocyte function [34] and increase HIV-1 replication in mononuclear cells [35]. Drug use may also increase HIV replication mediated through effects on immune activation [36]. Cocaine appears to promote HIV infection in vivo, interacting with host immunity, cell susceptibility and activating sigma-1 receptors [37]. Drug use may also affect the immune system and other host defenses that may predispose to OI-related morbidity and mortality. For example, smoking tobacco, which is frequently associated with drug use, is a risk factor for developing cryptococcal infections in AIDS [38]. Alcohol, in addition to smoking, may paralyze respiratory cilia function and predispose users to recurrent bacterial pneumonias [39,40]. Carrico et al. found that compared to non-users, weekly stimulant use (cocaine and methamphetamines) was associated with higher HIV viral loads, higher neopterin levels, a measure of immune activation, and lower tryptophan levels [41].

Cohorts of injection drug users in the pre-HAART era had similar rates of CD4 lymphocyte decline [42] and progression of AIDS compared with men who have sex with men [43]. Moore et al. found that HIV-infected drug users had similar risk of disease progression in the pre-HAART era but had higher rates of disease progression in the HAART era compared to non-drug users [17,44], suggesting that non-adherence may account for much of the difference

Our study had several limitations. Patients who achieve immunorestoration and choose to participate in a decade long observational study are likely atypical of other AIDS patients. Research volunteers have been shown to be less impulsive, more satisfied, and more positive than the general population [45]. As a result of this self-selection, our participants may under-represent the true prevalence of drug and alcohol abuse among patients with HIV in clinical practice and consequently, may have a lower likelihood of using illicit substances and alcohol than the average patient with HIV/AIDS on HAART in clinical practice. Patients who use drugs and alcohol may be more likely to underreport their drug use, miss study visits or prematurely discontinue the study compared to non-users; drug users tend to minimize or deny drug use and are more likely to discontinue HAART or the clinical trial if they were using drugs. Misclassification from this underreporting would reduce the power of our study.

We did not assess lifetime use of alcohol or tobacco, or other potential covariates such as homelessness, depression, health literacy, hepatitis status, insurance status, and recruitment and retention strategies used. Although self-reported measures of drug use are useful, we probably underestimated the use of drugs by not performing more other objective measures of drug use such as urine drug screening. We also did not ask about other drugs of abuse including amyl nitrates, marijuana, recreational use of prescription drugs or other drugs considered to be "party drugs."

This study of patients with advanced AIDS who had responded to HAART and were followed for close to ten years found a high prevalence of alcohol and drug use. Binge drinking and drug use was associated with increased risk of non-adherence that only partially explained poorer virologic control and increased risk of progression of AIDS or death. Our study highlights the need to routinely and continuously screen all patients with

HIV for current drug and alcohol use, and to offer alcohol and drug treatment services and other targeted interventions where appropriate to optimize HIV management and outcomes.

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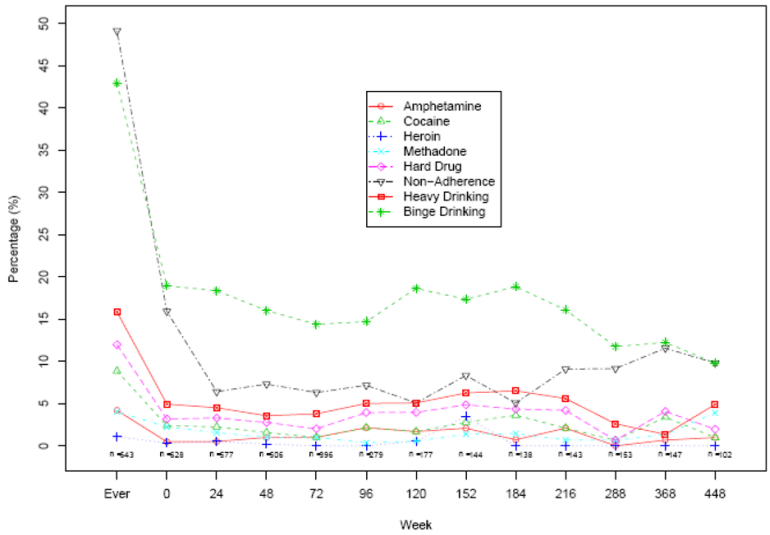

Figure 1. Percent of AIDS Patients in ACTG 362 Self-Reporting Drug Use[1] and Non-Adherence[2] During Study Follow-up

[1] Hard drug use: defined as reporting drug use within 30 days prior to entry or prior to any study visit.

[2] Non-adherence: defined as missing any antiretroviral therapy within the past week prior to entry or in the past 2 days at any study visit.

Table 1

Baseline and on Study Health Characteristics of AIDS Patients in ACTG 362, by Self-Reported Hard Drug Use During Study Follow-up

		Hard Drug User During Study[1]			
Characteristic		**Total (N=643)**	**No (N=566)**	**Yes (N=77)**	**P-Value[2]**
Age at entry (years)	Median	40	40	40	0.95
	< 35 years	135 (21%)	120 (21%)	15 (19%)	0.96
	35-39 years	184 (29%)	162 (29%)	22 (29%)	
	40-44 years	129 (20%)	112 (20%)	17 (22%)	
	45+ years	195 (30%)	172 (30%)	23 (30%)	
Gender	Male	559 (87%)	487 (86%)	72 (94%)	0.07
	Female	84 (13%)	79 (14%)	5 (6%)	
Race/Ethnicity	White Non-Hispanic	369 (57%)	320 (57%)	49 (64%)	0.22
	Black Non-Hispanic	131 (20%)	115 (20%)	16 (21%)	
	Hispanic	117 (18%)	105 (19%)	12 (16%)	
	Other	26 (4%)	26 (5%)	0 (0%)	
IV Drug Use (IVDU)	Never	544 (85%)	490 (87%)	54 (70%)	<0.001
	Current/Previous	99 (15%)	76 (13%)	23 (30%)	
Risk Behavior Category	MSM	354 (55%)	310 (55%)	44 (57%)	<0.001
	MSM and IVDU	38 (6%)	26 (5%)	12 (16%)	
	IVDU	61 (9%)	50 (9%)	11 (14%)	
	High risk Heterosexual Contact	117 (18%)	114 (20%)	3 (4%)	
	Others or Missing	73 (11%)	66 (12%)	7 (9%)	
Baseline CD4	Median	226	227	222	0.60
	<200	241 (37%)	209 (37%)	32 (42%)	
	200-299	208 (32%)	186 (33%)	22 (29%)	
	300+	194 (30%)	171 (30%)	23 (30%)	
Baseline Viral Load	500 or less	417 (65%)	371 (66%)	46 (60%)	0.54
	500-20,000 copies	112 (17%)	92 (16%)	20 (26%)	
	20,000 copies or more	100 (16%)	89 (16%)	11 (14%)	
	Missing	14 (2%)	14 (2%)	0 (0%)	
Antiretroviral Therapy at Entry	NRTI + PI based regimen	470 (73%)	417 (74%)	53 (69%)	0.91

Characteristic		Hard Drug User During Study[1] Total (N=643)	No (N=566)	Yes (N=77)	P-Value[2]
	NRTI + NNRTI + PI based regimen	105 (16%)	91 (16%)	14 (18%)	
	NNRTI + PI based regimen	30 (5%)	26 (5%)	4 (5%)	
	NRTI + NNRTI based regimen	14 (2%)	12 (2%)	2 (3%)	
	Other regimen	24 (4%)	20 (4%)	4 (5%)	
Self-reported Drinking:					
Baseline Binge Drinking		119 (19%)	97 (17%)	22 (29%)	0.02
Binge Drinking During Study		276 (43%)	227 (40%)	49 (64%)	<0.001
Baseline Heavy Drinking		31 (5%)	23 (4%)	8 (10%)	0.02
Heavy Drinking During Study		102 (16%)	81 (14%)	21 (27%)	0.01
Self-reported Baseline Drug Use[3]					
Baseline Cocaine Use		15 (2%)	---	15 (19%)	
Baseline Amphetamine Use		3 (0%)	---	3 (4%)	
Baseline Heroin Use		2 (0%)	---	2 (3%)	
Any Baseline Hard Drug Use		20 (3%)	---	20 (26%)	
Self-reported Drug Use During Study[4]:					
Cocaine Use During Study		57 (9%)	---	57 (74%)	
Amphetamine Use During Study		27 (4%)	---	27 (35%)	
Heroin Use During Study		7 (1%)	---	7 (9%)	
Baseline Non-adherence[5]	No	516 (80%)	459 (81%)	57 (74%)	0.31
	Yes	100 (16%)	85 (15%)	15 (19%)	
	Missing	27 (4%)	22 (4%)	5 (6%)	
Non-adherence During Study[6]		316 (49%)	266 (47%)	50 (65%)	0.003

MSM= men who have sex with men; IVDU=intravenous drug use; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor.

[1] Hard drug user: defined as reporting drug use (cocaine, heroin and/or amphetamine use) within 30 days prior to entry or prior to any study visit.

[2] P-value calculated by Fisher's Exact Test for binary characteristics, by Chi-Square test for categorical characteristics, and by Wilcoxon Rank Sum Test for continuous characteristics.

[3] Baseline drug use defined as use during the 30 days prior to entry for each individual drug, or for any hard drug (cocaine, heroin, amphetamines)

[4] Drug use during study defined as use during the 30 day prior to entry or any study visit

[5] Baseline non-adherence defined as self-reported non-adherence over 7 days prior to entry

[6] Non-adherence during study defined as self-reported baseline non-adherence as above, or in 2 days prior to any study visit

Table 2

Association between Hard Drug Use and Non-Adherence based on GEE Repeated Measures Models Adjusting for Within-Participant Correlation among Multiple Study Visits

Substance Use[1]	Adjusted Odds Ratio[2]	95% Confidence Interval	P-value
Recent Cocaine Use	2.60	(1.63, 4.13)	<0.001
Recent Heroin Use	1.94	(0.39, 9.58)	0.42
Recent Amphetamine Use	1.79	(0.73, 4.39)	0.20
Recent Methadone Treatment	2.33	(1.16, 4.69)	0.02
Recent Hard Drug Use (Cocaine, Amphetamine, or Heroin)	2.14	(1.36, 3.38)	0.001
Heavy Drinking	1.19	(0.72, 1.98)	0.50
Binge Drinking	1.53	(1.21, 1.95)	<0.001

[1] Defined as reported use in the 30 days prior to a visit.

[2] Each row represents a separate model for the specified substance use, adjusted for visit week, age, sex, and correlation among visits for a given participant.

Table 3

Association between Hard Drug Use and Risk of AIDS Progression or Death based on Cox Models for Time to Event

Recent Substance Use at Entry[1]	Adjusted Hazard Ratio[2]	95% Confidence Interval	P-value
Without adjusting for non-adherence:			
Recent Hard Drug Use (Cocaine, Heroin, or Amphetamine)	2.46	(1.06, 5.69)	0.04
Baseline Viral Load > 500 copies/mL	2.12	(1.38, 3.26)	<0.001
Karnofsky Score ≤ 80	2.01	(1.23, 3.28)	0.005
Adjusting for non-adherence reported at study entry:			
Recent Hard Drug Use (Cocaine, Heroin, or Amphetamine)	2.58	(1.11, 5.97)	0.03
Baseline Viral Load > 500 copies/mL	2.14	(1.39, 3.30)	<0.001
Karnofsky Score ≤ 80	2.07	(1.27, 3.39)	0.004
Non-adherence reported at entry	0.78	(0.50, 1.21)	0.26
Adjusting for non-adherence reported throughout study follow-up as time-dependent covariate:			
Recent Hard Drug Use (Cocaine, Heroin, or Amphetamine)	2.11	(0.90, 4.92)	0.08
Baseline Viral Load > 500 copies/mL	1.92	(1.24, 2.97)	0.003
Karnofsky Score ≤ 80	1.93	(1.18, 3.15)	0.01
Time-updated Non-Adherence	1.84	(1.15, 2.94)	0.01

[1] Defined as reported use in the 30 days prior to study entry.

[2] We adjusted for baseline HIV RNA>500 copies/ml and Karnofsky score only since all other covariates (age, sex, baseline CD4, non-white status, randomized treatment status [azithromycin versus placebo], years on antiretroviral therapy at entry, and prior AIDS defining event) had p>0.20 or higher.