



Alcohol Use and Incarceration Adversely Affect HIV-1 RNA Suppression Among Injection Drug Users Starting Antiretroviral Therapy

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ABSTRACT *We conducted this study among HIV-infected injection drug users to determine the effect of self-reported alcohol use and prior incarceration at the time of initiating antiretroviral therapy on subsequent HIV-1 RNA suppression. We examined the demographics, recent incarceration history, and drug and alcohol use history from the Vancouver Injection Drug User Study (VIDUS) questionnaire closest to the date of initiating antiretroviral therapy. We linked these data to the HIV/AIDS Drug Treatment Program. There were 234 VIDUS participants who accessed antiretroviral therapy through the Drug Treatment Program from August 1, 1996, to July 31, 2001. In terms of illicit drug use, 196 (84%) reported injecting heroin and cocaine at the time of initiating antiretroviral therapy. Multiple logistic regression revealed that in the 6 months prior to initiating antiretroviral therapy, alcohol use (adjusted odds ratio [AOR] 0.32; 95% CI 0.13–0.81) and incarceration (AOR 0.22; 95% CI 0.09–0.58) were independently associated with lower odds of HIV-1 RNA suppression. Factors positively associated with HIV-1 RNA suppression included: adherence (AOR 1.27; 95% CI 1.06–1.51); lower baseline HIV-1 RNA (AOR 1.30; 95% CI 1.01–1.66); highly active antiretroviral therapy (AOR 4.10; 95% CI 1.56–10.6); months on therapy (AOR 1.1; 95% CI 1.06–1.14). Among HIV-infected injection drug users who were on antiretroviral therapy, any alcohol use and incarceration in the 6 months prior to initiating antiretroviral therapy were negatively associated with achieving HIV-1 RNA suppression. In addition to addiction treatment for active heroin and cocaine use, the identification and treatment of alcohol problems should be supported in this setting. As well, increased outreach to HIV-infected drug users recently released from prison to ensure continuity of care needs to be further developed.*

KEYWORDS *Anti-HIV agents, HIV infections, Human, Logistic regression models, Substance abuse, Intravenous, Alcohol, Prison.*

INTRODUCTION

Heavy alcohol and active illicit drug use have been found to reduce the odds of being on antiretroviral therapy as well as the odds of HIV-1 RNA suppression,^{1,2} presumably through impaired adherence.³ In a prospective cohort study of 764 HIV-1-infected patients who attended an urban HIV clinic, Lucas et al. found that a higher proportion of active drug users were not on highly active antiretroviral

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therapy (HAART) compared to non-drug users (44% vs. 18%). Among participants who were taking antiretroviral therapy, active drug users were more likely to report medication nonadherence (34% vs. 24% of nonusers) and had a smaller median reduction in HIV-1 RNA from baseline.¹ In a longitudinal study of patients attending an inner-city clinic who completed at least two questionnaires, the authors found that switching from nonuse to substance use was strongly associated with worsening antiretroviral therapy use and adherence and less frequent HIV-1 RNA suppression compared to remaining free of substance use. They also found that switching from substance use to nonuse was strongly associated with improvements in antiretroviral therapy use and adherence and HIV-1 RNA suppression, compared to persisting with substance use.²

Substance use and HIV infection are not uncommon among the prison population. Although most inmates are already infected prior to arriving at prison, intra-prison transmission may occur via tattooing, injection drug use, and sex.⁴ A number of correctional systems have instituted routine HIV testing, and the administration of antiretroviral therapy under direct observation maximizes adherence in these settings. This widespread availability of HAART in the prison system has been responsible for the decrease in AIDS mortality, where the rate declined from 1,010/100,000 in 1995 to 20/100,000 in 1999.⁵ Although HIV-infected inmates may achieve viral suppression in prison, once they are released to the community, these advances may be attenuated.

Previous studies have not examined the effect of engagement in methadone maintenance therapy and recent incarceration on HIV treatment outcomes among injection drug users. We hypothesized that injection drug users who reported active substance (drug and alcohol) use and incarceration in the 6 months prior to initiating antiretroviral therapy would be less likely to achieve HIV-1 RNA suppression, whereas enrollment in methadone maintenance therapy would increase the likelihood of HIV-1 RNA suppression. Therefore, we conducted this study among HIV-infected injection drug users to determine the effect of these factors at the time of initiating antiretroviral therapy on subsequent HIV-1 RNA suppression.

METHODS

Study Subjects

The research design and methods of the Vancouver Injection Drug User Study (VIDUS) have been previously described.⁶ Briefly, VIDUS is an open cohort study of injection drug users that has enrolled over 1,400 participants since May 1996. Its primary aim was to determine the risk practices associated with HIV seroconversion. Subjects were eligible to participate if they had injected illicit drugs in the previous month and resided in the Greater Vancouver region. Most participants (82%) were recruited through word of mouth and street outreach. Participants responded to an interviewer-administered questionnaire semiannually and were reimbursed \$20 CDN for each study visit, at which time referrals were provided for medical care and available drug and alcohol counseling and treatment.

At each visit, HIV antibody testing was performed. Those who tested HIV positive at entry or who seroconverted during the follow-up period and were receiving antiretroviral therapy through the provincial HIV/AIDS Drug Treatment Program (described below) from August 1, 1996 to July 31, 2001 were included in this analysis. The VIDUS questionnaire closest to the date of initiating antiretroviral

therapy was used for this analysis. Non-nominal VIDUS cohort data were linked to Drug Treatment Program data.⁷

HIV/AIDS Drug Treatment Program

The British Columbia Centre for Excellence in HIV/AIDS supports a provincewide program referred to as the HIV/AIDS Drug Treatment Program that distributes antiretroviral agents at no cost to eligible HIV-infected individuals. Antiretroviral drugs are distributed based on specific guidelines generated by the Therapeutic Guidelines Committee. In July 1997, the guidelines were revised to recommend highly active antiretroviral therapy for all antiretroviral-naive individuals with HIV-1 RNA greater than 5,000 copies/mL or CD4 counts less than 500 cells/mm³. The Centre recommends that HIV-1 RNA be monitored at baseline, at 4 weeks after the start of antiretroviral therapy, and every 3 months thereafter. In 2000, the guidelines were updated in keeping with the updated recommendations of the International AIDS Society-USA Panel, in which highly active antiretroviral therapy was recommended for all antiretroviral-naive individuals with CD4 counts less than 300 cells/mm³.⁸ HIV-1 RNA was measured using the Amplicor HIV-1 Monitor, manufactured by Roche Diagnostic System (Branchburg, NJ). Physicians enrolling a patient in the program complete a questionnaire that collects patient baseline data.

Variable Definitions

The primary outcome was having at least two consecutive HIV-1 RNA levels below 500 copies/mL after the start of antiretroviral therapy.⁹ Our primary explanatory variables were drug use, specifically daily injection heroin use, daily injection cocaine use, and alcohol use in the previous 6 months. These categories were not mutually exclusive. Other specific independent variables assessed included: incarceration in the previous 6 months; age; gender; enrollment in a methadone maintenance program at the time of initiating antiretroviral therapy; baseline CD4 cell count; baseline log₁₀ HIV-1 RNA; initial antiretroviral therapy regimen with highly active antiretroviral therapy comprising three or more antiretroviral medications; months on therapy; and adherence to antiretroviral therapy, which was measured using pharmacy refill compliance data.^{7,9-11} In brief, we calculated adherence as the ratio of number of months the patients received antiretroviral therapy refills relative to total number of months of follow-up in year 1. The Providence Health Care Ethics Committee for Human Experimentation approved the data collection for this study.

Statistical Analysis

We compared the demographic and behavioral data of HIV-infected injection drug users who achieved HIV-1 RNA suppression to less than 500 copies/mL at least twice consecutively by chi-square for categorical variables and Wilcoxon rank sum for continuous variables. We created a multiple logistic model to examine the association of drug and alcohol use with our primary outcome. We adjusted for potential confounding factors by including in the model age (per year), jail, methadone maintenance therapy, baseline log₁₀ HIV-1 RNA, baseline CD4 cell count, initial antiretroviral regimen (HAART versus not), months on therapy, and adherence (per 10% increment). We also ran the same model excluding the baseline HIV-1 RNA, as there were missing values for 47 subjects.

RESULTS

There were 234 VIDUS participants who accessed antiretroviral therapy through the HIV/AIDS Drug Treatment Program from August 1, 1996 to July 31, 2001. In terms of illicit drug use, 196 (84%) reported injecting heroin and cocaine at the time of initiating antiretroviral therapy and 65% (128/196) injected heroin and/or cocaine on a daily basis. As well, over one third (82) of the participants reported alcohol use in the previous 6 months. Participant characteristics associated with achieving HIV-1 RNA suppression to 500 copies/mL twice consecutively are included in Table 1. Injection drug users who reported any alcohol use in the previous 6 months (29% vs. 42%, $P = .04$) and incarceration in the previous 6 months (19% vs. 40%, $P = .001$) were less likely to suppress their HIV-1 RNA. There were no differences in the proportion of injection drug users who suppressed their HIV-1 RNA by daily use of injected heroin or cocaine or enrollment in a methadone maintenance program at the time of initiating antiretroviral therapy. Highly active anti-

TABLE 1. Characteristics of injection drug users in the HIV/AIDS Drug Treatment Program who achieved HIV-1 RNA suppression

Characteristics	HIV-1 RNA Suppression		P-value
	Yes (N = 133)	No (N = 101)	
Drug and alcohol use*			
Daily heroin	35 (26)	28 (28)	.81
Daily cocaine	56 (42)	50 (50)	.26
Alcohol†	39 (29)	43 (42)	.04
Enrolled in methadone maintenance	35 (26)	19 (19)	.18
Jail†	25 (19)	40 (40)	.001
Age in years			
Median (IQR)	36 (30–42)	34 (30–40)	.02
Gender			
Female	52 (39)	37 (37)	.70
Unstable housing‡	76 (57)	48 (48)	.14
CD4 cell count‡			
Median (IQR)	270 (140–390)	305 (140–455)	.38
HIV-1 RNA level§			
Median viral load (IQR)	10.9 (10.1–12.4)	11.1 (10.3–13.8)	.76
Initial antiretroviral therapy			
HAART	86 (65)	47 (47)	.006
Months on therapy			
Median (IQR)	35 (24–48)	12 (5–22)	<.001
Adherence			
Median (IQR)	100 (83–100)	67 (33–100)	<.001

IQR, interquartile range.

*Not mutually exclusive categories.

†In the 6 months prior to starting antiretroviral therapy.

‡Cells $\times 10^6/L$ at baseline for 229 participants with available baseline CD4 cell counts.

§Per \log_{10} at baseline for the 187 participants with available baseline HIV-1 RNA levels.

retroviral therapy as the initial regimen (65% vs. 47%, $P = .006$), longer duration on antiretroviral therapy (35 months vs. 12 months, $P < .001$), and higher median adherence (100% vs. 67%, $P = .001$) as measured by pharmacy refill compliance was also positively associated with HIV-1 RNA suppression. We examined drug-using behaviors of the subjects at their next follow-up visit and found the following: the number of persons using heroin and cocaine daily was 126 (64%), which is similar to the finding at the initial observation. The number of subjects who reported any alcohol use declined from 82 at the initial observation to 59.

Multiple logistic regression results, presented in Table 2, show that in the 6 months prior to initiating antiretroviral therapy, alcohol use (adjusted odds ratio [AOR] 0.32; 95% confidence interval [CI] 0.13–0.81) and incarceration (AOR 0.22; 95% CI 0.09–0.58) were independently associated with lower odds of HIV-1 RNA suppression. Factors positively associated with HIV-1 RNA suppression included adherence (AOR 1.27; 95% CI 1.06–1.51), lower baseline HIV-1 RNA (AOR 1.30; 95% CI 1.01–1.66), highly active antiretroviral therapy (AOR 4.10; 95% CI 1.56–10.6), and months on therapy (AOR 1.1; 95% CI 1.06–1.14). Age, daily heroin use, daily cocaine use, and enrollment in a methadone maintenance program were not associated with HIV-1 RNA suppression among our cohort of injection drug users. In an analysis that did not include baseline HIV-1 RNA, these findings were unchanged (data not shown).

DISCUSSION

We found that alcohol use and being incarcerated in the 6 months prior to starting antiretroviral therapy were associated with lower odds of HIV-1 RNA suppression. Unlike other studies, we did not observe an association between ongoing injection of heroin or cocaine with HIV-1 RNA suppression.^{1–3} The number of injection drug users not actively using drugs (38/234) may have been insufficient to detect any difference by intensity of drug use, as observed by Lucas et al.¹ A recent study found that among HIV-infected drug users, active use of crack cocaine was nega-

TABLE 2. Multivariable logistic regression analysis of factors associated with HIV-1 RNA level suppression in 234 injection drug users taking antiretroviral therapy

Factor	Adjusted odds ratio	95% Confidence interval
Daily heroin vs. not*	0.99	0.37–2.63
Daily cocaine vs. not*	1.41	0.55–3.62
Alcohol use vs. not*	0.32	0.13–0.81
Jail vs. not*	0.22	0.09–0.58
Methadone enrollment vs. not*	1.30	0.46–3.66
Adherence (per 10%)	1.27	1.06–1.51
Age (per year)	1.04	0.98–1.10
HIV-1 RNA level†‡	1.30	1.01–1.67
HAART vs. not§	4.10	1.56–10.6
Months on therapy	1.10	1.06–1.14

*In the 6 months prior to starting antiretroviral therapy.

†Baseline.

‡Per log₁₀ decrement of HIV-1 RNA level.

§Highly active antiretroviral therapy.

tively associated with adherence, as measured by MEMS and HIV-1 RNA suppression.³ One small ($N = 94$) study compared the virologic outcomes of HIV-infected patients receiving highly active antiretroviral therapy by their daily alcohol intake; they found no significant difference in the proportion of patients who achieved HIV-1 RNA suppression.¹² Given the burden of coinfection of hepatitis C and HIV among injection drug users, however, those who also use alcohol may be less likely to adhere to anti-HIV therapy for behavioral reasons as well as due to their inability to tolerate antiretroviral therapy.¹³

The HIV Cost and Services Utilization Study estimated the prevalence of any alcohol consumption and heavy drinking among 2,864 HIV-infected patients in care. The prevalence of heavy drinking was 8% of the entire cohort. The odds of heavy drinking were significantly higher among users of cocaine or heroin (AOR 2.6; 1.3–5.3) and significantly lower among the better educated (college versus < high school, AOR 0.33; 0.16–0.68) and those with an AIDS-defining illness (AOR 0.56; 0.34–0.95).¹⁴ The relationship between problem drinking and medication adherence was also examined in a cross-sectional survey of 212 HIV-infected persons. They found that 19% of subjects reported problem drinking (binge,¹⁵ heavy and hazardous drinking¹⁶) during the past month, and that 30% did not take their medications as scheduled during the previous week. Problem drinkers were significantly more likely to report taking medicines off schedule (45% vs. 26%, $P = 0.02$). Among drinking subtypes, taking medications off schedule was significantly associated with both heavy drinking (high quantity or frequency)¹⁵ (AOR 4.7; 1.5–14.8) and hazardous drinking (score 8 of 40 points on the AUDIT)¹⁶ (AOR 2.6; 1.1–6.5).¹⁷ Unfortunately, we did not have data pertaining to frequency and quantity of alcohol consumed. To date, no published studies have assessed the effect of treatment of alcohol dependence on HIV-1 medication adherence and treatment outcomes. Our findings support that alcohol use may attenuate the effect of antiretroviral therapies, and future research should evaluate the effect of alcohol treatment programs on adherence to highly active antiretroviral therapy and virologic outcomes.

Incarceration in the 6 months prior to starting antiretroviral therapy was independently associated with lower odds of achieving HIV-1 RNA suppression. This variable may be a marker of life instability and may identify a group of injection drug users who need more tangible adherence support. A number of studies have highlighted the importance of the link between HIV specialists and correctional health care providers for ensuring that HIV-infected patients have optimal care both inside prison and after release.^{18,19} In terms of the prescription of antiretroviral therapies in prisons, one study found that 72% of those eligible for treatment ($N = 77$) in the San Francisco jail were on antiretroviral therapy and that 71% followed medical advice and picked up medication at release.²⁰ Programs that ensure continuity of care for HIV-infected patients after release clearly need to be established and further evaluated.²¹

Methadone use was not associated with HIV-1 RNA suppression in our sample of HIV-infected injection drug users. Less than 25% of the drug users were enrolled in a methadone maintenance therapy program. Numerous studies have found that drug users who are on methadone maintenance are more likely to access antiretroviral therapy.^{22–25} Little data exist on the relationship between being on methadone and HIV-1 treatment outcomes. Stein et al. surveyed 42 HIV-infected patients on methadone maintenance and found that ongoing illicit drug use was associated with lower self-reported adherence but did not affect HIV-1 RNA suppression.²⁶ The

interaction of methadone with highly active antiretroviral therapy may require higher doses of methadone²⁷⁻³⁰ and make management more complex. One study of drug users in France found that the opioid-replacement drug buprenorphine had no effect on HIV-1 RNA suppression.³¹

Limitations of our study include our inability to capture whether or not participants actually took their dispensed medication. However, we attempted to control for the difference in adherence to antiretroviral therapy based on refill compliance, a powerful predictor of virologic and clinical outcome^{9,10,32} and survival.¹¹ Likely, this will correctly identify nonadherence given that our program is the only source of free antiretroviral therapy in the province, although there is likely residual confounding in our measure. This bias, however, would be conservative and tend to overestimate adherence. Second, the participants in our study likely included drug users whom their physicians may have considered potentially more adherent to antiretroviral therapy relative to the larger pool of eligible HIV-infected injection drug users who are not receiving any treatment.⁷ Third, since our observation period included 1996–1997, 101 (43%) of the injection drug users were started on dual nucleoside therapy rather than HAART that, as expected, portended a lower likelihood of viral suppression. Fourth, the alcohol exposure variable used in this analysis is not refined enough to define alcohol dependence or abuse, and we have no information on quantity or frequency. Fifth, in our study, ongoing drug use was so prevalent that we could not discriminate its effect. We did find, however, a subgroup of drug users who also use alcohol, and we think this polysubstance use may be a marker for even worse adherence, either through behaviors incompatible with consistently taking antiretroviral therapy or inability to tolerate medication due to adverse effects, especially in light of the high prevalence of hepatitis C infection. Finally, the definition of virologic suppression is relative to the sensitivity of the assay. The assay-detection threshold of 500 copies/mL was commonly used when many of our participants started HAART, but it has recently decreased to 50 copies/mL.^{33,34}

In summary, we found that among HIV-infected injection drug users who were on antiretroviral therapy, any alcohol use and incarceration in the 6 months prior to initiating antiretroviral therapy were negatively associated with achieving HIV-1 RNA suppression. High level of adherence in the first year of therapy, longer time on therapy, lower baseline HIV-1 RNA level, and the use of HAART were also independently associated with superior virologic outcome. Our data highlight the negative impact that alcohol can have on drug injectors. Further research is needed to better understand the mechanism by which alcohol adversely affects HIV-1 treatment outcomes. In addition to addiction treatment for active heroin and cocaine use, the identification and treatment of coexistent alcohol problems should be supported in this setting. Finally, increased outreach to HIV-infected drug users recently released from prison to ensure continuity of care needs to be further developed. The integration of these strategies with adherence supports may allow more drug users to derive the full potential benefits of highly active antiretroviral therapy.

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