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Heroin Use and HIV Disease Progression: Results from a Pilot Study of a Russian Cohort

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Abstract

Opioids have immunosuppressive properties, yet their impact on HIV disease progression remains unclear. Using longitudinal data from HIV-infected antiretroviral therapy-naïve Russian individuals (n=77), we conducted a pilot study to estimate the effect of heroin use on HIV disease progression. Heroin use was categorized based on past 30 day self-report at baseline, 6 months and 12 months as none, intermittent or persistent. We estimated the effect of heroin use on HIV disease progression, measured as change in CD4 count from baseline to 12 months, using multivariable linear regression. Those with intermittent (n=21) and no heroin use (n=39) experienced mean decreases in CD4 count from baseline to 12 months (−103 cells/mm³ and −10

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cells/mm³, respectively; adjusted mean difference (AMD) -93, 95% CI: -245, 58). Those with persistent use (n=17) showed a mean increase of 53 cells/mm³ (AMD 63, 95% CI: -95, 220). Future studies exploring the effects of heroin withdrawal on HIV disease progression are warranted.

Keywords

heroin; HIV disease progression; HIV; CD4

INTRODUCTION

Globally, approximately 3 million people who inject drugs are estimated to be HIV-infected, with the highest numbers of injecting individuals in China, the United States and Russia [1]. Substance use impacts HIV progression by leading to decreased access and linkage to treatment [2], non-adherence to antiretroviral therapy (ART) [3, 4], and comorbidities [5]. Given heroin's immunosuppressive properties, one could hypothesize that it may hasten HIV disease progression [6, 7].

The specific impact of heroin, a pro-drug of morphine, on HIV disease progression remains unclear [8, 9]. Laboratory studies demonstrate that morphine impacts multiple aspects of the immune system [10], including promoting HIV-1 growth in cell cultures [11], inducing lymphocyte apoptosis [12] and increasing expression of the HIV entry co-receptors with increased HIV replication [13-15]. Animal [16-19] and human [20-26] studies are inconsistent, with only some studies demonstrating deleterious effects of opioids on HIV progression [22-28]. Human studies evaluating the impact of heroin use on HIV progression have been limited. Few include longitudinal designs where frequency of heroin use is measured [8, 20, 29, 10], and heroin use is often categorized with cocaine use, a drug that has already been associated with HIV disease progression and has a completely different mechanism of action [8, 30, 31]. Moreover, studies are unable to adjust for important confounders, such as ART use and adherence [8, 32].

Therefore, we conducted the current pilot longitudinal study to examine the association between self-reported heroin use and HIV disease progression in a sample of HIV-infected Russians who were ART-naïve. This represented a unique opportunity to examine these questions given that in Russia, a cohort of HIV-infected persons not on ART is accessible, heroin is the dominant illicit substance used [33], cocaine use is quite limited [34, 35], and chronic opioids for pain or as opioid agonist therapy are not prescribed [36], thus minimizing issues of confounding. The primary objective of this study was to estimate the effect of heroin use on HIV disease progression as measured by change in CD4 cell count over a 12 month period.

METHODS

Study Design and Participants

We conducted a longitudinal study to assess the effect of heroin use on change in CD4 cell counts in a prospective cohort of HIV-infected Russians. Participants were recruited

between January 2010 and March 2011 for the Drug Use - Investigating and Measuring Progression to AIDS in a Cohort Trial (IMPACT). This prospective cohort study in St. Petersburg was nested within the HIV Evolution in Russia – Mitigating Infection Transmission and Alcoholism in a Growing Epidemic (HERMITAGE) trial[37]. The HERMITAGE study recruited 700 HIV-infected heavy drinkers who reported recent unprotected sex from four clinical inpatient and outpatient HIV and addiction sites in St. Petersburg, Russia, including 1) Botkin Infectious Disease Hospital, 2) the St. Petersburg AIDS Center, 3) Pavlov State Medical University Clinics, and 4) the St. Petersburg State Drug Treatment Clinic. Participants were also recruited from non-clinical sources including a needle exchange program, and through “snowball recruitment” and referred to one of the clinical sites for eligibility assessment. Eligibility criteria for the HERMITAGE study included the following: 1) HIV-infection; 2) aged 18 to 70 years old; 3) any at-risk drinking, as defined by the US National Institute on Alcohol Abuse and Alcoholism (NIAAA) [38], 6 months prior to hospital admission; 4) anal or vaginal sex without a condom during the past 6 months; 5) free from cognitive impairment or acute illness; 6) not trying to get [partner] pregnant; 7) provision of contact details for self and two confidants to facilitate follow-up; 8) living within 150 kilometers of St. Petersburg; 9) no pending incarceration; and 10) able to provide informed consent.

The IMPACT study recruited HERMITAGE subjects when they returned for their 12-month follow-up visit. To eliminate the effect of ART on the study outcome, change in CD4 cell count, the analytic sample for the current study was restricted to patients who were ART naïve. Participants were also required to have CD4 cell count data available at both baseline and 12 months.

The study was approved by the institutional review boards of Boston University and First St. Petersburg Pavlov State Medical University. All subjects provided written informed consent and were reimbursed the equivalent of USD\$10 for their completion of the additional specific IMPACT survey at the HERMITAGE follow-up visit.

Assessments

Data were collected for the HERMITAGE study at baseline, 6 and 12-month follow-up. For this analysis, data from the HERMITAGE study were supplemented with specific IMPACT data that were collected at the 12-month follow-up, including a survey, CD4 cell count and urine toxicology testing.

Outcome

Change in CD4 cell count (cells/mm³) from baseline to 12 months was the primary outcome. Baseline CD4 cell count was ascertained based on chart review, using the value available closest in timing to the baseline assessment. CD4 cell count at 12 months was directly measured using a standard assay (Fluorescence-activated cell sorting/Flow Cytometry).

Primary Independent Variable: Pattern of Heroin Use

Self-reported substance use was assessed using a modified Risk Behaviors Survey (RBS) [39-41] at baseline, 6 and 12 months. Participants were asked specifically about use of heroin not in combination with other drugs and separately about their use of other opiates in the last 30 days. Based on responses across the three time points, the primary independent variable – pattern of heroin or other opioid use – was categorized into a 3-level variable as none (no reported heroin or other opioid use at baseline, 6 and 12 months), intermittent (reported both use and no use across baseline, 6 and 12 months) or persistent (reported heroin or other opioid use at baseline, 6 and 12 months). Given that heroin is the opioid used by the majority of participants, we refer to the main independent variable as “pattern of heroin use” throughout the manuscript. Participants were categorized accordingly regardless of whether opioid use occurred alone or in combination with other drugs. There were no missing data on heroin use at baseline or 12 months. However, there were eight participants with missing data at 6 months, each of whom had the same respective response at baseline and 12 months. For these subjects we assumed that use at 6 months was consistent with the response at the baseline and 12 month assessments. Of these eight participants, four reported use at baseline but no use at 12 months. These participants were classified as having intermittent use. For the remaining four participants (one who reported use at both baseline and 12 months and the other three who reported no use at both baseline and 12 months), we assumed use at 6 months was consistent with their reported use at baseline and 12 months.

Given the variability in types of opioids used in Russia[42], we also assessed whether participants ever used heroin by itself, other opioids (codeine, china white, methadone, fentanyl) by themselves, or heroin mixed with stimulants (Jeff, ephedrine, amphetamine, methamphetamine, cocaine or crack). In addition, we assessed the average number of injections and use without injection of heroin or other opioids in a given day over the prior 30 days at baseline, 6 and 12 months. To validate the self-report data, we conducted urine toxicology tests at 12 months to test for opiates, which were conducted on the same day as the survey.

Covariates

Socio-demographic variables included gender and age. Depressive symptoms in the past 2 weeks was evaluated using the Beck Depression Inventory-II defined as a score greater than 13 [43] at baseline. Pain was assessed using the SF-12 [44] and dichotomized based on the presence of at least moderate pain at baseline, 6 or 12-months. Past 30 day stimulant (typically ephedrine in Russia) and cannabis use, assessed with a modified RBS [39, 40], and binge drinking [38], determined with the interview-based 30-day Time-Line Follow Back (TLFB) [45], were analyzed as dichotomous variables based on the presence of any use at baseline, 6 or 12-months. Binge drinking was defined as the consumption of 5 or more drinks on any given occasion for men and 4 or more for women. Time between baseline and follow-up CD4 cell counts was included given an expected time-dependent decline in CD4 cell count in one with untreated HIV and variability in the time between CD4 cell count assessments.

Statistical Analysis

We performed descriptive statistics to characterize the demographic and clinical characteristics of the analytic sample, overall and stratified by heroin use (none; intermittent; persistent). Baseline characteristics were compared across heroin use groups using one way-ANOVA for continuous variables and chi-square or Fisher's exact test for categorical variables. We characterized opioid use among patients with intermittent or persistent use across all time points. Using urine toxicology results as the reference, we determined the sensitivity and specificity of self-reported opioid use. Correlation between variables was assessed using Spearman correlation (no pair of variables had $r > 0.50$). Linear regression models were constructed to estimate the association between pattern of heroin use and change in CD4 cell count from baseline to 12 months. We conducted a series of adjusted analyses to control for potential confounding factors. The first model included the covariates gender, age, baseline CD4 cell count, time between baseline and CD4 cell counts, and depressive symptoms. Additional models were fit controlling for pain, stimulant use, cannabis use, and binge drinking in addition to the above covariates. Adjusted mean differences for persistent and intermittent groups vs. no use are reported along with 95% confidence intervals. Secondary, we ran a sensitivity analysis, excluding those four participants with missing data who either had reported use at both baseline and 12 months ($n=1$) or had no reported use at both baseline and 12 months ($n=3$). Third analyses were performed categorizing heroin use as any vs. none. Finally, confirmatory analyses were performed using median regression [46, 47] as this method does not rely on the normality assumption and is more robust to outliers than linear regression. We considered statistical significance to be a $p < 0.05$. All analyses were performed using SAS version 9.3 (SAS Institute, Inc, NC, USA).

RESULTS

Participant Characteristics

Among the 700 participants in the HERMITAGE study, 135 completed the IMPACT survey at 12 months. Of these, 53 were on ART and 5 had missing CD4 cell count data, leaving a final analytic sample of 77 individuals for the current study as described in Table 1. Heroin use was common with 27% reporting intermittent use and 22% reporting persistent use. Participant characteristics included the following: 40% women; mean age of 30 years; diagnosed with HIV for less than 5 years on average; and a mean CD4 cell count of 543 cells/mm³. The mean baseline CD4 cell count was 574 cells/mm³ (standard deviation [SD] 211) among those with no heroin use, 517 cells/mm³ (SD 314) among those with intermittent use and 503 cells/mm³ (SD 351) among those with persistent use ($p=0.60$). The median duration between baseline and follow-up CD4 cell counts was 14 months (interquartile range=11,18). Depressive symptoms were the norm, particularly among those with intermittent (91%) and persistent (71%) heroin use. The majority reported pain (68%). Stimulant use was also more prevalent among those with persistent heroin use (30%) compared to those with intermittent (10%) or no (3%) heroin use. While cannabis use and binge drinking were more commonly reported among those with persistent heroin use than those with intermittent or no use, these differences were not statistically significant.

Self-Reported Heroin Use vs. Urine Toxicology Testing

Across all time points, the majority of patients with either intermittent or persistent heroin use reported heroin use by itself (79%); 18% reported using other opioids and 3% reported heroin used mixed with stimulants. Patients with intermittent or persistent heroin use predominantly reported use of heroin or other opioids by injection, with a median average number of injections per day of 2. Participants reported infrequent use of heroin or other opioids without injection (median average number of use without injection per day of 0; only one person (2.6%) reported using heroin or other opioids without injection and had an average daily use greater than zero.

Among the 24 participants who reported any opioid use in the past 30 days at 12 months, 23 were positive by urine toxicology testing. Among the 53 participants who reported no opioid use at 12 months, 3 were positive by urine toxicology testing; these 3 participants had all been classified as intermittent users based on self-report. The sensitivity of self-reported opioid use was 88.5%; the specificity was 98.0% using the urine tests as the gold standard.

Heroin Use and HIV Disease Progression

In the unadjusted analyses, those with intermittent and no heroin use experienced mean decreases in CD4 cell count from baseline to 12 months (-93 CD4 cells/mm³ and -24 CD4 cells/mm³, respectively; mean difference -69 , 95%CI: -225 , 87) (Table 2). Those with persistent heroin use experienced a mean increase of 52 cells/mm³ (mean difference 76 , 95%CI: -91 , 244).

The results were similar after adjusting for gender, age, baseline CD4 cell count, time between CD4 cell counts and depressive symptoms. Those with intermittent and no heroin use (comparison group) experienced mean decreases in CD4 cell count from baseline to 12 months (-103 cells/mm³ and -10 cells/mm³, respectively; adjusted mean difference [AMD] -93 , 95% CI: -245 , 58). Those with persistent heroin use showed a mean increase of 53 cells/mm³ compared to those with no use (AMD 63 , 95%CI: -95 , 220). After including pain in the model, the results were similar (AMD -93 , 95%CI: -245 , 58 for intermittent vs. no heroin use; AMD 60 , 95%CI: -99 , 218 for persistent vs. no heroin use). These patterns persisted in the models including stimulants, cannabis and binge drinking. In sensitivity analysis, excluding the one participant with reported use at both baseline and 12 months and the three who reported no use at both baseline and 12 months, findings were consistent. Analyses categorizing heroin use as any vs. none and confirmatory analyses using median regression models resulted in similar findings in terms of the directions of observed associations and lack of statistical significance (data not shown).

DISCUSSION

Among this sample of young, HIV-infected Russians with risky drinking, the magnitude and direction of the estimated association between heroin use and CD4 cell count change appeared to depend on whether the heroin use was intermittent or persistent. Although as anticipated in this pilot study with none of the observed differences being statistically significant, those with intermittent heroin use appeared to have larger decreases in CD4 cell

count between baseline and 12 months compared to those with no heroin use, while those with persistent heroin use appeared to have an increase in CD4 cell count over time. There are very limited human data examining the longitudinal association between CD4 cell counts and different patterns of heroin use among a sample naïve to ART and not currently using other non-heroin opioids. The current study seeks to examine this particular issue by including repeated measures of use of individual substances in a distinctive cohort who are naïve to ART and not using other opioids and relatively recently HIV-infected as suggested by the mean CD4 cell count. These analyses also include relevant covariates known to impact HIV disease progression (e.g. baseline CD4 cell count, depressive symptoms, stimulants).

Given the absence of opioid agonist therapy in Russia, intermittent opioid use is associated with recurrent withdrawal episodes. Thus, the observed decreases in CD4 cell count for intermittent heroin use compared to no heroin use and the observed increases in CD4 cell count for persistent heroin use support the notion that opioid withdrawal may be particularly harmful to the immune system while chronic opioid use may be associated with some degree of immune tolerance [48, 7, 16]. Preclinical studies support such a hypothesis. For example, one study of opioid dependent macaques found that stable opioid dependence was not associated with a decline in CD4 cells in comparison to the pre-morphine condition [49]. Precipitated opioid withdrawal or abstinence for 24 hours, however, was associated with a decrease in absolute lymphocyte counts as well as lymphocyte subsets, including CD4 cells, in comparison to both the pre-morphine and opioid-dependent states [49]. In addition, pilot data indicate that precipitated opioid withdrawal in monkeys led to a rise in circulating cells with simian immunodeficiency virus indicating that withdrawal may enhance viral replication [16].

Data from humans are mixed. One study of HIV-uninfected heroin users revealed that active use and early withdrawal (i.e., 15 to 21 days) was associated with a lower percentage and absolute count of CD4 cells in comparison to normal controls and those in late withdrawal (i.e., 6 to 24 months). Notably, those in early withdrawal had the lowest values though these differences were not statistically significant [50]. Data from the AIDS Link to Intravenous Experiences (ALIVE) cohort, which had careful ascertainment of injection drug use, did not find a significant impact of injection drug use pattern on CD4 cell count decline [51]. One reason our findings may differ from this study is their inclusion of a sicker population indicated by the fact that many of these patients developed AIDS and the fact that the issue examined was injection drug use rather than heroin use. Also, the ALIVE study was unable to focus on heroin use in the absence of other opioid use such as pain meds or opioid agonist treatment. In contrast, a study of the Women's Interagency HIV Study (WIHS) cohort demonstrated that progression to AIDS was greater among those with consistent, inconsistent and former drug use compared to never users [29]. Lucas et al. found that compared to nonusers, those with recent active use in the setting of intermittent use (AOR=2.3, 95% 1.5, 3.0), and those with persistent use (AOR=2.1, 95% 1.4, 3.1) were more likely to develop an opportunistic infection. Compared to nonusers, however, those with recent abstinence in the setting of intermittent use (AOR=1.4, 95% 1.0, 1.9) were not significantly more likely to develop an opportunistic infection [20]. Both of these studies included patients receiving ART and categorized heroin with other substances including

stimulants limiting interpretation of the findings [20, 29]. We specifically excluded patients on ART to avoid masking any effects of opioids on HIV progression in the setting of ART. While the precise mechanisms mediating the effects of opioids on the immune system remain to be elucidated, they are likely to involve both the hypothalamic-pituitary-adrenal axis as well as direct effects on various immune cells [49, 7, 48, 52, 6]. Moreover, intermittent opioid use may reflect financial insecurity, which may be associated with food insecurity and poor nutrition, and subsequent immune dysfunction.

We assessed whether pain symptoms impacted the association between heroin use and change in CD4 cell count because pain and heroin use are associated and pain as a source of stress may impact CD4 cell count; however, our findings persisted across these models [53]. Similarly, as depression has been found to be associated with HIV disease progression specifically among HIV-infected patients with injection drug use[54] we attempted to adjust for depressive symptoms in our models. While our study was not designed to specifically evaluate the impact of pain or depressive symptoms on HIV disease progression, prior work indicates the prevalence and importance of addressing these symptoms in this population [55, 53].

Stimulant [31, 30] and alcohol use [56, 57] have been reported to have deleterious effects on HIV disease progression with less clear effects of cannabis on HIV disease progression [58]. While the presence of any stimulant use varied across patterns of heroin use, the overall amount of use based on days of use was low across groups (data not shown). Again, results did not change after adjusting for use of these other substances. Consistent with our inclusion criteria, binge drinking was common across all categories of heroin use. Alcohol may be used in combination with opioids to moderate a high or to cope with withdrawal symptoms. Whether the timing of binge drinking relative to opioid use leads to differential effects on HIV disease progression warrants further investigation.

These findings should be interpreted in the context of some limitations. We lacked data on HIV viral load, which may have been a confounder. We relied on self-reported substance use, which may be subject to under-reporting. However, urine toxicology results were obtained to assess reliability of self-report and were found to be largely consistent with the self-report data. As the majority of the subjects in our sample were co-infected with HCV, we were unable to assess whether the effect of opioids on HIV disease progression varied by HCV status. Also, a single laboratory using consistent assays was not possible for the measurement of both the baseline and 12-month CD4 cell counts, with the possible consequence of decreasing the precision of these findings. We did not specifically ask about krokodil[42]. This opioid drug, however, has only been noted in St. Petersburg in recent years, after our study recruitment occurred. Finally, while the immunosuppressive effects of opioids may vary based on specific type of opioid[15, 52] and route of administration, our study was able to evaluate those effects mainly associated with injection use of heroin.

These limitations notwithstanding, these data support the need for further investigation of the effects of opioids and different patterns of heroin use on HIV disease progression. In particular, larger future studies assessing the differential effects of chronic use, intermittent use and the associated withdrawal, compared to no heroin use, might be quite informative.

In addition, whether the effects of heroin on HIV disease progression differ based on method of administration also deserves further evaluation. Despite the long-term recognition of the association between heroin use and HIV infection, important unanswered questions about the nature of the relationship in terms of HIV disease progression remain.

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Table 1
IMPACT Participant Demographic and Clinical Characteristics (n=77)

Characteristic	Pattern of Heroin Use over 12 Months				
	Overall	None n=39 (51%)	Intermittent n=21 (27%)	Persistent n=17 (22%)	p-value
Age, mean (SD)	30 (5)	29 (5)	30 (3)	31 (5)	0.48
Male Gender, n (%)	46 (60%)	25 (64%)	10 (48%)	11 (65%)	0.41
Months since 1st positive HIV test, median (IQR)	45 (13, 91)	46 (10, 87)	65 (22, 95)	42 (23, 93)	0.77
Hepatitis C, n (%)	71 (92%)	34 (87%)	20 (95%)	17 (100%)	0.21
Depressive Symptoms, n (%)	49 (64%)	18 (46%)	19 (91%)	12 (71%)	<0.05
Baseline CD4 cells/mm ³ , mean (SD)	543 (274)	574 (211)	517 (314)	503 (351)	0.60
Stimulant Use, n (%)	8 (10%)	1 (3%)	2 (10%)	5 (29%)	0.01
Cannabis Use, n (%)	14 (18%)	5 (13%)	4 (19%)	5 (29%)	0.33
Binge Drinking, n (%)	67 (87%)	32 (82%)	19 (91%)	16 (94%)	0.40
Pain, n (%)	52 (68%)	23 (59%)	15 (71%)	14 (82%)	0.21

* p<0.05 considered to be statistically significant.

Table 2
Results from Multiple Linear Regression Models Evaluating Association Between Pattern of Heroin Use and Changes in CD4 cell count (cells/mm³) from Baseline to 12 months

	No Heroin Use	Intermittent Heroin Use	Persistent Heroin Use	Intermittent Use vs. No Heroin Use		Persistent Use vs. No Heroin Use	
	Adjusted Means			Adjusted Mean Difference (95% CI)	p value	Adjusted Mean Difference (95% CI)	p value
Unadjusted Model	-24	-93	52	-69 (-225, 87)	0.38	76 (-91, 244)	0.37
Adjusted Model *	-10	-103	53	-93 (-245, 58)	0.23	63 (-95, 220)	0.44
Adjusted Model* + Pain	-13	-106	47	-93 (-245, 58)	0.23	60 (-99, 218)	0.46
Adjusted Model* + Stimulants	-47	-134	40	-87 (-239, 65)	0.26	87 (-84, 258)	0.32
Adjusted Model* + Cannabis	-22	-114	46	-92 (-243, 60)	0.24	68 (-92, 229)	0.40
Adjusted Model* +Binge	-41	-135	17	-94 (-244, 57)	0.22	58 (-99, 215)	0.47

* Adjusted for age, gender, depressive symptoms, baseline CD4 cell count, time between baseline and 12 month CD4 cell counts (in days)

(SENSITIVITY ANALYSIS). Adjusted Means and Adjusted Mean Difference in CD4 cell count (cells/mm³) from Baseline to 12 months by Pattern of Heroin Use – EXCLUDING 4 SUBJECTS WITH MISSING 6-MONTH HEROIN INFORMATION

Table 3

	No Heroin Use	Intermittent Heroin Use	Persistent Heroin Use	Intermittent Use vs. No Heroin Use**		Persistent Use vs. No Heroin Use**	
	Adjusted Means			Adjusted Mean Difference	95% CI	Adjusted Mean Difference	95% CI
Unadjusted Model	-12	-93	56	-81	-242, 81	69	-108, 246
Adjusted Model *	4	-125	50	-129	-288, 29	46	-119, 211
Adjusted Model* + Pain	-33	-156	38	-129	-287, 29	44	-121, 210
Adjusted Model* + Stimulants	8	-122	52	-123	-281, 36	71	-108, 250
Adjusted Model* + Cannabis	-29	-160	11	-130	-290, 29	44	-125, 212
Adjusted Model* + Binge	2	-127	46	-131	-288, 26	40	-124, 204

* Adjusted for age, gender, depressive symptoms, baseline CD4 cell count, time between baseline and 12 month CD4 cell counts (in days)

** no values reached statistical significance defined as a p<0.05