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# Pain is Associated with Heroin Use over Time in HIV-Infected Russian Drinkers

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## Abstract

**Aims—**This study evaluated whether pain was associated with increased risk of using heroin, stimulants or cannabis among HIV-infected drinkers in Russia.

**Design—**Secondary analysis of longitudinal data from the HERMITAGE study, a behavioral randomized controlled trial, with data collected at baseline, 6 month and 12 month visits.

**Setting—**Recruitment occurred at HIV and addiction treatment sites in St. Petersburg, Russian Federation.

**Participants—**Six-hundred and ninety-nine HIV-infected adult drinkers.

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**Meetings:** Preliminary results from this analysis were presented on June 10, 2012 at the College on Problems of Drug Dependence in Palm Springs, CA.

**Declarations of Interest:** The authors do not have financial conflicts of interest.

**Measurements—**The primary outcome was past month illicit drug use; secondary outcomes examined each drug (heroin, stimulants and cannabis) separately. The main predictor was pain that at least moderately interfered with daily living. General estimating equations (GEE) logistic regression models were used to evaluate the association between pain and subsequent illicit drug use adjusting for potential confounders.

**Findings—**Participants reporting pain appeared to have higher odds of using illicit drugs, although the results did not reach statistical significance (adjusted Odds Ratio [OR]=1.32; 95% CI: 0.99, 1.76, p=0.06). There was a significant association between pain and heroin use (OR=1.54; 95% CI: 1.11 to 2.15, p=0.01) but not other drugs (OR=0.75; 95% CI: 0.40 to 1.40, p=0.35 for stimulants and OR=0.70; 95% CI: 0.45 to 1.07, p=0.09 for cannabis).

**Conclusions—**HIV-infected Russian drinkers who reported pain were more likely to use heroin over time. Pain may be an unrecognized risk factor for persistent heroin use with implications for HIV transmission in Russia.

### Keywords

Pain; HIV; substance use; heroin

## Introduction

Pain is a common clinical problem among persons living with human immunodeficiency virus (HIV). The prevalence of pain in clinical samples of HIV-infected persons living in Western countries ranges from 30 to 90% [1-10] and a national survey of HIV-infected persons living in the United States found that 67% reported pain in the past week [11]. Less is known about the prevalence of pain among HIV-infected patients from non-Western countries, but research to date suggests a similar burden and a greater lack of resources for treatment [12]. The problem of chronic pain and painful symptoms in HIV-infected patients has major potential implications for patterns of substance use.

Pain and substance use frequently overlap [13-19]. Patients with HIV, many of whom became infected through injection drug use, represent a population at risk for these overlapping co-morbidities [20]. Substance use has been hypothesized to represent a maladaptive coping response to pain [21, 22]. As such, patients with pain may be less likely to refrain from using drugs and suffer worse addiction treatment outcomes. Some studies suggest that persistent pain is associated with worse substance use treatment outcomes over time [23, 24], though not all studies are consistent [25]. Little is known about the impact of pain on substance use behaviors in HIV-infected adults. In one study of HIV-infected men, pain was found to be significantly associated with illicit drug use and depression [26]. Because substance use is related to HIV-risk behaviors and non-adherence to HIV medications [27], understanding whether pain is associated with persistent drug use is especially relevant in this population.

To date, there is a lack of research on pain among HIV-infected persons in Russia and Eastern Europe. The HIV epidemic in the Russian Federation continues to grow, with an estimated 1 million individuals infected in 2009 [28]. The primary mode of HIV

transmission in Eastern Europe is injection drug use [28, 29], and it is estimated that up to a third of injection drug users in this region are infected with HIV [30]. Important differences in the management of pain and opioid addiction exist between the United States/Western Europe and Russia. The Russian Federation maintains restrictive policies toward the medical use of opioids. As a result opioids are less frequently prescribed for pain [31] and opioid agonist therapy for treatment of opioid addiction is unavailable [32]. Given that opioids are less commonly prescribed for treatment of pain, it is possible that drugs with pain-relieving properties, like heroin, might be more commonly used among patients with pain in Russia.

This study assessed the association between self-reported pain and subsequent use of illicit drugs (i.e., heroin, stimulants and cannabis) in a cohort of HIV-infected Russians with alcohol problems. We hypothesized that pain would be associated over time with later illicit drug use, particularly heroin use.

## Methods

### Study Design and Participants

We performed secondary analyses of longitudinal data from the HERMITAGE (HIV Evolution in Russia—Mitigating Infection Transmission and Alcoholism in a Growing Epidemic) study, a randomized controlled trial that tested a secondary HIV prevention intervention [33]. Of the 700 participants in the original study, 699 had complete data on pain and substance use at baseline and were included in the analysis. Participants were recruited from HIV and substance use care sites in St. Petersburg, Russia between 2007 and 2010. Eligibility criteria included the following: HIV-infection; 18-70 years old; any risky drinking by National Institute on Alcohol Abuse and Alcoholism (NIAAA) criteria [34] in the past 6 months (i.e. drinking greater than 14 standard drinks per week/greater than 4 drinks in a day for men; greater than 7 drinks in the past week/greater than 3 drinks in a day for women); unprotected vaginal or anal sex in the past 6 months; provision of contact information of two relatives or close friends who could assist with follow-up; stable address/ telephone; fluency in Russian; and ability to provide informed consent. Exclusion criteria were anticipated incarceration or trying to conceive. Both the Institutional Review Boards of Boston Medical Center and St. Petersburg Pavlov State Medical University approved this study.

### Data Collection

After eligibility assessment, all participants provided written informed consent. Data were collected at baseline, 6 month and 12 month visits via: (a) a face-to-face interview with a trained research associate and (b) a self-administered questionnaire for particularly sensitive questions. Review of pain and substance use behaviors occurred at each visit. Interviews were conducted in Russian using translated tools.

### Measures

**Outcome Measures—**The primary outcome of interest was any past month use of illicit drugs, which included use of heroin, stimulants (cocaine, amphetamines and ephedrine) or cannabis. Secondary outcomes were any past month use of each drug analyzed separately.

Use of these illicit drugs was assessed using the Risk Behavior Survey [35, 36], which we modified for the Russian setting by asking about drugs commonly used in Russia. Responses were modeled as dichotomous variables based on any use within the past month.

**Main Predictor—**The main predictor of interest was clinically significant pain in the past month, defined as pain that at least moderately interfered with daily living. This was based on a single question from the Short Form-12 (SF-12) [37], which asks, "During the past month, how much did pain interfere with your normal work, including housework?". The range of possible responses were "not at all/a little bit/moderately/quite a bit/extremely", and responses were dichotomized at the threshold of "moderately" or above.

**Covariates—**Covariates included in the analysis as potential confounders were: age, gender, education (≥9$^{th}$ grade), marital status, employment status, depressive symptoms, CD4 cell count (<350 cells/mm$^3$), current use of antiretroviral therapy (ART), hepatitis C virus (HCV) serostatus based antibody testing, recruitment site, time and randomization group. Depressive symptoms were assessed using the Beck Depression Inventory II (BDI-II) – Russian version and a threshold of 20 was used to define moderate to severe symptoms of depression [38].

## Statistical Analysis

Chi-square and Student's t tests were used to compare characteristics of participants with and without clinically significant pain at baseline. General estimating equations (GEE) logistic regression was used to calculate odds ratios and 95% confidence intervals for the association between reporting clinically significant pain in the past month and subsequent illicit drug use. The main exposure, self-reported pain, was lagged; therefore analyses assessed whether past-month self-reported pain (assessed at baseline and 6 months) was associated with substance use (also past month) at the subsequent 6-month visit (assessed at 6- and 12- months). The GEE approach was used to account for the correlation from using repeated observations from the same subject over time. An independence working correlation structure was used, and empirical standard errors are reported for all analyses. The same approach was used for the secondary analyses of individual drugs. Potential collinearity was assessed by calculating the correlation between independent variables and covariates, and no pair of variables had a Spearman correlation >0.40. A two-tailed p value <0.05 was considered statistically significant for all hypothesis testing. Final models were adjusted for all covariates. Pain, substance use, depressive symptoms and ART were modeled as time-dependent covariates; all other covariates (age, gender, education, marital status, employment, CD4 cell count, HCV serostatus, recruitment site and randomization group) were based on baseline values. Additional secondary analyses were conducted to examine whether pain was associated with the number of days of use of each particular substance in the past month using GEE overdispersed Poisson regression models. The number of days of drug use was modeled as count data and the Pearson chi-square correction was used to account for overdispersion in the data.

For each substance, we also performed secondary, confirmatory analyses that examined, among those who have not used a particular drug at baseline, the association between

baseline self-reported pain and use of the particular drug at follow-up. Logistic regression models calculated the relative odds and 95% confidence intervals for the association between having baseline pain and reporting each substance use outcome at either the 6- or 12- month visit. Models were adjusted for baseline values of covariates listed above. All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Inc., NC, USA).

## Results

Table 1 describes overall characteristics of the cohort, and shows differences at baseline between participants with and without significant pain. Nearly half (46%) of the 699 subjects had pain in the past month that at least moderately interfered with daily living at baseline, which decreased to 35% at subsequent visits. Just under half (47%) reported use of any illicit drugs in the past month. Heroin was the drug most often used (38%), followed by cannabis (21%) and stimulants (12%). Participants with pain were significantly more likely to be female, unemployed and to report moderate to severe depressive symptoms. Participants with pain were more likely to have reported using heroin in the past month, but not other drugs.

The longitudinal analysis included 1,013 observations from 699 participants. Results from the adjusted GEE models demonstrated that participants who reported at least moderate pain interference in the past month had 1.3 times the odds of any illicit drug use reported at the subsequent six month visit (Table 2), however the results did not reach statistical significance (p=0.06). In analyses that examined associations between pain and use of each drug separately, we observed a significant association between pain and heroin use. Individuals who reported at least moderate pain interference with daily living had approximately 1.5 times the odds of reporting current heroin use at the subsequent study visit. In contrast, there was no significant association between pain interference and later use of stimulant or cannabis. Overdispersed Poisson regression models that assessed associations between pain and frequency of drug use reported 6 months later showed similar results (Table 3). Reporting at least moderate pain interference was associated with a greater number of days use in the past month for heroin, but not other drugs.

Confirmatory analyses using adjusted logistic regression models to assess, among those who have not used a particular substance at baseline, the association between baseline pain interference and use of the particular substance at either the 6 or 12 month visit showed results that were consistent with prior analyses. Among study participants with no illicit drug use at baseline, those who reported pain at baseline appeared to have higher odds of reporting any illicit drug use at 6 or 12 months, although the results were borderline significant (OR=1.76 95% CI: 0.99 to 3.12, p=0.05). When analyzing each drug as a separate outcome, we observed a significant association between baseline pain and subsequent heroin use (OR=2.16; 95%CI: 1.16, 4.01), p=0.02), but not other drugs (OR=0.73; 95% CI: 0.30 to 1.78, p=0.48 for stimulants and OR=0.82; 95% 0.41 to 1.63, p=0.57 for cannabis).

## Discussion

This analysis of longitudinal data on HIV-infected Russian drinkers demonstrated that clinically significant pain (i.e. self-reported pain that at least moderately interfered with daily living) was associated with increased odds of using heroin over time, but not stimulants or cannabis. This study suggests an important link between pain and heroin use among HIV-infected persons, which may have implications for clinical practice and for strategies to reduce HIV transmission in Russia and possibly other countries with injection drug driven HIV epidemics.

This study provides important insights on the burden of pain and its impact on substance use among Russian persons infected with HIV. Russia is experiencing a growing epidemic of HIV, yet access to ART lags behind Western countries [28, 39] and absence of opioid agonist treatment thwarts efforts to effectively engage injection drug users [40]. This, coupled with restrictive policies for treatment of pain with opioids, has implications for pain experiences among HIV-infected patients in Russia. In this study, we found that one-third to one-half of the HIV-infected participants complained of pain that at least moderately interfered with daily living at each study visit. These results are comparable to what has been reported in the U.S. and Western Europe [1-6, 8, 9]. Although one might expect a higher prevalence of pain reported in a setting with limited access to ART and opioid pain medications, this may be consistent with prior research that has demonstrated that painful symptoms do not necessarily improve over time with effective HIV treatment [41] and that use of opioids is not associated with improved pain over time among individuals with HIV [42].

Our primary finding, that pain was associated with heroin use in this cohort of HIV-infected patients is consistent with some, but not all, prior research mostly among non-HIV infected populations. Similar to our findings, a multi-site cross-sectional study of 7,876 patients seeking treatment for substance use disorders found a significant association between pain and heroin use, but not use of cocaine or cannabis [43]. However, a smaller cross-sectional study of veteran patients seeking treatment for opioid dependence found that patients with pain were significantly more likely to report illicit use of prescribed narcotics and cannabis, but not heroin [15]. Russian patients have less access to prescription narcotics, both prescribed and illicit, and therefore may be more likely to use what is accessible, namely heroin. Longitudinal studies on the effect of pain on substance use have shown mixed results. A study of 397 adults in a residential detoxification program found that persistent pain was associated with increased odds for using heroin, but not cocaine, at the 24-month follow-up [24]. Similarly, a study of 582 veterans treated for substance dependence found that persistent pain was associated with a lower likelihood of being abstinent of alcohol or drugs at one year [23]. However, another study of veterans initiating methadone for treatment of opioid dependence did not find baseline pain to be predictive of substance-use related outcomes at one year [25]. In the one study identified among HIV-infected persons, the relationships between pain and substance use in a cohort of 1,940 men in the U.S. found that pain was significantly associated with cannabis and hard drug use (defined as cocaine or heroin use) [26]. Our study supports the hypothesis that pain can impact substance use patterns over time in HIV-infected men and women, and provides information to suggest

that the relationship between pain and heroin use may be unique, as compared to other illicit drugs.

While we hypothesized that pain may lead to substance use (in particular use of drugs with analgesic properties such as heroin) as an effort to self-medicate pain, there are other explanations for these study findings that must be considered. First, it is possible that the lifestyle associated with substance use could lead to trauma and co-morbidities that cause pain. However, in that case, one might expect to observe associations between pain and use of other substances (stimulants and cannabis) as well, which was not observed in this study. Likewise, substance use may lead to depression which is well-established to be associated with pain [44]. However, we found a persistent association between pain and heroin use, even after adjustment for depressive symptoms. Another possibility is that use of heroin could be causing pain either through withdrawal symptoms, which were not assessed in this study, or opioid-induced hyperalgesia. Opioid-induced hyperalgesia is a physiologic phenomenon whereby pain thresholds and tolerance are lowered by persistent administration of opioids [45]. While this phenomenon is well-characterized in animal studies, it is less well established in humans [46]. Our analyses, which test for associations by modeling pain as a lagged exposure, attempt to address this issue of direction of the association, but cannot rule out the opposite causal relationship (i.e. heroin leading to pain, rather than pain leading to heroin use). Furthermore, bi-directional relationships may concurrently exist and contribute to the persistence of both conditions. More nuanced research methods such as ecological momentary assessments which evaluate pain and drug use behaviors repeatedly in real-time may be appropriate for future research [47].

Given that all the participants in this study had HIV infection, which can cause painful symptoms, and they likely had limited access to opioids for pain treatment, it is plausible that pain may have been a factor leading to prolonged heroin use. As such, persistent pain may be an unrecognized barrier to risk reduction, and may be indirectly contributing to the spread of HIV in Russia. Injection drug use is the primary mode of transmission in Eastern Europe, and as such, efforts to slow the epidemic of HIV in this region must include interventions to reduce drug use and the harms associated with drug use. More research is needed to understand how pain and substance use are related, and to test the effectiveness of programs to help HIV-infected substance users reduce or manage their pain. In the United States, studies suggest that up to one-quarter of HIV-infected patients are prescribed opioids for chronic pain [48, 49]. However, the use of opioids for chronic pain is controversial. Aberrant prescription opioid behaviors are known to exist in HIV-infected populations as in other non-HIV patient populations [50]. A national study of HIV-infected persons in the U.S. showed an association between pain and complementary and alternative therapy, suggesting a desire for alternative treatments on the part of patients [51]. Additionally, research points to the importance of other potentially treatable factors that impact pain such as sleep disorders [52] and post-traumatic stress-disorder [53]. More research is needed to establish effective strategies for managing pain in HIV-infected populations, as well as research to examine the downstream effects of such interventions on substance use and HIV-risk behaviors.

A number of limitations to this study exist. Clinically significant pain was based on a single question from the SF-12; we did not have additional information on pain severity, duration, causes or treatment. Other studies similarly have utilized single question measurements on pain [42, 54], and have isolated pain questions from health-related quality of life instruments to measure pain [23, 24]. Furthermore, although our study focuses on pain interference, pain interference and pain severity have been shown to be highly correlated [7, 55]. Our study sample was comprised of HIV-infected persons who drank risky amounts of alcohol within the past 6 months, which could impact how our findings may be generalized. However, alcohol problems are more common among HIV-infected [56], with prevalence estimated at 40% in the U.S. [57-59]. Russia is one of the highest per capita alcohol consumption countries [60], and indeed, few HIV-infected persons did not meet this alcohol consumption entry criteria (only 12% of all potential candidates assessed). Therefore, our findings are of interest as they do appear to be broadly applicable to most HIV-infected, particularly those with lifetime injection drug use. As previously discussed, causality between pain and substance use cannot be definitively concluded and it remains possible that heroin use could also lead to pain, rather than vice versa. However our methodologic approach (i.e. modeling pain as a lagged exposure) provides some support for our research hypothesis.

In summary, this study of HIV-infected Russian patients found that perceived pain was associated with higher odds of using heroin over time. This study reinforces the close relationship between illicit opioid use and pain. In addition, it brings to light the possibility that pain may be an important and unrecognized risk factor for persistent heroin use among HIV-infected patients in Russia, which may indirectly be contributing to the spread of HIV. Additional research is needed to understand how the experience of pain contributes to on-going drug use, and to test interventions for managing pain and their impact on substance use among persons with HIV.

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**Table 1**

**Baseline Characteristics of HIV-infected HERMITAGE Study Participants (Overall and Stratified by Pain Status)**

| | Overall | No Significant Pain | Significant Pain | p-value |
|---|---|---|---|---|
| | (n=699) | (n=376) | (n=323) | |
| Age (Mean ±SD) | 30.1 (±5.2) | 29.8 (±5) | 30.4 (±5.5) | 0.18 |
| Female | 41% | 35% | 47% | <0.01 |
| ≥ 9th grade education | 78% | 79% | 76% | 0.37 |
| Married or living with a partner | 36% | 34% | 39% | 0.16 |
| Unemployed | 27% | 22% | 33% | <0.01 |
| Recruitment site | | | | |
| Pavlov Medical University | 30% | 35% | 25% | 0.04 |
| City Addiction Centers | 13% | 12% | 13% | |
| AIDs Centers | 57% | 53% | 62% | |
| ≥Moderate depressive symptoms* | 42% | 34% | 51% | <0.01 |
| Past month risky drinking** | 81% | 80% | 83% | 0.32 |
| HCV seropositive | 80% | 76% | 84% | 0.06 |
| CD4 <350 cells/mm$^3$ | 24% | 21% | 28% | 0.26 |
| Current ART | 17% | 17% | 18% | 0.82 |
| Years with HIV(Mean ±SD) | 4.4 (±3.6) | 4.2 (±3.5) | 4.6 (±3.6) | 0.12 |
| Lifetime heroin use | 83% | 81% | 85% | 0.11 |
| Past month injection drug use | 42% | 37% | 47% | <0.01 |
| Past month any illicit drug use† | 47% | 43% | 51% | 0.05 |

| | Overall | No Significant Pain | Significant Pain | p-value |
|---|---|---|---|---|
| | (n=699) | (n=376) | (n=323) | |
| Past month heroin use | 38% | 33% | 44% | <0.01 |
| Past month stimulant use | 12% | 10% | 14% | 0.12 |
| Past month cannabis use | 21% | 20% | 21% | 0.72 |

*Beck Depression Inventory II score ≥20

**Based on NIAAA definition

†Use of heroin, stimulants or cannabis

**Table 2**

**Regression Models for the Association between Pain and Subsequent Illicit Drug Use Over Time, Results from Fully Adjusted Longitudinal Generalized Estimating Equation Models with Lagged Exposure***

| | Any Illicit Drug Use | | Heroin Use | | Stimulant Use | | Cannabis Use | |
|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) | p-value | OR (95% CI) | p-value | OR (95% CI) | p-value | OR (95% CI) | p-value |
| ≥ Moderate Pain Interference | 1.32 (0.99, 1.76) | 0.06 | 1.54 (1.11, 2.15) | 0.01 | 0.75 (0.40, 1.40) | 0.35 | 0.70 (0.45, 1.07) | 0.09 |
| Twelve month visit (v. 6 mo.) | 0.97 (0.78, 1.19) | 0.76 | 1.01 (0.78, 1.31) | 0.91 | 1.30 (0.78, 2.17) | 0.35 | 0.93 (0.69, 1.25) | 0.62 |
| Intervention Group (v. control) | 1.11 (0.80, 1.55) | 0.53 | 1.20 (0.84, 1.72) | 0.32 | 0.86 (0.44, 1.69) | 0.67 | 1.26 (0.77, 2.06) | 0.36 |
| Site | | | | | | | | |
| Pavlov Medical University | 1.00 | 0.03 | 1.00 | 0.01 | 1.00 | 0.17 | 1.00 | 0.52 |
| City Addiction Centers | 0.53 (0.31, 0.90) | | 0.56 (0.32, 0.97) | | 1.18 (0.41, 3.39) | | 0.66 (0.29, 1.47) | |
| AIDs Centers | 0.70 (0.48, 1.03) | | 0.53 (0.35, 0.80) | | 2.22 (1.00, 4.97) | | 1.04 (0.58, 1.87) | |
| Age | 0.98 (0.94, 1.01) | 0.15 | 1.00 (0.96, 1.03) | 0.83 | 0.91 (0.85, 0.97) | 0.004 | 0.97 (0.92, 1.02) | 0.20 |
| Gender Male | 1.46 (1.00, 2.14) | 0.05 | 0.91 (0.60, 1.38) | 0.66 | 1.18 (0.56, 2.51) | 0.66 | 3.01 (1.58, 5.71) | <0.001 |
| Education level ≥ 9 grades | 0.81 (0.54, 1.22) | 0.32 | 0.72 (0.46, 1.13) | 0.17 | 0.93 (0.43, 2.02) | 0.86 | 1.01 (0.54, 1.87) | 0.98 |
| Married or partnered | 0.92 (0.64, 1.31) | 0.64 | 0.73 (0.49, 1.09) | 0.12 | 0.65 (0.31, 1.36) | 0.24 | 1.36 (0.81, 2.29) | 0.26 |
| Unemployed | 0.82 (0.55, 1.21) | 0.32 | 0.97 (0.63, 1.50) | 0.89 | 0.37 (0.13, 1.11) | 0.05 | 0.64 (0.33, 1.24) | 0.17 |
| ≥ Moderate depressive symptoms** | 2.42 (1.75, 3.33) | <0.001 | 3.11 (2.19, 4.43) | <0.001 | 1.79 (0.94, 3.40) | 0.10 | 1.44 (0.91, 2.28) | 0.13 |
| CD4 count < 350 | 1.37 (0.86, 2.17) | 0.18 | 1.25 (0.74, 2.10) | 0.40 | 0.71 (0.29, 1.74) | 0.46 | 1.68 (0.91, 3.10) | 0.10 |
| Current ART use (time varying) | 0.45 (0.30, 0.67) | <0.001 | 0.23 (0.14, 0.39) | <0.001 | 1.24 (0.56, 2.73) | 0.60 | 1.16 (0.67, 2.01) | 0.61 |
| HCV infected | 3.24 (1.26, 8.32) | 0.01 | 21.90 (4.19, 114.49) | <0.001 | 5.24 (0.72, 38.00) | 0.10 | 1.23 (0.44, 3.35) | 0.70 |

* 699 subjects, 1,013 observations

** Beck Depression Inventory II score ≥20

**Table 3**

**Overdispersed Poisson Regression Models for the Association between Pain and Subsequent Frequency of Illicit Drug Use* Over Time, Results from Fully Adjusted Models with Lagged Exposure***

| | Heroin Use | | Stimulant Use | | Cannabis Use | |
|---|---|---|---|---|---|---|
| | IRR (95% CI) | p-value | IRR (95% CI) | p-value | IRR (95% CI) | p-value |
| ≥ Moderate Pain Interference | 1.48 (1.15, 1.89) | 0.003 | 0.98 (0.50, 1.92) | 0.95 | 0.55 (0.28, 1.10) | 0.06 |
| Twelve month visit (v. 6 mo.) | 1.15 (0.97, 1.38) | 0.11 | 1.80 (0.79, 4.11) | 0.18 | 1.01 (0.70, 1.46) | 0.96 |
| Intervention Group (v. control) | 1.16 (0.89, 1.51) | 0.28 | 0.62 (0.27, 1.43) | 0.25 | 0.95 (0.50, 1.80) | 0.88 |
| Site | | | | | | |
| Pavlov Medical University | 1.00 | <0.001 | 1.00 | 0.09 | 1.00 | 0.31 |
| City Addiction Centers | 0.53 (0.34, 0.85) | | 1.67 (0.35, 7.97) | | 0.50 (0.19, 1.32) | |
| AIDs Centers | 0.53 (0.39, 0.72) | | 3.49 (1.33, 9.21) | | 0.74 (0.39, 1.40) | |
| Age | 0.98 (0.95, 1.01) | 0.28 | 0.92 (0.86, 0.99) | 0.03 | 0.98 (0.90, 1.05) | 0.51 |
| Gender Male | 0.82 (0.60, 1.14) | 0.24 | 1.07 (0.39, 2.92) | 0.89 | 3.38 (1.20, 9.48) | 0.005 |
| Education level ≥ 9 grades | 0.88 (0.65, 1.19) | 0.42 | 0.68 (0.28, 1.63) | 0.44 | 1.20 (0.55, 2.64) | 0.64 |
| Married or partnered | 0.66 (0.48, 0.92) | 0.01 | 1.21 (0.51, 2.88) | 0.68 | 1.67 (0.89, 3.15) | 0.14 |
| Unemployed | 1.11 (0.80, 1.55) | 0.52 | 0.11 (0.04, 0.32) | 0.003 | 0.37 (0.15, 0.90) | 0.04 |
| ≥ Moderate depressive symptoms* | 2.17 (1.66, 2.84) | <0.001 | 2.05 (0.86, 4.88) | 0.15 | 1.06 (0.56, 2.03) | 0.86 |
| CD4 count < 350 | 1.12 (0.74, 1.68) | 0.59 | 0.61 (0.22, 1.72) | 0.35 | 1.81 (0.75, 4.36) | 0.18 |
| Current ART use (time varying) | 0.28 (0.17, 0.45) | <0.001 | 1.01 (0.41, 2.52) | 0.98 | 1.33 (0.52, 3.44) | 0.56 |
| HCV infected | 7.86 (1.55, 39.90) | 0.01 | 11.09 (1.51, 81.28) | 0.02 | 4.34 (1.43, 13.14) | 0.01 |

*699 subjects, 1,012 observations

*Beck Depression Inventory II score ≥20