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Fatal and Non-Fatal Overdose After Narcology Hospital Discharge Among Russians Living with HIV/Aids who Inject Drugs[‡]

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Abstract

[‡]Preliminary data from this project was presented at the Association for Medical Education and Research in Substance Abuse 2014 Annual Conference in San Francisco, California and the College on Problems in Drug Dependence 2014 Annual Conference in San Juan, Puerto Rico.

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Authorship contributions: A.Y.W conceived the study question, led the analytic planning and wrote the first draft of the manuscript. D.M.C. was the biostatistician. E.K.Q. provided data management and conducted the analyses, with oversight from C.E.C. N.G. was the project manager in the United States. E.B. was the project manager and led the data collection in Russia. P.O.C. provided background expertise on the prevalence and incidence of overdose in Russia. E.K. led the Russian team and was the principal investigator in Russia. J.H.S. was the principal investigator of the parent study. All authors contributed to developing the analytic plan, reviewed, revised, and approved the submitted manuscript.

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Objectives—Among Russians living with HIV/AIDS who inject drugs, we examined the incidence of fatal and non-fatal overdoses following discharge from a narcology hospital and the associations with more advanced HIV infection.

Design—Prospective cohort study of data collected at baseline, 3 and 6 months from HIV-infected patients with a history of injection drug use who were not treated with anti-retroviral therapy. Participants were recruited between 2012-14 from a narcology (addiction) hospital in St. Petersburg, Russia.

Methods—Fatal overdose was determined based on contact reports to study staff in the year after discharge. Non-fatal overdose was self-reported at the 3- and 6-month assessments. The main independent variable for HIV severity was CD4 cell count at the baseline interview (<200 cells/mm³– 200 cells/mm³). Secondary analyses assessed time since HIV diagnosis and treated with anti-retroviral treatment (ART) prior to enrollment as independent variables. We fit Cox proportional hazards models to assess whether HIV severity is associated with either fatal or non-fatal overdose.

Results—Among 349 narcology patients, 18 participants died from overdose within one year after discharge (8.7%, 95% CI 3.4–14.2 by Kaplan-Meier); an estimated 51% [95% CI 34–68%] reported at least one non-fatal overdose within 6 months of discharge. HIV severity, time since HIV diagnosis and ever ART were not significantly associated with either fatal or non-fatal overdose events.

Conclusion—Fatal and non-fatal overdose are common among Russians living with HIV/AIDS who inject drugs after narcology hospital discharge. Overdose prevention interventions are urgently warranted among Russian narcology patients with HIV infection.

Keywords

Overdose; HIV; injection drug use; mortality; Russia

1.0 Introduction

In Russia, there are an estimated 1.8 million people who inject drugs (PWID) – a prevalence of 1.8% of the adult population, which ranks only behind Azerbaijan, Georgia, and Mauritius in prevalence worldwide (Mathers et al 2008). Among Russian PWID, 37% are HIV-infected. Russia has more HIV-infected PWID than any other country (Mathers et al 2008). Along with a high prevalence of HIV and PWID, Russians have no access to opioid agonist treatment, low and worsening access to clean syringes and low access to anti-retroviral treatment (ART) (Mathers et al. 2010, Degenhardt et al. 2014). The incidence of fatal overdose among Russians who use drugs has been estimated at greater than 2 per 100 person-years (Coffin 2008, Grau et al. 2009), whereas a meta-analysis of studies among PWIDs in other countries has found an overall overdose death rate of 0.62 per 100 person-years, with studies ranging from 0.12 to 4.71 deaths per 100 person-years (Mathers et al. 2013, Evans et al. 2015).

PWIDs living with HIV/AIDS have twice the risk for overdose as those who are not HIV-infected (Mathers et al. 2013, Green et al. 2012). In a previous study of Russians with HIV

infection and injection drug use primarily recruited from an inpatient hospital medical service, over three quarters (76%) reported a history of non-fatal overdose in their lifetime with 16% reporting non-fatal overdose in the past 3 months. Those with higher injection frequency and receiving ART were more likely to overdose (Walley et al. 2014a). Similarly, a study of nonfatal overdose among PWIDs with and without HIV infection in Vancouver did not show differences in non-fatal overdoses by HIV status or HIV severity (Escudero et al. 2016). It is not clear why people living with HIV/AIDS have a higher risk of fatal overdose than people without HIV. Considerations include co-morbid liver dysfunction, pulmonary dysfunction, riskier behaviors, and social isolation (Green et al 2012).

In Russia, opioid detoxification (detox) is provided by state-supported narcology hospitals, where 40% of patients are HIV-infected (Holt 2010). Studies of populations in several countries undergoing detox without further treatment have demonstrated relapse rates after detox as high as 90% at 12 months (Strang et al. 2003, Fischer et al. 2004, Davoli et al. 2007). Due to reduced tolerance and the high rate of relapse, detox is associated with markedly elevated rates of overdose and overdose mortality in the months after treatment (Strang et al. 2003). Thus, utilizing detox services carries very real risks for people who use opioids; the vast majority of PWIDs in Russia use opioids.

The objectives of this paper are the following: i) To assess the probabilities of fatal and non-fatal overdose among discharged narcology patients living with HIV/AIDS infection who inject drugs; and ii) To evaluate whether more advanced HIV infection is associated with either fatal or non-fatal overdose.

2.0 Methods

2.1 Population and Setting

We conducted a prospective, longitudinal cohort study using data from the Linking Infectious and Narcology Care (LINC) study, which is a randomized controlled trial of a strengths-based peer-led case management intervention designed to support and motivate HIV-infected narcology patients who inject drugs in St. Petersburg, Russia to initiate and remain in HIV medical care and ultimately improve their HIV outcomes. From July 2012 through May 2014, 349 narcology patients with HIV infection and a history of injection drug use were recruited into the LINC study. Eligibility criteria included: 1) age 18-70 years; 2) HIV-infected; 3) hospitalized at the narcology hospital; 4) history of injection drug use; 5) available for CD4 count testing; 6) have 2 contacts to assist with follow-up; 7) live within 100 km of St. Petersburg; 8) have a telephone. The following served as exclusion criteria for study enrollment: 1) currently on ART; 2) not fluent in Russian; 3) cognitive impairment precluding informed consent.

Study participants were recruited from the inpatient wards at the City Addiction Hospital in St. Petersburg, Russia, which is a 500-bed hospital that provides detoxification, early stabilization (treatment of co-morbid psychiatric and somatic disorders), and in-patient rehabilitation. Admitted patients have typical stays of one to three weeks. HIV-infected patients admitted to multiple designated floors at City Addiction Hospital were eligible for screening. HIV status is routinely collected upon admission and noted on the front of the

medical chart. Three times a week, a study nurse selected medical charts of HIV-infected patients who had not been previously screened for the LINC study. Patients were screened one to five days after admission to the narcology hospital. Research Assessors (RAs) who were City Addiction Hospital physicians with narcology sub-specialty training (i.e., narcologists) were trained on the research protocol and screened patients. To reduce the chance of therapeutic misconception, which is the misunderstanding by study participants that a study intervention is already proven to help them, only narcologists who were not involved with the patient's medical care could approach the patient to assess study eligibility. Once a patient was identified as being HIV-infected, without evident significant cognitive impairment, not on ART, and not previously approached about the LINC study, then the RA met with the patient in a private place (e.g. hospital room or exam room) to briefly describe the study, conduct the screening, offer study enrollment and document informed consent. Afterwards, the RA administered the baseline assessment and facilitated CD4 testing. The LINC study was approved by the Institutional Review Boards of Boston University Medical Campus and First St. Petersburg Pavlov State Medical University.

2.2 Data Collection

Study interviews were conducted face-to-face by trained research staff at baseline at the narcology hospital, at 6 months and 12 months post-enrollment at First St. Petersburg Pavlov State Medical University. In the event of readmission to the narcology hospital, follow-up interviews were occasionally conducted at the City Addiction Hospital. Study staff contacted study participants by telephone at 3 months post-enrollment to ascertain the number of times participants had overdosed since the baseline interview, and then contacted participants or their contacts prior to the 6-month and 12-month assessments to remind them about the assessment appointments.

2.2.1 Outcomes—The two main outcomes of interest were: i) time from discharge to fatal overdose and ii) time to first non-fatal overdose. The occurrence and dates of fatal overdoses were determined by interviewing participant-provided contacts. Time to fatal overdose was censored at the earliest of the following events: death not due to overdose, loss to follow-up (last date participant confirmed to be alive based on communication with either participant or their alternate contact), or study completion date. Nonfatal overdose was self-reported at the 3-month telephone assessment and the 6-month in-person assessment. At the 3-month telephone assessment, non-fatal overdoses were self-reported based on the question: “The following question refers to accidental overdose on drugs or alcohol. I am referring to unintentional overdose, not to suicide attempts that involve overdosing on purpose. An overdose is when you lose consciousness and your breathing stops or is slowed down. *How many times have you overdosed since you were discharged from the narcology hospital?*” At the 6-month in-person assessment, non-fatal overdoses were assessed using the following: “These next questions refer to accidental overdose on drugs or alcohol. I am referring to unintentional overdose, not to suicide attempts that involve overdosing on purpose. *How many times have you overdosed in the past 6 months?*” For the 6-month non-fatal overdose reports, we asked the date of the most recent non-fatal overdose. Because we did not specifically collect data on date of first non-fatal overdose, we approximated this variable using the date of the 3-month telephone call if a non-fatal overdose was reported, or the date

of most recent non-fatal overdose reported at 6 months, whichever was earlier. Time to nonfatal overdose was censored at the earliest of loss to follow-up with respect to nonfatal overdose assessment, due to death or study drop out, or study completion date. A confirmatory analysis was also conducted for the outcome time to any overdose (fatal or non-fatal).

2.2.2 Independent variables—The main independent variable was CD4 cell count at the baseline interview, a measure of HIV severity, dichotomized at less than 200 versus 200 or more. We chose this cut off because it is a CD4 count level that has other clinical implications with regard to comorbid illness. We conducted sensitivity analyses using 350 as alternate cut-off. Secondary analyses evaluated other measures of HIV severity including self-reported duration since HIV diagnosis and ever treated with ART prior to study enrollment (Prior ART).

2.2.3 Covariates—Due to the number of fatal overdose events (18), we adjusted only for age, gender, and randomization group as covariates. Age was defined as a continuous variable in years (Stoove et al. 2009, Hickman et al. 2003). Gender was dichotomized as male versus female. (Dietze et al. 2005, Brugal et al. 2005,). Because all the participants were enrolled in a randomized controlled trial adjusted models included randomization group as a covariate. We conducted additional sensitivity analyses that included education and unemployment as dichotomous variables. Education was dichotomized as those with at least 11 grades completed versus those with less than 11 grades.

2.3 Analysis

We calculated descriptive statistics to characterize the cohort and report these by overdose status: fatal overdose, non-fatal overdose (but no fatal overdose), and no overdose or censored. To estimate the probabilities of fatal and non-fatal overdoses within 6 months, we used the Kaplan-Meier method. For descriptive purposes, fatal and non-fatal overdose rates were also calculated using person-months of observation along with 95% confidence intervals.

Prior to regression analyses, we assessed the correlation between independent variables and covariates. No pair of variables included in the regression models had Spearman correlation >0.40 . To evaluate whether severity of HIV infection was associated with overdose, we fit separate Cox proportional hazards models for each overdose outcome, both unadjusted and adjusted for age, gender, and randomization group. The exact method (Kalbfleisch and Prentice 2002) was used to handle tied event times. Because all but one of the participants with a fatal overdose was not assessed for a non-fatal overdose, an additional exploratory analysis was conducted for the outcome any overdose (fatal or non-fatal) in order to include those with a fatal overdose and assess the consistency of findings. The proportional hazards assumption was evaluated by assessing time interactions for the main independent variables and covariates in the adjusted models. Specifically, we created interaction terms between the independent variables and covariates in the model with the log time to overdose and tested whether the interactions were significant. None of the interactions were significant, independently or collectively for either outcome, suggesting the data were consistent with

the proportional hazards assumption. Adjusted hazard ratios (HR) and 95% confidence intervals were calculated for all variables. Two-tailed tests and a significance level of 0.05 were used for all tests. Analyses were performed using SAS version 9.3 (SAS Institute, Inc., NC, USA).

3.0 Results

Among this cohort of narcology patients with HIV infection and injection drug use, the mean age was 34, almost three quarters were male, almost one third had CD4 cell count of less than 200, only 12% had been treated with ART prior to study enrollment, and the mean number of years since HIV diagnosis was 7. (Table 1)

The 349 narcology patients contributed 279 person-years of follow-up, during which 18 participants (Kaplan-Meier estimate of 8.7% [95%CI 3.4-14.2]) died from overdose. There were 11 people with no information after the interview at study entry who did not contribute follow-up time. The overdose death incidence rate was 6.44 per 100 person-years (95%CI 4.06-10.23), and an estimated 51% [95% CI 34-68%] reported at least one non-fatal overdose within 6- months from discharge.

Of 349 participants, 250 (71.6%) were interviewed at six month follow up: 27% reported 30-day use of multiple drugs, 27% had likely alcohol dependence by the AUDIT, 52% reported past 30-day injection drug use, 21% reported receptive sharing, and 21% had been arrested or incarcerated in the previous year. (Table 2) The median number of non-fatal overdoses reported by those reporting non-fatal overdose was one. Of the 35 who reported their last non-fatal overdose at six month follow-up, 57% (20/35) reported receiving any emergency treatment, 23% (8/35) reported receiving naloxone. One of these eight reported receiving naloxone from a non-medical person.

In unadjusted and adjusted Cox proportional hazards analyses for fatal overdose, we found no significant associations between years since diagnosis, prior ART or CD4 cell count (cut-off 200 or 350) and time to fatal overdose. (Table 3) Similarly in the Cox proportional hazards analyses for non-fatal overdose, we found no significant associations between any of the independent variables and time to non-fatal overdose. (Table 4) The models showed no substantive change in the magnitude or direction of the hazard ratios in sensitivity analyses that additionally controlled for education and employment as covariates. For the combined outcome of time to any overdose (non-fatal or fatal), we found no significant associations between any of the independent variables and time to non-fatal overdose. (Table 5)

There were 15 additional deaths, 3 from trauma and 12 from medical illness (including cancer, pneumonia, unspecified AIDS-related disease, tuberculosis, stroke, and sepsis) for a total of 33 known deaths among 349 study participants. The median time to death was 84 days (Interquartile range (IQR) 46, 178) for overdose, 82 days (IQR 15, 240) for other trauma and 239.5 days (IQR 152.5,309) for medical illness.

4.0 Discussion

Among this Russian sample living with HIV/AIDS who inject drugs released from a narcology hospital, we found very high fatal and non-fatal overdose rates. An estimated 8.7% died of an overdose within a year of discharge with an incidence of 6.44 overdose deaths per 100 person-years; estimated 51% reported at least one non-fatal overdose within 6 months after discharge. HIV severity, measured as CD4 count <200 cells/mm³, time since diagnosis or whether the participant had received ART previously, were not significantly associated with fatal or non-fatal overdose events.

This overdose mortality rate is more than double what has been previously reported in studies among Russians who use drugs (Coffin 2008, Grau et al. 2009). A meta-analysis of 43 studies among PWIDs from 16 countries found an overall overdose death rate of 0.62 per 100 person-years, with the highest overdose death rate among these studies reporting 4.71 per 100 person-years (Mathers et al. 2013). Similarly, the estimated rate of non-fatal overdose was 51% at 6 months. Two likely reasons explain the high overdose rates in this cohort. First, these are PWIDs with HIV infection. Meta-analyses have demonstrated an almost two fold risk of death among PWIDs with HIV infection (Mathers et al. 2013, Green et al. 2012, Brugal et al. 2005). Second, this cohort underwent detoxification and then was released with low tolerance. A study among 137 detoxification patients in England found 2.2% (3/137) died of overdose within 4 months after release (Strang et al 2003). A study of 10,454 Italian PWIDs recruited in treatment found 1 overdose death per 100 person-years overall, but 2.3 overdose deaths per 100 person-years among those in the 30 days after leaving treatment (Davoli et al. 2007). A study that followed 32,322 people in California with opioid dependence initiating either detoxification or maintenance treatment found 0.80 drug-related deaths per 100 person-years among those who left treatment compared to 0.23 drug-related deaths per 100 person-years among those during maintenance treatment (Evans et al. 2015). In our study, 50% of the overdose deaths occurred within 3 months of hospital discharge on 12-month follow-up.

Factors specific to the Russian setting also likely explain the high overdose death rate we found. In Russia, there is no opioid agonist treatment, little access to overdose prevention education and naloxone rescue kits, and inadequate availability of clean needles and syringes in the community (Mathers et al. 2010, Degenhardt et al. 2014, Federova et al. 2013). A qualitative study among PWID in St. Petersburg found knowledge about overdose, experiencing overdose, and witnessing overdose are common, but PWIDs do not feel empowered to prevent or address overdose death (Grau et al. 2009). Furthermore, the emergency system in Russia is not well equipped to respond to overdoses when they occur in the community (Green et al. 2009). Police are not trained as medical first responders. Ambulance services are infrequently equipped with naloxone. Finally, PWID may be subjected to threats of arrest at the scene of an overdose.

Although meta-analyses show that HIV infection is associated with greater overdose death, we did not detect an association between the severity of HIV infection and fatal or non-fatal overdose. This may be due to several reasons including: low statistical power due to the limited number of events, because severity of HIV does not contribute additional risk

beyond HIV infection, or that the contribution of HIV severity is small and difficult to detect among this population of recently discharged narcology patients with very high overdose risk. Furthermore, HIV disease and disease severity may impact fatal and non-fatal overdose differently. In the fatal overdose model, the hazard ratio for any prior use of ART was in the direction of increased risk of overdose, although not statistically significant. This unexpected finding is similar to our previous study looking at non-fatal overdose among a cohort of people with HIV and Russian medical patients and street recruited participants who used injection drugs (Walley et al. 2014). In our prior study, we proposed that the association between ART and increased odds of nonfatal overdose may have been due to periods of abstinence required by treatment providers to qualify for ART in Russia (Wolfe, 2007). But in the current study of narcology patients, they were all off ART and abstinent at the time of narcology discharge. Thus, risk due to a connection between ART use and abstinence was unlikely. We did not observe a substantial effect size from Prior ART in the non-fatal analyses. Explaining the relationship between ART and overdose in Russia is a puzzle that requires further study with larger cohorts of patients with varying exposure to ART and longer follow-up in order to obtain more overdose events.

Interventions likely to reduce the high overdose mortality of narcology patients in Russia that warrant research and implementation include overdose prevention education and medication for opioid use disorders. Overdose prevention education and naloxone rescue kits have been associated with reduced opioid overdose death rates in high-risk populations (Walley et al. 2013, Bird et al. 2016). Studies in the US and Russia have shown that distributing naloxone rescue kits would be highly cost-effective (Coffin and Sullivan 2013a, Coffin and Sullivan 2013b). How best to do this for narcology patients warrants implementation studies. Opioid agonist treatment is associated with reduced mortality among HIV-infected PWIDs receiving anti-retroviral treatment (Nosyk et al 2015). Providers and policy makers should advocate for access to methadone and buprenorphine in Russia, as opioid agonists are proven to reduce overdose death risk (Mathers et al. 2013, Degenhardt et al. 2011). Some access to naltrexone maintenance in Russia exists and this opioid antagonist may reduce overdose death risk when patients are taking it as indicated; this is as yet unproven. Whether it will have the retention in care and other benefits of opioid agonists is as yet unknown.

Study strengths included thorough measures of substance use and examination of a population at particularly high risk for overdose, not previously studied. We acknowledge the following limitations. First, although overdose was more common than expected, the number of deaths nevertheless limited power to detect potential associations for all factors of interest. Focusing on mortality after discharge from narcology hospital enabled us to examine relatively proximal behaviors and conditions, which may present opportunities for intervention. Second, the available potential covariates were limited, particularly for the fatal overdose analyses, and therefore the possibility of unmeasured confounding remains. Third, the fatal and non-fatal overdose definitions were not substance-specific which may have resulted in higher overdose rates than if the measure was limited to drug-related overdoses only. However, the overdose measure did explicitly focus on unintentional overdose and exclude intentional overdoses. Furthermore, all of the study participants had a history of injection drug use and therefore were at risk for drug-related overdose. Fourth, days re-

admitted narcology hospital (or any hospital) was not systematically collected as part of this cohort and therefore we were not able to censor people who were not in the community. Fifth, generalizability of our findings may be limited to HIV-infected PWID being discharged from Russian narcology hospitals though the specificity of our sample is also a strength, as it defines a sizable population worthy of targeted interventions.

5.0 Conclusions

This cohort of Russians living with HIV/AIDS who inject drugs undergoing detoxification and early treatment in narcology hospital had strikingly high rates of overdose mortality and non-fatal overdose. Measures of HIV disease severity (i.e. CD4 count, time since diagnosis, and ART use) were not significantly associated with either fatal or non-fatal overdose. Overdose prevention interventions, including naloxone rescue kits and medications for management of opioid use disorders, are warranted among Russian narcology patients with HIV infection.

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Figure 1. Kaplan-Meier survival curve for fatal overdose among HIV-positive Russian narcology patients who inject drugs

Figure 2. Kaplan-Meier survival curve for non-fatal overdose among HIV-positive Russian narcology patients who inject drugs

Baseline characteristics of HIV-infected Russians prior to discharge from narcology hospital**Table 1**

Characteristic	Total n=349	No Overdose or censored n=290	Non-Fatal Overdose ⁺ n=41	Fatal Overdose n=18	p-value [#]
Age Mean (Std Dev)	34.0 (4.8)	34.0 (4.8)	34.3 (5.0)	33.3 (3.9)	0.78
Male	73% (256)	74% (215)	68% (28)	72% (13)	0.73
Female	27% (93)	26% (75)	32% (13)	28% (5)	0.73
CD4 Count < 200	32% (105)	31% (84)	41% (16)	31% (5)	0.43
Prior ART	12% (43)	12% (35)	7.3% (3)	28% (5)	0.08
HCV Coinfection, Self-Report	99% (345)	99% (287)	98% (40)	100% (18)	0.66
Live alone	11% (39)	11% (33)	9.8% (4)	11% (2)	0.95
CES-D [*] Score > 24	42% (137)	41% (112)	53% (20)	31% (5)	0.27
Unemployed	54% (190)	53% (155)	61% (25)	56% (10)	0.66
Education: At least 11 Grades	70% (243)	71% (206)	63% (26)	61% (11)	0.44
Homelessness	2.8% (10)	2.4% (7)	12% (3)	0% (0)	0.16
Died during followup	9.5% (33)	4.8% (14)	2.4% (1)	100% (18)	<.01
Median Years Since HIV Diagnosis (Interquartile range) n=323	6.6 (3.9,11.5)	6.8 (4.0,11.4)	5.6 (3.7,11.5)	7.4 (3.3,12.2)	0.84

⁺ Non-Fatal OD reported at either 3- or 6-Month Assessment. The one participant who reported a non-fatal overdose and subsequently had a fatal overdose is included in the fatal overdose column.

[#] Proportions compared using chi-square tests, means compared using ANOVA, medians compared using Kruskal-Wallis test

^{*} A measure of depressive symptoms

Table 2
Six month follow-up characteristics of HIV-infected Russians after discharge from
narcology hospital (n=250^{*})

Characteristic	Total n=250	No overdose or censored n=210	Non-fatal overdose ⁺ n=40	p-value [#]
Initiated ART during follow-up	22% (54)	20% (43)	28% (11)	0.32
Use of Multiple Drugs, Past 30 Days	27% (67)	25% (53)	35% (14)	0.20
AUDIT: Alcohol Dependence	27% (67)	23% (49)	46% (18)	0.005
Injected drugs, Past 30 Days	52% (129)	49% (102)	68% (27)	0.03
Receptive Needle Sharing, Past 30 Days	21% (52)	19% (39)	33% (13)	0.30
Median times Injected Drugs, Past 30 Days (interquartile range)	1 (0,20)	0 (0,15)	15 (0,25)	0.86
Arrested or Incarcerated	21% (52)	19% (40)	30% (12)	0.12

^{*} Participants with 6-Month Follow-Up

[#] Proportions compared using chi-square tests, medians compared using Wilcoxon Rank Sum Test

⁺ Non-Fatal OD reported at either 3 or 6-Month Assessment.

Table 3
Cox proportional hazards models for fatal overdose

	Unadjusted Hazard Ratio (95% CI)	Adjusted ⁺ Hazard Ratio (95%CI)
Years since HIV diagnosis	1.00 (0.89, 1.12) (n=312)	1.01 (0.90 - 1.13) (n=312)
Prior ART	2.57 (0.92, 7.23) (n=338)	2.68 (0.95-7.59) (n=338)
CD4 Count <200	0.94 (0.33, 2.70) (n=318)	0.97 (0.34-2.79) (n=318)
CD4 Count <350	2.29 (0.74, 7.10) (n=318)	2.17 (0.70-6.79) (n=318)
Age per year	0.98 (0.88, 1.08) (n=338)	+
Male gender	0.90 (0.32, 2.54) (n=338)	+
Randomization group	2.10 (0.79 - 5.60) (n=338)	+

⁺Separate model fit for each independent variable, each adjusted for age, gender, and randomization group.

Table 4
Cox proportional hazards models for non-fatal overdose

	Unadjusted Hazard Ratio (95% CI)	Adjusted ⁺ Hazard Ratio (95%CI)
Years since HIV diagnosis	0.99 (0.92, 1.07) (n=268)	1.00 (0.92, 1.07) (n=268)
Prior ART	1.01 (0.36, 2.88) (n=290)	0.99 (0.35, 2.82) (n=290)
CD4 Count <200	1.62 (0.85, 3.06) (n=276)	1.72 (0.90, 3.28) (n=276)
CD4 Count <350	1.04 (0.55, 1.97) (n=276)	1.00 (0.52, 1.92) (n=276)
Age per year	1.01 (0.95, 1.08) (n=290)	+
Male gender	1.23 (0.62, 2.41) (n=290)	+
Randomization group	1.71 (0.92, 3.18) (n=290)	+

⁺Separate model fit for each independent variable, each adjusted for age, gender, and randomization group.

Table 5
Sensitivity Analysis Cox proportional hazards models for fatal OR non-fatal overdose

	Unadjusted Hazard Ratio (95% CI)	Adjusted ⁺ Hazard Ratio (95%CI)
Years since HIV diagnosis	0.98 (0.92, 1.05) (n=312)	0.98 (0.92, 1.05) (n=312)
Prior ART	1.09 (0.52, 2.30) (n=338)	1.09 (0.51, 2.31) (n=338)
CD4 Count <200	1.23 (0.71, 2.13) (n=318)	1.26 (0.73, 2.18) (n=318)
CD4 Count <350	1.22 (0.70, 2.13) (n=318)	1.17 (0.67, 2.05) (n=318)
Age per year	1.01 (0.96, 1.06) (n=338)	+
Male gender	0.84 (0.48, 2.26) (n=338)	+
Randomization group	1.55 (0.92 - 2.62) (n=338)	+

⁺Separate model fit for each independent variable, each adjusted for age, gender, and randomization group.