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Non-structured treatment interruptions (NTIs) among injection drug users in Baltimore, MD

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Abstract

Background—We characterized patterns of highly active antiretroviral therapy (HAART) use and predictors of non-structured treatment interruptions (NTIs) among injection drug users (IDUs) in Baltimore, MD.

Methods—335 IDUs who initiated HAART from 1996–2006 were studied. NTIs were defined as any subsequent six-month interval where HAART was not reported. Predictors of the first NTI and subsequent restart of HAART were examined using Cox regression.

Results—260 (78%) reported ≥ 1 NTI. Of 215 with ≥ 1 follow-up visit after the NTI, 44 (20%) never restarted HAART, 62 (29%) restarted and remained on HAART and 109 (51%) reported multiple NTIs. NTIs were less likely among those who initiated HAART in later calendar years and had a recent outpatient visit and more likely among women, persons with detectable HIV RNA at the prior visit and those who reported injecting daily. Among those with NTIs, interruptions occurred earlier in persons who were younger, did not have a prior AIDS diagnosis and were actively injecting; NTIs lasted longer in persons who had higher HIV RNA levels, were incarcerated and drinking alcohol. A recent outpatient visit and not actively injecting were associated with restarting HAART.

Conclusions—NTIs were common in this population and occurred most frequently in the setting of active drug use and disruption of health care. Effective linkages between primary care for HIV and substance abuse treatment may improve HAART outcomes in this population.

Keywords

Highly active antiretroviral therapy; injection drug users; treatment interruptions

BACKGROUND

Highly active antiretroviral therapy (HAART) has been associated with dramatic improvements in survival among HIV-infected persons.^{1–3} However, due to the frequent occurrence of toxicities and concerns about long-term effects of prolonged exposure to antiretroviral drugs, alternate strategies to continuous use of therapy (e.g., structured treatment interruptions) have been considered. Findings from clinical trials of prescribed, CD4-guided

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structured treatment interruptions (STIs) have been mixed⁴⁻⁶ but as a result of generally discouraging results, STI strategies have not been recommended for adoption to clinical practice. Nevertheless, unsupervised or non-structured treatment interruptions (NTIs) still occur in clinical settings. Observational studies tend to suggest that short limited interruptions are not associated with adverse outcomes⁷ whereas longer interruptions are associated with increased clinical disease progression.^{8,9}

Injection drug users (IDUs) have lagged behind other groups in terms of benefits associated with HAART. IDUs tend to take longer to initiate HAART and do so less often compared with other HIV-infected patient groups.¹⁰ In addition, observational studies have suggested that IDUs more often voluntarily interrupt HAART.^{7,8} We recently observed a high rate of inconsistent antiretroviral treatment among HAART initiators in a cohort of current and former IDUs that was associated with suboptimal immunologic and virologic response and in turn poorer survival.¹¹ The objective of the current study was to characterize patterns of HAART use and to identify predictors of non-structured treatment interruptions (NTIs) in a cohort of former and current IDUs in Baltimore, MD.

METHODS

Study population

The study sample derives from the AIDS Link to the IntraVenous Experience (ALIVE) cohort. Between 1988 and 1989, 2946 IDUs in Baltimore, MD were enrolled into a cohort study of the natural history of HIV-1 infection and followed at six-month intervals, as previously described.¹² Participants were 18 years of age and older, free of AIDS at entry into the study and acknowledged injection drug use within the prior 11 years. Additional periods of recruitment were in 1994-95, 1998 and 2000. Semi-annual data collection included standardized interviews with questions about reported HAART use, drug use and other risk behaviors, medical history, health care utilization, a clinical examination and a blood draw. The study was approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board and all subjects provided written informed consent. Seven hundred forty-eight HIV positive participants were in follow-up after July 1996, of whom 389 (52%) initiated HAART through July 2005. HAART use was defined as receiving one of the following combinations, 1) protease inhibitor (PI) + 2 nucleoside reverse transcriptase inhibitors (NRTIs), 2) non-nucleoside reverse transcriptase inhibitor (NNRTI) + 2 NRTIs, 3) abacavir in combination with lamivudine and zidovudine or stavudine (3 NRTI), 4) PI + NNRTI + NRTI. Individuals were excluded from the analysis if they did not have at least one follow-up visit after the initial report of HAART (n=34), reported initiating HAART prior to 1996 (n=9) or reported HAART use at entry into the study (n=11) leaving 335 (86%) for analysis.

Laboratory testing

HIV-1 antibodies were measured using a commercially available enzyme-linked immunosorbent assay (Genetic Systems, Seattle, Washington) and confirmed with Western Blot (Dupont, Wilmington, Delaware) using standard criteria. T-cell subpopulations were measured using whole-blood staining methods and flow-cytometry. Plasma HIV-1 RNA levels were quantified using RT-PCR (Roche Molecular Systems, Branchburg, NJ) according to manufacturer's specifications. The dynamic range of the assay was approximately 4 logs (on a base 10 scale) and the minimal detectable HIV-1 RNA level was 400 copies/ml. Specimens in which HIV-1 RNA was undetectable were classified for analysis as 200 copies/ml.

Statistical analysis

NTIs were defined as any six-month interval in which no HAART use was reported after the initial HAART report. The date of interruption was calculated as the midpoint between the last

visit where HAART was reported and the first visit where no HAART was reported. The primary analysis focused on time to the 1st NTI. Survival analysis methods (Cox regression) were used to identify predictors of treatment interruption. The time origin for the analysis was the estimated date of HAART initiation (midpoint of last date where no HAART was reported and first date where HAART was reported). Individuals were administratively censored at the last date of HAART report if no interruption was reported; Persons who died or were lost to follow-up were censored at date of last visit. Similar methods were used to evaluate factors associated with HAART resumption after the first interruption. Here, observations were censored at the last available follow-up visit.

Fixed exposure variables of interest included general demographics (e.g., age, gender, race). Time-varying exposures of interest included measures of socioeconomic status and stability (e.g., employment, homelessness, incarceration), health care utilization (e.g., health insurance, outpatient visit) and substance use (injection and non-injection drug use, alcohol use and drug treatment). All time-varying variables reflected behaviors in the prior six months. Employment, homelessness, health insurance, outpatient visit and drug treatment and non-injection drug use reflected any exposure/episode in the prior six months and injection drug use, alcohol use and incarceration were characterized according to frequency and duration in the prior six months, respectively. In addition, we also considered some HIV-related variables including type of initial HAART regimen, AIDS diagnoses, previous ART as well as CD4 cell count and HIV viral load, both of which were lagged one visit because they may have been influenced by the NTI. Variables considered in multivariate models included those associated at a level $p < 0.10$ in univariate analysis as well as those considered *a priori* to be important predictors. Variables were retained in final multivariate models if $p < 0.05$.

We further compared characteristics associated with earlier treatment interruptions (defined as those occurring within the first year) compared to later treatment interruptions and of longer interruptions (defined as those lasting more than 6 months) compared with shorter interruptions using multiple logistic regression. In these analyses, all covariates were taken from the visit where the interruption was first reported except for CD4 cell count and HIV RNA which were lagged one visit. Similar to the analysis described above, behaviors including drug and alcohol use as well as employment, incarceration and homelessness elicited at each visit refer to the previous 6 months. Model building strategies were similar to those described above.

Finally, we assessed the distribution of CD4 cell counts at the time of interruption and also characterized whether the distributions were different by whether the interruption occurred early vs. late and whether the duration was short vs. long using Mann Whitney tests. We also assessed whether any characteristics differentiated persons who stopped at CD4 cell counts < 200 cells/ μ l vs. ≥ 200 cells/ μ l using chi-square tests. Analysis was performed using SAS version. 9.12 (Cary, North Carolina).

RESULTS

Study population & patterns of HAART use

Characteristics of the study population at the time of HAART initiation are given in Table 1. The median age was 43 years, (interquartile range [IQR], 40-47), 28% were female, 96% were African-American and 47% were actively injecting drugs in the time period of HAART initiation. Of the 335 that initiated HAART, 53% started on a PI-based regimen; 17% started on an NNRTI-based regimen, 25% on a 3 NRTI regimen including abacavir and 5% on a regimen that included both a PI and an NNRTI.

Of the 335 who initiated HAART, 75 (22%) reported no treatment interruption and 260 (78%) at least one NTI (Figure 1). Among those who reported at least one NTI, the median time to

interruption was 11.9 months (IQR, 6.2-21.2). Of the 260 with at least one interruption, 215 had at least one follow-up visit after interruption for which we could document whether HAART was restarted. Forty-four (20%) participants never restarted HAART over a median of 18.4 months of follow-up. Sixty-two (29%) restarted HAART after a median of 8.9 months off of HAART and remained on HAART until their last follow-up visit. One hundred and nine (51%) participants had multiple NTIs. Of those with more than one interruption, the majority had only two NTIs (65%) with 22 (35%) having more than two. No baseline demographic characteristics, risk behaviors or clinical status variables distinguished the four groups (data not shown).

Predictors of 1st NTI

In univariate analysis, factors significantly associated with a higher risk of an NTI included female gender, lower CD4 cell count, higher HIV RNA level and daily injection drug use. Having a recent outpatient visit and initiating HAART in a later calendar year were significantly associated with lower risk of interruption. Younger age, being unemployed, using non-injection drugs, crack and heavy alcohol use were also associated with higher likelihood of an NTI, but these associations were not statistically significant. In multivariate analysis, having at least one outpatient visit (relative hazard [RH], 0.46; 95% confidence interval [CI], 0.35 - 0.62) and calendar year of initiation (RH, 0.89; 95% CI, 0.81 - 0.99) remained significantly associated with a lower likelihood of having an NTI; being female (RH, 1.36; 95% CI, 1.02 - 1.82), having detectable HIV RNA (RH for 400-10,000, 1.89; 95% CI, 1.30-2.73; RH for >10,000, 2.12; 95% CI, 1.51-2.96) and reporting daily injection drug use (RH, 1.43; 95% CI, 1.02-1.98) remained associated with a higher probability of having an NTI.

Among persons with at least one NTI, we further characterized whether the treatment interruption occurred within the 1st year of HAART use (early) or beyond 1 year (late, Table 2). One-hundred fifty-seven (60.4%) participants interrupted within the first year (median 6.5 months, IQR, 5.2-11.66) and 103 (39.6%) interrupted after the first year, a median of 24.1 months (IQR, 18.7-38.5) after initiation. Individuals were less likely to interrupt earlier if they were older and had a prior AIDS diagnosis while they were significantly more likely to interrupt earlier if they reported any (<daily or ≥daily) injection drug use, non-injection drug use or alcohol use. Other demographic, behavioral or clinical variables did not distinguish early versus later NTIs among those with at least one NTI (data not shown). In multivariate analysis, age (OR per 5 years, 0.66; 95% CI, 0.53-0.83), previous AIDS diagnosis (OR, 0.49; 95% CI, 0.26-0.91) and any injection drug use (OR, 1.80; 95% CI, 1.04-3.10) remained independent predictors of early compared to late interruption.

Once an NTI occurred, we compared those who interrupted for more than a six month interval (e.g., no HAART reported for more than one study visit) and those who interrupted for ≤6 months (Table 3). Compared to participants that interrupted for ≤6 months, those who interrupted for a longer interval were significantly more likely to inject drugs, report alcohol use and have been incarcerated. Persons with HIV RNA >10,000 copies/ml and those with CD4<200 tended to be more likely to interrupt for longer intervals. Other demographic, behavioral or clinical variables did not distinguish long versus short NTIs (data not shown). High HIV RNA levels (OR for >10,000, 2.23; 95% CI, 1.03 - 4.80), any alcohol use (OR, 2.46; 95% CI, 1.30-4.67) and being incarcerated (OR, 2.80; 95% CI, 0.97-8.12) remained in the final multivariate model.

Predictors of restarting HAART after the 1st interruption

Among the 260 participants who had at least one treatment interruption, 215 (83%) had at least one follow-up visit after interruption to characterize whether HAART was restarted. HAART was re-initiated in 171 (80%) at a median of 8.6 months (IQR, 6.0-18.8) after interruption.

Factors associated with HAART re-initiation in univariate analysis were having had an outpatient visit in the prior six months, having health insurance and not injecting drugs (Table 4). In multivariate Cox regression analysis, having an outpatient visit was associated with a higher likelihood of restarting HAART (RH, 3.30; 95% CI, 1.93-5.63) and active injection drug use was associated with a lower probability of restarting HAART (RH, 0.69; 95% CI, 0.49-0.97).

CD4 cell count

The median CD4 cell count at the time of HAART interruption was 191 cells/ul (IQR, 191-484). Among those who stopped, the CD4 at the time of interruption was <200 for 93 (47%), 200-350 for 64 (32%) and >350 for 42 (21%). There were no differences in the distribution of CD4 cell counts by whether interruptions occurred early after HAART initiation or later nor by whether the interruption was short or long. Those who stopped at CD4 cell counts <200 cells/ul were significantly less likely to have had a recent outpatient visit compared with those who stopped at CD4 >350 cells/ul (66% vs. 86%, $p=0.03$). Those who stopped at lower CD4 cell counts were also significantly more likely to report recent injection drug use compared with those who stopped at higher CD4 cell counts (52% vs. 22%, $p<0.001$).

Discussion

In this group of current and former IDUs, only a small minority of participants reported consistent HAART use throughout a median follow-up period of 4.5 years; the majority had at least one treatment interruption. We and others have previously demonstrated that inconsistent HAART use is associated with suboptimal virologic and immunologic response and poorer survival.^{8,9,11} Thus, understanding the factors associated with non-structured treatment interruptions will be important for IDUs to achieve maximum benefits from HAART use.

The observation of a high frequency of treatment interruptions is not entirely surprising and is consistent with prior observations which suggest that IDUs are less likely to initiate HAART,¹⁰ less likely to achieve virologic and immunologic response¹¹ and more likely to modify or discontinue their original HAART regimen.¹³ Many of the same factors that were associated with failure to initiate treatment and failure to achieve a response to HAART were also associated with treatment interruptions. For example, persons reporting heavy injection drug use were significantly more likely to interrupt HAART and tended to have NTIs that occurred shortly after initiation and that lasted for longer periods of time. Consistent with prior observations,^{14,15} persons injecting less frequently were no more likely than former injectors to report treatment interruptions. That being said, those injecting less frequently tended to parallel heavy injections in their patterns of having longer interruptions that happened earlier and any injection regardless of frequency was associated with a lower probability of restarting HAART.

However, it is important to note that the injection patterns in this cohort are dynamic.¹⁶ Although 50% were not actively injecting during the time period of HAART initiation, 45% of these individuals reported injecting at a subsequent follow-up visit at least once. Moreover, of those who were actively injecting at the time of initiation, 76% had at least one subsequent visit where they were not injecting. It is important for providers to understand the dynamic nature of injection drug use when decisions to initiate HAART among IDUs are made. Moreover, active injection was not the only risk factor for interruption. Other important predictors were poor initial response, the type of HAART regimen and frequency of contact with the health care system.

Persons with NTIs were more likely to have had initial suboptimal responses to HAART prior to the NTI, which may reflect poor adherence even prior to the interruption. We have previously demonstrated high rates of virologic and immunologic non-response associated with the first HAART regimen among IDUs,¹¹ and these results further suggest that high HIV RNA levels and low CD4 cell counts after HAART initiation were predictive of interrupting HAART. It was encouraging that persons initiating HAART in later calendar years - were less likely to have an NTI, indicating that perhaps simpler regimens are associated with improved adherence leading to IDUs being less likely to discontinue their HAART regimens.

Unfortunately, it was not possible in this analysis to distinguish between physician-guided structured treatment interruptions (STIs) and unplanned, non-structured treatment interruptions (NTIs) initiated by the patients themselves. However, the CD4 cell count at the time of interruption can provide some insight into the reason for interruption. Prior studies have demonstrated that interruptions occurring at higher CD4 cell counts are more likely to reflect physician-guided decisions whereas interruptions occurring at lower CD4 cell counts reflect patient decisions.⁹ In this group of IDUs, the majority interrupted at CD4 cell counts less than 350 cells/ul suggesting that most of the NTIs observed in this cohort were likely driven by patient rather than provider decisions. This conjecture is further supported by the observation that the absence of any outpatient visits was associated with a higher risk of interruption reflecting that interruptions in HAART most likely reflect interruptions in care. Additionally, incarcerations, which may also reflect interruptions in primary care, were associated with longer treatment interruptions. The main barrier to optimal HAART use appears not to be access to HIV care in general as most IDUs in this cohort reported having a regular HIV provider. Instead, strategies are needed to maintain continuity of care among this population, particularly as they enter and are released from correctional settings.

Surprisingly, being in substance abuse treatment, and in particular methadone maintenance, was not protective against treatment interruptions nor was it associated with restarting therapy. In general, prior studies have demonstrated that methadone maintenance is associated with stability and improved adherence to HAART as well as HIV RNA suppression and CD4 cell increases.^{17,18} Therefore, it could be hypothesized that being in methadone maintenance would also improve continuity of care and subsequent HAART use. The lack of positive effect of methadone maintenance may reflect our crude definition of any methadone treatment in the prior six months or the limited access/utilization of methadone maintenance by these patients as only 13% of participants reported being in methadone maintenance at the time of HAART initiation.

Another limitation is that we did not have information on the reasons for stopping HAART. Prior studies have observed that HCV co-infection is a common reason for interrupting HAART, some of which may be explained by higher rates of hepatotoxicity; however, we were not able to confirm this in our study. Further, reports of HAART use are collected at 6-month intervals and because of the way the questions are asked, it is possible that we missed interruptions that were less than six months in duration. However, these shorter interruptions are likely to have reflected non-adherence rather than true treatment interruptions.

These data, in conjunction with prior reports, suggest that there is still much work to be done to improve HAART outcomes among HIV-infected IDUs. Though progress has been made,¹⁹ IDUs are still far from achieving the maximum benefits of HAART. It is particularly concerning that the same factors have been associated with initiation, maintenance and response to HAART reinforcing a need for comprehensive interventions targeting these issues. Only with interventions that move beyond addressing each of these issues in isolation will we be able to successfully improve all aspects of HAART delivery to IDUs.

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Figure.

Patterns of HAART use among 290 HAART initiators with at least one study visit following a NTI. 75 (22%) reported consistent HAART use, 44 (13%) reported one NTI and never restarted HAART, 62 (19%) reported one NTI and restarted HAART and 109 (33%) reported multiple NTIs. In the figure, the labels represent median months (interquartile range) on and off HAART.

Table 1

Factors associated with 1st non-structured treatment interruption among 335 HAART initiators in the ALIVE study, 1996-2006, Baltimore, MD*

	Number (%) (n=335) [†]	Unadjusted RH (95% CI)	Adjusted RH (95% CI)
Sociodemographic			
Female gender	94 (28)	1.31(1.00 - 1.72)	1.36(1.02 - 1.82)
African American race	321 (96)	1.32(0.74 - 2.36)	
Baseline age (per 5 years)	43(40-47)	0.92(0.84 - 1.02)	
Employed	59 (18)	0.71(0.51 - 1.01)	
Homeless	38 (12)	1.24(0.87 - 1.79)	
Incarceration			
None	280 (85)	1.00	
≤ 30 days	8(3)	0.75(0.49 - 1.15)	
>30 days	40 (12)	1.44(0.68 - 3.08)	
HIV-related			
Initial HAART Regimen			
PI + 2NRTI	178 (53)	1	
3NRTI	83 (25)	1.35(1.01 - 1.82)	
NNRTI- based	58 (17)	0.80(0.57 - 1.12)	
CD4 count (cells/(μl)) [†]			
>350	81 (25)	1	
200-350	108 (33)	1.50(1.09 - 2.07)	
<200	140 (42)	1.44(1.06 - 1.95)	
HIV RNA(copies/mL) [†]			
<400	32 (13)	1	1
400-10,000	51 (21)	1.92(1.34 - 2.77)	1.89(1.30 - 2.73)
>10,000	164 (66)	2.24(1.61 - 3.11)	2.12(1.51 - 2.96)
Pre-HAART AIDS diagnosis	64(19)	1.06(0.78 - 1.44)	
Previous antiretroviral therapy	266 (79)	1.17(0.85 - 1.61)	
Health care utilization			
Health insurance	272 (82)	1.01(0.71 - 1.43)	
Outpatient visit	290 (87)	0.45(0.34 - 0.59)	0.46(0.35 - 0.62)
Hospitalization	73(22)	0.89(0.63 - 1.25)	
Substance use			
Injection drug use			
None	187 (57)	1	1
< Daily	88 (27)	0.94(0.68 - 1.30)	0.93(0.66 - 1.31)
≥Daily	55(17)	1.58(1.16 - 2.15)	1.43(1.02 - 1.98)
Any non injection drug use	91 (27)	1.26(0.96 - 1.66)	
Crack use	51(15)	1.32(0.97 - 1.81)	
Alcohol use			
None	175 (54)		
Light	128 (40)	0.97(0.74 - 1.27)	
Heavy	19(6)	1.58(0.92 - 2.70)	
Methadone maintenance	82 (25)	0.98(0.73 - 1.32)	
Detoxification	22(7)	1.54(0.94 - 2.53)	
Calendar year		0.92(0.84 - 1.01)	0.89 (0.81 - 0.99)

* HAART, highly active antiretroviral therapy; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; RH, relative hazard; CI, confidence interval; Frequencies reflect behaviors captured at the time of HAART initiation; In Cox regression models, all variables are treated as time-varying covariates and reflect behaviors in the prior six months except where otherwise indicated.

[†] CD4 cell count and HIV RNA are lagged six months

Table 2

Predictors of early (≤ 1 year) versus late (> 1 year) treatment interruption among 260 ALIVE participants with at least one NTI*

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Female gender	1.22 (0.70-2.11)	
Baseline age (per 5 years)	0.65(0.52 - 0.81)	0.66(0.53 - 0.83)
Previous AIDS diagnosis	0.42(0.23 - 0.76)	0.49(0.26 - 0.91)
Injection drug use		
None	1	1
<Daily	2.02(1.02 - 4.0)	
$\geq$ Daily	2.03(1.06 - 3.90)	1.80 (1.04 - 3.10) [†]
Non injection drug use	1.84(1.02 - 3.30)	
Alcohol use		
None	1	
Light	1.63(0.94 - 2.82)	
Heavy	1.55(0.51 - 4.73)	
Calendar year of initiation	0.88(0.77 - 1.01)	

* Data from the six months prior to when the treatment interruption was first reported; Only those variables associated with the outcome at a level $p < 0.10$ are listed in the table; OR, Odds ratio; CI, Confidence interval

[†] Categories were collapsed in multivariate analysis due to similar magnitude of effect and small cell sizes

Table 3

Predictors of long (>6 months) versus short (≤ 6 months) treatment interruptions among 215 ALIVE participants with at least one NTI*

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Female gender	0.90 (0.49 - 1.64)	
Age (per 5 years)	0.92(0.73 - 1.16)	
CD4 cell count (cells/ul) [†]		
>350	1	
200-350	0.97 (0.48-1.95)	
<200	1.90 (0.94-3.82)	
HIV RNA(copies/ml) [†]		
<400	1	1
400-10,000	1.41(0.63 - 3.18)	1.36(0.57 - 3.22)
>10,000	2.15(1.03 - 4.45)	2.23(1.03 - 4.80)
Injection drug use [‡]		
None	1	
<daily	2.77(1.27 - 6.05)	
$\geq$ daily	1.58(0.76 - 3.26)	
Alcohol use [‡]		
None	1	1
Light	1.98(1.09 - 3.61)	
Heavy	3.21(0.83 - 12.5)	2.46 (1.30 - 4.67) [§]
Incarcerated [‡]		
None	1	1
7-30 days	3.39(1.08 - 10.6)	
≥ 30 days	3.62(0.40 - 33.0)	2.80 (0.97 - 8.12) [§]

* 215/260 persons with one NTI had sufficient data to characterize the duration of the interruption; Only those variables associated with the outcome at a level $p < 0.10$ are listed in the table; OR, Odds ratio; CI, confidence interval

[†] Data are lagged six months from the visit before the treatment interruption

[‡] Data from the six months prior to when the treatment interruption was first reported

[§] Categories were collapsed in multivariate analysis due to similar magnitude of effect and small cell sizes

Table 4

Factors associated with treatment re-start after 1st HAART interruption among 215 persons with at least one NTI*

	Unadjusted RH (95% CI)	Adjusted RH (95% CI)
Sociodemographic		
Female gender	0.94 (0.67 - 1.32)	
African American race	0.58 (0.28 - 1.20)	
Baseline age (per 5 years)	0.99(0.88 - 1.11)	
Employed	0.91 (0.59 - 1.40)	
Homeless	0.97 (0.61 - 1.55)	
Incarceration		
None	1	
7-30 days	0.68(0.22 - 2.14)	
>30 days	0.62(0.33 - 1.14)	
HIV-related		
CD4 count (cells/(μ L)) [†]		
>350	1	
200-350	1.25(0.51 - 3.04)	
<200	0.75(0.50 - 1.13)	
HIV RNA(copies/mL) [†]		
<400	1	
400-10,000	0.97(0.59 - 1.59)	
>10,000	0.71(0.46 - 1.07)	
AIDS diagnosis	1.26(0.88 - 1.78)	
Health care utilization		
Health insurance	2.04(1.18 - 3.53)	
Outpatient visit	3.48(2.04 - 5.93)	3.30(1.93 - 5.63)
Hospitalization	1.05(0.70 - 1.58)	
Substance use		
Injection drug use		
None	1	1
< Daily	0.61(0.40 - 0.94)	
≥ Daily	0.62(0.40 - 0.98)	0.69 (0.49 - 0.97) [‡]
Any non injection drug use	0.63(0.42 - 0.95)	
Crack use	0.74(0.45 - 1.23)	
Alcohol use		
None	1	
Light	0.81(0.58 - 1.13)	
Heavy	0.62(0.30 - 1.27)	
Methadone maintenance	1.27(0.90 - 1.78)	
Detoxification	1.19(0.61 - 2.36)	

* 215/260 persons with at least one NTI had sufficient data to characterize HAART restart; HAART, highly active antiretroviral therapy; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; RH, relative hazard; CI, confidence interval; All variables are treated as time-varying covariates all variables are treated as time-varying covariates and reflect behaviors in the prior six months except where otherwise indicated.

[†] CD4 cell count and HIV RNA are lagged six months

[‡] Categories were collapsed in multivariate analysis due to similar magnitude of effect and small cell sizes