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Factors associated with discontinuation of antiretroviral therapy in HIV-infected patients with alcohol problems

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Abstract

Although mortality rates among HIV-infected populations have declined with the advent of combination antiretroviral therapy (ART), patients with substance use disorders have benefited less from these therapies. While adherence to ART has been well studied, less is known about factors associated with discontinuation of ART. The aim of this study is to investigate predictors of discontinuation of ART in HIV-infected patients with alcohol problems, focusing on their substance use and depressive symptoms. The study cohort ($n = 266$) was prospectively assessed with biannual standardised interviews between 2001 and 2005. Four predictor variables (cocaine, heroin, heavy alcohol use and substantial depressive symptoms) were assessed six months prior to the outcome (ART discontinuation). Longitudinal logistic regression models examined the association between predictor variables and ART discontinuation adjusting for age, gender, race/ethnicity, homelessness, CD4, HIV RNA and HIV Symptom Index. Subjects were 77% male; 43% black; 22% homeless; 45% used cocaine; 20% used heroin; 29% had heavy alcohol use; and 40% had substantial depressive symptoms. Discontinuation occurred in 135 (17%) of the observations ($n = 743$). In bivariate analyses, cocaine use, heroin use and depressive symptoms were significantly associated with ART discontinuation but heavy alcohol use was not. In the multivariable model, substantial depressive symptoms (adjusted odds ratio (AOR) = 1.66; 95% confidence interval (CI): 1.04, 2.65) but not cocaine (AOR = 1.28; 95% CI: 0.76, 2.16) or heroin use (AOR = 1.27 95% CI: 0.66, 2.44), remained significantly associated with ART discontinuation. Among HIV-infected adults with alcohol problems, depressive symptoms, but not substance use, predicted subsequent ART discontinuation. Recognition and treatment of depressive symptoms in this population may result in better maintenance of ART and its associated clinical benefits.

Introduction

Increasingly, researchers and health policy-makers are recognising the difficulty in translating medical treatment advances to vulnerable populations. Although mortality from HIV infection has declined with the advent of combination antiretroviral therapy (ART), patients with substance use disorders have benefited less (Lucas et al., 2006). Since patients with intermittent use of ART have higher mortality rates (Hogg et al., 2002; Riley et al., 2005), sustaining these drug regimens over long periods of time is one of the major challenges in the care of HIV-infected patients.

Studies of predictors of ART discontinuation among populations with HIV and addictions are limited. The impact of injection drug use (IDU) is often evaluated by analysing subjects' HIV transmission risk behavior (Chen et al., 2003; D'Arminio et al., 2005; Mocroft et al., 2005) and may assume that the impact of substance use is unaffected by its cessation. Evaluating IDU as a risk category does not account for the spectrum of use that may occur at different stages of a patient's addiction trajectory (McLellan et al., 2000). The relationship between the use of specific drugs of abuse and discontinuation of ART also has received little attention (Li et al., 2005; Yuan et al., 2006) despite the spectrum of biological and behavioural effects caused by individual stimulants and depressants. Also, there has been limited examination of the impact of alcohol use on ART discontinuation despite the high prevalence of alcohol use disorders among HIV-infected persons (Conigliaro et al., 2003; Galvan et al., 2002; Samet et al., 2004) and its association with suboptimal adherence (Braithwaite et al., 2005; Samet et al., 2004) and HIV disease progression (Samet et al., 2003). Furthermore, studies examining addictions and ART use frequently do not include information about depressive symptoms (Kerr et al., 2005; Riley et al., 2005; Yuan et al., 2006). This is important because of the high co-morbidity of substance use and mood disorders in the general population (Grant et al., 2004), which is even greater among HIV-infected patients (Galvan et al., 2003).

The aim of this study is to investigate predictors of discontinuation of ART in HIV-infected patients with alcohol problems, focusing on their substance use and depressive symptoms. We hypothesised that active substance use (cocaine, heroin and heavy alcohol use) and depressive symptoms would each be associated with a greater likelihood of ART discontinuation.

Methods

Study design and population

This study examines predictors of discontinuation of ART among subjects in the HIV-Longitudinal Inter-relationships of Viruses and Ethanol (HIV-LIVE) study. This was a prospective, observational cohort study of HIV-infected patients with past or current alcohol problems. Subjects were prospectively followed with biannual standardised interviews between August 2001 and March 2005.

The 400 subjects of the HIV-LIVE study were recruited from different sources including: (1) a previous cohort study (Samet et al., 2003) of people with HIV and alcohol problems ($n = 154$; 38%); (2) the Diagnostic Evaluation Unit (Samet et al., 1995), an intake clinic for HIV-infected patients at Boston Medical Center ($n = 88$; 22%); (3) the HIV Primary Care and Specialty Clinics at Beth Israel Deaconess Medical Center ($n = 31$; 8%); and (4) additional healthcare centres, homeless shelters, drug treatment programs, subject referrals and flyers ($n = 127$; 32%).

Eligibility criteria for the HIV-LIVE study included: (1) documented HIV antibody by ELISA confirmed by Western Blot; (2) two or more affirmative responses to the CAGE alcohol screening questionnaire (Buchsbbaum et al., 1991) or co-investigator physician diagnosis of

alcohol abuse or dependence; (3) ability to speak English or Spanish; and (4) at least one contact person who was likely to know their whereabouts. Exclusion criteria included: (1) scoring < 21 on the 30-item Mini-Mental State Examination (Smith et al., 2006); (2) trained interviewer assessment that the patient was incapable of comprehending informed consent or answering the interview questions; or (3) plans to move from the Boston area in the subsequent two years.

Subjects were included in the analyses if they reported being on ART at any study interview (hereafter referred to as T_N) and then returned six months later for the next scheduled interview (T_{N+1}).

Data collection

After enrolment, research associates interviewed subjects using a standardised instrument at baseline and biannually thereafter. For interviews conducted in Spanish, standardised scales in Spanish were used when available; the remainder of the questionnaire was translated from English into Spanish, back translated to check for accuracy and then corrected. CD4 cell counts and HIV RNA viral load measurements conducted as part of clinical care were recorded if within four months of the research interview. If they were not available through clinical care, blood samples were obtained and tested for these parameters.

All subjects provided written informed consent prior to enrolment. The Institutional Review Boards of Boston University Medical Center and Beth Israel Deaconess Medical Center approved this study. Additional privacy protection was secured by the issuance of a Certificate of Confidentiality by the Department of Health and Human Services to protect subjects from release of their research data even under a court order or subpoena.

Dependent variable

We defined discontinuation of ART as either: (1) being off ART medications at T_{N+1} (This was assessed with the question: 'Are you currently taking antiretroviral medications for HIV?'); or (2) stopping all ART medications for ≥ 30 days between T_N and T_{N+1} . This second criterion was included since some subjects who were taking ART medications on the day of the follow-up research interview (T_{N+1}) may have stopped them for an extended period of time since the last interview. This criterion was assessed with the questions: 'Did you stop taking all of your HIV medications for more than a day during the past six months (not including switching or changing medications)?' and, for those answering affirmatively, asking about the number of days without ART.

Main independent variables

The main independent variables were: (1) heavy alcohol consumption over the previous month using the National Institute on Alcohol Abuse and Alcoholism definition, which is more than 14 standard drinks per week (or more than four drinks in a day) for men or more than seven drinks per week (or more than three drinks in a day) for women; past month alcohol consumption was assessed using a validated calendar method (Sobell, 1992); (2) any cocaine use in the past six months using the Composite International Diagnostic Interview (CIDI), Short Form (Kessler et al., 1998); (3) any heroin use during the past six months using the CIDI, Short Form and (4) substantial depressive symptoms, defined as a score of ≥ 23 on the 20-item Center for Epidemiologic Studies-Depression scale (CES-D) (Radloff, 1977). This score indicates substantial depressive symptoms in patients with chronic medical conditions (Golub et al., 2004). All main independent variables were modelled as dichotomous variables.

To reduce the likelihood that we were measuring depressive symptoms rather than symptoms related to HIV infection, secondary analyses were performed using a modified version of the

CES-D (Ickovics et al., 2001) removing somatic complaints (fatigue, anorexia, lack of energy, insomnia and poor concentration).

Additional secondary analyses were performed to assess the association between a current diagnosis of alcohol dependence or drug dependence (in models that did not include substance use) and ART discontinuation. Current alcohol dependence was determined with the CIDI (Robins et al., 1988) at the baseline (recruitment) HIV-LIVE research interview and the CIDI, Short Form at subsequent interviews. Current drug dependence was assessed with the CIDI, Short Form at all research interviews.

Other independent variables

The following covariates were considered for inclusion in regression models based on clinical considerations and evidence from previous studies of ART use in patients with addictions: age; gender; race/ethnicity; homelessness (any night spent in a shelter or on the street in past six months) (Kertesz et al., 2005); time in jail (any in past six months); and HIV symptoms. We measured HIV-related symptoms using the 20-item HIV Symptom Index, which has been used to monitor symptoms in the AIDS Adult Clinical Trials Group (Justice et al., 2001). We observed a strong correlation between the CES-D and the HIV Symptom Index ($r = 0.47$); therefore, we used a modified HIV Symptom Index described in other studies (Kilbourne et al., 2002) excluding questions that overlap with the CES-D questionnaire (e.g. questions about sadness, anxiety, sleep problems, fatigue and memory loss). Laboratory parameters included CD4 cell count, HIV log₁₀ RNA and hepatitis C antibody status.

Statistical analysis

We used generalised estimation equations (GEE) (Zeger et al., 1988) and logistic regression methods to examine factors associated with ART discontinuation. Predictor variables were assessed at time T_N approximately six months prior to the outcome at T_{N+1} . Only observations where the subject was on ART at T_N contributed to analyses. Since subjects could contribute multiple pairs of observations, we used the GEE approach to adjust for the correlation between repeated measures from the same subject over time using a working independence correlation matrix. The empirical standard errors from the GEE approach were used for all analyses.

To avoid the potential for colinearity, we assessed the correlation between each pair of independent variables and none of the variables included in regression models were highly correlated (i.e. no correlation was greater than 0.40). Covariates were selected for inclusion in the multivariable models if their p -values were <0.10 in unadjusted analyses. To avoid linearity assumptions, continuous covariates were categorised based on descriptive statistics (e.g. median or tertiles) from the study sample. All predictor variables except for gender, age and race/ethnicity were allowed to vary with time. Health insurance status was not included in the models since 99% of all subjects had access to private, Medicaid or other publicly funded health insurance. For descriptive purposes, we calculated the proportion of subjects who ever discontinued ART during the study using Kaplan-Meier analyses. Subjects were censored if they did not complete a follow-up interview.

Analyses were conducted using two-sided tests and an alpha level of 0.05 was used to determine statistical significance. All analyses were carried out using SAS version 8.2 (SAS Institute, Cary, NC).

Results

Among the 400 HIV-LIVE subjects, 303 (76%) were on ART at least once during the study and therefore eligible for analysis. Thirty-seven of these 303 subjects (12%) were not included in this analysis because of a missed study visit at the subsequent follow-up. No significant

differences were found between the analytic sample (266/303; 88%) and those with incomplete follow-up (37/303; 12%) in terms of age, race/ethnicity, housing status, heavy alcohol consumption or cocaine or heroin use. A higher proportion of subjects with incomplete follow-up had substantial depressive symptoms ($\text{CES-D} \geq 23$) (27/37; 73%) compared to those in the analytic cohort (117/266; 44%) ($p = 0.001$).

Table I shows demographic and clinical characteristics of the study sample ($n = 266$) at baseline. The cohort was predominantly male (77%) and non-white (either black or Hispanic—43 and 23% respectively). Study participants were mostly poor (median income \$7,500) and a substantial minority (22%) was homeless. More than half (55%) of the cohort reported past injection drug use; a similar proportion (58%) tested positive for hepatitis C antibody. Almost half (45%) reported past six-month cocaine use and a quarter reported heroin use. Past month heavy alcohol consumption was reported by 29% of subjects. A significant proportion (40%) had substantial depressive symptoms ($\text{CES-D} \geq 23$). Twenty-three percent of the sample discontinued ART at least once during the study period.

Subjects were followed every six months for up to six visits, and the median number of observations per subject was three (interquartile range 2–4). For this analysis, the proportion of subjects who completed one, two, three, four, five and six observations during the three-year follow-up period was (# interviews/subjects): 20.3%; 22.6%; 20.3%; 14.3%; 15.0%; and 7.1%, respectively. Overall, the 266 subjects contributed a total of 743 observations to the longitudinal analyses. Discontinuation of ART was reported in 18% (135/743) of the observations; 12.4% (92/743) were not on ART at T_{N+1} , and 5.8% (43/743) had stopped ART for at least 30 days since T_N . The median number of days without ART in the previous six months for this last group was 60 (interquartile range 44–94).

We obtained information about reasons for ART discontinuation in 62% (84/135) of the cases. Subjects could specify multiple reasons for stopping ART from a checklist of responses. In about three-fourths of the cases of discontinuation (62/84; 74%), reasons other than ‘MD told me to’ were cited. The most common reason was ‘just took self off’ or ‘personal problems’ (41/84; 49%), followed by ‘MD told me to’ (21/84; 25%), ‘substance abuse’ (14/84; 17%), ‘meds made me sick’ (10/84; 12%) and issues related to lost medications or lack of refills (8/84; 10%).

As shown in Table II, factors associated with discontinuation of ART in the unadjusted analyses were: cocaine use (unadjusted OR = 1.86; 95% CI: 1.18, 2.94); heroin use (OR = 2.12; 95% CI: 1.25, 3.60); and depressive symptoms (OR = 2.26; 95% CI: 1.49, 3.43) but not heavy alcohol use. Other factors associated with discontinuation were: age less than 40; female gender; homelessness; higher viral load; and more HIV-related symptoms.

Cocaine, heroin and heavy alcohol use were not significant predictors of ART discontinuation in a multivariable model that adjusted for age, gender, homelessness, CD4 count, HIV viral load and HIV Symptom Index (Table II). Similarly, diagnoses of alcohol dependence (adjusted odds ratio (AOR) = 1.18; 95% CI: 0.71, 1.96) and drug dependence (AOR = 1.54; 95% CI: 0.88, 2.70) were not associated with ART discontinuation.

Subjects with substantial depressive symptoms were more likely to discontinue ART (AOR = 1.66; 95% CI: 1.04, 2.65). Similar results were found when analysing depressive symptoms with the modified CES-D (removing questions about somatic symptoms) (AOR = 1.82; 95% CI: 1.07, 3.11). Other factors independently associated with ART discontinuation were age <40, higher HIV viral load and higher HIV Symptom Index score (8–15).

Discussion

In this sample of HIV-infected adults with past or current alcohol problems, patients with substantial depressive symptoms had almost twice the likelihood of discontinuing ART six months later. Although HIV-infected patients with depression are more likely to have HIV-related symptoms (Kilbourne et al., 2002) and patients with HIV symptoms are more likely to discontinue ART, (Ahdieh et al., 2005; Mocroft et al., 2005), we found that the association between depression and ART discontinuation was independent of HIV symptoms. We did not detect an association between heroin, cocaine or heavy alcohol use and subsequent ART discontinuation in multivariable analyses that adjusted for depressive symptoms, clinical indicators of HIV disease severity and housing status.

To our knowledge, no other studies have examined the relationship between heavy alcohol use and ART discontinuation despite the former's high prevalence among HIV-infected drug users (Miguez et al., 2003) and its association with suboptimal adherence (Braithwaite et al., 2005; Samet et al., 2004). This study also differs from previous studies examining substance use and ART utilization in a number of respects: the current study (1) used validated instruments to assess substance use and substance use disorders rather than relying on physician detection in clinical care; (2) prospectively assessed predictor variables at least six months before the outcome suggesting a temporal relationship between depressive symptoms and discontinuation; (3) examined a measure of depressive symptoms highlighting the clinical importance of co-occurring affective disorders with substance use disorders; and (4) included an indicator of HIV quality of life (HIV Symptom Index) often missing in studies of antiretroviral medication use.

Our data are consistent with prior studies examining HIV-infected women (Ahdieh et al., 2005), gay men (Li et al., 2005) and homeless persons (Moss et al., 2004) in which depressive symptoms were found to be associated with discontinuation of ART. Based upon our results, this observation appears to apply to HIV-infected persons with past or current alcohol problems as well. Depression is common in HIV-infected patients (Bing et al., 2001; Fairfield et al., 2001). However, despite being prevalent and associated with higher mortality in this population (Cook et al., 2004; Ickovics et al., 2001), it is under-diagnosed in clinical practice. Asch et al. (2003) found that clinical depression was recognised in only about half of patients; patients with less education were more at risk for having depression under-recognised. Psychopharmacologic and psychotherapeutic treatments are associated with better ART utilization (Cook et al., 2006).

Since mood disorders commonly occur with substance use disorders (Conway et al., 2006; Grant et al., 2004), screening and management of depression in HIV-infected adults with alcohol problems are likely to be particularly important to maximise the benefits of ART. A growing body of evidence suggests that shared neurobiological pathways are involved in addiction and depression (Brady et al., 2005). Even previous alcohol dependence is associated with a fourfold higher risk of depression (Hasin & Grant, 2002). Co-occurring mental health and substance use disorders have worse psychiatric and addiction outcomes than either alone (Compton et al., 2003). This paper's findings suggest that depression may be associated with worse HIV outcomes in this population by means of its association with ART discontinuation.

We did not find an association between cocaine, heroin or heavy alcohol use and ART discontinuation in adjusted analyses. Since eligibility required being prescribed ART, this study examined a specific subgroup of substance users. It may be that physicians offered ART to certain patients with substance abuse based upon unmeasured factors thought to be predictive of better ART adherence. Among IDUs in Vancouver, patient's self-assessment of ability to meet challenges related to ART management (e.g. refilling prescriptions on time, continuing

ART when using drugs or in withdrawal etc.) was associated with sustaining ART use rather than frequency of heroin or cocaine use (Kerr et al., 2005). These findings suggest that substance use, per se, may not be reasonable justification for withholding ART on the basis of fears of medication treatment interruption. Instead an assessment of a patient's ability to sustain ART use should involve a careful evaluation for depressive symptoms, self-efficacy, unstable housing (Moss et al., 2004) and HIV-related somatic symptoms.

Similar to other studies (Ahdieh et al., 2001; Kerr et al., 2004; Mocroft et al., 2005), we found that more HIV symptoms predicted subsequent discontinuation of ART. This study adds to the growing literature demonstrating their clinical importance. HIV-related symptoms are common; patients reported an average of 12 in the previous year in one study (Heath et al., 2002). HIV-related symptoms are among the strongest predictors of health-related quality of life (Hays et al., 2000), hospitalisation and mortality (Kilbourne et al., 2002). Our study extends that literature by demonstrating their importance among people with alcohol problems.

The finding that a higher HIV viral load is associated with a greater likelihood of subsequent discontinuation is also consistent with other studies (Ahdieh et al., 2001; Li et al., 2005). Since higher viral loads are often found in patients with lower CD4 counts, this finding may be the consequence of patients with more advanced HIV disease having greater difficulty tolerating ART. However, since our analyses were adjusted for CD4 count and HIV symptoms, a higher viral load (which was measured at the first interview) may have indicated that the subject was already non-adherent prior to discontinuing therapy.

The following limitations should be considered when interpreting this study's findings. First, we did not have information about why patients discontinued ART in over a third of the cases. This is important as the dynamics of physician-recommended discontinuation because of, for example, intolerable medication side effects, may be different than those of patient-initiated discontinuation without physician consultation. However, the information that was available to us in terms of reasons for ART discontinuation was consistent with overall findings, namely that 49% reported discontinuing for personal reasons versus 17% for substance abuse. Second, we did not have information about provider or clinic characteristics that may have influenced the likelihood of ART discontinuation. Third, we did not have clinical or immunological information on the consequences of discontinuing ART as we have defined it in this study. Some subjects may have discontinued ART for 30 days and then restarted ART without negative clinical consequences such as acquisition of viral resistance mutations. However, prior studies have found higher mortality risk with intermittent use of ART (Riley et al., 2005). Also, because of the observational design of this study, conclusions about causal relationships cannot be inferred. However, information on predictor variables was prospectively assessed before the outcome, which supports a temporal association between depressive symptoms and ART discontinuation. Another study limitation, given the importance of depressive symptoms with regards to ART discontinuation, is that we did not have additional information on psychiatric diagnosis or antidepressant utilization. Finally, although in this analysis heavy alcohol use did not impact ART discontinuation, our sample did not include people without current or past alcohol problems, in whom heavy alcohol use could have an impact on ART utilization. The generalisability of this study's findings may be limited to HIV-infected persons with past or current alcohol problems who are prescribed ART.

In this study of HIV-infected adults with past or current alcohol problems, depressive symptoms predicted subsequent ART discontinuation. Their recognition and treatment may be important in maintaining ART and its associated clinical benefits in this patient population.

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Table I

Baseline characteristics of HIV-infected subjects with past or current alcohol problems on antiretroviral drugs ($n = 266$).

Characteristic	Total sample N (%)
Female	60 (23)
Race/ethnicity	
Black	115 (43)
Hispanic	64 (23)
White	90 (34)
Non-high school graduate	88 (33)
Homeless ^{a,b}	59 (22)
Jail ^a	45 (17)
Injection drug use, lifetime	146 (55)
Hepatitis C Ab positive	155 (58)
Substantial depressive symptoms ^c	117 (40)
Heavy alcohol use ^d	77 (29)
Cocaine use ^a	120 (45)
Heroin use ^a	101 (25)
Age, mean (SD) (years)	43.6 (7.2)
Income, median \$US (interquartile range) ^e	7500 (7500, 25000)
CD4 count (cells/ μ l), median (interquartile range)	378 (232, 606)
HIV log ₁₀ viral load, median	2.1 (UDT ^f , 3.9)

^a In the past six months.

^b $\geq$ one night in a shelter or on the street.

^c Center for Epidemiologic Studies Depression (CES-D) scale ≥ 23 .

^d More than 14 standard drinks per week (or more than four drinks in a day) for men or more than 7 drinks per week (or more than three drinks in a day) for women, in the past month.

^e Highest in past five years.

^f UDT = undetectable.

Table II
Predictors of discontinuation of antiretroviral therapy in unadjusted and adjusted analyses.

Variable	% Discontinued ART	OR (95%CI)	
		Unadjusted	Adjusted ^a
Heavy alcohol use ^b			
Yes	19	1.23 (0.77, 1.95)	1.01 (0.63, 1.63)
No	16	1	1
Cocaine use ^c			
Yes	23	1.86 (1.18, 2.94) **	1.28 (0.76, 2.16)
No	14	1	1
Heroin use ^c			
Yes	27	2.12 (1.25, 3.60) *	1.27 (0.66, 2.44)
No	17	1	1
Depressive symptoms ^d			
Yes	24	2.26 (1.49, 3.43) ***	1.66 (1.04, 2.65) *
No	12	1	1
Age (years)			
<40	24	1.96 (1.20, 3.22) **	1.82 (1.11, 2.94) *
≥40	14	1	1
Gender			
Female	25	1.93 (1.09, 3.42) *	1.69 (0.91, 3.12)
Male	15	1	1
Race/ethnicity			
Non-white	18	1.55 (0.92, 2.60)	—
White	13	1	1
Homeless			
Yes	26	1.95 (1.16, 3.29) *	1.34 (0.75, 2.40)
No	15	1	1
Jail			
Yes	24	1.62 (0.84, 3.11)	—
No	16	1	1
CD4 cell count			
<374 ^e	23	1.59 (0.99, 2.52)	1.07 (0.63, 1.84)
≥374	15	1	1
HIV log ₁₀ RNA			
≥2.1 ^e	27	2.73 (1.79, 4.18) ***	2.28 (1.47, 3.53) **
<2.1	12	1	1
HIV Symptom Index ^f			
8–15	25	2.74 (1.59, 4.75) ***	1.94 (1.05, 3.60) **
4–7	16	1.88 (1.12, 3.16) *	1.49 (0.85, 2.62)
0–3	10	1	1
Hepatitis C Ab positive			
Yes	17	1.04 (0.62, 1.61)	—
No	17	1	1

* p < 0.05.

** p < 0.001.

*** p < 0.0001.

^a Analyses based on 266 subjects contributing 743 observations. Multivariable model adjusted for heavy alcohol use, cocaine use, heroin use, depressive symptoms, age, gender, homelessness, CD4, HIV log₁₀ RNA and HIV Symptom Index score.

^b More than 14 standard drinks per week (or more than four drinks in a day) for men, or more than seven drinks per week (or more than three drinks in a day) for women, in the past month.

^c In the past six months.

^d Center for Epidemiologic Studies Depression (CES-D) scale in which ≥ 23 indicates substantial depressive symptoms.

^e Study sample median.

^f Modified HIV Symptom Index, in which questions that overlap with the CES-D questionnaire (e.g. questions about sadness, anxiety, sleep problems, fatigue and memory loss) were excluded. Variable was categorised by tertiles for the study sample.