HIV-associated cognitive performance and psychomotor impairment in a Thai cohort on long-term cART

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Abstract

Objectives: To assess cognitive performance and psychomotor impairment in an HIV-positive cohort, well-suppressed on combination antiretroviral therapy (cART), in an Asian resource-limited setting.

Methods: Cross-sectional sociodemographic and cognitive data were collected in 329 HIV-positive and 510 HIV-negative participants. Cognitive performance was assessed using the International HIV Dementia Scale (IHDS), Montreal Cognitive Assessment (MoCA), WAIS-III Digit Symbol, Trail Making A, and Grooved Pegboard (both hands). Psychomotor test scores in the HIV-positive participants were converted to Z-scores using scores of the HIV-negative participants as normative data. Psychomotor impairment was defined as performance on two tests more than 1 standard deviation (SD) from controls or more than 2 SD on one test. Multivariate linear and logistic regression analyses were used to investigate associations between HIV and non-HIV-related covariates and poorer cognitive performance and psychomotor impairment.

Results: HIV-positive participants, mean age 45 (SD 7.69) years received cART for a median of 12.1 years (interquartile range [IQR] 9.1–14.4). Median CD4 cell count was 563 cells/mm^3 (IQR 435–725), and 92.77% had plasma HIV RNA <40 copies/mL. The adjusted mean differences between HIV-positive versus HIV-negative cohorts indicated significantly inferior cognitive performance (tests all $P<0.001$) with increasing age and lower income, independently associated. Psychomotor impairment was found ($P<0.02$) in all tests except the Grooved Pegboard non-dominant hand ($P=0.48$). Psychomotor impairment prevalence was 43% in the HIV-positive cohort, associated with male gender and lower income.

Conclusions: In this study, in individuals with viral suppression rates >90% on long-term cART, we found that inferior cognitive performance and psychomotor impairment were primarily associated with non-HIV-related factors.

Keywords: cognitive performance, psychomotor impairment, Asia, HIV-infection, HAND

Introduction

The introduction of combination antiretroviral therapy (cART) in the late 1990s has had a strong impact on morbidity and mortality [1], including a decreasing prevalence of the most severe forms of HIV-associated neurocognitive disorders (HAND) [2]. The reported prevalence of HAND in settings with access to treatment, but not necessarily with suppression of plasma HIV RNA, ranges from 15% to 69% [3–10].

HAND is an umbrella term that categorises cognitive disorders by severity including two forms of milder impairment: in asymptomatic neurocognitive impairment (ANI), mild deficits occur in the absence of participants reporting an impact on daily functioning; and mild neurocognitive disorder where a similar degree of impairment is seen on testing, but participants endorse functional consequences. The most severe form of impairment continues to be HIV-associated dementia (HAD). The time and capacity required is often a barrier to gold standard diagnostic work-up in resource-limited settings.

Because of the global scale-up of HIV care and treatment programmes, the number of individuals receiving cART was expected to rise above 15 million in 2015 [11,12]. Successfully treated patients may presume a life expectancy approaching that of the general population [13]. However, ageing patients on cART appear disproportionally predisposed to developing chronic comorbidities associated with ageing. This is attributed to a complex milieu of ongoing inflammation, immune activation, cART-related toxicities, a higher prevalence of traditional risk behaviours such as tobacco and alcohol use, as well as psychological and socioeconomic factors [14–17]. Poor cognitive performance is a comorbidity [18,19], to which additional comorbidities (for example, depression, cardiovascular disease, and diabetes) may confound or contribute to a patients' clinical presentation [15,20–23]. A better understanding of prevalence, severity, determinants, and prognosis are needed to inform prevention and treatment strategies for resilient ageing in this expanding and vulnerable patient population [17,24,25].

Even in its mildest form, HAND can negatively impact cART adherence, quality of life, ability to perform activities of daily living and working capacity [5,25–28]. Increasing evidence describes cognitive performance as a changeable condition suggesting fluctuations, and possible decline may occur over time [2,29]. The current hypothesis is that the central nervous system harbours an HIV reservoir that may intermittently switch from a latent to replicative state, resulting in inflammation that exacerbates neurocognitive symptoms although the patient's plasma viraemia is suppressed [30].

Findings on poor cognitive performance from resource-rich countries may not be generalisable to resource-limited settings where the majority of patients reside. Inappropriate application of normative data captured from resource-rich settings, or use of unvalidated assessment tools in resource-limited settings may result in unreliable estimates of cognitive performance. Socio-economic,

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cultural and regional diversity as well as factors related to ethnicity may influence cognitive performance, negatively impacting sensitivity and specificity of unvalidated tools [31–33].

Owing to time constraints we were unable to assess participants with the full battery of testing necessary for the diagnosis of HAND according to Frascati criteria. Instead, we investigated factors associated with an inferior cognitive performance, with several tests specific to the psychomotor domain. Our cohort consists of long-term-treated HIV-positive participants located in Thailand. We employed tests from the WHO/NIMH International battery designed to minimise cultural biases and compared the testing performance of the HIV-positive participants to appropriate HIV-negative control data captured in Thailand among individuals with similar sociodemographic backgrounds [34].

Methods

Participants

The 329 HIV-positive participants enrolled consisted of individuals who presented for routine HIV-related follow-up appointments between January 2011 and December 2014. These participants were, at the time of enrolment, participating in the HIV-NAT 006 cohort (clinicaltrials.gov NCT00411983) at the Thai Red Cross AIDS Research Center (TRCARC), an urban care centre in Bangkok, Thailand. The 006 cohort comprises 1114 individuals who were previously enrolled in various clinical trial protocols. The cohort participants receive combination antiretroviral therapy (cART) and are followed for long-term health outcomes. Sociodemographic and clinical care data were extracted from the electronic health records or other source documents: age, gender, income, education, smoking status, CD4 cell counts (nadir and current), current plasma HIV RNA levels, CDC classification stage at treatment initiation, and cART regimens (previous and current). Participants with documented evidence of hepatitis B virus surface antigen or hepatitis C virus antibody either at, or prior to, baseline were assumed to have that condition at the time of their cognitive evaluation as HBV DNA and HCV RNA data were unavailable.

The 510 HIV-negative participants were recruited at the TRCARC between August 2006 and June 2013 as part of the SEARCH 002 study (clinicaltrials.gov NCT00713752) [35]. HIV-negative status was confirmed through serology testing at baseline and all were evaluated by a study physician. These normative cases were recruited from the same geographical area, had a similar sociodemographic background, and had a wide age and education range allowing for the development of normative tables for this study. Although individual income data was not obtained in the HIV-negative cohort, it was believed to correspond to Thai national statistics reporting an average individual monthly income of US$311.54 in 2012 and US$370.75 in 2014 [36], and it corresponds well with the reported monthly income in our HIV-positive cohort. Educational attainment was categorised as: primary school or less, secondary, high school, vocational, bachelor degree and higher. Current smoking status, hepatitis B and hepatitis C virus serology were not collected in the HIV-negative cohort.

Inclusion criteria for both cohorts included an age of 20 to 70 years and the ability to provide written informed consent. Exclusion criteria were the presence of any factors that could compromise cognitive functioning (i.e. a history of cerebral toxoplasmosis, CMV encephalitis, head injury with loss of consciousness >30 minutes, stroke, and current illicit substance use) as judged by the clinical investigators. The presence of depression was screened for using the Thai Depression Inventory (TDI). Self-reported data on current alcohol and illicit substance use were collected. Alcohol use was defined as the consumption of alcohol on more than 5 days per week. A participant's history of illicit substance use was defined as ever or never.

Both studies were approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

Data collection

Cognitive evaluation tests were administered by trained nurses. In the HIV-positive group, sociodemographic and clinical care data were extracted from the electronic health records or source documents.

Assessment tools were selected based on (1) screening feasibility in a time- and resource-constrained environment; (2) frequency of application in previous studies to aid comparability of our findings; and (3) results from previous studies demonstrating that cultural and educational influences on the assessment tool outcomes may be less pronounced. The following tests (and corresponding cognitive areas or domains) were evaluated:

- International HIV Dementia Scale (IHDS, global cognition);
- Montreal Cognitive Assessment (MoCA, global cognition);
- WAIS-III Digit Symbol (psychomotor speed);
- Trail Making Test A (psychomotor speed); and
- Grooved Pegboard Test (both hands, manual dexterity and fine motor functioning) [37–41].

Evaluations took approximately 1 hour per participant. Grooved Pegboard data was not collected in 63 (19%) of the HIV-positive participants owing to time constraints and other logistical barriers. MoCA data was not collected until later in the HIV-negative participants, being available only for the last 158 participants enrolled who did not differ socio-economically from the main group, and enrolment strategies remained consistent.

Statistical analysis

Statistical analyses were conducted with Stata 12 (College Station, TX, USA). Group differences between categorical characteristics were compared using chi-squared tests. An independent samples *t*-test was used to compare continuous variables between groups.

Cognitive performance differences were first assessed by calculating the difference in the mean of all tool scores (IHDS, MoCA, WAIS-III Digit Symbol, Trail Making Test A, and Grooved Pegboard tests) between the HIV-positive and HIV-negative cohorts using univariate and multivariate linear regression models adjusting for the predefined confounders of age, education, and gender.

Linear regression univariate models were then used to identify sociodemographic and HIV-related covariates potentially associated with inferior cognitive performance. Covariates included age, sex, income, education, hepatitis C status, CD4 nadir, current CD4 cell count, viral load and efavirenz use. Covariates with a *P*-value <0.2 were included in adjusted multivariate models. Separate models were constructed for each test.

A separate analysis was performed to determine the presence of significant impairment of the psychomotor domain as a sufficient number of tests results were available. Significant impairment of the psychomotor domain was defined as having test scores at least 1 standard deviation (SD) on two tests or a single test score of at least 2 SD below the mean score from the control group. Raw psychomotor test scores of the WAIS-III Digit Symbol, Trail Making Test A, and Grooved Pegboard tests were used to calculate Z-scores in the HIV-positive participants, employing the test scores in the

appropriate age and education strata from HIV-negative controls as the normative data. The MoCA and IHDS do not focus strictly on the psychomotor domain and were not designed as diagnostic but rather screening tests, and were, therefore, not included in the analysis of significant psychomotor impairment. Logistic regression models were used to determine contributions of HIV-related and unrelated covariates. When modelling continuous covariates, the linearity of the variable against the logit function was assessed and in the case of non-linearity, the covariate was grouped into quartiles. Adjacent categories were collapsed together if the odds ratio (OR) and 95% confidence intervals (95% CI) were similar. All covariates with a *P*-value <0.2 in the univariate model and previously identified co-infections and HIV-related factors were selected for inclusion in the multivariate adjusted model. Covariates with *P*-values <0.05 in the multivariate models for all tests were considered to be statistically significant independent associations.

Results

The mean age was 45 years in both cohorts, the SD was wider in the HIV-negative than the HIV positive cohort (7.7 *vs* 15.8) (Table 1). The HIV-positive cohort contained more men than the HIV-negative group (57.1% *vs* 44.3%, *P*<0.001). No significant differences between cohorts with regard to education, depression screening outcomes, current alcohol use or history of substance use were observed.

The median (IQR) duration HIV-positive participants were receiving cART was 12.1 (9.1–14.4) years. At the time of assessment 28% of cART regimens included efavirenz. The median CD4 nadir cell count and current CD4 cell count were 175 (69–241) and 563 (435–725) cells/mm^3, respectively. The majority of patients (93%) had undetectable plasma HIV RNA (<40 copies/mL) (Table 1). US$ personal monthly income categorisation and corresponding percentages were as follows: <US$138.60 (<฿5000, 21.4%), US$138.61–415.74 (฿5000–<฿15,000, 47.7%), US$415.75–554.32 (฿15,000–<฿20,000, 13.8%), and >US$554.32 (≥฿20,00, 17.1%).

Cognitive performance and psychomotor impairment comparisons by HIV status

The HIV-positive cohort's overall cognitive performance including the psychomotor subset tests were significantly inferior to the HIV-negative reference group across all but one (Grooved Pegboard Test non-dominant) tool in the multivariate linear models after adjusting for age, education and gender (Table 2). In the sensitivity analyses, which

Table 1. Sociodemographic characteristics of study participants

Characteristic	HIV-positive (*Total* = 329) *n*	HIV-negative (*Total* = 510) *n*	*P*-value
Mean age (years ± SD)	45.69 ± 7.69	45.29 ± 15.79	0.67
Male gender	188 (57.14%)	226 (44.31%)	<0.001
Educational level			
Primary or less	76 (25%)	121 (23.73%)	0.55
Secondary	50 (16.45%)	96 (18.82%)	
High school	37 (12.17%)	79 (15.49%)	
Vocational	58 (19.08%)	88 (17.25%)	
Bachelor degree and higher	83 (27.3%)	126 (24.71%)	
Missing data	25		
Mild-to-moderate depression	23 (7.03%)	26 (5.12%)	0.25
Alcohol use ≥5 times/week	9 (2.96%)	9 (1.76%)	0.26
History of drug use	4 (4/200, 2%)	12 (2.35%)	0.78
Monthly income (Thai baht)			
<5000	65 (21.38%)		
5000–<15,000	145 (47.7%)		
15,000–<20,000	42 (13.82%)		
≥20,000	52 (17.11%)		
Missing data	25		
CDC stage			
A	140 (45.9%)		
B	115 (37.7%)		
C	50 (16.39%)		
Missing data	29		
CD4 nadir (cells/mm^3)			
Median (IQR)	175 (69–241)		
≤100	96 (30.67%)		
101–200	92 (29.39%)		
≥201	125 (39.94%)		
Missing data	16		
Plasma HIV RNA (copies/mL)			
≤40	295 (92.77%)		
41–400	14 (4.40%)		
>400	9 (2.83%)		
Missing data	11		
CD4 cell count (cells/mm^3)			
Median (IQR)	563 (435–725)		
≥500	124 (37.69%)		
EFV-containing regimen	93 (28.26%)		
Smoking			
Current smoker	58 (19.02%)		
Missing data	25		
Chronic hepatitis B			
HBsAg positive	40 (12.31%)		
Missing data	4		
Chronic hepatitis C			
Anti-HCV positive	43 (14.1%)		
Missing data	25		

Table 2. Unadjusted and adjusted comparison of cognitive test scores in HIV-positive versus HIV-negative subjects

	Test score for HIV-positive, (mean± SD)	Test score for HIV-negative, (mean±SD)	Mean difference (95% CI)	*P*-value	Adjusted mean difference* (95% CI)	*P*-value
WAIS-III Digit Symbol**	49.07 ± 14.81	52.72 ± 17.99	–3.64 (–5.98 to –1.30)	0.002	–3.02 (–4.86 to –1.17)	<0.001
IHDS**	9.51 ± 1.54	11.36 ± 0.93	–1.85 (–2.01 to –1.67)	<0.001	–1.80 (–1.97 to –1.64	<0.001
MoCA**	22.24 ± 3.83	24.01 ± 3.22	–1.77 (–2.46 to –1.07)	<0.001	–2.82 (–3.60 to –2.06)	<0.001
Trail Making Test A***	39.98 ± 16.15	35.59 ± 15.03	4.39 (2.24–6.54)	<0.001	3.87 (2.05–5.69)	<0.001
Grooved Peg dominant hand ***	72.67 ± 16.51	69.34 ± 17.77	3.32 (0.75–5.90)	0.011	2.89 (0.54–5.24)	0.016
Grooved Peg non-dominant hand***	79.86 ± 19.62	78.22 ± 21.85	1.64 (–1.50–4.78)	0.31	1.04 (–1.86–3.94)	0.48

* Adjusted mean difference is adjusted for age, education, and gender; ** higher score indicates superior functioning; *** lower score indicates superior functioning.
IHDS: International HIV Dementia Scale; MoCA: Montreal Cognitive Assessment.

included only cases with suppressed plasma HIV RNA, the magnitude and direction of almost all findings were the same and remained statistically significant, except for the Grooved Pegboard dominant hand, the effect of which maintained direction but with decreased magnitude and lost statistical significance.

HIV-related factors associated with cognitive performance

Multivariate linear regression models explored the contribution of covariates related to cognitive testing performance (Table 3). Older age was significantly related to worse cognitive performance across all tests ($P<0.05$). Lower income was also associated with worse performance across all tests ($P<0.05$), with the exception of the Grooved Pegboard tests (both hands). The only HIV-related covariate that was associated with worse cognitive performance was current efavirenz use in the Grooved Pegboard non-dominant hand test ($P=0.02$). However, despite the lack of association of HIV-related characteristics (i.e. nadir CD4 cell count), HIV-positive status was independently associated with inferior performance in all but one of the cognitive tests after adjusting for age, education and gender (Table 3).

HIV-related factors associated with psychomotor impairment

Utilising the Z-scores of the tests of the psychomotor domain, 140/329 (43%) HIV-positive participants met the criteria for impairment. Impairment was driven predominantly by low scores in WAIS-III Digit Symbol (70% of patients scored more than 1 SD below the mean of the HIV-negative control group), Trail Making Test A (69%) and to a lesser degree by the Grooved Pegboard Test non-dominant (48%) and Grooved Pegboard Test dominant hand (46%). In a sensitivity analysis among participants with undetectable plasma HIV RNA, 41% met criteria for psychomotor impairment. Covariates associated with psychomotor impairment in HIV-positive patients in the univariate and multivariate logistic regression models are shown in Table 4: male gender and lower incomes were independent risk factors.

Discussion

Our key findings are first that cognitive performance and psychomotor impairment in an HIV-positive cohort treated with cART for an extended duration with viral suppression rates >90% in a resource-limited setting, were inferior to that of the HIV-negative control cohort from a similar socio-economic background and second that HIV-related covariates did not predict cognitive performance and psychomotor impairment. Our study is strengthened by sensitivity analyses showing, that limiting the group to those with viral suppression, our findings remain statistically significant. Moreover, 43% of HIV-positive participants met the criteria for significant impairment criteria in the psychomotor domain. Correlates of inferior cognitive performance and of significant psychomotor impairment included older age, male gender and lower income highlighting vulnerable groups.

Other studies have assessed cognitive performance in cohorts receiving cART and observed associations highlighting vulnerable sub-populations as opposed to HIV-related covariates. For example, Robertson *et al*. prospectively assessed HAND across multiple resources-limited settings over 192 weeks finding variations in cognitive performance improvement by country. However as the plasma viral load detection limit in this study was 400 copies/mL while in our study it was 40 copies/mL, it is difficult to directly compare their findings with ours [33]. Winston *et al.* found that black ethnicity, among virally suppressed HIV-positive participants residing in the UK, was associated with worse cognitive performance [7].

The number of studies addressing cognitive performance in resource-limited countries has increased over the last decade. However, sample sizes are often small, a limited testing battery is employed and normative comparison data is often not available, thereby precluding a formal diagnosis of HAND [42,43]. The strengths of our study were the larger sample size and the inclusion of an appropriate HIV-negative reference group. We were also bolstered by the long-term follow-up of these individuals within our clinic who have assured continued access and information regarding their long-term treatment. However, our study has limitations that may affect its generalisability. Our inability to formally diagnose HAND due to the insufficient number of domains assessed allows for the possibility that our findings may have been different if a full battery of tests had been utilised. Furthermore, missing data may have also led to under representation of outcomes.

Assessing cognitive performance can be challenging. Application of a comprehensive battery of neuropsychological tests, or referral to a neuropsychologist is often unfeasible due to time constraints, competing priorities and the limited human resource capacity available to assess, as well as interpret, neuropsychological testing results [43,44]. Furthermore, not all commonly used tests have been validated across cultures or languages [38]. Consensus on a consistent screening approach has not been reached, nor is there clarity regarding the most important risk factors in the era of cART, particularly among patients with suppressed plasma HIV RNA [37,38,45]. At present, there are no validated screening tools that can be uniformly applied across populations [21]. When used in isolation, cognitive screening tools exhibit low sensitivity for detecting HAND [37–39,46,47].

This study reflects the challenges in assessing cognitive performance and psychomotor impairment in a resource-limited, time constrained HIV treatment centre. Assessment tools were selected based on expected implementation feasibility; however,

Table 3. Multivariate linear regression analysis of covariates associated with cognitive performance in HIV-positive participants

Test	Covariate	Coefficient (95%CI)	*P*-value	Group *P*-value
WAIS-III Digit Symbol	Age (per year)	–0.59 (–0.78 to –0.40)	<0.001	
	Male gender	–2.88 (–5.8–0.09)	0.06	
	Income (Thai bhat)			<0.001
	<5000	(ref)		
	5000–14,999	2.81 (–1.07–6.69)	0.16	
	15,000–19,999	11.0 (5.88–16.1)	<0.001	
	≥20,000	16.3 (11.5–21.1)	<0.001	
IHDS	Age (per year)	–0.03 (–0.05 to –0.01)	0.01	
	Male gender	–0.11 (–0.44–0.23)	0.53	
	Income (Thai bhat)			
	<5000	(ref)		0.012
	5000–14,999	–0.02 (–0.47–0.42)	0.91	
	15,000–19,999	0.54 (–0.04–1.11)	0.07	
	≥20,000	0.51 (–0.03–1.05)	0.06	
	Chronic HCV	–0.42 (–0.92–0.09)	0.10	
MoCA	Age (per year)	–0.09 (–0.14 to –0.04)	<0.001	
	Male gender	–0.05 (–0.85–0.76)	0.91	
	Income (Thai bhat)			<0.001
	<5000	(ref)		
	5000–14,999	1.48 (0.41–2.55)	0.01	
	15,000–19,999	3.43 (2.04–4.82)	<0.001	
	≥20,000	3.41 (2.11–4.71)	<0.001	
	CD4 ≥500 (cells/mm^3)	1.20 (–1.32–3.73)	0.35	
	Viral load ≥401 (copies/mL)	0.76 (–0.09–1.62)	0.08	
Trail Making A	Age (per year)	0.36 (0.14–0.58)	<0.001	
	Male gender	0.44 (–2.90–3.79)	0.79	
	Income (Thai bhat)			<0.001
	<5000	(ref)		
	5000–14,999	–3.47 (–7.88–0.93)	0.12	
	15,000–19,999	–6.14 (–11.9 to –0.40)	0.04	
	≥20,000	–11.7 (–(17.0 to –6.28)	<0.001	
	Chronic HCV	4.57 (–0.43–9.58)	0.07	
Grooved Peg	Age (per year)	0.79 (0.50–1.07)	<0.001	
dominant hand	Male gender	2.64 (–1.44–6.73)	0.20	
	Income (Thai bhat)			0.039
	<5000	(ref)		
	5000–14,999	–2.18 (–7.56–3.19)	0.42	
	15,000–19,999	–6.79 (–13.89–0.30)	0.06	
	≥20,000	–5.72 (–12.28–0.84)	0.09	
Grooved Peg	Age (per year)	0.88 (0.57–1.18)	<0.001	
non-dominant hand	Male gender	–0.24 (–4.77–4.30)	0.92	
	Use of EFV	–5.92 (–10.88–0.96)	0.02	

HCV: hepatitis C virus; EFV: efavirenz; IHDS: International HIV Dementia Scale; MoCA: Montreal Cognitive Assessment.

in practice, the application of the Grooved Pegboard tool was not completed in 19% of HIV-positive participants, suggesting it may not be an ideal tool in a resource-constrained setting due to the length of time needed for setting up the test, patient instruction and test completion. Although there were missing data in the electronic health records (Table 1) as no pattern or selection biases were noted, it is unlikely to have compromised outcomes.

In summary, we observed a worse cognitive performance and a high prevalence of significant psychomotor impairment in Thai HIV-infected participants on long-term cART with a high rate of plasma HIV RNA suppression compared to an appropriate HIV-negative control group. Significant determinants included older age, lower income, and male gender, but not HIV-related parameters.

Table 4. Univariate and multivariate logistic regression analysis of covariates associated with psychomotor impairment in HIV-positive subjects utilising Z-scores

	Univariate models*				Multivariate model**	
	Covariate	Coefficient (95% CI)	*P*-value	Group *P*-value	Coefficient (95% CI)	*P*-value
Sex (male)		1.96 (1.25–3.08)	<0.001		2.16 (1.31–3.55)	<0.001
Income (Thai baht)	<5000	Ref		0.05	Ref	
	5000–<15,000	0.72 (0.40–1.30)	0.28		0.80 (0.44–1.49)	0.49
	15,000–<20,000	0.43 (0.19–0.98)	0.045		0.42 (0.18–0.98)	0.045
	>20,000	0.32 (0.15–0.72)	0.005		0.28 (0.12–0.65)	0.003
HCV		1.86 (0.97–3.57)	0.06		1.40 (0.66–2.95)	0.38
EFV		1.23 (0.76–2.00)	0.4		1.62 (0.94–2.80)	0.08
CD4 cell count (cells/mm^3)	>350	Ref				
	<350	1.26 (0.65–2.44)	0.5			
Viral load (copies/mL)	<400	Ref				
	>400	0.71 (0.17–2.88)	0.63			0.68

* Univariate models adjusting for age and education. ** Multivariate model adjusting for factors significant in univariate analysis at $P<0.2$ and known confounders (HCV and EFV use).
EFV: efavirenz; HCV: hepatitis C virus.

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