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Long-term efavirenz use is associated with worse neurocognitive functioning in HIV-infected patients

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Author contributions Dr. Ma is the primary author on this manuscript, and as such, he and Dr. Letendre were responsible for study conceptualization and design. All study data were available to them, and they planned the statistical analyses and performed the interpretation of the results. Drs. Ma and Letendre thereby assume responsibility for the accuracy of the data, analysis, and interpretation. Dr. Vaida assisted with the interpretation of results along with drafting and revising the manuscript. Ms. Wong assisted with the statistical analysis and interpretation of results. Ms. Sanders assisted with data collection, result interpretation, drafting, and revising the manuscript. Ms. Kao assisted with data collection, analysis, and result interpretation. Dr. Croteau made considerable contributions through management and coordination of the data collection and assisted with study design, analysis, and interpretation, as well as revisions to the manuscript. Dr. Clifford assisted with primary data collection, drafting, and revising the manuscript. Dr. Collier assisted with primary data collection, drafting, and revising the manuscript. Dr. Gelman assisted with primary data collection, drafting, and revising the manuscript. Dr. Marra assisted with primary data collection, drafting, and revising the manuscript. Dr. McArthur assisted with primary data collection, drafting, and revising the manuscript. Dr. Morgello assisted with primary data collection, drafting, and revising the manuscript. Dr. Simpson assisted with primary data collection, drafting, and revising the manuscript. Dr. Heaton significantly contributed to all aspects of the manuscript, including study design, statistical analysis, and interpretation of results. He also strongly contributed in revising the manuscript. Dr. Grant assisted with study design, drafting, and revising the manuscript. Dr. Letendre made considerable contributions through management and coordination of the laboratory data and assisted with study design, analysis, and interpretation, as well as revisions to the manuscript.

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Abstract

Neurocognitive (NC) complications continue to afflict a substantial proportion of HIV-infected people taking effective antiretroviral therapy (ART). One contributing mechanism for this is antiretroviral neurotoxicity. Efavirenz (EFV) is associated with short-term central nervous system (CNS) toxicity, but less is known about its long-term effects. Our objective was to compare NC functioning with long-term use of EFV to that of a comparator, lopinavir-ritonavir (LPV/r), in a cohort of well-characterized adults. Four hundred forty-five patients were selected from the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) cohort based on their use of either EFV (n=272, mean duration 17.9 months) or LPV/r (n=173, mean duration 16.4 months) and the lack of severe NC comorbidities. All patients had undergone standardized comprehensive NC testing. Univariable and multivariable analyses to predict NC outcomes were performed. Compared with LPV/r users, EFV users were more likely to be taking their first ART regimen (p<0.001), were less likely to have AIDS (p<0.001) or hepatitis C virus (HCV) coinfection (p<0.05), had higher CD4+ T cell nadirs (p<0.001), had lower peak (p<0.001) and current (p<0.001) plasma HIV RNA levels, and were less likely to have detectable HIV RNA in cerebrospinal fluid (CSF) (p<0.001). Overall, EFV users had worse speed of information processing (p=0.04), verbal fluency (p=0.03), and working memory (p=0.03). An interaction with HCV serostatus was present: Overall among HCV seronegatives (n=329), EFV users performed poorly, whereas among HCV seropositives (n=116), LPV/r users had overall worse performance. In the subgroup with undetectable plasma HIV RNA (n=269), EFV users had worse speed of information processing (p=0.02) and executive functioning (p=0.03). Substantial differences exist between EFV and LPV/r users in this observational cohort, possibly because of channeling by clinicians who may have prescribed LPV/r to more severely ill patients or as second-line therapy. Despite these differences, EFV users had worse functioning in several cognitive abilities. A potentially important interaction was identified that could indicate that the NC consequences of specific antiretroviral drugs may differ based on HCV coinfection. The complexity of these data is substantial, and findings would best be confirmed in a randomized clinical trial.

Keywords

Long-term antiretroviral therapy; Neurocognitive function; Efavirenz; Lopinavir/ritonavir; Neurotoxicity; Hepatitis C virus coinfection

Introduction

Despite advances in potent combination antiretroviral therapy (ART), milder forms of HIV-associated neurocognitive disorders (HAND) continue to affect nearly 50 % of HIV-infected individuals, suggesting that either current clinical management of HAND is inadequate, or HAND is irreversible, or both (Letendre 2011; Valcour et al. 2011). The pathogenesis of HAND remains incompletely understood. Several factors may contribute to the development of HAND, including aging (Ikezu 2009; Justice et al. 2004; Marquine et al. 2014), poor ART adherence, subtherapeutic distribution of ART into the central nervous system (CNS) (Letendre 2011; Winston et al. 2011), and neurotoxicity of antiretroviral drugs (Robertson et al. 2012a).

Efavirenz (EFV), a common component of first-line combination ART, is associated with CNS adverse effects. After treatment initiation, acute neuropsychological adverse reactions occur in a substantial proportion of individuals but generally resolve after a few weeks of continued use. Longer term (>6 months) CNS toxicity related to EFV was suggested in a cross-sectional cohort study showing an association between EFV use and neurocognitive (NC) impairment (Ciccarelli et al. 2011). The underlying mechanisms for EFV neurotoxicity are not fully understood, but recent data from 17 HIV-infected individuals receiving long-term therapy, ranging from 6 to 27 months, found a correlation between EFV plasma concentrations and CNS toxicity (Gutierrez et al. 2005). Furthermore, an 8-OH metabolite of EFV, recently identified as a potent neurotoxin in primary neuronal culture, can damage dendritic spines, suggesting a potential role of EFV neurotoxicity in the neuronal injury that may underpin HAND (Tovar-y-Romo et al. 2012; Brandmann et al. 2013). While many randomized clinical trials of EFV have been performed, none evaluated patients with the comprehensive, objective neurocognitive assessments that are required to determine the impact of treatment on specific cognitive abilities, largely relying instead on self-report, small batteries of simple NC tests, or symptom questionnaires. In addition, few comparisons of long-term EFV to a single comparator have been performed in observational cohorts of well-characterized HIV-infected patients (Clifford et al. 2005, 2009).

Complex drug-disease interactions might also contribute to NC decline. Although advanced HIV disease, hepatitis C virus coinfection, and EFV use have been widely suspected as risk factors for neurocognitive complications among HIV-infected individuals (Cherner et al. 2005; Letendre et al. 2005; Morgan et al. 2012), the interactions between these factors remain largely unknown. The purpose of the present study was to compare the impact of long-term use of EFV to a comparator, lopinavir (with ritonavir, LPV/r), on global and domain-specific NC functioning in a large cohort of well-characterized patients.

Methods

Study design and patients

This was a retrospective cohort study of 445 patients from the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) project, an observational cohort study examining the effects of HIV on the nervous system of HIV-infected individuals and based at academic medical centers in six US cities (Baltimore, MD; Galveston, TX; New York, NY; St. Louis,

MO; San Diego, CA; and Seattle, WA). Eligibility criteria for this analysis included current use of either EFV or LPV/r for at least 12 weeks, at least three antiretroviral agents in the ART regimen, and the absence of severe neuropsychiatric comorbidities that would confound attribution of NC impairment to other causes, such as HIVor ART toxicity. Of 445 HIV-infected patients included in this analysis, 269 qualified for the planned secondary analysis by having HIV RNA below 50 copies/mL (c/mL) in plasma. Three hundred fifty-seven (80.2 %) patients successfully underwent lumbar puncture and cerebrospinal fluid (CSF) collection using aseptic techniques. The study protocol was approved by the Human Subjects Protection Committees of each institution. Written informed consent was obtained from all study patients.

HIV disease and treatment characteristics

Blood CD4+ T cell counts were measured by flow cytometry, and HIV RNA concentrations in plasma and CSF were assayed by reverse transcriptase PCR (lower limit of quantitation 50 c/mL). Details of medical and treatment history including the dates, dose, and schedule for EFV and LPV/r were collected through self-report using a structured questionnaire or extracted from the medical records. The CNS penetration-effectiveness (CPE) estimate of each subject's current ART regimen was calculated according to the 2010 revision (Letendre 2011). Hepatitis C virus (HCV) serostatus was determined by commercial immunoassay. No patients took interferon-based therapy for HCV disease.

Neurocognitive assessment

All patients completed standardized comprehensive testing (Antinori et al. 2007) that assessed seven cognitive abilities known to be commonly affected by HIV disease (Heaton et al. 2010): (1) speed of information processing, (2) learning, (3) recall, (4) executive function, (5) verbal fluency, (6) working memory and attention, and (7) motor function (Heaton et al. 2010). Raw test scores were converted to demographically adjusted *T* scores based on published normative data to account for the influence of age, education, sex, and ethnicity when possible (Carey et al. 2004). *T* scores were then converted into deficit scores. The deficit scores from each of the NC test variables were then averaged to derive a global deficit score (GDS) for each subject. The GDS values range from 0 (entirely normal) to 5 (severely impaired); higher scores indicate worse NC functioning with a GDS value of greater than or equal to 0.50 indicating definite impairment (Carey et al. 2004). Mood was assessed using the Beck Depression Inventory (BDI-II) (Beck et al. 1996), a 21-item self-report measure that rates severity of depressive symptoms during the past 2 weeks.

Statistical analysis

Univariable analyses were performed to determine demographic and clinical differences between patients in the EFV and the LPV/r groups using Fisher's exact test for categorical variables and *t* tests for continuous variables. Continuous domain-specific and GDS and BDI-II values were compared between the EFV and LPV/r groups in univariable and multivariable analyses. The univariable analysis used the *t* test; the unadjusted mean difference in outcome between groups and 95 % confidence interval, and the *p* value was reported. Multivariable analysis was adjusted for relevant covariates. Covariates for

adjustment were chosen by backward model selection using the Akaike information criterion (AIC). The candidate covariates were age, HCV serostatus, estimated HIV disease duration, duration of the current ART regimen, self-reported adherence to ART (based on ACTG 4-day adherence assessment), past ART use prior to the current regimen (yes/no), total number of past ART drugs, AIDS status, current CD4+ T cells, nadir CD4+ T cells, plasma HIV RNA, peak plasma HIV RNA, and the other antiretroviral drugs in the treatment regimen, which included abacavir (ABC), didanosine (DDI), emtricitabine (FTC), lamivudine (3TC), stavudine (D4T), tenofovir (TDF), and zidovudine (ZDV). In addition to the continuous deficit scores, domain-specific and global impairment was analyzed as dichotomous outcomes, as defined in the preceding section. Univariable and multivariable logistic regression were used to compare the proportion of patients who were impaired in either the EFV or LPV/r groups. In the next stage of the analysis, differences between treatment groups were screened for first-order interactions on neurocognitive and mood outcomes by including the treatment group, the covariate, and their interaction in a linear model for continuous neurocognitive outcomes or a logistic model for dichotomous neurocognitive outcomes. When a statistically significant interaction was identified, both unadjusted and adjusted models are reported using covariate selection via the AIC. No correction for multiple comparisons was applied to the analyses. All analyses used the R statistical platform (version 3.0.1, R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographic and disease characteristics

The demographic and disease characteristics of 272 patients receiving EFV in comparison to those of 173 patients receiving LPV/r are summarized in Table 1. The two treatment groups did not differ in sex, ethnicity, age, or treatment duration. Compared with EFV users, however, LPV/r users had evidence of more advanced past and current HIV disease, including longer duration of HIV disease, greater AIDS prevalence, lower nadir and current CD4+ T cells, higher peak and current HIV RNA in plasma, and higher HIV RNA in CSF. LPV/r users also had longer durations of total ART use, were less likely to be taking their first ART regimen, reported worse recent ART adherence, and their regimens had higher CPE values.

Neurocognitive and mood outcomes

Overall, EFV users had worse performance in most neurocognitive abilities than LPV/r users, particularly verbal fluency (p=0.03) and working memory (p=0.03); there was also a trend for them to have worse speed of information processing (p=0.07) (Table 2). While the absolute differences appeared marginal, analyses of categorical impairment status revealed a more substantial association between EFV and speed of information processing impairment (87 % increased odds of speed of information processing impairment, p= 0.04). In the mood analyses, EFV users were 40 % less likely to have a lifetime diagnosis of major depressive disorder prior to study entry (p=0.02), although they did not have better BDI-II values at the time of assessment. In the subgroup of patients with plasma HIV RNA ≤50 c/mL (n=269), EFV users had significantly worse executive functioning (p=0.03) and speed of information processing (p=0.02).

Interaction with HCV serostatus

An interaction with HCV serostatus was identified in multivariable analyses (summarized in Table 3). Among HCV seronegative patients (n=328), EFV use was associated with consistently worse NC performance compared with LPV/r use, globally (p=0.02) and particularly in the speed of information processing (p=0.04) and executive functioning (p= 0.05) domains. In contrast, among HCV seropositive patients (n=117), long-term LPV/r use was associated with worse NC performance compared to EFV use globally (p=0.04) and particularly in learning (p=0.04), recall (p=0.01), and motor functioning (p=0.06), domains that entirely differed from those associated with EFV use.

Discussion

This analysis was primarily designed to compare EFV to a comparator on the NC functioning of people living with HIV disease and to our knowledge was the largest cohort-based analysis of long-term use of EFV- and LPV/r-containing regimens on cognition. Since EFV is more commonly used as first-line therapy for HIV than LPV/r, EFV users had less advanced HIV disease than individuals taking LPV/r, as expected. Specifically, EFV users had higher nadir and current CD4+ T cell counts and lower peak HIV RNA levels in plasma, were more likely to be taking their first ART regimen, reported better recent ART adherence, and were less likely to be HCV seropositive. In contrast, LPV/r users had many disease characteristics, e.g., lower nadir CD4+ T cell counts, HCV coinfection that are known to increase risk for NC impairment, providing a conservative bias in analyses assessing possible EFV neurotoxicity. Despite these differences favoring better neuropsychological performance among EFV users, they had worse verbal fluency in unadjusted analyses. Following adjustment for the many between-group differences noted in Table 1, additional disparities between groups emerged, with EFV users having worse performance in working memory and speed of information processing. EFV users performed worse than LPV/r users in three NC abilities, although the effect sizes were not large and the composite measure of global NC functioning did not differ between the groups in these initial analyses. The second-stage analyses involved analyzing first-order interactions that could influence our findings. This process identified an influential effect associated with HCV serostatus. Among HCV seronegative individuals, EFV users performed worse globally, especially in the executive function and speed of information processing abilities. Among HCV seropositive individuals, however, LPV/r users performed worse globally and especially in two abilities that differed from those above: learning and recall. EFV users were also 40 % less likely to have a lifetime diagnosis of major depressive disorder prior to study entry, although they did not have better BDI-II values at the time of assessment. This was suspected that physicians might be less likely to prescribe EFV in patients with a history of serious depression, even if they had no ongoing depression at the time of the study.

While the acute CNS side effects of EFV are well recognized, one long-term randomized study found that EFV had no chronic adverse effects on the CNS although these findings may have been impacted by subject drop-out. (Clifford et al. 2009). In our analysis, EFV use was associated with worse NC functioning, specifically in participants without HCV coinfection, with a mean duration of use approximately 1.5 years. This finding is consistent

with recent reports from smaller cohorts (Ciccarelli et al. 2011; Gutierrez et al. 2005; Winston et al. 2012). The biological mechanisms that might underlie worse neurocognitive performance in EFV users are not known but may be caused by neurotoxicity of EFV metabolites, 7-OH-EFV and 8-OH-EFV, producing morphological damage to dendritic spines in vitro (Tovar-y-Romo et al. 2012), which suggests potential synergy with synaptodendritic pathology that occurs in HIV-associated dementia and HAND (Ellis et al. 2007; Kaul et al. 2001). More recent studies also suggest an important role of EFV-induced oxidative stress and the increase of amyloid-beta production in its neurotoxicity (Brown et al. 2014). In contrast to EFV neurotoxicity, few investigations have focused on the possible neurotoxicity of LPV/r. In support of our findings of better neurocognitive performance in HCV seronegative patients taking LPV/r, a randomized study found that 48 weeks of LPV/r-containing ART reduced rates of NC impairment from baseline on multiple neurocognitive tests, suggesting that long-term use of LPV/r might lead to better NC outcomes (Bunupuradah et al. 2012). This conclusion is also supported by a study of LPV/r-containing ART for 96 weeks (Santos et al. 2013). Our study for the first time demonstrated that LPV/r may provide an effective alternative to EFV in HCV seronegative patients experiencing NC impairment or other symptoms of neurotoxicity.

The finding that the impact of EFV and LPV/r on NC functioning differed by HCV serostatus is novel and may have particular implications for regions where HCV coinfection is common. The impact of HCV disease on NC impairment has been suggested by several studies (Clifford et al. 2005; Letendre et al. 2005; Garvey et al. 2012; Thiyagarajan et al. 2010; Vivithanaporn et al. 2012; Winston et al. 2010). HCV disease might lead to NC impairment either directly (e.g., via infection of glial cells and production of viral proteins) or indirectly (e.g., via upregulated HIV replication and immune activation or substance use disorders that predispose to HCV transmission). These HCV-related factors, however, should have affected LPV/r and EFV users similarly. The main HCV-related finding in our analysis was that HCV combined with LPV/r was associated with worse NC functioning compared with HCV combined with EFV use. There are possible explanations for this finding including different hepatic functioning among LPV/r and EFV users; HCV-associated liver disease that could alter the pharmacokinetics of LPV/r and EFV; and potential alteration of CNS distribution of LPV/r and EFV by HCV coinfection, which warrant further investigations using CSF samples collected to test these hypotheses and determine if there is higher CSF viral load and inflammation in those on LPV/r and the interaction between HCV and different ART on NC performance.

Mounting evidence has suggested that HCV coinfection could alter the distribution of drugs into the CNS. HCV can infect a critical component of the blood–brain barrier (BBB) and brain microvascular endothelial cells (Fletcher et al. 2012) and was associated with reduced BBB permeability in a recent analysis (Letendre et al. 2011). Since EFV concentrations in CSF exceed the 50 % inhibitory concentration (IC_{50}) for wild-type HIV by approximately 25-fold (Best et al. 2011), a reduction of EFV distribution into the CNS by HCV coinfection might maintain therapeutic concentrations while reducing neurotoxicity, which has been linked to higher EFV concentrations. Since LPV/r concentrations in CSF exceed the IC_{50} by approximately 2- to 10-fold (Capparelli et al. 2005), a reduction in its distribution might result in subtherapeutic concentrations in the CNS, leading to low-level HIV replication and

neuroinflammation. This theory posits different mechanisms for CNS injury (HCV seronegative EFV users: drug neurotoxicity; HCV seropositive LPV/r users: HIV replication and neuroinflammation) and is consistent with the differing NC abilities affected by EFV and LPV/r in our analyses. Measurement of drug concentrations in the CSF would provide direct evidence to support this hypothesis but was not part of this nested analysis.

The least unlikely explanation is that the finding was artifactual. Even though our project had a priori hypotheses, type I error remains a legitimate concern, particularly since we did not specifically predict that HCV would reverse the direction of the observed associations. Imposing a Bonferroni correction of our HCV interaction analyses, however, did not eliminate the statistical significance of the differences between EFV and LPV/r users in global, recall, and motor functioning, supporting that the findings were not errant.

If confirmed, our findings could have an impact on prescribing patterns since these two drugs represent critical components of recommended first- and second-line regimens in WHO treatment guidelines that have been widely used in resource-limited settings (Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. World Health Organization. Geneva and Switzerland 2006). The long-term effects of these drugs on NC functioning are of particular relevance both to the management of HIV disease and to overall public health in these settings with a high HIV prevalence. Highlighting the importance of the finding, several recent reports have identified the high prevalence and severity of HAND in Sub-Saharan African and Asian countries (Kanmogne et al. 2010; Robertson et al. 2012b; Sacktor et al. 2006). The translation of our findings into practice should be proceeded with caution as the threshold of NC impairment warranting a regimen change remains to be determined. Additional data on self-reported day-to-day function are needed to determine if these apparently marginal differences in NC testing translate into impaired daily function.

In addition to the possibility of type I error, our study has several possible limitations that could affect the accuracy of our findings. Cross-sectional designs like ours have inherent bias that precludes attribution of causality. Although considered as the strength of our project, the diversity of the study population, which was representative of patients in care in HIV clinics in the USA, could introduce additional sources of bias and confound attribution of our finding to EFV and LPV/r. For example, while our analyses adjusted for many characteristics that differed between EFV and LPV/r users, they did not include other factors, such as substance-related disorders or indicators of persistent immune activation. The differences we did observe between EFV and LPV/r users, such as in peak HIV RNA and nadir CD4+ T cell counts, could reflect the clinical channeling that is known to occur in selection of ART regimens: Protease inhibitors, like LPV/r, tend to be reserved for patients with more severe disease or who are already ART-experienced. Accounting for these differences is critical to any comparison of a first-line drug like EFV with a second-line comparator. A randomized, controlled clinical trial of ART-naive adults would both address the limitations of our cross-sectional design and better ensure balance in important characteristics between treatment groups. This would also allow standardization of the other drugs in the regimen. However, conducting such a randomized clinical trial becomes less likely in the future since the use of LPV/r and EFV is decreasing. In our analysis, LPV/r

users received regimens that had higher estimated CNS effectiveness than EFV users, suggesting another possible regimen selection bias, possibly because LPV/r users had several characteristics that placed them at higher risk of HAND. One potential methodological issue is that our analysis invoked multiple comparisons without corrections, e.g., the Bonferroni correction. The rationale for such a lack of adjustment was primarily based on the fact that most NC variables tested were rather dependent whereas the Bonferroni correction would assume that all of the hypothesis tests were statistically independent. Nevertheless, with the Bonferroni correction, the interactions between HCV serostatus and ART use would remain significant but no remarkable differences between EFV and LPV/r groups, suggesting that this procedure might increase the risk of type II errors.

We conclude that long-term EFV use is associated with worse NC functioning than LPV/r but principally in HCV seronegative individuals. With HCV coinfection, LPV/r users perform worse for reasons that remain to be determined. Our findings may assist in the selection of ART regimens with low neurotoxicity for the long-term management of HIV disease in the USA and in resource-limited settings.

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Table 1

Demographic and disease characteristics

Variable		EFV (*N*=272)	LPV/r (*N*=173)	*P*[d]
Gender	Male, *N* (%)	221 (81 %)	137 (79 %)	0.625 F
Ethnicity	Black, *N* (%)	128 (47 %)	89 (51 %)	0.671 F
	Hispanic, *N* (%)	27 (10 %)	19 (11 %)	
	White, *N* (%)	109 (40 %)	62 (36 %)	
	Other, *N* (%)	8 (3 %)	3 (2 %)	
Age, years	Mean (SD)	43.9 (8.1)	45.1 (7.8)	0.113 T
Education, years	Mean (SD)	12.8 (2.4)	12.6 (2.5)	0.605 T
HCV serostatus	Positive, *N* (%)	63 (23 %)	54 (32 %)	0.046 F
ART use prior to current regimen	Naive, *N* (%)	99 (36 %)	24 (14 %)	<0.001 F
Estimated HIV duration, months	Mean (SD)	109.8 (75)	144 (68.4)	<0.001 T
Total ART duration, months	Mean (SD)	42.4 (47.7)	56.4 (56.3)	0.008 T
Current regimen duration, months	Mean (SD)	17.9 (19.6)	16.4 (14.5)	0.378 T
Drug-specific duration[a], months	Mean (SD)	27.6 (23.6)	25.1 (18.4)	0.202 T
Four-day adherence (≥95 %)	Adherence, *N* (%)	248 (92 %)	146 (85 %)	0.042 F
AIDS	Diagnosed, *N* (%)	173 (64 %)	142 (82 %)	<0.001 F
Current CD4+ T cells (/mm^3)	Mean (SD)	499 (279)	443 (290)	0.044 T
	≤200, *N* (%)	31 (11 %)	36 (21 %)	0.009 F
Nadir CD4+ T cells (/mm^3)	Mean (SD)	187 (157)	129 (130)	<0.001 T
	≤200, *N* (%)	166 (61 %)	127 (73 %)	0.008 F
Neuropsychiatric comorbidity severity[b]	Mild, *N* (%)	176 (65 %)	113 (65 %)	0.919 F
	Moderate, *N* (%)	96 (35 %)	60 (35 %)	
	Severe, *N* (%)	0 (0 %)	0 (0 %)	
HIV RNA—plasma ($\log_{10}$ c/mL)	Mean (SD)	2.1 (0.9)	2.6 (1.3)	<0.001 T
	≤1.7 $\log_{10}$ c/mL, *N* (%)	68.4 %	49.4 %	<0.001 F
Peak HIV RNA—plasma ($\log_{10}$ c/mL)	Mean (SD)	5.4 (5.6)	5.6 (6.0)	0.003 T
HIV RNA—CSF ($\log_{10}$ c/mL)[e]	Mean (SD)	1.8 (0.33)	2.0 (0.62)	<0.001 T
	≤1.7 log10 c/mL, *N* (%)	204 (92.3 %)	101 (74.3 %)	
Total ART ever used[c]	Mean (SD)	5.4 (2.5)	7.6 (3.0)	<0.001 T
CPE of current regimen	Mean (SD)	7.7 (1.3)	8.5 (2.1)	<0.001 T
Other drugs in regimen	ABC, *N* (%)	41 (15 %)	56 (32 %)	<0.001 F
	3TC, *N* (%)	108 (40 %)	88 (51 %)	0.024 F
	ZDV, *N* (%)	55 (20 %)	54 (31 %)	0.009 F
	DDI, *N* (%)	26 (10 %)	17 (10 %)	1.00 F
	D4T, *N* (%)	14 (5 %)	17 (10 %)	0.084 F
	FTC, *N* (%)	137 (50 %)	52 (30 %)	<0.001 F
	TDF, *N* (%)	186 (68 %)	105 (61 %)	0.103 F
	By drug combinations			
	ABC/3TC, *N* (%)	22 (8 %)	16 (9 %)	0.729 F

Variable		EFV (*N*=272)	LPV/r (*N*=173)	*P*[d]
	ABC/3TC/ZDV, *N* (%)	6 (2 %)	20 (12 %)	<0.001 F
	ZDV/3TC, *N* (%)	46 (17 %)	27 (16 %)	0.793 F
	TDF/FTC, *N* (%)	136 (50 %)	48 (28 %)	<0.001 F

EFV and LPV/r users had similar demographic characteristics but differed in many HIV disease and treatment characteristics

[a] Duration of EFV use for EFV group and LPV/r use for LPV/r group

[b] Individuals with confounding level were removed as part of exclusion criteria

[c] Ritonavir is excluded as an ART drug because its role is to boost other protease inhibitors

[d] *F* Fisher's exact test, *T* two-sample *t* test

[e] 357 (80.2 %) of the patients had CSF tested

EFV efavirenz, *LPV/r* lopinavir/ritonavir, *CSF* cerebrospinal fluid, *CPE* CNS penetration-effectiveness, *ART* antiretroviral therapy

Table 2

Analysis of neurocognitive outcomes without and with adjustment for statistically significant between-group differences in disease and treatment characteristics (Table 1: EFV vs. LPV/r)

		EFV group	LPV/r group	Unadjusted $\Delta_{E\text{-}L}$ (95 % CI), P or OR (95 % CI), P	Adjusted $\Delta_{E\text{-}L}$ (95 % CI), P or OR (95 % CI), P
Global functioning					
Deficit score	Mean (SD)	0.50 (0.51)	0.49 (0.46)	0.01 (−0.08, 0.1), 0.83	0.03 (−0.06, 0.13), 0.53
Impairment	*N* (%)	135 (50 %)	80 (46 %)	1.15 (0.78, 1.68), 0.49	1.17 (0.78, 1.77), 0.45
Verbal fluency					
Deficit score	Mean (SD)	0.35 (0.67)	0.22 (0.45)	0.13 (0.01, 0.24), **0.03**	0.13 (0.01, 0.25), **0.03**
Impairment	*N* (%)	44 (16 %)	22 (13 %)	1.32 (0.76, 2.30), 0.32	1.15 (0.64, 2.08), 0.63
Executive functioning					
Deficit score	Mean (SD)	0.63 (0.89)	0.54 (0.8)	0.09 (−0.07, 0.25), 0.28	0.15 (−0.02, 0.32), **0.08**
Impairment	*N* (%)	101 (37 %)	57 (33 %)	1.20 (0.80, 1.80), 0.37	1.28 (0.84, 1.96), 0.25
Speed of information processing					
Deficit score	Mean (SD)	0.31 (0.6)	0.23 (0.48)	0.08 (−0.03, 0.19), 0.15	0.11 (−0.02, 0.22), **0.07**
Impairment	*N* (%)	45 (17 %)	20 (12 %)	1.52 (0.86, 2.67), 0.15	1.87 (1.03, 3.38), **0.04**
Learning					
Deficit score	Mean (SD)	0.56 (0.74)	0.67 (0.75)	−0.1 (−0.25, 0.04), 0.15	−0.1 (−0.25, 0.05), 0.19
Impairment	*N* (%)	95 (35 %)	66 (38 %)	0.87 (0.59, 1.29), 0.49	0.96 (0.61, 1.49), 0.84
Recall					
Deficit score	Mean (SD)	0.57 (0.78)	0.66 (0.71)	−0.08 (−0.23, 0.06), 0.27	−0.04 (−0.18, 0.11), 0.62
Impairment	*N* (%)	81 (30 %)	58 (34 %)	0.85 (0.56, 1.27), 0.42	0.90 (0.60, 1.37), 0.64
Working memory					
Deficit score	Mean (SD)	0.54 (0.77)	0.46 (0.69)	0.09 (−0.05, 0.23), 0.23	0.15 (0, 0.3), **0.05**
Impairment	*N* (%)	78 (29 %)	43 (25 %)	1.22 (0.79, 1.88), 0.38	1.49 (0.9, 2.46), 0.12
Motor functioning					
Deficit score	Mean (SD)	0.47 (0.89)	0.46 (0.85)	0.01 (−0.16, 0.18), 0.90	0.06 (−0.12, 0.24), 0.52
Impairment	*N* (%)	61 (23 %)	37 (21 %)	1.07 (0.68, 1.7), 0.77	1.10 (0.69, 1.77), 0.69

Higher values indicate worse performance. In analyses of continuous outcomes, $\Delta_{E\text{-}L}$ indicates the difference between the EFV (E) and LPV/r (L) groups: Positive values indicate that EFV users performed worse than LPV/r users, and negative values indicate the opposite. In analyses of binary impairment outcomes, odds ratios (ORs) >1.0 indicate that EFV users performed worse than LPV/r users and ORs <1.0 indicate the opposite. *p* Values <0.10 are indicated in bold font

Covariates in adjusted analysis: 3TC, ABC, D4T, FTC, TDF, ZDV, adherence, age, AIDS, ART duration, CPE of current regimen, current CD4+ Tcells, current CD4+ T cells <200/mm^3, HCV serostatus, HIV duration, HIV RNA plasma, nadir CD4+ T cells, nadir CD4+ T cells <200/mm^3, peak HIV plasma HIV RNA, ART history prior to the current regimen, total ART drugs ever used

Table 3

Summary of HCV interaction analysis

Outcome		HCV− (*n*=328)	HCV+ (*n*=117)	*P* for interaction	Difference between Δ_{E-L} or ratio of ORs
		Δ_{E-L} (95 % CI) or OR (95 % CI)	Δ_{E-L} (95 % CI) or OR (95 % CI)		
Global DS	Δ_{E-L}	0.11 (0, 0.22)	−0.22 (−0.4, −0.05)	**0.002**	−0.33 (−0.54, −0.12)
Global impairment	OR	1.7 (1.07, 2.68)	0.44 (0.21, 0.93)	**0.003**	0.26 (0.11, 0.62)
Verbal fluency DS	Δ_{E-L}	0.15 (0.01, 0.28)	0.06 (−0.15, 0.28)	0.53	−0.08 (−0.34, 0.17)
Verbal fluency impairment	OR	1.54 (0.81, 2.94)	0.71 (0.22, 2.25)	0.25	0.46 (0.12, 1.73)
Executive functioning DS	Δ_{E-L}	0.16 (−0.03, 0.36)	−0.08 (−0.39, 0.23)	0.19	−0.24 (−0.61, 0.12)
Executive functioning impairment	OR	1.62 (0.99, 2.63)	0.63 (0.3, 1.32)	**0.04**	0.39 (0.16, 0.95)
Speed of information processing DS	Δ_{E-L}	0.16 (0.03, 0.28)	−0.12 (−0.32, 0.08)	**0.02**	−0.28 (−0.52, −0.04)
Speed of information processing impairment	OR	2.25 (1.11, 4.59)	0.53 (0.17, 1.59)	**0.03**	0.23 (0.06, 0.87)
Learning DS	Δ_{E-L}	−0.01 (−0.17, 0.16)	−0.35 (−0.62, −0.08)	**0.04**	−0.34 (−0.66, −0.02)
Learning impairment	OR	1.17 (0.73, 1.89)	0.43 (0.2, 0.92)	**0.03**	0.37 (0.15, 0.9)
Recall DS	Δ_{E-L}	0.06 (−0.11, 0.23)	−0.42 (−0.69, −0.15)	**0.004**	−0.47 (−0.79, −0.16)
Recall impairment	OR	1.24 (0.75, 2.03)	0.33 (0.15, 0.74)	**0.006**	0.27 (0.1, 0.69)
Working memory DS	Δ_{E-L}	0.14 (−0.03, 0.3)	0 (−0.27, 0.27)	0.40	−0.14 (−0.45, 0.18)
Working memory impairment	OR	1.51 (0.89, 2.58)	0.8 (0.36, 1.76)	0.19	0.53 (0.2, 1.37)
Motor functioning DS	Δ_{E-L}	0.16 (−0.03, 0.36)	−0.36 (−0.68, −0.05)	**0.006**	−0.53 (−0.9, −0.15)
Motor functioning impairment	OR	1.68 (0.93, 3.01)	0.42 (0.18, 1.0)	**0.01**	0.25 (0.09, 0.72)

In the HCV− and HCV+ columns, Δ_{E-L} indicates the difference between the EFV (E) and LPV/r (L) groups: Positive values indicate that EFV users performed worse than LPV/r users, and negative values indicate the opposite. In analyses of binary impairment outcomes, odds ratios (ORs) >1.0 indicate that EFV users performed worse than LPV/r users, and ORs <1.0 indicate the opposite. *p* Values <0.10 are bolded