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Switching from efavirenz to rilpivirine improves sleep quality and self-perceived cognition but has no impact on neurocognitive performances: results from a randomized controlled trial

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Abstract

Background: Efavirenz (EFV) association with neurocognitive (NC) impairment is debated. Whether switching away from EFV improves NC performances is still controversial.

Methods: In a randomized open-label controlled trial, patients under effective treatment with tenofovir disoproxil-fumarate (TDF), emtricitabine (FTC) and EFV, who had altered NC assessment (Z-transformed score below -1 in ≥1 cognitive domains), depression, anxiety or low sleep-quality, were randomized 1:1 to immediate or delayed (24-weeks) switch to TDF/FTC/rilpivirine (RPV). Treatment efficacy, NC function, symptoms and quality of life were evaluated 12, 24 and 48 weeks after randomization.

Findings: 74 patients were randomized to immediate (36 patients) or delayed switch (38 patients). At baseline, 63% and 25% of patients had z-scores below -1 in ≥1 NC or 2 domains, 31.1%, 17.6% and 44.6% had significant depression or anxiety symptoms or low sleep-quality. At week 24 (primary end-point), overall NC improvement was observed, with no statistically significant differences between arms, neither considering the global z-score (between arms difference +0.1; P=0.458), nor domain-specific z-scores. Patients switching away from EFV had significant greater improvement of sleep quality index (between arms difference -1.5; P=0.011), self-reported cognitive failures (-6.2; P=0.001) and CNS symptoms score (-5; P=0.002), but not of anxiety or depression. No protocol defined virological failure, grade ≥3 lab abnormalities or drug-related serious adverse events were reported.

Conclusions: Our results do not support the hypothesis that switching to RPV improves cognitive function in patient under stable treatment with EFV. Nonetheless, improvements in neuropsychiatric symptoms, sleep quality and self-perceived cognition were observed.

Keywords: Neurocognitive impairment; neurotoxicity; Antiretroviral treatment; Atripla; efavirenz; Rilpivirine; Complera; Eviplera; toxicity; central nervous system side effects

Background

Efavirenz (EFV) has long been one of the cornerstones of combination antiretroviral treatment and one of the most prescribed antiretroviral drugs worldwide, although limited by central nervous system (CNS) side-effects. In the last 5 years, EFV-based regimens have been progressively dismissed, in favor of more tolerated alternatives.[1–3] Despite the recent changes in the guidelines, several millions of patients worldwide are still currently receiving EFV. Whether those who are not experiencing overt toxicity and whose HIV-infection is well controlled merit to switch to more modern regimens is still debatable.

Though EFV-related CNS side-effects are generally well tolerated and wane after the first weeks, some patients may still experience mild, persistent disturbances.[4–8] Even if patients may not experience such effects or get used to them, there is concerns about a possible impact of EFV on neurocognitive (NC) function. As a matter of fact, worst NC performances have been associated with EFV in some cohort studies,[9,10] but not in others.[4,11–13] In a randomized trial, antiretroviral-naïve subjects treated with EFV had a significantly smaller NC improvement compared with those treated with a zidovudine and abacavir, but not with those treated with atazanavir/ritonavir.[14] Moreover, replacement of EFV was not found to be associated with cognitive improvement in a prospective uncontrolled study.[15] By converse, in a small prospective randomized study, modest improvements in some cognitive domains (namely attention and speed of information processing) were observed. [16]

Taken all together, these results suggest that the effect of EFV discontinuation on NC performances is yet to be determined. The answer to this question is very relevant to the many patients who are still treated with EFV and have no overt CNS side-effects nor other reasons to modify their antiretroviral treatment.

Methods

Patients

The Switch from Efavirenz/Atripla to Rilpivirine (SWEAR) study is a randomized, multicenter, open-label controlled trial conducted in five sites in Italy (Monza, Milan, Genova, Brescia and Turin). All consecutive HIV-1-infected patients presenting for care between July 1st 2015 and Dec 31st 2016 were evaluated for inclusion. Eligible participants were ≥18 years old, under stable (>6 months) and well-tolerated treatment with co-formulated tenofovir disoproxil-fumarate (TDF), emtricitabine (FTC) and EFV, had confirmed HIV-RNA <50 copies/ml and ≥200 CD4+/μL. Moreover, in order to select patients who could theoretically benefit from the switch, they had to have at least one among: (i) a Z-transformed score below -1 in at least 1 out of 6 NC domains; (ii) significant depression or anxiety symptoms, defined as a score >90th percentile in Beck Depression Inventory-II (BDI-II) or Beck Anxiety Inventory (BAI); (iii) low quality of sleep, defined as Pittsburgh Sleep Quality Index (PSQI) score >5. We excluded patients with selected laboratory alterations, those with previous antiretroviral failure or past evidence of resistance-mutations and those with current alcohol or substance dependence, major psychiatric disorders, dementia, recent AIDS defining condition, ongoing or predictable need for treatment with proton pump inhibitors or other medications contraindicated with study drugs.

Written informed consent was obtained from each patient before any screening procedures. The study was approved by the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) and by the ethics committees for each site. The study was registered with the European Clinical Trial Register (EudraCT), number 2014-003419-12 and with ClinicalTrials.gov, number NCT02042001.

Study design

Eligible patients were randomized 1:1, using a permuted-block randomization list with random block sizes, to receive co-formulated TDF/FTC/RPV 245/200/25 mg, 1 tablet once-daily with food (Switch arm) or continuing co-formulated TDF/FTC/EFV 245/200/600 mg, 1 tablet once-daily at bedtime, up to week 24 (Continuation arm). After 24 weeks, also patients in the Continuation arm were switched to co-formulated TDF/FTC/RPV. The assignment sequence was generated and kept centrally, by independent staff members, not involved in other study procedures. The patients were randomized using a computer-based procedure during baseline visits, thus protecting allocation concealment.

After randomization, patients were evaluated at baseline, week 4, week 12 and every 12 weeks, thereafter. Patients in the continuation arm underwent an additional visit at week 28 (4 weeks after the switch). We assessed safety at all study visits, recording all serious and non-serious adverse events (graded according to the Division of AIDS toxicity scales) and laboratory tests including complete blood count, fasting lipid profile, blood markers of liver and kidney toxicity and urinalysis. Differential T-lymphocyte count and plasma HIV-RNA were also evaluated.

All patients had a battery of tests assessing NC performances, symptoms, depression, anxiety, quality of sleep and quality of life at screening, week 12, week 24 and week 48.

Comprehensive NC assessment explored 6 cognitive abilities (Verbal, Executive Functioning, Motor Functioning, Speed of Info Processing, Memory/Delay Recall and Selective Attention) using the following tests: Rey auditory verbal learning test (immediate and delayed recall), Trail making test A and B, verbal fluency test (by word and by category), attentive matrices test and Grooved Peg-board test. Alternate version of the verbal learning and verbal fluency tests were used at different time-points, in order to decrease the learning effect due to frequent testing. Raw results were compared with appropriate normative data of

reference Italian populations, comparable for age, gender and education (where appropriate), and transformed into Z-scores.

The PSQI, BDI-II and BAI tests were administered to investigate quality of sleep, depression and anxiety symptoms. A questionnaire specifically designed to assess CNS symptoms, derived from the literature, was used.[11] Each CNS-related symptom was rated on a Likert scale, according to its intensity, and given a score from 0 ("Not at all") to 4 ("Extremely"). The sum of all single symptom scores returned the total symptom score. The Cognitive Failures Questionnaire (CFQ) was used to explore patients self-perceived cognition, measured as the frequency with which they experienced cognitive failures, such as slips and errors of perception, memory or motor functioning in the everyday life. It was scored as the sum of the ratings (from 0 "Never" to 4 "Very Often") of 25 individual items, yielding a score from 0-100.[17,18] Quality of life (QoL) was measured using MOS-HIV questionnaire and expressed as Mental Health Score (MHS) and Physical Health Score (PHS).

Preference of Medication (POM) questionnaire was administered at W4, W12 and W24 (Switch arm) or W28, W36 and W48 (Continuation arm). Treatment adherence was measured at all visits using a visual analogue scale (VAS), ranging from 0 to 100.

Outcomes

The primary study end-point was the proportion of patients with NC improvement in at least 1 domain altered at baseline and/or improvement of depression, anxiety or sleep quality at week 24. Secondary end-points were global and domain specific NC Z-scores changes and changes in PSQI, BDI-II and BAI scores at weeks 24 and 48. Secondary efficacy end-points were the proportion of patients with HIV-RNA <50 copies/ml and changes in CD4 T-cell counts after 24 and 48 weeks, in the intention-to-treat population. Secondary safety endpoint included the proportion of patients discontinuing the study treatment due to side-effects or

developing grade ≥3 adverse events. Health-related endpoints were patient reported outcomes on POM questionnaire, symptom questionnaire, CFQ and MOS-HIV at weeks 24 and 48.

Statistical analysis

We hypothesized that switching from EFV to RPV would have led to significant reduction in neuropsychological disorders and NC impairment. We proposed a sample size of 82 patients (41 per arm) to provide an 80% power with an alpha-error of 0.05, considering the Fisher exact test, to demonstrate a difference in the proportion of patients with NC or neuropsychological improvement, assuming an improvement in ≤5% of patients continuing EFV-based treatment and ≥30% of those switching to TDF/FTC/RPV. The factual group sizes were slightly smaller than the targeted numbers, but still enough to achieve a 76% power leaving the other parameters unchanged.

The composite primary end-point was analyzed using Fisher exact test. The mean change in the Z-scores of the NC performance tests during follow-up was calculated and compared between treatment arms using the T-test and visualized through boxplots. Similar procedures were adopted to compare PSQI, CNS symptoms, CFQ, anxiety, depression and quality of life scores. The proportions of patients with NC impairment, defined as at least NC domains with a z-score ≤ -1, were compared using the McNemar test. Paired T-test was used to evaluate the mean change in laboratory parameters in the two treatment arms.

Results

Patients

Among 124 screened patients, 74 were enrolled and randomized (36 to the Switch and 38 to the Continuation Arm). Patients disposition and reasons for screening failure or premature discontinuation are shown in Figure 1. In the presented analysis (intention-to-treat), one patient randomized in the Continuation arm but incorrectly switched to TDF/FTC/RPV was

included in the Continuation Arm, as randomized. A supplementary analysis with the patient included in the Switch Arm (as treated) did not significantly change the results.

Patients enrolled in the study were mostly male (89%), with a mean age of 47 (standard deviation [SD]:11) years. They had been treated with TDF/FTC/EFV for a mean of 5 (SD:2) years and their mean CD4 count was 746 (SD:261) cells/μL. These and other features at study enrollment are shown in Table 1. All characteristics were well balanced between the two arms, but nadir CD4+ T-cell count, slightly higher among patients in the Switch Arm (337 *versus* 257 cells/μL, P=0.045).

Patients reported high levels of adherence to TDF/FTC/EFV at baseline (mean VAS score 98.6% SD:3.8) and maintained high adherence throughout the trial in both arms.

Treatment efficacy and safety

The proportion of patients with HIV-RNA <50 copies/ml at weeks 24 and 48 was 97.2% and 97.1% in the Switch arm and 97.2% and 100% in the Continuation arm, respectively. No protocol defined virological failure occurred during the trial. However, one patient discontinued RPV at week 24, due to persisting detectable HIVRNA (although, always <200 cp/ml). No treatment emergent resistance was observed and the patient regained HIV-RNA suppression after switch to abacavir/lamivudine/dolutegravir.

At week 24, CD4+ T-cell counts did not significantly change in either arm (Mean change: +27 cells/μL; 95%CI -40 to +93; P=0.421 in the Switch arm and -21 cells/in; 95%CI -80 to +38; P=0.474 in the Continuation arm). Similar results were observed at week 48. No cases of AIDS-defining events or signs of HIV clinical progression were reported. Two serious adverse events occurred during the study (1 acute hepatitis A in the Continuation

arm and 1 depression worsening in the Switch arm), both of which were deemed not to be related to study drugs and resolved by the end of the trial. Apart from liver tests in the patient with acute hepatitis, no grade 3 laboratory abnormalities were reported. A significant reduction of eGFR by week 24 was observed in the Switch Arm (-9.4 ml/min; 95%CI -13.1 to -5.6; P<0.001) but not in the Continuation Arm (-1.5 ml/min; 95%CI -5.1 to +2.2; P=0.649). No patient developed Fanconi syndrome or signs of new-onset acute tubular injury. Total cholesterol and triglycerides significantly decreased among patients in the Switch Arm (-27 mg/dl; 95%CI -34 to -20; P<0.001 and -16 mg/dl; 95%CI -31 to -2.7; P<0.001, respectively) but not among those in the Continuation Arm.

Neurocognitive function, depression, anxiety and quality of sleep

The mean patient global z-score at baseline was -0.02 (SD:0.78) but 63% of the patients had z-scores below -1 in ≥1 domain and 25% in ≥2 domains. Memory (mean z-score -0.66, SD:0.88) and motor functioning (mean z-score -0.76, SD:1.84) were more commonly compromised. The proportion of patient with significant anxiety or depression was 17.6% and 31.1%, respectively. Mean (SD) PSQI score was 5.3 (3.5) and 44.6% of patients had a PSQI score >5.

At week 24, 68.6% and 50% improved NC performances, depression, anxiety or sleep quality (study primary end-point) in the Switch and Continuation arm, respectively (P=0.149). Although NC functioning significantly improved in both arms (+0.38 [95%CI 0.2-0.56] and +0.28 [95%CI 0.08-0.49]) no differences between arms were found, either considering global or domain-specific z-scores (Figure 2). The proportion of patients with ≧1 NC domain with z-score below -1 decreased to 40% and 47.2% in the Switch and Continuation arm, respectively, with no statistically significant difference between arms (P=0.674).

Patients with significant depression and anxiety reduced over time, but, again, there was no difference comparing the two arms (14.8% vs. 17.1%, P=1 and 0% vs. 8.3%, P=0.25). Regarding quality of sleep, PSQI score significantly improved in the Switch arm (mean change -1.6; 95%CI -2.5 to -0.7), while it remained unchanged in the Continuation arm (mean change -0.1; 95%CI -0.8 to +0.6).

Between weeks 24 and 48, no further significant changes in NC function, BAI, BDI and PSQI scores were observed.

Central nervous symptoms, perceived cognition and other health-related outcomes

At screening, one-third (35.5%) of the patients reported CNS-symptoms of significant intensity, the most common of which were dream alterations (30.8%), restless sleep or insomnia (22%) and drowsiness (7.3%). Only 5.4% of patients reported no CNS symptoms at all. The median CNS symptom score was 9 (IQR: 2-17). At week 24, patients switching away from EFV had a significant improvement in CNS symptom score (mean score change -7; 95%CI -9 to -4). Conversely, the score did not significantly change among those maintained on EFV treatment (-2; 95%C -5 to +1).

At screening, the median CFQ score was 24 (IQR: 13-36). Although the score improved in both arms at week 24, the improvement was significantly higher among patients switching to RPV (mean change -9; 95%CI -12 to -6) than among those maintaining EFV (mean change -4; 95%CI -7 to -1; Switch *versus* Continuation Arm P=0.018). (Table 2)

When questioned about their preference of medication, most of patients (65.7%) preferred TDF/FTC/RPV over TDF/FTC/EFV but only 31.3% of them considered it to be more convenient.

Quality of life was measured using the MOS-HIV questionnaire. After 24 weeks of observation, no significant changes were found in either arms regarding the Physical Health Score, whereas a slight improvement in the Mental Health Score was found among patients in the Switch arm (mean change +3.9; 95%CI +0.5 to +7.3) but not among those in the Continuation arm (mean change +0.9; 95%CI -1.4 to +3.1).

Discussion

Efavirenz plus tenofovir and emtricitabine (or lamivudine) has been, for over a decade, the recommended regimen for first-line antiretroviral treatment and, probably, the most commonly used regimen worldwide. Although its use has progressively reduced over the last years, many patients, particularly in low-income settings, are still receiving an efavirenz-based treatment. The need to change it, moving to efavirenz-sparing regimens, is debated.[19] As a matter of fact, despite a well-established long-term efficacy, it has been suggested that efavirenz can continue to exert a neurotoxic effect and impair patient neurocognitive function, even in absence of clearly reported symptoms.[20,21] Whether switching away from EFV can improve patients NC function, however, is yet to be demonstrated.

In our population of patients under stable treatment with TDF/FTC/EFV, switching to TDF/FTC/RPV was not associated with a significant benefit in terms of NC function. Although NC performances improved overall in the study population, we did not find any significant difference between patients switching to TDF/FTC/RPV and those maintaining TDF/FTC/EFV. Of note, the two arms did not differ in any of the explored NC domains.

The first, more obvious, interpretation for these findings is that EFV does not affect NC function. Whether EFV can actually impair NC function is, in facts, uncertain. Early studies failed to demonstrate a detrimental impact of EFV on NC performances, either in the short or in the long term.[4,22] Although a few studies suggested that patients treated with EFV have worse NC performances than others,[9,10][14] such studies have been contradicted by other observations.[12,13]

There is also a second possible explanation. Studies on animal models suggested that some antiretrovirals, including but not limited to EFV, have the potential to damage neurons, inducing mitochondrial dysfunction or cell metabolism alterations.[23,24] It cannot be excluded that, if EFV exerts a toxic effect on neuronal cells, such an effect could need more than 24 weeks to reverse (or even be non-reversible).

Regardless of the explanation, our results show that switching from EFV to RPV was not associated with NC improvement and suggest that the decision to discontinue TDF/FTC/EFV among otherwise healthy subjects should not be driven by the expectation of a cognitive improvement following the switch, because it is unlikely to occur. It should be noted, however, that although we tried to include patients with some form of neurocognitive or neuropsychological impairment who could have had benefit from EFV discontinuation, only 25% of the recruited patients had mild neurocognitive disease/asymptomatic neurocognitive impairment, according to the Frascati criteria.[25] Therefore, we can not exclude that more compromised patients can still benefit from EFV discontinuation.

Our findings are in line with a previous, smaller study, in which EFV withdrawal did not result in significant modification of neurocognitive function in 16 HIV-infected patients.[15] Conversely, Hakkers and colleagues reported a modest improvement in attention and speed of information processing among patients who switched to TDF/FTC/RPV, compared with

those who continued TDF/FTC/EFV.[16] When we examined the individual effect of EFV discontinuation on each NC domain, however, we could not confirm their results nor did we find any significant difference in any other explored domain. Since our study have a longer follow-up and a larger sample size with a larger control group, we believe our results to be more solid and reliable. In addition, unlike in ours, patients in the Hakkers study were included regardless of their baseline NC function or neuropsychological assessment. Therefore, the finding of a slight NC improvement among patients who had largely normal NC performances at baseline is unlikely to have any clinical relevance.

It cannot be excluded, however, that selected patients can still benefit from EFV discontinuation. It has been recently suggested that higher EFV plasma concentrations are associated with NC impairment.[26] Whether EFV discontinuation or dose reduction in those with high plasma concentration brings to NC improvement merits further investigation.

Notwithstanding the lack of objective improvement in NC function, switching away from EFV was associated with a significant reduction in self-reported cognitive failures in the everyday life, which paralleled a significant reduction of CNS symptoms and an improvement in the quality of sleep. Subjective cognitive impairment, even in presence of normal performance on objective measures of cognition and no impairment of daily functioning, can be disturbing for patients and lead to anger, stress or fear of dementia. Although it is unclear whether some of the patients presenting with subjective NC complaints have already a subclinical cognitive decline, our study showed that a symptomatic relief can be obtained by switching from EFV to RPV, even if patients had already received EFV for a long time. In addition, an improvement in the Mental Health Score was observed after the switch, supporting the usefulness of treatment modification in patients who still report mild CNS symptoms during EFV. As a matter of fact, these symptoms, even if tolerated for years, can still cause distress and interfere with patient quality of life.[5]

In our study, switching to TDF/FTC/RPV demonstrated to be safe and effective for as long as 48 weeks. Such strategy, can be considered a valid alternative to TDF/FTC/EFV in virologically controlled patients and with no evidence of previous virological failure. In addition, we confirmed that RPV has a favourable metabolic profile, compared with EFV. Both cholesterol and triglyceride significantly decreased in patients switching away from EFV, thus confirming that RPV can be an option among patients with dyslipidemia.

Our study has some limitations that merit to be acknowledged. First, the study was open-label and this could limit our ability to interpret changes in self-reported outcomes. Second, patients underwent repeated NC testing during the trial. Although we used alternate forms of the tests, such repeated testing translated into an overall improvement of patient NC performances, which was mainly due to a practice effect rather than to a true change in NC function. Practice effects are confounders of nearly all longitudinal studies on NC function. In our study, however, the use of a randomly selected control group allowed to weight their impact on the study results. Third, we failed to enroll the targeted number of patients, basing on the original sample size calculation. However, the group sizes were only slightly smaller than that originally anticipated and this only marginally reduced the power of the analysis. Given the small difference detected (<20%), we can exclude that an actual effect greater or equal to the minimum clinically relevant difference of 25% (as postulated during the study planning) was missed by our analysis. Fourth, the patients enrolled in the study were exposed to EFV for a very long time (more than 5 years, on average). It is therefore possible that some patients with NC decline could have been already switched to other alternative regimens, thus reducing our ability to demonstrate a beneficial effect of EFV discontinuation.

In conclusion, we found no evidence that switching to RPV improves the NC function of patients under long-term treatment with TDF/FTC/EFV. However, a beneficial effect on neuropsychiatric symptoms, quality of sleep and self-perceived cognition was observed.

Single tablet combination including RPV can be considered a valid alternative to EFV-containing regimens, particularly among patients who have self-perceived cognitive impairment or CNS side-effects, even if mild and tolerated for a long time.

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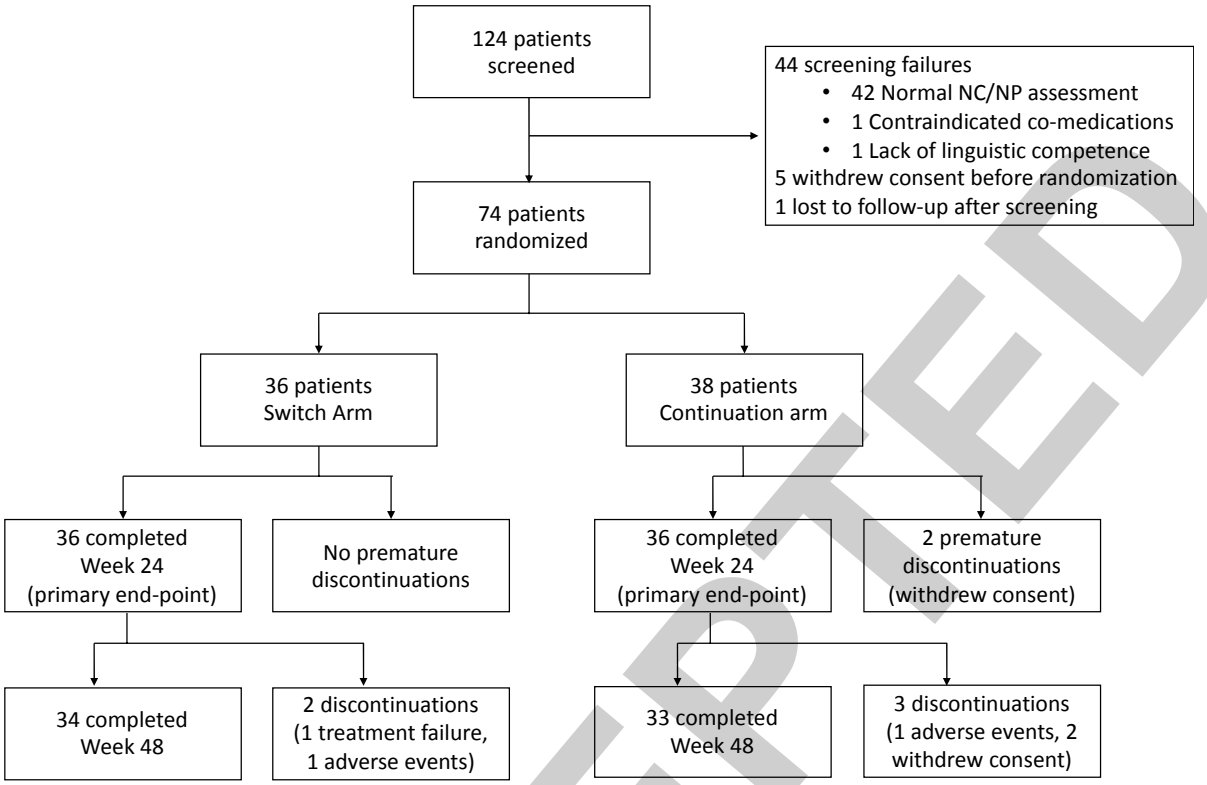
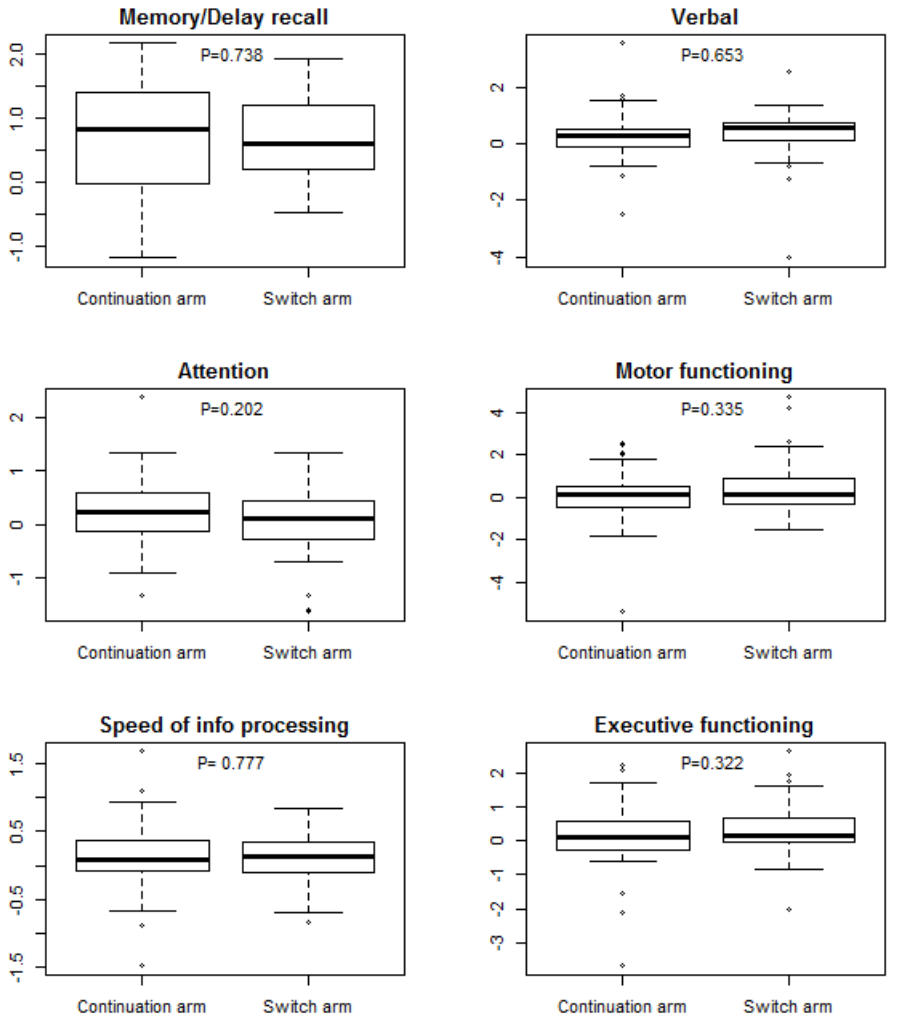
Figure 1: Patients disposition and trial profile



NC/NP = neurocognitive/neuropsychiatric

One patient randomized in the Continuation arm was incorrectly switched to tenofovir/emtricitabine/rilpivirine upon enrollment. In the presented analysis (intention-to-treat) his/her data are included in the Continuation Arm, as randomized. A supplementary analysis with the patient included in the Switch Arm (as treated) did not significantly change the results.

Figure 2: 24-weeks changes in domain-specific z-scores in the Continuation and in the Switch Arms.



Note to figure: All P show t-test comparison between z-score change since baseline in the Continuation versus the Switch arm

Table 1: Patients characteristics at enrollment.

Characteristic	Switch Arm (N=36)	Continuation Arm (N=38)	p	Overall (N=74)
Male gender, n (%)	31 (86.1)	35 (92.1)	0.474	66 (89.2)
Italian born, n (%)	36 (100.0)	34 (89.5)	0.115	70 (94.6)
Education, n (%)			0.328	
None	1 (2.8)	0 (0)		1 (1.4)
Basic school degree	0 (0)	2 (5.3)		2 (2.7)
Secondary school degree	22 (61.1)	20 (52.6)		42 (56.8)
High school degree	8 (22.2)	12 (31.6)		19 (25.7)
University degree	7 (22.2)	5 (13.2)		13 (13.5)
Age (years), mean (sd)	47.4 (10.3)	47.2 (11.4)	0.927	47.3 (10.8)
Hep C infection, n (%)	2 (5.7)	1 (2.8)	0.614	3 (4.2)
Hep B infection, n (%)	3 (8.3)	5 (13.2)	0.712	8 (10.8)
CD4+ nadir (cells/μL), mean (sd)	257 (139)	337 (193)	0.045	299 (173)
CDC clinical category C, n (%)	12 (33.3)	8 (21.1)	0.298	20 (27.0)
Risk factor for HIV, n (%)			0.263	
Omosexual intercourses	7 (19.4)	14 (36.8)		21 (28.4)
Heterosexual intercourses	19 (52.8)	16 (42.1)		35 (47.3)
Intravenous Drug Use	2 (5.6)	4 (10.5)		6 (8.1)
Other	1 (2.8)	0 (0.0)		1 (1.4)
Not reported	7 (19.4)	4 (10.5)		11 (14.9)
Time since HIV diagnosis (years), mean (sd)	10.5 (6.7)	11.1 (7.9)	0.743	10.8 (7.3)
Time under TDF/FTC/EFV (years), mean (sd)	4.9 (2.4)	5.1 (2.0)	0.731	5 (2.2)
BSL CD4+ count (cells/μL), mean (sd)	690 (271)	798 (243)	0.073	746 (261)

BSL CD4/CD8 ratio, mean (sd)	0.96 (0.44)	0.96 (0.39)	0.994	0.96 (0.41)
BSL HIV-RNA <50 copies/ml, n (%)	36 (100)	38 (100)	NA	74 (100)
BSL creatinine (mg/dl), mean (sd)	0.90 (0.15)	0.89 (0.12)	0.672	0.90 (0.14)
BSL ALT (UI/ml), mean (sd)	28 (16)	30 (19)	0.646	29 (18)
BSL AST (UI/ml), mean (sd)	26 (9)	26 (18)	0.99	26 (14)
BSL triglyceride (mg/dl), mean (sd)	107 (52)	121 (59)	0.26	114 (55)
BSL total cholesterol (mg/dl), mean (sd)	186 (25)	184 (35)	0.799	185 (30)
BSL HDL cholesterol (mg/dl), mean (sd)	53 (16)	50 (11)	0.416	51 (14)
BSL LDL cholesterol, mean (sd)	112 (23)	111 (30)	0.913	111 (26)
Visual analog scale of adherence to TDF/FTC/EFV treatment, mean (sd)	99.3 (2.3)	97.9 (4.8)	0.12	98.6 (3.8)
Z-score ≤ -1 in at least 1 NC domain, n (%)	22 (61.1)	25 (65.8)	0.676	47 (63.5)
Low sleep quality (i.e., PSQI score >5), n (%)	21 (58.3)	12 (31.6)	0.035	33 (44.6)
BDI-II score >90th percentile, n (%)	12 (33.3)	11 (28.9)	0.803	23 (31.1)
BAI score >90th percentile, n (%)	5 (13.9)	8 (21.1)	0.545	13 (17.6)

List of abbreviations: BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory-II; BSL, baseline; CD, cluster of differentiation; CDC, centers for disease control; HDL, high-density lipoprotein; Hep, hepatitis; LDL, low-density lipoprotein; sd, standard deviation; NC, neurocognitive; PSQI, Pittsburgh Sleep Quality Index; TDF/FTC/EFV, tenofovir disoproxil fumarate/emtricitabine/efavirenz.

Table 2: Total and domain-specific Z-scores and symptom scores across 24 weeks of observation, grouped by randomization arm.

	Treatment arm	Baseline mean(sd)	Week 12 mean(sd)	Week 24 mean(sd)	Change week 24 – baseline (95% CI)	P *A vs. B*
Neurocognitive test results (z-scores)						
Memory	A (Switch)	-0.64 (0.92)	-0.48 (1.2)	0.06 (1.07)	0.68 (0.44;0.92)	0.738
	B (Continuation)	-0.69 (0.86)	-0.56 (1.07)	0 (1.05)	0.74 (0.46;1.03)	
Language	A (Switch)	0.62 (1.12)	1.05 (1.13)	1.02 (1.39)	0.38 (0;0.75)	0.653
	B (Continuation)	0.69 (1.27)	0.93 (1.21)	0.86 (1.25)	0.26 (-0.06;0.59)	
Attention	A (Switch)	-0.05 (0.9)	-0.1 (0.8)	0.05 (0.79)	0.03 (-0.2;0.26)	0.202
	B (Continuation)	0.12 (0.88)	0.17 (1.01)	0.34 (0.65)	0.23 (0.01;0.45)	
Motor	A (Switch)	-0.62 (1.99)	-0.35 (1.57)	-0.18 (1.52)	0.46 (0;0.92)	0.335
	B (Continuation)	-0.89 (1.71)	-0.92 (1.53)	-0.77 (1.8)	0.15 (-0.31;0.61)	
Speed	A (Switch)	0.96 (0.36)	0.96 (0.56)	1.08 (0.4)	0.12 (-0.01;0.25)	0.806
	B (Continuation)	0.76 (0.6)	0.89 (0.53)	0.89 (0.51)	0.15 (-0.04;0.33)	
Executive	A (Switch)	0.26 (1.08)	0.48 (1.09)	0.55 (0.8)	0.31 (0.02;0.61)	0.322
	B (Continuation)	0.23 (1.06)	0.08 (2)	0.27 (1.59)	0.09 (-0.27;0.44)	
Global	A (Switch)	0.01 (0.84)	0.22 (0.78)	0.39 (0.70)	0.38 (0.2;0.56)	0.458
	B (Continuation)	-0.04 (0.73)	0.01 (0.86)	0.17 (0.83)	0.28 (0.08;0.49)	
Symptom scores						
PSQI	A (Switch)	6.03 (3.24)	4.75 (2.52)	4.44 (2.43)	-1.58 (-2.44;-0.72)	0.008
	B (Continuation)	4.71 (3.68)	4.46 (3.73)	4.61 (3.5)	-0.08 (-0.8;0.64)	
CNS	A (Switch)	12.69 (9.48)	6.06 (4.59)	6.19 (5.1)	-6.5 (-9.11;-3.89)	0.019
	B (Continuation)	10.82 (12.41)	9.71 (11.9)	8.58 (10.98)	-2.24 (-4.72;0.25)	
CFQ	A (Switch)	16.86 (11.11)	11.11 (7.34)	8.06 (5.67)	-8.81 (-11.81;-5.8)	0.018
	B (Continuation)	14.53 (14.82)	13.71 (14.08)	10.74 (12.08)	-3.79 (-6.75;-0.83)	

List of abbreviations: CFQ, cognitive failure questionnaire; CNS, central nervous system; PSQI, Pittsburgh Sleep Quality Index; sd, standard deviation.