Objective and Subjective Improvement of Cognition After Discontinuing Efavirenz in Asymptomatic Patients: A Randomized Controlled Trial

Charlotte S. Hakkers, MD, Joop E. Arends, MD, PhD,* Guido E. van den Berk, MD, PhD,† Monique H. M. Ensing, MSc,‡ Imke Hooijenga, BSc,† Matthijs Vink, PhD,§ Martine J. E. van Zandvoort, PhD,‡ and Andy I. M. Hoepelman, MD, PhD**

Background: Efavirenz is well known for its clinical cognitive side effects. Even asymptomatic patients who switch for other reasons than neurocognitive complaints have reported a subjective improvement in cognitive functioning after discontinuing efavirenz. The aim of this study was to assess the effect on cognition of switching Atripla (TDF/FTC/EFV) to Eviplera (TDF/FTC/RPV), hypothesizing an improvement when discontinuing efavirenz.

Setting: A randomized controlled design with a highly comparable comparator drug was used to minimize bias and to differentiate drug versus learning effects. An extensive sensitive neuropsychological assessment (NPA) was used to detect subtle changes.

Methods: Virologically suppressed, cognitively asymptomatic male HIV-infected patients on Atripla were included and randomized (2:1) to switch to Eviplera (switch group) or continue on Atripla (control group) for 12 weeks. At baseline and week 12, patients underwent an extensive NPA.

Results: Fourteen control and 34 switch subjects completed the study. There were no differences at baseline. Group analysis demonstrated a significantly better improvement for the switch group on the domains attention ($P = 0.041$) and speed of information processing ($P = 0.014$). Normative comparison analyses showed that 5 of the 34 patients who switched (15%) improved on NPA score as compared to the control group. Interestingly, subjective improvement after discontinuing efavirenz made 74% of the switch group chose for a regime without efavirenz after study completion.

Conclusions: Switching from Atripla to Eviplera resulted in objective cognitive improvement on the group level in cognitively asymptomatic patients. Discrepancies in objective and subjective cognitive complaints make it challenging to identify patients who would benefit from discontinuing efavirenz.

Key Words: HIV, cognition, efavirenz, cART, asymptomatic, NCI, toxicity

(*J Acquir Immune Defic Syndr* 2019;80:e14–e22)

INTRODUCTION

Neurocognitive impairment (NCI) is a frequently occurring complication of HIV infection, with a negative effect on quality of life, participation, and drug adherence.[1–6] The different presentations of NCI in HIV infection are summarized in the term HIV-Associated Neurocognitive Disorders (HAND), which is conventionally diagnosed with a neuropsychological assessment (NPA). The etiology of NCI in HIV is currently not yet fully elucidated. Evidence has pointed in the direction of an effect of the virus itself or an effect of immune activation, but this does not explain the fact that HIV patients who are being adequately treated suffer from NCI as well.[6] Even in the era of combination antiretroviral therapy (cART), HAND prevalence remains as high as 50%, and around 40% of patients in outpatient settings report subjective neurocognitive complaints.[4,7] Recently, a study found a beneficial effect of discontinuing cART on cognition, and additionally, several studies have suggested a direct negative effect of antiretroviral treatment on cognitive function.[8–10]

When investigating neurocognitive toxicity of cART, a good example is efavirenz, a drug that, although being one of the most frequently used antiretrovirals worldwide, has been associated with considerable neurocognitive complaints.[11–14] This is mostly visible in patients who experience evident side effects and subsequently quickly change their

Received for publication June 25, 2018; accepted September 10, 2018.

From the *Department of Internal Medicine, Section Infectious Diseases, University Medical Center Utrecht (UMCU), Utrecht University, Utrecht, the Netherlands; †Department of Infectious Diseases, OLVG Hospital, Amsterdam, the Netherlands; ‡Department of Neuropsychology, University Medical Center Utrecht (UMCU), Utrecht, the Netherlands; and §Department of Developmental and Experimental Psychology, Utrecht University, Utrecht, the Netherlands.

Supported by an unrestricted grant from Gilead.

Abstract accepted for presentation at AIDS 2018; July 24, 2018; Amsterdam, the Netherlands.

The authors have no conflicts of interest to disclose.

C.S.H.: data collection, statistical analysis, and writing manuscript. J.E.A.: study design, statistical analysis, and writing manuscript. G.E.B.: data collection and writing manuscript. M.H.M.E.: data collection and writing manuscript. I.H.: data collection. M.V.: statistical analysis and writing manuscript. M.J.E.Z.: study design, data collection, statistical analysis, and writing manuscript. A.I.M.H.: study design, data collection, and writing manuscript.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

Correspondence to: Charlotte Hakkers, MD, Department of Internal Medicine and Infectious Diseases, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, the Netherlands (e-mail: c.s.hakkers@umcutrecht.nl).

regimen.[9] This toxicity profile, along with the emergence of newer antiretrovirals, has resulted in a decline in Efavirenz' popularity in the Western world. However, efavirenz is still very much the drug of first choice in low income countries.[15,16] Furthermore, the most popular combination of efavirenz with other antiretrovirals in a single-tablet regime (STR), namely Atripla, has recently become generically available, making it a very attractive regimen for economical regions. Moreover, a substantial group of patients on efavirenz do not report cognitive complaints, ie, cognitively asymptomatic patients. Anecdotal evidence has suggested that the negative effect on cognition even in these "asymptomatic" patients seems reversible. That is, studies in asymptomatic patients did show an improvement in cognition, the amount of adverse events, and drug adherence after discontinuing efavirenz.[10,17] In addition, from clinical experience in our outpatient clinic, we have learned that patients often develop a subjective cognitive improvement after switching efavirenz for other reasons than cognitive side effects. Nevertheless, the effect of efavirenz in asymptomatic patients has not yet been properly studied. There are only 2 studies in asymptomatic patients investigating the effect of switching from an efavirenz-containing regime by means of an NPA.[18,19] These studies are however limited by their design (ie, observational or retrospective and no comparative control group), sample sizes, and/or measurements of cognition.

When studying cognition, the choice of the NPA used is very important. For example, HAND is diagnosed by an NPA measuring at least 5 cognitive domains with preferably at least 2 subtests per domain.[20] Because the current study focuses on asymptomatic patients, it is important to use a sensitive NPA that is not so much focused on impairment but on performance.[21] This can be accomplished with subtests designed to pick up subtle changes within the higher ranges of measured cognition. This is especially important when investigating (long-term) cART toxicity, seeing as patients with subtle complaints usually stay on their regime, rather than switching to a different regime altogether.

Given the attributed effects of efavirenz on cognition, the hypothesis of this study is that discontinuation of efavirenz leads to measurable improvement in neurocognitive functioning. The aim of this study is to investigate the effect of discontinuing efavirenz in stable, asymptomatic HIV patients, using an extensive and sensitive NPA together with inclusion of a control group.

METHODS

Participants

The ESCAPE (Effect of SwitChing AtriPla to Eviplera on neurocognitive and emotional functioning) study ran from May 2015 to December 2016. Stable HIV-infected patients on Atripla were recruited from the outpatient department of a large academic HIV treatment center (UMC Utrecht) and a large peripheral HIV treatment center (OLVG) in the Netherlands. To ensure a homogeneous study group, only patients on tenofovir/emtricitabine/efavirenz (Atripla) at time of inclusion were asked to participate. Patients were eligible if they were male, between 25 and 50 years old, were on Atripla for at least 6 months with an undetectable viral load on the last visit before inclusion, were fluent in Dutch, and without any subjective cognitive complaints in the past year. Exclusion criteria were: having active or past central nervous system opportunistic infections, active psychiatric of neurologic disorders, a history or evidence of alcohol or drug abuse, assessed with the Drug Abuse Screening Test (DAST-10), and/or anatomical abnormalities on a magnetic resonance imaging (MRI)-scan of the brain.[22]

After being screened for inclusion and exclusion criteria and receiving complete information on the study procedures, all patients signed written informed consent. The study was performed according to the Declaration of Helsinki,[23] was reviewed and approved by the medical ethical board of the University Medical Center Utrecht, and was registered at clinicaltrials.gov under number NCT02308332.

Study Design

Patients on Atripla were randomized to the switch group (S; Eviplera, ie, tenofovir/emtricitabine/rilpivirine) or the control group (C; continuing on Atripla) with an S:C ratio of 2:1. We chose to put the switch group on Eviplera because it is a STR like Atripla, with the same backbone (emtricitabine/tenofovir) and with a third agent within the same drug class of nonnucleoside reverse transcriptase inhibitors. One of the differences between the regimes is the dietary instructions of Eviplera, which has to be taken with a substantial meal (390 kcal and 12 g of fat). This, however, means patients experience more stringent lifestyle rules with Eviplera, with dietary consequences and a more strict regularity in timing and size of the main meal of the day.

Patients in both groups underwent study-related procedures at baseline and week 12 including an extensive NPA together with measurements of HIV-RNA loads and CD4 cell counts, and an MRI scan of the brain. In addition, plasma concentrations of efavirenz for all patients at baseline and either efavirenz or rilpivirine concentrations on week 12 depending on the switch or control group were determined. Finally, patients filled out questionnaires on quality of life, participation, and mood. As planned, patients in the switch group were seen at weeks 2 and 4 after the switch, to check for Eviplera side effects and to perform routine laboratory tests. After completion of the study, patients were given the explicit choice to either go back to their prestudy regime, remain on Eviplera, or switch to a different cART regime all together.

NPA

The NPA was conducted by a trained neuropsychologist (M.H.M.E.) and interpreted by a senior neuropsychologist (M.J.E.v.Z.), who were both blinded for treatment allocation. Afterward, data were further analyzed by the trial physician (C.S.H.).

The NPA comprised 16 subtests, testing for 7 cognitive domains. Because the ESCAPE study group consisted of asymptomatic patients, we specifically chose NPA tasks that

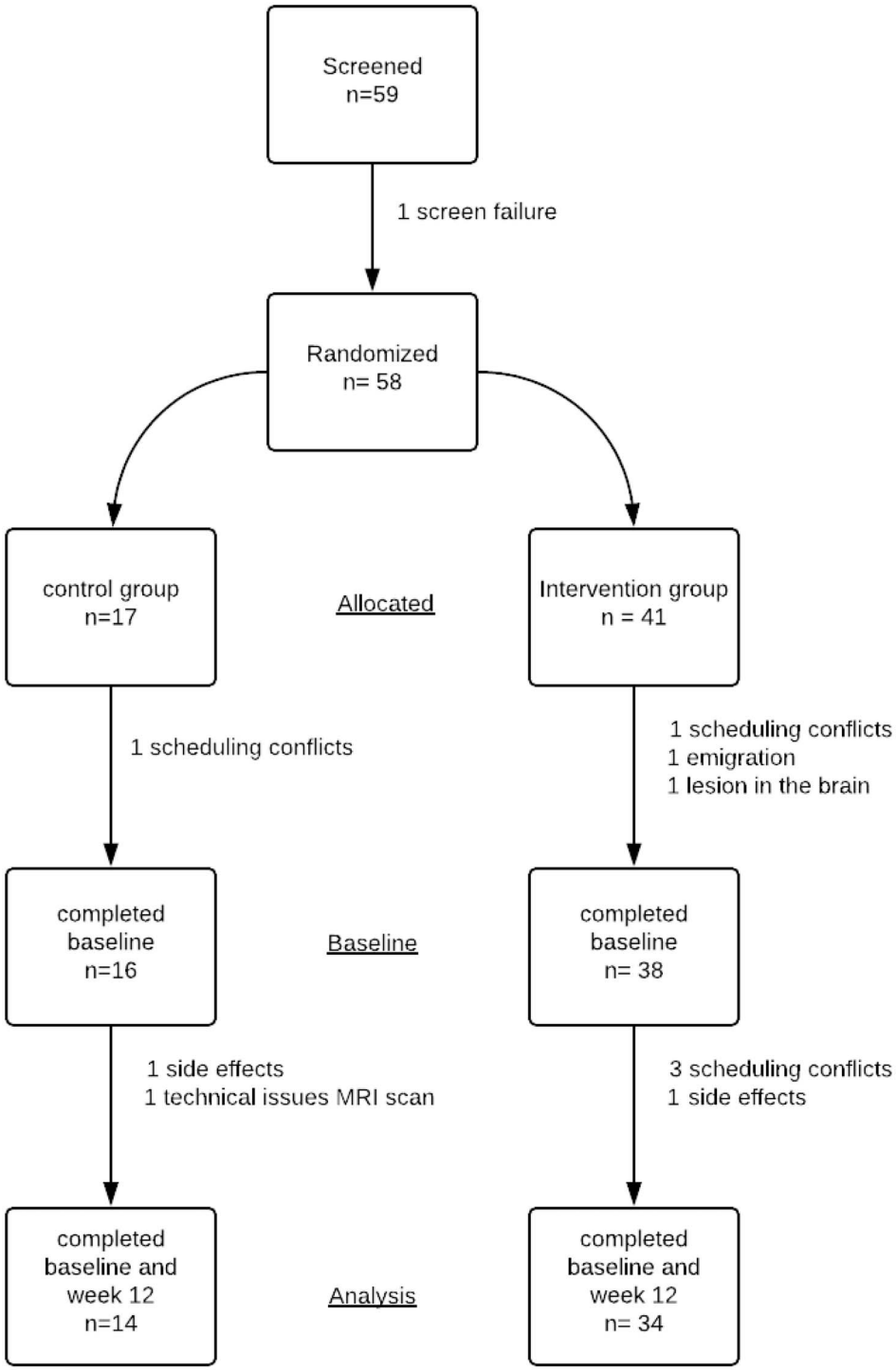

FIGURE 1. Inclusion flowchart.

can detect subtle changes. This means we focused on those tasks that are not only limited to detect cognitive impairment, but that can also chart performance without a ceiling effect; ie., tests without a predefined maximum or timed tests. The domains tested were language, learning and memory, executive functioning, attention/working memory, speed of information processing, and psychomotor speed. The subtests and their accompanying domains are given as Supplemental Digital Content 1, http://links.lww.com/QAI/B224. To control for test–retest effects, alternate test versions were used for the week-12 NPA. Dutch age- and education level–adjusted normative data were used to transform raw test scores into standardized z-scores to allow for further comparison between tests and domains. Cognitive domain scores were calculated by averaging the Z-scores of the different tests per domain, and a composite Z-score was calculated by

averaging all tests' Z-score. The change (improvement or worsening) of these domain and composite Z-scores in both groups were used to assess the effects of discontinuing efavirenz.

Questionnaires

Patients filled out questionnaires at baseline and at follow-up including the Short-Form Health Survey (SF-36) to investigate quality of life. The SF-36 is a survey constructed for self-administration made up by 36 items on quality of life, divided into 8 sections. It has been proven to be a practical, reliable, and valid instrument for use in chronically ill patients.[24,25] An important aspect of quality of life is how well an individual can function in society, eg, having a payed job, being able to interact with others, and the ability to run a household and practice self-care. This concept is also called participation. In this study, participation was measured using the Utrecht Scale for Evaluation of clinical Revalidation–Participation (USER-P), a brief well-validated instrument to rate objective and subjective participation consisting of 31 items on 3 scales: frequency, restrictions, and satisfaction. Outcomes were measured on a scale from 0 to 100 (most-positive outcome). The Hospital Anxiety and Depression Scale (HADS) was filled out to examine mood complaints. The HADS is a self-report screening scale developed to indicate the presence of anxiety and depressive states. It comprises a 7-item scale with a maximum of 21 points. A score of 11 points or more indicates a probable mood disorder. Furthermore, 4 short forms from the Patient-Reported Outcome Measurement Information System (PROMIS) were used (see http://www.assessmentcenter.net and http://www.dutchflemishpromis.nl). PROMIS questionnaires, or short forms, are a valid and reliable measurement system to measure patient-reported health outcomes. By using a dynamic system of item banks, multiple aspects of health and well-being can be tested. In this study, the short forms for anxiety, depression, sleep disturbances, and satisfaction with social roles and activities were used. The raw scores of the PROMIS short forms were transformed into T-scores with a mean of 50 and a SD of 10.

TABLE 1. Table of Baseline Patient Characteristics

	Control (16)	Intervention (38)	*P*
Age	41.6 (6.1)	41.3 (6.7)	0.76
CD4	699.3 (200.4)	665.4 (238.8)	0.91
Years of education	16.8 (0.8)	16.2 (1.7)	0.18
Education level Verhage*	5.8 (0.8)	5.5 (0.86)	0.95
CD4 nadir	263.3 (118.6)	293.4 (157.0)	0.38
Time since HIV diagnosis (mo)	108.4 (50.9)	89.2 (58.5)	0.29
Employed (in %)	88	97	0.21
Time on cART (mo)	63.9 (32.8)	62.7 (40.8)	0.99
Time on efavirenz (mo)	59.6 (25.7)	57.1 (30.2)	0.86
Comedication (in %)	0.77		
0	53	63	
1	37	31	
2 or more	10	6	
Previous cART regimes (in %)	0.35		
0	81	87	
1	19	8	
2 or more	0	5	
User-P satisfaction score (0–100)	80.8 (14.1)	74.3 (16.6)	0.21
User-P restrictions score (0–100)	99.1 (1.9)	97.9 (5.5)	0.42
SF-36 general health score (0–100)	72.2 (11.0)	77.5 (12.3)	0.30
SF-36 total score–physical	53.2 (5.0)	53.2 (7.2)	0.98
SF-36 total score–mental	53.2 (4.7)	51.1 (7.7)	0.33

All outcomes are shown in mean (SD), unless otherwise specified.
*Verhage education level: Dutch classification system including 7 categories from 1 (did not finish primary school) to 7 (university degree).

Statistical Analyses

Differences in baseline characteristics were evaluated using a χ^2 test in case of categorical variables, and an independent samples T test (for normal distribution) or Mann–Whitney *U* test (for skewed distribution) in case of continuous variables.

The main outcome measure was the change in NPA composite Z-score at 12 weeks after the switch compared with the control group. Effects of the switch were analyzed at the group level using a linear mixed effects model with composite and domain Z-scores as outcome measurement. The interaction between time (baseline or week 12) and group (switch or control) was used to assess the group effect (estimated difference) on Z-score. Missing data were accounted for by the model using maximum likelihood estimation. Models with random effects for intercept (per individual) and slope (for time) were evaluated for each score. Model diagnostics were performed by checking standardized residuals versus fitted values, residuals per subgroup and per individual, and by checking homoscedasticity of random intercepts. A 2-sided alpha level of 0.05 was used, and 95% confidence intervals were calculated. Moreover, to assess differences in improvement in the switch group compared with the control group at the individual level, analysis was performed on the delta (difference) of the Z-scores per individual using a corrected normative comparison (NC) developed by Huizenga et al.[26] This method, used for evaluating multiple neuropsychological tests by comparing them with a control group performing the same tests, uses step-down resampling as a correction for multiple comparisons. Questionnaires' outcomes were evaluated on a group level with a repeated-measures General Linear Model.

Mixed model analyses were performed using R Statistical Software version 3.3.2, and for the remaining analyses, IBM SPSS version 21 was used.

RESULTS

From all patients eligible for inclusion, 59 were willing to participate and were screened for inclusion (Fig. 1). The main reasons patients did not want to participate were because of time investment and reluctance to switch to a regime that had a dietary restriction. Four patients were excluded after screening, leaving 55 patients to complete the baseline visit.

TABLE 2. Change in Composite and Domain Z-Scores on Baseline and Week 12

A: Composite and Domain Z-Scores on Baseline and Week 12

	Baseline		Week 12	
Median Z-Score	**Control (16)**	**Intervention (38)**	**Control (14)**	**Intervention (34)**
Composite	0.358 (1.14)	0.186 (1.04)	0.670 (1.16)	0.520 (0.83)
Domain verbal	0.370 (1.67)	0.150 (1.45)	0.990 (1.90)	0.364 (1.18)
Domain memory	0.005 (0.66)	−0.015 (0.66)	−0.092 (1.52)	−0.227 (0.82)
Domain executive functioning	0.568 (1.66)	0.183 (1.23)	0.958 (1.29)	0.713 (0.80)
Domain attention	−0.298 (1.53)	−0.348 (1.81)	0.003 (1.08)	0.370 (1.79)
Domain speed	0.193 (2.01)	−0.122 (1.50)	0.345 (2.01)	0.307 (1.02)
Domain motor	0.395 (1.05)	−0.120 (1.79)	0.528 (1.26)	0.428 (1.19)
Domain learning	0.340 (1.15)	0.369 (1.12)	0.778 (1.44)	0.867 (1.34)

B: Corrected Estimated Difference in Composite and Domain Z-Scores

Type of Z-Score	**Z-Score Difference Estimate**	**95% CI**	***P***
Composite	0.152	−0.028 to 0.322	0.103
Domain verbal	0.118	−0.394 to 0.626	0.652
Domain memory	−0.149	−0.149 to 0.208	0.414
Domain executive functioning	−0.054	−0.363 to 0.256	0.735
Domain attention	0.368	0.023 to 0.714	0.041
Domain speed	0.371	0.084 to 0.657	0.014
Domain motor	0.364	−0.099 to 0.827	0.128
Domain learning	0.049	−0.504 to 0.603	0.859

All outcomes are shown as median (IQR).
CI, confidence interval.

Subsequently, due to a detected lesion in the brain on the anatomical MRI, an additional patient was excluded leading to randomization of 54 patients; 16 patients in the control and 38 patients in the switch group. Six patients did not have a week-12 visit because of side effects (1 control and 1 intervention), technical issues with the MRI scanner, or inability of the patient to comply with the time window of 12 weeks (Fig. 1). There was no significant difference between the switch and the control group at baseline with respect to age, years of education, and mean composite z-score (Table 1). The mean age was 41.6 years (SD 6.1) for the control group and 41.3 years (SD 6.7) for the switch group. Mean years of education was 16.8 (SD 0.8) for the control group and 16.2 (SD 1.7) for the switch group. Furthermore, patients had a high mean level of education according to the Verhage scale[27] (5.8 control and 5.5 switch) and scored well on subjective measurements of quality of life and participation. Moreover, unemployment rate was low (12% and 3%).

NPA Group Analysis

The main study outcome was the change in NPA composite Z-score for the switch group compared with the control group. At baseline, there was no significant difference in the mean composite Z-score between the control group 0.36 [interquartile range (IQR) 1.14] and the switch group 0.21 (IQR 1.04; $P = 0.40$). In addition, no significant difference was found at baseline between the groups on the 7 cognitive domain Z-scores (Table 2A). After 12 weeks, the mean composite Z-score for the control group improved to 0.67 (IQR 1.16) and for the switch group to 0.52 (IQR 0.83; $P = 0.40$). Both groups improved, although not significantly, on all domains except on the domain memory. Subsequently, the difference in change at week 12 between the 2 groups was assessed using a mixed model (Table 2B). No significant improvement was found on composite Z-score for the switch group compared with the control group (estimated Z-score difference = 0.15; P value = 0.10). However, the switch group improved significantly more than the control group on the domains attention (estimated Z-score difference = 0.37, $P = 0.04$) and speed of information processing (estimated Z-score difference = 0.37, $P = 0.01$) (Figs. 2A, B).

NPA NC Analysis

As an addition to the group analysis, an analysis at the individual level was conducted with the NPA scores of the control group as a NC group. Five of 34 patients (15%) in the switch group were found to improve significantly more on their NPA as compared to the control subjects. These 5 patients differed from the rest of the group on age (44.6 versus 40.8, $P = 0.049$) and body mass index (27.8 versus 24.1, $P = 0.02$).

Questionnaires

To investigate subjective difference, outcomes of the questionnaires were examined (Table 1). As shown in Table 1, according to the USER-P, a tool that measures a person's amount of participation in society, patients in both groups had

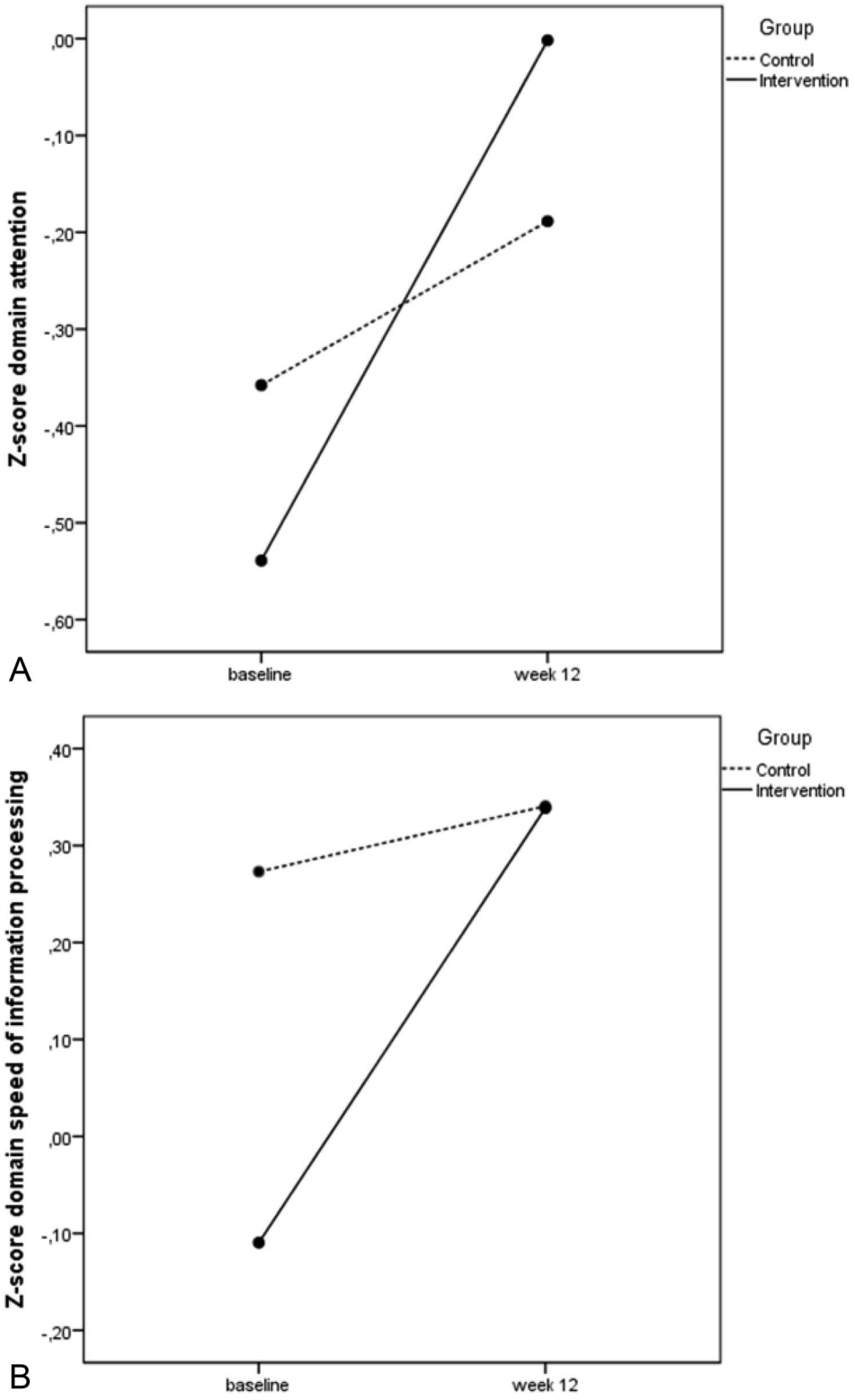

FIGURE 2. Change in NPA Z-score on domains attention and speed of information processing. A, Domain attention. B, Domain speed of information processing.

little to no restrictions in participation (switch: 98.5/100 and control: 97.4/100, $P = 0.45$) and a high satisfaction with their ability to participate (switch: 76.3/100 and control: 71.4/100, $P = 0.31$). After 12 weeks, the score for restrictions did not change significantly (switch: 97.4 and control: 96.2, $P = 0.68$), and the score for satisfaction stayed high as well (switch: 78.2, control: 72.1, $P = 0.23$). The USER-P also measures the frequency of participation, which remained

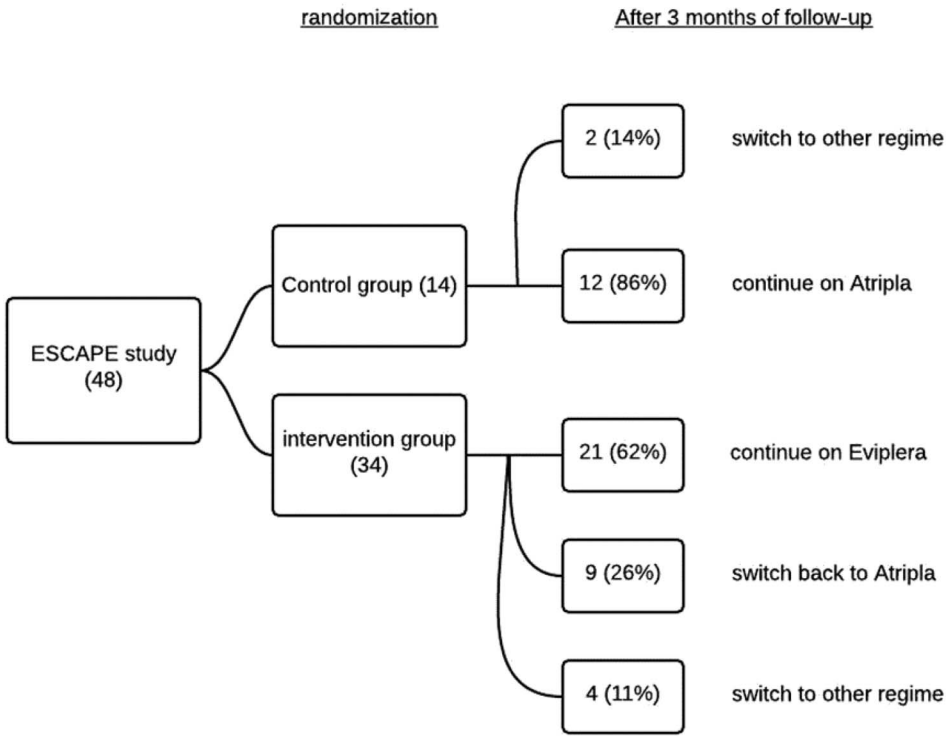

FIGURE 3. Choice of regime after 3 months of follow-up.

virtually the same from baseline to week 12 (switch: 41.5–42.4 and control: 41.0–41.0, $P > 0.05$). A similar pattern was seen while analyzing the SF-36, measuring different aspects of quality of life. The mean score was above 70/100 on all subdomains with no significant difference between groups or between baseline and week 12 (Table 1). Finally, patients did not show signs of depression or anxiety disorders according to the HADS at baseline (mean score 5/21). This was not significantly different between groups (switch: 5 and control: 7) and did not significantly change at week 12 (switch: 4 and control: 6).

At baseline, patients had a T-score on the PROMIS short forms for anxiety, depression, and sleep disorders of just below 50 (48, 46, and 47, respectively), and just above 50 on the short form for satisfaction with social roles (53). At week 12, the scores remained virtually the same (47, 46, 47, and 53) without a significant difference between the switch and control group at week 12.

Choice of Regime

After completion of the study, patients were asked whether they wished to switch back to their original Atripla (Fig. 3). Three months after discontinuation of the study, 74% (25/34) of patients in the switch group were on a non–efavirenz-containing regime versus 14% (2/14) of the controls ($P < 0.01$). This was mostly due to a subjective improvement in everyday life after switching from efavirenz noted by the treating physician in the patient file. Patients who did not experience a subjective change switched back to Atripla (n = 9) because it is a more convenient STR without a dietary restriction.

DISCUSSION

In this study, we aimed to investigate the effects of efavirenz use in cognitively asymptomatic highly educated HIV-infected patients. We found an objective improvement in 2 domains of cognitive functioning on the group level in those patients switching from Atripla to Eviplera. At an individual level, in 15% of the patients, performance on the NPA was significantly improved after switching. Moreover, 74% of patients experienced a subjective improvement, represented in their choice of regime after study completion.

The objective improvement on switching to efavirenz was significant in the cognitive domains attention and speed of information processing. This is consistent with previous literature investigating the effect of HIV on the brain.[28,29] An explanation for the fact that the most apparent effect was seen in these domains is that the subtests used for these 2 domains were the most challenging tests or timed tests. These tests do not have ceiling effects and, as such, are more sensitive to changes at the level of performance more than impairment. It is therefore likely that these tests are the most sensitive for detecting cognitive issues, and subsequently, the tests that show the first signs of cognitive decline. It is conceivable that patients who already struggle with cognitive complaints are the first to report negative cognitive effects of ART. Therefore, cognitive decline associated with efavirenz might be underreported when it is compensable in patients with sufficient cognitive reserve capacity, as might well be the case in our study sample. Previous studies have suggested a brain reserve theory for cognitive decline in HIV patients, proposing a negative effect on the brains' reserve capacity that is addressed when handling complex or challenging cognitive demands.[30,31] In this study, the effect of switching efavirenz

was largest on the more complex tests, which is in line with the brain reserve theory as well.

The next question is then how to distinguish within this total group of asymptomatic patients those who would cognitively benefit from switching versus those who would not. The fact that patients do not always report cognitive complaints poses a challenge for physicians treating HIV patients because they can not trust on the patients' clinical presentation to identify which group of patients would benefit. Importantly, individual analyses using NC identified a small but significant subgroup of 15% of the patients (5/34) who would particularly benefit from discontinuing efavirenz. In addition, no discriminatory clinical parameters were found that could identify these patients beforehand. There was also a discrepancy between the amount of patients with a subjective improvement and with an objective improvement. Even with Eviplera's dietary inconvenience, the majority of patients in the switch group chose to stay on Eviplera rather than switch back to Atripla as was reported by their treating physician in the patients' hospital file in the 0–3 months after completion of the study. It is important for future research to identify those patients at risk of efavirenz-induced negative effects on cognition because Atripla is currently generically available and therefore less expensive compared with non-generic cART in Western countries. More importantly, it is the drug of choice in most resource-limited settings, where the greater part of the HIV-infected population lives. Also, recent evidence suggests that efavirenz is not the only ART with negative neurocognitive effects. For instance, several studies have now demonstrated that neuropsychological and cognitive complaints appear frequently in dolutegravir and other members of the group of integrase strand transfer inhibitors as well.[32–34] This, together with the fact that this study showed that a negative effect can exist even in asymptomatic patients with assumed large cognitive reserve capacities, makes it sensible to investigate the matter of cART neurotoxicity further, to see if it is justified to empirically switch patients off ART with known neurocognitive side effects.

Studies on the effect of efavirenz on neurocognition using an NPA are hampered by methodological issues in particular to the extent of the used NPA. For example, in the earlier mentioned studies in cognitively asymptomatic HIV-infected patients on efavirenz, Payne et al used only 6 subtests and Tiraboschi et al only 3.[18,19] The current study used 14 internationally established neuropsychological tasks. Furthermore, this study uses strong methodological criteria to keep bias to a minimum. First, unlike previous studies, this study used a control group of patients remaining on Atripla. In this study, the control group improved on the NPA as well, albeit less than the switch group. This can be explained by a learning effect from performing an NPA for the second time. Previous studies who did not use a control group could have mistaken this learning effect for an improvement. Second, this study used a highly comparative antiretroviral drug as comparator for the switch group, namely Eviplera. Eviplera was chosen because it has the exact same backbone as Atripla, and a third agent in the same class as Efavirenz. And, although Eviplera has a dietary restriction and Atripla does not, the alternative, switching to a different drug class, will lead to differences in metabolism, the necessity for a booster, or multiple drug intake moments a day, creating an even bigger bias for the study. There are several limitations to this study. First, we studied patients who had been stable on efavirenz for a mean of 57.8 months, representing a group of patients who appear to tolerate the drug for long periods. The results in this group might henceforth be an underestimation of the degree or nature of neurocognitive decline of all patients on efavirenz. Second, the main outcome variable used in this study was a composite Z-score. Although this is a sensitive and broadly used outcome measurement, it does not take into account any sum to zero effects where negative and positive results cancel each other out, unlike for instance the global deficit approach. However, by also doing subanalyses on domain scores, and a NC analysis that uses a multivariate approach to NPA outcomes, this study sufficiently minimized this pitfall.

In conclusion, discontinuing efavirenz resulted in a subjective and objective improvement in neurocognitive functioning in a group of asymptomatic, high-functioning HIV patients. Discrepancies in subjective and objective results make it difficult to select patients who would benefit from a switch.

REFERENCES

1. Heaton RK, Velin RA, McCutchan JA, et al. Neuropsychological impairment in human immunodeficiency virus-infection: implications for employment. HNRC Group. HIV Neurobehavioral Research Center. *Psychosom Med.* 1994;56:8–17.
2. Barclay TR, Hinkin CH, Castellon SA, et al. Age-associated predictors of medication adherence in HIV-positive adults: health beliefs, self-efficacy, and neurocognitive status. *Heal Psychol.* 2007;26:40–49.
3. Kamal S, Locatelli I, Wandeler G, et al. The presence of human immunodeficiency virus-associated neurocognitive disorders is associated with a lower adherence to combined antiretroviral treatment. *Open Forum Infect Dis.* 2017;4:ofx070.
4. Heaton RK, Clifford DB, Franklin DR, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology.* 2010;75:2087–2096.
5. Robertson K, Smurzynski M, Parsons TD, et al. The prevalence and incidence of neurocognitive impairment in the HAART era. *AIDS.* 2016; 21:1915–1921.
6. Simioni S, Cavassini M, Annoni JMM, et al. Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *AIDS.* 2010; 24:1243–1250.
7. Hakkers CS, Kraaijenhof JM, van Oers-Hazelzet EB, et al. HIV and cognitive impairment in clinical practice: the evaluation of a stepwise screening protocol in relation to clinical outcomes and management. *AIDS Patient Care STDS.* 2017;31:363–369.
8. Shah A, Gangwani MR, Chaudhari NS, et al. Neurotoxicity in the post-HAART era: caution for the antiretroviral therapeutics. *Neurotox Res.* 2016;30:677–697.
9. Scourfield A, Zheng J, Chinthapalli S, et al. Discontinuation of Atripla as first-line therapy in HIV-1 infected individuals. *AIDS.* 2012;26:1399–1401.
10. Robertson KR, Su Z, Margolis DM, et al. Neurocognitive effects of treatment interruption in stable HIV-positive patients in an observational cohort. *Neurology.* 2010;74:1260–1266.
11. Kenedi CA, Goforth HW. A systematic review of the psychiatric side-effects of efavirenz. *AIDS Behav.* 2011;15:1803–1818.
12. Arendt G, de Nocker D, von Giesen HJ, et al. Neuropsychiatric side effects of efavirenz therapy. *Expert Opin Drug Saf.* 2007;6:147–154.
13. Abers MS, Shandera WX, Kass JS. Neurological and psychiatric adverse effects of antiretroviral drugs. *CNS Drugs.* 2014;28:131–145.

14. Muñoz-Moreno JA, Fumaz CR, Ferrer MJ, et al. Neuropsychiatric symptoms associated with efavirenz: prevalence, correlates, and management. A neurobehavioral review. *AIDS Rev.* 2009;11:103–109.
15. WHO. *Consolidated Guidelines on HIV Prevention, Diagnosis, Treatment and Care for Key Populations—2016*; 2016. Available at: http://www.ncbi.mlm.nih.gov/books/NBK379694. Accessed May 19, 2018.
16. Meintjes G, Moorhouse MA, Carmona S, et al. Adult antiretroviral therapy guidelines 2017. *South Afr J HIV Med ISSN.* 2017;18:a776.
17. Markowitz M, Hill-Zabala C, Lang J, et al. Induction with abacavir/lamivudine/zidovudine plus efavirenz for 48 weeks followed by 48-week maintenance with abacavir/lamivudine/zidovudine alone in antiretroviral-naive HIV-1-infected patients. *J Acquir Immune Defic Syndr.* 2005;39:257–264.
18. Tiraboschi J, Hamzah L, Teague A, et al. Short communication: the impact of switching from Atripla to darunavir/ritonavir monotherapy on neurocognition, quality of life, and sleep: results from a randomized controlled study. *AIDS Res Hum Retroviruses.* 2016;32:1198–1201.
19. Payne B, Chadwick T, Blamire A, et al. Does efavirenz replacement improve neurological function in treated HIV infection? *HIV Med.* 2017;18:690–695.
20. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology.* 2007;69:1789–1799.
21. Grant I, Franklin DR, Deutsch R, et al. Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline. *Neurology.* 2014;82:2055–2062.
22. Yudko E, Lozhkina O, Fouts A. A comprehensive review of the psychometric properties of the Drug Abuse Screening Test. *J Subst Abuse Treat.* 2007;32:189–198.
23. World Medical Association. World Medical Association Declaration of Helsinki. *JAMA.* 2013;310:2191.
24. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 1992;30:473–483.
25. Garratt A, Schmidt L, Mackintosh A, et al. Quality of life measurement: bibliographic study of patient assessed health outcome measures. *BMJ.* 2002;324:1417.
26. Huizenga HM, Smeding H, Grasman RPPP, et al. Multivariate normative comparisons. *Neuropsychologia.* 2007;45:2534–2542.
27. Verhage F. *Intelligentie en leeftijd: Onderzoek bij Nederlanders van twaalf tot zevenenzeventig jaar*. 1st ed. Assen: van Gorcum; 1964.
28. Grant I. Neurocognitive disturbances in HIV. *Int Rev Psychiatry.* 2008;20:33–47.
29. Reger M, Welsh R, Razani J, et al. A meta-analysis of the neuropsychological sequelae of HIV infection. *J Int Neuropsychol Soc.* 2002;8:410–424.
30. Hakkers CS, Arends JE, Barth RE, et al. Review of functional MRI in HIV: effects of aging and medication. *J Neurovirol.* 2017;23:20–32.
31. Foley JM, Ettenhofer ML, Kim MS, et al. Cognitive reserve as a protective factor in older HIV-positive patients at risk for cognitive decline. *Appl Neuropsychol.* 2012;19:16–25.
32. de Boer MGJ, van den Berk GEL, van Holten N, et al. Intolerance of dolutegravir-containing combination antiretroviral therapy regimens in real-life clinical practice. *AIDS.* 2016;30:2831–2834.
33. Menard A, Montagnac C, Solas C, et al. Neuropsychiatric adverse effects on dolutegravir. *AIDS.* 2017;31:1201–1203.
34. Kheloufi F, Allemand J, Mokhtari S, et al. Psychiatric disorders after starting dolutegravir. *AIDS.* 2015;29:1723–1725.