A randomized cross-over study to compare raltegravir and efavirenz (SWITCH-ER study)

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Background: Efavirenz (EFV) causes neuropsychiatric side-effects and an unfavorable blood lipid profile. We investigated the effect of replacing EFV with raltegravir (RAL) on patient preference, daytime sleepiness, sleep quality, anxiety, and lipid levels.

Method: Switch-ER was a randomized, double-blind, cross-over study. Patients who tolerated EFV, with less than 50 copies/ml HIV-RNA, were randomized into two groups: the RAL-first group started with RAL (400 mg twice daily) and EFV placebo, and the EFV-first group with EFV (600 mg once daily) and RAL placebo. After 2 weeks, both groups switched to the alternate regimen. The primary endpoint was patient preference for the first or the second regimen, assessed after 4 weeks.

Results: Fifty seven participants were enrolled with a median CD4 cell count 600/μl, and duration of previous EFV therapy 3.4 years. Fifty three participants completed the study. When asked about treatment preference after 4 weeks, 22 preferred RAL and 12 preferred EFV, whereas 19 did not express a preference. A significant difference in anxiety and stress scores favoring RAL ($P = 0.04$ and 0.03, respectively) was observed. Median plasma cholesterol levels decreased by 0.4 mmol/l (16 mg/dl, $P < 0.001$), triglycerides by 0.2 mmol/l (18 mg/dl, $P = 0.036$), and low-density lipoprotein by 0.2 mmol/l (8 mg/dl, $P = 0.004$) after replacing EFV with RAL. After study completion, 51% of patients switched to RAL.

Conclusion: Half of patients previously on a stable EFV preferred to switch to RAL, after double-blind exposure to RAL for 2 weeks. Substitution of EFV by RAL significantly impacted on lipid levels, stress, and anxiety scores.

AIDS 2011, **25**:1481–1487

Keywords: cross-over, efavirenz, neuropsychiatric side-effects, preference, raltegravir

Introduction

Efavirenz (EFV) is a nonnucleoside reverse transcriptase inhibitor (NNRTI) of proven effectiveness in the suppression of HIV-1 replication [1]. American and European guidelines recommend the use of EFV in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) as the preferred NNRTI-based regimen [2,3]. Acute central nervous system (CNS) effects are well recognized adverse events associated with

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Received: 14 March 2011; revised: 6 May 2011; accepted: 16 May 2011.

DOI:10.1097/QAD.0b013e328348dab0

EFV therapy and have been reported in up to 50% of patients within the first week after treatment initiation [4]. Abnormal dreams, sadness, irritability, nervousness, lightheadedness, and difficulty in sleeping were the most frequent adverse events reported [5–7]. They usually disappear within a few days of stopping EFV treatment. One prospective study showed discontinuation rates because of acute CNS symptoms in 13% of patients during the first 2 weeks of EFV treatment [5]. In patients who continue the drug, the adverse events are attenuated after the first month of therapy [1,6–8].

However, 13% of patients reported persistent neuropsychiatric disorders 1 year after starting EFV treatment [9]. Such patients experienced relief from switching to an alternative drug such as nevirapine (NVP) even months or years after initiation of EFV [10]. In the Swiss HIV Cohort study, among 8686 persons followed between 2008 and 2010, 93 of 2810 patients switched from EFV to NVP (3.3%). The median time on EFV before the switch to NVP was 482 days. The most common reason for switching were CNS symptoms (48 patients of 93 switched), emphasizing that EFV-linked CNS toxicity can persist.

Raltegravir (RAL) is an integrase strand transfer inhibitor (INSTI) given at a dosage of 400 mg twice daily. Phase II and III trials for treatment-experienced patients have shown excellent efficacy and safety data until 96 weeks. Notably, in phase II and phase III studies, no excess of abnormal dreams, nightmares, or depression occurred [11,12].

In view of the possible persistence of subtle neuropsychiatric side-effects even in well adjusted patients who have tolerated EFV for long periods of time and also with regard to results from the Switch-EE study [13], replacement of EFV with an alternative antiretroviral regimen is of potential interest. We replaced EFV in long-term users with RAL given twice daily and investigated the effect of such replacement on patient preference, sleep quality, daytime sleepiness, anxiety, and lipid levels.

Participants and methods

Study population

Participants were recruited within the Swiss HIV Cohort study (www.SHCS.ch) in six hospitals from Switzerland. Eligibility criteria were as follows: patients aged 18 years or older, on stable HAART including EFV, and with undetectable HIV-RNA [<50 copies by the Roche HIV Monitor test (Roche Diagnostic, Basel, Switzerland)] for at least 3 months. Pregnant women or patients with known or severe psychiatric illness were excluded. Patients were recruited from September 2009 until July 2010.

The protocol was approved by the Human Research Ethics Committees of participating hospitals and regulatory authorities. The study was conducted in accordance with the ethical principles laid out in the Declaration of Helsinki (1996) and Good Clinical Practice guidelines [Consolidated guidelines (E6) issued by the International Conference on Harmonization (ICH) in May 1996].

Study design and procedures

Switch-ER was a 4-week, randomized, double-blind cross-over study. Patients were randomized into two groups: the RAL-first group received RAL (400 mg twice daily) for 2 weeks, and EFV placebo. The EFV-first group received EFV first (600 mg, once daily), and RAL placebo for 2 weeks. After 2 weeks, both groups switched to the alternate regimen. The NRTI backbone was continued unchanged.

Assessments

The primary endpoint of the trial was patient preference for the first or the second regimen, elicited by a questionnaire after 4 weeks.

At each visit (week 0, week 2, week 4), patient anxiety and depression, sleepiness during the day, sleep quality, and antiretroviral satisfaction were recorded using standardized questionnaires (see below). Laboratory safety measurements including lipids levels as well as hepatic parameters and full blood count were also assessed at screening, at week 2, and 4. HIV-RNA was measured at week 0, week 2, and week 4, using Roche Taqman version 2.0 (Roche Diagnostic).

Plasma drug concentrations

Plasma drug concentration was measured in all patients on day 1, and at the end of both treatment phases. At least 8 h elapsed between last drug intake and blood sampling. Results were not communicated to the investigators in accordance with double-blind methodology.

EFV and RAL total plasma concentrations were determined by high-performance liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) after protein precipitation with acetonitrile (MeCN), using an adaptation of our published methods for EFV [14,15], and for RAL [16]. EFV provided by MSD (Merck Sharp & Dohme-Chibret AG, Glattbrugg, Switzerland) and RAL by Merck (Rahway, New Jersey, USA) were used to prepare calibration and quality control samples.

Questionnaires

Depression, anxiety, and stress

Symptoms of depression, anxiety, and stress were assessed with the Depression Anxiety and Stress Scale short version DASS21 [17]. This scale was chosen for its high internal consistency, temporal stability, and stable factor structure applying to clinical as well as normal samples

[17,18]. The scale is derived from the results of a standardized self-report questionnaire that distinguishes among normal, mild moderate, severe score, and extremely severe degrees of depression, anxiety, or stress.

Sleep assessment

Daytime sleepiness was measured using Epworth Sleep Score (ESS) and the Stanford Sleepiness Scale (SSS) [19,20]. Sleep quality was measured using the Groningen Sleep Quality Score (GSQS) [21].

The ESS asks eight questions about how often a person dozed during daily activities, with a 4-point scale from 0 equal to never doze to 3 equal to high chance of dozing. A total score at least 10 represents daytime sleepiness.

The SSS was used to measure subjective daytime sleepiness. Participants were asked to select one of the seven statements on the SSS that best described their typical sleepiness at work during the last week prior to visit. The directions to the SSS were adjusted for this study to assess sleepiness over the last week rather than current sleepiness.

The GSQS includes 15 questions about sleep the previous night, answered Yes (=1) or No (=0). A total score of 8 or less indicates disturbed sleep during the previous night.

Treatment preference

The patient preference questionnaire was used at the final visit, before unblinding. This questionnaire asked which treatment the patient preferred, comparing the one he or she received during the first 2 weeks and the last 2 weeks of the trial. Patients could also indicate that the treatments were equivalent. At week 6, 2 weeks after the last visit, we called patients to ask what treatment they were currently taking. In addition, satisfaction with the antiretroviral treatment was recorded with the HIV Treatment Satisfaction Questionnaire (HIVTSQc) [22] at week 0, week 2, and week 4. A simplified version with six questions instead of 10 items in the original version was used. Very satisfied was scored as six and very dissatisfied was scored as zero for each question. A sum of scores was obtained for all six questions at each visit.

German, French, Italian, and English questionnaires were used, as appropriate for the patient's mother tongue.

Statistical analysis

To calculate the sample size for this study, we assumed that two-thirds of the total population would express a preference. We assumed that in the remaining patients who expressed a preference, twice as many preferred one drug over the other, resulting in a final distribution of 33% no preference/not evaluable versus 44% preferring drug 1, and 22% preferring drug 2. To detect such a difference with a power of 80% and an alpha error of 5%, 54 patients need to be included.

Baseline characteristics were summarized using median and interquartile range (IQR) for quantitative variables and percentages for qualitative variables. Preference of treatment at week 4 (primary endpoint) and treatment taken at week 6 (phone call) were analyzed using χ^2 tests and McNemar χ^2 tests with threshold of 5%. We tested the order effect (EFV-first group versus RAL-first group, standard χ^2 tests) and the treatment effect (RAL versus EFV, McNemar χ^2 tests).

Differences in scores (quantitative variables) between the EFV period and the RAL period for DASS, SSS, ESS, and GSQS questionnaires, HIVTSQc questionnaire, lipids and safety parameters (liver function, lipids, and glycemic parameters) were analyzed with non-parametric Wilcoxon matched-pairs tests with a threshold of 5%.

Statistical analysis was performed using STATA Release 10.0 (Stata Statistical Software: Release 10.0; Stata Corporation, College Station, Texas, USA).

Results

Patients

Fifty-nine participants (87% men) were screened and 57 were randomized. Fifty-three participants completed the study (Fig. 1). Median age was 47 years (IQR 44–51), with a median duration of known HIV infection of 10 years (IQR 6.7–15.6) and CD4 cell count of 600 cells/μl (IQR 476–821). HIV-RNA was below 50 copies per μl for all patients at screening and enrollment. Patients had been on EFV for a median of 3.4 years (IQR 1.8–7.6). At baseline, median EFV plasma concentration was 1930 ng/ml (IQR 1471–2568). The most used antiretroviral for the background regimen was

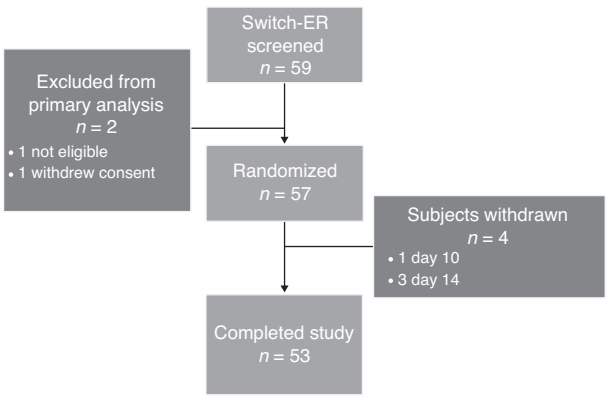

Fig. 1. Patient disposition.

tenofovir (TDF) in combination with emtricitabine (FTC; $n=29$, 54.7%), followed by abacavir in combination with lamivudine (3TC; $n=21$, 39.6%). Ten patients (18.9%) were on statins at start of study (Table 1).

The RAL-first and EFV-first groups were similar for all parameters listed in Table 1.

Treatment preference

After 4 weeks, of 53 patients, 34 (64%) expressed a preference for one or the other drug, whereas 19 (36%) said that the two treatments were equal. Of the 34 who expressed a preference, 12 patients preferred EFV (35%), and 22 preferred RAL (65%). No order effect was observed ($P=0.331$). Compared to the null hypothesis of equality of the two drugs, the preference expressed for RAL did not attain statistical significance (χ^2 McNemar test, $P=0.086$; Table 2).

At week 6, 2 weeks after unblinding, 26 (49%) patients indicated that they continued treatment with EFV, whereas 27 (51%) patients had switched to RAL (Table 2). No order effect was observed ($P=0.669$).

HIVTSQc questionnaire

Patients were also asked 'How satisfied are you with your current treatment?' at the end of each treatment period with the HIVTSQc questionnaire. Patients in the RAL-first group were more satisfied by RAL than by EFV ($P=0.002$). Patients in the EFV-first group also tended to prefer RAL, but this preference was not statistically significant.

Table 2. Patient's preference at week 4 and patient's treatment at week 6.

	Group of randomization		
	EFV-first $N=24$	RAL-first $N=29$	Total (n%)
Patient's preference at week 4			
Prefer EFV	7	5	12 (22%)
Prefer RAL	9	13	22 (42%)
No preference	8	11	19 (36%)
Patient's treatment at week 6 (phone call)			
On EFV	11	15	26 (49%)
On RAL	13	14	27 (51%)
No preference			

EFV, efavirenz; RAL, raltegravir.

Anxiety, depression, and sleep assessment

Quality of sleep (questionnaire GSQS, SSS) and depression (ESS) scores did not differ significantly between groups. We observed, however, a significant difference in anxiety and stress score (questionnaire DASS) favoring RAL ($P=0.04$ and 0.03, respectively; Table 3).

Table 1. Baseline characteristics of enrolled patients.

Characteristics	All population ($n=53$)	EFV first ($n=24$)	RAL first ($n=29$)
Age (years)	47 (44–51)	47.0 (43.0–50.5)	48 (45–53)
BMI (kg/m^2)	23.9 (22.2–25.8)	23.5 (21.9–25.7)	24.3 (22.3–26.6)
Men, *n* (%)	39 (73.58)	16 (66.67)	23 (79.31)
CDC category A, *n* (%)	24 (45.28)	10 (41.67)	14 (48.28)
CDC category B, *n* (%)	16 (30.19)	8 (33.33)	8 (27.59)
CDC category C, *n* (%)	13 (24.53)	6 (25.00)	7 (24.14)
HIV duration (years)	10.2 (6.7–15.6)	13.2 (6.7–16.3)	8.8 (5.5–12.4)
HIV viral load (copies/μl)	20 (20–20)	20 (20–20)	20 (20–20)
CD4 cells/μl	600 (476–821)	597 (483–810)	637 (476–852)
Lipid and glycemic parameters			
Total cholesterol (mmol/l)	5.2 (4.8–5.9)	5.2 (4.8–5.9)	5.2 (5.0–5.9)
Triglycerides (mmol/l)	1.44 (1.04–1.92)	1.58 (1–20.63)	1.4 (1.07–1.80)
HDL[a] cholesterol (mmol/l)	1.3 (1.09–1.57)	1.245 (1.09–1.90)	1.3 (1.10–1.55)
LDL[b] cholesterol (mmol/l)	3.11 (2.55–3.85)	3.11 (2.60–3.50)	3.25 (2.45–4.20)
Glucose (mmol/l)	5.34 (4.97–5.90)	5.1 (4.78–5.55)	5.6 (5.02–5.96)
Liver function			
Alanine aminotransferase (U/l)	28 (21–39)	25.5 (17.0–39.5)	29 (26–36)
HAART[c] *n* (%)			
TDF + FTC	29 (54.7)	9 (37.5)	20 (69.0)
ABC + 3TC	21 (39.6)	13 (54.2)	8 (27.6)
Others[d]	3 (5.7)	2 (8.3)	1 (3.4)
EFV plasma concentration (ng/ml)	1930 (1471–2568)	1894 (1378–2438)	2182 (1522–2616)
Above P75[e] (EFV plasma concentration) *n* (%)	12 (23.5)	4 (18.2)	8 (27.6)
Statin *n* (%)	10 (18.9)	5 (20.8)	5 (17.2)

If not indicated differently, data are median (IQR). 3TC, lamivudine; ABC, abacavir; DDI, didanosine; EFV, efavirenz; FTC, emtricabine; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TDF, tenofovir; ZDV, zidovudine.
[a]LDL-cholesterol: low-density lipoprotein cholesterol.
[b]HDL-cholesterol: high-density lipoprotein cholesterol.
[c]TDF, 3TC, and ABC treatments are the most used.
[d]Others: ABC + DDI; 3TC + ZDV; 3TC + TDF.
[e]P75, the 75th percentile, value concentration including 75% of our study population.

Table 3. Change in Depression Anxiety and Stress Scale questionnaire (in median, interquartile range).

DASS items	End of EFV period (W2 or W4) $n=53$ median	End of RAL period (W2 or W4) $n=53$ median	Change between RAL and EFV periods $n=53$ median	Order effect *P* values	Treatment effect *P* values
Anxiety	4	2	0	0.8914	0.0400
Depression	6	4	0	0.5530	0.1956
Stress	10	6	−2	0.4886	0.0298

DASS, Depression Anxiety and Stress Scale; EFV, efavirenz; RAL, raltegravir.

Lipids

Table 4 reports median metabolic changes between the two treatments. We observed a significantly lower total cholesterol (median change −0.4 mmol/l or −16 mg/dl, IQR −0.9 mmol/l to −0.1 mmol/l, $P<0.0001$), low-density lipoprotein (LDL)-cholesterol (median change −0.2 mmol/l or −8 mg/dl, IQR −0.6 mmol/l to 0.2 mmol/l, $P=0.004$), triglycerides levels (median change −0.2 mmol/l or −18 mg/dl, IQR −0.6 to 0.1, $P=0.036$), high-density lipoprotein (HDL)-cholesterol (median change −0.1 mmol/l or −4 mg/dl, IQR −0.2 to 0, $P=0.005$), and LDL/HDL ratio (median change −0.1, IQR −0.4 to 0.3, $P=0.966$) in patients on RAL, when compared to patients on EFV.

Safety parameters

No loss of virological suppression was observed over the study period (3 months). At baseline, median EFV plasma concentration was 1930 ng/ml (IQR 1471–2568). At the switch visit, median EFV plasma concentration was 2163 ng/ml (IQR 1650–2520) among EFV-first group and RAL plasma concentration was 193 ng/ml (IQR 61–429) among RAL-first group. At final visit, median RAL plasma concentration was 235 ng/ml (IQR 111–446) and median EFV plasma concentration was 2312 ng/ml (IQR 1848–3027) among EFV-first and RAL-first groups, respectively. The optimal therapeutic range for EFV is 1000–4000 ng/ml [23] with a large interindividual pharmacokinetic variability of 55%, and a smaller intraindividual variability of 26%. For RAL, no therapeutic range has been established yet, but average concentrations measured in our study correspond to the concentrations observed in the previous study [24].

One serious adverse event (SAE) was observed. The patient experienced a pulmonary embolism and was withdrawn from the study on investigator's decision. This SAE was considered nonrelated to the study drugs.

Discussion

Our study tested the hypothesis that subclinical neuropsychiatric effects of EFV might persist over the initial period of treatment, and that patients might, therefore, prefer RAL to EFV. Indeed, 51% of patients in our study switched to RAL after being exposed to the drug in a double-blind fashion for 2 weeks.

Patients were eligible for our study when they were on a stable, effective, EFV-containing regimen. They had tolerated EFV for a median time of 3.4 years. The baseline questionnaire underlined that our patients were experiencing no clinical significant adverse events at the time of enrollment. The high proportion of switchers stands out against this background, which 'stacks the deck' against RAL, and when considering that switching to RAL meant accepting a twice-daily regimen while forgoing the convenience of the once-daily, one-pill triple combination (Atripla).

Table 4. Changes in metabolic parameters (in median, interquartile range).

Metabolic parameters	End of EFV period (W2 or W4) $n=53$ median	End of RAL period (W2 or W4) $n=53$ median	Change between RAL and EFV periods $n=53$ median	Treatment effect *P* values
Liver function				
Alanine aminotransferase (U/l)	30	26	−1	0.2623
Lipid and glycemic parameters				
Total cholesterol (mmol/l)	5.3	4.7	−0.4	<0.0001
Triglycerides (mmol/l)	1.4	1.1	−0.2	0.0362
HDL cholesterol (mmol/l)	1.3	1.2	−0.1	0.0052
LDL cholesterol (mmol/l)	3.1	2.8	−0.2	0.0036
LDL/HDL ratio (mmol/l)	3.3	2.4	−0.1	0.9664
Glucose (mmol/l)	5.4	5.2	−0.2	0.0887

EFV, efavirenz; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RAL, raltegravir.

EFV is one of the preferred drugs when initiating HAART. Its efficacy and safety were established in several large randomized trials [1]. The most notable adverse events associated with EFV are rash and CNS symptoms, the latter being reported between 25 and 70% of exposed patients [25,26]. The prevalence of CNS symptoms declines within a few weeks if therapy is continued and disappears within a few days if therapy is interrupted. In a minority of patients, neuropsychiatric symptoms persist for several months or longer. The durability of EFV therapy was recently questioned as several observational cohorts reported high rate of EFV discontinuations due to adverse neuropsychiatric events [27,28].

In 2010, the Switch-EE study [13] investigated the effect of replacing EFV with etravirine (ETR) on patient preference, sleep, anxiety, and lipid levels, with methods very similar to the present Switch-ER study. The main difference was that in Switch-EE, the two treatment periods were 6 weeks long, compared to 2 weeks in Switch-ER. After 12 weeks, 16 patients preferred EFV and 22 patients preferred ETR, whereas 17 did not express a preference. Fifteen of 21 (71%) of those who continued EFV during the first phase of the trial preferred EFV, whereas patients who started with ETR were more likely to prefer ETR ($n = 16/17$, 94%). This order effect may have been due to the disappearance of the cytochrome enzyme induction caused by EFV. Thus, patients who were on EFV before the trial, and on ETR followed by EFV during the trial, experienced EFV adverse events again, and therefore preferred ETR. To avoid this confusing order effect, we shortened treatment periods to 2 weeks in Switch-ER, and indeed we did not observe an order effect.

Efficacy of RAL was well established in the BENCHMRK [29] and Switchmark trials [12]. SPIRAL [30] showed improvement of lipid profiles. In SPIRAL, the average triglyceride level fell by 23% in the RAL arm while rising by 5% in the protease inhibitor (lopinavir or atazanavir) continuation arm. Total and LDL cholesterol decreased more than HDL among switchers, producing a more favorable total-to-LDL ratio [30]. Lipid profile improvement was also observed in Switch-EE study in patients switching from EFV to ETR [13].

This study has limitations. These include its small size and that few women were included. By design, patients who could not tolerate EFV were excluded. In addition, none of the participants had a history of major neurologic or psychiatric disorders, such as depression; these could conceivably be a risk factor for experiencing EFV-induced side-effects.

In conclusion, approximately half of patients previously on a stable EFV preferred to switch to RAL, after double-blind exposure to RAL for 2 weeks. Switching to RAL was associated with a significant improvement in anxiety and stress, as measured by the DRESS scale, and improvement in lipid profile.

Acknowledgements

B.H. contributed to study concept and design. C.D., A.N., A.C., B.H. contributed to the analysis and interpretation of data. A.C. contributed to the drafting of the article. All authors contributed to the critical revision of the article for important intellectual content. C.D. contributed to the statistical analysis. B.H. contributed to study supervision. The authors do not have an association that might pose a conflict of interest.

The study was funded in part by Merck Sharp & Dohme-Chibret AG and conducted within the Swiss HIV Cohort Study. The SHCS is financed in the framework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation.

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