A randomized crossover study to compare efavirenz and etravirine treatment

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\textbf{Background:} Efavirenz (EFV) causes neuropsychiatric side-effects and an unfavourable blood lipid profile. We investigated the effect of replacing EFV with etravirine (ETR) on patient preference, sleep, anxiety and lipid levels.

\textbf{Method:} Study participants did not complain of side-effects, had tolerated EFV for at least 3 months, with less than 50 copies/ml HIV-RNA. After randomization, the ETR-first group started with ETR (400 mg four times daily) with EFV-placebo and the EFV-first group with EFV with ETR-placebo. After 6 weeks, both groups switched to the alternate regimen. Nucleoside reverse transcriptase inhibitors were continued without any change. The primary end point was patient preference for the first or the second regimen, assessed after 12 weeks.

\textbf{Results:} Fifty-eight patients were enrolled with a median CD4 cell count of 589 cells/\textmu{}l and the duration of previous EFV therapy was 3.9 years. Fifty-five patients completed the study. When asked about treatment preference after 12 weeks, 16 preferred EFV and 22 preferred ETR, whereas 17 did not express a preference ($P$¼ NS). Patients who continued EFV during the first phase of the trial preferred EFV (15/21, 71%), whereas patients who started with ETR were more likely to prefer ETR (n = 16/17, 94%). This order effect was strongly significant ($P$ < 0.0001). Quality of sleep, depression, anxiety and stress scores did not differ significantly between groups. Median plasma cholesterol levels decreased by 0.7 mmol (29 mg/100 ml) after replacing EFV with ETR ($P$ < 0.002).

\textbf{Conclusion:} After substitution of EFV by ETR, patients did not express a significant preference for ETR. There was no measurable effect on neuropsychiatric symptoms and sleep. Cholesterol decreased.

\textbf{Keywords:} crossover, efavirenz, etravirine, neuropsychiatric side-effects, preference

\textbf{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 NRTIs as the preferred NNRTI-based regimen [2,3]. Acute central nervous system (CNS)
effects are well recognized adverse events associated with 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 side-effects 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 experience 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 7129 persons followed in 2006 or in 2007, 104 of 2471 patients switched from EFV to NVP (4.2%). The median time on EFV before the switch to NVP was 364 days. The most common reason for switching were CNS symptoms (40 patients of 104 switched), emphasizing that EFV-linked CNS toxicity can persist. Etravirine (ETR) is a next-generation NNRTI indicated at a dosage of 200 mg twice daily. Phase IIb and III trials for treatment-experienced patients have shown excellent efficacy and safety data until 96 weeks, notably without occurrence of abnormal dreams, nightmares or depression. The type and incidence of adverse events in the phase III trials on experienced patients after 96 weeks of treatment [11–13] did not differ from placebo, with the exception of rash which was significantly more frequent in the ETR group (21 vs. 12%, P < 0.0001). Once daily dosage of ETR, as used in this study, was based on the pharmacokinetics of ETR which – in multiply dosed patients – has a terminal half-life of 36 h [14]. Switching from EFV to ETR does not require a dose adjustment of ETR [15].

In view of the possible persistence of subtle neuropsychiatric side-effects even in well adjusted patients who have tolerated EFV for long periods, replacement of EFV with ETV is of interest. We replaced EFV in long-term users with ETR given once 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 five 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. Persistent EFV-related neuropsychiatric side-effects were not an inclusion criterion. Pregnant women or patients with known or severe psychiatric illness were excluded. Patients were recruited from October 2008 to June 2009.

The protocol was approved by the Human Research Ethics Committees of participating hospitals. 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 Harmonisation (ICH) in May 1996).

Study design and procedures

Switch-EE was a 12 weeks randomized, double-blind crossover study.

Patients were randomized into two groups; the ETR-first group received ETR (400 mg once daily) for 6 weeks with EFV placebo and the EFV-first group received EFV first (600 mg once daily) with ETR placebo for 6 weeks. After 6 weeks, both groups switched to the alternate regimen. The NRTI backbone was continued unchanged. ETR was administered once daily.

Assessments

The primary end point of the trial was patient preference for the first or the second regimen, elicited by questionnaire after 12 weeks.

At each visit, patient anxiety and depression, sleepiness during the day, sleep quality and antiretroviral satisfaction were recorded using standardized questionnaires (see below). Laboratory safety measurements including lipid levels, hepatic parameters and full blood count were also assessed at screening, at week 6 and 12. HIV-RNA was measured at baseline, 6 and 12 weeks after study initiation, using Roche Taqman version 2.0 (Roche Diagnostic, Basel, Switzerland).

Plasma therapeutic drug concentration

Plasma drug concentration was collected in all patients on day 1 and at the end of both treatment phases. Results were not communicated to the investigators in compliance with double-blind methodology.

EFV and ETR 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 previously reported methods for EFV [16,17], and our recently published method for ETR [18]. EFV and ETR pure substance was provided by Merck Sharp & Dohme-Chibret AG (Glattpugg, Switzerland) or Tibotec (Melchelen, Belgium), respectively, 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 (DASS) [19]. This scale was chosen for its high internal consistency, temporal stability and stable factor structure applying to clinical and normal samples [19,20]. The scale is derived from the results of a standardized self-report questionnaire that distinguishes among normal, mild, moderate, severe and extremely severe degrees of depression, anxiety or stress.

Sleep quantity and quality assessment
Daytime sleepiness was measured using Epworth Sleep Score (ESS) and the Stanford Sleepiness Scale (SSS) [21,22]. Sleep quality was measured using the Groningen Sleep Quality Score (GSQS) [23].

The ESS asks eight questions about how often a person dozed during daily activities, with a 4-point scale from 0 (never doze) to 3 (high chance of dozing). A total score of more than 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 less than 8 indicates disturbed sleep during the previous night.

Treatment preference
The patient preference questionnaire was used at the final visit only, before unblinding. This questionnaire asked which treatment the patient preferred, comparing the one they received during the first 6 weeks and the last 6 weeks of the trial. Patients could also indicate that the treatments were equivalent. In addition, satisfaction with the antiretroviral treatment was recorded with the HIV Treatment Satisfaction Questionnaire (HIVTSQc) [24]. A simplified version with six questions instead of 10 items in the original version was used. German, French, Italian and English questionnaires were used, as appropriate for the patient’s mother tongue. Each questionnaire was answered during each visit, except the treatment preference questionnaire which was filled during the final visit only. All questionnaires were administered by a trained study nurse at each site.

Statistical analysis
Baseline characteristics were summarized using median and interquartile range for quantitative variables and percentages for qualitative variables. Preference of treatment at week 12 (primary end point), prescription of treatment after the closure of the trial and scores in three classes of the HIVTSQc were analysed using a McNemar’s \( \chi^2 \) test with a threshold of 5%. We tested the treatment effect (ETR vs. EFV) and the order effect (EFV-first group vs. ETR-first group) in the patient groups who expressed a preference. Difference in scores (quantitative variables) for DASS, SSS, ESS and GSQS questionnaires and safety parameters (liver function, lipids and glycaemic parameters) were analysed as follows: treatment effects with a nonparametric Wilcoxon matched pairs test with a threshold of 5% and group effects with a nonparametric Mann–Whitney test with a threshold of 5%.

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

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

Results

Patients
Fifty-eight patients (87% men) were randomized. Fifty-five patients completed the study (Fig. 1). Median age was 47 years [interquartile range (IQR) 42–55], with a median duration of known HIV infection of 11.3 years (IQR 6.3–15.4) and CD4 cell counts of 589 cells/\( \mu \)l (IQR 420–785). HIV-RNA was below 50 copies/fil for all patients at screening and enrolment. Patients had been on EFV for a median of 3.9 years (IQR 1.9–6.6). At baseline, EFV plasma concentration was 2058 ng/ml (IQR 1588–2648). The most used antiretroviral for the background regimen was tenofovir in combination with emtricitabine (FTC) \((n=28, 48.3\%)\), followed by abacavir (ABC) in combination with lamivudine (3TC) \((n=20, 34.5\%)\) (Table 1).

![Fig. 1. Patient disposition. Switch-EE; trt, treatment. *One patient withdrawal at visit week 6 in arm 1 and two patients withdrawal before visit week 6 in arm 2.](image-url)
Table 1. Baseline characteristics of enrolled patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All population (n = 58)</th>
<th>EFV first (n = 30)</th>
<th>ETR first (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47 (42–55)</td>
<td>47 (43–52)</td>
<td>47.5 (41–57)</td>
</tr>
<tr>
<td>BMI, kg/m² in median (IQR)</td>
<td>23.2 (22.1–26.7)</td>
<td>22.7 (21.2–25.3)</td>
<td>24.4 (22.3–28.1)</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>51 (87.9)</td>
<td>26 (86.7)</td>
<td>25 (89.3)</td>
</tr>
<tr>
<td>CDC category A, n (%)</td>
<td>25 (43.3)</td>
<td>14 (46.7)</td>
<td>11 (39.3)</td>
</tr>
<tr>
<td>CDC category B, n (%)</td>
<td>17 (29.3)</td>
<td>7 (23.3)</td>
<td>10 (35.7)</td>
</tr>
<tr>
<td>CDC category C, n (%)</td>
<td>16 (27.6)</td>
<td>9 (30.0)</td>
<td>7 (25.0)</td>
</tr>
<tr>
<td>HIV duration: years (IQR)</td>
<td>11.3 (6.3–15.4)</td>
<td>12.1 (6.3–14.9)</td>
<td>9.0 (6.2–16.8)</td>
</tr>
<tr>
<td>HIV viral load, log₁₀ copies/µl in median (IQR)</td>
<td>40 (40–40)</td>
<td>40 (40–40)</td>
<td>40 (40–40)</td>
</tr>
<tr>
<td>CD4 cells/µl, in median (IQR)</td>
<td>589.5 (420.0–785.5)</td>
<td>592.0 (474.0–721.5)</td>
<td>547.5 (387.0–800.5)</td>
</tr>
<tr>
<td>Lipid and glycaemic parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/l in median (IQR)</td>
<td>5.6 (4.7–6.1)</td>
<td>5.7 (4.8–6.1)</td>
<td>5.3 (4.5–6.2)</td>
</tr>
<tr>
<td>Triglycerides, mmol/l in median (IQR)</td>
<td>1.8 (1.3–2.9)</td>
<td>1.8 (1.4–2.8)</td>
<td>1.7 (1.3–2.9)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L in median (IQR)</td>
<td>1.1 (0.9–1.4)</td>
<td>1.1 (1.0–1.4)</td>
<td>1.1 (0.9–1.4)</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/l in median (IQR)</td>
<td>3.3 (2.6–4.0)</td>
<td>3.3 (2.6–4.1)</td>
<td>3.3 (2.6–3.8)</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>5.4 (5.0–6.1)</td>
<td>5.3 (5.0–6.2)</td>
<td>5.4 (5.1–5.8)</td>
</tr>
<tr>
<td>Liver function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase, U/L in median (IQR)</td>
<td>34.5 (22.0–49.0)</td>
<td>37.0 (22.0–48.0)</td>
<td>31.0 (21.0–55.0)</td>
</tr>
<tr>
<td>HAART n (%)</td>
<td>58 (100)</td>
<td>30 (100)</td>
<td>28 (100)</td>
</tr>
<tr>
<td>TDF–FTC n (%)</td>
<td>28 (48.3)</td>
<td>14 (46.7)</td>
<td>14 (50.0)</td>
</tr>
<tr>
<td>ABC–3TC n (%)</td>
<td>20 (34.5)</td>
<td>9 (30.0)</td>
<td>11 (39.3)</td>
</tr>
<tr>
<td>EFV plasma concentration, ng/ml in median (IQR)</td>
<td>2058 (1588–2648)</td>
<td>2022 (1558–2648)</td>
<td>2112 (1609–2774)</td>
</tr>
<tr>
<td>Up to P75 (EFV plasma concentration), n (%)</td>
<td>15 (26)</td>
<td>8 (21)</td>
<td>7 (21)</td>
</tr>
</tbody>
</table>

Table 2. Patient’s preference and drug prescription at week 12.

<table>
<thead>
<tr>
<th>Randomization of EFV-first group (n = 28)</th>
<th>Randomization of ETR-first group (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s preference:</td>
<td></td>
</tr>
<tr>
<td>Prefer EFV</td>
<td>15*</td>
</tr>
<tr>
<td>Prefer ETR</td>
<td>1</td>
</tr>
<tr>
<td>No preference</td>
<td>7</td>
</tr>
<tr>
<td>Prescribed:</td>
<td></td>
</tr>
<tr>
<td>EFV</td>
<td>12</td>
</tr>
<tr>
<td>ETR</td>
<td>15</td>
</tr>
</tbody>
</table>

EFV, efavirenz; ETR, etravirine.  
*P < 0.0001 (15/21; 71% vs. 16/17; 91%).

Treatment preference
After 12 weeks, 16 patients preferred EFV and 22 preferred ETR, whereas 17 did not express a preference (P = 0.331). Patients who started with EFV were more likely to prefer EFV (15/21, 71%), whereas patients who started with ETR were more likely to prefer ETR (n = 16/17, 94%) (Table 2). This order effect was strongly significant (P < 0.0001, Fisher’s exact test).

Patients in the ETR-first group were 3.4 times more likely to prefer ETR at week 12 than the EFV-first group [Relative risk (RR), RR = 3.4 for preferring ETR (95% confidence interval 1.7–6.9, P < 0.00001)].

Patients were asked ‘how satisfied are you with your current treatment?’ at the end of each treatment period. Of 54 patients who were receiving ETR, 32 expressed satisfaction, nine were neutral, whereas 13 expressed dissatisfaction with their current treatment. Of 55 receiving EFV, 23 expressed satisfaction, 15 were neutral, whereas 17 expressed dissatisfaction (P = 0.19 for groups comparison).

At week 12 after unblinding, 35 patients chose to continue on a prescription of EFV and 20 patients chose to continue on a prescription of ETR; again, we observed a significant treatment order effect (P = 0.04) as 75% of the patients who chose ETR had started with ETR (15/20, 75%) and 66% of the patients who have chosen EFV started with EFV (23/35, 66%) (Table 2).

Anxiety, depression and sleep assessment
None of the questionnaires detected any significant differences among depression, anxiety, sleepiness or sleep quality between the two study periods (see supplementary materials, http://links.lww.com/QAD/A105).

Safety and laboratory parameters
Two serious adverse events (SAE) were reported, but were considered not related to either of the study drugs. One patient was hospitalized for 2 days for a previously scheduled resection of distal clavicle. The patient did not stop the study. The second SAE was a hospital admission for diagnostic work-up of pelvic pain. The patient had testicular cancer in 1992, and the examination revealed pelvic metastasis. The patient stopped the study and commenced chemotherapy. Table 3 reports median metabolic changes between the two treatments. We observed a significantly lower total cholesterol (median change -0.7 mmol/l; IQR -1.1, -0.2; P < 0.0001), low-density lipoprotein (LDL)–cholesterol (median change -0.6 mmol/l; IQR -0.7, -0.1; P < 0.00001)
and triglycerides levels (median change $-0.3$ mmol/l; IQR $-0.9$, $-0.1$; $P=0.0002$) in patients on ETR when compared with patients on EFV. This cholesterol-lowering effect of switching to ETR was observed irrespective of initial cholesterol levels and irrespective of whether patients were treated with statins or not (results not shown).

### Discussion

Our study tested the hypothesis that subclinical neuropsychiatric effects of EFV might persist over the initial period of treatment and that patients who switched to ETR might, therefore, prefer the newer to the older drug. However, this did not turn out to be the case.

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 tends to decline within a few weeks if therapy is continued and 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 included. By design, patients who could not tolerate EFV for a median time of 3.9 years. Although the presence of neuropsychiatric side-effects was not required, we expected that patients with symptoms or treatment dissatisfaction would be more willing to participate. However, the baseline questionnaire and the baseline EFV concentrations [EFV-first 2022 ng/ml (1558–2648) and ETR-first 2112 ng/ml (1609–2774), respectively] underlined that our patients were experiencing no clinically significant side-effects at the time of the enrolment.

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 3.9 years. Although the presence of neuropsychiatric side-effects was not required, we expected that patients with symptoms or treatment dissatisfaction would be more willing to participate. However, the baseline questionnaire and the baseline EFV concentrations [EFV-first 2022 ng/ml (1558–2648) and ETR-first 2112 ng/ml (1609–2774), respectively] underlined that our patients were experiencing no clinically significant side-effects at the time of the enrolment.

Multiple, validated questionnaires did not confirm a significant preference of ETR over EFV. There was, however, statistically significant order effect in the crossover design in those patients receiving ETR first preferred ETR and patients receiving EFV first preferred EFV. We assume that this was due to the recrudescence of symptoms when EFV was restarted after a 6 weeks break in the ETR-first group. EFV is a strong inducer of hepatic cytochrome P450 (CYP450), a group of enzymes involved in the metabolism of numerous drugs, including EFV itself [29]. ETR also induces CYP450, but to a lesser extent when compared with EFV [29,30]. Our study suggests that CYP450 induction by ETR does not replace induction by EFV: when patients are again exposed to EFV, they may be prone to experience CNS symptoms again.

This study has limitations: there were few women included. By design, patients who could not tolerate EFV were excluded. In addition, few, if any, had a history of neurological or psychiatric disorders, such as depression; these could conceivably be a risk factor for experiencing EFV-induced side-effects.

### Table 3. Changes in metabolic parameters.

<table>
<thead>
<tr>
<th>Safety parameters</th>
<th>End of ETR period at week 6 or week 12 ($n=55$) median (IQR)</th>
<th>End of EFV period at week 6 or week 12 ($n=55$) median (IQR)</th>
<th>Change between ETR and EFV periods ($n=55$) median (IQR)</th>
<th>Treatment effect ($P$ values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>37.0 (26.0; 64.0)</td>
<td>33.0 (24.0; 55.5)</td>
<td>0.0 (−5.5; 6.0)</td>
<td>0.223</td>
</tr>
<tr>
<td>Lipid and glycaemic parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.6 (3.9; 5.5)</td>
<td>5.5 (4.7; 6.3)</td>
<td>−0.7 (−1.1; −0.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.4 (1.0; 1.9)</td>
<td>1.7 (1.2; 2.4)</td>
<td>−0.3 (−0.9; −0.1)</td>
<td>0.0002</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.1 (0.9; 1.3)</td>
<td>1.07 (0.9; 1.4)</td>
<td>−0.02 (−0.1; 0.1)</td>
<td>0.400</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>2.8 (2.1; 3.3)</td>
<td>3.3 (2.6; 3.8)</td>
<td>−0.6 (−0.7; −0.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>5.5 (4.9; 6.1)</td>
<td>5.4 (4.9; 6.0)</td>
<td>0.0 (−0.7; 0.5)</td>
<td>0.870</td>
</tr>
</tbody>
</table>

Changes are in median, IQR. EFV, efavirenz; ETR, etravirine; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; U/L, unit per litre.
Switching to ETR had a masked effect on cholesterol levels; total cholesterol, LDL-cholesterol and triglycerides were all lowered during the ETR period and increased significantly when the patients were on EFV. No clinical trial has so far compared EFV and ETR regarding lipid levels; trials in more experienced patients with salvage therapy may be confounded by the lipid effects of other antiretroviral drugs. Our results indicate that ETR may represent an interesting therapeutic option for patients with lipid abnormalities [31].

In this study, ETR was used once daily, in accordance with its long half-life. We did not observe any viral breakthrough, but should emphasize that this reassuring results only represents a 6-week treatment in 55 patients.

In conclusion, patients on long-term EFV do not, as a rule, prefer ETR after a switch. In patients who have tolerated an EFV regimen for extended periods, switching to an ETR regimen is of limited benefit insofar, as neuropsychiatric side-effects are a concern. Patients on ETR, however, had a better lipid profile. The order effect observed in our trial could be linked to recrudescence of symptoms once EFV is reintiated.

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The analysis and interpretation of data was performed by C.D., A.N., A.C. and B.H.

The drafting of the manuscript was performed by A.C. and B.H.

Critical revision of the manuscript for important intellectual content was performed by all authors. The statistical analysis was performed by C.D. and the study was supervised by B.H.

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