A phase IV, double-blind, multicentre, randomized, placebo-controlled, pilot study to assess the feasibility of switching individuals receiving efavirenz with continuing central nervous system adverse events to etravirine

Laura Waters\textsuperscript{a}, Martin Fisher\textsuperscript{b}, Alan Winston\textsuperscript{c}, Chris Higgs\textsuperscript{a}, Wendy Hadley\textsuperscript{b}, Lucy Garvey\textsuperscript{c}, Sundhiya Mandalia\textsuperscript{a}, Nicky Perry\textsuperscript{b}, Nicola Mackie\textsuperscript{c} and Mark Nelson\textsuperscript{a}

\textbf{Background:} Two nucleoside reverse transcriptase inhibitors (NRTIs) and efavirenz (EFV) is a recommended initial regimen for HIV-1. Most EFV-related central nervous system (CNS) toxicity resolves early though symptoms may persist; we studied switching to etravirine (ETR) in these individuals.

\textbf{Methods:} A randomized, double-blind trial in patients with viral suppression but ongoing CNS adverse events after more than 12 weeks EFV. Patients received 2NRTI/EFV/ETR-placebo (delayed switch) or 2NRTI/ETR/EFV-placebo (immediate switch) for 12 weeks followed by 12-week open-label phase (2NRTI/ETR). Primary end-point was percentage with G2-4 CNS adverse events at 12 weeks.

\textbf{Results:} Thirty-eight men; 20/18 were randomized to immediate switch/delayed switch; median CD4 was 444/498 cells/\mu{l}, respectively. Baseline CNS adverse events were similar. Nineteen immediate switch patients completed follow-up (one lost to follow-up) and 13 on delayed switch (two lost to follow-up, two withdrawn consent, one adverse event). Immediate switch G2-4 CNS adverse event: 90\% at baseline, 60\% at week 12 ($P=0.041$). Delayed switch G2-4 CNS adverse event: 88.9\% at baseline, 81.3\% at week 12 ($P=\text{ns}$). Combined (both arms) percentage decline in G2-4 CNS adverse event after 12 weeks of ETR was significant for overall adverse events, insomnia, abnormal dreams and nervousness ($P=0.009, 0.016, 0.001, \text{and} 0.046, \text{respectively}$). All participants on study maintained HIV-RNA below 50 and median week 24 CD4 was 593 and 607 cells/\mu{l} on immediate switch and delayed switch. Two participants experienced new G3-4 adverse events [delayed switch: G3 flatulence on EFV); immediate switch: G4 viral URTI on ETR (SAE)].

\textbf{Conclusion:} Switching EFV to ETR led to a significant reduction in overall G2-4 CNS adverse events, including insomnia, abnormal dreams and nervousness as individual adverse event. Lack of improvement for some events suggests other causative factors.


\textbf{Keywords:} adverse events, central nervous system, efavirenz, etravirine, neuro-psychiatric, switch, toxicity

\textsuperscript{a}Chelsea & Westminster Hospital, London, \textsuperscript{b}Royal Sussex County Hospital, Brighton, and \textsuperscript{c}St Mary’s Hospital, London, UK.

Correspondence to Dr Laura Waters, Department of HIV/GU Medicine, Chelsea and Westminster Hospital Foundation Trust, 369 Fulham Road, London SW10 9NH, UK.

Tel: +44 20 8846 6503; fax: +44 20 8746 5628; e-mail: lwaters@nhs.net

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Introduction

Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that, in combination with two nucleoside reverse transcriptase inhibitors (NRTIs), is a recommended first-line regimen for the treatment of HIV-1 infection [1–3]. Antiretroviral toxicity is the most common reason for modification of first-line therapy [4,5]. Central nervous system (CNS) toxicity is a common side effect of EFV: 19.4% of patients experience at least moderate CNS adverse events on EFV compared with 9% on control regimens [6]; CNS toxicity is one of the most frequent reasons for switching or discontinuing highly active antiretroviral therapy (HAART) [4].

Although most CNS toxicity resolves after 2–4 weeks of EFV [6] some patients experience ongoing symptoms [7] and chronic low-grade CNS toxicity may be underestimated. Higher levels of stress, anxiety and abnormal dreams were reported in patients on stable EFV-containing HAART compared with matched controls [8] and long-term (184 week) follow-up of a subset of patients from ACTG5095 showed EFV was associated with bad dreams and anxiety compared with baseline [9].

Etravirine (ETR) is a second-generation NNRTI licensed for treatment–experienced HIV–1–infected adults [10]. Rates of nervous system and psychiatric adverse events were similar when ETR was compared with placebo in treatment–experienced patients, each in combination with optimized background therapy [11]. ETR has a higher genetic barrier to resistance than first-generation NNRTI. Although ETR licensed for twice daily (b.i.d.) administration, pharmacokinetic data support once-daily (q.d.) dosing; 200 mg b.i.d. and 400 mg q.d. achieve similar 24-h exposure and minimum plasma concentrations in healthy volunteers [12]. EFV reduces ETR concentrations by 30–40%, demonstrated in a healthy volunteer pharmacokinetic study, but this reduction was not considered clinically significant as all participants maintained plasma concentrations well above the IC50 for wild-type virus. The authors concluded that no dose adjustment is necessary when switching directly from EFV to ETR, whether the ETR was dosed q.d. or b.i.d. [13].

The aim of this study was to assess the impact of switching from EFV to ETR q.d. on CNS symptoms in patients on a stable, fully suppressive, EFV-based regimen.

Methods

HIV–1–infected adults who had received at least 12 weeks of EFV and two NRTIs with ongoing CNS symptoms were recruited from three UK sites (Chelsea and Westminster and St Mary's Hospitals, London and The Royal Sussex County Hospital, Brighton). Patients were required to have an undetectable plasma viral load (less than 50 copies/ml) and CD4 cell count greater than 50 cells/μl at screening. Exclusion criteria included previous exposure to etravirine or rilpivirine, a serious medical or psychiatric condition, acute viral hepatitis, an active AIDS–defining illness, significant laboratory abnormality, disallowed concomitant medication (as per the summary of product characteristics for EFV and ETR), resolution of CNS toxicity between screening and baseline, and patients who were pregnant or breastfeeding. All patients provided written, informed consent and ethics approval was granted by local Research Ethics Committees for each study site.

The study comprised of two phases as outlined in Fig. 1. Eligible patients were randomized at baseline to one of two arms:

1. Immediate switch: 2 NRTI + ETR 400 mg q.d. + EFV-placebo
2. Delayed switch: 2 NRTI + EFV 600 mg q.d. + ETR-placebo

Study assessments

At each study visit patients underwent urine macroanalysis and blood sampling for plasma HIV–RNA (Chiron bDNA), CD4 cell count and percentage, CD8 cell count and percentage, biochemistry (hepatic, renal and bone profiles), haematology (full blood count and differential), fasting lipids (total, high-density lipoprotein (HDL) and low–density lipoprotein (LDL) cholesterol, total: HDL cholesterol ratio and triglycerides) and fasting glucose. Adverse events were based on the summary of product characteristics and local clinical experience; these were documented at each visit and graded in a manner based on the to the AIDS Clinical Trials Group (ACTG) Division of AIDS scale (2004). The following CNS adverse events were investigated:

1. Dizziness
2. Depression
3. Insomnia

Fig. 1. Study design. EFV, efavirenz; ETR, etravirine; NRTI, nucleoside reverse transcriptase inhibitor; q.d., once daily.
Impact of switching to etravirine on efavirenz-related CNS toxicity

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(4) Anxiety
(5) Impaired concentration
(6) Headache
(7) Somnolence
(8) Fatigue
(9) Abnormal dreams
(10) Nervousness
(11) Hallucinations

Study participants were specifically questioned by a research doctor at each study visit about each neuro-psychiatric and CNS adverse events as listed above; these were graded on a four-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening). CNS adverse events were described as the proportion of patients with any grade 2–4 adverse events and individual grade 2–4 adverse events; the median number of grade 2–4 CNS adverse event was also calculated. A 'CNS score' was calculated based on the sum total of all grades of CNS adverse events; for example, a patient with grade 1 depression, grade 3 anxiety, grade 2 insomnia and no other CNS adverse events would have a CNS score of 6.

The primary endpoint of the study was change in the proportion of patients experiencing grade 2–4 CNS toxicity at week 12. Secondary endpoints were as follows:

(1) Change in CNS score
   (a) At week 12 and week 24
   (b) Combined (immediate switch and delayed switch) after 12 weeks on ETR

(2) Median number of grade 2–4 CNS adverse events
   (a) At week 12 and week 24
   (b) Combined (immediate switch and delayed switch) after 12 weeks on ETR

(3) Viral suppression at week 12 and week 24
(4) CD4 change at week 12 and week 24
(5) Fasting lipids
(6) Safety and non-CNS tolerability

Statistical analyses
All data analyses were performed in SAS V9 (SAS Institute Inc., Cary, North Carolina, USA). Quantitative data with hypergeometric distribution is presented as medians with interquartile ranges (IQRs); qualitative data have been presented as proportions. Between-group quantitative comparisons were analysed with Mann–Whitney U test, between-groups qualitative comparisons with chi-squared testing (+/− Yates’ correction for small numbers). Within–participant changes over time were analysed using: Wilcoxon signed–rank test (quantitative data) or McNemar’s chi–squared test (qualitative data). Due to the relatively small sample size, P values are presented as Yate’s corrected; all P values are two-tailed.

Results

Thirty-eight men were enrolled; median age was 43 years (range 26–64) and median duration of EFV exposure at baseline was 21.4 months (range 3.5–117.5 months). Median baseline CD4 cell count was 510 cells/μl (IQR 365–611 cells/μl) and plasma viral load was less than 50 copies/ml in all patients at screening and baseline. Twenty patients were randomized to immediate switch and 18 to delayed switch; patient disposition is illustrated in Table 1. NRTI backbones were: tenofovir/emtricitabine fixed-dose combination [60% immediate switch arm, 61% delayed switch arm (50% as Atripla in each arm)], abacavir/lamivudine fixed-dose combination (35% immediate switch arm, 22% delayed switch arm), abacavir/tenofovir (5% immediate switch arm, 11% delayed switch arm) and tenofovir/lamivudine (6% delayed switch arm); none of the differences in backbone use between the two study arms were statistically significant.

Central nervous system adverse events
Rates of baseline CNS toxicity were similar in the two arms (Table 2); 90% in the immediate switch arm and 88.9% in the delayed switch arm had at least one grade 2–4 CNS adverse event and the frequency of individual grade 2–4 CNS adverse events were similar with the exception of insomnia (75% in the immediate switch arm compared with 39% in the delayed switch arm; P = 0.024). Baseline CNS score was 14 (IQR 6–17.5) in the immediate switch arm and 10 (IQR 5.5–17.5) in the delayed switch arm; this difference was not significant (P = 0.534).

Change from baseline to week 12
At week 12 (Table 3) the proportion of patients with grade 2–4 CNS adverse events (primary endpoint) had declined to 60% in the immediate switch arm and remained unchanged (81.3%) in the delayed switch arm (P = 0.041 and P = 0.999 compared with baseline, respectively). In terms of individual grade 2–4 CNS adverse events there were no significant changes in the delayed switch arm; the proportion experiencing abnormal dreams declined significantly in the immediate switch arm (from 50% at baseline to 20% at week 12; P = 0.041) and was significantly less than in the delayed switch arm (62.5%; P = 0.009). The median number of grade 2–4 CNS adverse events at baseline was 4 in the

Table 1. Subject disposition.

<table>
<thead>
<tr>
<th></th>
<th>Immediate switch</th>
<th>Delayed switch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baselined</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Completed</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Withdrawal of consent</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Adverse event</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Virological failure</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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immediate switch arm and 3 in the delayed switch arm and at week 12 this had changed to 1.5 in the immediate switch arm ($P = 0.003$) and was unchanged in the delayed switch arm. Finally, CNS score declined from 14 at baseline to 6 at week 12 in the immediate switch arm ($P = 0.001$) and from 10 to 7.5 in the delayed switch arm ($P = 0.192$).

**Change from week 12 to week 24**

In the immediate switch arm there was no further significant change in overall or individual grade 2–4 CNS adverse events from week 12 to week 24 ($P$ values for week 12 vs. week 24 not presented). In the delayed switch arm there was a numerical reduction in proportion of patients with any grade 2–4 CNS adverse events in the delayed switch arm from week 12 to week 24, although this was not statistically significant; there was, however, a significant reduction in abnormal dreams in delayed switch arm from week 12 to week 24 ($P = 0.023$). In terms of median number of grade 2–4 CNS adverse events at week 24 there was a further small reduction compared with week 12 from 1.5 to 1 in the immediate switch arm ($P = 0.085$) and a decline from 3 to 1 in the delayed switch arm ($P = 0.003$).

**Combined analyses**

Combined analyses were performed to calculate the change in CNS adverse events after 12 weeks of ETR; changes from baseline to week 12 in the immediate switch arm and from week 12 to week 24 in the delayed switch arm were combined for statistical analysis. After 12 weeks of ETR there were significant reductions in the proportion of patients reporting any grade 2–4 CNS adverse events ($P = 0.009$), grade 2–4 insomnia ($P = 0.016$), abnormal dreams ($P = 0.001$) and nervousness ($P = 0.046$) compared with baseline. Combined change in other CNS events was not significant. Median number of grade 2–4 CNS adverse events declined from 3 at baseline to 1 at 12 weeks ($P < 0.001$) and CNS score from 10 to 7 ($P = 0.001$).

**Virological and immunological efficacy**

All participants on study maintained viral suppression (less than 50 copies/ml) at all visits. By on-treatment analysis

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### Table 2. Rates of overall and individual central nervous system events in immediate switch and delayed switch arms.

<table>
<thead>
<tr>
<th>Grade 2–4 CNS conditions at baseline</th>
<th>IS (n = 20) (%)</th>
<th>DS (n = 16) (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion with any grade 2–4 CNS AE</td>
<td>15 (75.0%) 95% CI 63–88%</td>
<td>16 (88.9%) 95% CI 65–98.6%</td>
<td>0.676</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (35.0%)</td>
<td>3 (6.7%)</td>
<td>0.544</td>
</tr>
<tr>
<td>Depression</td>
<td>7 (35.0%)</td>
<td>6 (33.3%)</td>
<td>0.914</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3 (15.0%)</td>
<td>4 (22.2%)</td>
<td>0.386</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2 (10.0%)</td>
<td>2 (10.0%)</td>
<td>0.480</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (25.0%)</td>
<td>4 (22.2%)</td>
<td>0.302</td>
</tr>
<tr>
<td>Somnolence</td>
<td>4 (20.0%)</td>
<td>2 (10.0%)</td>
<td>0.386</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (50.0%)</td>
<td>12 (66.7%)</td>
<td>0.299</td>
</tr>
<tr>
<td>Impaired concentration</td>
<td>1 (5.0%)</td>
<td>1 (5.6%)</td>
<td>0.939</td>
</tr>
<tr>
<td>Nervousness</td>
<td>2 (10.0%)</td>
<td>4 (22.2%)</td>
<td>0.192</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (10.0%)</td>
<td>4 (22.2%)</td>
<td>0.302</td>
</tr>
<tr>
<td>Somnolence</td>
<td>8 (40.0%)</td>
<td>6 (33.3%)</td>
<td>0.671</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (45.0%)</td>
<td>8 (44.4%)</td>
<td>0.973</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>10 (50.0%)</td>
<td>12 (66.7%)</td>
<td>0.299</td>
</tr>
<tr>
<td>Anxiety</td>
<td>7 (35.0%)</td>
<td>5 (27.8%)</td>
<td>0.633</td>
</tr>
<tr>
<td>Hallucinations (auditory)</td>
<td>0</td>
<td>0</td>
<td>0.683</td>
</tr>
</tbody>
</table>

AE, adverse event; CI, confidence interval; CNS, central nervous system.

### Table 3. Rates of grade 3–4 CNS events at week 12 and week 24 by study arm ($P$ values refer to difference at each time point compared with event rates at baseline).

<table>
<thead>
<tr>
<th>Overall CNS events</th>
<th>IS (n = 20) (%)</th>
<th>DS (n = 16) (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>3 (15.0%)</td>
<td>3 (18.8%)</td>
<td>0.618</td>
</tr>
<tr>
<td>Depression</td>
<td>4 (20.0%)</td>
<td>3 (18.8%)</td>
<td>0.372</td>
</tr>
<tr>
<td>Insomnia</td>
<td>10 (50.0%)</td>
<td>7 (43.8%)</td>
<td>0.999</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5 (25.0%)</td>
<td>7 (43.8%)</td>
<td>0.999</td>
</tr>
<tr>
<td>Impaired concentration</td>
<td>6 (30.0%)</td>
<td>5 (31.3%)</td>
<td>0.999</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (5.0%)</td>
<td>4 (25%)</td>
<td>0.617</td>
</tr>
<tr>
<td>Somnolence</td>
<td>6 (30.0%)</td>
<td>5 (31.3%)</td>
<td>0.999</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (35.0%)</td>
<td>7 (43.8%)</td>
<td>0.999</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>4 (20.0%)</td>
<td>10 (62.5%)</td>
<td>0.724</td>
</tr>
<tr>
<td>Nervousness</td>
<td>2 (10%)</td>
<td>4 (25%)</td>
<td>0.617</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>0 (0%)</td>
<td>1 (6.7%)</td>
<td>0.480</td>
</tr>
</tbody>
</table>

CNS, central nervous system; DS, delayed switch; IS, immediate switch.
viral suppression rates were 100% at weeks 12 and 24 for both treatment arms.

Week 12 CD4 rise from baseline was $+40$ cells/µl in the immediate switch arm and $+6$ cells/µl in the delayed switch arm; at week 24 CD4 rises from baseline were $+68$ cells/µl and $+60$ cells/µl, respectively. In the combined analysis the median CD4 rise after 12 weeks of ETR was $+43$ cells/µl ($P = 0.027$ compared with baseline).

**Lipids**

Lipid changes are illustrated in Table 4. Analysing the two arms of the study individually, there was a significant reduction in total cholesterol in each arm after 12 weeks of ETR ($-0.64$ mmol/l in the immediate switch arm and $-0.63$ mmol/l in the delayed switch arm; $P = 0.017$ and $P = 0.024$, respectively). In addition there was a significant reduction in LDL-cholesterol in the immediate switch arm after 12 weeks of ETR ($-0.74$ mmol/l; $P = 0.043$). There were no significant changes in HDL-cholesterol or triglycerides.

When the changes after 12 weeks of ETR in each arm were combined (i.e. the change from baseline to week 12 in the immediate switch arm and from week 12 to week 24 in the delayed switch arm) reductions in total cholesterol and LDL-cholesterol were significant at $-0.64$ mmol/l ($P < 0.001$) and $-0.58$ mmol/l ($P = 0.021$), respectively.

In terms of lipid-lowering agents, at baseline 3 participants in the immediate switch arm were on a statin. In the delayed switch arm two patients were receiving a statin at baseline and one was taking fish oil supplements. Lipid-lowering drug use remained stable during the study and no new agents were started.

**Non-central nervous system adverse events and laboratory abnormalities**

There were two new grade 3/4 adverse events: one patient in the delayed switch arm developed grade 3 flatulence (deemed probably drug-related) during the blinded phase (i.e. on EFV with ETR placebo) and one patient in the immediate switch arm was hospitalized during the blinded phase with a viral upper respiratory tract infection [grade 4 (serious adverse event); not drug-related]. Patient subsequently experienced full recovery.

All other adverse events were grade 2 or less. Grade 2 adverse events deemed at least probably study drug related are outlined in Table 5.

There were no changes in liver function tests, no grade 2 or greater nausea and no cases of rash at any time point in the study.

**Discussion**

The study demonstrates an improvement in several measures of CNS toxicity when switching from EFV to ETR in patients stable on an EFV-based regimen. All
patients were required to have been on EFV for at least 12 weeks but the median EFV exposure at study entry was much longer (21.4 months). These data further confirms the persistence of CNS toxicity in some EFV-treated patients as demonstrated in other studies and cohorts.

Although the study was open to male and female patients, by chance all recruited patients were men; this was consistent with the patient demographics across the three sites. The study population reported high rates of CNS toxicity at baseline; majority of individuals had at least one grade 2–4 CNS adverse event and a median of three grade 2–4 CNS adverse events in total. By definition our study selected patients with persistent CNS toxicity and it is possible that the time commitment required of participants, and the higher pill burden (six pills or more during the blinded phase), further selected individuals with more severe toxicity. The prevalence of CNS toxicity cannot therefore be applied to the general clinic population.

Switching to ETR most improved sleep-related CNS adverse events (abnormal dreams and insomnia), as well as nervousness, but yielded no significant improvement in other CNS adverse events. The study was not powered to detect significant differences for each of the individual adverse event. It may be that individuals with other possible EFV-related CNS adverse events, such as depression, had already switched away to alternative regimens or were less likely to enter the study. Alternatively, some CNS symptoms on stable EFV regimen may be secondary to other factors and not drug-related. Although the difference in baseline CNS score between the two arms was not statistically significant it was numerically higher in the immediate switch arm; we cannot exclude that improvement in the CNS score at week 12 in the immediate switch arm was secondary to regression to the mean rather than an effect of treatment switch.

The study also provides limited data supporting the use of ETR as a q.d. agent. Once-daily dosing is unlicensed but supported by the pharmacokinetic profile of ETR [12,13]. No virological failures occurred in the 19 and 15 patients completing 24 and 12 weeks of once-daily ETR-based HAART, respectively. However, the study population was small and all patients were virologically suppressed, most for more than 48 weeks, prior to switching to ETR. These results cannot necessarily be extrapolated to patients with viraemia. Additionally all patients had baseline resistance tests demonstrating full NNRTI susceptibility; switching to q.d. ETR may not be appropriate for patients with any evidence of NNRTI resistance.

In addition we described an improvement in lipids with significant reductions in total and LDL-cholesterol after 12 weeks of ETR. EFV is known to be associated with lipid changes [14]; ETR, like other new agents including maraviroc [15] and raltegravir [16,17], is associated with better lipid parameters and may be a switch option for metabolic reasons.

Several studies have shown that switching therapy in patients with viral suppression maintains efficacy [18–20]. Until recent years the switch options available to patients with EFV-related CNS toxicity were mainly limited to protease inhibitors. Switching from efavirenz to nevirapine results in improvements in CNS toxicity [21] and lipids [22] but is limited by the CD4 restrictions for NVP use [23]. The advent of newer, once-daily agents should encourage active questioning about CNS toxicity in patients on EFV. Proactive switch away from EFV may yield significant reductions in CNS toxicity. Patients can be reassured that, in the absence of noticeable improvement, they can resume an EFV-containing regimen.

In conclusion, once-daily etravirine offers an efficacious, tolerable and lipid-friendly alternative to efavirenz in patients with persistent CNS toxicity.

Acknowledgement

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References


