A comparison of neuropsychiatric adverse events during 12 weeks of treatment with etravirine and efavirenz in a treatment-naive, HIV-1-infected population

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\textbf{Background:} Although efavirenz is a universally recommended treatment for naive HIV-infected individuals, neuropsychiatric adverse events are common.

\textbf{Methods:} The Study of Efavirenz NeuropSychiatric Events versus Etravirine (SENSE) trial is a double-blind, placebo-controlled study in which 157 treatment-naive individuals with HIV-RNA higher than 5000 copies/ml were randomized to etravirine 400 mg once daily (n = 79) or to efavirenz 600 mg once daily (n = 78), with two investigator-selected nucleoside reverse transcriptase inhibitors (NRTIs). The primary end point was the percentage of patients with grade 1–4 drug-related treatment-emergent neuropsychiatric adverse events up to week 12.

\textbf{Results:} The study population were 81\% men and 85\% whites, with a median age of 36 years, baseline CD4 cell counts of 302 cells/\mu l and HIV-RNA of 4.8 log_{10} copies/ml. In the intent-to-treat analysis, 13 of 79 individuals (16.5\%) in the etravirine arm and 36 of 78 individuals (46.2\%) in the efavirenz arm showed at least one grade 1–4 drug-related treatment-emergent neuropsychiatric adverse event (P < 0.001). The number with at least one grade 2–4 drug-related treatment-emergent neuropsychiatric adverse event was four of 79 individuals (5.1\%) in the etravirine arm and 13 of 78 individuals (16.7\%) in the efavirenz arm (P = 0.019). The change in HIV-RNA to week 12 was $-2.9 \log_{10}$ in both treatment arms. The median rise in CD4 cell counts was 146 cells/\mu l in the etravirine arm and 121 cells/\mu l in the efavirenz arm.

\textbf{Conclusions:} After 12 weeks, first-line treatment with etravirine 400 mg once daily with two NRTIs was associated with significantly fewer neuropsychiatric adverse events when compared with efavirenz with two NRTIs. The virological and immunological efficacy profile was similar between the two arms.

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Introduction

The most widely recommended nonnucleoside reverse transcriptase inhibitor (NNRTI) for first-line use is efavirenz [1,2], owing to the consistently high rates of HIV-RNA suppression observed in trials [3–5]. However, efavirenz is associated with an increased risk of developing nervous system or psychiatric adverse events, particularly dizziness and sleep disorders [6]. Several head-to-head studies in treatment-naive populations have shown a higher risk of grade 1–4 neuropsychiatric (NPS) adverse events for efavirenz when compared with other antiretrovirals, as measured by the Division of AIDS [7] 2007 grading scale [5,8–10], but increases in grade 3 or 4 (severe or life-threatening) adverse events have been smaller [11,12].

Etravirine (TMC125, ETR) is an NNRTI with activity against both wild-type and NNRTI-resistant HIV [13]. Etravirine was first evaluated in treatment-naive and treatment-experienced individuals as a monotherapy for 7 days [14,15]. In the TMC125 to Demonstrate Undetectable Viral Load in Patients Experiencing with ARV Therapy (DUET) studies, treatment-experienced populations receiving etravirine 200 mg twice daily with background antiretrovirals had higher HIV-RNA suppression rates than those receiving placebo with background antiretrovirals. The percentage developing NPS adverse events was similar in the etravirine and placebo arms. [16]. More recent studies have evaluated etravirine at a dose of 400 mg once daily [17,18]. In a 24-week study, 40 individuals with NPS toxicities while taking efavirenz showed improvements in these toxicities when switched to etravirine 400 mg once daily [17].

The Study of Efavirenz NeuropSychiatric Events versus Etravirine (SENSE) trial was designed to evaluate whether 12 weeks of once-daily etravirine with two nucleoside reverse transcriptase inhibitors (NRTIs) would be associated with fewer NPS adverse events than efavirenz with two NRTIs.

Methods

The SENSE trial recruited 157 antiretroviral treatment-naive individuals with HIV-RNA levels above 5000 copies/ml and no genotypic or phenotypic resistance to study antiretrovirals at the screening visit [19]. The planned duration of the trial was 48 weeks, with the primary analysis of neuropsychiatric adverse events at week 12. Patients were randomized to receive either etravirine 400 mg once daily or efavirenz, with two investigator-selected NRTIs (either tenofovir/emtricitabine, abacavir/lamivudine or zidovudine/lamivudine). Etravirine was administered as four 100 mg tablets once daily (or matching placebo), and efavirenz as a single 600 mg tablet once daily (or matching placebo).

Individuals were instructed to take etravirine or matching placebo in the morning with breakfast, and then efavirenz or matching placebo in the evening on an empty stomach, ideally at bedtime.

Efficacy and safety assessments

Patients attended study visits at screening, baseline and at weeks 2, 6 and 12. Plasma HIV-RNA was measured using the Roche Amplicor HIV-1 Monitor assay (version 1.5, Roche Molecular Systems, Branchburg, New Jersey, USA). Viral genotype and predicted phenotype were evaluated at screening and baseline, using the virco TYPE HIV-1 assay (Virco BVBA, Beerse, Belgium). The presence of NRTI, NNRTI or protease inhibitor mutations at screening [19] was used to assess primary HIV drug resistance. Clinical and laboratory abnormalities were classified using the Division of AIDS grading tables [7]. This system classifies adverse events as either grade 1 (mild), grade 2 (moderate), grade 3 (severe) or grade 4 (life-threatening).

Written informed consent was obtained from all participating individuals prior to study entry. The trial protocol was reviewed and approved by the appropriate institutional ethics committees and health authorities, and the trial was undertaken in accordance with the Declaration of Helsinki and Good Clinical Practice.

Statistical methods

The primary end point was the percentage of individuals with at least one grade 1–4 treatment-emergent, drug-related NPS adverse event at the week 12 analysis. Twelve weeks duration of therapy was used for the primary analysis, as differences in NPS events between efavirenz and other antiretrovirals have been detected at this point of time in previous studies. Estimates of the rate of grade 1–4 drug-related NPS adverse events from the TMC278-C204 trial (TMC278 versus efavirenz) were used for the sample size calculations [10], assuming 90% power and a two-sided significance level of 0.05.

The primary end point was analyzed using logistic regression, adjusted for the stratification variable of screening HIV-RNA. All analyses were performed on the intent-to-treat (ITT) population.

Results

Baseline characteristics

Of 193 screened, 157 individuals were randomized and treated (79 in the etravirine arm and 78 in the efavirenz arm) and were included in the ITT analysis. Overall, 81% of the patients were men with a median age of 36 years,
mean weight of 73 kg and median CD4 cell counts of 302 cells/μl (Table 1). Baseline characteristics were well balanced between the two treatments, with the exception of the number of International AIDS Society-USA defined NRTI and NNRTI mutations which were detected more frequently in the etravirine arm (Table 1). However, these mutations were mainly polymorphisms which did not affect phenotypic sensitivity of etravirine. Nucleoside analogues used at baseline were tenofovir with emtricitabine (60%), abacavir with lamivudine (26%) and zidovudine with lamivudine (14%).

Ten patients in the etravirine arm and eight in the efavirenz arm discontinued by week 12 (Table 1). Four patients in the etravirine arm and eight in the efavirenz arm discontinued study medication for adverse events. One patient in the etravirine arm and five in the efavirenz arm discontinued study medication with NPS adverse events.

Neuropsychiatric adverse events
Figure 1 shows the percentage of individuals with graded NPS adverse events up to the week 12 analysis in the etravirine and efavirenz arms. In the primary analysis, the percentage with treatment-emergent grade 1–4 drug-related NPS adverse events was 16.5% in the etravirine arm and 46.2% in the efavirenz arm (P < 0.001). In addition there was a significant difference between the arms for the end points of all cause grade 1–4 NPS events (P < 0.001) (Fig. 1a), and grade 2–4 drug-related treatment-emergent NPS events (P = 0.019), but not for grade 2–4 NPS adverse events (all cause) (Fig. 1b).

The NPS adverse events were divided into nervous system disorders and psychiatric complications. The percentage with at least one grade 1–4 nervous system disorder (all cause) was 20.2% in the etravirine arm versus 33.4% in the efavirenz arm. The most common adverse event of the nervous system was dizziness, reported in three patients (4%) in the etravirine arm and 15 patients (19%) in the efavirenz arm. The percentage with at least one grade 1–4 psychiatric disorder was 11% with etravirine and 39% with efavirenz. The most common psychiatric adverse events were sleep disorder (abnormal dreams, nightmares, sleep disorders or insomnia) which was observed in seven patients (9%) in the etravirine arm and 25 patients (32%) in the efavirenz arm. One patient receiving etravirine and four receiving efavirenz reported grade 1–4 depression. The prevalence of grade 1–4 NPS adverse events showed a peak at week 2 (21.5% with etravirine and 43.6% with efavirenz), but at the week 12 visit, the percentage with an ongoing drug-related grade 1–4 all cause NPS adverse event remained different between the arms (11.6% with etravirine and 30.0% with efavirenz, P = 0.015).

Safety
Up to week 12, five individuals receiving etravirine had experienced a serious adverse event versus three receiving efavirenz. There were no deaths in the study population.

Sixteen individuals receiving etravirine (20.3%) experienced at least one drug-related grade 2–4 adverse event versus 25 (32.1%) receiving efavirenz. Eight individuals (10.1%) in the etravirine arm and nine (11.5%) in the efavirenz arm experienced a grade 2–4 skin or
subcutaneous adverse event. Four patients in each treatment group discontinued the trial because of subcutaneous adverse events (two patients in each arm discontinued due to grade 2 rash and two per arm because of grade 3 rash). There were fewer grade 2–4 elevations in total cholesterol and low-density lipoprotein cholesterol in the etravirine arm (three and six individuals, respectively) compared with the efavirenz arm (18 and 13 individuals, respectively).

HIV-RNA and CD4 cell counts
The mean change in HIV-RNA to week 12 was $-2.9\log_{10}$ in both treatment arms. The percentage of patients achieving HIV-RNA levels below 400 copies/ml at week 12 was 87.9% with etravirine and 92.6% with efavirenz. A single patient in the efavirenz arm with persistently high HIV-RNA levels during the trial (owing to suboptimal levels of adherence) and developed NRTI and NNRTI mutations. The median rise in CD4 cell counts was 146 cells/µl in the etravirine arm and 121 cells/µl in the efavirenz arm ($P = \text{NS}$).

Discussion
In the SENSE trial, the percentage of individuals experiencing grade 1–4 drug-related NPS adverse events was significantly lower in antiretroviral-naive individuals treated with etravirine 400 mg once daily with two NRTI (16.5%) when compared with those treated with efavirenz with two NRTI (46.2%). The 12-week virological and immunological responses were similar.

A benefit of etravirine over efavirenz in the primary analysis was observed when NPS adverse events were analyzed using several different methods: grade 1–4 all cause NPS adverse events, grade 1–4 drug-related events and grade 2–4 drug-related events. The most commonly observed nervous system adverse event associated with efavirenz was dizziness, whereas the most common psychiatric adverse events were sleep disorders (nightmares, insomnia, sleep disorders or somnolence). This is consistent with previous studies which have also shown an excess of dizziness and/or sleep disorders in those receiving efavirenz when compared with other antiretrovirals [5,6,9,10].

The improved NPS adverse event profile of etravirine may improve long-term adherence to antiretroviral treatment. The clinical implications of the more neutral lipid profile are unknown.

Although there was a statistically significant benefit for etravirine over efavirenz for NPS adverse events, most of these adverse events were grade 1 (mild) or grade 2 (moderate) in intensity. There was no significant difference between the arms in the number discontinuing treatment for NPS adverse events. The SENSE trial includes a short-term evaluation of NPS adverse events. Longer term follow-up is required to determine whether the safety benefits of etravirine are sustained, and if there is also durable HIV-RNA suppression. The trial is continuing to week 48. With a sample size of 157 patients, the SENSE trial is not large enough to determine whether etravirine shows equivalent rates of HIV-RNA suppression when compared with efavirenz: noninferiority trials to evaluate relative efficacy normally include 600–800 patients [20]. The SENSE trial recruited mainly white homo/bisexual men, and further clinical experience of first-line etravirine is needed in other populations. In nonwhites, there is a higher prevalence of genetic polymorphisms in CYP2B6 metabolism which may lead to elevated efavirenz levels and possible increases in adverse events [21,22]. The analysis of NPS adverse events is complex because there is a high-background incidence of underlying NPS problems in the HIV-infected population, associated with HIV disease itself, recreational drug use and other factors [23,24].

In summary, 12 weeks therapy with etravirine 400 mg once daily with two NRTIs led to significantly fewer NPS adverse events.
adverse events, compared with efavirenz with two NRTIs. Longer term follow-up is required to determine whether the safety benefits of etravirine compared with efavirenz are sustained. Also the longer term efficacy and resistance profiles after virological failure will help to guide decisions on sequencing of these two nonnucleosides.

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References


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