

Phase 2 double-blind, randomised trial of etravirine versus efavirenz in treatment-naïve patients: 48 week results

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Background: The SENSE Trial compared etravirine with efavirenz in treatment-naïve patients. The primary endpoint was neuropsychiatric (NPS) adverse events (AEs) up to Week 12; HIV RNA suppression at Week 48 was a secondary endpoint.

Methods: Patients with HIV RNA >5000 copies/mL were randomised to etravirine 400 mg OD (n = 79) or efavirenz (n = 78), plus two nucleoside analogues. HIV RNA <50 copies/mL at Week 48 was analysed using the Time to Loss of Virological Response (TLOVR) algorithm. Drug resistance at treatment failure and safety endpoints were also evaluated.

Results: At baseline, the median CD4 count was 302 cells/uL and HIV RNA 4.8 log₁₀ copies/mL. In the ITT TLOVR analysis at Week 48, 60/79 (76%) patients on etravirine versus 58/78 (74%) on efavirenz had HIV RNA <50 copies/mL. In the On Treatment analysis, there were 92% with HIV RNA <50 copies/mL for etravirine versus 89% for efavirenz: etravirine showed non-inferior efficacy versus efavirenz in both analyses (p < 0.05). Four patients had virological failure in the etravirine arm: none developed resistance to nucleoside analogues or non-nucleosides. Seven patients had virological failure in the efavirenz arm: three developed treatment-emergent resistance to nucleoside analogues and/or non-nucleosides. At the Week 48 visit, the percentage with ongoing neuropsychiatric adverse events was 6.3% for etravirine and 21.5% for efavirenz, p = 0.011).

Conclusions: First-line treatment with etravirine 400 mg OD + 2NRTIs led to similar rates of HIV RNA suppression, compared with efavirenz + 2NRTIs. None of the patients with virological failure in the etravirine arm developed resistance to NRTIs or NNRTIs.

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Introduction

International HIV treatment guidelines recommend first-line use of two nucleoside analogues (NRTIs) with either a non-nucleoside (NNRTI) or a boosted protease

inhibitor (PI) [1–3]. Of the non-nucleosides, efavirenz 600 mg once daily is the most widely recommended, owing to the high rates of efficacy seen in large randomized trials. The alternative non-nucleoside is nevirapine, which has shown levels of efficacy close to,

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but not equivalent with efavirenz[4]. Nevirapine has recently been reformulated to a 400 mg once daily extended release dosing, which has shown non-inferior efficacy to the original dose of 200 mg twice daily in treatment-naïve patients [5].

There are several concerns over the safety profiles of these two non-nucleosides. Efavirenz showed teratogenicity in animal models, and it is uncertain whether the use of efavirenz in pregnancy could increase the risk of birth defects if used in pregnant women [6]. Efavirenz also causes a range of neuropsychiatric adverse events – in particular dizziness, mood and sleep disorders [7,8]. These adverse events are mild and short-term in most patients, but a minority has long-lasting neuropsychiatric problems. Efavirenz also causes rises in lipids and there is a risk of rash [9,10]. Nevirapine is associated with severe skin reactions in a minority of patients, which can lead to Stevens-Johnsons syndrome, particularly if used in patients with high CD4 counts [6,11]; hepatotoxicity is an additional risk [12]. Patients with virological failure while taking first-line efavirenz or nevirapine have a high risk of developing resistance to non-nucleosides and nucleoside analogues, which can restrict future treatment options [12–14].

The non-nucleoside etravirine has *in vitro* activity versus both NNRTI-naïve and resistant virus [15,16]. Etravirine was evaluated in the DUET trials of highly treatment-experienced patients, and this led to regulatory approval for treatment-experienced patients at the 200 mg twice daily dose [17]. In the DUET trials, there was no increase in neuropsychiatric adverse events or lipids for patients in the etravirine arm versus placebo; there was a small rise in the risk of rash in the etravirine arm [17].

A proof-of-concept trial showed significant reductions in HIV RNA for treatment-naïve patients given etravirine as monotherapy for seven days [18]. The long half-life of etravirine (30–40 hours) supports once daily dosing, and pharmacokinetic studies have evaluated the 400 mg once daily dose of etravirine [19]. The SENSE trial was designed to evaluate the safety and preliminary efficacy of first-line use of etravirine versus the standard control arm of efavirenz, both combined with two nucleoside analogues, for 48 weeks. The primary endpoint of the trial was to compare the neuropsychiatric adverse events at Week 12 between the arms, and this was published previously [20]. This paper will concentrate on the efficacy, resistance and safety outcomes at Week 48.

Methods

Design, randomisation and dosing

The SENSE trial recruited 157 antiretroviral treatment-naïve individuals with HIV RNA levels above

5000 copies/mL and no genotypic or phenotypic resistance to study antiretrovirals at the screening visit [20]. The patients were recruited from Europe, Russia and Israel. Patients were randomised to receive either etravirine 400 mg once daily or efavirenz 600 mg once daily, together with two investigator selected N(t)RTIs (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). The randomisation was stratified for screening HIV RNA – either at/less than or more than 100,000 copies/mL.

Efficacy and safety assessments

Patients attended study visits at screening, baseline and then Weeks 2, 6, 12, 24, 36 and 48. There was a follow up visit 2–8 weeks after Week 48 when the patients were unblinded.

Plasma HIV RNA was measured using the Roche Amplicor HIV-1 Monitor assay (version 1.5, Roche Molecular Systems, Branchburg, 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 PI mutations at screening [21] was used to assess sensitivity to the study drugs. During the trial, patient samples were genotyped for several reasons: (i) if the patient discontinued the trial with detectable HIV RNA levels (ii) if the HIV RNA level had not fallen by 1 log₁₀ by Week 12, or was above 400 copies/mL at this time (iii) if the patient had HIV RNA above 50 copies/mL at the Week 48 visit, or had shown virological failure (HIV RNA >50 copies/mL) by the Time to Loss of Virological Response (TLOVR) algorithm.

Clinical and laboratory abnormalities were classified using the Division of AIDS grading tables [22]. This system classifies adverse events as either Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe) or Grade 4 (life-threatening). Investigators recorded the duration of adverse events, and judged whether they were related to randomised medication. The medRA coding dictionary was then used to classify adverse events into System Organ Classes and individual categories.

Written informed consent was obtained from all participating individuals prior to study entry. Trial protocols were reviewed and approved by the appropriate institutional ethics committees and health authorities, and were undertaken in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP). The Data Safety Monitoring Board reviewed the safety data after all patients had completed Week 12 or discontinued prematurely, and recommended continuation of the trial.

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Role of the funding source

The trial was designed and conducted by Janssen EMEA Medical Affairs, a division of Janssen International N.V., acted as the study sponsor. The statistical analysis was conducted independently by an external statistician (SGS, Mechelen, Belgium), and was reviewed and validated by the trial statistician (AH). The authors had full access to the data and the corresponding author had the final responsibility to submit the manuscript for publication.

Statistical methods

The primary endpoint was the percentage of patients with at least one Grade 1–4 treatment-emergent, drug-related neuropsychiatric adverse event at the Week 12 analysis.

The treatment arms were compared using the protocol defined endpoint of Time to Loss of Virological Response (TLOVR) [23]. Using this endpoint, success is two consecutive HIV RNA levels below 50 copies/mL up to Week 48, with no subsequent confirmed rebound. Treatment failure is defined as two consecutive HIV RNA levels above 50 copies/mL at Week 48, or discontinuation of randomised treatment for either adverse events or other reasons.

The treatment arms were compared for non-inferiority, using multiple logistic regression adjusting for the stratification variable of baseline HIV RNA. A delta estimate of –12% was used for the non-inferiority analysis, which is consistent with other recently published HIV clinical trials [24,25]. It should be noted that the SENSE trial was not statistically powered to demonstrate non-inferior efficacy of etravirine versus efavirenz – this would require a sample size in the region of 300–400 patients per arm [26].

Results

Baseline characteristics

Of 193 screened, 157 individuals were randomised and treated (79 in the etravirine arm and 78 in the efavirenz arm) and were included in the ITT analysis. Genotypic resistance testing at screening was used to exclude patients with evidence of transmitted drug resistance. Among the 36 who were screen failures, the main reasons were the presence of NRTI, NNRTI or PI drug resistance (14 patients), lack of predicted phenotypic sensitivity to NRTIs and NNRTIs (4 patients), or HIV RNA levels below 5000 copies/mL at screening (5 patients). Of the 36 screen failures, 10 patients had either genotypic or phenotypic resistance to efavirenz, but no patients showed either genotypic or phenotypic resistance to etravirine.

Baseline characteristics of the 157 randomised patients are shown in Table 1 and were well balanced between the treatment arms. The patients were predominantly male Caucasians, with a mean age of 38 years. The most common mode of HIV transmission was MSM (79 patients, 50%). The nucleoside analogues used with randomized NNRTIs were tenofovir plus emtricitabine for 94 patients (60%), abacavir plus lamivudine for 41 patients (26%) and zidovudine plus lamivudine for 22 patients (14%) and. At baseline, the median HIV RNA level was 4.8 log₁₀ copies/mL and the median CD4 count was 302 cells/uL. The baseline HIV RNA level was above 100,000 copies/mL for 34% of patients. At the baseline visit, 12 patients in the etravirine arm and four in the efavirenz arm had single IAS-USA NNRTI mutations. These NNRTI mutations were E138A (n=5), V106I (n=4), V108I (n=1) and V90I (n=6). None of these NNRTI mutations was in the

Table 1. Baseline characteristics by treatment arm and patient disposition at Week 48.

	Etravirine arm n = 79	Efavirenz arm n = 78
Mean age, years	38 (18–63)	38 (19–66)
Gender (% male)	67 (85%)	60 (77%)
Race (% Caucasian)	73 (92%)	66 (85%)
MSM (%)	42 (53%)	35 (45%)
Median HIV RNA (log ₁₀ copies/mL)	4.8	4.8
HIV RNA ≤ 100,000 (%)	54 (68%)	52 (67%)
HIV RNA >100,000 (%)	25 (32%)	26 (33%)
Median (range) CD4 count (cells/uL)	319 (74–638)	273 (91–722)
CD4 count <200 cells/uL (%)	12 (15%)	18 (23%)
HIV Sub-Type B virus	54 (68%)	45 (58%)
At least 1 IAS-USA NNRTI mutation	13 (16%)	4 (5%)
At least 1 Bennett NNRTI mutation	0 (0%)	0 (0%)
At least 1 IAS-USA NRTI mutation	5 (6%)	0 (0%)
At least 1 Bennett NRTI mutation	3 (4%)	0 (0%)
Etravirine sensitive (Virtual Phenotype)	79 (100%)	78 (100%)
Efavirenz sensitive (Virtual Phenotype)	77 (97%)	77 (99%)

IAS-USA NRTI mutations: M41L, A62V, K65R, D67N, 69ins, K70E/r, L74V, F77L, Y115F, F116Y, Q151M, M184I/V, L210W, T215Y/F, K219Q/E
Bennett NRTI mutations: M41L, K65R, D67E/G/N, T69D, 69ins, K70E/R, L74I/V, V75A/M/S/T, F77L, Y115F, F116Y, Q151M, M184I/V, L210W, T215C/D/E/F/I/S/V/Y, K219E/N/R/Q
IAS-USA NNRTI mutations: V90I, A98G, L100I, K101E/H/P, K103N, V106A/I/M, V108I, E138A, V179D/F/T, Y181C/I/V, Y188C/H/L, G190A/S, P225H, M230L
Bennett NNRTI resistance mutations: L100I, K101E/P, K103N/S, V106A/M, V179F, Y181C/I/V, Y188C/H/L, G190A/E/S, P225H, M230L

Bennett list of transmitted drug mutations used to exclude patients from the trial [21]. Almost all patients were phenotypically sensitive to the NNRTI they were randomized to (Table 1). There were five patients in the etravirine arm with IAS-USA NRTI mutations at baseline, of whom three also had Bennett NRTI mutations – these three patients were protocol violators. No patient in the efavirenz arm had NRTI mutations at baseline.

Efficacy

Figure 1 shows the percentage of patients with HIV RNA <50 copies/mL at Week 48, by the Time to Loss of Virological Response (TLOVR) algorithm. Results are shown for the overall trial population (Fig. 1a) and for the pre-defined subgroups with baseline HIV RNA ≤100,000 copies/mL (Fig. 1b) and >100,000 copies/mL (Fig. 1c). Two analyses are shown for each Figure – the main TLOVR analysis includes all patients who discontinued treatment for adverse events or other reasons as treatment failures. The “non-VF censored” analysis excludes data from patients who discontinued for adverse events or other reasons – only the virological failures are included.

In the overall trial population (Fig. 1a), the percentage with HIV RNA suppression was similar in the two treatment arms. In the etravirine arm, 60/79 (75.9%) patients had HIV RNA <50 copies/mL at Week 48. Of the 19 treatment failures, four had virological failure, six discontinued for adverse events and nine discontinued for other reasons. In the efavirenz arm, 58/78 (74.4%) patients had HIV RNA <50 copies/mL at Week 48. Of the 20 treatment failures, seven had virological failure, 13 discontinued for adverse events and 2 discontinued for other reasons. In the main TLOVR analysis, the difference in suppression rates was +1.6% in favour of the etravirine arm, with 95% confidence intervals of –12.0% to +15.2%, which met the criteria for non-inferiority with a delta of –12% ($p < 0.05$). In the non-VF censored analysis (including only virological failures), the difference in suppression rates also favoured the etravirine arm (+2.9%) with 95% confidence intervals of –5.8% to +11.7%. This result also showed non-inferiority for etravirine versus efavirenz ($p = 0.001$, delta = –12%).

In the pre-defined subgroups by baseline HIV RNA, the response rates were similar in two arms (Fig. 1b–1c). Given the small number of patients in each sub-group, statistical testing was not performed to compare the treatment arms.

Table 2 shows the details of the 11 patients who had virological failure by the TLOVR algorithm up to Week 48. There were four patients in the etravirine arm: none showed evidence of treatment-emergent NRTI or NNRTI mutations. The levels of HIV RNA in these

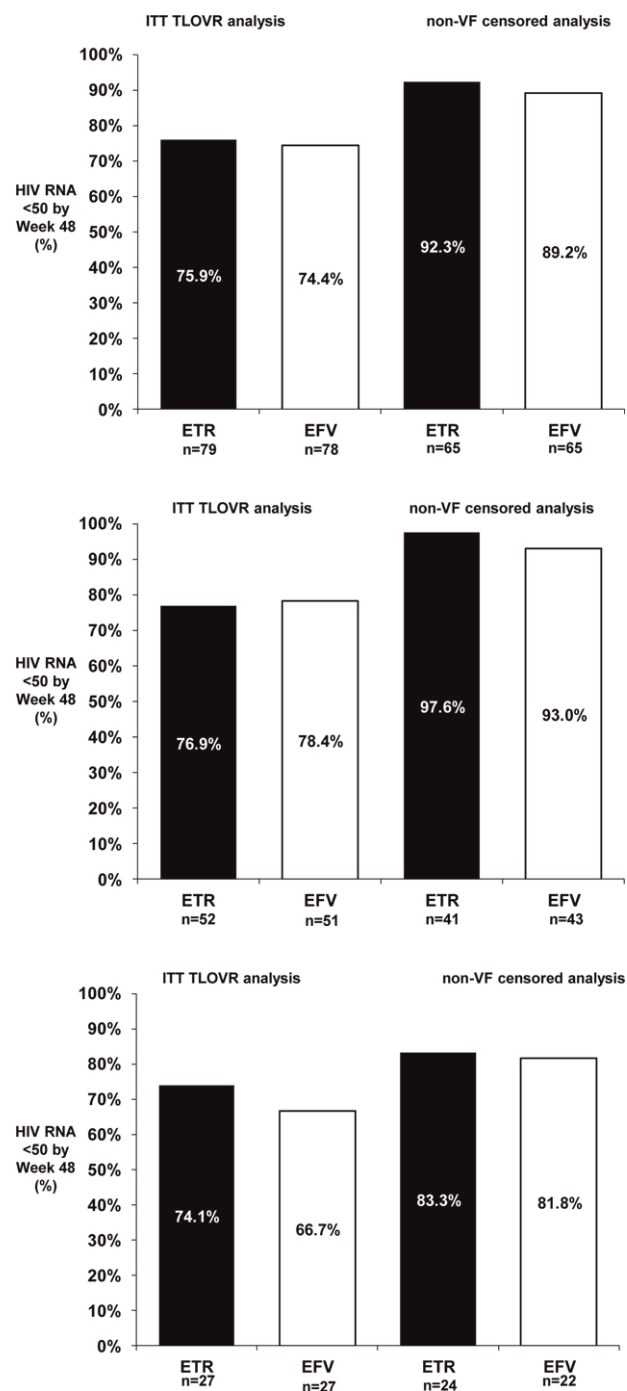


Fig. 1. HIV RNA <50 copies/mL at Week 48, for all patients (1a), baseline HIV RNA ≤100,000 copies/mL (1b), baseline HIV RNA >100,000 copies/mL (1c).

four patients tended to be low – three of the four patients had HIV RNA below 200 copies/mL at Week 48, but were defined as failures because of earlier rises in HIV RNA, or from not having two consecutive HIV RNA levels below 50 copies/mL at the end of the trial.

There were seven patients with virological failure in the efavirenz arm: three developed treatment-emergent

Table 2. Virological Failures by treatment arm: HIV RNA levels and detection of genotypic resistance (IAS-USA or Bennett lists).

Patient	HIV RNA				FU	Resistance mutations
	Baseline	Wk 24	Wk 36	Wk 48		
Etravirine arm (n = 4) ^a						
1	122,000	<50	<50	700	124	None
2	78,800	<50	100, 104	<50	<50	None
3	178,000	<50	85	68	<50	None
4	118,000	<50	114	<50	50	None
Efavirenz arm (n = 7)						
1	48,900	<50	104	<50	10,700	None
2	3,160	<50	1,350	240, 62	<50, 73	None
3	397,000	123	111	<50	81	None
4	3,810,000	107	129	56	<50	Not amplified
5	240,000	<50	<50	2180	missing	V106I + M184I
6	82,800	<50	72	<50	81,600	K103N
7	412,000	33,400	51,800	26,100	discontinued	K103N+M184V + P225H

Numbers in bold show samples which were successfully genotyped (amplified)

^aThere was one additional patient in the etravirine arm with full HIV RNA suppression <50 copies/mL from Week 16 to Week 48, but with a single NNRTI mutation at Week 12 (V90I): this viralsample was phenotypically sensitive to etravirine by Virtual Phenotype.

NRTI or NNRTI mutations. One patient developed the NNRTI mutation V106I together with the 3TC mutation M184I. One patient developed the NNRTI mutation K103N alone, and the third patient developed the NNRTI mutations K103N plus P225H, and the 3TC mutation M184V. The HIV RNA levels at the time of virological failure tended to be higher in the efavirenz arm than the etravirine arm (Table 2).

In addition to the patients genotyped at virological failure, seven patients in the etravirine arm and two in the efavirenz arm were genotyped at discontinuation, with HIV RNA >50 copies/mL: eight of these nine patients developed no new NRTI or NNRTI mutations. There was a single patient in the etravirine arm, who had a single NNRTI mutation (V90I) at Week 12, when the HIV RNA level was 501 copies/mL. This patient sample remained phenotypically sensitive to etravirine by Virtual Phenotype and the HIV RNA fell to <50 copies/mL at the next visit, remaining fully suppressed to Week 48 with no changes in randomized treatment.

In the etravirine arm, there were 16 patients with either an IAS-USA NRTI or NNRTI mutation at baseline in

the etravirine arm: 14 had HIV RNA <50 copies/mL at Week 48. Ten of these 16 patients had only NNRTI mutations (E138A: n = 3, V106I, n = 3, V90I: n = 3, V108I: n = 1); all 10 patients had HIV RNA below 50 copies/mL at Week 48. Four patients had NRTI mutations only – three had HIV RNA <50 copies/mL at the week 48 visit and the other discontinued for adverse events at Week 2. Two patients had both NRTI and NNRTI mutations at baseline: one had HIV RNA <50 at Week 48 and one was lost at follow up after the baseline visit.

In the efavirenz arm there were four patients with IAS-USA NNRTI mutations at baseline (E138A, n = 2, V90I, n = 1, V106I: n = 1): all four patients had HIV RNA <50 copies/mL at Week 48.

The mean rise in CD4 count by Week 48 was +232 cells/uL in the etravirine arm and +236 cells/uL in the efavirenz arm (observed data analysis).

Neuropsychiatric adverse events

The primary endpoint of the trial was the percentage of patients with Grade 1–4 treatment-emergent neuropsychiatric adverse events at Week 12. Figure 2 shows the percentage of patients with ongoing Grade 1–4 drug-related adverse events at each study visit to Week 48. The prevalence of Grade 1–4 drug-related neuropsychiatric AEs peaked at Week 2 (13.9% in the ETR arm and 39.7% in the EFV arm, $p < 0.001$); at the Week 48 visit, the percentage with ongoing neuropsychiatric adverse events was 6.3% for ETR and 21.5% for EFV, $p = 0.011$).

Table 3 shows the percentage of patients with Grade 2–4 drug-related neuropsychiatric adverse events at any time during the trial: this analysis excludes the Grade 1 (mild) adverse events. The percentage of patients with at least one Grade 2–4 drug-related nervous system adverse event was 1/79 (1%) in the etravirine arm and 13/78 (17%) in

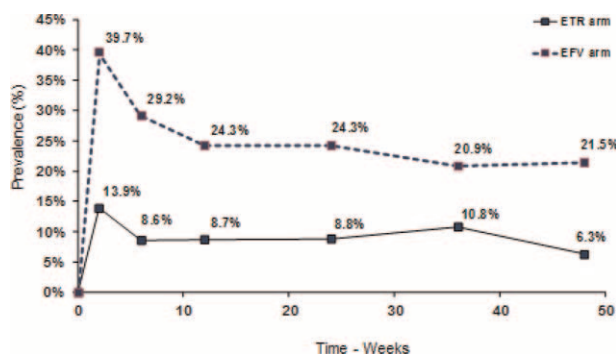


Fig. 2. Prevalence of neuropsychiatric adverse events by treatment arm, to Week 48.

the efavirenz arm ($p < 0.01$). The most common nervous system adverse event in the efavirenz arm was dizziness ($n = 7$). The percentage of patients with at least one Grade 2–4 drug-related psychiatric adverse event was 4/79 (5%) in the etravirine arm versus 12/78 (15%) in the efavirenz arm ($p < 0.05$). The most common psychiatric adverse events in the efavirenz arm were related to sleep (insomnia: $n = 4$, nightmare: $n = 3$, sleep disorder, $n = 2$). Four patients discontinued from the efavirenz arm for nervous system or psychiatric adverse events, versus none in the etravirine arm.

Clinical and laboratory adverse events

Table 3 shows the number of patients in each arm with Grade 2–4 drug-related clinical adverse events or Grade 3–4 laboratory abnormalities during the trial. The clinical adverse events are presented by System Organ Class. There were 21/79 (27%) patients in the etravirine arm with at least one Grade 2–4 drug-related clinical adverse event, versus 33/78 (42%) in the efavirenz arm. The main differences between the arms were for nervous system disorders and psychiatric disorders. There were nine patients in each arm with Grade 2–4 drug-related skin/subcutaneous adverse events. Of these patients, four per arm discontinued the trial for these adverse events (two in each arm with Grade 2 skin/subcutaneous adverse events, two in each arm for Grade 3 events).

The main difference between the arms in Grade 3–4 laboratory abnormalities was for lipids: there was one patient in the etravirine arm with a Grade 3 elevation in total cholesterol versus six (8%) in the efavirenz arm; two patients had Grade 3 elevations in LDL in the etravirine arm versus eight (10%) in the efavirenz arm. Use of lipid-lowering drugs in the trial was infrequent: one patient in the etravirine arm used fish oil, while six patients in the efavirenz arm used lipid-lowering drugs (two used pravastatin, four used fish oil).

Discussion

In the SENSE trial of treatment-naïve patients, there were similar rates of HIV RNA suppression at Week 48 for patients taking etravirine 400 mg once daily and efavirenz 600 mg once daily, both with two nucleoside analogues. In addition, there was a lower risk of neuropsychiatric adverse events in the etravirine arm that persisted over time, and there were also fewer lipid elevations in the etravirine arm. The risk of skin or subcutaneous adverse events was similar in the two treatment arms.

Etravirine showed non-inferior efficacy to efavirenz in the ITT TLOVR and non-VF censored analyses, and the results were consistent for the pre-defined subgroups of patients with HIV RNA above versus equal or below

100,000 copies/mL. However, the primary endpoint of the SENSE trial was neuropsychiatric adverse events, and the trial was not statistically powered to demonstrate non-inferior efficacy of etravirine versus efavirenz. Clinical trials to demonstrate non-inferior rates of HIV RNA suppression normally require from 300–400 patients per treatment arm [26], and several recently conducted trials have used a non-inferiority margin of -10% [27–29], rather than the wider -12% margin used in this trial: clearly, a larger trial would be required to establish the efficacy and safety profile of etravirine in treatment-naïve patients at the 400 mg once daily dose.

The SENSE trial involved a detailed analysis of drug resistance, with all samples tested when HIV RNA rebounded above 50 copies/mL or was above 50 copies/mL at Week 48, at the time of discontinuation, or if initial reductions in HIV RNA were judged to be sub-optimal. In the etravirine arm, none of the four patients with protocol defined virological failure had treatment-emergent NRTI or NNRTI resistance. By contrast in the efavirenz arm, three of the seven patients with virological failure developed NRTI and/or NNRTI mutations, associated with phenotypic resistance. There was one patient in the etravirine arm who developed a single IAS-USA NNRTI mutation while the HIV RNA was declining, but the patient had full HIV RNA suppression < 50 copies/mL from the next visit onwards, with no change in treatment and was not classified as a virological failure. The percentage of patients in the efavirenz arm of the SENSE trial who developed treatment-emergent resistance to NRTIs and NNRTIs is consistent with a recent meta-analysis of clinical trials evaluating first-line NNRTI-based HAART [12].

Additional trials would be needed to support the findings from this study which suggest that etravirine could lower the risk of NRTI and NNRTI resistance emergence after first-line treatment failure. Results using standard population sequencing should be repeated using more sensitive methods, such as Ultra-Deep Sequencing. A reduction in the risk of treatment-emergent drug resistance could have important long-term implications for the preservation of treatment options. This potential benefit could be especially important in developing countries where the monitoring of HIV RNA and drug resistance is limited. In the DUET trials, treatment-experienced patients were treated with either etravirine or placebo, and a background regimen which included darunavir/ritonavir for all patients. In the etravirine arm, there was a lower risk of treatment-emergent resistance to darunavir, suggesting that etravirine may protect other drugs from the development of resistance [30].

At baseline, there were more patients with NRTI or NNRTI mutations in the etravirine arm ($n = 16$), versus the efavirenz arm ($n = 4$). There was no correlation between baseline mutations and HIV RNA suppression at

Table 3. Clinical and laboratory adverse events by treatment arm.

	Etravirine arm n = 79	Efavirenz arm n = 78
Grade 2–4 drug-related clinical adverse events ^a :		
Total	21 (27%)	33 (42%)
Gastrointestinal	4 (5%)	4 (4%)
General disorders	1 (1%)	7 (9%)
Investigations	1 (1%)	4 (5%)
Metabolism and nutrition	1 (1%)	5 (6%)
Skin/subcutaneous disorders	9 (11.4%)	9 (11.5%)
Nervous system disorders	1 (1%)	13 (17%)
Psychiatric disorders	4 (5%)	12 (15%)
Grade 2–4 drug-related nervous system adverse events ^b		
Total	1 (1%)	13 (17%)
Cognitive disorder	0	1 (1%)
Disturbance in attention	1 (1%)	3 (4%)
Dizziness	0	7 (9%)
Headache	0	5 (6%)
Memory impairment	0	1 (1%)
Neuralgia	0	1 (1%)
Somnolence	1 (1%)	1 (1%)
Grade 2–4 drug-related psychiatric adverse events ^b		
Total	4 (5%)	12 (15%)
Aggression	0	1 (1%)
Anxiety	0	1 (1%)
Attention deficit / hyperactivity	0	1 (1%)
Depression	1 (1%)	2 (3%)
Insomnia	1 (1%)	4 (5%)
Decreased libido	0	1 (1%)
Altered mood	0	1 (1%)
Nightmare	2 (3%)	3 (4%)
Sleep disorder	0	2 (3%)
Suicidal ideation	0	1 (1%)
Grade 3–4 laboratory abnormalities ^a :		
Hypophosphataemia	0	4 (5%)
Neutropenia	6 (8%)	3 (4%)
Elevated ALT	2 (3%)	1 (1%)
Elevated AST	1 (1%)	2 (3%)
Elevated Total Cholesterol	1 (1%)	6 (8%)
Elevated LDL	2 (3%)	8 (10%)
Elevated triglycerides	0	2 (3%)

^aAt least 2 patients in either treatment arm.^bAll neuropsychiatric adverse events.

Week 48 in either treatment arm. However, patients with key NRTI or NNRTI mutations (in the Bennett list) had already been excluded from the trial. A recent study has shown no correlation between “minor” NNRTI mutations and the risk of virological failure [31].

In this study, 100 mg etravirine tablets were used, but a new 200 mg formulation of etravirine has recently been approved in North America [32] and is under regulatory review in Europe. This will improve the convenience of etravirine dosing.

In the SENSE trial, there were significantly fewer nervous system or psychiatric adverse events in the etravirine arm compared with the efavirenz arm, and this difference was still statistically significant at the Week 48 visit. Some clinical trials have shown a higher risk of neuropsychiatric adverse events for efavirenz only in the first few weeks of treatment [28,33]. Results from a “stepped dose” trial of efavirenz suggest that the short-term risk of neuropsychiatric adverse events can be lessened by gradually raising

the dose of efavirenz during the first six weeks of treatment [34]. However results from another double-blind trial show that long-term Grade 2 (moderate) neuropsychiatric adverse events may resolve after patients switch from efavirenz to etravirine [35]. In a trial recruiting patients with or without neuropsychiatric adverse events on efavirenz, there was no significant improvement after the switch to etravirine [36].

There were greater rises in lipids in the efavirenz arm of the SENSE trial. The clinical implications of rises in lipids during treatment with efavirenz are unknown. Efavirenz treatment has been associated with lipid elevations similar to protease inhibitors [9] and an elevated risk lipodystrophy compared with lopinavir/ritonavir [14]. The risk of Grade 2–4 skin or subcutaneous adverse events was similar in the two arms of the SENSE trial. A “Dear Doctor” letter was sent to the trial investigators during the recruitment to the trial, reporting two cases of severe rash on etravirine detected from routine drug surveillance [37]. Consequently, there was a review of all cases of rash

during the early stages of the SENSE trial. However the final results at Week 48 showed no increased risk of Grade 2–4 skin or subcutaneous rash for etravirine relative to efavirenz; there was a slightly higher risk of mild (grade 1) rash in the etravirine arm. These results are consistent with the DUET trials, where most cases of rash on etravirine were mild and resolved within the first six weeks of treatment [17].

In summary, etravirine showed a lower risk of neuropsychiatric adverse events and lipid elevations than efavirenz in the SENSE trial: both safety benefits were sustained through Week 48. There were similar rates of HIV RNA suppression in the two treatment arms, and none of the patients with virological failure in the etravirine arm developed resistance to NRTIs or NNRTIs.

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