J Antimicrob Chemother 2012; **67**: 685–690
doi:10.1093/jac/dkr533 Advance Access publication 29 December 2011

Journal of Antimicrobial Chemotherapy

Lipid profiles for etravirine versus efavirenz in treatment-naive patients in the randomized, double-blind SENSE trial

G. Fätkenheuer[1]*, C. Duvivier[2], A. Rieger[3], J. Durant[4], D. Rey[5], W. Schmidt[6], A. Hill[7], Y. van Delft[8] and S. Marks[8] on behalf of the SENSE Study Team†

[1]*First Department of Internal Medicine, University Hospital of Cologne, Cologne, Germany;* [2]*Hôpital Necker, AP-HP, Infectious Diseases Department, Centre d'Infectiologie Necker-Pasteur, Paris, France;* [3]*University Clinic, Vienna, Austria;* [4]*Hopital Archeti, Nice, France;* [5]*Hopitaux Universitaires, Strasbourg, France;* [6]*Praxis, Berlin, Germany;* [7]*Pharmacology Research Laboratories, Liverpool University, Liverpool, UK;* [8]*Janssen, Tilburg, The Netherlands*

*Corresponding author. Tel: +492214785860; Fax: +49221478591; E-mail: g.faetkenheuer@uni-koeln.de
†Members of the SENSE Study Team are listed in the Acknowledgements section.

Received 5 September 2011; returned 4 October 2011; revised 17 November 2011; accepted 19 November 2011

Background: Etravirine is approved for use in treatment-experienced patients at a dose of 200 mg twice daily. Efavirenz has been associated with greater increases in serum lipids compared with other non-nucleosides in randomized trials of first-line treatment.

Methods: In this double-blind, placebo-controlled trial, 157 treatment-naive patients with HIV RNA >5000 copies/mL were randomized 1:1 to either 400 mg of etravirine once daily ($n=79$) or 600 mg of efavirenz once daily ($n=78$) plus two nucleoside analogues (either abacavir/lamivudine, zidovudine/lamivudine or tenofovir/emtricitabine) for 48 weeks. Lipids were measured under fasting conditions at baseline and all visits to Week 48. Clinicaltrials.gov identifier: NCT00903682.

Results: Overall, the patients had a median baseline CD4 count of 302 cells/mm^3 (range 74–722) and a median HIV RNA of 4.8 $\log_{10}$ copies/mL (range 3.5–6.6). Both the non-nucleosides and the nucleoside analogues used caused changes in serum lipids. In the efavirenz arm, patients showed significantly larger increases in high-density lipoprotein (HDL) (+0.15 mmol/L, $P=0.004$), low-density lipoprotein (LDL) (+0.35 mmol/L, $P=0.005$), total cholesterol (+0.61 mmol/L, $P<0.0001$) and triglycerides (+0.33 mmol/L, $P=0.03$) at Week 48 compared with the etravirine arm. Across the two arms, patients taking abacavir/lamivudine showed greater increases in total cholesterol (+0.47 mmol/L, $P=0.005$) compared with patients taking tenofovir/emtricitabine. There were fewer grade 3/4 elevations in total cholesterol, LDL and triglycerides in the etravirine arm (2 patients, 1 patient and 0 patients, respectively) versus the efavirenz arm (8 patients, 6 patients and 2 patients, respectively).

Conclusions: In the SENSE trial, first-line treatment with 400 mg of etravirine once daily plus two nucleoside analogues led to fewer grade 3 or 4 lipid elevations compared with efavirenz plus two nucleoside analogues.

Keywords: non-nucleoside reverse transcriptase inhibitors, antiretroviral treatment, lipid elevations, cholesterol, nucleoside analogues

Introduction

International HIV treatment guidelines recommend first-line use of two nucleoside reverse transcriptase inhibitors (NRTIs) with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a boosted protease inhibitor (PI) to achieve full HIV RNA suppression below assay detection limits.[1–3] Of the non-nucleosides, 600 mg of efavirenz once daily is the most widely recommended, owing to the high rates of efficacy seen in large randomized trials.[1–3] The main risks associated with the use of efavirenz are neuropsychiatric adverse events,[4] rash[5] and increases in lipids.[6] While these problems may be mild and self-limiting for most patients, there is the risk of serious and/or long-term toxicity in a small percentage of patients.[4–6] There is also the potential for teratogenicity if efavirenz is used in pregnant women.[7]

The association between increases in serum lipids during antiretroviral treatment and the risk of cardiovascular disease or lipodystrophy is not well understood. However, people with HIV typically have a high prevalence of other pre-existing risk factors for cardiovascular disease,[8] and long-term elevations in lipids above accepted thresholds[9,10] should be avoided where possible.

In randomized clinical trials, first-line treatment with efavirenz has been associated with greater mean increases in total

cholesterol than the non-nucleosides nevirapine[11] and rilpivirine,[12,13] the integrase inhibitor raltegravir[14] and the CCR5 antagonist maraviroc.[15] In the ACTG 5202 trial, mean increases in lipids during first-line treatment with efavirenz were significantly larger than with the protease inhibitor atazanavir/ritonavir.[16] In a systematic review of first-line trials, first-line use of efavirenz led to similar increases in total cholesterol compared with atazanavir/ritonavir or darunavir/ritonavir, but these increases were smaller compared with other protease inhibitors, i.e. lopinavir/ritonavir or fosamprenavir/ritonavir.[6] Among the nucleoside analogues, treatment with tenofovir/lamivudine or tenofovir/emtricitabine leads to smaller increases in lipids compared with abacavir/lamivudine or zidovudine/lamivudine.[6]

The non-nucleoside etravirine is currently approved for use in treatment-experienced patients at the 200 mg twice daily dose. Pharmacokinetic studies have evaluated the 400 mg once daily dose of etravirine.[17] In the DUET trials, conducted in highly treatment-experienced patients, there was no difference in mean lipid elevations between the etravirine and placebo arms.[18]

The SENSE trial was designed to evaluate the safety and preliminary efficacy of first-line use of etravirine versus the standard of care of efavirenz, both combined with two investigator-selected 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 the results have been published previously.[19,20] In addition, the SENSE trial was designed to evaluate the preliminary efficacy and safety of first-line treatment with etravirine 400 mg once daily plus two nucleoside analogues. The purpose of this analysis was to compare the changes in lipids from first-line treatment with efavirenz or etravirine given in combination with different nucleoside analogues.

Methods

The SENSE trial recruited 157 antiretroviral treatment-naive individuals from Europe, Russia and Israel with HIV RNA levels >5000 copies/mL.[19,20] Patients were randomized to receive either 400 mg of etravirine once daily or 600 mg of efavirenz once daily, together with two investigator-selected nucleoside analogues (either tenofovir/emtricitabine, abacavir/lamivudine or zidovudine/lamivudine). Etravirine was administered as four 100 mg tablets once daily (or matching placebo) and efavirenz was administered as a single 600 mg tablet once daily (or matching placebo). Subjects 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.

Randomization was conducted centrally, with the sequence generated by the trial statistician. Randomized blocks were generated for each stratum (HIV RNA >100 000 versus <100 000 copies/mL at screening).

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. Samples were drawn for measurement of lipids under fasting conditions. Patient samples were tested for total cholesterol, low-density lipoprotein (LDL, direct), high-density lipoprotein (HDL) and triglycerides at a central laboratory. Adverse events were recorded on the Case Report Form. At the Week 48 visit, there were 56 patients in the etravirine arm and 62 in the efavirenz arm with lipids evaluated; the remaining patients had discontinued trial medication before Week 48.

Clinical and laboratory abnormalities were classified using the Division of AIDS grading tables.[10] This system classifies adverse events as 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 randomized medication. The MedDRA coding dictionary was then used to classify adverse events into system organ classes and individual categories.

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 sample size was determined assuming 90% statistical power, a two-sided significance level of 5% and rates of neuropsychiatric adverse events consistent with previous clinical trials of efavirenz.[4–6] Analysis of lipids was a secondary endpoint. The analyses of lipids were included in the trial protocol and statistical analysis plan, with no changes made during the course of the trial.

Mean changes from baseline in each parameter were calculated by treatment arm and according to the use of investigator-selected nucleoside analogues. Multiple linear regression was used to correlate changes in lipids with treatment arm and use of nucleoside analogues. The number of patients with grade 3 or 4 elevations in lipids was analysed by treatment arm.

Ethics

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). Clinicaltrials.gov identifier: NCT00903682.

Results

Baseline characteristics of the 157 randomized 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 men having sex with men (79 patients, 50%). The nucleoside analogues used were tenofovir plus emtricitabine for 94 patients (60%), abacavir plus lamivudine for 41 patients (26%) and zidovudine plus lamivudine for 22 patients (14%). Lipid levels were well balanced between the treatment arms. At baseline, 44% of patients in each treatment arm had HDL levels <1.06 mmol/L (40 mg/dL), which is an accepted cut-off level by the ATP-III classification system.[9]

Figure 1 shows the mean lipid levels during the 48 weeks of the trial. There was an increase in total cholesterol in the efavirenz arm, from 4.2 to 5.2 mmol/L, compared with a smaller increase in the etravirine arm, from 4.3 to 4.7 mmol/L. In univariate analysis, the increase in total cholesterol to Week 48 was significantly larger in the efavirenz arm ($P<0.001$). There was also an increase in LDL cholesterol (direct) from baseline to Week 48 in the efavirenz arm, from 2.4 to 3.0 mmol/L, compared with a smaller increase in the etravirine arm, from 2.6 to 2.8 mmol/L. In univariate analysis, this increase was also significantly larger in the efavirenz arm ($P=0.001$). The mean levels of HDL rose significantly more in the efavirenz arm (from 1.0 mmol/L at baseline to 1.3 mmol/L at Week 48) than in the etravirine arm (from 1.1 mmol/L at baseline to 1.2 mmol/L at Week 48) ($P=0.028$). Consequently, the mean ratio of total to HDL cholesterol declined from baseline to Week 48 by −0.3 in the etravirine

Table 1. Baseline characteristics by treatment arm

	Etravirine arm, $n=79$	Efavirenz arm, $n=78$
Age (years), mean (range)	38 (18–63)	38 (19–66)
Gender (male), *n* (%)	67 (85%)	60 (77%)
Race (Caucasian), *n* (%)	73 (92%)	66 (85%)
MSM, *n* (%)	42 (53%)	35 (45%)
Median HIV RNA (log_{10} copies/mL)	4.8	4.8
HIV RNA $\leq$100 000 copies/mL, *n* (%)	54 (68%)	52 (67%)
HIV RNA >100 000 copies/mL, *n* (%)	25 (32%)	26 (33%)
CD4 count (cells/mm^3), median (range)	319 (74–638)	273 (91–722)
Nucleoside analogues used, *n* (%)		
TDF/FTC	49 (62%)	45 (58%)
ABC/3TC	18 (23%)	23 (29%)
ZDV/3TC	12 (15%)	10 (13%)
Total cholesterol (mmol/L), mean (SD)	4.3 (0.83)	4.2 (0.86)
LDL cholesterol (mmol/L), mean (SD)	2.6 (0.76)	2.4 (0.74)
HDL cholesterol (mmol/L), mean (SD)	1.1 (0.41)	1.0 (0.29)
Triglycerides (mmol/L), mean (SD)	1.5 (1.14)	1.7 (2.19)
Total cholesterol/HDL ratio, mean (SD)	4.4 (1.71)	4.6 (2.65)
Use of lipid-lowering drugs during the trial, *n* (%)	1 (1)	6 (8)

ZDV, zidovudine; 3TC, lamivudine; ABC, abacavir; TDF, tenofovir; FTC, emtricitabine; MSM, men who have sex with men.

arm and −0.4 in the efavirenz arm. There was no difference between the arms in this ratio at Week 48.

Table 2 shows results from an exploratory multivariate analysis to determine the relative impact of nucleoside analogues used versus non-nucleosides on increases in lipids to Week 48. In these analyses, the use of efavirenz remained a significant predictor of larger increases in total cholesterol (+0.61 mmol/L compared with etravirine, $P<0.001$), but the use of abacavir/lamivudine also led to larger increases in total cholesterol (+0.47 mmol/L, $P=0.005$) compared with tenofovir/emtricitabine. Use of efavirenz was also a significant predictor of larger increases in LDL cholesterol (+0.35 mmol/L compared with etravirine, $P=0.005$); the additional effect of abacavir/lamivudine was borderline significant (+0.24 mmol/L compared with tenofovir/emtricitabine, $P=0.09$). Efavirenz was associated with larger increases in HDL cholesterol (+0.15 mmol/L compared with etravirine, $P<0.001$) and triglycerides (+0.33 mmol/L compared with etravirine, $P=0.033$); there was no additional effect of different nucleoside analogues on changes in these lipid parameters.

Table 3 shows the number of patients in each arm with grade 3–4 laboratory abnormalities at any time during the trial. 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. Two patients in the efavirenz arm had grade 3 elevations in triglycerides, versus none in the etravirine arm. At Week 48, the percentage of patients with HDL <40 mg/dL (<1.06 mmol/L) was 20/56 (36%) in the etravirine arm, versus 9/62 (15%) in the efavirenz arm; at baseline, the percentage with HDL <1.06 mmol/L was 44% in both treatment arms.

During the trial, 21/79 patients in the etravirine arm (27%) and 33/78 patients in the efavirenz arm (42%) reported at least one grade 2–4 adverse event judged to be at least possibly related to randomized treatment by the investigator. Seven of these 54 patients had lipid-related grade 2–4 adverse events. One patient in the etravirine arm had palpitations, while six patients in the efavirenz arm had elevations in lipids also reported as adverse events.

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). The analyses were repeated, excluding patients who were taking lipid-lowering drugs. The mean changes in lipids were consistent with the main analyses after exclusion of these patients (data not shown).

Discussion

In the SENSE trial, there were larger mean increases in total cholesterol, LDL, HDL and triglycerides for patients randomized to efavirenz compared with those on etravirine. There was an additional effect of nucleoside analogues on lipid elevations—patients receiving abacavir/lamivudine had greater increases in total cholesterol and LDL compared with patients receiving tenofovir/emtricitabine. In addition, more patients in the efavirenz arm had grade 3 or 4 elevations in total cholesterol, LDL or triglycerides. However, the mean ratio of total cholesterol to HDL remained stable over the 48 weeks of the trial in both arms.

The differences in lipids between etravirine and efavirenz in the SENSE trial are consistent with other randomized trials of first-line treatment, where efavirenz has shown larger mean increases in lipids than other non-nucleosides.[11–13] Other studies have also shown similar effects of nucleoside analogues on lipid elevation.[6] In the SENSE trial, the number of patients receiving each of the three combinations of nucleoside

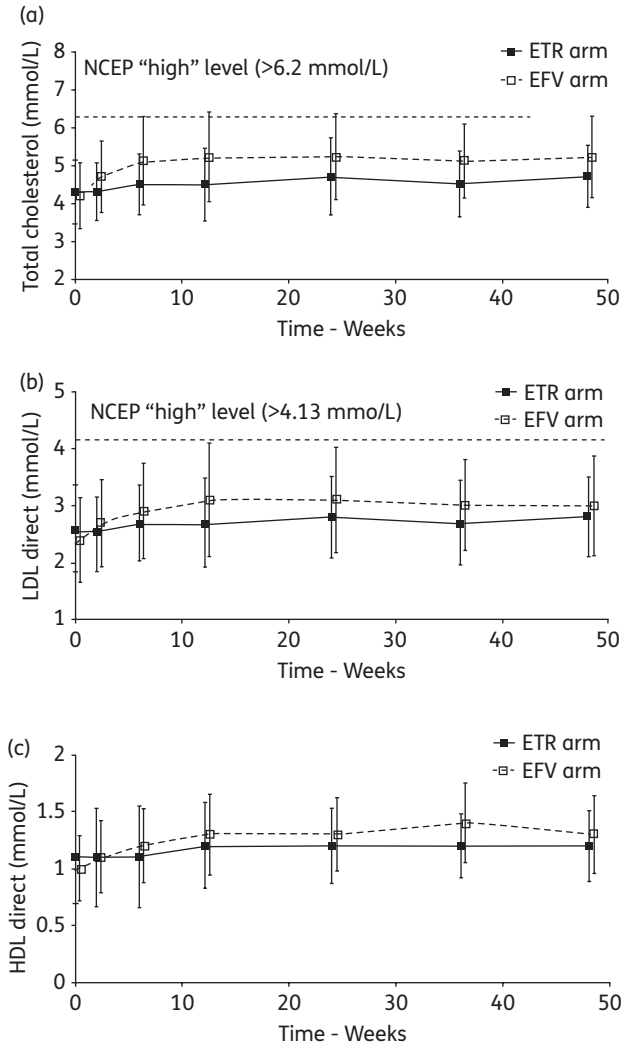

Figure 1. Mean and standard deviation of lipid parameters versus time by treatment arm in the SENSE trial. (a) Total cholesterol; (b) LDL cholesterol; (c) HDL cholesterol. ETR, etravirine; EFV, efavirenz; NCEP, National Cholesterol Education Programme.

Table 2. Multivariate analysis of changes in lipids to Week 48

Lipid parameter (mmol/L)	Predictive factor	Estimate (SEM)	*P* value
Total cholesterol	etravirine	0 (reference)	
	efavirenz	+0.611 (0.142)	<0.001
	tenofovir/emtricitabine	0 (reference)	
	abacavir/lamivudine	+0.466 (0.163)	0.005
	zidovudine/lamivudine	+0.335 (0.213)	0.118
LDL cholesterol	etravirine	0 (reference)	
	efavirenz	+0.354 (0.125)	0.005
	tenofovir/emtricitabine	0 (reference)	
	abacavir/lamivudine	+0.243 (0.142)	0.089
	zidovudine/lamivudine	+0.187 (0.187)	0.310
HDL cholesterol	etravirine	0 (reference)	
	efavirenz	+0.148 (0.041)	<0.001
	tenofovir/emtricitabine	0 (reference)	
	abacavir/lamivudine	0.063 (0.047)	0.182
	zidovudine/lamivudine	0.065 (0.061)	0.282
Triglycerides	etravirine	0 (reference)	
	efavirenz	+0.334 (0.155)	0.033
	tenofovir/emtricitabine	0 (reference)	
	abacavir/lamivudine	+0.256 (0.176)	0.154
	zidovudine/lamivudine	+0.035 (0.234)	0.879

Table 3. Grade 3 or 4 elevations in lipids during the SENSE trial, by treatment arm

Treatment arm	Etravirine, *n*=79	Efavirenz, *n*=78
Elevated total cholesterol (>7.8 mmol/L)	1 (1%)	6 (8%)
Elevated LDL (>4.9 mmol/L)	2 (3%)	8 (10%)
Elevated triglycerides (>8.5 mmol/L)	0	2 (3%)

analogues was limited, and this limits the statistical power to detect differences between nucleoside analogues. The SENSE trial did not include analysis of other lipid markers, such as apolipoproteins, which have been evaluated in other studies.[21]

The clinical implications of increases in lipids during treatment with efavirenz are unknown. Long-term follow-up in large-scale cohort studies has shown a higher cardiovascular risk from treatment with abacavir and certain protease inhibitors, but not from efavirenz treatment.[22] No difference in cardiovascular risk between efavirenz and nevirapine has been shown in cohort studies.[23] Whereas there were greater increases in total cholesterol and LDL in the efavirenz arm of the SENSE trial, there were also greater increases in HDL, and the ratio of total cholesterol to HDL did not differ between the arms at Week 48. Conventional cardiovascular risk equations use a combination of total cholesterol and HDL to predict cardiovascular risk,[24,25] while some also use LDL.[26] It is unclear whether a patient with elevations in both total cholesterol and HDL, but no difference in the ratio, will have an increased risk of cardiovascular disease. In a study of first-line treatment similar to the SENSE trial evaluating nevirapine and atazanavir/ritonavir, the changes in lipids observed were not large enough to affect Framingham scores for cardiovascular risk.[21] Patients may be able to reverse elevated lipids during antiretroviral treatment by changes in lifestyle,[27] although lipid-lowering drugs may not be as effective as in patients without HIV infection.[28]

In the SENSE trial, there were fewer grade 2–4 drug-related adverse events in the etravirine arm, in addition to the observed benefits in lipids. In addition to lipid elevations, there may be other adverse events that influence decisions on using non-nucleosides, such as neuropsychiatric adverse events or rash. The main benefit of etravirine over efavirenz in the SENSE trial was a lower risk of neuropsychiatric adverse events.[19,20] In the 2NN trial there were fewer elevations in lipids for patients

taking nevirapine versus efavirenz, but there was a higher risk of rash in the nevirapine arm.[11] The SENSE trial only involved 157 patients in total, and larger, long-term trials are needed to establish the safety and efficacy of etravirine 400 mg once daily; currently this non-nucleoside is approved for use in treatment-experienced patients at the 200 mg twice daily dose.

Acknowledgements

We thank the investigators, study coordinator (Marjolein Janssen), site and data managers, and the patients for their contributions.

SENSE Study Team

Austria: A. Rieger (Vienna), N. Vetter (Vienna) and R. Greil (Salzburg); Denmark: C. Pedersen (Odense) and M. Storgaard (Aarhus); France: P. Morlat (Bordeaux), C. Katlama (Paris), J. Durant (Nice), L. Cotte (Lyon), C. Duvvier (Paris) and D. Rey (Strasbourg); Germany: S. Esser (Essen), C. Stellbrink (Hamburg), W. Schmidt (Berlin), M. Stoll, (Hannover), C. Stephan (Frankfurt), G. Fatkenheuer (Cologne), A. Stoehr (Hamburg) and J. Rockstroh (Cologne); Hungary: D. Banhegyi (Budapest); Israel: L. Itzchak (Ramat-Gan), E. Shahar (Haifa), S. Maayan (Jerusalem) and D. Turner (Tel-Aviv); Italy: A. Lazzarin (Milan), A. Antinori (Rome), G. Carosi (Brescia), L. Minoli (Pavia), G. di Perri (Turin), G. Filice (Pavia) and M. Andreoni (Rome); Romania: D. Duiculescu (Bucharest), S. Rugina (Constanta), S. Erscoiu (Bucharest) and A. Streinu (Bucharest); Russia: A. Pronin (Moscow), V. Pokrovsky (Moscow), B. Gruzdev (Moscow), A. Yakovlev (St Petersburg) and E. Voronin (St Petersburg); Spain: B. Clotet (Barcelona), J. Gatell (Barcelona), J. Arribas, (Madrid), D. Podzamczer (Barcelona), P. Domingo (Barcelona), C. Miralles Alvarez (Vigo) and J. Hernandez Quero (Granada); Switzerland: H. Furrer (Berne) and J. Feher (Zurich); UK: M. Johnson (London), J. Fox (London), M. Nelson (London), M. Fisher (Brighton) and C. Orkin (London).

Funding

The work was supported by Janssen Europe.

Transparency declarations

A. H. has received consultancy payments from Janssen, which developed etravirine. Y. v. D. and S. M. are employees of Janssen. All other authors: none to declare.

The trial was designed and conducted by Janssen EMEA Medical Affairs, a division of Janssen International N.V., which 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 (A. H.). The authors had full access to the data and the corresponding author had the final responsibility to submit the manuscript for publication.

Author contributions

G. F., C. D., A. R., J. D., D. R. and W. S. were investigators in the SENSE trial, who also provided critical review of the trial manuscript. A. H. wrote the first draft of the manuscript and compiled comments from the other authors. Y. v. D. and S. M. set up and coordinated the SENSE trial, and also provided critical review of the trial manuscript.

References

1 Thompson M, Aberg J, Cahn P *et al*. Antiretroviral treatment of adult HIV infection. 2010 recommendations of the International AIDS Society-USA panel. *JAMA* 2010; **304**: 321–33.

2 US Department for Health and Social Security. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents—January 10, 2011*. http://www.aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=7 (17 October 2011, date last accessed).

3 European AIDS Clinical Society. *Guidelines for the Clinical Management of HIV Infected Adults in Europe*. http://www.europeanaidsclinicalsociety.org/index.php?option=com_content&view=article&id=59&Itemid=41 (17 October 2011, date last accessed).

4 Munoz-Moreno J, Fumaz C, Ferrer M *et al*. Neuropsychiatric symptoms associated with efavirenz: prevalence, correlates and management. A neurobehavioural review. *AIDS Rev* 2009; **11**: 103–9.

5 Squires K, Lazzarin A, Gatell J *et al*. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine as initial therapy for patients infected with HIV. *J Acquir Immune Defic Syndr* 2004; **36**: 1011–9.

6 Hill A, Sawyer A, Gazzard B. Effects of first-line use of nucleoside analogues, efavirenz, and ritonavir-boosted protease inhibitors on lipid levels. *HIV Clin Trials* 2009; **10**: 1–12.

7 Perinatal HIV Guidelines Working Group. *Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States—April 29, 2009*. http://www.emcureaidsinfo.com/pdf/PerinatalGL_2009.pdf (17 October 2011, date last accessed).

8 Law M, Friis-Moller N, El-Sadr W *et al*. The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D:A:D study. *HIV Medicine* 2006; **7**: 218–30.

9 Grundy S, Cleeman J, Merz N *et al*. Implications of recent clinical trials for the national cholesterol education programme adult treatment panel III guidelines. *Circulation* 2004; **110**: 227–39.

10 DAIDS. *Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*. 2004. http://rsc.tech-res.com/safetyandpharmacovigilance/ (17 October 2011, date last accessed).

11 van Leth F, Phanuphak P, Ruxrungtham K *et al*. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet* 2004; **363**: 1253–63.

12 Pozniak A, Morales-Ramirez J, Katabira E *et al*. Efficacy and safety of TMC278 in antiretroviral-naive HIV-1 patients: week 96 results of a phase IIb randomised trial. *AIDS* 2010; **24**: 55–65.

13 Cohen C, Molina JM, Cahn P *et al*. Pooled week 48 efficacy and safety results from ECHO and THRIVE, two double-blind, randomised phase III trials comparing TMC278 versus efavirenz in treatment-naïve, HIV-1-infected patients. In: *Abstracts of the Eighteenth IAS Conference, Vienna, Austria, 2010*. Oral Abstract Late Breaker THLBB206.

14 Lennox J, DeJesus E, Lazzarin A *et al*. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naïve patients with HIV-1 infection: a multicentre, double-blind randomized controlled trial. *Lancet* 2009; **374**: 796–806.

15 Sierra-Madero J, Di Perri G, Wood R *et al*. Efficacy and safety of maraviroc versus efavirenz, both with zidovudine/lamivudine: 96-week results from the MERIT study. *HIV Clin Trials* 2010; **11**: 125–32.

16 Sax P, Tierney C, Collier A *et al*. Abacavir/lamivudine versus tenofovir DF/emtricitabine as part of combination regimens for initial treatment of HIV: final results. *J Infect Dis* 2011; **204**: 1191–201.

17 Lalezari J, DeJesus E, Osiyemi O *et al*. Pharmacokinetics of once-daily etravirine (ETR) without and with once-daily darunavir/ritonavir (DRV/r) in antiretroviral-naïve HIV-1 infected adults. In: *Abstracts of the Ninth International Conference on HIV Treatment, Glasgow, Scotland, 2008*. Abstract PO413.

18 Katlama C, Haubrich R, Lalezari R *et al*. Efficacy and safety of etravirine in treatment-experienced, HIV-1 patients: pooled 48 week analysis of two randomized, controlled trials. *AIDS* 2009; **23**: 2289–300.

19 Nelson M, Stellbrink H, Podzamczer D *et al*. A comparison of neuropsychiatric adverse events during 12 weeks of treatment with etravirine and efavirenz in a treatment-naive, HIV-1-infected population. *AIDS* 2011; **25**: 335–40.

20 Gazzard B, Duvivier C, Zagler C *et al*. Phase 2 double-blind, randomized trial of etravirine versus efavirenz in treatment-naive patients: 48-week results. *AIDS* 2011; **25**: 2249–58.

21 Podzamczer D, Andrade-Villanueva J, Clotet B *et al*. Lipid profiles for nevirapine versus atazanavir/ritonavir both combined with tenofovir disoproxil fumarate and emtricitabine over 48 weeks, in treatment naïve HIV-1-infected patients (the ARTEN study). *HIV Med* 2011; **12**: 374–82.

22 D:A:D Study Group. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet* 2008; **371**: 1417–26.

23 DAD Study Group. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* 2007; **356**: 1723–35.

24 Anderson K, Odell P, Wilson P. Cardiovascular disease risk profiles. *Am J Heart Assoc* 1990; **124**: 293–8.

25 Hense H. Observations, predictions and decisions: assessing cardiovascular risk assessment. *Int J Epidemiol* 2004; **33**: 235–9.

26 Wilson P, D'Agostino R, Levy D *et al*. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; **97**: 1837–47.

27 Fitch K, Anderson E, Hubbard J *et al*. Effects of a lifestyle modification program in HIV-infected patients with the metabolic syndrome. *AIDS* 2006; **20**: 1843–50.

28 Silverberg M, Leyden W, Hurley L *et al*. Response to newly prescribed lipid-lowering therapy in patients with and without HIV infection. *Ann Intern Med* 2009; **150**: 301–3.