Efficacy and safety of efavirenz 400 mg daily versus 600 mg daily: 96-week data from the randomised, double-blind, placebo-controlled, non-inferiority ENCORE1 study

*ENCORE1 Study Group**

Summary

Background The week 48 primary analysis of the ENCORE1 trial established the virological non-inferiority and safety of efavirenz 400 mg compared with the standard 600 mg dose, combined with tenofovir and emtricitabine, as first-line HIV therapy. This 96-week follow-up of the trial assesses the durability of efficacy and safety of this treatment over 96 weeks.

Methods ENCORE1 was a double-blind, placebo-controlled, non-inferiority trial done at 38 clinical sites in 13 countries. HIV-infected adult patients (≥16 years of age) with no previous antiretroviral therapy, a CD4 cell count of 50–500 cells per μL, and plasma HIV-1 viral load of at least 1000 copies per mL were randomly assigned (1:1) by an electronic case report form to receive fixed-dose daily tenofovir 300 mg and emtricitabine 200 mg plus efavirenz either 400 mg daily or 600 mg daily. Participants, physicians, and all other trial staff were masked to treatment assignment. Randomisation was stratified by HIV-1 viral load at baseline (≤ or >100 000 copies per mL). The primary endpoint was the difference in the proportions of patients in the two treatment groups with a plasma HIV-1 viral load below 200 copies per mL at week 96. Treatment groups were deemed to be non-inferior if the lower limit of the 95% CI for the difference in viral load was above –10% by modified intention-to-treat analysis. Non-inferiority was assessed in the modified intention-to-treat, per-protocol, and non-completer=failure (NC=F) populations. Adverse events and serious adverse events were summarised by treatment group. This study is registered with ClinicalTrials.gov, number NCT01011413.

Findings Between Aug 24, 2011, and March 19, 2012, 636 eligible participants were enrolled and randomly assigned to the two treatment groups (324 to efavirenz 400 mg and 312 to efavirenz 600 mg). The intention-to-treat population who received at least one dose of study drug comprised 630 patients: 321 in the efavirenz 400 mg group and 309 in the efavirenz 600 mg group. 585 patients (93%; 299 in the efavirenz 400 mg group and 286 in the 600 mg group) completed 96 weeks of follow-up. At 96 weeks, 289 (90·0%) of 321 patients in the efavirenz 400 mg group and 280 (90·6%) of 309 in the efavirenz 600 mg group had a plasma HIV-1 viral load less than 200 copies per mL (difference –0·6, 95% CI –5·2 to 4·0; p=0·72), which suggests continued non-inferiority of the lower efavirenz dose. Non-inferiority was recorded for thresholds of less than 50 and less than 400 copies per mL, irrespective of baseline plasma viral load. Adverse events were reported by 291 (91%) of 321 patients in the efavirenz 400 mg group and by 285 (92%) of 309 in the 600 mg group (p=0·48). The proportions of patients reporting an adverse event that was definitely or probably related to efavirenz were 126 (39%) for efavirenz 400 mg and 148 (48%) for efavirenz 600 mg (p=0·03). The number of patients who reported serious adverse events did not differ between the groups (p=0·20).

Interpretation Our findings confirm that efavirenz 400 mg is non-inferior to the standard dose of 600 mg in combination with tenofovir and emtricitabine as initial HIV therapy over 96 weeks. Fewer efavirenz-related adverse events were reported with the 400 mg efavirenz dose than with the 600 mg dose. These findings support the routine use of efavirenz 400 mg. The coadministration of rifampicin and efavirenz 400 mg needs further investigation.

Funding Bill & Melinda Gates Foundation, and UNSW Australia.

Lancet Infect Dis 2015; 15: 793–802

Published Online
April 13, 2015
http://dx.doi.org/10.1016/S1473-3099(15)70060-5

This online publication has been corrected. The corrected version first appeared at thelancet.com/infection on May 1, 2015

See Comments page 749

*Members are listed at the end of the paper

Correspondence to:
Dr Dianne Carey, The Kirby Institute, UNSW Australia, Sydney, NSW 2052, Australia
dcarey@kirby.unsw.edu.au

Introduction

Efavirenz is the most widely used non-nucleoside reverse transcriptase inhibitor (NNRTI) and is a preferred first-line drug in adult HIV treatment guidelines.[1–3] Efavirenz 600 mg daily was granted accelerated approval by the US Food and Drug Administration in 1998 on the basis of surrogate endpoint analyses from short-term studies.[4] A phase 2 study of efavirenz 600 mg, 400 mg, 200 mg, or placebo plus nucleosides showed no significant difference in viral suppression rates across the different efavirenz groups at 24 weeks,[5] which suggests that lower doses of this drug can control viral replication, at least in the short term.

In 2011, the UN announced its objective to scale up antiretroviral treatment to 15 million people by 2015.[6] At the end of 2013, roughly 12·9 million patients with HIV were receiving treatment, including 11·7 million from low-income and middle-income countries.[7] However,

this figure represents only a third of those with HIV infection worldwide.[7] The 2013 WHO treatment guidelines recommend a first-line regimen comprising daily efavirenz with tenofovir and lamivudine or emtricitabine for adults and adolescents with HIV infection.[3] Recommendations to initiate treatment at a CD4 cell threshold of 500 cells per μL pose enormous challenges for expanding provision and retention in long-term care, since substantial increases in investments are needed at a time when donor funds and health-care resources either remain static or are decreasing.

Reduced antiretroviral drug prices have made HIV treatment expansion more affordable, but costs still remain substantial. On the premise that efavirenz dose reduction could provide a way of further decreasing drug costs given its pivotal role in first-line regimens and might contribute to reduced toxic effects, we designed the ENCORE1 study to compare the efficacy and safety of reduced dose (400 mg) versus standard dose (600 mg) efavirenz in treatment-naive adults with HIV infection. The week 48 primary analysis showed non-inferiority of efavirenz 400 mg when combined with tenofovir and emtricitabine as initial therapy.[8] In this Article, we report the durability of efficacy and safety of this therapy from the 96-week extended follow-up.

Methods

Study design and participants

ENCORE1 was a randomised, double-blind, placebo-controlled, non-inferiority trial. Participants for the study were recruited from 38 clinic and hospital sites in Argentina, Australia, Chile, Germany, Hong Kong, Israel, Malaysia, Mexico, Nigeria, Singapore, South Africa, Thailand, and the UK. Eligibility criteria were documented HIV-1 infection, age 16 years or older, no previous antiretroviral therapy, CD4 cell count between 50 and 500 cells per μL, and plasma HIV-1 viral load of at least 1000 copies per mL. Participants were excluded if they had previous AIDS-defining illness, any uncontrolled opportunistic infection or malignancy, used illegal drugs likely to adversely affect participation, or if they were pregnant or breastfeeding. Laboratory exclusion criteria were absolute neutrophil count lower than 500 cells per μL, haemoglobin concentration lower than 70 g/L, platelet count lower than 50 000 cells per μL, serum transaminases more than five-times the upper limit of normal, and an estimated creatinine clearance of 50 mL/min or lower. Individuals diagnosed with active *Mycobacterium tuberculosis* infection less than 2 years before their HIV diagnosis were also ineligible.[9,10] During the study, the protocol was amended to allow efavirenz use during pregnancy;[11] participants continuing the pregnancy were switched to open-label efavirenz 600 mg for the duration of the pregnancy. Previously, participants had replaced masked efavirenz with another agent for the duration of the pregnancy.

The study protocol was approved by St Vincent's Hospital, Sydney human research ethics committee and the UNSW human research ethics committee, by local research ethics committees or institutional review boards, and, when required, national regulatory authorities. All participants provided written informed consent.

Randomisation and masking

At baseline, participants were randomised centrally by an electronic case report form in a 1:1 ratio to receive fixed-dose daily tenofovir 300 mg and emtricitabine 200 mg (Truvada; Gilead Sciences, Foster City, CA, USA) plus either efavirenz 600 mg as three 200 mg tablets or efavirenz 400 mg as two 200 mg tablets plus one placebo tablet of identical appearance. Drugs (efavirenz and tenofovir–emtricitabine) were packaged into kits that had an individual kit number plus a detachable A or B label which was removed by independent site pharmacists at the time of dispensing (leaving only the kit number). To ensure that treatment assignment was concealed, only the study statistician had access to dose allocation. Randomisation was stratified by clinical site and screening plasma HIV-1 viral load (≤100 000 *vs* >100 000 copies per mL).

Procedures

A detailed description of the study methods has been reported in the week 48 primary efficacy comparison;[8] here, we provide a brief description of the 96-week methods. After week 48, participants were assessed at weeks 60, 72, 84, and 96. Safety assessments at all visits were clinical adverse events, concomitant medications, physical examination, full blood count, biochemistry (electrolytes, liver enzymes, and creatinine), and measurement of plasma HIV-1 viral load (for clinical management) and T-lymphocyte subsets; women of childbearing potential also underwent β human chorionic gonadotrophin testing. Fasting lipids, insulin, glucose, and estimated insulin resistance (by homoeostasis model assessment [HOMA]) were assessed at weeks 72 and 96. At week 96, health-related quality of life (on the 12-item Short-Form Health Survey [SF-12]),[12] depression, anxiety, and stress (on the 21-item Depression Anxiety Stress Scales [DASS-21]),[13] and treatment adherence[14] were self-reported. Plasma HIV-1 viral load was measured centrally (at St Vincent's Centre for Applied Medical Research, Sydney, Australia) with the Abbott m2000 Real Time HIV-1 Test (Abbott Molecular, Des Plaines, IL, USA; lower limit of detection 40 copies per mL) for efficacy assessment. Central genotypic resistance assay analysis was done on baseline samples and after week 24 for participants with virological failure. We interpreted results to week 48 with the Stanford genotypic resistance interpretation algorithm version 6.3.1, and after week 48 version 7.0 was used.[15] Owing to the nominal limit of assays, genotyping was only done on viral isolates from participants with two consecutive central plasma HIV-1 viral load recordings of 500 copies per mL or higher.

Outcomes

The primary endpoint was the comparison of the proportion of participants in each randomly assigned treatment group with a plasma HIV-1 viral load less than 200 copies per mL at week 96. Secondary endpoints included comparisons of the proportion of participants in each treatment group with a plasma HIV-1 viral load lower than 50 and 400 copies per mL; other secondary endpoints were comparisons between the treatment groups of time to loss of virological response (plasma HIV-1 viral load ≥200 copies per mL); mean change from baseline in $\log_{10}$ plasma HIV-1 viral load; mean change in CD4 cell counts; mean or median change from baseline in biochemical, haematological, and fasting lipid and glycaemic parameters; rates, types, and severity of adverse events and serious adverse events; and rates of opportunistic infections, serious non-AIDS-defining illnesses, and deaths. Other secondary endpoints were between-group comparisons of change from baseline in health-related quality-of-life scores; depression, anxiety, and stress scores; and self-reported adherence to treatment.

Statistical analysis

Statistical methods for the week 48 analysis have previously been published.[8] The week 96 analysis used the same methods, which we summarise briefly.

At week 96, we assessed virological outcomes in three populations: the modified intention-to-treat population (defined as all participants who received at least one dose of study treatment and attended at least one follow-up visit, irrespective of treatment received); the per-protocol population; and the non-completer=failure (NC=F) population (which is equivalent to the Food and Drug Administration snapshot algorithm). For intention-to-treat assessment of viral suppression, participants with missing data or treatment changes because of virological failure were classified as failures. The per-protocol analysis included only participants on randomised therapy and with available data, whereas in the NC=F analysis, participants with treatment changes for any reason or missing data were classed as failures.

All analyses were prespecified. Non-inferiority of efavirenz 400 mg was defined as the lower 95% CI of the between-group difference in the proportion of patients with plasma HIV-1 viral load below 200 copies per mL at 96 weeks lying above a threshold of –10%. Virological outcomes were stratified by screening plasma HIV-1 viral load (≤ or >100 000 copies per mL) and assessed at thresholds of 50, 200, and 400 copies per mL. Time to loss of virological response was measured as time from randomisation to the first of two plasma HIV-1 viral load values of 200 copies per mL or higher following suppression, cessation of randomly assigned treatment, death, or withdrawal, or was recorded as 0·5 days in participants who did not achieve virological suppression (ie, those who never achieved a plasma HIV-1 viral load <200 copies per mL). The primary endpoint at 96 weeks was comparison of the proportion of participants in each treatment group with plasma HIV-1 viral load below 200 copies per mL.

Safety analyses were clinical and laboratory adverse events. Investigators assessed the occurrence of adverse events and whether or not these were related to the study drug; adverse events were recorded as drug related if they were judged by the investigator to be definitely or probably related to the study drugs. Adverse event severity was graded according to the Division of AIDS table for grading adult adverse event severity (2004/2009 clarification). The numbers of adverse events were compared by the zero-inflated negative binomial method.

Analyses were done after all randomly assigned participants had completed at least 96 weeks of

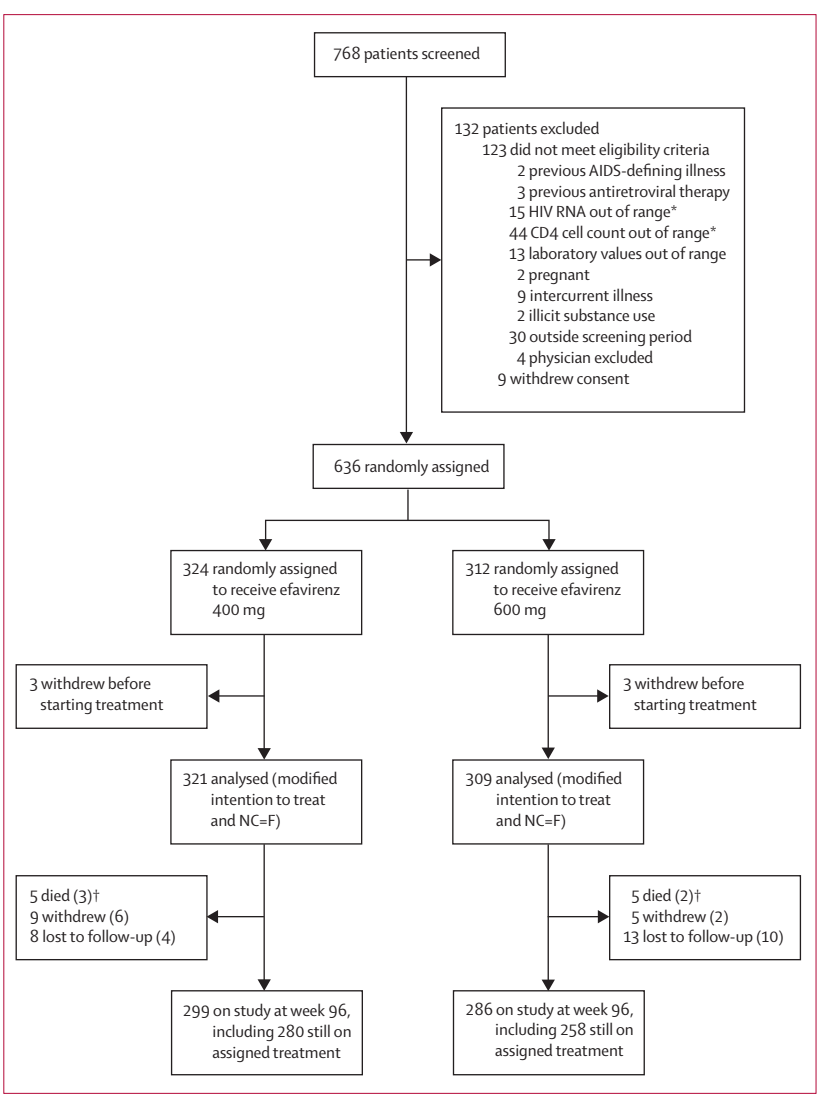

Figure 1: **Trial profile**
NCF=F represents non-completer=failure. *One patient with two events. †Numbers in brackets represent events occurring after week 48.

follow-up or were permanently lost to follow-up. Differences in the proportions between randomised groups were summarised as n (%) in each group and percentage difference with 95% CIs, and were tested with a Pearson's χ^2 or Fisher's exact test-derived p value. The *t* test was used to compare mean change from baseline. Time-to-event endpoints were summarised as incidence rates and randomised groups were compared with a Cox regression analysis with a hazard ratio (HR) estimated, and the Wald test was used to compare estimates between groups. The proportional hazards assumption was examined graphically and the assumption validated; therefore HRs are presented. Resistance mutations in reverse transcriptase at baseline were summarised by drug and treatment group. Treatment-emergent NNRTI mutations present at the time of failure were summarised by treatment group.

Only the primary endpoint was assessed in terms of non-inferiority. All other comparisons were tests for superiority. A two-sided α of 0·05 was used to define statistical significance. No adjustments were made for multiple comparisons. Stata version 13.1 and SAS version 9 were used for data analyses.

This study is registered with ClinicalTrials.gov, number NCT01011413.

	Efavirenz 400 mg group (n=321)	Efavirenz 600 mg group (n=309)
Men	221 (69%)	206 (67%)
Age (years)	36·1 (10·0)	35·8 (10·0)
Ethnic origin		
African	118 (37%)	116 (37%)
Asian	106 (33%)	103 (33%)
White	97 (30%)	90 (29%)
Aboriginal or Torres Strait Islander	0	1 (<1%)
Transmission		
Heterosexual contact	156 (49%)	156 (50%)
Homosexual/bisexual contact	138 (43%)	134 (43%)
Injection drug use, not known	27 (8%)	20 (7%)
Estimated time since infection (weeks)	151 (189)	167 (203)
CDC category		
A	264 (82%)	265 (86%)
B	46 (14%)	33 (11%)
C	11 (3%)	11 (4%)
Median (IQR) plasma HIV-1 viral load in $\log_{10}$ copies per mL	4·76 (4·37–5·26)	4·73 (4·35–5·20)
Plasma HIV RNA copies per mL		
0 to <1000	3 (1%)	4 (1%)
1000 to <10 000	55 (17%)	49 (16%)
10 000 to <100 000	156 (49%)	149 (48%)
≥100 000	107 (33%)	107 (35%)
CD4 T-cell count (cells per μL)	273 (97)	272 (101)
<100	9 (3%)	13 (4%)
100–200	68 (21%)	66 (21%)
>200–350	176 (55%)	158 (51%)
>350–500	68 (21%)	72 (23%)
Nadir CD4 T-cell count (cells per μL)	248 (88)	252 (90)
Hepatitis B virus surface antigen positive*	15 (5%)	12 (4%)
Hepatitis C virus antibody positive†	5 (2%)	3 (1%)
Creatinine clearance (mL/min)	117·4 (29·7)	120 (32·4)
Total cholesterol (mmol/L)	4·24 (0·95)	4·15 (0·93)
HDL cholesterol (mmol/L)	1·04 (0·32)	1·03 (0·31)
LDL cholesterol (mmol/L)	2·54 (0·93)	2·47 (0·84)
Triglycerides (mmol/L)	1·25 (0·72)	1·24 (0·69)
Insulin (pmol/L)	57·37 (89·59)	57·50 (67·37)
Glucose (mmol/L)	4·66 (0·98)	4·84 (1·78)
Current smoker	82 (26%)	87 (28%)
Body-mass index (kg/m²)	24·0 (4·7)	24·3 (5·2)

Data are n (%) or mean (SD), unless otherwise indicated. CDC=Centers for Disease Control and Prevention. *218 patients (68%) in the efavirenz 400 mg group and 206 (67%) in the efavirenz 600 mg group were tested for hepatitis B virus surface antigen. †213 patients (66%) in the efavirenz 400 mg group and 197 (64%) in the efavirenz 600 mg group were tested for hepatitis C virus. Table reproduced from ENCORE1 Study Group,[8] by permission of Elsevier Limited, 2015.

Table 1: **Baseline characteristics**

Role of the funding source

Representatives of the funding source (the Bill & Melinda Gates Foundation) reviewed the study design, statistical analysis, and reporting. They were not involved in study management or data collection. They reviewed study reports, final report, and the draft document before publication. The writing group had full access to all the study data and had final responsibility for the decision to submit for publication.

Results

Between Aug 24, 2011, and March 19, 2012, 636 eligible participants were enrolled and randomly assigned to the two treatment groups (324 to efavirenz 400 mg and 312 to efavirenz 600 mg). Of these individuals, 321 in the 400 mg group and 309 in the 600 mg group received at least one dose of study drug and attended one follow-up visit and therefore comprised the modified intention-to-treat population at week 96 (figure 1). Baseline characteristics were well balanced across the treatment groups (table 1). 234 (37%) of 630 participants were African, 209 (33%) were Asian, and 187 (30%) were white. The mean age of the participants was 36 years (SD 10·0) and 203 (32%) were women. At week 96, 585 (93%) of 630 participants (299 in the efavirenz 400 mg group and 286 in the 600 mg group) remained in follow-up.

At week 96, the modified intention-to-treat analysis showed that 289 (90·0%) of 321 patients in the efavirenz 400 mg group and 280 (90·6%) of 309 in the 600 mg group had a plasma HIV-1 viral load less than 200 copies per mL (difference –0·6% [95% CI –5·2 to 4·0]; relative risk 0·99 [95% CI 0·94 to 1·05]), which fulfilled the predetermined non-inferiority criteria (figure 2). Quantitatively similar results were recorded for the NC=F and per-protocol population analyses (figure 2). At the less than 50 copies per mL threshold, the modified intention-to-treat analysis showed that 277 (86·3%) of 321 patients in the efavirenz 400 mg group and 268 (86·7%) of 309 in the efavirenz 600 mg group achieved

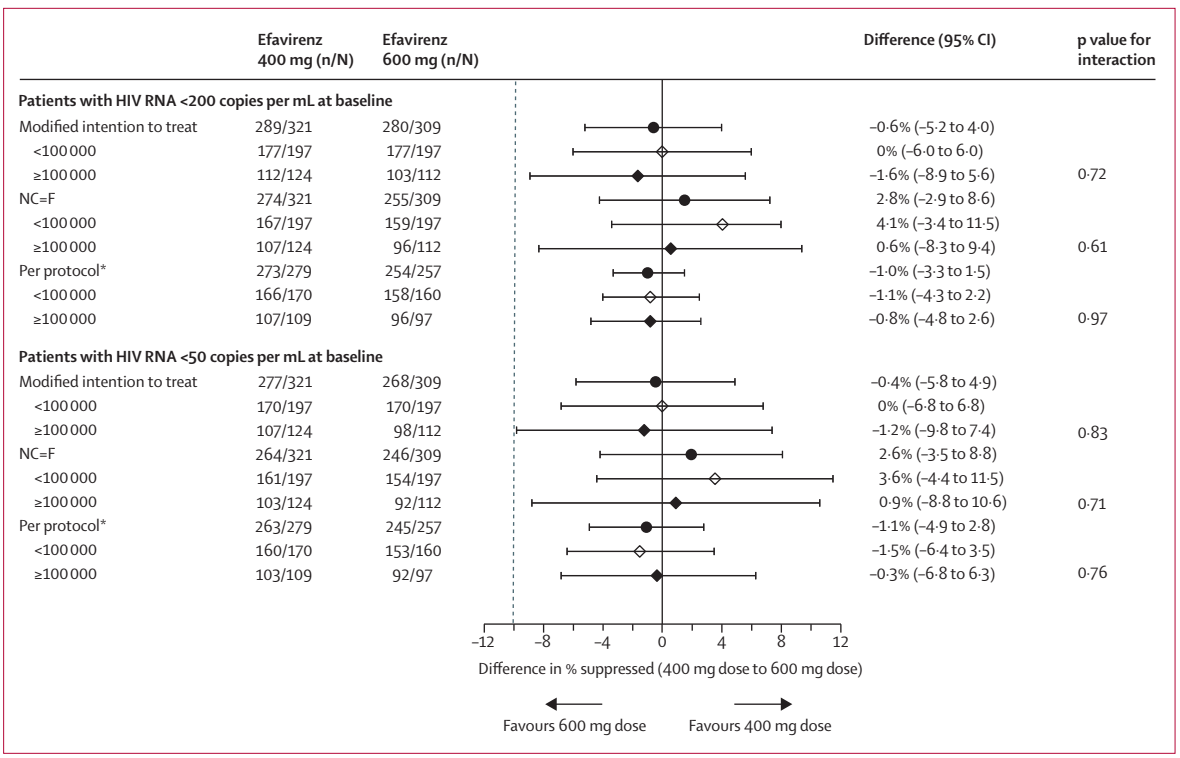

***Figure 2*: Results of non-inferiority comparisons at week 96 of HIV RNA viral load less than 200 copies per mL and less than 50 copies per mL by population and baseline HIV RNA strata**

The x-axis is the difference in the percentage of patients with plasma viral HIV RNA load less than 200 copies per mL or less than 50 copies per mL. Point estimates are the difference in the percentage of participants with viral load suppression less than 200 copies and less than 50 copies per mL at week 96. The primary comparison (circle) is stratified by plasma HIV RNA strata at screening (≤100 000 copies per mL [open diamond] *vs* >100 000 copies per mL [black diamond]) and is presented for modified intention-to-treat, NC=F, and per-protocol populations. The dotted vertical line at –10% is the non-inferiority boundary. NC=F represents non-completer=failure. *Error bars are 95% Agresti-Caffo exact CIs for point estimates. The test for interaction is presented for viral load strata only.

virological suppression (difference –0·4% [95% CI –5·8 to 4·9]), also fulfilling the non-inferiority criteria. Results for the NC=F and per-protocol analyses were similar (figure 2). Findings were consistent across baseline plasma viral load strata (≤ or >100 000 copies per mL) and in the fewer than 400 copies per mL threshold analysis (data not shown), and all results showed non-inferiority of the efavirenz 400 mg dose.

Mean change from baseline to week 96 in $\log_{10}$ plasma HIV-1 viral load did not differ between the groups in the modified intention-to-treat analysis (efavirenz 400 mg –3·0 [95% CI –3·09 to –2·92] *vs* efavirenz 600 mg –2·98 [–3·07 to –2·89]; difference –0·02 [–0·14 to 0·10], p=0·74) (figure 3) or per-protocol analysis (efavirenz 400 mg –3·05 [–3·14 to –2·97], efavirenz 600 mg –3·05 [–3·14 to –2·96]; difference 0·00 [–0·12 to 0·12], p=0·98). Analysis of time to loss of virological response at the fewer than 200 copies per mL threshold included 58 events (in the 400 mg group) and 62 events (in the 600 mg group); no between-group difference was recorded (rate per 100 participant-years 0·21 [95% CI 0·16–0·27] in the 400 mg group *vs* 0·24 [0·19–0·31] in the 600 mg group; HR 1·14 [95% CI 0·80–1·63], p=0·47). During the first 48 weeks, 80 (12·7%) of the 630 participants in the study

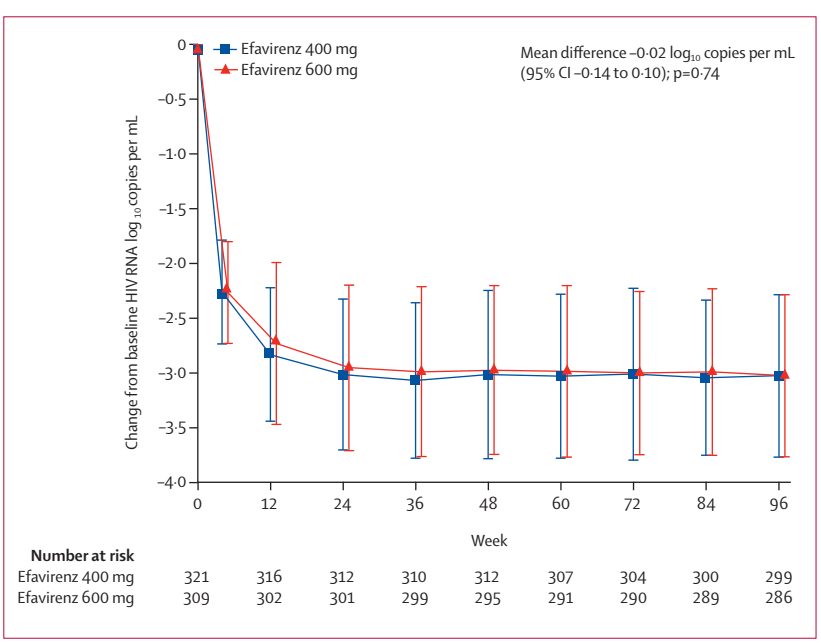

***Figure 3*: Mean change in HIV RNA viral load from baseline to week 96 for the modified intention-to-treat population**

Plotted points are mean $\log_{10}$ copies per mL; error bars are SDs.

population experienced a loss of virological response event, with an additional 40 (6·3%) experiencing an event in the subsequent 48 weeks. At week 96, 280 (87·2%) of 321 participants assigned to efavirenz 400 mg and 258 (84·5%) of 309 assigned to 600 mg remained on their assigned treatment (difference 3·7% [95% CI –1·8 to 9·3], p=0·18; figure 1). Time to efavirenz cessation did not differ between the groups, with rates per 100 person-weeks of 0·15 for efavirenz 400 mg and 0·19 for efavirenz 600 mg (HR 1·32 [95% CI 0·9–2·0]; p=0·18).

See Online for appendix

Mean CD4 cell counts increased in both groups. At week 96, mean change from baseline was 235 cells per µL (95% CI 218–252) in the efavirenz 400 mg group and 209 cells per µL (194–226) in the 600 mg group (figure 4). The mean change was significantly higher with the 400 mg dose of efavirenz in both the modified intention-to-treat population (difference 25 cells per µL [95% CI 2–48]; p=0·03) and the per-protocol population (difference 30 cells per µL [5–55]; p=0·018). The mean change in CD4 cell percentage did not differ between the groups (p=0·47), and neither did the mean change in CD8 cell counts (p=0·74) or total lymphocyte counts (p=0·79).

Over 96 weeks, the proportions of patients who ever reported an adverse event did not differ between the groups, and most events were of grade 1 or 2 severity (table 2). Adverse events definitely or probably attributable to efavirenz were significantly more common in the efavirenz 600 mg group than in the efavirenz 400 mg group (table 2). More participants who received efavirenz 600 mg stopped efavirenz treatment after an efavirenz-related adverse event than did those who received the 400 mg dose (table 2). The median time to first adverse event was 1 day (IQR 0·5–9) for efavirenz-related events and 24 days (2–98) for other events.

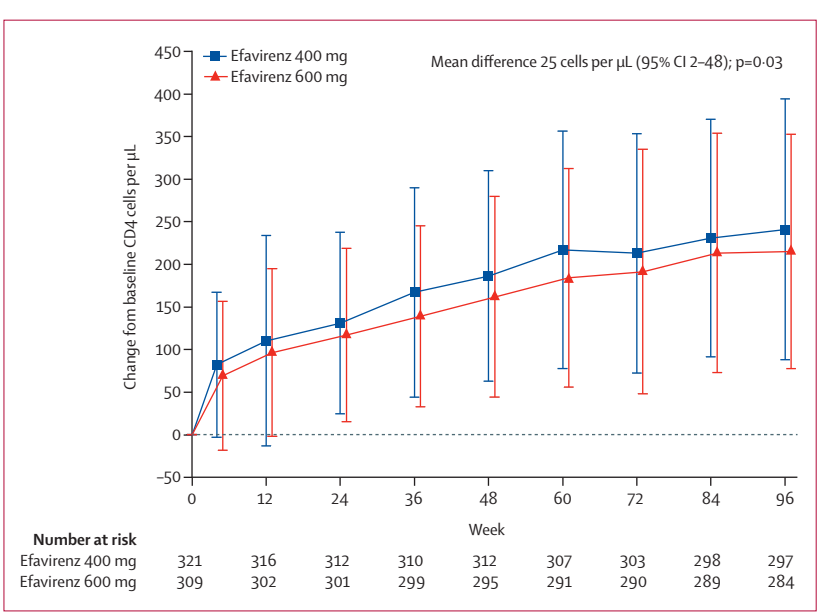

Figure 4: **Mean change in CD4 T cells from baseline to week 96 for the modified intention-to-treat population**
Plotted points are mean cells per µL; error bars are SDs.

Efavirenz-related adverse event severity was not dissimilar to overall adverse event severity, with 472 (93%) of 509 events being grade 1 or 2, whereas 37 (7%) were grade 3, and four (1%) were of grade 4 severity. Neuropsychiatric adverse events were less common after week 48; in the 400 mg dose group, these accounted for 48 (16%) of 292 of these events reported over 2 years, compared with 52 (15%) of 336 in the 600 mg dose group. Adverse events as categorised in the efavirenz product information were more frequent in the 600 mg group than in the 400 mg group (appendix p 1).[16] The frequency of serious adverse events was similar in the two groups (table 2). Seven serious adverse events were judged to be definitely or probably related to efavirenz; the numbers of participants who had these events did not differ significantly between the groups (p=0·44; table 2).

During the 96 weeks of follow-up, five deaths occurred in each treatment group. In the 400 mg group, these deaths were caused by non-Hodgkin lymphoma, probable primary CNS lymphoma, acute myocardial infarction, stab wounds, and pancreatic cancer, whereas in the 600 mg group the deaths were attributable to septic shock possibly caused by an adverse drug reaction, acinetobacter pneumonia, suicide, childbirth, and gun-shot wound. Three serious non-AIDS events occurred in each group (pancreatic cancer, acute myocardial infarction, and diabetes mellitus in the efavirenz 400 mg group; stroke, testicular seminoma, and pulmonary thromboembolism in the 600 mg group). In total, 21 AIDS events were reported (14 in the 400 mg group and seven in the 600 mg group), five of which occurred after week 48. Overall, pulmonary *Mycobacterium tuberculosis* infection (nine participants), non-Hodgkin lymphoma (five), and Kaposi's sarcoma (three) were the most common AIDS events. The proportions of participants who had an AIDS event during follow-up did not differ between the groups (p=0·14).

Self-reported quality of life, assessed by the SF-12, improved in both groups, with no significant between-group difference in improvement recorded for either the Physical Component Score (median change from baseline of 3·4 [IQR –3·0 to 14·3] in the 400 mg group *vs* 2·4 [–3·6 to 11·3] in the 600 mg group, p=0·20) or Mental Component score (median change from baseline of 3·3 [IQR –5·1 to 13·5] *vs* 3·6 [–4·1 to 17·3], p=0·25; appendix p 2). At 96 weeks, change in DASS-21 depression, anxiety, and stress *Z* scores did not differ between the groups (appendix p 2). Adherence to treatment at week 96 did not differ between the groups, with 271 (93%) of 292 participants in the 400 mg group and 256 (91%) of 280 in the 600 mg group reporting 100% adherence in the previous week (p=0·25).

At 96 weeks, a significant between-group difference for the mean change in alkaline phosphatase was recorded (21·2 U/L [95% CI 17·4–25·1] in the 400 mg group *vs* 26·8 U/L [22·9–30·6] in the 600 mg group; p=0·046). No other between-group differences were recorded for the

	Efavirenz 400 mg group (n=321)	Efavirenz 600 mg group (n=309)	Difference (95% CI)	p value
Adverse events (total=3337)				
Total number of adverse events	1653 (49·5%)	1684 (50·5%)	..	0·42
Grade 1	1202 (73%)	1236 (73%)	..	..
Grade 2	381 (23%)	363 (22%)	..	..
Grade 3	62 (4%)	77 (5%)	..	..
Grade 4	8 (1%)	8 (1%)	..	..
Patients reporting adverse events	291 (91%)	285 (92%)	−1·6 (−2·8 to 5·9)	0·48
Patients with adverse event related to efavirenz*	126 (39%)	148 (48%)	−8·6 (−16·4 to −0·9)	0·03
Patients stopping efavirenz because of treatment-related adverse event*†	16 (13%)	34 (23%)	−10·3 (−19·2 to −1·4)	0·03
Serious adverse events				
Total number of serious adverse events	32 (40%)	48 (60%)	..	..
Patients reporting serious adverse events	24 (8%)	32 (10%)	−2·9 (−7·3 to 1·5)	0·20
Patients reporting serious adverse events related to efavirenz*‡	2 (1%)	4 (1%)	−0·7 (−2·4 to 1·1)	0·44

Data are n (%) unless otherwise indicated. *Definitely or probably related to efavirenz. †Relationship interaction p=0·046. ‡Events included grade 3 dizziness and possible Stevens-Johnson Syndrome with the 400 mg dose; and rash with fever, septic shock possibly due to an adverse drug reaction, rash with labial oedema, suicide, and attempted suicide with the 600 mg dose (one event each in three patients, except for rash with fever and septic shock, which occurred in the same patient).

Table 2: **Adverse events and serious adverse events**

mean change in other biochemical or haematological parameters, or estimated creatinine clearance (appendix p 3). Fasting total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride concentrations increased modestly, but mean changes did not differ between the groups at 96 weeks. Changes in fasting glucose and insulin concentrations, and HOMA scores also did not differ between the groups (appendix p 3).

Baseline genotypic resistance data were available for 570 participants (appendix p 4). High-level NNRTI resistance was identified in ten participants in the efavirenz 400 mg group and in eight in the 600 mg group; one person (in the 400 mg group) had high-level emtricitabine resistance (appendix p 4). No participant had resistance to tenofovir. During the study, five of the 18 participants with NNRTI resistance (three in the efavirenz 400 mg group and two in the 600 mg group) had virological failure, and one participant stopped taking efavirenz because of depression. At 96 weeks, 13 participants (six in the 400 mg group and seven in the 600 mg group) had a plasma HIV-1 viral load below 50 copies per mL, including 12 individuals who remained on their randomly assigned treatment (appendix p 4).

36 participants with virological failure (two consecutive plasma HIV-1 viral load measurements >500 copies per mL) were eligible for assessment of NNRTI-emergent resistance. Of the 23 participants with HIV reverse transcriptase gene sequences that enabled interpretation of resistance, 14 had virological failure after week 48 (appendix p 5). Ten of the 23 participants had received efavirenz 400 mg and 13 had received 600 mg. NNRTI-emergent resistance was detected in two participants in the 400 mg dose group and three in the 600 mg dose group (appendix p 5); no evidence of NNRTI resistance mutations was found in the remainder of the participants.

Discussion

In this 96-week follow-up of the ENCORE1 study, our results show that a reduced 400 mg dose of efavirenz remains virologically non-inferior to the standard 600 mg dose when given with tenofovir and emtricitabine as initial antiretroviral therapy over 96 weeks. This finding was consistent across several efficacy endpoints and all plasma HIV-1 viral load thresholds assessed, irrespective of baseline viral load. Although the frequency and severity of adverse events did not differ with dose, adverse events attributable to efavirenz were significantly less common with the 400 mg dose than with the 600 mg dose, and contributed to fewer treatment-related discontinuations. We recorded no difference in treatment adherence; quality of life improvements; or depression, anxiety, and stress scores between the treatment groups.

Our findings confirm the durable virological non-inferiority of efavirenz 400 mg. Fewer participants experienced loss of virological response during the second 48 weeks of study than during the first 48 weeks. Rates of viral suppression were similar to those reported in recent studies of efavirenz in antiretroviral therapy-naive adults with HIV infection.[17–19] As with the present study, participants were from diverse geographical areas across high-income, middle-income, and low-income countries; therefore, our findings are broadly generalisable. We noted greater increases in mean CD4 cell counts with the 400 mg dose than with the 600 mg dose. The clinical significance of this difference is unclear. However, it is consistent with efavirenz-mediated lymphocyte toxic effects, which has previously been reported.[20]

Reduction of the efavirenz dose did not affect the overall frequency or severity of adverse events. Most events were mild to moderate in severity and were consistent with those that have been reported previously.[16,18,19] However, dose affected the likelihood of treatment-related adverse

Panel: **Research in context**

Systematic review

We searched Medline, Embase, PubMed, and the Cochrane Central Register of Controlled Trials for prospective, randomised trials of at least 24 weeks duration of efavirenz as initial antiretroviral therapy published from Jan 1, 2000, to Dec 31, 2014. Clinical trial registry and regulatory site searches included the National Institutes of Health Clinical Trials Registry, the ISRCTN registry, and clinical trials at AIDSinfo. Our main search terms were: "efavirenz", "dose reduction", "reduced dose", and "randomised controlled trial". We assessed the quality of methods used in the studies for inclusion using Cochrane-based criteria,[29] including method of sequence generation, allocation concealment, blinding, incomplete outcome data, absence of selective reporting, and adherence to the intention-to-treat principle. We identified only one population-based, randomised controlled study, which was the week 48 primary analysis of the present study.[8] This analysis established the non-inferiority of efavirenz 400 mg to 600 mg as initial therapy over 48 weeks and indicated improved safety and tolerability with the lower dose.

Interpretation

The week 96 analysis of this large, randomised, double-blind, placebo-controlled, non-inferiority study in ethnically and geographically diverse adults with HIV infection confirmed the durable virological non-inferiority of efavirenz 400 mg to the standard 600 mg dose when given as initial therapy with tenofovir and emtricitabine. Compared with the 600 mg dose, the lower 400 mg dose was associated with fewer efavirenz-related adverse events and fewer treatment discontinuations: both these outcomes offer potential for improved adherence, which is a factor crucial in determining the success or failure of a treatment regimen. The efficacy and safety findings of this study provide robust evidence to redefine the efavirenz dose for first-line HIV treatment. A recognised challenge to rollout of the 400 mg dose will involve further investigation of its use in pregnancy and with tuberculosis treatment, since these patient groups were not included in the present study. Universal access as recommended in the WHO guidelines[3] poses enormous challenges, especially in low-income and middle-income countries where the disease burden is high, since total drug costs will increase substantially. Dose optimisation provides an opportunity to reduce drug costs, enabling scarce financial resources to be deployed elsewhere within the health-care system. Prompt adoption of a 400 mg dose of efavirenz in international guidelines is therefore paramount, and international regulatory agencies should remove obstacles to ensure timely review of these compelling data. Amendment of treatment guidelines needs a considered approach, but agencies must not create obstacles to translating new research findings to updated recommendations. Such barriers can only lead to loss of benefits for those most in need.

events occurring, with significantly more efavirenz-related adverse events reported with the 600 mg dose than with the 400 mg dose: a finding consistent with previous publications that recorded fewer CNS adverse events at lower efavirenz doses than at higher doses.[4,21,22] We also observed fewer treatment-related discontinuations with efavirenz 400 mg. This finding is consistent with observations in an earlier study in which significantly higher rates of early termination due to adverse events were reported with efavirenz 600 mg than with lower (400 mg or 200 mg) doses or placebo.[5]

Self-reported adherence was higher than 90% in both treatment groups, which is consistent with the good virological outcomes suggesting the four-tablet daily pill burden was not a limiting factor in this treatment-naive population. Health-related quality of life improved modestly over 96 weeks. Although more participants in the 600 mg group reported efavirenz-related CNS adverse events, this outcome did not present itself as differences in DASS-21 scores, with no differences recorded between treatment groups at week 96.

The mean change in alkaline phosphatase was higher in recipients of the 600 mg dose than in those given the 400 mg dose; however, mean levels remained within the normal range in both groups. Both tenofovir and efavirenz can increase alkaline phosphatase concentrations.[23] Our observation probably represents a dose-dependent effect of efavirenz, since the tenofovir dose was the same in both treatment groups; however, the clinical significance of the increase is unclear.

Evidence of transmitted NNRTI resistance was uncommon, occurring in less than 3% of participants—a finding consistent with published data suggesting that NNRTI resistance in treatment-naive adults varies between countries but remains stable at around 5–8%.[24,25] We found no evidence to suggest that baseline NNRTI resistance led to different treatment failure rates between the two groups. Most participants who continued efavirenz treatment maintained virological suppression to week 96, suggesting that transmitted efavirenz resistance does not preclude virological control, especially when combined with potent nucleoside or nucleotide reverse transcriptase inhibitors such as tenofovir and emtricitabine—an observation consistent with previous studies.[26–28] Furthermore, we noted no evidence of greater rates of emergent NNRTI resistance in recipients of the 400 mg dose than in those who received the standard dose. Interestingly, more than three-quarters of those with virological failure did not have NNRTI resistance mutations, which suggests that treatment adherence was less than optimum.

Antiretroviral drug costs have fallen in low-income and lower-middle-income countries in recent years, assisted by the continuing expansion of treatment programmes, better predictability of demand, and increased competition between manufacturers. Although treatments are now more affordable than they were in the past, drug costs remain substantial. Expansion of treatment towards universal access as recommended in the WHO 2013 guidelines[3] will significantly increase total drug costs. Dose reduction provides a means of further lowering costs.

This large, well designed, double-blind, placebo-controlled study in HIV-infected adults with no previous exposure to antiretroviral therapy provides robust evidence of the virological non-inferiority of efavirenz 400 mg compared with the standard 600 mg dose when combined with tenofovir and emtricitabine over 96 weeks. Additionally, compared with the 600 mg dose, the lower dose of efavirenz was associated with fewer drug-related adverse events and fewer treatment discontinuations. This study provides strong evidence to redefine the first-line treatment dose of efavirenz (panel). Rollout of reduced dose efavirenz will involve challenges.

Assessment of its use in situations in which potential exists for reduced drug exposure, such as when rifampicin is needed for tuberculosis treatment and during pregnancy, will be crucial to reduce the risk of virological failure and drug resistance. However, we note recent data suggesting increased efavirenz trough concentrations with coadministration of efavirenz and rifampicin-based tuberculosis treatment.[30] Additional investigations in adolescents and malnourished patients might also be needed. Studies investigating the pharmacokinetic, pharmacodynamics, and pharmacogenetic characteristics of both efavirenz doses done during the course of ENCORE1 will be published separately. Importantly, widespread adoption of the 400 mg dose would reduce drug costs and enable scarce resources to be deployed elsewhere within health-care systems. However, uptake needs responsible normative agencies and international regulators to remove administrative blocks to review and decision making for emergent data such as these. For people with HIV infection, access to treatment and care saves lives and seems to offer population benefits through reductions in HIV transmission.

The strength of evidence derived from this trial is no less robust than that which is needed to license a new HIV treatment. Although a cautious approach is sensible when amending treatment guidelines, the societal and individual benefits foregone when agencies create impediments to the translation of new research findings should not be underestimated. Delay in recommending efavirenz 400 mg through normative guidelines must carry a burden of responsibility by the agencies involved.

Contributors

DC did protocol review, study coordination, data review, document drafting, and manuscript review. RP did protocol drafting and review, study coordination and management, drug sourcing and management, data review, and manuscript review. JA did protocol review, randomisation, statistical analysis, and manuscript review. ML and PP did protocol review, study coordination and management, recruited patients and followed the protocol, and reviewed the manuscript. SF, LM, BC-R, HJ, SK, AW, M-PL, and WB reviewed the protocol, recruited patients and followed protocol, and reviewed the manuscript. DAC did executive coordination, protocol review, recruited patients and followed the protocol, and reviewed the data and manuscript. SE did executive coordination, protocol drafting, protocol review, study coordination and management, and reviewed the data and manuscript.

Writing committee

Dianne Carey, Rebekah Puls, Janaki Amin, Marcelo Losso, Praphan Phanupak, Sharne Foulkes, Lerato Mohapi, Brenda Crabtree-Ramirez, Heiko Jessen, Suresh Kumar, Alan Winston, Man-Po Lee, Waldo Belloso, David A Cooper, and Sean Emery.

ENCORE1 Study Group

Protocol Steering Committee: Janaki Amin, Stephen Becker, Waldo Belloso, Marta Boffito, David Cooper, Brenda Crabtree-Ramirez, Chris Duncombe, Sean Emery, Sharne Foulkes, Andrew Hill, Heiko Jessen, Suresh Kumar, Man-Po Lee, Marcelo Losso, Chidi Nwizu, Praphan Phanuphak, Tim Read, Jim Rooney, Kim Schaffer, Eduardo Shahar, Alan Winston, Marcelo Wolff, and Barnaby Young. *Project team:* Cecilia Abela, Janaki Amin, Anchalee Avihingsanon, Waldo Belloso, Mark Boyd, Dianne Carey, Amanda Clarke, David Cooper, Kymme Courtney-Vega, Marina Delfino, Anna Donaldson, Sean Emery, Natalie Espinosa, Tanya Johannesen, Enmoore Lin, Marcelo Losso, Alejandra Moricz, Sarah Pett, Praphan Phanupak, Rebekah Puls, Kanitta Pussadee, Parinya Sutheerasak, Louise Tomlins, and Sasiwimol Ubolyam. *Site investigators*: Waldo Belloso, Raja Iskandar Shah bin Raja Azwa, Emiliano Bissio, Liliana Calanni, Ploenchan Chetchotisakd, David Cooper, Brenda Crabtree-Ramirez, Nicholas Doong, Julian Elliott, Sharne Foulkes, Brian Gazzard, Heiko Jessen, Mark Kelly, Suresh Kumar, Hector Laplume, Man-Po Lee, Marcelo Losso, Norma del Carmen Luna, Sergio Lupo, Oscar Garcia Messina, Lerato Mohapi, Richard Moore, David Nolan, Chidi Nwizu, Catherine Orrell, Carlos Perez, Praphan Phanuphak, Tim Read, Jürgen Rockstroh, Diane Rowling, Eduardo Shahar, Khuanchai Supparatpinyo, Don Smith, Jaime Andrade Villanueva, Emanuel Vlahakis, Alan Winston, Marcelo Wolff, and Barnaby Young. *Central laboratory:* Tony Kelleher, Philip Cunningham, Kate Merlin, Julie Yeung, Ansari Shaik, Bertha Fsadni, Alex Carrera, and Melanie Lograsso. *Data safety and monitoring board:* Roy Gulick, David Dunn, and Matthew Dolan.

Declaration of interests

ML has received research grants from the Kirby Institute/UNSW. LM has received grants from Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, the Kirby Institute/UNSW, Merck Sharp & Dohme, and Pfizer. BC-R has received personal fees from Bristol-Myers Squibb and Stendhal. AW has received honoraria or research grants, or been a consultant or investigator in clinical trials sponsored by, Abbott/AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen Cilag, Roche, Pfizer, and ViiV Healthcare. DAC has received research grants from the Bill and Melinda Gates Foundation and Gilead Sciences Inc. SE has received research grants from the Bill & Melinda Gates Foundation. DC, RP, JA, PP, SF, HJ, SK, M-PL, and WB declare no competing interests.

Acknowledgments

The study was funded through an investigator-driven unrestricted grant from the Bill & Melinda Gates Foundation (grant ID 51040). The Kirby Institute is funded in part by the Australian Government Department of Health and Ageing. The views expressed do not necessarily represent the position of the Australian Government. Gilead Sciences donated Truvada, and Mylan Inc provided Efamat and donated matched placebo. The Kirby Institute is affiliated with the Faculty of Medicine, UNSW Australia. We thank all participants for their time and commitment.

References

1 Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services, November, 2014. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf (accessed Nov 15, 2014).

2 European AIDS Clinical Society. Guidelines. Version 7.02. June 2014. http://eacsociety.org/Portals/0/140601_EACS%20EN7.02.pdf (accessed Sept 28, 2014).

3 WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization. June, 2013. http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf?ua=1 (accessed Sept 19, 2014).

4 US Food and Drug Administration. Center for Drug Evaluation and Research Medical Review Application number 20-972. Oct 19, 1998. http://accessdata.fda.gov/drugsatfda_docs/nda/98/20972clinical_review.pdf (accessed Sept 10, 2014).

5 Haas D, Hicks C, Seekins D, et al. A phase 2, double-blind, placebo-controlled, dose-ranging study to assess the antiretroviral activity and safety of efavirenz (DMP 266) in combination with open-label zidovudine and lamivudine at 24 weeks (DMP 005). Fifth Conference on Retroviruses and Opportunistic Infections; Chicago, IL, USA; Feb 1–5, 1998. Abstract 698.

6 United Nations General Assembly. Political declaration on HIV and AIDS: intensify our efforts to eliminate HIV and AIDS, 65/277. June, 2011. http://un.org/en/ga/search/view_doc.asp?symbol=A/RES/65/27 (accessed Sept 1, 2014).

7 WHO. Global update on the health sector response to HIV. July, 2014. Executive Summary. Geneva: World Health Organization. http://apps.who.int/iris/bitstream/10665/128196/1/WHO_HIV_2014.15_eng.pdf?ua=1 (accessed Oct 2, 2014).

8 ENCORE1 Study Group. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. *Lancet* 2014; **383:** 1474–82.

9 WHO. Interim WHO clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance. African Region. June 16, 2005. http://who.int/hiv/pub/guidelines/clinicalstaging.pdf (accessed Aug 26, 2014).

10 Centers for Disease Control and Prevention. Revised classification system for HIV infection and expanded surveillance sase definition for AIDS among adolescents and adults. Dec 18, 1992. http://cdc.gov/mmwr/preview/mmwrhtml/00018871.htm (accessed Aug 28, 2014).

11 WHO. Technical update on treatment optimization: use of efavirenz during pregnancy: a public health perspective. June, 2012. http://apps.who.int/iris/bitstream/10665/70920/1/9789241503792_eng.pdf?ua=1 (accessed Sept 1, 2014).

12 Ware J Jr, Kosinski M, Keller SD. A 12-item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996; **34:** 220–33.

13 Henry J, Crawford J. The short-form version of the Depression Anxiety Stress Scales (DASS-21): construct validity and normative data in a large non-clinical sample. *Br J Clin Psychol* 2005; **44:** 227–39.

14 Chesney M, Ickovics J, Chambers D, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). *AIDS Care* 2000; **12:** 255–66.

15 Stanford University. HIV drug resistance database. http://hivdb.stanford.edu (accessed Aug 28, 2014).

16 Merck Sharp & Dohme (Australia). Stocrin Product Information. June, 2014. http://secure.healthlinks.net.au/content/msd/pi.cfm?product=mkpstocr (accessed Sept 3, 2014).

17 Puls RL, Srasuebkul P, Petoumenos K, et al. Efavirenz versus boosted atazanavir or zidovudine and abacavir in antiretroviral treatment-naive, HIV-infected subjects: week 48 data from the Altair study. *Clin Infect Dis* 2010; **51:** 855–64.

18 Cohen CJ, Andrade-Villanueva J, Clotet B, et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. *Lancet* 2011; **378:** 229–37.

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

20 Pilon AA, Lum JJ, Sanchez-Dardon J, Phenix BN, Douglas R, Bradley AD. Induction of apoptosis by a nonnucleoside human immunodeficiency virus type 1 reverse transcriptase inhibitor. *Antimicrob Agents Chemother* 2002; **46:** 2687–91.

21 Lanzafame M, Bonora S, Lattuada E, Vento S. Efavirenz dose reduction in HIV-infected patients. *HIV Med* 2012; **13:** 252–53.

22 Gutierrez-Valencia A, Viciana P, Palacios R, et al. Stepped-dose versus full-dose efavirenz for HIV infection and neuropsychiatric adverse events: a randomized trial. *Ann Intern Med* 2009; **151:** 149–56.

23 Welz T, Childs K, Ibrahim F, et al. Efavirenz is associated with severe vitamin D deficiency and increased alkaline phosphatase. *AIDS* 2010; **24:** 1923–28.

24 Frentz D, Boucher CA, van de Vijver DA. Temporal changes in the epidemiology of transmission of drug-resistant HIV-1 across the world. *AIDS Rev* 2012; **14:** 17–27.

25 Parikh UM, Kiepiela P, Ganesh S, et al. Prevalence of HIV-1 drug resistance among women screening for HIV prevention trials in KwaZulu-Natal, South Africa (MTN-009). *PLoS One* 2013; **8:** e59787.

26 Kuritzkes DR, Lalama CM, Ribaudo HJ, et al. Preexisting resistance to nonnucleoside reverse-transcriptase inhibitors predicts virologic failure of an efavirenz-based regimen in treatment-naive HIV-1-infected subjects. *J Infect Dis* 2008; **197:** 867–70.

27 Li JZ, Paredes R, Ribaudo HJ, et al. Low-frequency HIV-1 drug resistance mutations and risk of NNRTI-based antiretroviral treatment failure: a systematic review and pooled analysis. *JAMA* 2011; **305:** 1327–35.

28 Lee GQ, Bangsberg DR, Muzoora C, et al. Prevalence and virologic consequences of transmitted HIV-1 drug resistance in Uganda. *AIDS Res Hum Retroviruses* 2014; **30:** 896–906.

29 Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions.Version 5.1.0 (updated March, 2011). The Cochrane Collaboration, 2011. http://handbook.cochrane.org (accessed Jan 10, 2015).

30 Leutkemeyer AF, Rosenkranz SL, Lu D, et al. Relationship between weight, efavirenz exposure, and virologic suppression in HIV-infected patients on rifampicin-based tuberculosis treatment in the AIDS Clinical Trials Group A5221 STRIDE study. *Clin Infect Dis* 2013; **57:** 586–93.