Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial

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Summary

Background Efavirenz with tenofovir-disoproxil-fumarate and emtricitabine is a preferred antiretroviral regimen for treatment-naive patients infected with HIV-1. Rilpivirine, a new non-nucleoside reverse transcriptase inhibitor, has shown similar antiviral efficacy to efavirenz in a phase 2b trial with two nucleoside/nucleotide reverse transcriptase inhibitors. We aimed to assess the efficacy, safety, and tolerability of rilpivirine versus efavirenz, each combined with tenofovir-disoproxil-fumarate and emtricitabine.

Methods We did a phase 3, randomised, double-blind, double-dummy, active-controlled trial, in patients infected with HIV-1 who were treatment-naive. The patients were aged 18 years or older with a plasma viral load at screening of 5000 copies per mL or greater, and viral sensitivity to all study drugs. Our trial was done at 112 sites across 21 countries. Patients were randomly assigned by a computer-generated interactive web response system to receive either once-daily 25 mg rilpivirine or once-daily 600 mg efavirenz, each with tenofovir-disoproxil-fumarate and emtricitabine. Our primary objective was to show non-inferiority (12% margin) of rilpivirine to efavirenz in terms of the percentage of patients with confirmed response (viral load <50 copies per mL intention-to-treat time-to-loss-of-virological-response [ITT-TLOVR] algorithm) at week 48. Our primary analysis was by intention-to-treat. We also used logistic regression to adjust for baseline viral load. This trial is registered with ClinicalTrials.gov, number NCT00540449.

Findings 346 patients were randomly assigned to receive rilpivirine and 344 to receive efavirenz and received at least one dose of study drug, with 287 (83%) and 285 (83%) in the respective groups having a confirmed response at week 48. The point estimate from a logistic regression model for the percentage difference in response was –0·4 (95% CI –5·9 to 5·2), confirming non-inferiority with a 12% margin (primary endpoint). The incidence of virological failures was 13% (rilpivirine) versus 6% (efavirenz; 11% *vs* 4% by ITT-TLOVR). Grade 2–4 adverse events (55 [16%] on rilpivirine *vs* 108 [31%] on efavirenz, p<0·0001), discontinuations due to adverse events (eight [2%] on rilpivirine *vs* 27 [8%] on efavirenz), rash, dizziness, and abnormal dreams or nightmares were more common with efavirenz. Increases in plasma lipids were significantly lower with rilpivirine.

Interpretation Rilpivirine showed non-inferior efficacy compared with efavirenz, with a higher virological-failure rate, but a more favourable safety and tolerability profile.

Funding Tibotec.

Introduction

Many antiretroviral regimens with similar antiviral activity are available for treatment-naive individuals infected with HIV-1.[1–4] Treatment selection is increasingly based on the tolerability profile and convenience of the regimen. Several treatment guidelines recommend the non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz, in combination with tenofovir-disoproxil-fumarate and emtricitabine.[1–4] However, efavirenz is associated with several adverse events.[5,6] Furthermore, efavirenz is contraindicated for pregnant women because of concerns over potential teratogenicity.[1,5,6]

Rilpivirine (Tibotec Pharmaceuticals, Co Cork, Ireland) is an NNRTI that has been approved for use in the USA.[7] It is a potential alternative to efavirenz for treatment-naive patients infected with HIV-1. This drug does not seem teratogenic in non-primate animals.[8] In a large, phase 2b, randomised trial (TMC278-C204)[9] in 368 treatment-naive patients, all once-daily doses of rilpivirine (25 mg, 75 mg, and 150 mg) showed antiviral efficacy similar to that recorded with once-daily 600 mg efavirenz, when either drug was given in combination with two nucleoside/nucleotide reverse transcriptase inhibitors (N[t]RTIs). Both rilpivirine and efavirenz had similar, sustained efficacy over 192 weeks.[10] Rash and neurological and psychiatric adverse events were reported less commonly with rilpivirine than with efavirenz, and lipid increases were smaller. The once-daily 25 mg dose of rilpivirine was selected for further development, because it had the best benefit–risk balance, with the lowest incidence of discontinuations due to adverse events and rashes.[9] Further, once-daily 25 mg rilpivirine had no effect on QTc interval in a thorough QT trial.[11,12] In our trial, Efficacy Comparison in Treatment-naive,

HIV-infected Subjects of TMC278 and Efavirenz (ECHO), our aim was to assess the efficacy, safety, and tolerability of rilpivirine versus efavirenz, each combined with a background regimen of tenofovir-disoproxil-fumarate and emtricitabine. We present data from our primary 48-week analysis.

Methods

Participants

We did a 96-week (April 21, 2008, to Jan 4, 2011), phase 3, double-blind, double-dummy, active-controlled randomised trial, to assess the efficacy, safety, and tolerability of once-daily 25 mg rilpivirine versus once-daily 600 mg efavirenz with a background regimen of tenofovir-disoproxil-fumarate and emtricitabine. Our trial was done at 112 sites across 21 countries (USA, Canada, Australia, South Africa, ten countries in Europe, three in Asia, and four in Latin America).

Our main inclusion criteria were patients aged 18 years or older, who had not been previously treated with antiretroviral drugs, a plasma viral load at screening of 5000 copies per mL or greater, and viral sensitivity to tenofovir-disoproxil-fumarate and emtricitabine (assessed with the resistance genotype virco TYPE HIV-1 assay; Virco BVBA, Beerse, Belgium). Further exclusion criteria included infection with HIV-2, documented evidence of at least one NNRTI resistance-associated mutation (RAM) from a list of 39 (A98G, L100I, K101E/P/Q, K103H/N/S/T, V106A/M, V108I, E138A/G/K/Q/R, V179D/E, Y181C/I/V, Y188C/H/L, G190A/C/E/Q/S/T, P225H, F227C, M230I/L, P236L, K238N/T, and Y318F),[13] any active clinically significant disease (eg, pancreatitis, cardiac dysfunction, active and significant psychiatric disorder, adrenal insufficiency, hepatic impairment), renal impairment (estimated glomerular filtration rate based on creatinine <50 mL per min), and, for women, pregnancy or breastfeeding.

All patients gave written consent before any trial-related procedure. Our protocol was reviewed and approved by independent ethics committees and institutional review boards, and our trial was done in accordance with the principles of good clinical practice and the Declaration of Helsinki.

Randomisation and masking

Patients infected with HIV-1 were randomly assigned (1:1) by a computer-generated interactive web response system to receive either once-daily 25 mg rilpivirine or once-daily 600 mg efavirenz, both given in combination with a fixed-dose background regimen of once-daily 300 mg tenofovir-disoproxil-fumarate and once-daily 200 mg emtricitabine. The investigator, sponsor, and patient did not know which NNRTI treatment the patient was assigned to receive. Randomisation was stratified by screening viral load (≤100 000 copies per mL, >100 000 to ≤500 000 copies per mL, and >500 000 copies per mL). Our double-dummy design required that rilpivirine (or matching placebo) be taken with a meal, whereas efavirenz (or matching placebo) was required to be taken on an empty stomach in the evening.

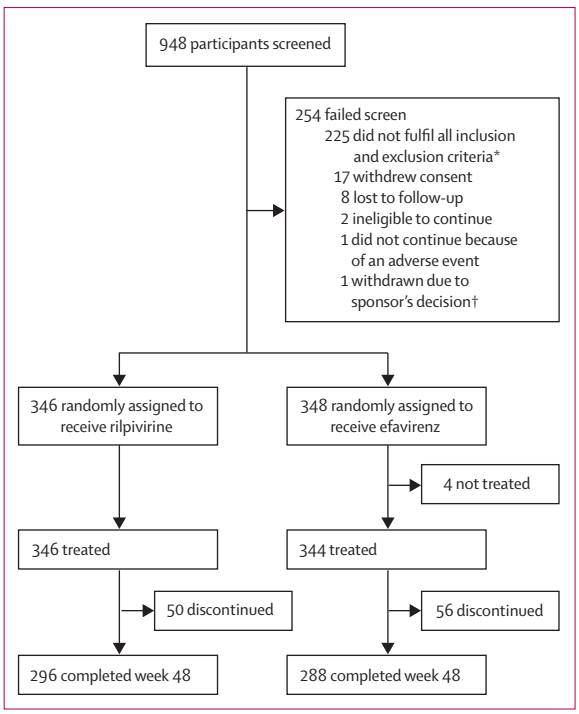

Figure 1: **Trial profile**
*The primary reasons screened patients did not meet our inclusion or exclusion criteria were the presence of non-nucleoside reverse transcriptase inhibitor resistance-associated mutations and a viral load of less than 5000 copies per mL. †Discontinued because more than 6 weeks elapsed between screening and baseline.

Procedures

Our trial consisted of a 6-week screening period, a 96-week treatment period, and a 4-week follow-up period. The results of a companion phase 3 trial, TMC278 against HIV, in a once-daily regimen versus efavirenz (THRIVE),[14] are reported separately.

Disallowed drugs included those which could reduce exposure to rilpivirine (ie, potent cytochrome 3A4-inducers and proton-pump inhibitors); drugs disallowed for efavirenz or tenofovir-disoproxil-fumarate and emtricitabine, as per the package inserts; any anti-HIV treatment other than drugs used in our trial; and all investigational drugs. Antacids (given at least 2 h before or at least 4 h after rilpivirine) and histamine H_2-receptor antagonists (given at least 12 h before or at least 4 h after rilpivirine) were permitted. Switches of N(t)RTIs were only allowed if there was N(t)RTI intolerance, and in accordance with the drug susceptibility profile; treatment was judged to have not failed in these patients.

Our primary objective was to show non-inferiority of treatment with once-daily 25 mg rilpivirine compared

	Rilpivirine group N=346	Efavirenz group N=344
Number of women	78 (23%)	69 (20%)
Median age (years; range)	36 (18–78)	36 (19–67)
Race		
White	214 (62%)	206 (60%)
Black	89 (26%)	80 (23%)
Asian	33 (10%)	48 (14%)
Other or not allowed to ask	10 (3%)	10 (3%)
Median viral load (log_{10} copies per mL; range)	5 (2–7)	5 (3–7)
Categorised viral load (copies per mL)		
≤100 000	181 (52%)	163 (47%)
>100 000 to ≤500 000	131 (38%)	134 (39%)
>500 000	34 (10%)	47 (14%)
Median CD4 cell count (cells per μL; range)	240 (1–888)	257 (1–757)
Centers for Disease Control and Prevention category		
A	249 (72%)	242 (70%)
B	83 (24%)	79 (23%)
C	14 (4%)	23 (7%)
Clade B	247 (71%)	243 (71%)
Active co-infection*		
Hepatitis B	11/341 (3%)	19/342 (6%)
Hepatitis C	8/332 (2%)	11/332 (3%)

Data are n (%) unless otherwise stated. *Hepatitis B infection status was confirmed by positive hepatitis B surface antigen. The hepatitis C virus (HCV) infection status was established by HCV antibody and qualitative HCV RNA if the test for HCV antibodies was positive or if patients were immunocompromised (CD4 cell count <100 cells per μL).

Table 1: **Baseline demographics and disease characteristics**

	Rilpivirine group	Efavirenz group	Percentage difference (95% CI)
ITT-TLOVR outcome	N=346	N=344	..
Viral load less than 50 copies per mL	287 (83%)	285 (83%)	0·1 (–5·5 to 5·7)
VF_{eff}	38 (11%)	15 (4%)	..
Rebounders	16 (5%)	8 (2%)	..
Never suppressed	22 (6%)	7 (2%)	..
Discontinuation due to adverse events*	6 (2%)	25 (7%)	..
Discontinuation due to reason other than an adverse event†	15 (4%)	19 (6%)	..
Model-predicted response‡	83%	84%	–0·4 (–5·9 to 5·2)
Per-protocol–TLOVR outcome	N′=335	N′=330	..
Viral load less than 50 copies per mL	282 (84%)	275 (83%)	0·8 (–4·8 to 6·5)

Data are n (%) unless otherwise stated. N=number of patients. TLOVR=time-to-loss of virological response. VF_{eff}=virological failure for the efficacy (ITT-TLOVR) endpoint (never suppressed [no confirmed response before week 48] or rebounders [confirmed response before week 48 with confirmed rebound at or before week 48]). N′=number of assessable patients in each treatment group. ITT=intention-to-treat. *As per investigator, irrespective of viral-load value at time of discontinuation. †Lost to follow-up, non-compliance, withdrew consent, ineligible to continue, or sponsor's decision. ‡Logistic regression (ITT-TLOVR outcome <50 copies per mL) adjusted for baseline viral load.

Table 2: **Treatment outcome at week 48**

with once-daily 600 mg efavirenz in terms of the percentage of patients with confirmed response (according to the intention-to-treat time-to-loss-of-virological-response [ITT-TLOVR] algorithm) at week 48, with a non-inferiority margin of rilpivirine versus efavirenz of 12% (based on the lower limit of the two-sided 95% CI). Our selected non-inferiority margin was chosen in accordance with US Food and Drug Administration guidelines for HIV drug development that suggest a margin ranging from 10% to 12%.[15]

Our secondary endpoints were non-inferiority at a 10% margin, superiority (if non-inferiority was shown), durability of antiviral activity, changes from baseline in CD4 cell count, safety, tolerability, HIV genotypic and phenotypic characteristics (in virological failures), adherence (measured with the Modified Medication Adherence Self-Report Inventory [M-MASRI]), pharmacokinetics, and pharmacokinetic and pharmacodynamic relations.

Patients attended scheduled trial visits at weeks 2 and 4, every 4 weeks until week 16, and then every 8 weeks. We collected urine and blood samples for urinalysis, haematology and biochemistry, immunology, plasma viral load, and viral genotype and phenotype determinations. We established plasma viral load (HIV-1 RNA concentration) with the Amplicor HIV-1 Monitor Test version 1·5 (Roche, Basel, Switzerland).

In our ITT-TLOVR analysis, non-responders were patients who discontinued the trial prematurely for any reason, or who had virological failure. We categorised patients with virological failure as either never suppressed (never achieving viral load <50 copies per mL before week 48) or as a rebounder (after having achieved two consecutive viral load values of <50 copies per mL but then having viral load ≥50 copies per mL at two consecutive timepoints).

We established virological failure according to our resistance analysis in our intention-to-treat (ITT) population and included all treatment failures in the database, irrespective of time of failure (whether at, before, or after week 48), treatment status, or reason for discontinuation, provided these criteria were met: never achieved two consecutive viral-load values less than 50 copies per mL and had an increase in viral load of 0·5 log_{10} copies per mL or greater above the nadir (never suppressed) or first achieved two consecutive viral-load values less than 50 copies per mL with two subsequent consecutive (or single, when last available) viral-load values of 50 copies per mL or greater (rebounder). Viral phenotypic and genotypic assessments were done by Virco BVBA (Mechelen, Belgium), with Antivirogram and Virco TYPE HIV-1 assays, respectively.

An independent data and safety monitoring board monitored the safety of patients during the trial. The Medical Dictionary for Regulatory Activities (version 11·0) was used to code adverse events, and adverse-event severity was assessed with the Division of Acquired Immunodeficiency Syndrome grading scale.[16] Included in our assessment of adverse events were those whose association with NNRTIs are well described: neurological events of interest and psychiatric events of interest. Neurological events of interest are defined as cluster headache, cranial neuropathy, disturbance in attention,

dizziness, facial palsy, headache, lethargy, memory impairment, mononeuropathy, paraesthesia circumoral, photophobia, restlessness, sensation of pressure in ear, somnolence, uveitis, vertigo, or blurred vision. Psychiatric events of interest are defined as abnormal dreams, affective disorder, aggression, agitation, anxiety, confusional state, depressed mood, depression, euphoric mood, homicidal ideation, insomnia, irritability, libido decreased, major depression, mood swings, nervousness, nightmare, panic attack, phobia, post-traumatic stress disorder, sleep disorder, social phobia, sopor, stress symptoms, or suicide attempt.

We estimated glomerular filtration rate (GFR), based on serum creatinine, with the Modification of Diet in Renal Disease trial formula ($eGFR_{creat}$).[17] An electrocardiograph was recorded at screening and at weeks 2, 12, 24, and 48.

Statistical analysis

The population for primary analysis was our ITT population (ie, all who had received a study drug). We did an additional analysis on our per-protocol population (ie, as ITT but excluding major protocol violations). Our sample-size calculations took into account response rates in previous trials with efavirenz.[18–24] Given an expected response rate of 75% at week 48, we needed 340 patients in each treatment group to establish non-inferiority of rilpivirine to efavirenz with a maximum allowable difference of 12% at 95% power. We also did a logistic-regression analysis for our primary efficacy endpoint adjusted for the stratification factor, baseline $\log_{10}$ plasma viral load (≤100 000, >100 000 to ≤500 000, and >500 000 copies per mL). We did a sensitivity analysis on the subpopulation censored for non-virological failure according to our resistance analysis, excluding patients who discontinued for reasons other than virological failure according to our resistance analysis.

In our analysis of mean change in absolute CD4 cell count from baseline, for premature discontinuations data were assigned the baseline value (non-completer equalled failure). For other missing values, our last observation was carried forward.

We preplanned all presented statistical analyses. We used Fisher's exact test (5% significance level) to compare prespecified adverse events for which a significant difference had been recorded in the phase 2b trial.[9] We applied no adjustment for multiple comparisons between groups. We did a non-parametric Wilcoxon rank-sum test to compare lipid changes between our two treatment groups.

Role of the funding source

The study sponsor was involved in the design and conduct of the trial, and in the collection and analysis of the data. All authors had full access to the 48-week clinical trial report. The corresponding author had final responsibility to submit the manuscript for publication.

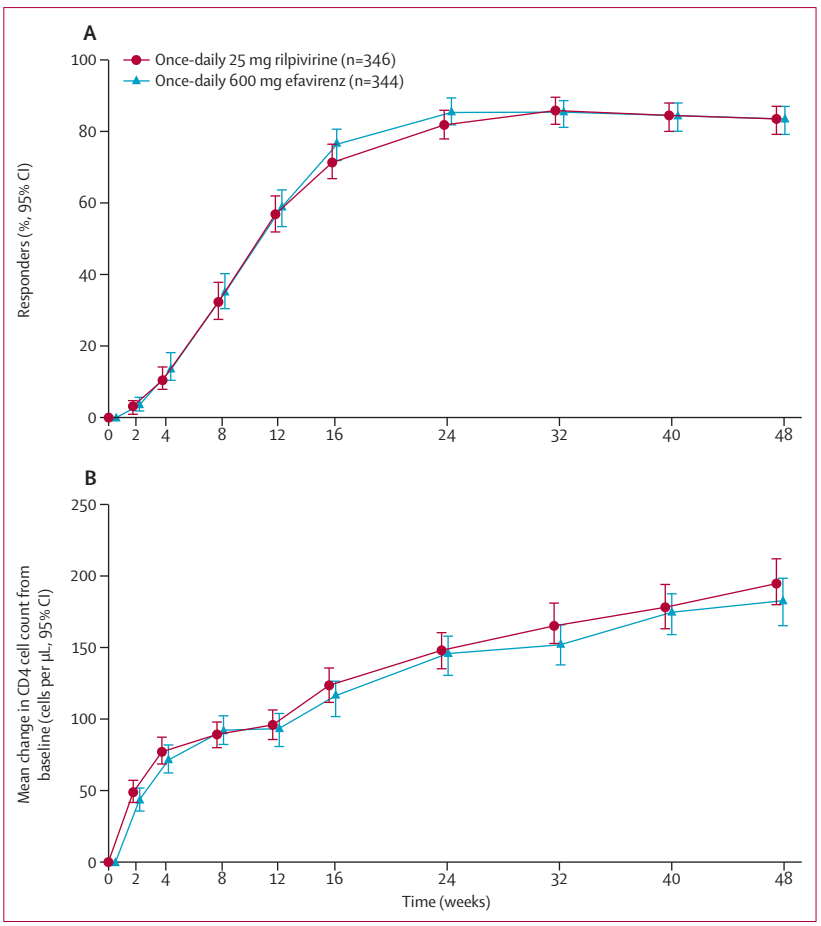

Figure 2: **Percentage of patients with a viral load of less than 50 copies per mL from baseline to week 48 (A) and mean change in absolute CD4 cell count from baseline (B)**

(A) Intention-to-treat time-to-loss-of-virological-response algorithm. (B) At week 48, mean change in absolute CD4 cell count from baseline was 196 cells per µL (95% CI 179–212) for rilpivirine and 182 cells per µL (165–198) for efavirenz (p=0·13).

Results

Figure 1 shows the trial profile. Our ITT analyses included the 690 patients who received at least one dose of study drug. 106 patients (15%) discontinued treatment before week 48, and reasons for discontinuations, as reported by the investigators, were balanced between groups, with the exception of adverse events (eight in the rilpivirine group *vs* 28 in the efavirenz group) and investigator-reported virological failure (23 *vs* six, respectively). The incidence of major protocol violations was similar in each group (11 of 346 patients in the rilpivirine group *vs* 14 of 344 in the efavirenz group) and included use of a disallowed drug in the treatment period (six *vs* nine), deviation of background treatment (three *vs* five), selection criteria not met (two *vs* none), and non-compliance with study drug intake (one *vs* two). One patient assigned to receive efavirenz switched background regimen to abacavir plus lamivudine because of renal impairment.

Overall, demographic and baseline characteristics were balanced between the two groups (table 1). Most

	Rilpivirine group N=346	Efavirenz group N=344
VF_{res}	45 (13%)	19 (6%)
VF_{res} with resistance data at time of failure	40	13
VF_{res} with any treatment-emergent NNRTI RAM	26/40 (65%)	8/13 (62%)
VF_{res} with any treatment-emergent IAS-USA N(t)RTI RAM[25]	28/40 (70%)	4/13 (31%)
VF_{res} with any treatment-emergent NNRTI or IAS-USA N(t)RTI RAM[25]	29/40 (73%)	8/13 (62%)
NNRTI RAM incidence in patients who failed with NNRTI mutations*	n=26	n=8
E138K	18 (69%)	0
K101E	5 (19%)	0
Y181C	5 (19%)	0
V90I	4 (15%)	0
H221Y	4 (15%)	0
V189I	3 (12%)	0
E138Q	2 (8%)	0
K103N	0	7 (88%)
IAS-USA N(t)RTI RAM incidence in patients who failed with N(t)RTI mutations†	n=28	n=4
M184I, V, or both	26 (93%)	4 (100%)
M184I only	20 (71%)	1 (25%)
M184V only	4 (14%)	2 (50%)
M184I/V mixtures	2 (7%)	1 (25%)
K65R	3 (11%)	0
K219E	3 (11%)	0
Y115F	2 (7%)	0

Data are n (%). VF_{res}=virological failure established with the resistance analysis defined as any patient in the intention-to-treat population experiencing treatment failure irrespective of time of failure, treatment status, or reason for discontinuation providing the following criteria were met: never achieved two consecutive viral-load values of less than 50 copies per mL and had an increase in viral load of 0.5 log_{10} copies per mL or greater above the nadir (never suppressed), or first achieved two consecutive viral-load values of less than 50 copies per mL with two subsequent consecutive (or single, when last available) viral load values of 50 copies per mL or greater (rebounder). N=number of patients in each treatment group. n=number of observations. NNRTI=non-nucleoside reverse transcriptase inhibitor. RAM=resistance-associated mutation. IAS-USA=International AIDS Society-USA. N(t)RTI=nucleoside/nucleotide reverse transcriptase inhibitor. *One patient receiving efavirenz had V108I (8%), as did one patient receiving rilpivirine (3%). †K70E was reported in one patient in the rilpivirine group versus no patients in the efavirenz group.

Table 3: **Most prevalent treatment-emergent NNRTI and N(t)RTI RAMs (in two or more patients with available resistance data) at the time of week 48 analysis**

patients (400; 58%) were from the USA, Canada, Europe, and Australia.

At week 48, 83% of patients from both groups had confirmed response (ITT-TLOVR algorithm; table 2). There were proportionally more virological failures in the rilpivirine group than in the efavirenz group (table 2). Our model-predicted responses, with the covariate log_{10} baseline plasma viral load, were similar to the ITT-TLOVR responses (table 2). The estimated difference in ITT-TLOVR response from our logistic-regression model was –0·4% (95% CI –5·9% to 5·2%). Since the lower limit of the 95% CI for the difference between rilpivirine and efavirenz was greater than both –12% (p<0·0001) and –10% (p=0·0007), we established non-inferiority at the 12% (primary endpoint) and 10% margins. However, we did not show superiority at the 5% significance level. Analysis of our per-protocol population confirmed that rilpivirine was non-inferior to efavirenz in confirmed response (table 2). In a sensitivity analysis excluding patients who discontinued for reasons other than virological failure according to our resistance analysis (ITT-TLOVR, population censored for non-virological failure), response rates were 86% (287 of 333) in our rilpivirine group and 94% (285 of 303) in our efavirenz group (difference –7·9%, 95% CI –12·5% to –3·2%). The percentage of responders for the two treatments increased over time, with no notable differences between the two groups (figure 2). Figure 2 also shows a steady increase from baseline in mean CD4 cell count.

The proportion of responders in the group of patients who self-reported greater than 95% adherence (M-MASRI; although data were not available for all patients) was 86% (236 of 275) for rilpivirine and 87% (229 of 262) for efavirenz. For patients who were 95% adherent or less, the proportion of responders was 68% (30 of 44) versus 73% (41 of 56), respectively. The median adherence of patients in the 95% adherent or less category who were treated with rilpivirine was 91% (n=44) and in patients treated with efavirenz was 92% (n=56).

The proportion of responders for patients with baseline viral load of 100 000 copies per mL or less was 90% (162 of 181) for rilpivirine versus 83% (136 of 163) for efavirenz. The proportion of responders for baseline viral load of 100 000 copies per mL to 500 000 or less copies per mL, was 79% (104 of 131) versus 83% (111 of 134), respectively. For baseline viral load of greater than 500 000 copies per mL, the proportion of responders was 62% (21 of 34) versus 81% (38 of 47). However, since some of the numbers of patients in these categories are small, the results in patients with 95% or less M-MASRI adherence and high baseline viral load should be interpreted with caution.

There was a greater proportion of virological failures according to our resistance analysis in the rilpivirine group versus the efavirenz group (table 3). At the time of failure, a similar high proportion of virological failures in each treatment group developed at least one treatment-emergent NNRTI RAM, whereas the proportion of virological failures with one or more treatment-emergent International AIDS Society-USA (IAS-USA) N(t)RTI RAM[25] was higher in the rilpivirine group (table 3). The most common treatment-emergent NNRTI RAM in the rilpivirine group was E138K; in the efavirenz group K103N was the principal NNRTI RAM. M184I, V, or both were the most common IAS-USA N(t)RTI RAMs in both groups.

Our safety analysis included data from patients treated beyond week 48 (table 4). Adverse events were generally mild-to-moderate (grade 1 or 2). The incidence of grade 2 or greater adverse events possibly related to treatment was greater for efavirenz (p<0·0001 rilpivirine *vs* efavirenz; Fisher's exact test, preplanned analysis). The most commonly reported grade 2 or greater adverse events possibly related to treatment in 2% or greater of patients in either group were dizziness, abnormal dreams

and nightmares, insomnia, nausea, and any rash (table 4). The incidences of serious adverse events, irrespective of relatedness, were similar between groups. There was one death in the efavirenz group due to Burkitt's lymphoma, which was unrelated to treatment (table 4). The incidence of discontinuations due to adverse events was greater for efavirenz (table 4).

Neurological events of interest (55 [16%] of 346 patients in the rilpivirine group *vs* 126 [37%] of 344 in the efavirenz group; p<0·0001) and psychiatric events of interest (50 [15%] *vs* 86 [25%], respectively; p=0·0006) possibly related to treatment (any grade) were at a significantly lower incidence with rilpivirine than with efavirenz. Individual neurological adverse events in 2% or greater of patients were dizziness (22 of 346 *vs* 85 of 344; p<0·0001), headache (22 *vs* 15), somnolence (12 *vs* 21), and disturbance in attention (two *vs* ten). Psychiatric adverse events in 2% or greater of patients were abnormal dreams and nightmares (32 of 346 *vs* 49 of 344; p=0·045), insomnia (14 *vs* 23), depression (six *vs* nine), anxiety (two *vs* eight), and sleep disorder (two *vs* 11). Most neurological and psychiatric adverse events of interest were grade 1 or 2 in severity, and the prevalence of these adverse events declined after the first 4–8 weeks of treatment in both groups.

The incidence of any rash possibly related to treatment (any grade) was lower (p<0·0001) for rilpivirine (4%; 12 of 346) than for efavirenz (15%; 50 of 344); most rashes were grade 1 or 2. Grade 3 rash was reported in one patient treated with rilpivirine and two patients treated with efavirenz, and no grade 4 rash was reported. One patient on rilpivirine discontinued because of a treatment-related rash versus three on efavirenz. Rash resolved with continuous dosing in both treatment groups in those who remained on study treatment.

Treatment-emergent grade 3 or 4 laboratory abnormalities happened at an incidence of 10% with rilpivirine compared with 16% for efavirenz. With the exception of hypophosphataemia, individual grade 3 or 4 laboratory abnormalities happened in a lower proportion of patients treated with rilpivirine versus those treated with efavirenz (table 4).

There were no relevant increases from baseline at week 48 in mean low-density lipoprotein-cholesterol (LDL-C) and triglyceride concentrations for rilpivirine (table 5). However, LDL-C and triglycerides increased with efavirenz (table 5). Rilpivirine was associated with lower increases than efavirenz in total cholesterol and high-density lipoprotein-cholesterol (HDL-C; table 5). There was no difference in the change from baseline at week 48 in the total cholesterol over HDL-C between groups.

There was a small increase from baseline in mean serum creatinine concentration for rilpivirine at our first on-treatment assessment, but then the concentration remained stable over the 48-week treatment period (range 5·69–9·07 μmol/L), whereas values remained around baseline for efavirenz (range 0·10–2·38 μmol/L). Consequently, $eGFR_{creat}$ remained slightly below baseline levels with rilpivirine, but within normal limits (mean decreases were 8–11 mL/min per 1·73 m²), and at about baseline levels with efavirenz. We did not record grade 3 or 4 abnormalities in creatinine, and no abnormalities

	Rilpivirine group N=346	Efavirenz group N=344	p value*
Median treatment duration (weeks; range)	56 (0–87)	56 (1–88)	..
Adverse events			
Any adverse event	303 (88%)	317 (92%)	..
Any treatment-related adverse event of grade 2 or greater	55 (16%)	108 (31%)	<0·0001
Adverse event leading to permanent discontinuation	8 (2%)	27 (8%)	..
Any serious adverse event (including death)	23 (7%)	31 (9%)	..
Death	0	1 (0%)	..
Most common treatment-related adverse event of grade 2 or greater in 2% or greater of patients in either group†			
Dizziness	4 (1%)	23 (7%)	..
Abnormal dreams or nightmares	5 (1%)	18 (5%)	..
Insomnia	5 (1%)	10 (3%)	..
Nausea	3 (1%)	8 (2%)	..
Rash‡	6 (2%)	26 (8%)	0·0002
Treatment-emergent grade 3§ or 4 laboratory abnormalities in greater than 2% of patients in either group	N′=345	N′=340	..
Any grade 3 or 4 laboratory abnormality	34 (10%)	55 (16%)	..
Increased pancreatic amylase	11 (3%)	16 (5%)	..
Increased aspartate aminotransferase	8 (2%)	12/339 (4%)	..
Hypophosphataemia	6 (2%)	4/339 (1%)	..
Increased alanine aminotransferase	4 (1%)	12 (4%)	..
Increased LDL-C¶	3 (1%)	8/339 (2%)	..
Increased triglycerides	1 (0%)	5/339 (2%)	..
Increased total cholesterol	1 (0%)	6/339 (2%)	..

Data are n (%) unless otherwise stated. N=number of patients in each treatment group. N′=number of assessable patients in each treatment group. LDL-C=low-density lipoprotein-cholesterol. *Rilpivirine versus efavirenz, Fisher's exact test, preplanned analysis. †Not including laboratory abnormalities reported as an adverse event. ‡Defined as rash, erythema, allergic dermatitis, macular rash, urticaria, maculopapular rash, papular rash, pustular rash, drug eruption, exanthem, scaly rash, toxic skin eruption, or urticaria papular. §The grade 3 cutoff values for each term were >2·0 to ≤5·0 × upper limit of normal for pancreatic amylase, >5·0 to ≤10·0 × upper limit of normal for aspartate aminotransferase and alanine aminotransferase, 0·32–0·64 mmol/L for serum phosphate, ≥4·91 mmol/L for LDL-C (fasting), 8·49–13·56 mmol/L for triglycerides (fasting), and >7·77 mmol/L for total cholesterol (fasting). ¶Combined total of calculated values and directly measured values (if the triglyceride level was too high for LDL-C to be calculated).

Table 4: **Overview of treatment-emergent adverse events and laboratory abnormalities at the time of week 48 analysis**

	Rilpivirine group	Efavirenz group	p value*
Total cholesterol (mmol/L)	0·03 (–0·06 to 0·11)	0·63 (0·53 to 0·73)	<0·0001
HDL-C (mmol/L)	0·07 (0·04 to 0·10)	0·24 (0·21 to 0·27)	<0·0001
Total cholesterol/HDL-C	–0·14 (–0·33 to 0·05)	–0·24 (–0·40 to –0·09)	0·25
LDL-C (mmol/L)	–0·04 (–0·10 to 0·03)	0·31 (0·23–0·39)	<0·0001
Triglycerides (mmol/L)	–0·10 (–0·19 to –0·01)	0·16 (–0·07 to 0·38)	0·01

Data are mean (95% CI). Lipid samples were taken fasting. HDL-C=high-density lipoprotein-cholesterol. LDL-C=low-density lipoprotein-cholesterol. *Rilpivirine versus efavirenz, Wilcoxon rank-sum test, preplanned analysis.

Table 5: **Change in lipid variables from baseline to 48 weeks**

Panel: **Research in context**

Systematic review

A recent Cochrane review[30] stated that the non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz and nevirapine are equally effective in suppressing infection with HIV but cause side-effects that can limit their use, highlighting a need for additional first-line NNRTIs with a better safety profile. We searched PubMed for supporting evidence up to May, 2011, with the search term "rilpivirine"; we selected randomised controlled trials and clinical trials published in English. Rilpivirine has only been assessed in one phase 2b study (NCT NCT00110305; TMC278-C204). This study showed that rilpivirine provided long-term (longer than 96 weeks) efficacy and tolerability in treatment-naive adults infected with HIV-1, with response rates similar to efavirenz. In this study, all rilpivirine doses resulted in similar response rates. Grade 2–4 adverse events at least possibly related to study medication, including nausea, dizziness, abnormal dreams/nightmare, rash, somnolence, and vertigo, were less common with TMC278 than with efavirenz in the context of an open-label trial (only the dose of rilpivirine was blinded).[9]

Interpretation

In combination with the THRIVE trial,[14] which assessed the safety and efficacy of rilpivirine with three different background regimens (tenofovir-disoproxil-fumarate plus emtricitabine, zidovudine plus lamivudine, or abacavir plus lamivudine) versus efavirenz, our data suggest that once-daily rilpivirine is probably a valuable treatment option for antiretroviral-naive patients infected with HIV-1.

were reported as adverse events. There were no discontinuations due to renal adverse events.

Overall, QT interval corrected according to Fridericia's formula (QTcF) increased over time up to week 48 for both rilpivirine and efavirenz, with no relevant difference between groups. The mean changes from baseline were 10·9 ms (95% CI 9·0–12·8) versus 12·0 ms (10·1–13·7), respectively. There were few adverse events potentially related to conduction abnormalities or to rate and rhythm disturbances (one of 346 *vs* two of 344; these were grade 1 in severity).

Discussion

Once-daily oral 25 mg rilpivirine showed non-inferior efficacy compared with once-daily 600 mg efavirenz at 48 weeks in our trial. Both study drugs achieved response rates (table 2) that are among the highest compared with earlier studies of efavirenz in combination with tenofovir-disoproxil-fumarate and emtricitabine in treatment-naive patients.[24,26] More patients discontinued treatment because of intolerability with efavirenz, although more discontinued because of virological failure with rilpivirine. The CD4 cell count increased to a similar extent in both groups. These efficacy results are consistent with those reported in the companion phase 3 trial, THRIVE,[14] although virological failure rates for rilpivirine were lower in THRIVE, and the difference in virological failures with efavirenz was smaller.

Our finding of more virological failures in the rilpivirine group than in the efavirenz group differs from the phase 2b study.[9] Although self-reported, suboptimum adherence (<95% by M-MASRI) was associated with lower responses in both treatment groups, this alone might not fully explain the difference in virological failure rates between patients on the two study drugs. The lower response in patients on rilpivirine with baseline viral load greater than 500 000 copies per mL compared with efavirenz probably contributed to these findings. Analyses are ongoing to better understand the role of factors such as adherence, drug exposure, and baseline viral load in virological failure. Because of the statistical power limitations for the individual trials, results of additional exploratory analyses of response factors will be reported in pooled analyses of data from ECHO and THRIVE. Additionally, pharmacokinetics and pharmacokinetic and pharmacodynamic relations will be presented elsewhere for the pooled data.

Consistent with other NNRTI regimens,[27] at the time of failure, the proportion of patients with at least one NNRTI RAM was high and similar in both groups. The most prevalent treatment-emergent NNRTI RAMs were consistent with data from TMC278-C204[9,10] and THRIVE.[14] Consequently, cross-resistance exists between rilpivirine and etravirine—initial findings from the pooled ECHO and THRIVE resistance analysis have shown that, of the 31 patients on rilpivirine who experienced virological failure and were phenotypically resistant to rilpivirine, 28 (90%) were cross-resistant to etravirine, 27 (87%) to efavirenz, and 14 (45%) to nevirapine.[28] Studies are in progress to further characterise the effect of specific combinations of NNRTI RAMs that are found in viruses emerging from selection with rilpivirine, on the antiviral activity of etravirine. Of the 12 patients on efavirenz who experienced virological failure and were phenotypically resistant to efavirenz, all were resistant to nevirapine but remained sensitive to etravirine.

Treatment-emergent IAS-USA N(t)RTI RAMs were more common in the rilpivirine group than in the efavirenz group among virological failures. The most common treatment-emergent N(t)RTI RAMs in both groups were M184I and V, which are associated with reduced susceptibility to emtricitabine and lamivudine.[29] An analysis of phenotypic sensitivity to NNRTIs will be presented separately for the pooled data.

As we anticipated from the phase 2b data (panel),[9,10] the safety and tolerability profile of rilpivirine was better than that of efavirenz. Discontinuations due to adverse events were less common with rilpivirine than with efavirenz (table 4). The incidence of any grade 2 or higher adverse events possibly related to treatment in the rilpivirine group was lower than in the efavirenz

group (table 4). Additionally, incidences of rash, neurological adverse events of interest and psychiatric adverse events of interest were lower for rilpivirine than efavirenz. Increases in some proatherogenic lipid variables were also smaller with rilpivirine, but the difference was not substantial in the total cholesterol to HDL-C ratio. Increases in creatinine for rilpivirine were small, and might be related to a rilpivirine effect on the disposition of creatinine, rather than to renal toxicity. Indeed, with the use of cystatin C, thought to be a better indicator of GFR than creatinine,[31] rilpivirine did not decrease GFR in THRIVE.[14] Rilpivirine might increase the exposure to tenofovir after tenofovir-disoproxil-fumarate, but this increase is not thought clinically relevant.[32] Long-term follow-up and assessment is available from the phase 2b trial and will be provided by the week-96 analysis of these phase 3 trials.

There are several limitations to our trial. First, our study used only one N(t)RTI background regimen (tenofovir-disoproxil-fumarate and emtricitabine). However, the THRIVE trial also assessed zidovudine with lamivudine or abacavir with lamivudine, as well as tenofovir-disoproxil-fumarate and emtricitabine selected by the investigator. The consistent findings, irrespective of N(t)RTI background, show the possibility of combining rilpivirine with other antiretroviral drugs. Second, our trial was not powered to assess comparisons of efficacy in various subsets of patients, and therefore it is difficult to generalise our findings to the overall population of patients. However, subgroup analyses of the combined ECHO and THRIVE populations by sex, region, ethnic origin, clade, and hepatitis B and C co-infection[28,33,34] show that the efficacy of rilpivirine and efavirenz are similar, suggesting broader applicability of these data. Furthermore, in routine clinical practice, patients might harbour transmitted resistance, which could reduce response rates. For our trial, we used a comprehensive NNRTI RAM list to screen out patients potentially resistant to NNRTIs. The present prevalence of E138K in routine clinical resistance testing is low (<1%).[35] Finally, since our trial had a double-dummy design, patients had to take their study medication twice daily, rather than the normal once-daily dosing for both NNRTIs, although we did not know what effect this design feature had on response rates. Also, patients were required to take rilpivirine (or matching placebo) with a meal. This recommendation might have been overlooked in our double-blind trial, resulting in some patients taking rilpivirine on an empty stomach and a lower rilpivirine exposure than expected in some cases.

The selection of rilpivirine will rely on assessing individual benefits and risks for individual patients. These data suggest that once-daily rilpivirine, perhaps as a single-tablet regimen in combination with tenofovir-disoproxil-fumarate and emtricitabine,[36] is expected to be a valuable treatment option for patients infected with HIV who have not been previously treated with antiretroviral drugs.

Contributors

All authors substantially contributed to the study's conception, design, and performance. J-MM, PC, BG, AL, AM, MS, KS, and SW all participated in recruiting substantial numbers of patients to the trial and reported data for those patients. HC, LT, SV, and KB were involved in the data analyses. All authors were involved in the development of the primary manuscript, interpretation of data, and have read and approved the final version.

Conflict of interest

J-MM has acted as a consultant, participated in advisory boards, has received speaker fees and has been an investigator for clinical trials for Tibotec, ViiV Healthcare, Gilead, Bristol-Myers Squibb (BMS), Abbott, Boehringer Ingelheim (BI), and Merck, Sharp & Dohme (MSD). PC has received grant research support, advisory and speaker fees from Abbott, Avexa, BI, Gilead, MSD, Tibotec, Janssen, GlaxoSmithKline (GSK), and ViiV Healthcare. BG has participated in advisory boards, has received speaker fees and has been an investigator for clinical trials for Tibotec, BMS, ViiV Healthcare, and MSD. AL has acted as a consultant, participated in advisory boards, speaker bureaus and has been an investigator in for clinical trials for Abbott, BMS, BI, Gilead, MSD, Tibotec, Pfizer, ViiV Healthcare, GSK, and Roche. AM has served on advisory boards and speaker bureaus for Tibotec, GSK, BMS, Gilead, BI, MSD, and ViiV Healthcare, and has received research funding from Tibotec. MS has received consulting fees, research support, or both from BMS, BI, GSK, MSD, Pfizer, Pain Therapeutics, Tibotec/J&J, Vertex, and ViiV Healthcare. SW has received consultancy fees or lecture sponsorships from Abbott, BI, Gilead, MSD, ViiV Healthcare, and Tibotec. HC, LTR, SV, and KB are all full-time employees of Tibotec. KS declares no conflicts of interest.

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