# 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

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## Summary

**Background** The non-nucleoside reverse transcriptase inhibitor (NNRTI), rilpivirine (TMC278; Tibotec Pharmaceuticals, County Cork, Ireland), had equivalent sustained efficacy to efavirenz in a phase 2b trial in treatment-naive patients infected with HIV-1, but fewer adverse events. We aimed to assess non-inferiority of rilpivirine to efavirenz in a phase 3 trial with common background nucleoside or nucleotide reverse transcriptase inhibitors (N[t]RTIs).

**Methods** We undertook a 96-week, phase 3, randomised, double-blind, double-dummy, non-inferiority trial in 98 hospitals or medical centres in 21 countries. We enrolled adults (≥18 years) not previously given antiretroviral therapy and with a screening plasma viral load of 5000 copies per mL or more and viral sensitivity to background N(t)RTIs. We randomly allocated patients (1:1) using a computer-generated interactive web-response system to receive oral rilpivirine 25 mg once daily or efavirenz 600 mg once daily; all patients received an investigator-selected regimen of background N(t)RTIs (tenofovir-disoproxil-fumarate plus emtricitabine, zidovudine plus lamivudine, or abacavir plus lamivudine). The primary outcome was non-inferiority (12% margin on logistic regression analysis) at 48 weeks in terms of confirmed response (viral load <50 copies per mL, defined by the intent-to-treat time to loss of virologic response [TLOVR] algorithm) in all patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT00543725.

**Findings** From May 22, 2008, we screened 947 patients and enrolled 340 to each group. 86% of patients (291 of 340) who received at least one dose of rilpivirine responded, compared with 82% of patients (276 of 338) who received at least one dose of efavirenz (difference 3·5% [95% CI –1·7 to 8·8]; $p_{non\text{-}inferiority}<0·0001$). Increases in CD4 cell counts were much the same between groups. 7% of patients (24 of 340) receiving rilpivirine had a virological failure compared with 5% of patients (18 of 338) receiving efavirenz. 4% of patients (15) in the rilpivirine group and 7% (25) in the efavirenz group discontinued treatment due to adverse events. Grade 2–4 treatment-related adverse events were less common with rilpivirine (16% [54 patients]) than they were with efavirenz (31% [104]; p<0·0001), as were rash and dizziness (p<0·0001 for both) and increases in lipid levels were significantly lower with rilpivirine than they were with efavirenz (p<0·0001).

**Interpretation** Despite a slightly increased incidence of virological failures, a favourable safety profile and non-inferior efficacy compared with efavirenz means that rilpivirine could be a new treatment option for treatment-naive patients infected with HIV-1.

**Funding** Tibotec.

*Lancet* 2011; 378: 229–37

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## Introduction

Recent changes in treatment guidelines[1,2] for HIV-1 recommend early initiation of highly active antiretroviral therapy. For first-line treatment in particular, short-term and long-term tolerability are very important for initiation and staying on treatment. Efavirenz-based regimens are recommended for individuals infected with HIV-1 who are treatment naive.[1,2] However, efavirenz is associated with neurological and psychiatric adverse events, rash, teratogenicity, and increases in concentrations of LDL cholesterol and triglycerides.[3,4]

Rilpivirine (TMC278[Edurant]; Tibotec Pharmaceuticals, County Cork, Ireland) is a US FDA-approved non-nucleoside reverse transcriptase inhibitor (NNRTI),[5] which can be given once per day.[6] In a phase 2b dose-ranging trial[7] of treatment-naive patients with HIV-1, once-daily rilpivirine showed much the same efficacy to once-daily efavirenz for 96 weeks, both given with a background regimen of two nucleoside or nucleotide reverse transcriptase inhibitors (N[t]RTIs). Equivalent efficacy of rilpivirine and efavirenz was sustained for 192 weeks.[8] Rilpivirine had a better neurological, rash, and lipid profile than did efavirenz,[7,8] and did not show teratogenic potential in preclinical studies.[9]

TMC278 against HIV, in a once-daily regimen versus efavirenz (THRIVE) was a 96-week trial that aimed to

assess the efficacy, safety, and tolerability of rilpivirine versus efavirenz, with two investigator-chosen background N(t)RTIs in treatment-naive patients with HIV-1 infection. We aimed to show non-inferiority of rilpivirine compared with efavirenz in terms of the percentage of patients with confirmed response (viral load <50 copies per mL defined by the time-to-loss of virological response [TLOVR] algorithm). Because choice of N(t)RTI is often made in clinical practice on the basis of characteristics of patients and local availability, THRIVE was designed to assess rilpivirine with one of three combination N(t)RTI regimens. In this analysis, we report data from the primary analysis at 48 weeks. The results of a companion phase 3 trial (ECHO),[10] which compared rilpivirine with efavirenz with a background regimen of tenofovir-disoproxil-fumarate and emtricitabine, are reported separately.

## Methods

### Trial design and patients

We undertook our phase 3, randomised, double-blind, double-dummy, active-controlled trial in 98 academic medical centres, independent non-profit centres, or hospitals in 21 countries (USA and Puerto Rico, Canada, Australia, Europe [seven countries], South Africa, Asia [four countries], and Latin America [6 countries]). The trial had a 6-week screening period, a 96-week treatment period, and a 4-week follow-up period.

Eligible patients were adults (≥18 years) who were naive to antiretroviral therapy, with a screening plasma viral load of 5000 copies per mL or more and viral sensitivity to the background N(t)RTIs, as assessed with the vircoTYPE HIV-1 assay. Main exclusion criteria were HIV-2 infection, documented presence of at least one of 39 NNRTI resistance-associated mutations (RAMs)[11] active clinically significant disease (eg, pancreatitis, cardiac dysfunction, active and significant psychiatric disorder, adrenal insufficiency, or hepatic impairment), renal impairment, and for women, pregnancy or breastfeeding.

The protocol was reviewed and approved by independent ethics committees and institutional review boards at participating sites or at a central institutional review board for some sites (eg, in the USA), and the trial was undertaken in accordance with the principles of good clinical practice and the Declaration of Helsinki. All patients provided written consent.

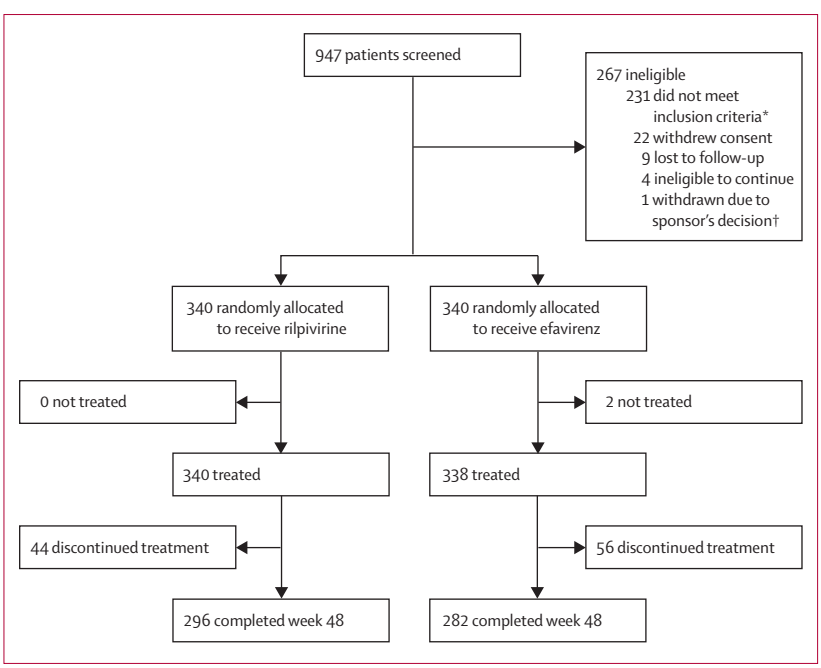


*Figure 1:* **Trial profile**
*Eg, presence of non-nucleoside reverse transcriptase inhibitor resistance-associated mutations and viral load fewer than 5000 copies per mL. †Discontinued because time between screening and baseline was more than 6 weeks.

### Randomisation and masking

We randomly allocated patients with a computer-generated interactive web-response system in a one-to-one ratio to receive oral rilpivirine 25 mg once daily or efavirenz 600 mg once daily after investigator selection of the background N(t)RTI regimen, which included tenofovir-disoproxil-fumarate plus emtricitabine, zidovudine plus lamivudine, or abacavir plus lamivudine. Randomisation was stratified by background regimen and screening viral load (≤100 000 copies per mL, 100 001–500 000 copies per mL, and >500 000 copies per mL). Investigators, the sponsor, and patients were masked to NNRTI treatment assignment.

### Procedures

We used a double-dummy regimen in which rilpivirine (or matching placebo) was taken with a meal, whereas efavirenz (or matching placebo) was taken on an empty stomach in the evening. N(t)RTIs were taken according to the locally applicable procedures and package inserts, but preferably at the same time as rilpivirine or efavirenz for abacavir plus lamivudine and tenofovir-disoproxil-fumarate plus emtricitabine. For zidovudine plus lamivudine (taken twice daily), the first dose was preferably taken in the morning with rilpivirine (or placebo), and the second dose was preferably taken in the evening with efavirenz (or placebo).

Disallowed drugs were all investigational drugs, drugs that could reduce rilpivirine exposure (eg, those with a potent cytochrome 3A4-inducing effect or proton-pump inhibitors), drugs disallowed for efavirenz or the background regimen (as per the package inserts) and any anti-HIV therapy other than those used in the trial. Antacids (≥2 h before or ≥4 h after) and histamine $H_2$-receptor antagonists (≥12 h before or ≥4 h after) after rilpivirine were allowed. Switches between N(t)RTIs were allowed only if intolerance occurred and were guided by resistance testing.

Our primary outcome was non-inferiority of rilpivirine to efavirenz in terms of percentage of all patients who received at least one dose of rilpivirine or efavirenz who had a confirmed virological response (defined by the

intent-to-treat TLOVR algorithm) at 48 weeks. We used a non-inferiority margin of 12% (lower limit of two-sided 95% CI) to establish non-inferiority of rilpivirine from efavirenz, which is in accordance with the margin of 10–12% suggested by the FDA for HIV drug development.[12] Secondary outcomes were non-inferiority with a 10% margin and superiority (if non-inferiority was shown), antiviral activity in time, changes from baseline in CD4 cell count, safety, tolerability, HIV genotypic and phenotypic characteristics (in virological failures), adherence (assessed by the Modified Medication Adherence Self-Report Inventory), pharmacokinetics, and pharmacokinetic and pharmacodynamic relations.

We followed-up patients at weeks 2, 4, 8, 12, and 16, and every 8 weeks thereafter. We collected urine and blood samples for haematology and biochemistry, urinalysis, immunology, plasma viral load, and viral genotype and phenotype assessments. We assessed plasma viral load (concentration of *HIV-1* RNA) with the Amplicor HIV-1 monitor test version 1.5 (Roche, Basel, Switzerland).

In the primary analysis, patients were regarded as non-responders if they discontinued treatment prematurely for any reason or if they had virological failure. Patients with virological failure were classified as never suppressed (never achieving viral load <50 copies per mL before week 48) or as rebounder (after achievement of two consecutive viral load values of <50 copies per mL but then having viral load ≥50 copies per mL at two consecutive assessments).

Virological failure in the resistance analysis was assessed in all patients who had received at least one dose of study drug and included all failures of treatment in the database, irrespective of time of failure (at, before, or after week 48), treatment status or reason for discontinuation, provided the following criteria were met: never achieved two consecutive viral load values of fewer than 50 copies per mL and had an increase in viral load 0·5 $\log_{10}$ copies per mL or more above the nadir (never suppressed) or first achieved two consecutive viral load values <50 copies per mL followed by two consecutive (or single, when last available) viral load values of 50 copies per mL or more (rebounder).

Virco (Mechelen, Belgium) did the viral phenotypic assessments with the Antivirogram assay and genotypic assessments with the VircoTYPE HIV-1 assay. We coded adverse events with MedDRA (version 11.0), and established severity of adverse events according to the division of AIDS grading scale.[13] An independent international data and safety monitoring board monitored safety and efficacy throughout the trial.

We estimated glomerular filtration rate at baseline, weeks 2, and 24 on the basis of serum creatinine ($eGFR_{creat}$) with the modification of diet in renal disease trial formula[14] and serum cystatin C concentrations ($eGFR_{cyst}$) with the Hoek formula.[15] We did an electrocardiograph at screening and weeks 2, 12, 24, and 48.

## Statistical analysis

We assessed non-inferiority of rilpivirine to efavirenz in patients who received at least one dose of rilpivirine or efavirenz, irrespective of protocol adherence, and in a per-protocol population of all randomly allocated patients who received study drugs, excluding those with major protocol violations.

Assuming a response rate of 75% at week 48 for both treatment groups,[16–22] we needed to enrol 340 patients in each group to establish non-inferiority of rilpivirine to efavirenz, with a maximum allowable difference of 12% at 95% power. We assessed the primary efficacy endpoint with a predicted-response analysis by use of a logistic regression analysis adjusted for the stratification factors (baseline $\log_{10}$ plasma viral load and background N[t]RTIs). We also did a sensitivity analysis for the subpopulation, excluding patients who discontinued for reasons other than virological failure according to the resistance analysis criteria.

In the analysis of mean change in absolute CD4 cell count from baseline, for premature discontinuations, we

| | Rilpivirine group (n=340) | Efavirenz group (n=338) |
|---|---|---|
| Women | 90 (26%) | 94 (28%) |
| Median age, years | 36 (19–62, 29–42) | 36 (19–69, 29–43) |
| Race | | |
| White | 206/338 (61%) | 204/338 (60%) |
| Black | 76/338 (22%) | 76/338 (22%) |
| Asian | 45/338 (13%) | 49/338 (14%) |
| Other races/unable to ask | 11/337 (3%) | 9/338 (3%) |
| Median viral load, $\log_{10}$ copies per mL | 5 (3–7, 4·5–5·3) | 5 (3–7, 4·5–5·4) |
| Categorised viral load, copies per mL | | |
| ≤100 000 | 187 (55%) | 167 (49%) |
| 100 001–500 000 | 118 (35%) | 136 (40%) |
| >500 000 | 35 (10%) | 35 (10%) |
| Median CD4 cell count, cells per μL | 263 (2–744, 177–342) | 263 (1–1137, 171–353) |
| US Centers for Disease Control and Prevention category | | |
| A | 237 (70%) | 232 (69%) |
| B | 82 (24%) | 90 (27%) |
| C | 21 (6%) | 16 (5%) |
| Clade B | 238 (70%) | 219 (65%) |
| Active co-infection* | | |
| Hepatitis B | 12/338 (4%) | 13/336 (4%) |
| Hepatitis C | 18/336 (5%) | 20/333 (6%) |
| Combination of N(t)RTIs in background regimen | | |
| Tenofovir-disoproxil-fumarate plus emtricitabine | 204 (60%) | 202 (60%) |
| Zidovudine plus lamivudine | 101 (30%) | 103 (30%) |
| Abacavir plus lamivudine† | 35 (10%) | 33 (10%) |

Data are n (%), median (range, IQR), or n/n assessed (%). N(t)RTI=nucleoside or nucleotide reverse transcriptase inhibitor. *Hepatitis B infection status was confirmed by hepatitis B surface antigen; hepatitis C virus infection status was determined by hepatitis C virus antibody and qualitative *HCV* RNA if the test for hepatitis C viral antibodies was positive or if patients were immunocompromised (CD4 cell count <100 cells per μL). †HLAB57*01 or HLAB57*01 hypersensitivity testing was required for abacavir selection.

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

| | Rilpivirine group (n=340) | Efavirenz group (n=338) | Difference, % (95% CI) |
|---|---|---|---|
| **Patients who received at least one drug dose** | | | |
| Viral load <50 copies per mL | 291 (86%) | 276 (82%) | 3·9% (–1·6 to 9·5) |
| Virological failure (efficacy endpoint) | 24 (7%) | 18 (5%) | .. |
| Rebounders* | 8 (2%) | 7 (2%) | .. |
| Never suppressed† | 16 (5%) | 11 (3%) | .. |
| Discontinuation due to adverse event or death‡ | 9 (3%) | 24 (7%) | .. |
| Other discontinuation§ | 16 (5%) | 20 (6%) | .. |
| Predicted response (%)¶ | 87% | 83% | 3·5% (–1·7 to 8·8) |
| **Per-protocol population** | | | |
| Viral load <50 copies per mL | 287/334 (86%) | 273/332 (82%) | 3·7% (–1·9 to 9·3) |

Data are n (%), n/n assessed (%), unless otherwise stated. *Confirmed response before week 48 with confirmed rebound at or before week 48. †No confirmed response before week 48. ‡Investigator adjudicated, irrespective of viral load value at time of discontinuation. §Lost to follow-up, non-compliance, withdrew consent, ineligible to continue, or sponsor's decision. ¶Primary analysis adjusted for baseline viral load and background nucleoside or nucleotide reverse transcriptase inhibitors.

***Table 2:*** **Treatment outcomes (defined by the TLOVR algorithm) at week 48**

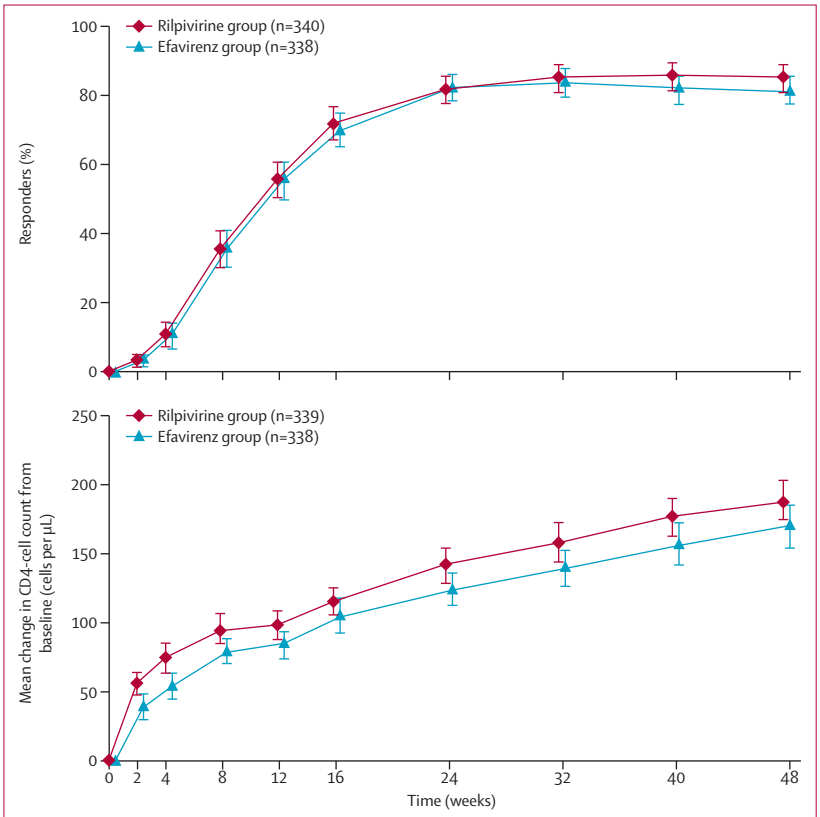


***Figure 2:*** **Outcomes for all patients who received at least one dose of rilpivirine or efavirenz**
(A) Patients with a viral load of fewer than 50 copies per mL (defined by the intent-to-treat TLOVR algorithm) from baseline to 48 weeks (B). Mean change in absolute CD4 cell count from baseline. For premature discontinuations, data were imputed with baseline value (non-completer was failure). For other missing values we used the last observation carried forward method. Error bars are 95% CI.

imputed data with baseline values (non-completer was classified as failure). For other missing values, we used the last observation carried forward method.

We undertook preplanned statistical analyses with Fisher's exact test (5% significance level) for prespecified adverse events that reported a significant difference in the phase 2b trial.[7] For adverse events, we made no adjustment for multiple comparisons between groups. We used a non-parametric Wilcoxon rank-sum test to compare changes in lipid concentrations between treatment groups.

This study is registered with ClinicalTrials.gov, number NCT00543725.

### Role of the funding source

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

## Results

Figure 1 shows the trial profile and table 1 shows the baseline characteristics of patients. The study started on May 22, 2008. The cut-off date for the 48-week analysis was Jan 28, 2010, and for the 96-week analysis was Jan 7, 2011. 326 patients (48%) were from the USA, Canada, Europe, and Australia. As reported by the investigators, discontinuations were mainly due to adverse events (15 of 340 [4%] in the rilpivirine group compared with 25 of 338 [7%] in the efavirenz group), virological failure (investigator-reported virological failure; 13 [4%] *vs* 8 [2%]), loss to follow-up (10 [3%] *vs* 6 [2%]), and withdrawn consent (2 [1%] *vs* 11 [3%]). Six patients (2%) in each group had major protocol violations, which included use of a disallowed drug (5 [1%] *vs* 4 [1%]), use of disallowed background therapy (1 [<1%] in both groups), or selection criteria not met (0 *vs* 1 [<1%]).

One of 204 (<1%) patients in the rilpivirine group switched from the initial background regimen of tenofovir-disoproxil-fumarate plus emtricitabine, five of 101 (5%) switched from zidovudine plus lamivudine, and one of 35 (3%) switched from abacavir plus lamivudine; the corresponding values in the efavirenz group were one of 202 (<1%) patients, five of 103 (5%) patients, and one of 33 (3%) patients.

In the primary analysis, 86% of patients (291 of 340) assigned to receive rilpivirine had a confirmed viral load of fewer than 50 copies per mL at 48 weeks, compared with 82% (276 of 338) for efavirenz (table 2). The lower 95% CI of estimated difference in confirmed response at 48 weeks in the logistic regression model was greater than –12% and –10%, confirming non-inferiority at the 12% (primary endpoint) and 10% margins ($p<0·0001$). However, we did not note superiority. 7% (24 of 340) of patients in the rilpivirine group had virological failure compared with 5% (18 of 338) in the efavirenz group. Results from the predicted-response analysis that adjusted for stratification factors were equivalent to those for the main analysis (table 2). Rilpivirine remained non-inferior

to efavirenz in the per-protocol analysis (table 2). Figure 2 shows percentages of responders in both groups from baseline to 48 weeks (primary analysis).

In a sensitivity analysis excluding patients who discontinued for reasons other than virological failure (defined as in the resistance analysis), 91% (291 of 319) patients in the rilpivirine group responded, compared with 93% (276 of 296) in the efavirenz group (difference –2·0%, 95% CI –6·3 to 2·2).

Mean CD4 cell counts continuously increased from baseline to 48 weeks for rilpivirine and efavirenz (figure 2). At week 48, the mean change from baseline in CD4 cell count was 189 cells per µL (95% CI 174–203) with rilpivirine and 171 cells per µL (155–187) with efavirenz (p=0·09).

The Modified Medication Adherence Self-Report Inventory data were not available for all patients. 89% (243 of 272) of patients who self-reported better than 95% adherence responded to treatment in the rilpivirine group as did 90% (206 of 230) in the efavirenz group. 64% (23 of 36) of patients who were less than or equal to 95% adherent responded in the rilpivirine group (median adherence 92·2%), compared with 62% (24 of 39) in the efavirenz group (median adherence 91·5%). In the rilpivirine group, 91% (170 of 187) of patients with a baseline viral load of 100 000 copies per mL or fewer responded, compared with 80% (94 of 118) for 100 001–500 000 copies per mL, and 77% (27 of 35) for more than 500 000 copies per mL; the corresponding numbers for the efavirenz group were 84% (140 of 167), 82% (112 of 136), and 69% (24 of 35). The background N(t)RTI regimen had no significant effect on response. However, given the small numbers of patients with low (≤95%) adherence as assessed by the Modified Medication Adherence Self-Report Inventory and high baseline viral loads, findings from such patients should be interpreted with caution.

8% of patients (27 of 340) in the rilpivirine group had virological failure according to the resistance analysis (including those without emerging mutation at failure) compared with 6% (20 of 338) in the efavirenz group (table 3).

We did safety analyses with all available data, including those for patients treated beyond 48 weeks. Adverse events were generally mild-to-moderate (grade 1 or 2). Prevelance of any grade 2–4 adverse events at least possibly related to treatment was lower in the rilpivirine group than it was in the efavirenz group (table 4). Rash was the main adverse event leading to discontinuation in the efavirenz group (five patients), but no discontinuations related to rash occurred in the rilpivirine group. All other adverse events that caused discontinuation from various system organ classes occurred in less than 1% of patients in either group.

Neurological events of interest (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) possibly related to treatment (any grade) occurred in 18% of patients (62 of 340) in the rilpivirine group compared with 39% (132 of 338) in the efavirenz group (p<0·0001). Individual neurological adverse events occurring in 2% or more of patients included dizziness (10% of patients [33 of 340] in the rilpivirine group *vs* 28% [94 of 338] in the efavirenz group; p<0·0001), headache (6% [20] *vs* 8% [27]), somnolence (4% [13] *vs* 8% [28]), and disturbance in attention (1% [three] *vs* 2% [seven]). Psychiatric events of interest (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) at least possibly related to treatment (any grade) occurred in 15% of patients (52 of 340) in the rilpivirine group compared with 20% (69 of 338) in the efavirenz group (p=0·09). Psychiatric adverse events occurring in 2% of

| | Rilpivirine group (n=340) | Efavirenz group (n=338) |
|---|---|---|
| Virological failure (resistance analysis) | 27 (8%) | 20 (6%) |
| Virological failure (resistance analysis) with resistance data at time of failure | | |
| With any treatment-emergent NNRTI RAM | 13/22 (59%) | 7/15 (47%) |
| With any treatment-emergent IAS–USA N(t)RTI RAM[23] | 14/22 (64%) | 5/15 (33%) |
| With any treatment-emergent NNRTI and/or IAS–USA N(t)RTI RAM[23] | 15/22 (68%) | 8/15 (53%) |
| NNRTI RAM incidence in patients who failed with NNRTI mutations | | |
| E138K | 10/13 (77%) | 0/7 |
| K101E | 3/13 (23%) | 1/7 (14%) |
| V189I | 2/13 (15%) | 0/7 |
| H221Y | 2/13 (15%) | 0/7 |
| K103N | 0/13 | 4/7 (57%) |
| V106M | 0/13 | 2/7 (29%) |
| Y188C | 0/13 | 2/7 (29%) |
| IAS–USA N(t)RTI RAM incidence in patients who failed with N(t)RTI mutations | | |
| M184I and/or V | 12/14 (86%) | 3/5 (60%) |
| M184V only | 5/14 (36%) | 3/5 (60%) |
| M184I only | 4/14 (29%) | 0/5 |
| M184I/V mixtures | 3/14 (21) | 0 |
| K65R | 0 | 2/5 (40) |

Data are n (%) or n/n assessed (%). Virological failure (resistance analysis) was defined as any patient who received at least one dose of drug who had a 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 fewer than 50 copies per mL and had an increase in viral load of 0·5 $\log_{10}$ copies per mL or more above the nadir (never suppressed) or first achieved two consecutive viral load values of fewer than 50 copies per mL followed by two consecutive (or single, when last available) viral load values 50 copies per mL or more (rebounder). NNRTI=non-nucleoside reverse transcriptase inhibitor. RAM=resistance-associated mutation. IAS=international AIDS society. N(t)RTI=nucleoside or nucleotide reverse transcriptase inhibitor.

***Table 3:*** **Treatment-emergent NNRTI and N(t)RTI RAMs (occurring in two or more patients with available resistance data in either treatment group) at 48 weeks**

| | Rilpivirine group (n=340) | Efavirenz group (n=338) | p value* |
|---|---|---|---|
| Median treatment duration, weeks | 55 (2–83, 53–64) | 55 (0–84, 53–63) | .. |
| Adverse events | | | |
| Any | 313 (92%) | 312 (92%) | .. |
| Treatment-related adverse events (≥ grade 2) | 54 (16%) | 104 (31%) | <0·0001 |
| Adverse events leading to permanent discontinuation | 15 (4%) | 25 (7%) | .. |
| Serious adverse events (including death) | 22 (7%) | 24 (7%) | .. |
| Death | 1 (<1%) | 3 (1%) | .. |
| Most common treatment-related adverse events (≥grade 2)†‡ | | | |
| Insomnia | 7 (2%) | 6 (2%) | .. |
| Headache | 5 (1%) | 9 (3%) | .. |
| Nausea | 2 (1%) | 9 (3%) | .. |
| Dizziness | 0 | 20 (6%) | .. |
| Rash§ | 1 (<1%) | 30 (9%) | <0·0001 |
| Treatment-emergent grade 3 or 4 laboratory abnormalities† | | | |
| Any grade 3 or 4 laboratory abnormality | 41/340 (12%) | 63/330 (19%) | .. |
| Increased pancreatic amylase¶ | 9/340 (3%) | 11/330 (3%) | .. |
| Increased alanine aminotransferase‖ | 6/340 (2%) | 11/330 (3%) | .. |
| Increased aspartate aminotransferase‖ | 6/340 (2%) | 7/330 (2%) | .. |
| Reduced white blood cell count** | 7/340 (2%) | 5/329 (2%) | .. |
| Increased LDL-C†† | 2/340 (1%) | 19/327 (6%) | .. |
| Increased lipase (fasting)‡‡ | 2/340 (1%) | 5/330 (2%) | .. |
| Increased triglycerides (fasting)§§ | 1/340 (<1%) | 10/329 (3%) | .. |
| Increased total cholesterol (fasting)¶¶ | 0/340 | 11/329 (3%) | .. |

Data are median (range, IQR), n (%), or n/n assessed (%). ULN=upper limit of normal. *Rilpivirine versus efavirenz, Fisher's exact test, preplanned analysis. †Occurring in ≥2% of patients in either group. ‡Not including laboratory abnormalities reported as an adverse event. §Rash, erythema, allergic dermatitis, macular rash, urticaria, maculopapular rash, papular rash, pustular rash, drug eruption, exanthem, scaly rash, toxic skin eruption, or urticaria papular. ¶>2·0–5·0 × ULN. ‖>5·0–10·0 × ULN. **1·000 × $10^9$–1·499 × $10^9$ cells per L. ††≥4·91 mmol/L; a combination of calculated values and directly measured values were used if the triglyceride concentration was too high for LDL-C to be calculated. ‡‡>3·0–5·0 × ULN. §§8·49–13·56 mmol/L. ¶¶>7·77 mmol/L.

***Table 4:*** **Treatment-emergent adverse events and laboratory abnormalities at 48 weeks**

| | Rilpivirine group | Efavirenz group | p value |
|---|---|---|---|
| Total cholesterol (mmol/L) | 0·08 (–0·01 to 0·16) | 0·79 (0·69 to 0·90) | <0·0001 |
| HDL-C (mmol/L) | 0·11 (0·08 to 0·13) | 0·27(0·24 to 0·30) | <0·0001 |
| Total cholesterol/HDL-C | –0·36 (–0·48 to –0·25) | –0·28 (–0·38 to –0·17) | 0·25 |
| LDL-C (mmol/L) | –0·02 (–0·09 to 0·05) | 0·44 (0·34 to 0·53) | <0·0001 |
| Triglycerides (mmol/L) | –0·07 (–0·17 to 0·04) | 0·14 (0·01 to 0·26) | <0·0001 |

Analyses were done with the Wilcoxon rank-sum test in a preplanned analysis.

***Table 5:*** **Mean change in fasting lipid parameters from baseline to 48 weeks**

patients or more were abnormal dreams or nightmares (7% [24 of 340] patients in the rilpivirine group *vs* 11% [38 of 338] in the efavirenz group; p=0·06), insomnia (6% [20] *vs* 5% [16]), and sleep disorder (2% [seven] *vs* 3% [nine]). Most neurological (98%) and psychiatric (96%) adverse events of interest were grade 1 or 2.

3% of patients (nine of 340) in the rilpivirine group had rash at least possibly related to treatment (any grade), compared with 13% (43 of 338) in the efavirenz group (p<0·0001). Of all treatment-related rashes (grouped term), 100% were grade 1–2 in the riplivirine group, with 99% grade 1–2 and 1% grade 3 in the efavirenz group. Rash resolved with continued dosing in both treatment groups, apart from for five patients who discontinued because of rash in the efavirenz group.

Table 4 shows rates of serious adverse events and treatment-emergent grade 3–4 laboratory abnormalities. There was one death in the rilpivirine group (bronchopneumonia) and three in the efavirenz group (one cerebral toxoplasmosis and dysentery, one cerebrovascular accident, and one respiratory failure). All four deaths were unrelated to treatment. With the exception of increased LDL-cholesterol (6% with efavirenz), individual grade 3–4 laboratory abnormalities occurred in 3% or less of patients.

Mean increases in total cholesterol, LDL-cholesterol, and triglyceride concentrations from baseline to week 48 were significantly lower with rilpivirine than they were with efavirenz (p<0·0001; table 5). The mean increase in HDL-cholesterol was significantly lower with rilpivirine than it was with efavirenz (p<0·0001). The ratio of total cholesterol to HDL-C did not differ between groups.

We noted a small increase from baseline in mean serum creatinine at the first on-treatment assessment, which remained stable over 48 weeks with rilpivirine (range 4·11–7·16 µmol/L), but no change with efavirenz. Treatment-associated changes in glomerular filtration rate differed according to the estimation used. There was a maximum mean decrease in $eGFR_{creat}$ of 5–9 mL/min per 1·73 $m^2$ from baseline during treatment with rilpivirine, corresponding to the change in creatinine concentration, with glomerular filtration rate remaining in the healthy range for all patients. $eGFR_{cyst}$ increased in both groups at week 2 (3 mL/min for rilpivirine *vs* 5 mL/min for efavirenz) and at week 24 (22 mL/min *vs* 31 mL/min). There were no grade 3–4 creatinine abnormalities, abnormalities reported as adverse events, or renal-related trial discontinuations.

Overall, QT-intervals corrected according to Fridericia's formula (QTcF) increased from baseline to week 48 in both groups, with no notable differences between groups; mean increases were 12·0 ms (95% CI 10·1–13·8) for rilpivirine and 14·1 ms (12·3–16·0) for efavirenz. There were few adverse events potentially related to conduction abnormalities or to rate and rhythm disturbances (two patients in the rilpivirine group and six in the efavirenz group). One patient in the rilpivirine group discontinued because of a grade 3 QT prolongation (QTcF increased >60 ms [77 ms] at week 48), which was reported by the investigator as an asymptomatic adverse event. No concomitant medications were regarded as having caused the increase in QTcF.

## Discussion

We showed that oral rilpivirine once daily is non-inferior in terms of efficacy to efavirenz at 48 weeks when given in combination with background N(t)RTIs. Both rilpivirine and efavirenz had high response rates. In our

study, response rates to efavirenz were among the highest reported when compared with earlier studies in treatment-naive patients (panel).[25–29] For both groups, the proportion of patients with virological failure was low. Within these virological failures, the rate of rebound after suppression was also low and much the same between groups with less than 5% of patients never suppressed in either group. The proportion of patients who discontinued due to adverse events and other reasons was lower for rilpivirine than it was for efavirenz, resulting in similar response rates.

Although our study was not powered to assess within-group significance, response rates seemed highest in the rilpivirine group for patients with lowest baseline viral loads, and background N(t)RTI regimen seemed to have no significant effect on responses. The slightly higher virological failure rate noted with rilpivirine than with efavirenz might be explained by a greater effect of suboptimum adherence on virological failure with rilpivirine than with efavirenz. Because of statistical power limitations in the separate ECHO and THRIVE studies, however, results of additional exploratory analyses of effects of factors on response and virological failure will be reported separately for pooled data analyses. Furthermore, pharmacokinetic and pharmacodynamic relationships will be reported elsewhere for the pooled data.

The proportion of virological failures (according to the resistance analysis criteria) with at least one treatment-emergent NNRTI RAM was much the same in both groups, whereas the proportion with at least one treatment-emergent international AIDS society–USA N(t)RTI RAM[23] was higher in the rilpivirine group than it was in the efavirenz group. Consistent with reports from the phase 2b TMC278-C204 trial,[7,8] E138K was the most prevalent NNRTI RAM in the rilpivirine group and K103N was in the efavirenz group, whereas M184I/V were the most prevalent N(t)RTI RAMs in both groups. Phenotypic testing in the pooled analysis showed that 28 of 31 (90%) patients who had virological failure in the rilpivirine group and were phenotypically resistant to rilpivirine were cross-resistant to etravirine.[30] A pooled analysis of sensitivity to NNRTIs will be presented separately.

Rilpivirine was well tolerated, with a more favourable overall profile than efavirenz considering grade 2–4 adverse events at least possibly related to treatment, rash, dizziness, and smaller increases in some proatherogenic lipid parameters, but there was no significant difference in the ratio of total cholesterol to HDL-cholesterol between groups. These data support the more favourable safety profile for rilpivirine compared with efavirenz that was reported in the phase 2b TMC278-C204 trial[7,8] and in the phase 3 ECHO trial.[10] By use of cystatin C, which is an alternative indication of renal function,[31] rilpivirine did not have a clinically relevant effect.

One limitation of our trial was that it was not powered to assess comparisons of efficacy in the various subsets of patients. Moreover, a comprehensive NNRTI RAM list was used to screen out patients potentially resistant to NNRTIs because the trial was double-blinded. Response rates might have been higher in this trial than they would be in the

### *Panel:* Research in context

#### Systematic review

Before approval of rilpivirine, two main non-nucleoside reverse transcriptase inhibitors (NNRTIs) were available for the first-line treatment of patients with HIV-1 infections in combination with reverse transcriptase inhibitors: efavirenz and nevirapine. Both drugs are equally effective in suppression of HIV infection[24] but cause different side-effects that can restrict their use. Treatment with efavirenz can lead to rash, impaired mental function, vertigo, abnormal dreams, and fetal malformations, whereas nevirapine treatment is associated with severe rash and liver damage due to hypersensitivity reactions. These adverse effects emphasise the unmet need for additional first-line NNRTI treatment options with a good safety profile.

We searched the PubMed database to May, 2011, for randomised controlled trials and clinical trials published in English with the search term "rilpivirine". Rilpivirine has only been assessed in one phase 2b study.[7,8] This randomised, controlled, dose-finding study of 368 patients showed that rilpivirine provided long-term (96 weeks) efficacy and tolerability in treatment-naive adults with HIV-1 infections, with comparable response rates with efavirenz. In this study, all daily rilpivirine doses (25 mg, 75 mg, and 150 mg) resulted in much the same response rates. Grade 2–4 adverse events at least possibly related to study medication, including nausea, dizziness, abnormal dreams or nightmares, rash, somnolence, and vertigo were less frequent with TMC278 than they were with efavirenz in the context of an open-label trial (only the dose of rilpivirine was masked).[7]

#### Interpretation

The phase 3 ECHO[10] and THRIVE trials were independently undertaken and powered to investigate the non-inferior efficacy of rilpivirine 25 mg once daily in combination with different reverse transcriptase inhibitors backbones for first-line therapy in adults with HIV-1 infection, compared with efavirenz, the preferred NNRTI for treatment-naive patients. Both studies met the primary objective of non-inferiority and also showed rilpivirine to have a more favourable side-effect profile versus efavirenz, with a reduced incidence of rash and central nervous system adverse reactions. However, the virological failure rate was slightly higher with rilpivirine than it was with efavirenz, and exploratory analyses are ongoing to examine the reasons for this difference in more detail.

Rilpivirine was better tolerated than was efavirenz in terms of lower incidences of discontinuations due to adverse events, especially due to central nervous system side-effects such as insomnia, depression, dizziness, or due to rash, when compared with patients taking efavirenz. Consequently, rilpivirine might be suitable for use in some treatment-naive patients, which efavirenz is not, such as women of child bearing age or potential and patients with certain pre-existing psychiatric conditions.

The ECHO trial[10] examined rilpivirine with emtricitabine and tenofovir-disoproxil-fumarate, a combination that has been submitted for marketing approval as a fixed-dose combination for antiretroviral-naive patients with HIV-1 infection. If this fixed-dose single-tablet is approved, it would be an alternative to the currently licensed once-daily single tablet, ATRIPLA combining emtricitabine and tenofovir-disoproxil-fumarate to efavirenz.

THRIVE 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. Based on these data and the findings in ECHO, rilpivirine 25 mg tablets have been approved in the USA in combination with other antiretroviral drugs for the first-line treatment of HIV infection.

Taken together, these data suggest that once-daily rilpivirine is likely to be a valuable treatment option for antiretroviral-naive patients with HIV-1 infection.

clinic where patients might harbour transmitted resistance. However, E138K has a low prevalence in routine clinical resistance testing (<1%).[32] Our trial had a double-blind, double-dummy design, meaning that patients had to take study treatment twice daily, rather than once daily, although the effect of this design feature on response rates is not known. A further limitation of the study was that, in common with most clinical HIV studies,[33] some populations of patients were under-represented (eg, women). Nevertheless, subgroup analyses of the combined ECHO and THRIVE populations by sex, region, race, clade, and co-infection with hepatitis B and C,[30,34,35] show that the efficacy of rilpivirine and efavirenz are equivalent, suggesting broader applicability of our data.

Thus, on the basis of our data and those from the companion phase 3 trial, ECHO,[10] rilpivirine is expected to be a valuable treatment option for antiretroviral-naive patients infected with HIV-1.

#### Contributors

All authors contributed substantially to the study's conception, design, and undertaking. CJC, JA-V, BC, JF, MAJ, KR, HW, and CZ all participated in recruiting patients to the trial and reported data for those patients. HC, LTR, SV, and KB all had a substantial involvement in the data analyses. All authors were involved in the development of the first manuscript, interpretation of data, have read and approved the final version, and have met the criteria for authorship as established by the International Committee of Medical Journal Editors.

#### Conflicts of interest

CJC has received research funding from Tibotec, Gilead, Bristol-Myers Squibb, Merck, Sharp & Dohme, Tobira, and ViiV Healthcare; has received speakers' honoraria from Tibotec, Gilead, Bristol-Myers Squibb, and Merck, Sharp & Dohme; and is on advisory boards for Gilead, Tibotec, Merck, Sharp & Dohme, Abbott, Tobira, and Bristol-Myers Squibb. JA-V has received research grants or honoraria for participation in advisory boards or conferences from Boehringer Ingelheim, Bristol-Myers Squibb, Tibotec Therapeutics, Abbott, Merck, Sharp & Dohme, and ViiV Healthcare. BC has received research funding, consultancy fees, lecture sponsorships from, or has served on advisory boards for Abbott, Boehringer Ingelheim, Gilead, GlaxoSmithKline, ViiV Healthcare, Janssen-Cilag, Merck, Sharp & Dohme, and Pfizer. JF and HW declare no conflicts of interest. MAJ has received honoraria from Bristol-Myers Squibb, GlaxoSmithKline, Tibotec, ViiV Healthcare, Abbott, and Merck, Sharp & Dohme. KR has received consultancy fees, or honoraria, travel grants, or research grants from Tibotec, F Hoffmann-La Roche, Merck, Sharp & Dohme, Bristol-Myers Squibb, Gilead, Abbott, and GlaxoSmithKline; has received the Professional Researcher Strengthen Grant from the National Science and Technology Development Agency, BIOTEC, Ministry of Science and Technology, Thailand, the National Research University Project of CHE, and the Ratchadaphiseksomphot Endowment Fund (HR1161A). CZ has received grants or research support from Pfizer, Tibotec, Bristol-Myers Squibb, Avexa, and Advent, and received consultancy fees from Tibotec. HC, LTR, SV, and KB are all full time employees of Tibotec.

#### Acknowledgments

We thank the patients and their families for their participation and support during the trial, the investigators, trial centre staff, and trial coordinators from every centre, Tibotec trial personnel, and Eric Lefebvre, Guy De La Rosa, Dave Anderson, Ines Adriaenssen, Yaswant Dayaram, Ralph DeMasi, Deborah Schaible, Kati Vandermeulen, and Peter Williams. The TMC278 against HIV, in a once-daily Regimen Versus Efavirenz (THRIVE) trial was designed and conducted by Tibotec, the trial sponsor and developer of rilpivirine. The authors received medical writing support and assistance in coordinating and collating author contributions from Ian Woolveridge (Gardiner-Caldwell Communications, Macclesfield, UK), which was funded by Tibotec.

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