Journal of Antimicrobial Chemotherapy

J Antimicrob Chemother 2012; **67**: 2020–2028
doi:10.1093/jac/dks130 Advance Access publication 24 April 2012

Efficacy and safety of rilpivirine in treatment-naive, HIV-1-infected patients with hepatitis B virus/hepatitis C virus coinfection enrolled in the Phase III randomized, double-blind ECHO and THRIVE trials

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Received 20 October 2011; returned 8 December 2011; revised 8 March 2012; accepted 16 March 2012

Objectives: The efficacy and hepatic safety of the non-nucleoside reverse transcriptase inhibitors rilpivirine (TMC278) and efavirenz were compared in treatment-naive, HIV-infected adults with concurrent hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection in the pooled week 48 analysis of the Phase III, double-blind, randomized ECHO (NCT00540449) and THRIVE (NCT00543725) trials.

Methods: Patients received 25 mg of rilpivirine once daily or 600 mg of efavirenz once daily, plus two nucleoside/nucleotide reverse transcriptase inhibitors. At screening, patients had alanine aminotransferase/aspartate aminotransferase levels $\leq 5\times$ the upper limit of normal. HBV and HCV status was determined at baseline by HBV surface antigen, HCV antibody and HCV RNA testing.

Results: HBV/HCV coinfection status was known for 670 patients in the rilpivirine group and 665 in the efavirenz group. At baseline, 49 rilpivirine and 63 efavirenz patients [112/1335 (8.4%)] were coinfected with either HBV [55/1357 (4.1%)] or HCV [57/1333 (4.3%)]. The safety analysis included all available data, including beyond week 48. Eight patients seroconverted during the study (rilpivirine: five; efavirenz: three). A higher proportion of patients achieved viral load <50 copies/mL (intent to treat, time to loss of virological response) in the subgroup without HBV/HCV coinfection (rilpivirine: 85.0%; efavirenz: 82.6%) than in the coinfected subgroup (rilpivirine: 73.5%; efavirenz: 79.4%) (rilpivirine, $P=0.04$ and efavirenz, $P=0.49$, Fisher's exact test). The incidence of hepatic adverse events (AEs) was low in both groups in the overall population (rilpivirine: 5.5% versus efavirenz: 6.6%) and was higher in HBV/HCV-coinfected patients than in those not coinfected (26.7% versus 4.1%, respectively).

Conclusions: Hepatic AEs were more common and response rates lower in HBV/HCV-coinfected patients treated with rilpivirine or efavirenz than in those who were not coinfected.

Keywords: TMC278, efavirenz, hepatitis, hepatic safety, non-nucleoside reverse transcriptase inhibitors, HBV, HCV

Introduction

As HIV type-1 (HIV-1), hepatitis B virus (HBV) and hepatitis C virus (HCV) share transmission routes, patients with HIV are frequently coinfected with HBV or HCV. Approximately 2–4 million HIV-infected people worldwide have chronic HBV and 4–5 million have chronic HCV coinfection.[1] In Western Europe and the USA, chronic HBV infection has been found in 6%–14% and HCV infection in 25–30% of HIV-positive individuals.[1] Data suggest that coinfection affects the overall survival of

HIV-infected patients, with a 3.6- to 8-fold increased risk of liver-related mortality in HIV/HBV-coinfected individuals.[2,3] Furthermore, in both HCV- and HBV-infected patients, HIV coinfection has been associated with more rapid progression of viral hepatitis-related liver disease (e.g. cirrhosis, end-stage liver disease, hepatocellular carcinoma and liver failure).[3–5]

Antiretroviral drugs (ARVs) that are active against HIV and HBV, such as tenofovir, lamivudine and emtricitabine, can directly suppress HBV replication and thus prevent or slow the progression of liver disease.[6–8] Although HCV replication is not inhibited by antiretroviral treatment, HCV treatment outcomes can improve as a result of suppressed HIV replication and increased CD4 cell count.[9] Based on these findings, current HIV therapy guidelines recommend that HIV patients with HBV, and possibly with HCV coinfection, begin highly active antiretroviral treatment (HAART), regardless of their CD4 cell count.[10–12]

Several studies have shown that hepatotoxicity can occur with any antiretroviral and the risk of severe toxicity following initiation of HAART is higher in HBV- or HCV-coinfected individuals.[13–20] Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been associated with hepatotoxicity, both in clinical trials and in practice.[21–25] Liver-related adverse events (AEs) occur less frequently with efavirenz than with nevirapine. The frequency of severe elevations in liver transaminases ranges from 1% to 8% in patients receiving efavirenz[26–33] compared with from 4% to 18% in patients receiving nevirapine.[23,29–34] In addition, nevirapine hepatotoxicity has been more frequent in females and in individuals with higher CD4 cell counts at the initiation of HAART.[25,35]

The NNRTI rilpivirine (TMC278; EDURANT®) has recently been approved for use in the USA, Canada and Europe in combination with other ARVs in HIV-1-infected treatment-naive adult patients.[36–38] Rilpivirine has been compared with efavirenz, each in combination with two nucleoside/nucleotide reverse transcriptase inhibitors [N(t)RTIs], in two Phase III, randomized, double-blind, double-dummy trials [ECHO (TMC278-C209, NCT00540449) and THRIVE (TMC278-C215, NCT00543725)] in treatment-naive, HIV-1-infected adults. In the pooled week 48 primary analysis of the two trials, compared with efavirenz, rilpivirine had non-inferior efficacy and a more favourable tolerability profile, with lower overall incidences of treatment-related grade 2–4 AEs, rash and neuropsychiatric AEs, and smaller lipid increases.[39]

Given that HIV patients coinfected with HBV and/or HCV have a higher risk of developing hepatic-related AEs with NNRTIs,[32,40] we analysed the efficacy and safety of rilpivirine compared with efavirenz in this subgroup of patients, using pooled week 48 Phase III data from the ECHO and THRIVE trials.

Methods

Trial design

ECHO and THRIVE were two Phase III, double-blind, double-dummy, international randomized trials in treatment-naive, HIV-1-infected adults (NCT00540449 and NCT00543725, respectively; www.clinicaltrials.gov). Their primary objective was to determine whether rilpivirine was non-inferior to efavirenz in overall response [confirmed viral load <50 copies/mL, intent to treat, time to loss of virological response (ITT-TLOVR), 12% non-inferiority margin] at week 48. The trial design and methods have been reported in detail for the individual trials.[41,42]

The main inclusion criteria were viral load ≥5000 copies/mL, absence of NNRTI resistance-associated mutations (based on a list of 39 out of 44 known NNRTI mutations)[41–43] and susceptibility to the N(t)RTIs in the background regimen as determined by virco®TYPE HIV-1 (Virco, Beerse, Belgium). Patients with clinically significant hepatic impairment or alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels that were five times above the upper limit of normal were excluded from the trials. Patients diagnosed with acute clinical viral hepatitis during the trial were withdrawn. The HBV and HCV status was determined at baseline by HBV surface antigen, HCV antibody and HCV RNA testing.

The patients were randomized 1:1 to receive 25 mg of rilpivirine once daily or 600 mg of efavirenz once daily, plus a combination of two N(t)RTIs: tenofovir/emtricitabine in the ECHO trial and investigator-selected tenofovir/emtricitabine, zidovudine/lamivudine or abacavir/lamivudine in the THRIVE trial.

Written informed consent was obtained from all participants. Trial protocols were reviewed and approved by the appropriate institutional Ethics Committees and Health Authorities, and the trials were conducted in accordance with the Declaration of Helsinki.

AEs were assessed using the Clinical Trials Group's 'Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events' (version 1.0, December 2004).[44] Reported AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA version 11.0).[45]

Trial and subanalysis assessments

Efficacy and safety data were analysed according to HIV/HBV and/or HIV/HCV coinfection status. The efficacy analysis included only patients with HBV/HCV status available at baseline and data gathered up to week 48. The safety analysis included all patients and all available data, including those beyond week 48. The cut-off date for this analysis was 28 January 2010 for THRIVE and 1 February 2010 for ECHO. In addition, patients who seroconverted for HBV/HCV during the trials were considered as HBV/HCV coinfected in the safety analysis. Pharmacokinetic data were collected and population-based pharmacokinetic parameters determined.

The ITT population was used for all efficacy analyses and all evaluations were performed on pooled data from the two trials. Response rate (defined as the proportion of patients with viral load <50 copies/mL) at week 48 was determined using the TLOVR algorithm. In *post-hoc* analyses, Fisher's exact test was used to compare differences in the response rates between different subgroups and the Wilcoxon signed-rank test was used for differences in the CD4 cell counts. The incidences of hepatic AEs and laboratory abnormalities were assessed on all available safety data from the trials. Fisher's exact test (*post-hoc* analysis) was used to compare safety differences between the treatment groups. The Wilcoxon rank-sum test (*post-hoc* analysis) was used to compare population pharmacokinetic data.

Results

Baseline patient characteristics

A total of 1368 patients were randomized and treated in the two trials ($N=686$ in the rilpivirine group and $N=682$ in the efavirenz group; Figure 1). At baseline, the median viral load was 5.0 $\log_{10}$ copies/mL and the median CD4 cell count was 256 cells/mm^3. Demographics and baseline characteristics were well-balanced between the treatment groups within each trial; the median treatment duration was 56 weeks in both groups.[39]

At baseline, the HIV/HBV and/or HIV/HCV coinfection status was determined in 1335 patients ($N'=670$ in the rilpivirine group and $N'=665$ in the efavirenz group). A total of 8.4%

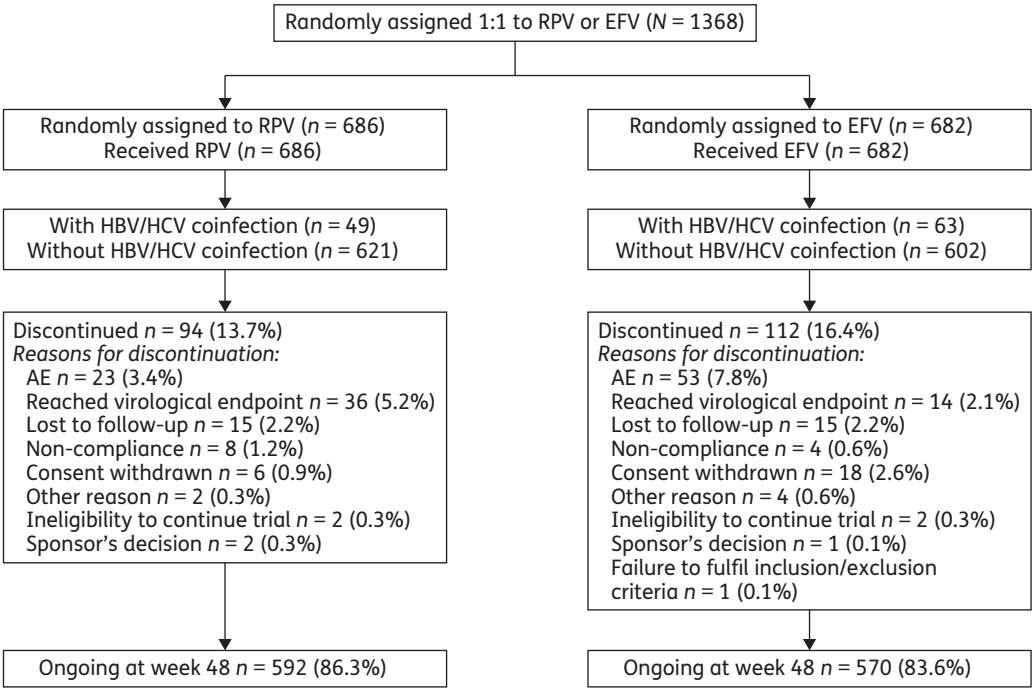

Figure 1. CONSORT diagram showing patient disposition for the pooled primary analysis of ECHO and THRIVE. RPV, rilpivirine; EFV, efavirenz.

Table 1. ECHO and THRIVE: baseline characteristics of patients according to HBV and/or HCV coinfection status at baseline (*N*=1335)

	HIV patients with HBV/HCV coinfection		HIV patients without HBV/HCV coinfection	
Parameter	25 mg of RPV once daily, *N*=49	600 mg of EFV once daily, *N*=63	25 mg of RPV once daily, *N*=621	600 mg of EFV once daily, *N*=602
Patient demographics				
male, %	77.6	73.0	75.2	76.4
Caucasian/white, %	46.9	50.8	62.6	60.6
age (years), median (range)	38 (25–78)	35.5 (22–63)	36 (18–74)	36 (19–69)
Disease characteristics				
HIV-1 viral load (log_{10} copies/mL), median (range)	5.2 (3.2–6.2)	5.0 (3.2–6.1)	4.9 (2.2–7.3)	5.0 (3.0–6.7)
HIV-1 viral load >100000 copies/mL, %	61.2	47.6	44.8	51.8
CD4 count (cells/mm^3), mean (95% CI)	230 (198–263)	246 (216–276)	262 (251–273)	274 (262–285)
CDC category C, %	8.2	4.8	4.5	5.8

RPV, rilpivirine; EFV, efavirenz.

(112/1335) of patients were coinfected with HBV and/or HCV: 7.3% (49/670) of patients in the rilpivirine group and 9.5% (63/665) in the efavirenz group. HBV and HCV coinfection occurred at similar frequencies, with 55/1357 patients (4.1%) being HBV positive and 57/1333 patients (4.3%) being HCV positive.

During the trial, an additional eight patients seroconverted for HBV/HCV (five patients in the rilpivirine group and three in the efavirenz group). Data from these patients were included in the coinfected subgroup in the safety analysis.

Table 1 shows the baseline characteristics of patients with known HIV/HBV and/or HIV/HCV coinfection status. The baseline disease characteristics were suggestive of a slightly more advanced HIV infection stage in patients in the rilpivirine-coinfected group than in the other groups (Table 1).

Efficacy outcomes by treatment group at week 48

The response rate was greater overall in the subgroup of HIV patients without HBV/HCV coinfection than in the subgroup of

Table 2. Pooled week 48 efficacy outcomes for patients with known HBV and/or HCV coinfection status at baseline ($N=1335$)

	HIV patients with HBV/HCV coinfection		HIV patients without HBV/HCV coinfection	
Efficacy parameters at week 48[a]	25 mg of RPV once daily, $N=49$	600 mg of EFV once daily, $N=63$	25 mg of RPV once daily, $N=621$	600 mg of EFV once daily, $N=602$
Patients with viral load <50 copies/mL (ITT-TLOVR), % (95% CI)	73.5 (61–86)	79.4 (69–90)	85.0 (82–88)	82.6 (80–86)
Virological failures, *n* (%)	5 (10.2)	3 (4.8)	55 (8.9)	30 (5.0)
Discontinuation due to AE/death, *n* (%)	2 (4.1)	6 (9.5)	13 (2.1)	40 (6.6)
Discontinuation due to reason other than AE[b], *n* (%)	6 (12.2)	4 (6.3)	25 (4.0)	35 (5.8)
Change in CD4 count (NC=F[c]) from baseline (cells/mm^3), mean (95% CI)[d]	+137 (100–175)	+192 (147–238)	+197 (186–209)	+173 (161–185)

RPV, rilpivirine; EFV, efavirenz.
[a]Patients included in efficacy analysis were those with baseline HBV/HCV assessments.
[b]Lost to follow-up, non-compliance, withdrew consent, ineligible to continue, sponsor's decision.
[c]NC=F, non-completer=failure: missing values after discontinuation imputed with change=0; last observation carried forward otherwise.
[d]$N'=48$ for rilpivirine for HBV- and/or HCV-coinfected patients.

HIV/HBV- and/or HIV/HCV-coinfected patients ($P=0.06$; Fisher's exact test) (Table 2). Among patients with HIV/HBV and/or HIV/HCV coinfection, 73.5% and 79.4% of patients in the rilpivirine and efavirenz groups, respectively, achieved viral load <50 copies/mL, whereas in non-coinfected patients the response rates were 85.0% and 82.6%, respectively (Table 2). This difference between coinfected and non-coinfected patients was significant for rilpivirine ($P=0.04$), though not for efavirenz ($P=0.49$, Fisher's exact test).

Similarly, for rilpivirine the mean improvement in the CD4 cell count was higher in the subgroup of HIV patients without coinfection than in the subgroup of patients with HBV/HCV coinfection (Table 2). In patients with coinfection, the mean increase in the absolute CD4 cell count from baseline was lower in the rilpivirine group than in the efavirenz group (although the 95% confidence intervals overlapped), while in non-coinfected patients the mean increase was higher in the rilpivirine group (with no overlap in the confidence intervals, Table 2). The change from baseline in the CD4 cell count was statistically significant for each of the four subgroups ($P<0.0001$; Wilcoxon signed-rank test).

HBV or HCV coinfection did not significantly influence rilpivirine or efavirenz pharmacokinetics, with no effect on the area under the concentration–time curve (AUC_{24}) of rilpivirine or efavirenz compared with non-coinfected patients (rilpivirine, $P=0.45$; efavirenz, $P=0.71$; Wilcoxon rank-sum test).

Hepatic safety and tolerability by treatment group in the overall patient population

The overall incidence of hepatic AEs was low [5.5% (38/686) for rilpivirine versus 6.6% (45/682) for efavirenz]. Hepatic AEs considered at least possibly related to treatment by the investigator (treatment-related AEs) occurred in 2.2% (15/686) of patients in the rilpivirine group and 2.1% (14/682) of patients in the efavirenz group. Increased AST [rilpivirine: 2.3% (16/686) versus efavirenz: 2.8% (19/682)] and increased ALT [1.9% (13/686) versus 2.8% (19/682), respectively] were the most commonly reported hepatic AEs (regardless of causality). All other hepatic AEs occurred in <1% of patients in each treatment group. Most hepatic AEs were asymptomatic grade 1 or 2 increases in transaminase levels.

Serious hepatic AEs (regardless of causality) occurred infrequently in both treatment groups [rilpivirine: 0.4% (3/686) versus efavirenz: 0.7% (5/682)]. Two serious treatment-related hepatic AEs occurred. Both were in the efavirenz group and led to discontinuation: one was a grade 3 increase in both ALT and AST, and one a grade 3 increase in ALT. Hepatic AEs infrequently led to treatment discontinuation, with three patients stopping treatment permanently in the rilpivirine group (0.4%) compared with nine patients in the efavirenz group (1.3%). No fatal hepatic AEs occurred.

Regarding treatment-emergent hepatic laboratory abnormalities, there was a lower incidence of grade 2–4 ALT and AST elevations in the rilpivirine group than in the efavirenz group [ALT: 5.1% (35/685) for rilpivirine versus 9.9% (66/670) for efavirenz, $P=0.0009$; AST: 4.8% (33/685) versus 9.0% (60/669), respectively, $P=0.003$; Fisher's exact test]. The incidence of grade 2–3 total hyperbilirubinaemia was higher in the rilpivirine group [3.1% (21/685) versus 0.4% (3/670) for efavirenz, $P=0.0003$; Fisher's exact test].

Hepatic AEs by HIV/HBV and/or HIV/HCV coinfection status

Compared with patients without HBV/HCV coinfection, coinfected patients developed more hepatic AEs and laboratory abnormalities reported as AEs in both treatment groups (Table 3). These were mostly increases in AST and ALT levels.

Of the two serious hepatic AEs that occurred in the overall population and considered at least possibly related to treatment, one was in a coinfected patient (grade 3 increase in ALT while receiving efavirenz) and led to discontinuation. The other (grade 3 increase in ALT and AST) was in a non-coinfected patient receiving efavirenz.

Table 3. Frequency of treatment-emergent hepatic AEs by HBV and/or HCV coinfection status ($N=1368$)[a]

	HIV patients with HBV/HCV coinfection		HIV patients without HBV/HCV coinfection	
Treatment-emergent hepatic AEs, *n* (%)	25 mg of RPV once daily, $N=54$	600 mg of EFV once daily, $N=66$	25 mg of RPV once daily, $N=632$	600 mg of EFV once daily, $N=616$
Any hepatic AE	15 (27.8)	17 (25.8)	23 (3.6)	28 (4.5)
Hepatobiliary disorders[b]	3 (5.6)	7 (10.6)	6 (0.9)	9 (1.5)
cholelithiasis	—	—	4 (0.6)	1 (0.2)
cytolytic hepatitis	—	1 (1.5)	—	—
abnormal hepatic function	—	3 (4.5)	—	—
hepatic steatosis	—	2 (3.0)	—	—
hepatitis	1 (1.9)	—	—	1 (0.2)
acute hepatitis	—	—	—	1 (0.2)
hepatomegaly	1 (1.9)	1 (1.5)	1 (0.2)	3 (0.5)
hyperbilirubinaemia (total)	1 (1.9)	—	1 (0.2)	1 (0.2)
hypertransaminasaemia	—	—	1 (0.2)	2 (0.3)
Incident cases of HBV or HCV[c]	3 (5.6)	5 (7.6)	—	—
HBV	1 (1.9)	1 (1.5)	—	—
HCV	2 (3.7)	4 (6.1)	—	—
Hepatic laboratory abnormalities reported as an AE[d]	9 (16.7)	8 (12.1)	19 (3.0)	21 (3.4)
abnormal ALT	—	—	1 (0.2)	—
increased ALT	6 (11.1)	7 (10.6)	7 (1.1)	12 (1.9)
increased AST	7 (13.0)	5 (7.6)	9 (1.4)	14 (2.3)
increased blood alkaline phosphatase	—	—	—	3 (0.5)
increased blood bilirubin	—	—	4 (0.6)	—
increased unconjugated blood bilirubin	—	—	1 (0.2)	—
increased hepatic enzyme	1 (1.9)	1 (1.5)	—	1 (0.2)
abnormal liver function test	—	—	2 (0.3)	1 (0.2)
increased transaminases	1 (1.9)	—	1 (0.2)	4 (0.6)

RPV, rilpivirine; EFV, efavirenz.
[a]Patient numbers are higher than for the efficacy analyses because the safety analyses were performed using all available data, including beyond week 48.
[b]Selection of preferred terms from the System Organ Class, as defined by MedDRA.
[c]Patients who seroconverted for HBV/HCV during the study were also included in the subgroup of HIV/HBV- and/or HIV/HCV-coinfected patients.
[d]Selection of preferred terms reported under the System Organ Class of investigations, not hepatobiliary disorders.

Three patients in the rilpivirine group discontinued for hepatic AEs; two were HBV/HCV coinfected and one patient had an unknown coinfection status. Of the nine patients in the efavirenz group who discontinued for this reason, six were HBV/HCV coinfected and one patient had an unknown coinfection status. The reason for discontinuation in the two HBV/HCV-coinfected patients in the rilpivirine group was a grade 3 or 4 increase in AST and/or ALT levels (as required by the protocol). One of the six HBV/HCV-coinfected patients in the efavirenz group also discontinued for this reason and the other five discontinued for HCV ($n=2$), cytolytic HCV ($n=1$), elevated hepatic enzymes ($n=1$) and abnormal hepatic function ($n=1$).

Hepatic laboratory abnormalities by HIV/HBV and/or HIV/HCV coinfection status

In both treatment groups, grade 2–4 increases in hepatic laboratory abnormalities were observed more frequently in HBV/HCV-coinfected patients than in patients who were not coinfected (Table 4). The majority of patients had increased indirect bilirubin above the normal limit. In HBV/HCV-coinfected patients, 3/54 patients (5.6%) in the rilpivirine group and 1/66 patients (1.5%) in the efavirenz group had a treatment-emergent indirect bilirubin level above normal. In patients without HBV/HCV coinfection, the proportions were 32/631 patients (5.1%) versus 2/603 (0.3%), respectively.

Discussion

Analysis of the pooled 48 week data from the ECHO and THRIVE trials showed that rilpivirine and efavirenz have comparable efficacy and hepatic safety profiles in antiretroviral treatment-naive patients coinfected with HIV-1 and HBV or HCV. Response rates were similar for rilpivirine and efavirenz within the HBV/HCV-coinfected and non-coinfected groups. Overall, the response rate was lower in HBV/HCV-coinfected patients than in patients

Table 4. Frequency of grade 2–4 treatment-emergent hepatic laboratory abnormalities occurring in ≥2% of patients per treatment group by HIV/HBV and/or HIV/HCV coinfection status ($N=1368$)[a]

	HIV patients with HBV/HCV coinfection		HIV patients without HBV/HCV coinfection	
Laboratory parameter, *n* (%)	25 mg of RPV once daily, $N=54$	600 mg of EFV once daily, $N=66$	25 mg of RPV once daily, $N=631$[b]	600 mg of EFV once daily, $N=604$[b]
Increased alkaline phosphatase				
all grades	4 (7.4)	13 (19.7)	16 (2.5)	75 (12.4)
grade 2–3[c]	0	2 (3.0)	1 (0.2)	6 (1.0)
Increased ALT				
all grades	27 (50.0)	28 (42.4)	114 (18.1)	161 (26.7)
grade 2–4	18 (33.3)	19 (28.8)	17 (2.7)	47 (7.8)
Increased AST[d]				
all grades	22 (40.7)	24 (36.4)	94 (14.9)	146 (24.7)
grade 2–4	11 (20.4)	12 (18.2)	22 (3.5)	48 (7.9)
Hyperbilirubinaemia (total)[e]				
all grades	7 (13.0)	1 (1.5)	50 (7.9)	4 (0.7)
grade 2–3[c]	4 (7.4)	1 (1.5)	17 (2.7)	2 (0.3)

RPV, rilpivirine; EFV, efavirenz.
[a]Patient numbers are higher than for the efficacy analyses because the safety analyses were performed using all available data, including beyond week 48; patients who seroconverted for HBV/HCV during the study were also included in the subgroup of HIV/HBV- and/or HIV/HCV-coinfected patients.
[b]Number of patients with data.
[c]No grade 4 laboratory abnormality observed.
[d]Data available for 603 patients in the efavirenz non-coinfected group.
[e]The majority of patients had increased indirect bilirubin above the normal limit.

who were not coinfected, with the difference being statistically significant for rilpivirine. The lower overall response rate in coinfected than in non-coinfected patients in the rilpivirine group was due to more discontinuations for reasons other than AEs (12.2% discontinuations for coinfected versus 4.0% for non-coinfected patients, respectively). For efavirenz, the main reason for the lower response rate in coinfected than in non-coinfected patients was a higher discontinuation rate due to AEs (9.5% versus 6.6% for non-coinfected patients). Virological failure rates were similar within each treatment group, regardless of the HIV/HBV and/or HIV/HCV coinfection status (10.2% in coinfected patients versus 8.9% in non-coinfected patients for rilpivirine, and 4.8% and 5.0%, respectively, for efavirenz).

In general, both rilpivirine and efavirenz were well tolerated, with no hepatic safety differences observed. Rilpivirine was, however, associated with a lower incidence of grade 2–4 increases in liver function test enzymes compared with efavirenz. While hyperbilirubinaemia (grade 1–3) was more frequent in the rilpivirine group compared with the efavirenz group, the majority of patients had an increased indirect bilirubin above the normal limit, which is not indicative of hepatic toxicity. This could be due to an interaction with a transporter or due to conjugation, but additional *in vitro* experiments would be required to explore this further. There have been no signs of haemolysis in preclinical or clinical studies. There were no grade 4 cases of hyperbilirubinaemia in either group. Consistent with observations from previous studies,[13–19,32,40] hepatic AEs occurred more frequently in HBV- and/or HCV-coinfected patients than in those patients who were not coinfected (26.7% versus 4.1%, respectively). Our results suggest that the liver safety profile of rilpivirine is similar to that of efavirenz.

Hepatotoxicity can lead to morbidity, mortality and the discontinuation of antiretroviral therapy in HIV patients, and those who are coinfected with HBV or HCV are more vulnerable.[40] Although varying degrees of drug-related liver injury have been associated with almost every antiretroviral regimen, previous reports suggest that NNRTIs tend to cause a slight increase in the cumulative incidence of hepatotoxicity with prolonged use, especially in HBV/HCV-coinfected patients.[21,40,46] However, this analysis showed that liver-related AEs were uncommon with rilpivirine or efavirenz over ≥48 weeks of treatment. Moreover, most of the hepatic AEs reported were laboratory abnormalities, generally asymptomatic grade 1 or 2 increases in transaminase levels, rather than clinical hepatic AEs. These findings are similar to those of other studies on the safety of NNRTIs.[32,47]

The current pooled analysis of two trials has several limitations. The individual trials were not designed to compare rilpivirine with efavirenz in coinfected patients. In addition, patients entering the trials were highly selected, e.g. those with clinically significant hepatic impairment or ALT and/or AST levels five times above the upper limit of normal were excluded. As such, this subpopulation was restricted to mild-to-moderately hepatically impaired

patients, and thus the proportion of HBV/HCV-coinfected patients (8.4%) was different (smaller) compared with the incidence of coinfection previously reported in Western Europe and the USA (HCV coinfection: 25%–30%; HBV coinfection: 6%–14%).[1] However, treatment comparison within the study remains valid. Also, this exclusion criterion meant the safety of rilpivirine or efavirenz in patients with more advanced liver disease at baseline was not explored. The small numbers preclude: separate analyses of the HBV- and HCV-coinfected patients; further study of the effect on response and safety of other baseline risk factors; or further study of the background N(t)RTIs that have anti-HBV activity (tenofovir, lamivudine and emtricitabine). Lastly, it is beyond the scope of this analysis to determine the reasons for the differences in the virological response and tolerability profile between HBV/HCV-coinfected patients and non-coinfected patients, e.g. whether or not they are due to an intrinsic effect of the NNRTIs.

The results of the analysis suggest that hepatic AEs are more common and the response rates lower in HBV/HCV-coinfected patients than in patients with HIV who are not coinfected, when treated with rilpivirine or efavirenz. Rilpivirine demonstrated an efficacy and hepatic safety profile similar to that of efavirenz in both coinfected and non-coinfected individuals. Standard clinical monitoring is considered adequate when HBV/HCV-coinfected patients receive a HAART regimen that includes rilpivirine. Finally, clinical practice will also be guided by the extensive drug interactions study programme being conducted with rilpivirine, particularly in the light of the known drug interactions between some current ARVs and certain HCV therapies.

Acknowledgements

Data contained in this article were presented during the 10th International Congress on Drug Therapy in HIV Infection, Glasgow, UK, 2010 (Abstract P210) and at the Seventh International Workshop on HIV and Hepatitis C Co-infection, Milan, Italy, 2011 (Abstract O_02).

We are very grateful to the patients and their families for their participation and support during the study, the ECHO and THRIVE study teams from Janssen, the study centre staff and principal investigators, and the members of the Janssen TMC278 team, in particular Guy De La Rosa, David Anderson, Eric Lefebvre, Peter Williams and Eric Wong, for their input.

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THRIVE

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Funding

This study was sponsored by Janssen Pharmaceuticals. The medical writing support and assistance in coordinating and collating author contributions from Ian Woolveridge (principal writer) of Gardiner-Caldwell Communications was funded by Janssen.

Transparency declarations

M. N. has acted as consultant and received educational and research grants from Merck Sharpe & Dohme (MSD), GlaxoSmithKline (GSK), Bristol-Myers Squibb (BMS), Gilead Sciences, Johnson & Johnson, Janssen, Abbott Laboratories, Boehringer Ingelheim (BI), Schering-Plough, Pfizer and Roche. N. C. has participated as an expert or investigator for Abbott Laboratories, BI, Gilead Sciences, GSK, MSD, Pfizer, Roche and Janssen. C. A. da C. has received research support from BMS, Janssen, Gilead Sciences and Schering-Plough. In addition, he has served as consultant and speaker for BMS, Janssen-Cilag, Gilead Sciences, Abbott Laboratories, MSD and Roche. D. J. has been an investigator and/or scientific advisor (Review Panel or Advisory Committee) for Janssen, BMS, Gilead Sciences, BI and GSK. He has received research support from Janssen, BMS, Roche and GSK, and speaker honorarium from Janssen, BMS, Gilead Sciences, BI, Roche and GSK. He has served as a consultant for Janssen, BMS, Gilead Sciences, Roche and GSK, and has been on the Speaker's Bureau for Janssen, BMS, Gilead Sciences, BI and GSK. P. J. has received consulting fees and or grants from Abbott Laboratories, Gilead Sciences, Merck, Janssen, ViiV Healthcare and BMS. P. T. has received consulting fees from GSK, Merck and, more than 1 year since publication, Pfizer and Janssen. M. S., S. V. and K. B. are full-time

employees of Janssen. M. S. owns stock in Johnson and Johnson. A. B. is a contractor for Janssen. G. A. and T. L. declare no conflicts of interest.

The authors received medical writing support and assistance in coordinating and collating author contributions from Ian Woolveridge (senior medical writer) of Gardiner-Caldwell Communications, Macclesfield, UK.

Author contributions

All authors substantially contributed to the study's conception, design and performance. Mark Nelson, Gerardo Amaya, Nathan Clumeck, Clovis Arns da Cunha, Dushyantha Jayaweera, Patrice Junod, Taisheng Li and Pablo Tebas all participated in recruiting significant numbers of patients to the trial and reported data for those patients. Marita Stevens, Annemie Buelens, Simon Vanveggel and Katia Boven all had a significant involvement in the data analyses. All authors were involved in the development of the primary manuscript, interpretation of the data, have read and approved the final version, and have met the criteria for authorship as established by the ICMJE.

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