Rilpivirine in the treatment of HIV infection: evidence from the ECHO and THRIVE studies

Pedro Cahn
Fundación Huesped, Buenos Aires, Argentina
Tel.: +54 11 4981 7777
Fax: +54 11 4982 4024
E-mail: pcahn@huesped.org.ar

Rilpivirine (RPV) is a once-daily (qd) non-nucleoside reverse transcriptase inhibitor that was evaluated in antiretroviral treatment-naive, HIV-1-infected adults (with two nucleotide reverse transcriptase inhibitors) in two international, double-blind, double-dummy, Phase III trials (ECHO and THRIVE). Both trials met their primary objective of demonstrating noninferior efficacy of RPV 25-mg qd versus efavirenz 600-mg qd regarding the proportion of patients with a confirmed response (viral load <50 copies/ml, intention-to-treat time-to-loss-of-virologic-response) at week 48. Pooled trial responses were 84 versus 82%, respectively. While RPV was associated with more virologic failures overall (9 vs 5%) and conveyed a greater risk of resistance-associated mutations developing, in patients with baseline viral load ≤100,000 copies/ml, virologic failures rates were similar (4 vs 3%). RPV was associated with fewer discontinuations due to adverse events (2 vs 7%) and a better tolerability profile, particularly regarding neurologic/psychiatric events and rash. qd RPV is a valuable option for antiretroviral treatment-naive patients, particularly those with viral load ≤100,000 copies/ml.

Keywords: antiretroviral therapy • efavirenz • reverse transcriptase inhibitors • rilpivirine • TDF-1 • treatment naive

All treatment guidelines recommend the non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz, in combination with tenofovir disoproxil fumarate (TDF) and emtricitabine as a preferred first-line option for antiretroviral treatment-naive adults [1,2,101–103]. While efavirenz is efficacious in this setting [1,2,101–103], it possesses a distinct side-effect profile that can limit its use in certain patients. For example, efavirenz has been associated with CNS toxicities, rash, metabolic changes, such as increases in cholesterol and triglycerides, and potential teratogenic effects that prohibit its use in pregnant women (during the first trimester) or in women with high pregnancy potential [1–3,101–104].

In all cases, the choice of antiretroviral regimen should be individualized according to virologic efficacy, toxicity, pill burden, dosing frequency, drug–drug interaction potential, resistance profile and comorbid conditions [1,101]. Of these factors, toxicity and dosing frequency are key considerations, as once-daily (qd), well-tolerated antiretroviral regimens may facilitate better adherence and the decision to initiate treatment earlier. The recommendation for earlier treatment initiation is in current TDF-1 treatment guidelines [1,2,101–103]. Toxicity is also a major cause of discontinuations in patients receiving first-line antiretroviral therapy [4] so a better-tolerated treatment option is less likely to lead to treatment discontinuations. In a 96-week follow-up study of 427 antiretroviral treatment-naive patients placed on a single-tablet regimen of efavirenz, tenofovir and emtricitabine, 19% of patients (89/427) discontinued treatment after a median...
duration of 294 days; the majority (71%) of the discontinuations were due to CNS toxicity [5].

Rilpivirine (RPV) is a new, recently approved, qd NNRTI that may prove to be a valuable alternative to efavirenz for antiretroviral treatment-naive adults with TDF-1 infection [105,106]. In addition, a single-tablet regimen, consisting of RPV combined with TDF and emtricitabine, has also recently been approved [107,108]. Approval of RPV and the single-tablet regimen in Europe is for antiretroviral treatment-naive adults with baseline viral load ≤100,000 copies/ml [106,108].

In a Phase IIb, dose-ranging, randomized trial (TMC278-C204), involving 368 antiretroviral treatment-naive adults, all RPV doses (25-, 75-, and 150-mg qd) resulted in similar virologic response rates at 48 and 96 weeks that were similar to that seen with efavirenz 600-mg qd, when given in combination with two nucleoside/nucleotide reverse transcriptase inhibitors (N[t]RTIs) [6]. Moreover, the efficacy observed with RPV 25-mg qd and efavirenz was sustained over 192 weeks [7]. Notably, RPV was associated with an improved tolerability profile compared with efavirenz. In particular, rash, and neurologic and psychiatric adverse events (AEs) were less common with RPV than with efavirenz, and lipid increases were smaller [6,7].

The efficacy and safety of RPV demonstrated in this Phase IIb study led to the initiation of two pivotal Phase III trials in antiretroviral treatment-naive adults with TDF-1 infection: ECHO (TMC278-C209, NCT00540449) and THRIVE (TMC278-C215, NCT00543725) [8–10]. For these two trials, the 25-mg qd dose of RPV was selected for investigation as it showed the best benefit–risk balance based on the Phase IIb study [6]. Importantly, the 25-mg qd dose of RPV had no significant effect on QTc interval in a thorough electrocardiographic study in TDF-negative volunteers [11]. This review evaluates the week-48 outcomes from these two Phase III trials (including outcomes from a preplanned pooled analysis [12]), discusses how the results impact treatment choices for antiretroviral treatment-naive patients with TDF-1 infection, and explores future avenues of development for the drug.

**ECHO & THRIVE**

**Study designs**

ECHO and THRIVE were both 96-week, international, randomized, double-blind, double-dummy, Phase III trials with the primary objective of showing noninferiority of RPV versus efavirenz, when used in combination with two N(t)RTIs, in treatment-naive, TDF-1-infected adults [8,9]. These two studies, which were nearly identical (except for background antiretroviral regimen and trial site) were designed to maximize the reliability of the efficacy data and strengthen conclusions regarding the safety/tolerability profile of RPV. The global distribution of the sites led to a diverse patient population.

To be eligible for the trials, all patients had to have a viral load ≥5000 copies/ml and confirmed sensitivity to the N(t)RTIs in the background regimen. Patients with NNRTI resistance-associated mutations (RAMs), based on a list of 39 NNRTI RAMs [8,9,13] were excluded. This exclusion criterion was included to avoid bias, as many of these NNRTI RAMs are known to decrease susceptibility to efavirenz [14].

Patients were randomized to receive RPV 25-mg qd or efavirenz 600-mg qd, in combination with a fixed-dose, background N(t)RTI regimen of TDF/emtricitabine (ECHO), or investigator-selected TDF/emtricitabine (60% of THRIVE patients), zidovudine/lamivudine (30% of THRIVE patients) or abacavir/lamivudine (10% of THRIVE patients; Figure 1) [8,9]. As part of the randomization process, patients were stratified according to their screening viral load (≤100,000, >100,000 to ≤500,000 and >500,000 copies/ml) in both studies, and by N(t) RTI background regimen in THRIVE. To maintain the double-blind, double-dummy design, RPV/RPV placebo was taken with food (as is recommended) and efavirenz/efavirenz placebo was taken on an empty stomach, at bedtime; hence, study medication was not administered using a true qd dosing regimen, a factor that may have affected treatment adherence (which was shown to be a predictor of treatment response in these trials).

The primary objective of both studies was to demonstrate the noninferiority (with a 12% margin, based on recent trials and US FDA guidelines [15–18,109]) of RPV versus efavirenz with regard to the proportion of patients with a confirmed response (viral load <50 copies/ml, according to the intention-to-treat time-to-loss-of-virologic-response [ITT-TLOVR] algorithm [109]) at week 48 [8,9]. Secondary objectives included evaluation of: noninferiority with a 10% margin and superiority (if noninferiority was shown); durability of antiviral activity; immunologic response; safety/tolerability; TDF genotypic and phenotypic characteristics (in virologic failures [VFs]); treatment adherence (measured using the Modified Medication Adherence Self-Report Inventory [M-MASRI]); and pharmacokinetics/pharmacodynamics. The M-MASRI questionnaire asks patients to report, by means of a horizontal visual analogue scale ranging from 0–100%, their estimation of the percentage of doses of RPV, efavirenz and the background regimen taken during the past 30 days. Exploratory analyses...
were also undertaken to investigate changes in serum 25-hydroxyvitamin D levels (a standard indicator of vitamin D status [110] ) in ECHO only, and substudies of body fat distribution and bone mineral density (whole body dual energy x-ray absorptiometry) during treatment in both trials [19,20].

As the two trials had an almost identical design, a preplanned, pooled week-48 analysis was undertaken after the week-48 data had been reported for both studies [12]. Due to the larger sample size, this analysis provided greater statistical power than each trial individually and particularly permitted more detailed analysis of the trial data in selected patient subgroups. These pooled data will form the primary focus of the discussion for the remainder of this article.

**Efficacy of RPV in ECHO & THRIVE**

Across ECHO and THRIVE, 686 patients were randomized to receive RPV 25-mg qd and 682 were randomized to receive efavirenz 600-mg qd [12]. Patient demographics and baseline characteristics were well balanced between the two treatment groups, and were representative of a typical treatment-naïve, TDF-1-infected patient population. Among all patients (24% female, 61% Caucasian/white, 8% with hepatitis B and/or C co-infection), median baseline viral load was 5.00 log10 copies/ml and median CD4 cell count was 256 cells/mm3 [12].

Analysis of efficacy revealed high and similar response rates in both treatment groups that were at least as high as those reported for other antiretroviral agents in this setting (Figure 2 & Table 1) [8,9,13-16,21-23]. The two trials also independently achieved their primary objective of demonstrating the noninferiority of RPV versus efavirenz with regard to the proportion of patients with a confirmed response (ITT-TLOVR outcome) at week 48 (Table 1) [8,9]. In ECHO, 83% of patients treated with either RPV or efavirenz achieved confirmed viral load <50 copies/ml at week 48 (difference: 0.1%; 95% CI: -5.5–5.7), while in THRIVE, 86% of RPV-treated patients and 82% of efavirenz-treated patients achieved a response (difference: 3.9%; 95% CI: -1.6–9.5) [8,9]. In the pooled analysis, confirmed responses were observed in 84 and 82% of patients, respectively (Figure 2 & Table 1) [12]. Importantly, these response data were confirmed in the various sensitivity analyses employed (model adjusted ITT-TLOVR, per-protocol-TLOVR, and ITT-snapshot) [12].

While the response rates with the two study drugs were similar, RPV was associated with a higher incidence of VFs than efavirenz at week 48 (pooled VFeff: 9 vs 5%, respectively; Table 1) [12]. Looking across both studies, the increase in VFs with RPV versus efavirenz was more evident in ECHO (VFeff: 11 vs 4%, respectively) than in THRIVE (VFeff: 7 vs 5%, respectively) [8,9]; the reasons for this difference are unclear. Nonetheless, the virologic failure rates associated with either drug were still within the range described in recent trials of antiretroviral therapy in antiretroviral treatment-naïve, TDF-infected patients [15,24,25]. In addition, RPV was associated with a lower rate of discontinuations than efavirenz (pooled data: 7 vs 13%, respectively), primarily due...
to a lower incidence of discontinuations occurring as a result of AEs/deaths (pooled data: 2 vs 7%, respectively) [12].

Potential factors influencing virologic outcomes were investigated in a pooled week 48 logistic regression analysis with generalized additive models [26]. As observed in previous studies [27–32], higher treatment adherence (assessed according to pill count as reported by the investigator or M-MASRI), higher drug exposure and lower baseline viral load were the most important factors associated with increased likelihood in achieving virologic response in both treatment groups [26]. In the pooled subgroup analysis, lower levels of adherence and higher viral load had a more pronounced effect on RPV than on efavirenz in achieving virologic response and conversely causing virologic failure. In patients with a baseline viral load of ≤100,000 copies/ml, virologic response rates were 90% with RPV and 84% with efavirenz, in patients with a baseline viral load >100,000 to ≤500,000 copies/ml, virologic response rates were 80 versus 83%, respectively, and in patients with a baseline viral load >500,000 copies/ml, they were 70 versus 76%. It should also be noted that as the number of patients

Table 1. Response rates and VF_{eff} rates at week 48 in ECHO and THRIVE (pooled data).

<table>
<thead>
<tr>
<th>Response or VF_{eff} rate</th>
<th>RPV (25-mg qd)</th>
<th>EFV (600-mg qd)</th>
<th>Percentage difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT-TLOVR (n)</td>
<td>686</td>
<td>682</td>
<td>–</td>
</tr>
<tr>
<td>Viral load &lt;50 copies/ml (%)</td>
<td>84</td>
<td>82</td>
<td>2.0 (-2.0–6.0)</td>
</tr>
<tr>
<td>VF_{eff} (%)</td>
<td>9</td>
<td>5</td>
<td>–</td>
</tr>
<tr>
<td>ITT-TLOVR by self-reported adherence using M-MASRI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M-MASRI adherence &gt;95% (n)</td>
<td>547</td>
<td>492</td>
<td>–</td>
</tr>
<tr>
<td>Viral load &lt;50 copies/ml (%)</td>
<td>88</td>
<td>88</td>
<td>-0.8 (-4.8–3.1)</td>
</tr>
<tr>
<td>VF_{eff} (%)</td>
<td>7</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>M-MASRI adherence ≤95% (n)</td>
<td>80</td>
<td>95</td>
<td>–</td>
</tr>
<tr>
<td>Viral load &lt;50 copies/ml (%)</td>
<td>66</td>
<td>68</td>
<td>-2.2 (-16.1–11.8)</td>
</tr>
<tr>
<td>VF_{eff} (%)</td>
<td>19</td>
<td>9</td>
<td>–</td>
</tr>
<tr>
<td>ITT-TLOVR by baseline viral load</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤100,000 copies/ml (n)</td>
<td>368</td>
<td>330</td>
<td>–</td>
</tr>
<tr>
<td>Viral load &lt;50 copies/ml (%)</td>
<td>90</td>
<td>84</td>
<td>6.6 (1.6–11.5)</td>
</tr>
<tr>
<td>VF_{eff} (%)</td>
<td>4</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>&gt;100,000 to ≤500,000 copies/ml (n)</td>
<td>249</td>
<td>270</td>
<td>–</td>
</tr>
<tr>
<td>Viral load &lt;50 copies/ml (%)</td>
<td>80</td>
<td>83</td>
<td>-3.1 (-9.8–3.7)</td>
</tr>
<tr>
<td>VF_{eff} (%)</td>
<td>13</td>
<td>5</td>
<td>–</td>
</tr>
<tr>
<td>&gt;500,000 copies/ml (n)</td>
<td>69</td>
<td>82</td>
<td>–</td>
</tr>
<tr>
<td>Viral load &lt;50 copies/ml (%)</td>
<td>70</td>
<td>76</td>
<td>-6.0 (-20.4–8.3)</td>
</tr>
<tr>
<td>VF_{eff} (%)</td>
<td>22</td>
<td>11</td>
<td>–</td>
</tr>
<tr>
<td>ITT-TLOVR by hepatitis B/C co-infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n)</td>
<td>49</td>
<td>63</td>
<td>–</td>
</tr>
<tr>
<td>Viral load &lt;50 copies/ml (%)</td>
<td>73</td>
<td>79</td>
<td>N/A</td>
</tr>
<tr>
<td>VF_{eff} (%)</td>
<td>10</td>
<td>5</td>
<td>–</td>
</tr>
<tr>
<td>No (n)</td>
<td>621</td>
<td>602</td>
<td>–</td>
</tr>
<tr>
<td>Viral load &lt;50 copies/ml (%)</td>
<td>85</td>
<td>83</td>
<td>N/A</td>
</tr>
<tr>
<td>VF_{eff} (%)</td>
<td>9</td>
<td>5</td>
<td>–</td>
</tr>
</tbody>
</table>

VF_{eff} included rebounders: confirmed response before week 48 with confirmed rebound at or before week 48 or never suppressed: patients with no confirmed response before week 48.

Patients included in efficacy analysis were those with baseline assessments for the hepatitis B and C viruses.

EFV: Efavirenz; ITT: Intent-to-treat; M-MASRI: Modified Medication Adherence Self-Report Inventory; qd: Once daily; RPV: Rilpivirine; TLOVR: Time-to-loss-of-virologic-response; VF_{eff}: Virologic failure for the efficacy (ITT-TLOVR) end point.

with suboptimal adherence (M-MASRI ≤95%) and/or a very high baseline viral load (>500,000 copies/ml) was low, any conclusions made should only be regarded as tentative, although the evidence for using RPV in patients with low viral load is particularly compelling.

Hepatitis B and C co-infection, an important determinant of survival and disease progression in TDF patients [33–36], also resulted in lower response rates in both treatment groups (Table 1) [37]. The response rate was numerically (but not statistically) lower with RPV than efavirenz in co-infected patients. While this was due in part to a higher rate of VFeff with RPV than efavirenz (10 vs 5%, respectively), it was primarily because of more discontinuation due to reasons other than AEs (lost to follow up, noncompliance, withdrew consent, ineligible to continue or sponsor’s decision) in the RPV group (12 vs 6%). Discontinuation due to AEs/death occurred less frequently with RPV (4 vs 10%). VFeff rates appeared to be unaffected by co-infection status (Table 1) [37].

Responses were also similar for RPV and efavirenz irrespective of background regimen, gender and race, and were comparable with those seen in the overall patient population (Table 2) [12]. In accordance with previously published data [38–40], response rates were lowest in black/African–American patients in both treatment groups and highest in Asian patients. Discontinuations for other reasons were also highest in black/African–American patients (RPV and efavirenz 1%, respectively), it was primarily because of more discontinuation due to reasons other than AEs (lost to follow up, noncompliance, withdrew consent, ineligible to continue or sponsor’s decision) in the RPV group (12 vs 6%). Discontinuation due to AEs/death occurred less frequently with RPV (4 vs 10%). VFeff rates appeared to be unaffected by co-infection status (Table 1) [37].

In terms of immunologic response, the mean change in CD4 cell count from baseline increased continuously over the 48-week study period with both treatments, with the mean imputed CD4 cell count being 192 cells/mm³ higher than baseline in the RPV group and 176 cells/mm³ higher in the efavirenz group [12]. These results indicate an ongoing improvement in immune status with RPV and efavirenz.

Virology data

Consistent with the efficacy analysis [12], in the resistance analysis – in which a broader definition of virologic failure was applied (VFeff) – a higher proportion of patients who received RPV experienced virologic failure compared with those who received efavirenz (VFeff: 10 [72/686] vs 6% [39/682], respectively) [12,41]. When the data were analyzed by viral load category, however, the proportions of RPV (19/368) and efavirenz (16/330) VFeff were shown to be the same (5%) in patients with a baseline viral load ≤100,000 copies/ml, indicating a low propensity for virologic failure with RPV in patients with a low viral load [41]. In patients with a baseline viral load >100,000 copies/ml, the rate of VFeff was 17% in the RPV group and 7% in the efavirenz group.

Analysis of the overall resistance profiles for the two study regimens were in accordance with other similar NNRTI-based therapies [42], and showed that a similar percentage of RPV and efavirenz VFeff had treatment-emergent NNRTI RAMs (63 [39/62]; 54% [15/28], respectively) [41]. In contrast, RPV VFeff had a higher rate of treatment-emergent N(t) RTI RAMs than efavirenz VFeff (68 [42/62] vs 32% [9/28], respectively). As with the overall VFeff rate, baseline viral load also influenced the development of RAMs, with less common occurrence of NNRTI and N(t)RTI RAMs in RPV VFeff with a viral load ≤100,000 copies/ml (NNRTI: 38% [6/16]; N(t)RTI: 44% [7/16]) compared with those with a viral load >100,000 copies/ml (NNRTI: 72% [33/46]; N(t)RTI: 76% [35/46]) [41].

Table 2. Response rates at week 48 (viral load <50 copies/ml, intent-to-treat-time-to-loss-of-virologic-response) by subgroups in ECHO and THRIVE (pooled data).

<table>
<thead>
<tr>
<th>Background N(t)RTI regimen</th>
<th>RPV (25-mg qd) n</th>
<th>Response (%)</th>
<th>EFV (600-mg qd) n</th>
<th>Response (%)</th>
<th>Percentage difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC</td>
<td>550</td>
<td>83</td>
<td>546</td>
<td>82</td>
<td>1.0 (-3.4–5.5)</td>
</tr>
<tr>
<td>AZT/3TC</td>
<td>101</td>
<td>87</td>
<td>103</td>
<td>81</td>
<td>6.5 (-3.6–16.7)</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>35</td>
<td>89</td>
<td>33</td>
<td>85</td>
<td>3.7 (-12.7–20.1)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>518</td>
<td>85</td>
<td>519</td>
<td>82</td>
<td>2.7 (-1.9–7.2)</td>
</tr>
<tr>
<td>Female</td>
<td>168</td>
<td>83</td>
<td>163</td>
<td>83</td>
<td>-0.1 (-8.2–7.9)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian/white</td>
<td>420</td>
<td>85</td>
<td>410</td>
<td>83</td>
<td>2.5 (-2.4–7.5)</td>
</tr>
<tr>
<td>Black/African–American</td>
<td>165</td>
<td>75</td>
<td>156</td>
<td>74</td>
<td>0.8 (-8.8–10.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>78</td>
<td>95</td>
<td>97</td>
<td>93</td>
<td>2.1 (-5.2–9.4)</td>
</tr>
<tr>
<td>Other†</td>
<td>14</td>
<td>93</td>
<td>12</td>
<td>92</td>
<td>1.2 (-20.4–22.8)</td>
</tr>
</tbody>
</table>

Other† includes patients whose race was other than those presented.

TT: Lamivudine; ABC: Abacavir; AZT: Zidovudine; EFV: Efavirenz; FTC: Emtricitabine; N(t)RTIs: Nucleoside/nucleotide reverse transcriptase inhibitors; qd: Once daily; RPV: Rilpivirine; TDF: Tenofovir disoproxil fumarate.

K103N (39%; 11/28), a clinically important RAM that is associated with 20- to 50-fold resistance to NNRTIs (except etravirine) [41,111]. These findings indicate that $V_F$ with RPV or efavirenz results in distinct genotypic patterns of NNRTI resistance. With regard to treatment-emergent N(t)RTI RAMs, the most prevalent were M184I (RPV 47% [29/62]; efavirenz 7% [2/28]) and M184V (RPV 23% [14/62]; efavirenz 21% [6/28]) in both treatment groups. Following virologic failure (defined as confirmed plasma viral load $>50$ copies/ml 6 months after starting therapy [initiation or modification] in patients who remain on antiretroviral therapy), when RAMs are detected, the EACS guidelines generally recommends that at least two, preferably three, active drugs should be used in a new regimen. Regimens consisting of at least one fully active ritonavir-boosted protease inhibitor plus one drug from a class not used previously are recommended [102]. N(t)RTIs are to be avoided if multiple N(t)RTI resistance is demonstrated. The continuation of lamivudine or emtricitabine even with documented M184V/I RAMs is not ruled out, albeit their use is only relevant in particular situations and depends on the availability of other treatment options [102].

Of the efavirenz $V_F$ with phenotypic resistance to efavirenz (12/28), all had cross-resistance with nevirapine, and none had cross-resistance with RPV or etravirine [41]. The proportions of efavirenz patients with cross-resistance between efavirenz and nevirapine were independent of patient’s baseline viral load. Of the RPV $V_F$ with phenotypic resistance to RPV (31/62), 90% (28/31) had cross-resistance with etravirine, 87% (27/31) with efavirenz, and 45% (14/31) with nevirapine. However, almost all of these RPV $V_F$ with cross-resistance between RPV and efavirenz (or etravirine) had a baseline viral load $>100,000$ copies/ml (27/29) compared with only two RPV $V_F$ with baseline viral load $<100,000$ copies/ml that had any NNRTI cross-resistance develop (one with cross-resistance to etravirine and one with cross-resistance to efavirenz). The clinical implications of all these findings have yet to be elucidated. In total, 15 NNRTI RAMs are associated with decreased susceptibility or response to RPV: K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, H221Y, F227C, M230I/L. Thus, the presence of any one of these 15 RPV RAMs should be considered when initiating a RPV-based regimen [41].

### Safety & tolerability of RPV in ECHO & THRIVE

The safety analyses in ECHO and THRIVE, which included data from beyond 48 weeks (median 56 weeks), were consistent with the Phase IIb safety data [6], and showed that RPV-based treatment was generally well tolerated in this antiretroviral treatment-naive patient population with an improved safety/tolerability profile compared with efavirenz-based therapy [8,9,12].

**Table 3. Adverse-event profile of rilpivirine and efavirenz in ECHO and THRIVE (pooled analysis).**

<table>
<thead>
<tr>
<th>AE profile</th>
<th>RPV 25-mg qd</th>
<th>EFV 600-mg qd</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Any AE</td>
<td>616</td>
<td>90</td>
</tr>
<tr>
<td>Any treatment-related AE ≥ grade 2</td>
<td>109</td>
<td>16*</td>
</tr>
<tr>
<td>AE leading to permanent discontinuation</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td>Any serious AE (including death)</td>
<td>45</td>
<td>7</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Treatment-related AEs ≥ grade 2 occurring in ≥2% of patients</td>
<td>117</td>
<td>17*</td>
</tr>
<tr>
<td>Any neurologic AE</td>
<td>55</td>
<td>8*</td>
</tr>
<tr>
<td>Any psychiatric AE</td>
<td>102</td>
<td>15**</td>
</tr>
<tr>
<td>Abnormal dreams/nightmares</td>
<td>56</td>
<td>8***</td>
</tr>
<tr>
<td>Rash</td>
<td>21</td>
<td>3*</td>
</tr>
</tbody>
</table>

*p <0.0001; **p <0.001; ***p <0.05 vs EFV, Fisher’s Exact test, preplanned analysis.

Number of patients in treatment group = 686.

Number of patients in treatment group = 682.

Not including laboratory abnormalities reported as an AE.

Rash is defined as one of the following terms: rash, erythema, allergic dermatitis, macular rash, urticaria, maculopapular rash, papular rash, pustular rash, drug eruption, exanthema, scaly rash, toxic skin eruption, urticaria papular.

Well-described AEs associated with current non-nucleoside reverse transcriptase inhibitors.

Neurologic events of interest are defined as one of the following terms: cluster headache, cranial neuropathy, disturbance in attention, dizziness, facial palsy, headache, lethargy, memory impairment, mononeuropathy, parasthesia circumpalmaris, photophobia, restlessness, sensation of pressure in ear, somnolence, uveitis, vertigo, blurred vision.

Psychiatric AEs are defined as one of the following terms: 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, suicide attempt.

AE: Adverse event; EFV: Efavirenz; n: Number of observations; qd: Once daily; RPV: Rilpivirine.

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Of $V_F$ with phenotypic resistance to efavirenz (12/28), all had cross-resistance with nevirapine, and none had cross-resistance with RPV or etravirine [41]. The proportions of efavirenz patients with cross-resistance between efavirenz and nevirapine were independent of patient’s baseline viral load. Of the RPV $V_F$ with phenotypic resistance to RPV (31/62), 90% (28/31) had cross-resistance with etravirine, 87% (27/31) with efavirenz, and 45% (14/31) with nevirapine. However, almost all of these RPV $V_F$ with cross-resistance between RPV and efavirenz (or etravirine) had a baseline viral load $>100,000$ copies/ml (27/29). Compared with only two RPV $V_F$ with baseline viral load $<100,000$ copies/ml that had any NNRTI cross-resistance develop (one with cross-resistance to etravirine and one with cross-resistance to efavirenz). The clinical implications of all these findings have yet to be elucidated. In total, 15 NNRTI RAMs are associated with decreased susceptibility or response to RPV: K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, H221Y, F227C, M230I/L. Thus, the presence of any one of these 15 RPV RAMs should be considered when initiating a RPV-based regimen [41].

- Safety & tolerability of RPV in ECHO & THRIVE

The safety analyses in ECHO and THRIVE, which included data from beyond 48 weeks (median 56 weeks), were consistent with the Phase IIb safety data [6], and showed that RPV-based treatment was generally well tolerated in this antiretroviral treatment-naive patient population with an improved safety/tolerability profile compared with efavirenz-based therapy [8,9,12].

- Compared with efavirenz, RPV was associated with a significantly lower incidence of treatment-related

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grade 2–4 AEs, any rash, neurologic AEs of interest (including dizziness), psychiatric AEs (including abnormal dreams/nightmares; p <0.05; Table 3) [12]. These data suggest that RPV might be particularly suitable for use in patients with certain pre-existing psychiatric, neurologic and dermatologic conditions. The rate of AEs leading to discontinuation was also lower with RPV than with efavirenz (3 vs 8%, respectively), reflecting better tolerance (Table 3). Deaths were infrequent and not considered to be related to study medication.

RPV was also associated with an improved lipid profile compared with efavirenz [12]. Significantly smaller mean changes from baseline in total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride levels were observed with RPV compared with efavirenz (Figure 3). However, the changes in total cholesterol/HDL-cholesterol ratio were similar between the two treatment groups.

In terms of other safety parameters, neither treatment was associated with a clinically relevant change in endocrine parameters, QTc interval or glomerular filtration rate [12]. In ECHO, evaluation of changes in vitamin D status was performed. Vitamin

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Figure 3. Mean (±95% CI) change from baseline. (A) Total cholesterol, (B) LDL-cholesterol, (C) HDL-cholesterol, (D) total cholesterol/HDL-cholesterol ratio, and (E) triglycerides over 48 weeks in ECHO and THRIVE (pooled analysis).

*p value vs EFV at week 48.
EFV: Efavirenz; RPV: Rilpivirine.
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D deficiency/insufficiency is very common among TDF-infected individuals, and can be exacerbated by the use of antiretroviral agents such as efavirenz. Vitamin D deficiency/insufficiency is associated with muscle weakness, immune dysfunction, decreased myocardial contractility, hypertension, diabetes and cancer [43–47]. While efavirenz reduced serum 25-hydroxyvitamin D levels, in accordance with prior data [44–46], serum levels remained unchanged with RPV [19], indicating that RPV is unlikely to worsen any TDF- or antiretroviral-related vitamin D deficiency.

Additionally, loss of body fat and reduced bone-mineral density have been reported during antiretroviral therapy, including efavirenz-based regimens [48–51], both of which may have clinical implications, particularly in underweight patients and those with osteoporosis or conditions with altered bone metabolism. In the ECHO/THRIVE dual energy x-ray absorptiometry substudies, overall changes in body fat and bone-mineral density were similar and modest in both treatment groups [20]. Furthermore, only a small percentage of patients had a ≥20% reduction (definition of lipoatrophy from ACTG study 5142 [49]) in limb fat (RPV 4%; efavirenz 6%) or a 6% decrease (indicative of a clinically significant change [51]) in bone mineral density (RPV 3%; efavirenz 2%) at week 48 [20].

Clinical perspective
The results of the ECHO and THRIVE studies show that similar, high response rates can be achieved over 48 weeks when antiretroviral treatment-naive adults with TDF-1 infection receive either RPV 25-mg qd or the current recommended first-line NNRTI, efavirenz, in combination with two N(t)RTIs (most commonly tenofovir/emtricitabine) [8,9,12]. Furthermore, data from the final analysis of both studies (pooled data) indicate that this similar high response can be sustained for up to 96 weeks [10]. Although the virologic failure rate is higher with RPV than with efavirenz overall, there was a similar, low virologic failure rate with both treatments in patients with a baseline viral load ≤100,000 copies/ml. Cross-resistance to etravirine was more common with RPV treatment failures who were phenotypically resistant torilpivirine compared with efavirenz treatment failures, who were phenotypically resistant to efavirenz, which is influential in the strategic sequencing of TDF-1 treatment regimens [12,41]. However, the clinical implications of all these findings have yet to be elucidated. RPV was also associated with fewer discontinuations due to AEs and a better tolerability profile than efavirenz, particularly relating to neurologic and psychiatric AEs, skin rash, lipid abnormalities and changes in vitamin D levels.

Taken together, these data suggest that RPV 25-mg qd is a valuable additional treatment option for antiretroviral treatment-naive patients with TDF-1 infection, including patients with certain pre-existing neurologic, psychiatric or dermatologic conditions, dyslipidemia, or severe vitamin D deficiency. RPV may be particularly suitable for antiretroviral treatment-naive patients with a low pretreatment viral load. RPV did not show any teratogenic potential in animal studies [53] and does not interact with the oral contraceptives norethindrone and ethinylestradiol [54]. Patients deemed unsuitable to receive efavirenz (e.g., women with a high pregnancy potential) or other NNRTIs may therefore be candidates for RPV-based therapy. However, adequate and well-controlled trials of RPV in pregnant women have not been conducted, and therefore, RPV should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus [105,106].

Based on the efficacy and safety data from ECHO and THRIVE, RPV as a 25-mg qd tablet for use in combination with other antiretrovirals and a single-tablet regimen consisting of RPV combined with tenofovir and emtricitabine were approved in the USA, Canada and Europe for treatment of TDF-1 infection in treatment-naive adults [105–108]. The approvals in Europe are for the treatment of antiretroviral treatment-naive TDF-1-infected adults with a viral load ≤100,000 copies/ml [106,108]. The efficacy and safety of the single-tablet regimen versus the single-tablet regimen of efavirenz and tenofovir/emtricitabine (ATRIPLA®, Bristol-Myers Squibb, NY, USA and Gilead Sciences, CA, USA) is currently being investigated in a Phase IIIb, randomized, open-label study in approximately 700 TDF-1-infected, antiretroviral treatment-naive adults [112].

Future perspective
The results from ECHO and THRIVE establish RPV as a valuable treatment option for TDF-1-infected antiretroviral treatment-naive patients. However, the profile of RPV suggests that with appropriate evaluation it may also be suitable for use as a switch agent from other first-line regimens, particularly in cases of intolerance. In this regard, a 48-week, Phase IIb pilot study has recently been undertaken to evaluate the effects of switching from a single-tablet regimen containing efavirenz and tenofovir/emtricitabine to the single-tablet regimen containing RPV and tenofovir/emtricitabine in 50 patients with viral load <50 copies/ml [55,113]. Week 24 results showed that all patients who switched remained virologically suppressed (viral load <50 copies/ml) 24 weeks after switching [55]. The RPV and tenofovir/emtricitabine single-tablet regimen was also well tolerated and none of the patients experienced...
an AE that resulted in discontinuation. A second ongoing, 48-week, randomized, open-label, Phase III study is evaluating switching from a ritonavir-boosted protease inhibitor plus two N(t)RTIs based regimens to the RPV and tenofovir/emtricitabine single-tablet regimen in 476 virologically suppressed, TDF-1-infected patients with viral load <50 copies/ml [56,114]. Over 24 weeks, switching to RPV/tenofovir/emtricitabine was noninferior to remaining on a ritonavir-boosted protease inhibitor plus two N(t)RTIs, regardless of baseline viral load while antiretroviral-treatment naive prior to treatment initiation. Switching to RPV/tenofovir/emtricitabine resulted in an improvement in fasting lipids [56].

Executive summary

Rilpivirine

Rilpivirine (RPV) is a new, once-daily non-nucleoside reverse transcriptase inhibitor (NNRTI) that has been evaluated for the treatment of antiretroviral treatment-naive adults with tenofovir disoproxil fumarate-1 infection in two pivotal Phase III trials: ECHO and THRIVE.

ECHO & THRIVE

ECHO and THRIVE were both 96-week, international, randomized, double-blind, double-dummy trials designed to assess the efficacy and safety of RPV versus efavirenz, when used in combination with two nucleoside/nucleotide reverse transcriptase inhibitors (N[t]RTIs; most commonly tenofovir/emtricitabine). The primary objective of both studies was to demonstrate the noninferiority of RPV 25-mg qd versus efavirenz 600-mg qd with regard to the proportion of patients with a confirmed virologic response (intention-to-treat time-to-loss-of-virologic-response outcome) at week 48.

Efficacy

Analysis of efficacy at week 48 revealed high and similar response rates in both treatment groups and noninferior efficacy of RPV compared with efavirenz was confirmed for both trials. Pooled response rates were 84% in the RPV group and 82% in the efavirenz group.

Resistance

While the response rates with the two study drugs were similar, RPV was associated with a higher overall incidence of virologic failures than efavirenz at week 48 (VF_{eff}: 9 vs 5%, respectively), and a greater risk of development of reverse transcriptase resistance-associated mutations (RAMs). However, RPV was associated with a lower rate of discontinuations than efavirenz (pooled data: 7 vs 13%, respectively), due primarily to a lower incidence of discontinuations due to adverse events (AEs)/deaths (2 vs 7%, respectively). Additionally, there was a similar, low virologic failure rate with both treatments in patients with a low viral load (baseline viral load ≤100,000 copies/ml; VF_{eff}: 4 vs 3%, respectively).

The most common treatment-emergent NNRTI RAMs in RPV VF_{eff} were E138K and K101E, while the most prevalent treatment-emergent N(t)RTI RAMs were M184I and M184V. NNRTI and N(t)RTI RAMs occurred less frequently in RPV VF_{eff} with a viral load ≤100,000 copies/ml compared with those with a viral load >100,000 copies/ml.

Safety & tolerability

RPV had a better tolerability profile than efavirenz, with a significantly lower incidence of treatment-related grade 2–4 AEs, grade 2–4 rash, any rash, any neurologic AEs of interest (including dizziness), and any psychiatric AEs (including abnormal dreams/nightmares). RPV was also associated with fewer lipid abnormalities than efavirenz and, unlike efavirenz, did not reduce serum vitamin D levels.

Clinical perspective

These results suggest that once-daily RPV 25 mg is a valuable treatment option for antiretroviral treatment-naive patients with tenofovir disoproxil fumarate-1 infection including those with certain comorbidities and may be particularly suitable for women and patients with a viral load ≤100,000 copies/ml.

Future perspective

A single-tablet regimen, consisting of RPV combined with tenofovir and emtricitabine, has also recently been approved for use in antiretroviral treatment-naive patients and is currently under investigation as a switch regimen for patients who fail to tolerate other first-line antiretroviral therapies, including NNRTI- and ritonavir-boosted protease inhibitor-based regimens.
Gilead Sciences, Inc., GlaxoSmithKline, Merck and Co, Inc., Pfizer Inc., and Tibotec Therapeutics. The author has served as a ban investigator for Abbott, Aventis, Ltd., Boehringer Ingelheim Pharmaceuticals (BI), Inc., Gilead Sciences, GlaxoSmithKline, Merck and Co., Inc., Pfizer Inc., Pharmasset, Inc., Roche Laboratories and Tibotec Therapeutics. The author’s institution has received honoraria for speaking or chairing engagements from Abbott Laboratories, Bristol-Myers Squibb, GlaxoSmithKline, Merck and Co, Inc., Pfizer Inc. and Tibotec Therapeutics. The author was an investigator for the ECHO trial, which, along with the THRIVE trial, was designed, sponsored and conducted by Tibotec, the developer of rilpivirine. The author has received grant research support, advisory and speaker fees from Abbott Laboratories, Aventis, Ltd., Boehringer Ingelheim, Gilead Sciences, Merck, Sharp and Dohme, Tibotec, Janssen, GlaxoSmithKline and Viiv Healthcare. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Papers of special note have been highlighted as:  
- of interest  
- of considerable interest


9 Primary report of data from the ECHO study, which evaluated the efficacy and safety of rilpivirine 25-mg once daily versus efavirenz, in combination with tenofovir and emtricitabine in 690 treatment-naive adults infected with HIV-1.  

10 Primary report of data from the THRIVE study, which evaluated the efficacy and safety of rilpivirine 25-mg once daily versus efavirenz, in combination with two investigator-selected background nucleoside/nucleotide reverse transcriptase inhibitors, in 678 treatment-naive adults infected with HIV-1.


Rilpivirine in the treatment of HIV infection


Knochel H, Guelar A, Carmona A et al.


Pooled analysis of week-48 data from the ECHO and THRIVE studies describing efficacy and safety outcomes according to whether or not patients were co-infected with the hepatitis B and/or C virus.


Pooled week-48 analysis of data from the ECHO and THRIVE studies describing the genotypic and phenotypic characterization of HIV-1 isolates obtained from rilpivirine virologic failures.


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