Triple-combination rilpivirine, emtricitabine, and tenofovir (Complera™/Eviplera™) in the treatment of HIV infection

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Abstract: The combination rilpivirine (RPV)/emtricitabine (FTC)/tenofovir (TDF) is a once-daily, single-tablet regimen (STR) containing one nonnucleoside reverse-transcriptase inhibitor associated with two nucleos(t)ide reverse transcriptase inhibitors. It is approved by regulatory agencies (eg, US Food and Drug Association, European Medicines Agency) in all countries in which it is manufactured, except Switzerland, as first-line highly active antiretroviral therapy (HAART) for the treatment of naïve patients with HIV infection and a viral load HIV-RNA level of $\leq 100,000$ copies/mL. Two large trials (ECHO and THRIVE) comparing RPV with efavirenz, along with different background regimens, led to approval of the drug, while a more recent trial (STaR) explored the use of STR. RPV showed noninferiority to efavirenz in all the studies, including superiority as an STR in patients with HIV-RNA $\leq 100,000$ copies/mL in the STaR study. A positive CD4 cell response was observed in all the studies, both in the RPV and efavirenz groups. The incidence of virologic failures was higher for RPV, but was mostly referred to patients with HIV-RNA $> 100,000$ copies/mL. There were fewer adverse events (AEs) with the RPV-based regimens versus efavirenz-based regimens, with a lower discontinuation rate because of AEs, especially psychiatric–neurological AEs, and a significantly lower rate of blood-lipid abnormalities. In the SPIRIT study (a switch study), significantly greater improvements from baseline in serum total cholesterol, low-density lipoprotein cholesterol, and triglyceride were demonstrated in patients switching to RPV/FTC/TDF from a ritonavir-boosted protease inhibitor (PI/r)-based regimen, than in those who continued treatment with a PI/r regimen. RPV's better tolerability, associated with its once-daily STR formulation, is key to improving patients' adherence and quality of life, which are among the most important factors affecting the therapeutic efficacy of an antiretroviral regimen. In summary, RPV/FTC/TDF STR is a valuable treatment option for the majority of antiretroviral-naïve HIV-infected patients. Furthermore, the use of this STR in the therapeutic switch, like in the SPIRIT study, can result in another valuable option by which to reduce AEs and improve patients' quality of life.

Keywords: rilpivirine or RPV, HIV, treatment-naïve, once-daily, single-tablet regimen

Introduction

Highly active antiretroviral therapy (HAART) plays a key role in mitigating the HIV/AIDS epidemic by reducing morbidity and mortality. Furthermore, extensive use of treatment may reduce the incidence of HIV infection, as the risk of transmission of the virus is lower in those receiving antiretrovirals than in naïve patients.¹ However, HAART regimens are often complex and require careful consideration on drug–drug interactions and toxicities, all of which potentially lead to poor patient compliance/adherence and, as a consequence, to the emergence of resistance that may limit the long-term efficacy.²

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Current combination treatment options for naïve HIV patients

According to international guidelines,¹ all adults with HIV infection should be offered HAART regardless of CD4 cell count. Although there is no CD4 cell-count threshold at which starting therapy is contraindicated, the strength of the recommendation and the quality of the evidence supporting initiation of therapy increase as the CD4 cell count decreases and when specific clinical conditions, such as AIDS-defining illnesses, coinfections with hepatitis B virus/hepatitis C virus, or pregnancy are present.^{3,4} The options for initial therapy in naïve adults with confirmed drug-susceptible virus continue to expand, with new drugs and coformulations available (Table 1).¹ Because therapy can be expected to last indefinitely, regimen choice must consider patient convenience, potential toxicities, and tolerability, all of which may affect adherence. The aim of therapy is the constant, lifelong suppression of HIV replication, with the aims of preventing emergence of resistance, facilitating optimal immune recovery, and improving health. Interactions are a growing challenge as persons with HIV age and require additional medications for comorbid conditions.⁵⁻⁷

Initial therapy continues to be based on a combination of two nucleos(t)ide reverse-transcriptase inhibitors (NRTIs) and a potent third agent, generally a non-NRTI (NNRTI), a ritonavir-boosted protease inhibitor (PI/r), or an integrase strand transfer inhibitor (INSTI). Coformulations of drugs or complete regimens in fixed-dose combinations (FDCs) are preferred to enhance convenience and medication adherence.^{4,8,9}

Overview of pharmacology

Rilpivirine (RPV) is a diarylpyrimidine NNRTI that inhibits HIV reverse transcriptase by binding to it noncompetitively.¹⁰

NNRTIs bind reverse transcriptase near the active site of the enzyme, within a small hydrophobic pocket, inducing changes in enzyme conformation depending on the specific drug's chemical structure, its size, and its mode of binding.¹¹ These conformational changes inhibit the catalysis of viral RNA to DNA by the transcriptase, thereby decreasing replication of HIV. The second-generation NNRTIs etravirine and RPV are flexible and adapt to changes in the NNRTI-binding pocket associated with resistance mutations, a characteristic that may help to explain their high barrier to resistance.^{12,13} RPV does not inhibit human cellular DNA polymerases α , β or γ ,¹⁰ which may be advantageous, as inhibition of these enzymes is implicated in the major mitochondrial toxicity observed with NRTI use.¹⁴

In a multiple-dose-escalating study, orally administered RPV was rapidly absorbed. After 7 days of RPV 25 mg once daily, the mean maximum plasma RPV concentration (C_{max}) was 263 ng/mL, the mean plasma area under the concentration–time curve from time 0 to 24 hours (AUC_{0-24}) was 3659 ng h/mL, and the median time to C_{max} was 4 hours,¹⁵ which is consistent with a general estimate of 4–5 hours across various studies.^{10,16} At steady state, the average plasma concentration of RPV was 152 ng/mL. Across dosage groups, RPV was detectable in plasma in most patients for up to 168 hours after administration.¹⁵ RPV should always be taken with a meal to ensure adequate exposure.^{10,16} The reduction in RPV bioavailability when taken after fasting is $\approx 40\%$ when compared with ingestion after a normal caloric or high-fat, high-caloric meal. There is no difference in RPV exposure when taken with a standard versus a high-fat breakfast. However, compared with administration with a meal, bioavailability was reduced by 50% when taken with only

Table 1 Recommended and alternative initial antiretroviral regimens, including strength of recommendations and quality of evidence

	Recommended regimens	Alternative regimens	Comments
NNRTI plus NRTIs	Efavirenz/tenofovir/emtricitabine (AI). Efavirenz plus abacavir/lamivudine (AI) in HLA-B 5701-negative patients with baseline plasma HIV-RNA <100,000 copies/mL.	Nevirapine plus tenofovir/emtricitabine or abacavir/lamivudine (BI).	Severe hepatotoxicity and rash with nevirapine are more common in initial therapy when CD4 cell count is >250/ μ L in women and >400/ μ L in men.
PI/r plus NRTIs	Darunavir/r plus tenofovir/emtricitabine (AI). Atazanavir/r plus tenofovir/emtricitabine (AI). Atazanavir/r plus abacavir/lamivudine (AI) in patients with plasma HIV-RNA <100,000 copies/mL.	Darunavir/r plus abacavir/lamivudine (BIII). Lopinavir/r plus tenofovir/emtricitabine (BI) (or abacavir/lamivudine) (BI).	Other alternative PIs include fosamprenavir/r and saquinavir/r, but indications to use these options for initial treatment are rare.
INSTI plus NRTIs	Raltegravir plus tenofovir/emtricitabine (AI).	Raltegravir plus abacavir/lamivudine (BI).	Raltegravir is given twice daily.

Notes: Fixed-dose combinations are recommended when available and appropriate. Current fixed-dose combinations available are: efavirenz/tenofovir/emtricitabine; tenofovir/emtricitabine; abacavir/lamivudine; lopinavir/ritonavir.

Abbreviations: INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleos(t)ide reverse-transcriptase inhibitor; PI, protease inhibitor; /r, ritonavir-boosted; AI, strong support for the recommendation - evidence from one or more randomized controlled clinical trials; BI, moderate support for the recommendation - evidence from one or more randomized controlled clinical trials; BII, moderate support for the recommendation - evidence from nonrandomized clinical trials or cohort or case control studies; BIII, moderate support for the recommendation - recommendation based on the panel's analysis of the accumulated available evidence; RNA, ribonucleic acid.

a protein-rich nutritional drink.^{10,16} In vitro, RPV is $\approx 99.7\%$ bound to plasma proteins, chiefly to albumin, whereas its distribution outside plasma is unknown.^{10,16}

RPV undergoes oxidative metabolism in the liver, chiefly mediated by the hepatic CYP3A system.^{10,16} It is excreted mostly in the feces, with minimal excretion via the kidneys.¹⁷ RPV has a terminal elimination half-life of ≈ 50 hours.^{10,16}

As RPV is metabolized by CYP3A enzymes, drug interactions are possible when it is coadministered with inducers or inhibitors of these enzymes.¹⁰

The coadministration with the following drugs is contraindicated: anticonvulsants (strong CYP3A inducers), rifampicin, rifabutin, antifungals, proton pump inhibitors, systemic dexamethasone (except as a single dose), and St John's wort.¹⁶

RPV has been shown to cause a prolongation of the QTc interval at supratherapeutic doses, so caution is required when it is used with drugs known to be associated with Torsades de pointes.^{10,16}

Coadministration of drugs raising gastric pH should be avoided, as plasma concentrations can be decreased by higher gastric pH.¹⁰ No adjustment of the dosage is required when paracetamol, atorvastatin, raltegravir, ribavirin, maraviroc, methadone, and oral contraceptives are coadministered.¹⁰

Tenofovir (TDF) and emtricitabine (FTC), the two NRTIs coformulated with RPV, have long been available as a once-daily FDC. FTC and TDF are phosphorylated by cellular enzymes to the active moieties FTC triphosphate and TDF diphosphate, respectively, which competitively inhibit HIV reverse transcriptase, leading to DNA chain termination.^{18,19} Both of these active moieties are weak inhibitors of mammalian DNA polymerases α , β , and mitochondrial DNA polymerase γ . Both drugs may be taken without food restrictions. TDF is well tolerated, but has been associated with kidney injury, which appears to increase in incidence with long-term administration and concurrent PI/r use.^{20–22}

Therapeutic efficacy

The efficacy of oral RPV as a component of combination antiretroviral therapy in antiretroviral-naïve patients with HIV infection was evaluated in a Phase II, randomized, multinational, dose-ranging study²³ and in the Phase III ECHO (Efficacy Comparison in Treatment-naïve HIV-infected Subjects of TMC278 and Efavirenz) (NCT00540449)²⁴ and THRIVE (TMC278 against HIV, in a once-daily regimen versus efavirenz) (NCT00543725)²⁵ trials.

In the Phase II, dose-ranging study, patients received once-daily RPV 25 mg ($n = 93$), 75 mg ($n = 95$), or 150 mg ($n = 91$) or once-daily efavirenz 600 mg ($n = 89$). Patients

and investigators were blinded to the RPV dosage, whereas the open design was used for efavirenz. Background regimens for this study were zidovudine/lamivudine or TDF/FTC.²³ In the Phase II study, RPV reduced plasma HIV-RNA levels over the short term more than placebo.¹⁵ Patients with an HIV-RNA level of > 5000 copies/mL and a CD4 cell count of 75–500 cells/mL ($n = 47$) were randomized 3:1 to receive an oral solution of RPV (25, 75, or 150 mg) or placebo once daily as monotherapy for 7 days before commencement of standard antiretroviral therapy. There was a significantly greater reduction in HIV-RNA levels with all RPV dosages (median $-1.199 \log_{10}$ copies/mL in RPV groups combined) compared to placebo ($+0.002 \log_{10}$ copies/mL) ($P < 0.01$).¹⁵

ECHO and THRIVE were independent, randomized, double-blind, double-dummy, multinational trials of almost identical design.^{24,25} Included patients underwent a 6-week screening period, after which they were randomized to 96 weeks of treatment with RPV 25 mg once daily or efavirenz 600 mg once daily, plus a fixed-dose background regimen.^{24,25} In the ECHO trial, the backbone was an FDC of TDF/FTC, while backbones in the THRIVE study were, at the physician's discretion, TDF/FTC, zidovudine/lamivudine, and abacavir/lamivudine. Randomization was stratified by HIV-RNA level at screening ($\leq 100,000$, $100,000$ – $500,000$, or $\geq 500,000$ copies/mL)^{24,25} and, in the THRIVE trial, by backbone regimen as well.²⁵ The primary analysis in both trials was a logistic regression analysis (adjusted for stratification factors) that predicted response rates at 48 weeks based on an intent-to-treat time-to-loss-of-virological-response (ITT-TLOVR) algorithm.^{24,25} Noninferiority of RPV to efavirenz was established if the lower limit of the two-sided 95% confidence interval (CI) for the difference in response rates was within a 12% margin. Patients who never achieved an HIV-RNA level of < 50 copies/mL, had a level of ≥ 50 copies/mL at two consecutive assessments, or discontinued treatment prematurely were classified as nonresponders.^{24,25} At 48 weeks, $\geq 83\%$ of RPV and efavirenz recipients in both trials achieved the goal of an HIV-RNA level of < 50 copies/mL (Figure 1A).^{24,25} In the primary analyses, the predicted response rates in the RPV group met the noninferiority criterion versus efavirenz. There were no significant between-group difference in response rates in either trial.

In both trials, there was a virological response to treatment with RPV or efavirenz within 2–4 weeks from baseline and this increased steadily during the first 6 months of treatment, with no apparent between-treatment difference in the timing

Figure 1 Efficacy of oral rilpivirine as a component of combination therapy in antiretroviral-naïve patients with HIV infection.

Notes: Response rates (**A**) in the full modified intent-to-treat populations (primary end point) and (**B**) in descriptive subgroup analyses according to baseline HIV-RNA level. Results are from the randomized, double-blind, double-dummy, multinational ECHO ($n = 690$)²⁴ and THRIVE ($n = 678$)²⁵ trials, which compared rilpivirine 25 mg once daily with efavirenz 600 mg once daily, plus background regimens. For the primary analysis, the noninferiority margin (rilpivirine vs efavirenz) for the lower bound of the 95% CI was −12%. In the ECHO and THRIVE trials, 344 and 354, 265 and 254, and 81 and 70 patients, respectively, had baseline HIV-RNA levels of $\leq 100,000$, 100,000–500,000, and $>500,000$ copies/mL.

Abbreviations: BR, background regimen; BVL, baseline viral load; CI, confidence interval; EFV, efavirenz; RPV, rilpivirine; RNA, ribonucleic acid.

of response.^{24,25} Response rates were $>80\%$ by 24 weeks in all treatment groups.^{24,25} Similar results were obtained when the analyses were performed on the per-protocol populations.^{24,25}

In descriptive subgroup analyses, response rates in RPV recipients were higher in those with a lower baseline HIV-RNA level ($\leq 100,000$ copies/mL) than in those with higher viral loads (Figure 1B).^{24,25}

The proportion of virological failures (VFs) in Phase III trials was higher among patients treated with RPV (10%) compared with those who received efavirenz (6%).^{24–26}

A subanalysis based on baseline viral load demonstrated that the proportion of VFs was the same for RPV and efavirenz (5%) recipients with baseline HIV-RNA $\leq 100,000$ copies/mL, but was higher in RPV (17%) compared to efavirenz (7%) among those patients with a baseline HIV-RNA $>100,000$ copies/mL.

Among patients with VF who had evaluable post-baseline resistance data at week 48, 63% (39 of 62) and 54% (15 of 28) in the RPV and efavirenz groups, respectively, had treatment-emergent NNRTI resistance-associated mutations (RAMs). NRTI RAMs occurred at a significantly ($P = 0.003$; post hoc analysis) higher rate in RPV 68% (42 of 62) than efavirenz 32% (9 of 28) recipients.

In RPV recipients with $\leq 100,000$ HIV-RNA copies/mL at baseline, eight of 16 (50%) patients had any NNRTI and/or NRTI RAM, compared with 36 of 46 (78%) patients with $>100,000$ HIV-RNA copies/mL at baseline.²⁶ Specific NNRTI and NRTI RAMs occurring in ≥ 2 patients with VF at week 48 are shown in Figure 2.

Although the resistance profile for RPV has not been completely defined, the presence of a single NNRTI RAM seems to only marginally affect susceptibility to the drug. By far, E138 K was the most frequently selected (45%) mutation in antiretroviral-naïve patients that failed on RPV therapy in the ECHO²⁴ and THRIVE²⁵ studies. Interestingly, this substitution was generally associated with M184I mutation (34%), which confers lamivudine and FTC resistance.²⁶ The combination E138K/M184I confers a 6.7-fold reduced phenotypic susceptibility to RPV compared with a 2.8-fold reduction for E138K alone. Mutation K103N, which is associated with clinical resistance to efavirenz and nevirapine, does not reduce susceptibility to RPV.

Drug-resistance interpretation systems (ie, Stanford [<http://hivdb.stanford.edu/>], Agence Nationale de Recherches sur le Sida [www.hivfrenchresistance.org] [French National Agency for AIDS Research]) have recently incorporated predictions of virological response to RPV. The Drug Resistance Platform of the Spanish AIDS Research Network has weighted NNRTI RAMs²⁷ so that, for considering resistance to RPV, at least two mutations must be present. Mutations with the greatest impact on RPV susceptibility are at four codons K101E/P/T, E138A/G/K/R, Y181C/I/V, and M230 L. Changes in the other nine positions display a lower impact (V90I, L100I, V106A/I, V108I, V179F/I/L, Y188I, G190E, H221Y, and F227C/L). However, in the presence of M184I, the selection of either E138K or K101E is sufficient to induce high-level RPV resistance.

Figure 2 Resistance-associated mutations occurring in ≥ 2 patients at time of virological failure with (A) once-daily oral rilpivirine 25 mg plus a background regimen or (B) efavirenz 600 mg plus a background regimen.

Notes: Data are from a pooled analysis²⁶ of the Phase III ECHO²⁴ and THRIVE²⁵ trials. Patients with evaluable post-baseline resistance data at 48 weeks were included and the data are presented according to baseline HIV viral load.

Abbreviations: NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside/nucleotide-reverse transcriptase inhibitor; RNA, ribonucleic acid.

Overall, the change in sensitivity to RPV ranges from 3.7- to 554-fold in the presence of a combination of two or three RAMs.¹⁰

VFs with RPV compared to efavirenz (EFV) were more likely to show cross-resistance with all NNRTIs.¹⁰ After VF with RPV, 89% of patients were resistant to etravirine and efavirenz and 63% were resistant to nevirapine, whereas none of the efavirenz recipients with VF were cross-resistant to etravirine.¹⁰

Response rates were higher in patients who were more adherent to RPV- or efavirenz-based regimens (86%–90% in those with $>95\%$ adherence versus 62%–73% in those with $\leq 95\%$ adherence).^{24,25}

RPV was associated with a positive immunological response. In both ECHO and THRIVE trials, the CD4 cell count steadily increased over time. At 48 weeks, the CD4 mean increment in RPV recipients was 190 cells/mcL (ECHO) and 189 cells/mcL (THRIVE), while in efavirenz-treated patients, the same values were 180 cells/mcL and 171 cells/mcL, respectively.

In generalized additive modeling, adherence to treatment, systemic exposure to the NNRTI, and lower baseline viral load were the most important predictors of virological response (persistence of an HIV-RNA level of <50 copies/mL) to both RPV and efavirenz at 48 weeks.²⁸ In descending order of importance, the prognostic variables in the final RPV model were: adherence; plasma RPV C_{trough} ; baseline viral load; baseline fold change in viral load with RPV; baseline CD4 cell count; undetectable plasma level of RPV at any time point (a proxy of poor adherence); and trial (ECHO or THRIVE). For efavirenz, in descending order of importance, the variables in the final model were: undetectable plasma level of efavirenz at any time point; adherence; baseline viral load; plasma efavirenz C_{trough} ; baseline fold change in viral load with efavirenz; and background regimen.²⁸

The results of a post hoc pooled analysis of the ECHO and THRIVE trials restricted to the subset of patients receiving RPV or efavirenz plus FTC/TDF showed that RPV plus FTC/TDF was noninferior to efavirenz plus FTC/TDF at both 48 and 96 weeks.²⁹ ITT-TLOVR response rates were high, both at 48 weeks (83.5% vs 82.4%) and at 96 weeks (77% in both groups). Response rates in RPV/FTC/TDF recipients were higher in those with a lower baseline HIV-RNA level ($\leq 100,000$ copies/mL) than in those with higher viral loads at 48 and 96 weeks (Figure 3).^{30,31}

Rationale for combination of the individual components in RPV/FTC/TDF

The single-tablet formulation of RPV, FTC, and TDF (Complera™/Eviplera™; Gilead, Foster City, CA, USA) was developed on the grounds that, compared with multiple-tablet regimens, single-tablet regimen (STRs) are preferred by patients and are likely to be associated with increased adherence. RPV/FTC/TDF comprises FTC 200 mg, TDF 300 mg, and RPV 25 mg, and has met bioequivalence criteria, being the geometric least squares mean plasma C_{max} , AUC from time 0 to infinity, and AUC time 0 to the last dose for each of the constituent drugs of the combined tablet, within an 80–125 percentage margin of the 90% CI compared to

Figure 3 Virological response in antiretroviral-naïve patients with HIV infection receiving oral rilpivirine plus emtricitabine/tenofovir.

Notes: Proportion of patients with confirmed HIV-RNA levels <50 copies/mL at 48 weeks (intent-to-treat time-to-loss-of-virological-response analysis) and 96 weeks (intent-to-treat snapshot analysis) in all patients stratified according to baseline HIV-RNA levels. Results are shown for patients receiving rilpivirine plus emtricitabine/tenofovir ($n = 550$) or efavirenz plus emtricitabine/tenofovir ($n = 546$) in pooled subset analyses²⁹ of the ECHO²⁴ and THRIVE²⁵ trials.

Abbreviations: BVL, baseline viral load; EFV, efavirenz; FTC/TDF, emtricitabine/tenofovir; pts, patients; RPV, rilpivirine; RNA, ribonucleic acid.

the same parameters calculated for the separate formulations of each drug.³²

The STR RPV/FTC/TDF has been studied in clinical trials, both in naïve patients starting their first HAART and as a simplification regimen for chronically treated subjects.

The Single-Tablet Regimen study (STaR) is the first study comparing the efficacy, safety, and tolerability of the two STRs so far marketed in Europe: RPV/FTC/TDF and EFV/FTC/TDF. It is a multicenter, international, randomized, open-label, Phase IIIb, 96-week study, the primary endpoint of which is virological efficacy as defined by the proportion of patients with HIV-RNA <50 copies/mL at week 48. The study aims to demonstrate noninferiority of RPV/FTC/TDF compared to EFV/FTC/TDF with a noninferiority margin of 12%. The snapshot analysis of 48-week results demonstrated noninferiority for the overall population. Patients treated with STR RPV/FTC/TDF presented virologic suppression in 86% of cases and virologic failure in 8% and were categorized as missing data in 6%, the same figures for patients treated with EFV/FTC/TDF were 86%, 6%, and 13%, respectively. A subanalysis performed according to the baseline HIV-RNA value demonstrated that the RPV/FTC/

TDF STR was superior to EFV/FTC/TDF in subjects with a baseline HIV-RNA $\leq 100,000$ copies/mL (virologic response 89% vs 82%) and noninferior in subjects with higher HIV-RNA (100,000–500,000 copies/mL: 83% vs 82%; $\geq 500,000$ copies/mL: 72% vs 80%). The proportions of VFs were very low in patients with HIV-RNA $\leq 100,000$ copies/mL (5% vs 3%) and HIV-RNA 100,000–500,000 copies/mL (10% vs 9%), but rose in those subjects with higher HIV-RNA levels (HIV-RNA $\geq 500,000$ copies/mL: 25% vs 16%).³³

The STaR study, in contrast to the previous ECHO and THRIVE studies, seems to indicate that the risk of VF with the combination of RPV/FTC/TDF rises when the baseline HIV-RNA is very high ($>500,000$) and, therefore, the currently approved use (patients with HIV-RNA $\leq 100,000$) can be considered safe. On the other hand, the same study indicates that, for lower HIV-RNA values, the STR combination of RPV/FTC/TDF may be superior to EFV/FTC/TDF. One of the driving forces of this result is certainly the elevated tolerability of the new drug combination, but the use of the STR itself may have played a relevant role by enhancing patients' adherence. Although RPV has so far been approved only as first-line treatment for antiretroviral therapy-naïve patients, the drug is currently being considered in other clinical scenarios, such as switch and simplification strategies.

The SPIRIT (Switching boosted PI to Rilpivirine in combination with Truvada as an STR) study³⁴ is a multicenter, international, randomized, open-label, Phase IIIb, 48-week study aiming to demonstrate the noninferiority of a RPV/FTC/TDF switch compared to a continuing PI/r + 2 NRTIs therapy. According to a 24-week snapshot analysis, switching to RPV/FTC/TDF was noninferior to remaining on PI/r + 2 NRTI (93.7% vs 89.9%); moreover, at the same time point, lower rates of VF were observed in subjects switching to RPV/FTC/TDF (0.9%) compared to those remaining on PI/r + 2 NRTI (5.0%).³⁴

The possibility of switching to RPV/FTC/TDF (STR) from EFV/FTC/TDF (STR) has been explored by the GS-264-111 study.³⁵ The virological results of the trial showed that the transient efavirenz inductive effects on RPV metabolism do not appear to be clinically relevant in suppressed patients. Overall, virological suppression was maintained in 100% of cases, analyzed after 24 weeks. RPV mean C_{trough} was within historic range in 2 weeks.³⁵

Altogether, the switch studies indicate that the RPV/FTC/TDF STR is a favorable choice also in a planned simplification strategy. Its use in this indication is not yet approved, but, on the basis of the results of these studies, an

application to regulatory agencies (eg, US Food and Drug Association, European Medicines Agency) has been filed and the approval of the new indication is expected by the mid-2013.

Safety and tolerability

General

In the ECHO and THRIVE trials, the RPV-based treatment regimen was generally well tolerated, with a more favorable profile with respect to psychiatric, neurological, and metabolic adverse events (AEs) compared to the efavirenz-based regimen.^{24,25} In the pooled analysis, conducted after a median treatment duration of 55.7 and 55.6 weeks in the RPV and efavirenz groups, 2% and 4% of patients, respectively, discontinued treatment because of AEs.¹⁰

The most common AEs leading to discontinuation were any rash (0.1% of RPV vs 1.8% of efavirenz patients) and depression (0.3% vs 0.6% of patients, respectively). Pregnancy led to discontinuation in 0.4% of patients in each group.³⁶

The incidence of any rash at least possibly related to treatment was significantly lower in the RPV group than in the efavirenz group. The incidence of rash was higher in the first 4 weeks of treatment. The majority of rashes were of severity grade 1 or 2 and there were no grade 4 rashes.³⁶

RPV recipients were also less likely to have psychiatric AEs (24% vs 29%; $P = 0.03$) and treatment-related psychiatric AEs (15% vs 23%; $P = 0.006$). The between-group differences in neurological and psychiatric AEs were chiefly due to the higher proportion of efavirenz recipients reporting dizziness or abnormal dreams and nightmares. Grades 3 or 4 neurological and psychiatric AEs were infrequent ($\leq 1\%$ of patients in any group).³⁷

AEs of severity grade 2–4 occurring at 48 weeks in $\geq 2\%$ of patients in at least one treatment group in the ECHO and THRIVE trials are shown in Figure 4. The most frequent grade 2–4 AEs were depressive disorders, headache, rash, and insomnia in RPV recipients, and rash, dizziness, abnormal dreams, depressive disorders, headache, insomnia, and nausea in efavirenz recipients.¹⁰ Occurrence of treatment-related grade 2–4 AEs was time dependent. Analyzing the first 12 weeks of treatment, the incidence of these AEs was 9.6% and 22.3% (weeks 0–4), 1.6% and 3.4% (weeks 5–8) and 1.2% and 2.5% (weeks 9–12) in RPV and efavirenz recipients, respectively.³⁸

In the ECHO and THRIVE trials, there were five deaths, one in the RPV group (grade 3 bronchopneumonia) and four in the efavirenz group (grade 3 Burkitt's lymphoma,

Figure 4 Tolerability of oral rilpivirine as a component of combination therapy in antiretroviral-naïve patients with HIV infection.

Notes: Pooled descriptive data¹⁰ from the ECHO²⁴ and THRIVE²⁵ trials, which compared rilpivirine 25 mg once daily with efavirenz 600 mg/day, plus background regimens. Adverse events (grade ≥ 2 level of severity) occurring in $\geq 2\%$ of patients in at least one group during 48 weeks of treatment.

Abbreviations: BR, background regimen; EFV, efavirenz; RPV, rilpivirine.

grade 4 cerebral toxoplasmosis/respiratory failure, grade 4 dysentery, grade 4 cerebrovascular accident), none of which was considered related to treatment.³⁶

In the subgroups with FTC/TDF as a backbone, at 96 weeks the tolerability profile of RPV was more favorable than that of EFV, according to pooled data from the ECHO and THRIVE trials.³⁸ Rates of treatment-related AEs of grade 2–4 severity well known to be associated with NNRTI use occurred in significantly fewer RPV/FTC/TDF recipients than EFV/FTC/TDF recipients, especially in those with HIV-RNA $\leq 100,000$ copies/mL.²⁹

The majority of treatment-related AEs occurred during the first year of treatment.³⁶ For example, treatment-related AEs of grade 2–4 severity occurred in 17% and 33% of RPV/FTC/TDF and EFV/FTC/TDF recipients, respectively, during the first year of treatment, and only in 2.5% and 3.7% of patients, respectively, during the second year of treatment.²⁹

From clinical trial results, it seems unlikely that RPV at therapeutic dosages will increase the QTc interval.³⁹ The actual 25 mg dosage of RPV has been selected because, in the Phase II dose-ranging study,²³ an increment of QTc interval was observed. The increment in QTc interval corrected according to Fridericia's formula (QTcF) was gradual up to week 48, was slightly more pronounced with either efavirenz or RPV 75 mg or 150 mg than with RPV 25 mg, and stabilized

in all groups from week 48 up to week 96. The alteration was seen in patients receiving lamivudine/zidovudine but not in those treated with FTC/TDF.²³ In a confirmatory thorough QT study in HIV-negative volunteers, compared with placebo, the upper limit of the 90% CI for time-matched differences in QTcF was <10 milliseconds at all time points for the RPV 25 mg once daily and efavirenz 600 mg/day groups, whereas this limit was exceeded for the active control, moxifloxacin 400 mg/day.³⁹ The QTc interval of the electrocardiogram, corrected using QTcF interval increased over time in both groups; mean (95% CI) increases were +11 (10–13) milliseconds and 13 (12–14) milliseconds, respectively. There were no QTcF intervals >500 milliseconds.³⁶

Laboratory abnormalities

In the ECHO trial, there was no significant change from baseline to 48 weeks in serum calcifediol (hydroxylated vitamin D [25(OH)D]) levels in RPV recipients, whereas 25(OH)D levels were significantly ($P < 0.0001$) lower in efavirenz recipients.⁴⁰ In the RPV group, severe 25(OH)D deficiency (serum 25[OH]D level of <25 nmol/L) was observed in 4.8% of patients at baseline and 4.5% at 48 weeks compared to 5.2% and 9.0% of efavirenz recipients ($P = 0.032$).⁴⁰

There was a small decrease from baseline to week 48 in basal cortisol of 13.1 nmol/L for RPV and a small increase of 9.0 nmol/L for efavirenz. The proportions of patients with at least two consecutive (treatment-emergent) abnormal cortisol responses to an adrenocorticotrophic hormone test (≤ 500 nmol/L) during the trial were 1.7% (11 of 643) in the RPV group and 0% in the efavirenz group. No patient had signs or symptoms of adrenal insufficiency or discontinued the study secondary to abnormal adrenocorticotrophic hormone test results. There were no clinically relevant changes from baseline to week 48 in androstenedione, dehydroepiandrosterone sulfate, luteinizing hormone, total testosterone, or progesterone.³⁶

Serum creatinine was elevated in 1% and 2% of RPV and efavirenz recipients.¹⁰ In both ECHO and THRIVE trials, RPV recipients showed an initial increase in mean serum creatinine levels (4–9 mmol/L) that thereafter remained stable up to 48 weeks. Mean values remained close to baseline in efavirenz recipients.^{24,25} There were no clinically significant changes in the glomerular filtration rate measured using the serum creatinine (ECHO and THRIVE) or the Hoek formula based on serum cystatin C concentrations (THRIVE). There were also no renal-related AEs or renal-related discontinuations in either treatment group.^{24,25}

RPV was associated with significantly smaller mean changes from baseline in aspartate aminotransferase, alanine aminotransferase, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels than efavirenz (Figure 5). Both mean LDL cholesterol and triglyceride levels did not increase above baseline values with RPV, but did with efavirenz. There was no between-group statistical difference in the change from baseline to week 48 of the total/HDL cholesterol ratio.³⁶

Grade 3–4 severity lipid abnormality rates (week 48) were significantly ($P = 0.001$) lower in RPV-treated patients compared to efavirenz recipients (total cholesterol: 0.1% vs 3%; LDL cholesterol: 1% vs 4%; triglycerides: 0.3% vs 2%). These differences in lipid abnormalities were independent of background treatment regimens.⁴¹ There was no significant between-group difference in the Framingham Coronary Heart Disease relative risk score.⁴¹ Similarly, in the 96-week descriptive analysis, in the RPV and efavirenz groups, serum lipid abnormalities of grade 3–4 severity occurred in 0.1% and 3.2% of patients (total cholesterol), 1.5% and 5.1% of patients (LDL cholesterol), and 0.6% and 3.2% of patients (triglycerides), respectively.⁴²

Figure 5 Laboratory abnormalities and changes in blood lipids associated with oral rilpivirine as a component of combination therapy in antiretroviral-naïve patients with HIV infection.

Notes: Pooled descriptive data¹⁰ from the ECHO²⁴ and THRIVE trials²⁵ are for severity-level grades 2–4 laboratory abnormalities or changes in blood lipids occurring in $\geq 2\%$ of patients in at least one group after 48 weeks of treatment. Values shown as <1 at a particular grade level of severity in the original reference were rounded up to 1 when summing to obtain totals for grade 2–4 levels.

Abbreviations: BR, background regimen; EFV, efavirenz; LDL, low-density lipoprotein; RPV, rilpivirine; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Focusing on the RPV/FTV/TDF and EFV/FTC/TDF subgroups, at 96 weeks the proportion of patients with treatment-related laboratory abnormalities was significantly ($P < 0.001$) lower for RPV than for EFV, with regard to both grade 2–4 (50% vs 60%) and grade 3–4 (13% vs 21%).³⁶ The most commonly observed abnormalities were hypophosphatemia (14% of RPV/FTC/TDF recipients vs 15% of EFV/FTC/TDF recipients), increased pancreatic amylase (9% vs 10%), and hyperglycemia (8% vs 6%).²⁹ Grade 2–4 lipid abnormalities were also significantly less common with RPV/FTC/TDF than with EFV/FTC/TDF ($P < 0.002$ for each individual grade of total cholesterol and LDL cholesterol abnormality). The proportion of patients who received lipid-lowering therapy was significantly lower in the first group than in the second (3% vs 6%; $P = 0.025$).²⁹

In confirmation of these results, in the SPIRIT study, patients switching to RPV/FTC/TDF had significantly ($P < 0.001$) greater improvements from baseline in serum total cholesterol, LDL cholesterol and triglyceride levels than patients who continued treatment with PI/r regimen.³⁴

Patient perspective

When selecting a first-line antiretroviral therapy regimen, the potential for development of resistance and cross-resistance is an important factor to consider, along with sustained efficacy, favorable tolerability, and convenience.¹

Parianti et al investigated treatment adherence with once-daily regimens, assessing eleven randomized, controlled trials with a total of 3029 subjects.⁴³ In this meta-analysis, adherence rates were modestly better with once-daily regimens (+2.9%; 95% CI: 1.0%–4.8%; $P = 0.003$) than with twice-daily regimens. The effect size was more pronounced for HAART-naïve patients and when all medications were taken once daily. Of note, 48-week virologic suppression with once- and twice-daily regimens was similar (77% vs 76%, respectively). More recent studies comparing once-daily regimens to more frequently dosed regimens continue to support the positive impact of once-daily regimens on HAART adherence.⁴⁴

Pill burden is another important factor affecting adherence. The ADONE (Adherence to ONE pill) study verified the effect of a reduced number of pills on adherence and quality of life; patients did not change their therapy in terms of active molecules or doses of the same molecules, but simply reduced the daily number of pills in their regimen from three or two to one. This approach was made possible by the use of an FDC pill combining all the drugs previously taken by the patients as separated entities (FTC

lamivudine, TDF, efavirenz). One month post-switch to STR, the adherence rate increased significantly to 96.1% from a baseline value of 93.8% ($P < 0.01$); the increase was steadily maintained throughout the study (96.2% at 6 months). Quality of life also improved over time, from 68.8% to 72.7% ($P = 0.042$), and was significantly associated with the perception of health status, presence of AEs, and number of reported AEs. Quality of life significantly influenced adherence ($P < 0.0001$).⁴⁵

Dosing frequency and pill burden have also been identified as important treatment characteristics for treatment persistence.⁴⁶ Distinct from but related to medication adherence, persistence reflects the duration of time from initiation to discontinuation of therapy, and can be measured at the regimen or patient level. In developed countries, improved regimen persistence, or durability, has been observed with regimens dosed once daily and containing fewer pills.⁴⁷ In the ECHO and THRIVE trials,^{24,25} adherence to treatment was one of the most important factors associated with virological response. In the pooled analysis in patients with baseline HIV-RNA levels $\leq 100,000$ copies/mL at 48 weeks, response rates were $\approx 20\%$ higher in patients with $>95\%$ adherence than in those with $\leq 95\%$ adherence in both the RPV/FTC/TDF and EFV/FTC/TDF groups;³⁰ similar results were derived from pooled 96-week data.²⁹ The RPV/FTC/TDF STR, as well as having a convenient once-daily administration schedule as a single tablet, is well tolerated, which may also improve adherence and patients' quality of life.

Health care system perspective

The RPV/FTC/TDF STR has not yet been thoroughly evaluated in terms of cost-effectiveness; however, the price of the STR in Europe makes it one of the cheapest treatment options for naïve patients. As an example from the Italian market, starting a patient on the RPV/FTC/TDF STR compared to the use of the same NNRTI backbone plus any boosted protease inhibitor ensures a monthly saving of about €150. More generally, recent studies have shown that the HAART regimens based on only one tablet a day (STR) are associated with significantly better adherence and a lower hospitalization risk in comparison to the administration of three or more tablets a day.⁹ In this regard, STRs present potential benefits for patients and, in the end, for the health care system.⁴⁸

According to Markov models, the economic value of the improved response by patients to the STR has been quantified in terms of quality of life and in terms of cost per gained quality-adjusted life year. Owing to the better quality of life

perceived by patients, the incremental cost-effectiveness ratio is more favorable and often dominating when STRs are used compared to more complex, although highly active, regimens.^{44,49–51}

Place in therapy

Although clinical trials of the STR are lacking, RPV/FTC/TDF was an effective and generally well-tolerated regimen in two clinical trials^{24,25} in treatment-naïve patients with HIV infection.⁵²

Generally speaking, within the approved indications,¹ RPV/FTC/TDF STR may prove an advantageous choice for first-line therapy in HIV-positive patients. Certain patient populations, in particular, could benefit from this regimen, including:

- Women of child-bearing potential. There are no clinically significant drug interactions between RPV/FTC/TDF and oral contraceptives. Moreover, RPV has a US Food and Drug Administration use-in-pregnancy rating of category B (no evidence of harm to the fetus in animal studies, but no adequate and well-controlled studies in pregnant women).¹⁰
- Patients with an increased risk of central nervous system events in which other specific drugs (eg, efavirenz) may be contraindicated.
- Patients with high cardiovascular risk, as the RPV/FTC/TDF combination has shown an excellent lipid profile.
- Patients on methadone substitutive therapy, because there is no need to adjust the dosage of methadone, as there are no clinically significant drug interactions.
- Patients with mild or moderate hepatic impairment, because there is no need of dosage adjustment, although caution is required in patients with moderate hepatic impairment.

Conclusion

The once-daily STR of FTC, TDF, and RPV (Complera™/Eviplera™) provides a convenient option for antiretroviral therapy-naïve patients with HIV infection.

Disclosure

FM has served as a consultant on advisory boards for Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck Sharp and Dome, Roche, Tibotec; has received lecture fees from Abbott, Bayer, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck Sharp and Dome, Pfizer, and Roche; and has received research and educational grants from Boehringer Ingelheim,

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