Combination therapies, effectiveness, and adherence in patients with HIV infection: clinical utility of a single tablet of emtricitabine, rilpivirine, and tenofovir

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Abstract: A recent addition to the anti-human immunodeficiency virus armamentarium of drugs is rilpivirine, which is a potent non-nucleoside reverse transcriptase inhibitor. This review focuses on the clinical utility of rilpivirine in terms of efficacy and virologic suppression, drug resistance, drug-drug interactions, and safety. The rilpivirine-tenofovir-emtricitabine combination is a safe and effective regimen for use in most patients who are ready to start first-line anti-human immunodeficiency virus therapy. Although drug resistance can be a problem in patients who initiate therapy on rilpivirine-based regimens with viral loads > 100,000 copies of viral RNA/mL, this problem can be alleviated by first starting therapy with efavirenz-tenofovir-emtricitabine for several months to suppress viral load to <50 copies/mL before switching to rilpivirine-based therapy. E138K is the most important mutation associated with resistance against rilpivirine and its development must be avoided whenever possible, because this mutation confers broad cross-resistance against all approved members of the non-nucleoside reverse transcriptase inhibitor family of drugs.

Keywords: non-nucleoside reverse transcriptase inhibitors, rilpivirine, human immunodeficiency virus, treatment, resistance

Introduction

Nevirapine and efavirenz were the first non-nucleoside reverse transcriptase inhibitors (non-NRTIs) to be approved for therapy and are able to bind to a hydrophobic pocket of human immunodeficiency virus (HIV)-1 close to the catalytic site of the enzyme.[1] However, these two agents have a low barrier to the development of resistance, because a single mutation within this pocket (eg, K103N) can render both drugs ineffective. This cross-resistance resulted in efforts to circumvent the loss of non-NRTI activity, leading to the development of two new non-NRTI agents (rilpivirine and etravirine), both of which are now approved by numerous regulatory agencies. Rilpivirine is also the latest non-NRTI to be approved for use in combination antiretroviral therapy for HIV-infected patients previously untreated by other antiretroviral drugs and is available as part of a single tablet in which it is coformulated with two nucleoside antagonists of HIV-1 reverse transcriptase, ie, tenofovir and emtricitabine. The approval of rilpivirine was granted on the basis of two Phase III triple combination studies, known as ECHO and THRIVE, in which rilpivirine was studied in combination with two nucleoside drugs (most commonly tenofovir and emtricitabine), in comparison with the use of a different non-NRTI, ie, efavirenz, to suppress viral load in antiretroviral-naïve individuals.[2]

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Antiviral activity

Tissue culture studies have shown that rilpivirine is currently the most potent anti-HIV non-NRTI available and possesses an EC_{50} of 0.73 nM compared with 1.73 nM for efavirenz and 2.73 nM for etravirine.[3] It is possible that the unique molecular structure of rilpivirine permits better binding to HIV-1 reverse transcriptase than other non-NRTIs.

Several large multicenter Phase III trials were performed to determine whether rilpivirine would be noninferior to efavirenz in HIV-infected adults enrolled into these studies, ie, ECHO and THRIVE, with viral loads $\geq$ 5000 copies of viral RNA per mL of plasma. Noninferiority was defined as a 12% margin in the percentage of subjects with confirmed virologic response, ie, viral load < 50 copies/mL based on an intention-to-treat time to loss of virologic response algorithm. The results of the ECHO trial, in which patients were randomized to receive either rilpivirine 25 mg once daily (n = 346) or efavirenz 600 mg once daily (n = 344), together with tenofovir and emtricitabine,[4] showed that 83% of patients in both arms had a positive response, with a viral load < 50 after 48 weeks (Table 1). Noninferiority was confirmed with a point estimate from logistic regression for a percent response difference of −0.4 (95% confidence interval −5.9 to 5.2, P < 0.0001). However, it was surprising that virologic failures were more common in the rilpivirine group (13% versus 6% and 11% versus 4% by intention-to-treat time to loss of virologic response) than in the efavirenz group.

In contrast, THRIVE was a study in which patients were randomized to receive either rilpivirine 25 mg once daily or efavirenz 600 mg once daily (n = 340 in both groups), together with an investigator-selected regimen of background NRTIs (tenofovir plus emtricitabine, zidovudine plus lamivudine, or abacavir plus lamivudine).[2,5] The study included a greater proportion of women (27%) than is common in most HIV trials. The results showed that 86% of patients who received rilpivirine and 82% of patients who received

efavirenz had a virologic response to below 50 copies/mL (difference 3.5%, 95% confidence interval −1.7 to 8.8, P < 0.0001 for noninferiority) after 48 weeks (Table 1). Increases in CD4 counts were also monitored and mean increases were similar between groups (189 cells/μL versus 171 cells/μL in the rilpivirine versus efavirenz arms, respectively), and virologic failures occurred with similar frequency in both groups (7% for patients receiving rilpivirine, 5% for patients receiving efavirenz, Table 1).

The results of a pooled data analysis from both studies confirmed the results of the individual studies,[5] showing that rilpivirine had a high virologic response rate that was noninferior to efavirenz after 48 weeks.[2–4] Furthermore, virologic response status at predefined time points and intention-to-treat time to loss of virologic response rates were similar between treatment groups (76% and 77% versus 78% and 78%, for the rilpivirine and efavirenz groups, respectively) after 96 weeks.[2–4] Increases in mean CD4 counts were also noted from baseline in both treatment groups, with that in the rilpivirine group being 228 cells/μL versus 219 cells/μL in the efavirenz arm.[5,6] NRTI regimens were balanced between the two arms of the analysis.

Virologic failure rates in the intention-to-treat population, as defined by confirmed rebound at or before week 96, were 12% and 6% in the rilpivirine and efavirenz arms, respectively,[3,4] as determined by time to loss of virologic response. With regard to rebounders, virologic failure rates were 6% and 4%, respectively, and were 5% and 2% in the never suppressed group. Not surprisingly, suboptimal adherence was associated with reduced virologic response in both study arms.[3,4] Although overall response rates were lower among black patients entered into the ECHO and THRIVE trials,[7] this seemed to be mostly related to higher rates of virologic failure and discontinuation among black patients, an unexplained finding that could potentially be the result of pharmacogenetic or sociodemographic factors.[7] At a baseline viral load $\leq$ 100,000, response rates appeared to be higher in the rilpivirine group, whereas the impact of suboptimal adherence and higher baseline viral load was less apparent in the efavirenz arm than in the rilpivirine arm.[2] Food intake can affect rilpivirine absorption, and the role of food in subsequent virologic failure must also be considered.

Clinical usefulness of rilpivirine

Rilpivirine is marketed as Edurant™ and has now been approved in the US and the European Union for the treatment of drug-naïve HIV-1-infected individuals. It is available as single pill fixed-dose formulation with tenofovir and emtricitabine

Table I Summary data from the ECHO and THRIVE Phase III studies

	THRIVE		ECHO		Combined information	
	EFV	**RPV**	**EFV**	**RPV**	**EFV**	**RPV**
Number of patients	340	340	344	346	682	686
Virologic failures (%)	5	7	6	13	9	13
Virologic response (48 weeks) (%)	82	86	83	83	82	84
CD4 count increase (48 weeks)	263	263	257	240		

Abbreviations: EFV, efavirenz; RPV, rilpivirine.

(marketed as Complera™ in the US and Eplivera™ in the European Union). Guidelines of the US Department of Health and Human Services now include rilpivirine as an agent to be considered in combination antiretroviral regimens for treatment-naïve subjects. Despite the fact that rilpivirine has been approved for use in first-line therapy, very little information is available on the potential for switching other non-NRTIs to rilpivirine after treatment initiation, and such strategies may be reasonable in situations in which drug intolerance and/or toxicities have occurred. In one study, 49 patients were switched from efavirenz to rilpivirine after having first been suppressed to <50 copies/mL for at least 8 weeks while remaining on the combination of emtricitabine and tenofovir.[8] The results showed that patients continued to have virologic suppression after 12 weeks on rilpivirine-emtricitabine-tenofovir, despite the fact that rilpivirine levels in the first week were lower than expected from the Phase III trials, possibly because of residual efavirenz-induced cytochrome P450 (CYP)3A activity. Similar pharmacological findings had previously been obtained in a small pilot study of 20 subjects who switched from efavirenz monotherapy to rilpivirine.[9]

In combination therapy, rilpivirine has only been studied in the ECHO and THRIVE studies together with tenofovir-emtricitabine, abacavir-lamivudine, and zidovudine-lamivudine. Information is lacking in regard to the use of rilpivirine in combination with protease inhibitors, integrase inhibitors, and other classes of antiretrovirals, and tissue culture data indicate that rilpivirine is unaffected by some of the resistance-associated mutations, including K103N, that markedly impair the activity of efavirenz and nevirapine.[3] Furthermore, patients with virologic failure on rilpivirine in ECHO and THRIVE did not have K103N mutations,[2,4] and this finding is not unexpected because rilpivirine does not select for the K103N mutation in tissue culture. It also follows that rilpivirine should be expected to be useful in patients who possess K103N at baseline due to transmitted resistance. Despite this, clinical data have not yet been published on the use of rilpivirine in patients with evidence of transmitted or acquired resistance to NRTIs and non-NRTIs, so rilpivirine is not recommended in such settings. In contrast, other mutations such as Y181C that diminish sensitivity to efavirenz and nevirapine can also cause cross-resistance to rilpivirine.

In addition, only limited data exist with regard to use of rilpivirine in coinfections with HIV. Even though a small number of patients enrolled in ECHO and THRIVE had active hepatitis B virus or hepatitis C virus (HCV) infection, no studies specifically addressed safety issues and response

rates in these individuals, although patients coinfected with HIV-1 and hepatitis B and/or C viruses and receiving rilpivirine or efavirenz had a higher incidence of hepatic enzyme elevation than patients who were not coinfected.[2,10] The pharmacokinetic exposure of rilpivirine in coinfected patients was similar to that in patients infected only by HIV-1, but new HCV therapies may complicate use of rilpivirine in this population (see later under drug-drug interactions and pharmacokinetics of rilpivirine). Similarly, no information is currently available on the use of rilpivirine in patients with tuberculosis, but interactions with rifamycins are likely to preclude the use of rilpivirine in patients coinfected with HIV and tuberculosis.

Use of rilpivirine in the clinic

C204 was an international, multicenter, dose-ranging study that randomized 368 treatment-naïve adults with viral loads > 5000 copies/mL to receive one of three once-daily doses of rilpivirine (25, 75, or 150 mg) or efavirenz 600 mg.[11] One of two NRTI regimens was used based on investigator preference as the antiretroviral backbone, ie, fixed-dose combination tenofovir-emtricitabine or zidovudine-lamivudine. Fixed-dose combination adjustments and substitutions for NRTIs for reasons of tolerability were allowed. The results showed that all of the doses of rilpivirine employed were efficacious and that the antiviral effect was maintained over 96 weeks. No dose-response relationship was observed for rilpivirine after 48 weeks and the proportion of rilpivirine-treated patients who responded with viral loads < 50 copies/mL was similar to that in efavirenz recipients (76.9%–80.0% versus 80.9%) after 48 weeks, with similar findings also being obtained after 96 weeks (71.4%–76.3% versus 70.8%). Median CD4 counts in the rilpivirine-treated group increased from about 110 cells/μL to about 145 cells/μL after 48 weeks versus an increase after 96 weeks from about 120 cells/mL to 170 cells/mL in the efavirenz-treated group, and the proportion of patients with viral loads < 400 copies/mL and a $\log_{10}$ reduction in viral load from baseline were also similar between both arms.

Furthermore, the relationship between virologic response and either baseline viral load or background NRTI regimen after both 48 and 96 weeks was not statistically significant ($P = 0.060$). Although the reasons for this include the fact that small numbers of patients were studied at each dose and only 32 patients possessed viral loads > 100,000 at baseline, all patients were switched after 96 weeks to open-label rilpivirine, ie, 75 mg once daily plus two NRTIs for weeks 96–144, and then 25 mg plus two NRTIs until week 240.[12]

Virologic response rates after 192 weeks had declined to 59% in the rilpivirine group versus 61% in individuals who had started on efavirenz, presumably due to discontinuations for reasons other than virologic failure, and mean CD4 counts had continued to increase to 210 cells/μL and 225 cells/μL in the rilpivirine and efavirenz groups, respectively, by week 192. A dose of 25 mg once daily was recommended for rilpivirine based on these results.

Resistance to rilpivirine

Rilpivirine has a unique chemical structure, suggesting that it might be less prone to the development of resistance than other non-NRTIs.[13–15] Furthermore, there is hope that rilpivirine might act efficiently against viruses that contain mutations associated with resistance against efavirenz and nevirapine, the older non-NRTIs. However, the fact that rilpivirine is extensively protein-bound (99.7%) could also offset any potential advantage in this regard.

Virologic failure due to resistance was rare in the C204 dose-ranging study[11] referred to above (ie, 6% of rilpivirine-treated patients versus 7% of efavirenz-treated patients), and the proportion of individuals with treatment-emergent non-nucleoside reverse transcriptase inhibitor mutations was similar (ie, 53% and 50% in the rilpivirine and efavirenz arms, respectively) among failures in the two study arms, with E138K and K103N being the most common mutations. The number of virologic failures after 192 weeks remained low, ie, 11% of patients in the rilpivirine group and 9% in the efavirenz arm ($P = 0.7$),[12] and the M184V mutation associated with resistance to lamivudine and emtricitabine was not present in any of the efavirenz patients but was found in 33% of patients in the rilpivirine failure group.

In general, rilpivirine-treated patients also had higher rates of virologic failure than efavirenz-treated patients in the Phase III ECHO and THRIVE trials, ie, 10% versus 6%,[11] and Table 2 shows that the most common mutations among the rilpivirine failures were E138K and M184I. E138K is known to confer resistance against all members of the non-NRTI family of drugs, including etravirine and rilpivirine,[14–16] but the appearance of E138K has not commonly been seen for other non-NRTIs except in tissue culture studies.[14,15] Nonetheless, it does not appear likely that patients who fail a first-line rilpivirine-based regimen with the E138K mutation will be able to benefit from etravirine if the latter drug is included in a second-line regimen. Virologic failure was also less frequent in efavirenz-treated than in the rilpivirine-treated patients (7% versus 17%)[16] in subjects who initiated therapy with high baseline viral load

Table 2 Frequently detected resistance mutations in the Pooled ECHO and THRIVE Phase III trials

	RPV arm	EFV arm
NRTI or N(t) RTI mutations		
Most frequent	M184I	M184V
Less frequent	M184V, K219E, K65R, Y115F, K65N, A62V	M184I, K65R
NNRTI mutations		
Most frequent	E138K	K103N
Less frequent	K101E, H221Y, V90IY181C, V189I, L100I, V179I, E138Q, F227C	V106M, Y188C, K101E, L100I

Abbreviations: RPV, rilpivirine; EFV, efavirenz; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; N(t) RTI, nucleotide reverse transcriptase inhibitor.

(≥100,000 copies/mL). Thus, virologic failure occurred more frequently in the rilpivirine than in the efavirenz arms of the ECHO and THRIVE trials in patients who initiated therapy with high viral loads, suggesting that patients with high plasma viremia who receive rilpivirine would need to be evaluated closely for potential development of resistance.

The basis for the emergence of resistance with rilpivirine seems to be that both the M184V and M184I mutations can impair HIV replicative fitness,[17] with M184I usually arising first, because it derives from a G to A (ATG to ATA) hypermutation. Subsequently, M184V develops because of an independent substitution within the same triplet codon (ATG to GTG), and viruses containing M184V then outcompete those containing M184I because of superior replication fitness.

Seemingly, the E138K mutation can compensate for the fitness deficits of both M184I and M184V, thus restoring the replicative capacity of viruses containing M184I/V together with E138K,[18,19] and the absence of M184V in the ECHO and THRIVE trials seems attributable to the stabilization effect of E138K on viruses containing M184I, thus obviating the need for development of the M184V mutation. These findings also explain the higher levels of treatment failure among rilpivirine-treated patients in the ECHO and THRIVE clinical trials, although other work suggests that viruses containing both the E138K and M184I viruses do not have high replicative fitness.[20] It is possible that use of the 25 mg once-daily dose may also have played a role in the higher rates of virologic failure in the rilpivirine arm of the ECHO and THRIVE trials because, in contrast, the C204 dose-ranging study also employed multiple doses of rilpivirine. Although the use of such higher doses may have been associated with QT interval prolongation, they may also have contributed to a more robust antiviral effect

that limited treatment failure and the development of drug resistance.

Safety of rilpivirine
Adverse events

Although rilpivirine was well tolerated in the Phase II and III clinical trials performed in 965 HIV-1-infected individuals, the most common adverse events for rilpivirine after 12 weeks of therapy in the ECHO and THRIVE studies were nausea, dizziness, abnormal dreams, nightmares, insomnia, and rash.[2–4,11] Nightmares, abnormal dreams, and dizziness were the most common adverse events at weeks 48 and 96, and most of these were only mild to moderate. It is important to note that rilpivirine had a better safety profile than efavirenz in treatment-naive subjects, with fewer grade 2–4 adverse events and discontinuations at weeks 12, 48, and 96.[2,5] Indeed, the incidence of serious adverse events was similar between the rilpivirine and efavirenz arms, with most such events occurring during the first 4 weeks of drug exposure.[5] Furthermore, baseline viral load had no impact on incidence of treatment-related adverse events, but nausea was more common among women than men in the ECHO and THRIVE studies. In contrast, nightmares and abnormal dreams were more frequent in men than women, regardless of whether patients had received rilpivirine or efavirenz.[7]

Abnormalities in metabolism

Efavirenz had a less benign effect on serum lipids than rilpivirine after 48 weeks in treatment-naïve subjects in the THRIVE and ECHO studies.[2] This benefit continued to 96 weeks,[2,5] with grade 3–4 laboratory abnormalities being significantly fewer in the rilpivirine arm (10.9% versus 17.6%, $P \leq 0.001$). Moreover, fewer patients treated with rilpivirine than efavirenz had increases in total cholesterol (0.1% versus 2.5%, $P < 0.0001$), low-density lipoprotein (LDL) cholesterol (0.7% versus 4.1%, $P < 0.0001$), and triglycerides (0.3% versus 2.2%, $P \leq 0.001$), and increased alanine aminotransferase levels were also rarer in the rilpivirine group (1.5% versus 3.4%, $P < 0.05$). Indeed, similar results had been reported in the C204 dose-ranging study, with increases in LDL cholesterol and triglycerides that were significantly higher in the efavirenz group than in the rilpivirine group after 96 weeks.[11] Consistently, a small increase in serum creatinine was also noted in the 49-patient switch study after 4 weeks, similar to results in the ECHO and THRIVE trials, wherein a similar early increase that then stabilized was noted.[2,3,11] Toxicity-related drug discontinuations were not seen in the switch study, suggesting that these effects were not of clinical significance.

QT interval prolongation

During its development, rilpivirine encountered a problem in regard to QT interval prolongation, which is an indicator of risk of ventricular tachycardia. A double-blind Phase I study of HIV-negative volunteers receiving rilpivirine show that the QT interval was corrected by heart rate using the Fridericia formula (QTcF = QT/RR), but no QTcF prolongation was found when rilpivirine was used at 25 mg once daily or when efavirenz is used at 600 mg once daily.

Indeed, in the ECHO study, QTcF increased over time up to week 48 in both the rilpivirine and efavirenz groups, with no relevant differences between the means (10.9 msec versus 12.0 msec),[3] and only three grade 1 adverse events were reported that might have been related to conduction abnormalities or to rate or rhythm disturbances.

Similar results were observed in the THRIVE trial, with an increased QTcF of 12.0 msec for rilpivirine versus 14.1 msec for efavirenz,[8] although in a few patients adverse events were reported (two in the rilpivirine arm and six in the efavirenz arm), that were potentially related to conduction abnormalities or to rate or rhythm disturbances. A single patient in the rilpivirine arm discontinued due to a grade 3 asymptomatic QT prolongation (QTcF increased > 60 msec by week 48), while QTcF intervals increased more in the C204 dose-ranging study in patients who received efavirenz, rilpivirine 75 mg, and rilpivirine 150 mg than in the rilpivirine 25 mg group,[11] with stabilization seen in all groups by week 96. These increases were also mainly observed in patients who received zidovudine-lamivudine but not tenofovir-emtricitabine.

Rash

The incidence of rash in the ECHO trial was lower among rilpivirine recipients than efavirenz recipients (4% versus 15%, $P < 0.0001$),[3] with grade 3 rash reported in one rilpivirine-treated patient and in two efavirenz-treated individuals, and no grade 4 rash was reported. A single rilpivirine-treated patient discontinued due to grade 3 rash compared with three efavirenz discontinuations, and these rashes resolved over time. Similar results were found in the THRIVE study, with no discontinuations because of rash in the rilpivirine group versus five in the efavirenz arm.[4] The same trends were also seen in the C204 dose-ranging study, with rash of any type being more common in the rilpivirine 150 mg and 75 mg groups than in the 25 mg group.[11] A single case of grade 3 rash was observed in a patient treated with 75 mg rilpivirine after 24 weeks on treatment, and this led to treatment discontinuation, but this may also have been caused by use of dapsone in this person.

Miscellaneous safety issues

No teratogenicity due to rilpivirine has been found in rats and rabbits, and, although no human data on exposure to rilpivirine during pregnancy or breastfeeding are available, the drug has been placed into a pregnancy category B by the US Food and Drug Administration, meaning that animal studies have not revealed risk to the fetus.[21,22] The efficacy and safety of rilpivirine have not been studied in patients with severe hepatic impairment, and the clinical experience in patients with mild or moderate hepatic impairment is inadequate to date. Given that rilpivirine metabolism is mediated by the Cytochrome P system, it is not surprising that the area under the concentration versus time curve for rilpivirine was increased by 47% in subjects with mild hepatic impairment and by 8% in subjects with moderate hepatic impairment. Data are not yet available for those with severe hepatic impairment, so caution is recommended in regard to use of rilpivirine in this population.

Further, the safety and efficacy of rilpivirine has not been studied in patients with renal impairment, although modeling data indicate that no clinically significant effect on the pharmacokinetics of rilpivirine should be seen in such individuals. Accordingly, dose adjustments are not required in patients with mild to moderate renal impairment, but caution is recommended in patients with several renal impairment and/or end-stage renal disease who may experience problems with drug absorption, metabolism, and distribution. Furthermore, rilpivirine is unlikely to be removed by hemodialysis or peritoneal dialysis because 99.7% of rilpivirine is plasma protein-bound. Rilpivirine has also not been studied in pediatric populations.

Drug-drug interactions and pharmacokinetics of rilpivirine

Table 3 summarizes some of the drug interactions and pharmacokinetics of rilpivirine that have been described extensively in the scientific literature. Very importantly, the absorption of rilpivirine is affected by food intake and a substantial fat-containing meal has been shown to have the least impact on rilpivirine exposure (8% reduction in area under the concentration versus time curve versus 43% in fasting subjects and 50% in people who ate a high-protein supplement). This is an important observation, because a decreased plasma concentration of rilpivirine could result in loss of virologic suppression, leading to possible development of resistance against rilpivirine, which is metabolized primarily by the CYP system. Accordingly, drugs that induce or inhibit CYP3A may affect the clearance of rilpivirine and coadministration of rilpivirine with drugs that induce CYP3A may result in decreased plasma concentrations of rilpivirine. Coadministration of rilpivirine with drugs that inhibit CYP3A may also result in increased plasma concentrations of rilpivirine.

Substances such as anticonvulsants (phenytoin, phenobarbital, oxcarbazepine, carbamazepine) and antimycobacterials (rifabutin, rifampin, rifapentine) that induce CYP3 enzymes can also cause significant decreases in plasma rilpivirine concentrations, as can St John's wort and dexamethasone. Hence, the use of these agents with rilpivirine is not recommended. In addition, proton pump inhibitors, including such agents as omeprazole, rabeprazole, lansoprazole, esomeprazole, and pantoprazole, significantly decrease rilpivirine plasma concentrations by increasing gastric pH and reducing rilpivirine absorption. Other gastric acid-reducing agents (including antacids and H2 receptor antagonists) can also cause significant decreases in plasma rilpivirine concentrations, and so should be used with appropriate timing of dosing and caution.

Relevant clinical interactions are not expected between rilpivirine and members of the NRTI class (abacavir, emtricitabine, lamivudine, stavudine, and zidovudine), the CCR5

Table 3 Important RPV drug-drug Interactions

Drug	Recommendation	Levels of RPV plasma concentration	Mechanism
Antacids	Caution advised	⇓	Increase gastric pH and reduce absorption
Azole antifungals	Caution advised	⇑	Inhibit CYP3A
HIV protease inhibitors	Caution advised	⇑	Inhibit CYP3A
HCV protease inhibitors	Caution advised	⇑	Inhibit CYP3A
H2-receptor antagonists	Caution advised	⇓	Increase gastric pH and reduce absorption
Anticonvulsants	Contra-indicated	⇓	Induce CYP3A
Proton pump inhibitors	Contra-indicated	⇓	Increase gastric pH and reduce absorption
Dexamethasone	Contra-indicated	⇓	Induces CYP3A
NNRTIs	Contra-indicated	⇓/⇑	Induce/inhibit CYP3A
Rifamycins	Contra-indicated	⇓	Induce CYP3A
Macrolides	Contra-indicated	⇑	Inhibit CYP3A

Abbreviations: RPV, rilpivirin; NNRTIs, non-nucleoside reverse transcriptase inhibitor; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

antagonist, maraviroc, or the integrase strand transfer inhibitor, raltegravir. Furthermore, dose adjustments are not necessary when rilpivirine is administered together with didanosine, but timing related to food is important. In rare instances in which didanosine is used as part of a treatment regimen, it should be administered on an empty stomach at least 2 hours before or at least 4 hours after rilpivirine administration, and the simultaneous use of two non-NRTIs is never appropriate. In addition, rilpivirine concentrations increase with delavirdine administration and decrease when other non-NRTIs (efavirenz, etravirine, nevirapine) are given, and rilpivirine concentrations can also be increased by protease inhibitors, whether boosted or unboosted. Studies on interactions between rilpivirine and darunavir-ritonavir and lopinavir-ritonavir found rilpivirine increases of 2.3–3.8-fold and 1.52-fold, respectively, but no dose adjustments appear to be necessary for other members of the protease inhibitor class.[21,22]

Attention must be paid to concurrent use of either azole antifungal agents (eg, ketoconazole, fluconazole, itraconazole, posaconazole, and voriconazole) with regard to antibiotics and antifungals that inhibit CYP3A, as well as macrolide antibiotics (eg, clarithromycin and erythromycin), because these may also elevate rilpivirine levels. New protease inhibitor agents developed for HCV, such as telaprevir and boceprivir, may also increase rilpivirine concentrations.

Dose adjustments for rilpivirine are needed when methadone is coadministered, although clinical monitoring is recommended because methadone maintenance therapy may require adjustment for some patients in whom methadone levels are diminished. Clinically relevant interactions are not expected for ribavirin, HMG-CoA reductase inhibitors, ethinylestradiol, norethindrone, or sildenafil, and grapefruit and/or grapefruit juice can inhibit CYP3A enzyme activity, so should be avoided in rilpivirine-treated patients.[21,22]

New clinical developments

An important trial recently presented was STaR, in which coformulated rilpivirine-tenofovir-emtricitabine was directly compared against coformulated efavirenz-emtricitabine-tenofovir over 48 weeks in drug-naïve individuals from the standpoint of virologic suppression.[23] The results demonstrated a significant difference in efficacy among patients with low baseline viral loads, ie, <100,000 copies/mL, when individuals began therapy with rilpivirine-tenofovir-emtricitabine. In contrast, a result of noninferiority was attained in individuals who initiated therapy with viral loads > 100,000 copies/mL. However, rates of virologic failure were higher among individuals

who began therapy with rilpivirine-emtricitabine-tenofovir with viral loads > 100,000 copies/mL. While overall rates of virologic failure were similar in both groups, ie, 8% for rilpivirine-emtricitabine-tenofovir versus 6% for efavirenz-emtricitabine-tenofovir through 48 weeks of treatment, the rates were 5% versus 3% in individuals initiating therapy with viral load < 100,000 copies/mL for rilpivirine-emtricitabine-tenofovir versus efavirenz-emtricitabine-tenofovir, respectively. At viral loads of 100,000–500,000, the rates were 10% versus 9% for rilpivirine-emtricitabine-tenofovir versus efavirenz-emtricitabine-tenofovir, respectively. In individuals initiating therapy with >500,000 copies/mL, the rates were 25% virologic failure for rilpivirine-emtricitabine-tenofovir and only 16% for efavirenz-emtricitabine-tenofovir. This notwithstanding, the coformulation of rilpivirine-emtricitabine-tenofovir was very well tolerated and involved fewer nervous system and adverse psychiatric events than did efavirenz-emtricitabine-tenofovir. In addition, there were fewer treatment discontinuations due to adverse events in the STaR study.

In a different study known as SPIRIT, 476 individuals who had initiated therapy as part of a first-line or second-line regimen with a boosted protease inhibitor plus two nucleosides, and who had been on that regimen for at least 6 months and attained a viral load below 50 copies of viral RNA per mL, were randomized to either switch to coformulated rilpivirine-emtricitabine-tenofovir or to remain on their boosted protease inhibitor regimen over a 24-week period.[24] Thereafter, all individuals in the study received coformulated rilpivirine-emtricitabine-tenofovir over an additional 24 weeks. The primary endpoint of the study was noninferiority in regard to viral load reductions to <50 copies/mL and secondary endpoints were maintenance of viral loads < 50 copies/mL after 48 weeks, as well as evaluations of safety and efficacy in the study population, including changes in lipid parameters and CD4 counts. The results demonstrated that virtually all patients, ie, greater than 90% of individuals, maintained viral loads < 50 copies/mL at 24 weeks and that individuals in the delayed switch arm of the study also maintained viral loads < 50 copies/mL in over 90% of cases. After 24 weeks, the results showed that switching to rilpivirine-emtricitabine-tenofovir was noninferior to remaining on a boosted protease inhibitor regimen. Virologic suppression was maintained in the delayed switch arm through 24 weeks. In the delayed switch arm, virologic suppression was also maintained through 48 weeks in almost 90% of individuals. This notwithstanding, a lower overall rate of

virologic failure was observed in individuals switching to rilpivirine-emtricitabine-tenofovir compared with remaining on the boosted protease inhibitor regimen at 24 weeks, ie, 0.9% of patients versus 5% of patients. A low rate of virologic failure was also seen in the delayed switch arm, and rilpivirine-emtricitabine-tenofovir maintained a low rate of virologic failure, ie, 2.5% over the 48 weeks of the study. Resistance developed in fewer than 1% of subjects who were switched to rilpivirine-emtricitabine-tenofovir, and this switch also resulted in improvements in fasting lipids and adverse events; the latter benefits were maintained through the 48-week period of the study.

These results are important and give credence to a similar switch study that has enrolled substantial numbers of individuals and involves a switch from initiation of therapy with coformulated efavirenz-tenofovir-emtricitabine to coformulated rilpivirine-tenofovir-emtricitabine. The goal is similar to that which was attained in the SPIRIT study, ie, to suppress patients on efavirenz-tenofovir-emtricitabine to <50 copies viral RNA per mL and then switch to coformulated rilpivirine-tenofovir-emtricitabine in order to benefit from the superior safety profile of the latter regimen. At the same time, this switch would obviate the problem of initiating therapy with an rilpivirine-based regimen at high viral loads and presumably avoid the problem of M184I/E138K drug resistance in such populations.

Summary

Rilpivirine is effective at reducing viral load and increasing CD4 cell counts in treatment-naïve patients over 96 weeks. The drug is well tolerated and safe and is an attractive treatment option relative to efavirenz due to its superior neurologic and lipid profile, making rilpivirine an important component of a combination antiretroviral single-dose tablet for drug-naïve HIV-infected subjects. Appropriate food intake at the time of drug administration and avoidance of gastric pH-reducing agents are key to its long-term effectiveness, and great caution must be exercised in the use of rilpivirine in patients with viral loads > 100,000/mL at baseline, due to higher numbers of virologic failures reported in this group. Also of concern is that the patients who developed resistant viruses in the ECHO and THRIVE studies commonly had mutations at both the E138K and M184I positions in the HIV reverse transcriptase gene, leading to dual resistance against both rilpivirine and emtricitabine. The fact that E138K causes cross-resistance among all currently approved members of the non-NRTI family of drugs, including rilpivirine, etravirine, efavirenz, and nevirapine, while M184I confers resistance against both

emtricitabine and lamivudine, is also disconcerting.[14–16] Thus, patients who fail on a rilpivirine-based regimen may be bereft of multiple future therapeutic options that involve the use of non-NRTIs, while simultaneously becoming resistant to both emtricitabine and lamivudine, and may be at risk of transmitting such multiply drug-resistant viruses. This is also a concern because of reports that viruses containing both M184I and E138K may have high replicative fitness. In general, the most likely correlate of the ability of a resistance mutation to survive and become dominant in a newly-infected host is if such a mutation does not have a significant impact on viral replicative capacity.

As stated above, a new clinical trial is now fully enrolled, initiating individuals with high viral loads onto a regimen of tenofovir-emtricitabine-efavirenz for several months, following which they are switched to tenofovir-emtricitabine-rilpivirine in order to avoid efavirenz-related toxicities. Hopefully, the use of tenofovir-emtricitabine-efavirenz to suppress viral load to below 50 copies of viral RNA per mL prior to the switch to tenofovir-emtricitabine-rilpivirine regimen will also result in an absence of treatment-related drug resistance, and prolonged use of tenofovir-emtricitabine-rilpivirine will successfully keep viral loads below levels of detection.

Disclosure

The author reports no conflict of interest in this work.

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