

Rilpivirine: a new non-nucleoside reverse transcriptase inhibitor

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Rilpivirine is a new non-nucleoside reverse transcriptase inhibitor (NNRTI) that is approved for HIV-1 treatment-naïve adult patients in combination with other antiretroviral agents. The recommended dose is a 25 mg tablet once daily taken orally with a meal. Due to cytochrome P450 3A4 enzyme induction or gastric pH increase, rilpivirine cannot be coadministered with a number of other drugs (anticonvulsants, rifabutin, rifampicin, rifapentine, proton pump inhibitors, systemic dexamethasone and St John's wort). Rilpivirine should be used with caution when coadministered with a drug with a known risk for torsade de pointes. Rilpivirine has a better tolerability than a comparative NNRTI, efavirenz, in clinical trials, with fewer central nervous system adverse effects, rashes, lipid abnormalities and discontinuation rates. Virological failure occurs more commonly with higher baseline viral loads (>100 000 copies/mL) and lower baseline CD4 counts (<50 cells/mm³). Seventeen NNRTI mutations have been associated with decreased susceptibility to rilpivirine: K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, H221Y, F227C, M230I/L, Y188L and the combination L100I+K103N. Resistance to rilpivirine largely excludes future use of the NNRTI class.

Keywords: NNRTIs, TMC 278, HIV-1

Introduction

Non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as efavirenz and nevirapine, are important components of highly active antiretroviral therapy. Combination therapy including an NNRTI has become a standard of care because of the low pill burden, improved adherence and high potency. Although NNRTIs are generally well tolerated, they also have a number of associated safety concerns, including hepatotoxicity and rash with nevirapine and neuropsychiatric disorders with efavirenz.^{1–3}

In January 2008, the US FDA approved etravirine for use in patients infected with HIV-1. Etravirine was the first next-generation NNRTI that was approved for the treatment of HIV infection in patients who have experienced virological failure while receiving an NNRTI-containing regimen.⁴ Rilpivirine (TMC278) is another NNRTI, which was approved by the FDA in May 2011.⁵ The once-daily, fixed-dose combination of rilpivirine/tenofovir/emtricitabine was approved in August 2011.⁶ Rilpivirine plus emtricitabine/tenofovir has been added as an alternative NNRTI option for initial therapy in treatment-naïve patients in the Department of Health and Human Service guidelines.³ We will review the pharmacological characteristics, *in vitro* activity, clinical data and adverse events associated with rilpivirine.

Pharmacology and pharmacokinetics

Rilpivirine is a diarylpyrimidine NNRTI like etravirine and inhibits HIV-1 replication by non-competitive inhibition of HIV-1 reverse

transcriptase and has high activity against wild-type and mutant virus strains, including K103N. The chemical name for rilpivirine hydrochloride is 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile monohydrochloride (Figure 1).^{5–12} Each tablet contains 27.5 mg of rilpivirine hydrochloride, which is equivalent to 25 mg of rilpivirine, and the recommended dose is 25 mg once daily, orally with meals. The coformulated tablet contains 25 mg of rilpivirine, 300 mg of tenofovir and 200 mg of emtricitabine.⁶

After oral administration, the maximum plasma concentration is achieved within 4–5 h, with a terminal half-life of 34–55 h. At 25 mg dosing, the C_{max} averaged 171.8 (± 69.22) ng/mL and the mean AUC₂₄ was 2808 (± 1281) ng·h/mL on day 14.^{5,11,13,14}

The exposure to rilpivirine is ~40% lower in a fasted condition and 50% lower with protein-rich drinks as compared with a normal or a high-caloric meal; it therefore should not be administered in a fasting state or with a high-protein meal. Rilpivirine is 99.7% bound to plasma proteins *in vitro*, primarily to albumin.

Rilpivirine is a substrate and inducer of cytochrome P450 (CYP) 3A4 and only 0.03% is eliminated as unchanged drug in the urine. Rilpivirine is primarily metabolized by CYP3A and drugs that induce or inhibit CYP3A may thus affect the clearance of rilpivirine.

The solubility and systemic absorption is pH dependent, as demonstrated by an increased bioavailability in an acidic environment. When coadministered with acidic suppressants, a significant reduction in drug absorption is observed. Rilpivirine should

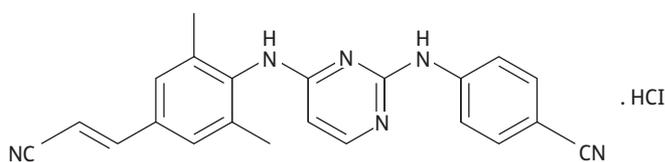


Figure 1. Chemical structure of rilpivirine (obtained from http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202022s000bl.pdf).

not be coadministered with proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole. An H_2 -receptor antagonist may be coadministered if spaced appropriately (Table 1). Besides proton pump inhibitors, rilpivirine should not be coadministered with the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital and phenytoin, the antimycobacterials rifabutin, rifampicin and rifapentine, the glucocorticoid systemic dexamethasone (more than a single dose) and St John's wort (*Hypericum perforatum*), as significant decreases in rilpivirine plasma concentrations may occur due to CYP3A enzyme induction. A summary of the significant drug interactions for rilpivirine is provided in Table 1.^{5,6,11–13,15–21}

No clinically relevant drug–drug interactions are expected when rilpivirine is coadministered with maraviroc, raltegravir or the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) abacavir, emtricitabine, lamivudine, stavudine and zidovudine.

Rilpivirine is classified as pregnancy class B; however, there are no well-controlled studies in pregnant women. Rilpivirine should be used during pregnancy only if potential benefit justifies the potential risk to the foetus. To monitor foetal outcomes, an Antiretroviral Pregnancy Registry has been established. Because of both the potential for HIV transmission and the potential for adverse reactions in nursing infants, mothers should be instructed not to breastfeed while on rilpivirine.

No dose adjustment is required in patients with mild renal impairment. There is insufficient information regarding the pharmacokinetics of rilpivirine to make dosing recommendations in patients with moderate or severe renal impairment or in patients with end-stage renal disease. Rilpivirine concentrations may be increased due to the alteration of drug absorption, distribution and metabolism secondary to renal dysfunction.

Rilpivirine should be used with caution in patients with severe renal impairment or end-stage renal disease. As rilpivirine is highly bound to plasma proteins, it is unlikely to be significantly removed by haemodialysis or peritoneal dialysis. The coformulated tablet containing tenofovir and emtricitabine should not be prescribed in patients with moderate, severe or end-stage renal disease or in those requiring dialysis (creatinine clearance <50 mL/min), as tenofovir and emtricitabine are eliminated by the kidneys through active tubular secretion and glomerular filtration.

No dose adjustment is required in patients with mild or moderate hepatic impairment (Child–Pugh score A or B) and there are no data regarding patients with severe hepatic impairment (Child–Pugh score C). Safety and effectiveness in paediatric patients have not been established.^{5,6}

In vitro activity

Rilpivirine is a potent NNRTI with a median 50% effective concentration (EC_{50}) for wild-type HIV-1 virus of 0.73 nM (0.27 ng/mL).

It is active against both wild-type and NNRTI-resistant strains of HIV due to flexibility at the NNRTI binding site of HIV-1 reverse transcriptase. Rilpivirine demonstrates greater *in vitro* activity against a variety of resistant HIV isolates and retains an EC_{50} of <1 nM against mutations L100I, K103N, V106A, G190A and G190S. Rilpivirine demonstrated antiviral activity against a broad panel of HIV-1 group M (subtypes A, B, C, D, F, G and H) primary isolates, with EC_{50} values ranging from 0.07 to 1.01 nM (0.03–0.37 ng/mL), and was less active against group O primary isolates, with EC_{50} values ranging from 2.88 to 8.45 nM (1.06–3.10 ng/mL). Rilpivirine has limited activity in cell culture against HIV-2.^{5–13}

Clinical studies

Phase II studies

A Phase IIa randomized, double-blind, placebo-controlled, multiple-dose escalation trial randomized 47 HIV-1 seropositive, antiretroviral-naïve adult males to receive one of four doses of rilpivirine monotherapy (25, 50, 100 or 150 mg daily) or placebo for 7 days, after which subjects commenced standard antiretroviral therapy. The change in the HIV-1 viral load from baseline was significantly greater with rilpivirine than placebo (median viral load decrease, 1.2 log) and good antiviral response was demonstrated across all rilpivirine doses.²²

TMC278–C204, a large Phase IIb randomized trial in 368 treatment-naïve patients, was extended to investigate long-term efficacy and safety. It consisted of two parts: an initial 96 weeks, partially blinded dose-finding part (25, 75 and 150 mg of rilpivirine) followed by a long-term, open-label once-daily doses of 75 mg of rilpivirine at week 96 and then 25 mg at week 144. Subjects in the control arm received 600 mg of efavirenz once daily, while both drugs were given in combination with two NRTIs. At week 48, intention-to-treat analysis demonstrated similar virological response (HIV viral load <50 copies/mL) with all doses of rilpivirine (76.9%–80%) and efavirenz (81%), respectively. The mean increase from baseline in CD4 cell counts was 146 cells/mm³ in subjects receiving 25 mg of rilpivirine and 160 cells/mm³ in subjects receiving efavirenz.²³ At 192 weeks, 59% of rilpivirine and 61% of subjects in the control group maintained HIV RNA <50 copies/mL.²⁴ Since the 25 mg dose had similar virological and immunological efficacy with fewer side effects than the higher doses, this dose was chosen for Phase III studies due to its favourable risk–benefit profile.

Currently, an open-label Phase IIb study (ClinicalTrials.gov identifier: NCT01286740) enrolling patients in switching from efavirenz/emtricitabine/tenofovir single-tablet regimen to rilpivirine/emtricitabine/tenofovir in virologically suppressed, HIV-1-infected patients is continuing. The primary objective was to evaluate the efficacy after switching in maintaining HIV RNA <50 copies/mL at week 12; the study is continuing for 48 weeks. Rilpivirine/emtricitabine/tenofovir was well tolerated, with no adverse events leading to discontinuation of the study drug. All subjects switching remained virologically suppressed at 12 weeks.²⁵ In the current study, rilpivirine troughs reached the target range within 2 weeks of dosing, averaging 52 ng/mL at 2 weeks after the switch. Because of the long half-life of efavirenz, average efavirenz troughs remained above the 50% inhibitory concentration for ~4 weeks. From weeks 4 to 12, rilpivirine troughs averaged 66–84 ng/mL.

Table 1. Significant drug interactions with rilpivirine

Drug	Drug dose	Rilpivirine dose	Effect on rilpivirine			Effect on drug			Recommendation
			C_{max}	AUC	C_{min}	C_{max}	AUC	C_{min}	
Darunavir/ritonavir	800 mg/100 mg qd	150 mg qd ^a	↑79%	↑130%	↑178%	↓10%	↓11%	↓11%	no adjustment
Lopinavir/ritonavir	400 mg/100 mg bid	150 mg qd ^a	↑29%	↑52%	↑74%	↓4%	↓1%	↓11%	no adjustment
Didanosine	400 mg qd	150 mg qd ^a	↔	↔	↔	↓4%	↑12%	NA	no adjustment
Tenofovir	300 mg qd	150 mg qd ^a	↓4%	↑1%	↓1%	↑19%	↑23%	↑24%	no adjustment
Acetaminophen	500 mg single dose	150 mg qd ^a	↑9%	↑16%	↑26%	↓3%	↓8%	NA	no adjustment
Atorvastatin	40 mg qd	150 mg qd ^a	↓9%	↓10%	↓10%	↑35%	↑4%	↓15%	no adjustment
Chlorzoxazone	500 mg single dose	150 mg qd ^a	↑17%	↑25%	↑18%	↓2%	↑3%	NA	no adjustment
Ethinylestradiol	0.035 mg qd	25 mg qd	↔	↔	↔	↑17%	↑14%	↑9%	no adjustment
Famotidine	40 mg 12 h before ^b	150 mg qd ^a	↓1%	↓9%	NA	↔	↔	↔	H ₂ -receptor antagonist to be administered 12 h before or 4 h after rilpivirine
	40 mg 2 h before ^b	150 mg qd ^a	↓85%	↓76%	NA				
	40 mg 4 h after ^b	150 mg qd ^a	↑21%	↑13%	NA				
Ketoconazole	400 mg qd	150 mg qd ^a	↑30%	↑49%	↑76%	↓15%	↓24%	↓66%	no adjustment, monitor for breakthrough fungal infections
(R)-Methadone	60–100 mg qd	25 mg qd	↔	↔	↔	↓14%	↓16%	↓22%	monitor for withdrawal of methadone
(S)-Methadone	60–100 mg qd	25 mg qd	↔	↔	↔	↓13%	↓16%	↓21%	
Omeprazole	20 mg qd	150 mg qd ^a	↓40%	↓40%	↓37%	↓14%	↓14%	NA	reduced rilpivirine due to gastric pH increase, contraindicated
Rifabutin	300 mg qd	150 mg qd ^a	↓35%	↓46%	↓49%	↔	↔	↔	reduced rilpivirine due to CYP3A4 induction, contraindicated
Rifampicin	600 mg qd	150 mg qd ^a	↓69%	↓80%	↓89%	↑2	↓1	NA	reduced rilpivirine due to CYP3A4 induction, contraindicated
Sildenafil	50 mg qd	75 mg qd ^a	↓8%	↓2%	↑4%	↓7%	↓3%	NA	no adjustment

AUC, area under the plasma concentration time curve; C_{max} , maximum concentration; C_{min} , minimum concentration; ↑, increase; ↓, decrease; ↔, no change; NA, not available; qd, once daily; bid, twice daily.

^aInteraction study performed with a higher dose than the recommended 25 mg dose for rilpivirine.

^bIn relation to rilpivirine dosing.

Phase III studies

Two major international Phase III [TMC278-209 (ECHO) and TMC278-215 (THRIVE)] double-blind, double-dummy, active-controlled randomized trials to assess the efficacy, safety and tolerability of 25 mg of rilpivirine versus 600 mg of efavirenz in HIV-1 treatment-naïve patients were performed. In ECHO, 346 patients were randomly assigned to receive rilpivirine and 344 to receive efavirenz. In THRIVE, 340 patients were randomly assigned to receive rilpivirine and 340 to receive efavirenz. The NRTI backbone comprised tenofovir/emtricitabine in the ECHO study and abacavir/lamivudine, tenofovir/emtricitabine or lamivudine/zidovudine in the THRIVE protocol. The primary endpoint was to demonstrate non-inferiority between rilpivirine-based and efavirenz-based regimen by virological response at week 48 (percentage of patients who achieved viral load <50 copies/mL). The secondary endpoints included safety, tolerability, change in CD4 cell count, pharmacokinetics, adherence and drug resistance. The included patients were ≥ 18 years of age and had a plasma viral load at screening of ≥ 5000 copies/mL and viral sensitivity to all study drugs. The baseline characteristics were similar, with a median baseline viral load of 5.0 log₁₀ copies/mL within each trial.

Table 2 depicts the baseline viral load, CD4 cell count with virological response and CD4 cell change. The incidence of virological failures was 13% (rilpivirine) versus 6% (efavirenz) in the ECHO study, whereas the incidence of virological failures was 8% (rilpivirine) versus 6% (efavirenz) in the THRIVE study.^{26,27} There was no significant change in the absolute CD4 count from baseline for rilpivirine versus efavirenz ($P=0.13$) in the ECHO study and ($P=0.19$) in the THRIVE study.^{26,27}

The response rate for pooled data at 48 weeks from both the above combined studies for rilpivirine ($n=686$) versus efavirenz ($n=682$) for baseline viral load of ≤ 100000 copies/mL was 90% ($n=368$) versus 84% ($n=330$) (6.6, 95% CI 1.6–11.5), >100000 copies/mL to ≤ 500000 copies/mL was 80% ($n=249$) versus 83% ($n=270$) (–3.1, 95% CI –9.8 to 3.7) and at ≥ 500000 copies/mL was 70% ($n=69$) versus 76% ($n=82$) (–6.0, 95% CI –20.4 to 8.3), respectively. The response rate was lower with baseline CD4 counts of <50 cells/mm³ for rilpivirine (59%, $n=34$) than for efavirenz (81%, $n=36$) (–21.7, 95% CI –43.0 to –0.5).²⁸

The 24 week results are available from an open-label clinical trial [ClinicalTrials.gov identifier: NCT0125290 (SPIRIT)] in which 476 NNRTI-naïve participants with undetectable viral load taking a ritonavir-boosted protease inhibitor (PI) plus two NRTIs were randomly assigned to either remain on their current regimen ($n=159$) or to switch to a rilpivirine/emtricitabine/tenofovir regimen ($n=317$). Some 93.7% of participants who switched versus 89.9% who stayed on their PI regimen had viral load <50 copies/mL at 24 weeks. Similar increases in the CD4 count from baseline were seen in both groups ($P=0.28$).²⁹

Drug toxicity

The most common significant adverse effects associated with the first-generation NNRTIs are cutaneous reactions (including Stevens–Johnson syndrome), hepatotoxicity with nevirapine and neuropsychiatric adverse effects with efavirenz.

Table 2. Baseline viral load, CD4 cell count with virological and CD4 cell count change at week 48 from Phase III trials

	TMC278-209 (ECHO)		TMC278-215 (THRIVE)	
	rilpivirine ($n=346$)	efavirenz ($n=344$)	rilpivirine ($n=340$)	efavirenz ($n=338$)
Baseline HIV-1 RNA copies/mL				
≤ 100000	52%	47%	55%	49%
100001–500000	38%	39%	35%	40%
>500000	10%	14%	10%	10%
Virological responders HIV-1 RNA copies/mL				
≤ 100000	90%	83%	91%	84%
100001–500000	79%	83%	80%	82%
>500000	62%	81%	77%	69%
virological failure	13%	6%	8%	6%
baseline median CD4 cells/mm ³	240	257	263	263
mean change in CD4 cells/mm ³ from baseline	196	182	189	171

Adapted from Molina *et al.*²⁶ and Cohen *et al.*²⁷

In the Phase Iib (TMC278-C204) trial, the incidence of any grade 2–4 adverse events related to rilpivirine or efavirenz was lower in the rilpivirine group than in the efavirenz group (20.4% versus 37.1%, respectively; $P=0.003$). The most commonly reported grade 2–4 adverse events included dizziness, vertigo, abnormal dreams/nightmares, somnolence and rash, which were less frequent with rilpivirine than with efavirenz. Overall, the most frequently reported adverse events were nausea (3.6% versus 5.6%) and dizziness (1.1% versus 3.4%).

Neurological adverse events (32.6% versus 59.6%) and psychiatric adverse events (16.1% versus 21.3%), irrespective of grade, as well as grade 2–4 neurological (6.5% versus 14.6%; $P<0.05$) and psychiatric (7.9% versus 11.2%; $P<0.05$) adverse events occurred at a lower incidence in the rilpivirine group than in the efavirenz group. The majority of adverse events were grade 1 or 2. The incidence of grade 2–4 rash was lower in the rilpivirine combined group (3.2%) or 25 mg of rilpivirine group (2.2%) than in the efavirenz group (11.2%; $P<0.05$). Grade 3 or 4 laboratory abnormalities in haemoglobin occurred in 2.2% of patients, all in the rilpivirine groups. However, haemoglobin levels declined for all groups and recovered throughout the course of the trial, returning to baseline levels in all groups and even increasing above baseline at week 96.²³

Adverse events leading to treatment discontinuation occurred in 11.5% versus 9.0% of patients in the rilpivirine combined group and efavirenz group, respectively, and more frequently in the 150 mg (14.3%) and 75 mg of rilpivirine (11.6%) groups than in the 25 mg group (8.6%). For rilpivirine, the majority of these adverse events were related to laboratory test results, most commonly alanine aminotransferase (ALT) and aspartate aminotransferase elevations. For efavirenz, the major reasons for treatment discontinuation were pregnancy, psychiatric disorders, and skin and subcutaneous tissue disorders. There was a

gradual mean increase from baseline in the QT interval up to week 48 only, which appeared greater with efavirenz and 75 mg and 150 mg of rilpivirine than with 25 mg of rilpivirine, and then stabilized in all groups up to week 96. This increase was seen in patients receiving abacavir/lamivudine, but not with tenofovir/emtricitabine.²³ The 25 mg dose of rilpivirine was selected based on the results of the lowest discontinuation rate due to adverse effects, rash and low incidence of prolonged QT intervals.^{23,24}

Over 96 weeks using pooled data from Phase III (ECHO and THRIVE) trials, the overall cumulative incidence of neuropsychiatric events was significantly lower with rilpivirine than with efavirenz (43% versus 60%; $P < 0.0001$). The most frequently reported neurological event was dizziness (8% versus 27%; $P < 0.0001$) and the most frequently reported psychiatric events were abnormal dreams/nightmares (8% versus 13%; $P = 0.004$). Most neurological (98%) and psychiatric (96%) adverse events of interest were grade 1 or 2.^{30,31}

The incidence of any rash related to treatment was lower with rilpivirine than with efavirenz (4.2% versus 15.1%; $P < 0.0001$).³² Grade 1 adverse events were most frequent in the first 4 weeks of treatment in both treatment groups. Rilpivirine was associated with a lower incidence of grade 1 adverse events than efavirenz over the first 12 weeks.³³

Grade 2–4 adverse events related to treatment were lower with rilpivirine than with efavirenz (16.9% versus 33.1%; $P < 0.0001$). Rilpivirine produced a lower incidence of increase in grade 3 or 4 ALT than efavirenz (1.5% versus 3.4%; $P = 0.02$). There was a minimal increase from baseline in mean serum creatinine at week 2, which remained stable over week 48, with rilpivirine (0.09 mg/dL), but there was no change with efavirenz.^{26,27}

At 48 weeks, the mean decrease in the baseline cortisol was 13.1 nM with rilpivirine, whereas a mean increase of 9 nM was seen with efavirenz. An abnormal cortisol response to adrenocorticotropic hormone stimulation was seen in 1.7% of the rilpivirine group, whereas none was seen with efavirenz. No serious adverse event or treatment discontinuation was related to adrenal insufficiency.²⁸

Rilpivirine produced minimal changes from baseline in total cholesterol, low-density lipoprotein cholesterol and triglyceride levels and an increase in high-density lipoprotein cholesterol (HDL-C) through to 96 weeks, whilst efavirenz produced significantly greater increases in all four lipid parameters (all $P < 0.0001$). There was no difference in the total cholesterol/HDL-C ratio between the groups ($P = 0.17$).²⁹ Switching to rilpivirine/emtricitabine/tenofovir improved the Farmington Risk Score at week 24 versus a ritonavir-boosted PI with two NRTIs. Mean changes from baseline in the lipid parameters were more favourable in the rilpivirine arm than in the boosted PI arm ($P < 0.001$).²⁹

The mean QT interval using Fridericia's formula (QTcF) increased, with no difference between rilpivirine (11.9 ms) and efavirenz (13 ms).^{26,27} No QTcF interval > 500 ms was seen.³¹ Fewer patients discontinued therapy due to adverse effects with rilpivirine than with efavirenz (4.1% versus 8.5%; $P < 0.001$).³²

Resistance

A lower cut-off for rilpivirine resistance has been set at a 2-fold change in the 50% inhibitory concentration with the use of a phenotypic assay.²² The prevalence of E138K, the most

common rilpivirine-associated mutation,^{23,26,27,34–36} including samples from treatment-naïve patients with NNRTI resistance-associated mutations (RAMs), is 0.6% in the USA.³⁵ In the pooled resistance analysis from the Phase III studies among patients with virological failures, NNRTI RAMs were higher for rilpivirine (63%; 39 out of 62) than for efavirenz (54%; 15 out of 28). The most prevalent NNRTI RAMs were E138K (45%) and K101E (13%) in the rilpivirine arm, whereas the most prevalent treatment-emergent NNRTI RAM in the efavirenz virological failure group was K103N (39%).^{26,27,36}

More rilpivirine-associated virological failures had treatment-emergent NRTI RAMs than did efavirenz virological failures (68% versus 32%, respectively), most commonly M184I and M184V.

Fifteen NNRTI RAMs have been identified as being associated with decreased susceptibility to rilpivirine: K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, H221Y, F227C and M230I/L.^{23,26,27,36}

The single NNRTI substitutions K101P, Y181I and Y181V conferred 52-, 15- and 12-fold decreased susceptibility to rilpivirine, respectively.⁵ The combination of E138K and M184I has shown 4.1-fold reduced susceptibility to rilpivirine compared with 2.4-fold for E138K alone.³⁷

The K103N substitution did not show reduced susceptibility to rilpivirine. Combinations of two or three NNRTI RAMs decreased susceptibility to rilpivirine (fold change range of 3.7–554) in 38% and 66% of mutants, respectively.⁵

Cross-resistance to efavirenz, etravirine and/or nevirapine is likely after virological failure and development of rilpivirine resistance. Of 31 patients with rilpivirine virological failure and rilpivirine resistance, 90% were resistant to etravirine, 87% to efavirenz and 45% to nevirapine. In the efavirenz arm, none of the 15 efavirenz-resistant virological failures was resistant to etravirine. Subjects experiencing virological failure on rilpivirine developed more NNRTI resistance-associated substitutions conferring more cross-resistance to other NNRTIs.^{26,27,35}

The prevalence of rilpivirine-associated mutations in 15 991 US clinical samples received for routine resistance testing was $\leq 3\%$ with the exception of Y181C, which had a prevalence of 7.11%. The combination of L100I+K103N and Y188L additionally was associated with reduced susceptibility to rilpivirine in a recent study, besides the above-mentioned 15 RAMs.³⁸ Thus, the presence of any 1 of these 17 RAMs should be considered when initiating a rilpivirine-based regimen.^{23,26,27,36,38}

Summary

Rilpivirine is the second drug from the new generation of NNRTIs. Rilpivirine is an efficacious and safe alternative to efavirenz in the treatment of antiretroviral-naïve patients infected with HIV-1 and is associated with fewer side effects. The drug has demonstrated efficacy when added to an optimized regimen containing two NRTIs and is approved by the FDA for use in antiretroviral-naïve patients. A lower baseline CD4 count of < 50 cells/mm³ and a high viral load at baseline of $> 100\,000$ copies/mL are associated with a lower rate of response. Virological failure, particularly in the setting of higher viral load and subsequent drug resistance, appears to limit the use of rilpivirine.

Due to drug interaction, patients on H₂-receptor antagonists will need to be well informed on dosing intervals. The major advantages and disadvantages of rilpivirine are given in Table 3.

Table 3. Advantages and disadvantages of using rilpivirine

Advantages	Disadvantages
Single pill formulation	decreased efficacy on an empty stomach or with protein-rich meals
Pregnancy category B ^a	currently recommended to be used for HIV-1 treatment-naïve patients only
Better tolerability leading to less drug discontinuation ^b	treatment failure more frequent with higher viral loads (>100 000 copies/mL) and low CD4 cell count (<50 cells/mm ³)
Fewer adverse effects (rash, dizziness and abnormal dreams) ^b	contraindicated with anticonvulsants, rifamycins and proton pump inhibitors
Less increase in lipids ^b	H ₂ -receptor antagonist needs to be carefully administered
Can be used as switch therapy in HIV-1 viral load-suppressed patients	coformulation cannot be used if creatinine clearance <50 mL/min
	resistance precludes further use of NNRTIs

^aRegister in Antiretroviral Pregnancy Registry to monitor foetal outcomes.

^bComparative arm, efavirenz.

The major role of prescribing rilpivirine will be in antiretroviral-naïve patients with viral load of <100 000 copies/mL. Due to its favourable lipid profile, rilpivirine may be beneficial in patients with cardiovascular risk factors. Switching from a PI-based regimen in virologically suppressed, HIV-1-infected patients to rilpivirine/emtricitabine/tenofovir resulted in favourable changes in lipid parameters. Additionally, clinicians may find rilpivirine of use in switching therapy from a efavirenz/emtricitabine/tenofovir single-tablet regimen to rilpivirine/emtricitabine/tenofovir in the setting of virologically suppressed, HIV-1-infected patients who have had an adverse reaction to efavirenz; however, larger studies are necessary to ensure efficacy after switch, due to drug interaction between efavirenz and rilpivirine. During child-bearing age or during pregnancy, as efavirenz is category D and rilpivirine is category B, rilpivirine may be an option of care.

Resistance to rilpivirine (including the E138K mutation, also associated with etravirine resistance) largely precludes future use of the NNRTI class, whereas for those on efavirenz who develop NNRTI resistance (predominantly the K103N mutation), etravirine and rilpivirine remain an option.

Transparency declarations

None to declare.

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