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REVIEW

Safety, efficacy, and pharmacokinetics of rilpivirine: systematic review with an emphasis on resource-limited settings

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Abstract: The vast majority of people living with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome reside in the developing world, in settings characterized by limited health budgets, critical shortages of doctors, limited laboratory monitoring, a substantial burden of HIV in children, and high rates of coinfection, in particular tuberculosis. Therefore, the extent to which new antiretrovirals will contribute to improvements in the management of HIV globally will depend to a large extent on their affordability, ease of use, low toxicity profile, availability as pediatric formulations, and compatibility with tuberculosis and other common drugs. We undertook a systematic review of the available evidence regarding drug interactions, and the efficacy and safety of rilpivirine (also known as TMC-278), and assessed our findings in view of the needs and constraints of resource-limited settings. The main pharmacokinetic interactions relevant to HIV management reported to date include reduced bioavailability of rilpivirine when coadministered with rifampicin, rifabutin or acid suppressing agents, and reduced bioavailability of ketoconazole. Potential recommendations for dose adjustment to compensate for these interactions have not been elaborated. Trials comparing rilpivirine and efavirenz found similar outcomes up to 96 weeks in intent-to-treat analysis; failure of rilpivirine was mainly virological, whereas failure among those exposed to efavirenz was mainly related to the occurrence of adverse events. Around half of the patients who fail rilpivirine develop non-nucleoside reverse transcriptase inhibitor resistance mutations. The incidence of Grade 2–4 events was lower for rilpivirine compared with efavirenz. Grade 3–4 adverse events potentially related to the drugs were infrequent and statistically similar for both drugs. No dose-response relationship was observed for efficacy or safety, and the lowest dose (25 mg) was selected for further clinical development. The potential low cost and dose of the active pharmaceutical ingredient means that rilpivirine can potentially be manufactured at a low price. Moreover, its long half-life suggests the potential for monthly dosing via nonoral routes, with promising early results from studies of a long-acting injectable formulation. These characteristics make rilpivirine an attractive drug for resource-limited settings. Future research should assess the potential to improve robustness and assess the clinical significance of interaction with antituberculosis drugs.

Keywords: rilpivirine, TMC-278, efficacy, pharmacology, safety

Introduction

Combination antiretroviral therapy has transformed the prognosis and life expectancy of people living with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) in both resource-rich[1] and resource-limited[2] settings. For patients to be able to benefit from these gains in the long term, antiretroviral medicines must be convenient, safe, tolerable, effective, and affordable. The main drug-related challenges to remaining on a particular regimen include side effects, interactions with other

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medications, safety during pregnancy, dosing schedules, pill burden, and degree of robustness against development of drug resistance.[3]

International treatment guidelines recommend using efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI), as part of the standard first-line regimen. Efavirenz is potent, relatively well tolerated, and easy to monitor. However, its use is limited by its low genetic barrier to development of resistance, its potential for central nervous system toxicity, concerns about safety in the first trimester of pregnancy,[4] and its relatively high cost. Among the alternative NNRTIs in development, rilpivirine has received attention as a potentially important drug for use in resource-limited settings because of its low manufacturing cost, its ability to be coformulated with other antiretrovirals, and its favorable safety profile.

A number of expert reviews have been published summarizing various characteristics of rilpivirine.[5–8] In order to update and complement these expert reviews, we undertook a systematic review of the available evidence regarding the safety, efficacy, and pharmacokinetics of rilpivirine, and discuss here the potential implications of this drug for resource-limited settings.

Search strategy

We searched the following databases from inception to March 2011 for articles containing rilpivirine or TMC-278: Medline via PubMed, Embase, Lilics, Toxnet, and the Cochrane Central Register of Controlled Trials. We also searched the websites of major HIV conferences, ie, all international AIDS society conferences (up to Vienna, August 2010), all conferences on retroviruses and opportunistic infections (up to Boston, March 2011), and all abstracts from the international congresses on drug therapy in HIV infection (up to Glasgow, November 2010). No language restrictions were applied. We included all articles reporting original data on pharmacokinetics, tolerability, safety, and efficacy. This information was crosschecked against data presented in secondary reports (nonsystematic reviews, opinion articles, and news items). We also searched in the clinical trial.gov website to obtain information about ongoing studies. Finally, we complemented the search by reviewing bibliographies of relevant papers.

Our initial search yielded 292 articles and 31 conference abstracts. After screening out duplicates and items that did not meet our inclusion criteria, we retained six full-length articles and 16 conference abstracts. Articles comprised three clinical trials,[9–11] one pharmacokinetic study,[12] and two formulation studies.[13,14] Conference abstracts yielded additional data from two clinical trials,[15,16] 13 pharmacokinetic studies,[17–29] and one bioequivalence study.[30] All studies were published in English.

Pharmacology

The mode of action of rilpivirine is at the stage of viral genome replication, inhibiting HIV reverse transcriptase by binding to a hydrophobic pocket near the active site of the enzyme and thus preventing transcription of viral RNA. Rilpivirine is active against HIV-1 in a variety of NNRTI-resistant clinical isolates, and the relatively high potency of rilpivirine compared with the older generation of NNRTIs is thought to be due to its internal conformational flexibility ("wiggling") and the plasticity of its interaction with the binding site ("jiggling").[31]

Pharmacokinetics

Rilpivirine is highly protein-bound, and more than 99% may be bound to human plasma proteins in a concentration-dependent manner.[31] Under fasting conditions, the maximum plasma concentration of rilpivirine (C_{max}) decreased by 46% and the area under the rilpivirine plasma concentration curve (AUC) decreased by 43%. Similarly, rilpivirine C_{max} and AUC are reduced by 50% when given with a protein-rich nutritional drink.[32] As a consequence, it is recommended to take rilpivirine with food but avoid taking after a protein-rich drink. In a 7-day pharmacokinetic study of oral administration of rilpivirine 25 mg, 50 mg, 100 mg, and 150 mg once daily, C_{max} was generally reached 3–4 hours after dosing.[32] Plasma concentrations were increased 2–3-fold from day 1 to day 7. Drug elimination from the plasma was slow, with a terminal half-life of 34–55 hours.[22] At higher doses, there was a trend towards greater interindividual pharmacokinetic variability, but plasma concentrations did not increase proportionately with dose. A pediatric granule formulation has been developed, and its exposure under fasting conditions was comparable with the tablet formulation if taken with food (the AUC_{∞} was 26% higher when taken with food[19]). The main clearance of rilpivirine is via oxidative metabolism followed by sulfate conjugation or O-glucuronidation and N-glucuronidation in animal studies.[32] Metabolic studies in human hepatocytes showed slow metabolic clearance, and $\leq$0.03% was found unchanged in the urine.[22]

Drug–drug interactions

The main results of drug–drug interaction studies are described below and summarized in Table 1.

Interaction with key drugs in the management of HIV/AIDS

Tuberculosis drugs

Two pharmacokinetic studies have investigated the interaction between rilpivirine and two drugs commonly used to treat tuberculosis, ie, rifampicin and rifabutin. Rifampicin dosed at 600 mg once daily together with rilpivirine 150 mg once daily was found to reduce rilpivirine AUC_{24h}, C_{max}, and C_{min} by 80%, 69%, and 89%, respectively, when given to 16 HIV-negative volunteers for 7 days.[22] No significant change was seen in the pharmacokinetics of rifampicin. The study investigators concluded that concurrent administration of rilpivirine and rifampicin is not recommended.

In an 11-day study of rilpivirine 150 mg once daily and rifabutin 300 mg once daily in 18 HIV-negative volunteers, the AUC_{24h}, C_{max}, and C_{min} of rilpivirine was reduced by 46%, 35%, and 49%, respectively. The AUC_{24h} of rifabutin and its metabolite, 25-O-desacetyl-rifabutin, were not affected by coadministration of rilpivirine.[18]

Both of these interactions are important for high-HIV burden settings where rates of tuberculosis/HIV coinfection are high.[23] Clinical and dose-adjustment studies of rilpivirine coadministered with rifabutin or rifampicin are needed before coadministration is definitively ruled out.

Antiretrovirals

Several studies have assessed the pharmacokinetic interaction between rilpivirine and other antiretrovirals. A study of rilpivirine and tenofovir, a nucleoside reverse transcriptase inhibitor (NRTI), in 15 healthy volunteers did not show any significant difference in the exposures of both drugs. The AUC_{24h} of tenofovir was increased by 24%; while this increase was statistically significant, it was not considered to be clinically relevant.[33] Another study looking at rilpivirine 150 mg once daily dosed concomitantly with darunavir/ritonavir 800/100 mg once daily in 16 HIV-negative volunteers found an important increase in rilpivirine exposure (AUC_{24h} 130%, C_{max} 79%, C_{min} 178%).[29] Three participants discontinued the study due to Grade 2 adverse events of diarrhea and abdominal pain (one volunteer on rilpivirine alone) and enteritis and maculopapular rash (volunteers on rilpivirine and darunavir/ritonavir). The effect of increased rilpivirine exposure when coadministered with darunavir/ritonavir was confirmed by a second study which concluded that this was due to cytochrome P450 (CYP)3A4 inhibition.[24] No clinically significant change in the pharmacokinetics of darunavir/ritonavir was seen. The clinical significance of this interaction and magnitude at lower doses of rilpivirine has not been assessed.

Antifungals

Ketoconazole, an azole antifungal, is a known inhibitor of CYP3A4, and coadministration (400 mg once daily) with rilpivirine 150 mg once daily in 16 HIV-negative volunteers resulted in an increase in AUC_{24h}, C_{max}, and C_{min} by 49%, 30%, and 76%, respectively, for rilpivirine.[34] Conversely, the AUC_{24h}, C_{max}, and C_{min} of ketoconazole decreased by 24%, 15%, and 66%, respectively. It is unknown if the final marketed dose of rilpivirine 25 mg once daily warrants dose adjustment when these two drugs are coadministered.

Methadone

A modest change in the pharmacokinetics of methadone was observed when coadministered with rilpivirine 25 mg once daily in a pharmacokinetic study involving 13 HIV-negative volunteers on dose-individualized methadone therapy. The C_{min}, C_{max}, and AUC_{24h} of R-methadone and S-methadone were found to decrease by 24%, 14%, 16%, respectively, and by 21%, 13%, and 16%, respectively.[25] Rilpivirine pharmacokinetics remained within normal range in the presence of methadone. As a result of this study, clinical monitoring for methadone withdrawal symptoms is recommended because methadone maintenance therapy may need to be adjusted in some patients.

Interactions with other drugs

Both rilpivirine and atorvastatin (a HMG-CoA reductase inhibitor) are substrates of CYP3A. A study in 16 HIV-negative volunteers administered rilpivirine 150 mg once daily and atorvastatin 40 mg once daily found no changes in rilpivirine exposures.[26] However, atorvastatin exposures were increased with the sum of atorvastatin and its two active metabolites, ie, AUC_{24h} increased by 21% while C_{max} increased by 35%. All volunteers completed the study, with no Grade 3 or 4 adverse events reported, so no dose adjustment was recommended.

Rilpivirine is shown to have decreased solubility at increased pH in vitro, and coadministration of famotidine 40 mg once daily 2 hours before rilpivirine 150 mg once daily in a study of 24 HIV-negative subjects resulted in reduced exposures of rilpivirine AUC_{∞} and C_{max} by 76% and 85%, respectively.[35] The rilpivirine AUC_{∞} was increased by 13% when famotidine was administered 4 hours after rilpivirine. No significant changes in the pharmacokinetics of either drug were noted when famotidine was administered 12 hours before rilpivirine. The conclusion of this study was that administration of acid-suppressing agents should be adequately spaced apart.

Table 1 Interactions between rilpivirine and other drugs

Coadministered drug	Participants	Duration	Dose	
			Rilpivirine	Coadministered drug
Rifabutin[18]	18 HIV-negative volunteers	11 days	150 mg qd	300 mg qd
Rifampicin[22]	16 HIV-negative volunteers	7 days	150 mg qd	600 mg qd
Darunavir/ritonavir[24]	16 HIV-negative volunteers	Session 1 – RIL 11 days Session 2 – DVR/r 22 days, RIL 11 days	150 mg qd	800 mg/100 mg qd
Tenofovir[33]	15 healthy volunteers	Session 1 – RIL 8 days Session 2 – TDF 16 days, RIL 8 days	150 mg qd	300 mg qd
Atorvastatin[26]	16 HIV-negative volunteers	Session 1 – Atorvastatin 4 days Session 2 – RIL 14 days, atorvastatin 4 days	150 mg qd	40 mg qd
Ketoconazole[34]	16 healthy subjects	11 days	150 mg qd	400 mg qd
Famotidine[35]	24 HIV-negative subjects	Famotidine administered 2 hours before, 12 hours before and 4 hours after rilpivirine	150 mg qd	40 mg qd
Sildenafil[28]	16 HIV-negative male volunteers	12 days RIL 75 mg qd and 50 mg sildenafil on day 12	75 mg qd	50 mg one dose
Ethinylestradiol and norethindrone[27]	18 HIV-negative female volunteers	3 oral contraceptive cycles	25 mg qd	Ethinylestradiol 35 µg and norethindrone 1 mg
Methadone[25]	13 HIV- negative volunteers		25 mg qd	60–100 mg dose individualized

A pharmacokinetic study of 18 HIV-negative female volunteers on oral contraceptives (norethindrone 1 mg and ethinylestradiol 35 µg) and rilpivirine (25 mg once daily) was carried out for three cycles[27] and found no significant pharmacokinetic changes in any of the drugs. There was an increase of 17% in the C_{max} of ethinylestradiol in the presence of rilpivirine, but this was not considered to be clinically relevant. Serum levels of progesterone, luteinizing hormone, and follicle-stimulating hormone taken on days 1 and 14 of the cycle were within normal ranges. Therefore, no dose adjustment is recommended during coadministration of rilpivirine and norethindrone/ethinylestradiol-based contraceptives.

Finally, a study assessing the pharmacokinetics of rilpivirine (75 mg once daily for 12 days) when coadministered with sildenafil (50 mg on day 12) and its active metabolites found no significant change when both were coadministered in a study of 16 HIV-negative male volunteers.[28]

Clinical efficacy

Data on the clinical efficacy of rilpivirine have been reported from three completed trials and two ongoing trials (Table 2).

Antiviral activity and safety was established in a Phase IIa trial that randomized 47 antiretroviral-naïve adult males to rilpivirine monotherapy or placebo. In this trial, rilpivirine achieved a statistically significant median viral load reduction, and 12.1% of participants (4/36) in the rilpivirine groups reached a viral load of <400 copies/mL on day 8 compared with no subjects in the placebo group.[9] No changes in viral genotype or phenotype of the treated subjects were identified.

PK Rilpivirine			PK Coadministered drug			Comments
C_{max}	AUC_{24h}	C_{min}	C_{max}	AUC_{24h}	C_{min}	
35%	46%	49%	NC	NC	NC	Reduced rilpivirine exposure due to CYP3A4 induction by rifabutin
69%	80%	89%	NC	NC	NC	Reduced rilpivirine exposure due to CYP3A4 induction by rifampicin
↑79%	↑130%	↑178%	10%	11%	11%	Increased rilpivirine exposure due to CYP3A4 inhibition; the increase is not clinically relevant and no dose modification is recommended
3%	↑2%	NC	↑21%	↑24%	↑24%	Increase in TDF exposure is not clinically relevant and no dose modification is recommended
NC	NC	NC	↑35%	↑21% (total HMG-CoA reductase activity)	NC	No dosage adjustment needed
↑30%	↑49%	↑76%	15%	24%	66%	Increased RIL exposure due to CYP3A4 inhibition by ketoconazole
85% (2 hours before)	AUC_{∞} 76% (2 hours before)	?	NC	NC	NC	Acid suppressing agent such as famotidine reduce bioavailability of RIL and therefore should be adequately space apart when given together
NC	NC	NC	NC	NC	NC	No dosage adjustment needed
NC	NC	NC	EST: ↑17% NE: NC	EST: NC NE: NC	EST: NC NE: NC	No dosage adjustment needed
NC	NC	NC	R-methadone: 14% S-methadone: 13%	R-methadone: 16% S-methadone: 16%	R-methadone: 24% S-methadone: 21%	Clinical monitoring for methadone withdrawal symptoms is recommended

Abbreviations: AUC_{24h}, area under the curve over 24 hours; AUC_{∞}, area under the curve zero to infinity; C_{max}, maximum concentration; C_{min}, minimum concentration; DRV, darunavir; EST, ethinylestradiol; NE, norethindrone; NC, no change; P, pharmacokinetics; qd, once daily; RIL, rilpivirine; TDF, tenofovir.

This study was followed by a Phase II open-label trial evaluating the antiviral activity of rilpivirine administered at three different doses (25 mg, 50 mg, or 150 mg) replacing either the protease inhibitor or an NNRTI of an ongoing failing treatment regimen.[10] In this nonrandomized, noncomparative trial, 36 patients were assessed for short-term (7-day) changes in viral load. Overall, the median change from baseline was −1.19 $\log_{10}$ copies/mL in the protease inhibitor-substituted therapy group and −0.71 $\log_{10}$ copies/mL in the NNRTI-substituted therapy group, demonstrating that rilpivirine has significant antiviral activity against HIV-1 in treatment-experienced patients.

A large, randomized Phase IIb dose-ranging study that compared the antiviral activity of rilpivirine (25 mg, 75 mg, or 150 mg) and efavirenz administered as triple therapy in treatment-naïve patients at 48 weeks and 96 weeks found no statistically significant difference in viral suppression or CD4 gain.[11] Virological failure was similar for both groups (6% for rilpivirine vs 7% for efavirenz). The proportion of patients developing treatment-emergent NNRTI resistance-associated mutations was similar between the groups.

Finally, in a large pooled analysis of two ongoing randomized Phase III trials (1368 patients) rilpivirine showed noninferior efficacy compared with efavirenz at 48 weeks.[15] Virological failure was higher in the rilpivirine group (9% vs 4.8%), while the incidence of adverse events leading to trial discontinuation was higher in the efavirenz group (8% vs 3%). A difference in virologic response favoring efavirenz was noted for patients in whom HIV RNA was >100,000 copies at study initiation. An effect

Table 2 Summary of studies evaluating safety and efficacy of TMC-278

Study	Participants	Design	TMC-278	Comparison	Reporting period	Efficacy	Safety
Goebel et al[9]	47 ARV- naïve men (median age 34)	Phase IIa randomized, double-blind, placebo-controlled trial	TMC-278 monotherapy (25, 50, 100, and 150 mg qd) as triple therapy (NRTI backbone)	Placebo (polyethylene glycol)	7 days	Median viral load change TMC-278: −1.199 log(10) copies/mL Placebo: +0.002 log(10) copies/mL	No Grade 4 abnormalities or serious adverse events
Arastéh et al[10]	36 ARV-experienced adults on a failing regimen	Phase II, open-label trial	TMC-278 (25–150 mg qd)	None	7 days	Median viral load change PI-substituted group: −1.19 log(10) copies/mL NNRTI-substituted group: −0.71 log(10) copies/mL	No Grade 4 abnormalities or serious adverse events
Pozniac et al[11]	368 ARV-naïve adults (median age 35, 33% female)*	Phase IIb randomized, open-label trial	TMC-278 (25, 75, and 150 mg qd) as triple therapy (NRTI backbone)	Efavirenz 600 mg qd as triple therapy (NRTI backbone)	96 weeks	Viral load <50 copies/mL TMC278: 71.4%–76.3% Efavirenz: 70.8%	Incidence of serious and Grade 3 or 4 adverse events similar between groups
Crauwels et al[19]	1368 ARV-naïve adults	Phase III, randomized, double-blind trial	TMC-278 25 mg qd as triple therapy (NRTI backbone)	Efavirenz 600 mg qd as triple therapy (NRTI backbone)	48 weeks	Viral load <50 copies/mL TMC-278: 85% Efavirenz: 83%	Adverse events leading to discontinuation TMC-278: 3% Efavirenz: 8%

Note: *Intent-to-treat population.
Abbreviations: ARV, antiretroviral; qd, once daily; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

of low-dose rilpivirine could not be excluded in the intent-to-treat analysis, in which discontinuation due to adverse events, death, and other reasons, was considered as failure. Failure on rilpivirine was due to virological failure, exposing patients to resistant mutations both for NNRTI and for NRTI, whereas failure among those exposed to efavirenz was related to the occurrence of adverse events, with no risk for compromising future treatment options. Among successfully genotyped patients, 68% of patients exposed to rilpivirine and 32% of patients exposed to efavirenz had emergent NRTI mutations, the most frequent NRTI mutation with rilpivirine being M184I (the lamivudine/emtricitabine mutation that often precedes and is replaced by M184V). Rates of emerging NNRTI-related mutations were similar between the two groups (50% for rilpivirine vs 43% for efavirenz). The most frequent NNRTI mutation to emerge upon rilpivirine failure was E138K, a mutation associated with resistance to etravirine, efavirenz, and nevirapine in vitro, whereas the K103N was most frequent for efavirenz.[16] This trial is planned to continue through to 96 weeks.

Further studies underway include a comparison of the safety, efficacy, and tolerability of rilpivirine in adolescents (Clinical trials.gov identifier: NCT0799864), a Phase III trial to evaluate the new combination of tenofovir/emtricibitane and rilpivirine as a fixed-dose combination in treatment-naïve patients (NCT00540449), and two trials to evaluate switching from regimens consisting of a ritonavir-boosted protease inhibitor and two NRTIs or efavirenz and two NRTIs to a fixed-dose combination of emtricitabine, rilpivirine, and tenofovir (NCT01252940, NCT01286740). A bioavailability study in healthy adult volunteers to evaluate three pediatric formulations of rilpivirine (a solution, a suspension, and granules) compared with an adult tablet formulation has recently been completed (Trial NCT00812292), but has yet to be reported.

Safety and tolerability

The most extensive safety and tolerability data to date come from the 96-week Phase IIb trial, in which the median duration of follow-up extended to over 100 weeks.[11] This study reported that rilpivirine was safe and well tolerated across a range of doses from 25 mg to 150 mg.

The overall incidence of Grade 2–4 events potentially related to the drug was lower for patients receiving rilpivirine compared with efavirenz (20.4% vs 37.1%, $P = 0.003$). Events included nausea, dizziness, abnormal dreams/nightmare, dyspepsia, asthenia, rash, somnolence, and vertigo. None of these events were reported in more

than 4% of patients, and all were less frequently reported in patients receiving rilpivirine compared with efavirenz. Incidence of Grade 2–4 rash was also statistically significantly lower among patients randomized to rilpivirine (3.2% versus 11.2%, $P < 0.05$).

Grade 3 or 4 adverse events potentially related to the drugs were infrequent and statistically similar (5.4% for rilpivirine and 7.9% for efavirenz). Grade 3 or 4 laboratory abnormalities in hemoglobin occurred in 2.2% of patients, and all were in the rilpivirine groups. However, hemoglobin 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. Incident anemia developed predominantly in the subgroup of patients using zidovudine/lamivudine as the NRTI backbone.[11]

Incidence of serious adverse events was similar at 12.2% for rilpivirine and 14.6% for efavirenz. Events considered at least possibly related to study medication occurred in one patient receiving efavirenz (arthralgia) and five patients receiving rilpivirine (aspartate aminotransferase/alanine aminotransferase increase/cytolytic hepatitis, blood amylase increase, abdominal pain/constipation, attempted suicide, and anemia).

There were no consistent or clinically relevant changes in vital signs among patients on rilpivirine. Increases in QT_c interval had been observed at week 48 with all rilpivirine doses and with efavirenz, but these changes stabilized from week 48 onwards. This increase was seen in patients receiving zidovudine/lamivudine, but not with tenofovir/emtricitabine.[11] The smallest increases to QT_c were observed with the 25 mg rilpivirine dose.[29,36] The clinical significance of the QT_c prolongation in patients with and without established cardiac conditions is not known.

Further evidence of the side effect profiles of rilpivirine and efavirenz comes from the 48-week interim pooled analysis of the two ongoing Phase III trials.[15] In this analysis, rilpivirine resulted in fewer discontinuations for adverse events and fewer instances of neurologic and psychiatric adverse events, lipid elevations, and rash, compared with efavirenz (Table 3). In view of similar efficacy and safety across treatment arms, the 25 mg dose was selected for Phase III development.

Safety in pregnancy has not been directly assessed because pregnant women are excluded from clinical trials, in keeping with prevailing ethical norms. However, studies in rats and rabbits have not found any adverse effect of rilpivirine on fertility, embryonic development, prenatal and postnatal development, or the immune system.[37] To date, there are no published data on the incidence of lipodystrophy in patients exposed to rilpivirine.

Table 3 Summary of adverse event data from Phase III trials[15]

	TMC-278 (686 patients)	Efavirenz (682 patients)	*P* value
Median treatment duration, weeks	56	56	
Grade 2–4 adverse events (%)	16	31	<0.0001
Discontinuation due to adverse events	3	8	0.0005
Most common adverse events			
Any neurological adverse events	17	38	<0.0001
Dizziness	8	26	<0.0001
Any psychiatric adverse events	15	23	0.0002
Abnormal dreams/nightmares	8	13	0.0061
Rash (any type)	3	14	<0.0001

Perspectives for resource-limited settings

The choice of preferred antiretroviral drug regimens in resource-limited settings depends on a number of characteristics and constraints common to these settings. First, regimens must be efficient and robust. Second, the regimens must be as affordable as possible. Third, because care is mainly provided at the primary care level by lesser-trained health workers with minimal laboratory monitoring, they must have minimal side effects. Fourth, they should be compatible with other commonly used drugs, in particular tuberculosis medications. Fifth, they should be safe and effective for patient groups that are more commonly in need in resource-limited settings, in particular women of childbearing age and children. Finally, they should be available as fixed-dose combinations to maximize adherence.[4] Rilpivirine has some, but not all, of these characteristics.

Clinical trial data reported to date demonstrate good efficacy, but the fact that around half of patients who fail rilpivirine develop NNRTI resistance mutations is a cause for concern.

The cost of the active pharmaceutical ingredients of antiretroviral drugs can account for between 5%–99% of direct manufacturing costs.[38] In the case of rilpivirine, the active pharmaceutical ingredient can be manufactured at a very low price, as low as $US10 per patient/year. The lower dosage also allows for coformulation with other drugs.

A fixed-dose of rilpivirine, emtricitabine, and tenofovir has been evaluated and found to have comparable bioequivalence

with the individual drugs.[30] For resource-limited settings, the combination of rilpivirine, lamivudine, and tenofovir could potentially cost at least one-third less than the alternative combination of efavirenz, lamivudine, and tenofovir (US$114 vs US$ 176 per patient/year).[39] However, current licensing arrangements for generic manufacture are too restrictive because they are limited to specific companies and exclude a number of high HIV-burden countries,[40] including South Africa and Brazil, which account for a substantial proportion of the total number of people receiving antiretroviral therapy in low-income and middle-income countries.[41] In order to facilitate the development of fixed-dose combinations and encourage reduced prices through increased competition, a number of international agencies, including the World Health Organization, the Joint United Nations Programme on HIV/AIDS, and the Médecins Sans Frontières, have called for the inclusion of rilpivirine into the Medicines Patent Pool.[42]

The long half-life of rilpivirine suggests a potential for monthly dosing via nonoral formulations. An injectable nanosuspension of rilpivirine has been developed and showed a promising pharmacokinetic profile in both animals and humans.[12,17] A 600 mg intramuscular injection was found to result in sustained release of rilpivirine, and simulation of the pharmacokinetic profile predicted a once-monthly delivery similar to oral dosing with 25 mg once daily.[17] Unfortunately, a clinical trial aimed at determining the safety, tolerability, and long-term plasma exposure over time of a one-dose regimen of four monthly subcutaneous doses of a long-acting formulation of rilpivirine (NCT00741741) has been terminated prematurely, although the results of this trial have yet to be placed in the public domain. The benefit of such a long-acting formulation in terms of adherence would depend on coadministration with other drugs that could be administered at similar intervals. Drugs currently in development that show potential for combination with rilpivirine in a long-acting formulation include GSK-572, GSK-744, CMX-157, and elvucitabine (although currently no further clinical development is planned for the latter drug).

The clinical efficacy of the lowest drug dose has to be proven over the long term. Trial data suggest that use of rilpivirine in patients with high viral load at treatment initiation may be precluded.[15] The side effect profile of rilpivirine is at least equivalent to and potentially even better than nevirapine and efavirenz, the two most common antiretroviral medications used in resource-limited settings.[15]

However, the safety and efficacy of rilpivirine in specific patient groups remains to be evaluated. No studies have yet been undertaken to assess rilpivirine in children under 12 years of age, although a bioavailability study evaluating a solution, suspension, and granules compared with adult rilpivirine tablets has been completed (NCT00812292).

Rilpivirine as prevention, treatment, or both?

Several recent studies have demonstrated the potential for antiretrovirals in preventing HIV infection. One study (the Pre-Exposure Prophylaxis Initiative [IPreX]) found that men who have sex with men taking daily tenofovir/emtricitabine as pre-exposure prophylaxis were 44% less likely to become HIV-infected compared with those taking placebo.[43] The good tolerability of oral tenofovir as pre-exposure prophylaxis among men who have sex with men was confirmed by a second study (CDC-4323),[44] while a third study (Center for the AIDS Program of Research in South Africa [CAPRISA] 004) demonstrated that tenofovir applied as a vaginal gel reduced the risk of contracting HIV by 39% in women.[45]

Antiretroviral medications such as rilpivirine that can be administered as long-acting formulations have particular interest as prevention interventions because they provide the potential for weekly or monthly administration. This advantage is evident from the results of the IPreX trial, in which poor adherence to daily tenofovir treatment compromised the overall effect size of the trial. A preclinical evaluation of the potential prophylactic application of rilpivirine at a range of intervals would be the logical first step.

There are also broader considerations. The use of any antiretroviral as pre-exposure prophylaxis will require administering these drugs to many more people than for treatment alone, and this raises a number of ethical concerns, including fair allocation (who is prioritized for pre-exposure prophylaxis, and who will pay), and the potential for speeding up the development of resistance to drugs used for pre-exposure prophylaxis, which may lead to recommendations to withhold a drug with preventive potential from being used in treatment.[46] Given the potential usefulness of rilpivirine as both prevention and treatment, careful consideration will be needed in order to ensure that this drug is used to the greatest benefit.

Conclusion

The vast majority of people living with HIV/AIDS reside in the developing world, in settings characterized by limited health budgets, critical shortages of doctors, limited laboratory monitoring, a substantial burden of pediatric HIV, and high rates of coinfection, in particular with tuberculosis. Therefore, the extent to which new antiretrovirals will

contribute to improvements in the management of HIV globally will depend to a large extent on their affordability, ease of use, limited toxicity, pediatric formulations, and compatibility with tuberculosis and other drugs that are commonly prescribed for people living with HIV/AIDS.

The development of rilpivirine to date has taken many, but not all, of these issues into account. Overall, the low dose (allowing for low cost and coformulation), good efficacy and safety profile, and potential for formulation in fixed-dose combinations, and ongoing development of pediatric formulations, makes rilpivirine an attractive drug for resource-limited settings. Disadvantages of this drug include limited robustness and important potential drug-to-drug interactions, in particular with antituberculosis drugs. Future research should consider the potential for increasing robustness without increasing toxicity using higher doses, the clinical significance of the interaction between rilpivirine and tuberculosis drugs, and the safety and efficacy of pediatric formulations. Finally, policies are needed to overcome intellectual property barriers to the development of fixed-dose combinations and to ensure access and affordability for all people living with HIV/AIDS.

Disclosure

The authors report no conflicts of interest in this work.

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