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REVIEW

An update on clinical utility of rilpivirine in the management of HIV infection in treatment-naïve patients

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Abstract: Non-nucleoside analog reverse transcriptase inhibitors (NNRTIs) are an important component of combination antiretroviral regimens. Amongst the NNRTIs, efavirenz is commonly recommended for initial regimens in treatment-naïve HIV patients, but its use in some settings is limited by adverse effects, particularly those affecting the central nervous system and lipid metabolism. Rilpivirine is a new second-generation NNRTI that is recommended as an alternative to efavirenz in treatment-naïve HIV patients. Evidence of the clinical efficacy of rilpivirine versus efavirenz, in combination with two nucleoside or nucleotide analog reverse transcriptase inhibitors in treatment-naïve patients, is derived from the THRIVE and ECHO studies. These studies demonstrated that rilpivirine 25 mg once daily was potent and non-inferior to efavirenz 600 mg once daily using an intention-to-treat time-to-loss-of-virologic-response (ITT-TLOVR) endpoint. Although virologic failure was higher in subjects treated with rilpivirine, study discontinuations due to adverse effects were more common in subjects treated with efavirenz. In addition, the virologic response to rilpivirine was suboptimal in patients with a baseline viral load >100,000 copies/mL. The overall incidence of adverse events and grade 2–4 adverse events was lower in the rilpivirine than in the efavirenz groups. Patients with rilpivirine failure were more likely to have resistance mutations that confer cross-resistance to other NNRTIs, including etravirine. Rilpivirine is currently available as a fixed-dose combination that allows for once-daily administration as a single pill, and is approved for use in treatment-naïve patients. This drug is contraindicated when co-administered with rifamycins or proton-pump inhibitors.

Keywords: rilpivirine, HIV infection, treatment-naïve

Introduction

Advances in antiretroviral therapy (ART) have ultimately improved the survival of HIV-infected patients, but the viral latency of HIV is a barrier for HIV eradication or cure.[1–3] Currently used antiretroviral regimens can control HIV replication and maintain maximal viral suppression if patients adhere to this chronic and life-long treatment. However, various factors can compromise HIV treatment success. First, after a long duration of exposure to ART, some patients experience long-term adverse effects from antiretroviral agents.[4,5] Second, adherence to prolonged ART may decrease over time.[6] Some ART regimens contain a higher pill burden that may further compromise adherence,[7,8] but most of the antiretroviral agents currently recommended for treatment-naïve patients are potent, durable, easy to administer, and have a low incidence of toxicity.[9] New agents should be safe for use in particular settings such as pregnancy or childbearing women. In this review, we aim to update the evidence base about a

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novel non-nucleoside analog reverse transcriptase inhibitor (NNRTI), rilpivirine, in treatment-naïve HIV patients, with data from relevant clinical trials.

The discovery of the second-generation NNRTI

Antiretroviral regimens usually consist of two nucleoside analog reverse transcriptase inhibitors (NRTI) plus a third agent. The recommended drug classes for selection of the third agent are protease inhibitors (PIs), NNRTIs, and integrase strand transfer inhibitors.[9,10] Although there are numerous choices available within these classes, only some agents are widely used and recommended in treatment-naïve patients as preferred third agents. More specifically, atazanavir boosted with ritonavir, darunavir boosted with ritonavir, efavirenz, and raltegravir are recommended in treatment-naïve patients as preferred third agents in the highly active ART (HAART) combination for developed countries. Amongst the NNRTIs, efavirenz and nevirapine have high potency and tolerability,[11] but efavirenz is recommended as the preferred third agent in the NNRTI class, because of demonstrated high efficacy in many clinical trials, lower rates of toxicity, and pharmacokinetic properties that allow for once-daily dosing.[9] Efavirenz has been assigned as a gold standard or comparator for study of the efficacy of new antiretroviral agents. However, its use can be limited by central nervous system (CNS) adverse effects,[12] cutaneous eruptions, and alterations in lipid metabolism.[5] In addition, efavirenz is teratogenic in animals, and might be associated with congenital anomalies in humans.[13] Other preferred 'third agents' for treatment-naïve patients also have limitations. PIs such as boosted atazanavir or boosted darunavir may cause dyslipidemia.[14,15] Raltegravir is potent but still requires twice-daily dosing.[16] Because of the limitations of current preferred agents in some clinical settings, there has been a search for effective new agents with improved toxicity profiles. Etravirine is the first of the second-generation NNRTIs that has showed efficacy in controlling HIV replication in treatment-experienced patients, in combination with other active agents.[17–19] In this review, we provide an update on the clinical use of rilpivirine, the second of the second-generation NNRTIs, a recommended alternative third agent for treatment-naïve patients.

The pharmacological properties of rilpivirine

Rilpivirine acts at the hydrophobic position near the NNRTI-binding site, causing inactivation of the reverse transcriptase enzyme, thus terminating DNA synthesis of the HIV virus.[20,21] Rilpivirine shares some chemical similarities with etravirine and hence these two agents have potential cross-resistance.[22] Etravirine has a higher genetic barrier to resistance and may be more suitable for use in treatment-experienced patients, while rilpivirine has a long terminal half-life, allowing for once-daily dosing, and is therefore a suitable choice for treatment-naïve patients.[23] Rilpivirine 25 mg once daily is the only dose licensed by the US Food and Drug Administration (FDA), due to suspected QT interval problems with higher doses in Phase I and II studies.[24]

Evidence of rilpivirine efficacy from clinical trials

In dose-finding studies, 25 mg of rilpivirine had viral suppression comparable to that of efavirenz through 96 weeks.[24,25] Efficacy of rilpivirine was subsequently determined in the THRIVE (TMC278 against HIV, in a once daily RegImen Versus Efavirenz) and ECHO (Early Capture HIV Cohort Study) studies.[26,27] These two similar Phase III, multinational, double-blinded, randomized, placebo-controlled, non-inferiority studies compared the efficacy of rilpivirine versus efavirenz in combination with a 2-NRTI backbone. The primary endpoint of both studies was an 'intention-to-treat time to loss-of-virologic response' (ITT-TLOVR) algorithm, and the secondary endpoints were rates of adverse effects, changes in HIV-1 viral load, CD4 cell counts, lipid parameters from baseline and patterns of drug resistance-associated mutations. The choice of backbone regimen in THRIVE was at the investigators' discretion, but, in ECHO, the backbone was tenofovir/emtricitabine. The response rate in both trials was stratified by backbone regimens and baseline viral load (<100,000 copies/mL, 100,001–500,000 copies/mL, and >500,000 copies/mL). A total of 1,368 subjects were enrolled in both studies, and 1,062 subjects were followed to week 48; 80% of subjects were male, with a balanced gender ratio in both studies, and approximately 50% of subjects had a baseline HIV-1 viral load greater than 100,000 copies/mL. The backbone regimens in THRIVE were tenofovir/emtricitabine, zidovudine/lamivudine, and abacavir/lamivudine. The mean HIV-1 viral load was 5 $\log_{10}$ copies/mL, and median CD4 cell count was 250 cells/mm.[3,28]

In the THRIVE study, the observed response rates were 86% for rilpivirine- and 82% for efavirenz-treated subjects. The ECHO study also showed similar results, with response rates of 83% and 83% for rilpivirine and efavirenz, respectively. In pooled analysis, the response

rate for rilpivirine was 78% and for efavirenz was 78%.[29] Rilpivirine was potent and non-inferior to efavirenz in both studies. The ITT-TLOVR primary outcome included subjects who had virologic failure (rebound/never suppressed) or discontinued study drug for any reason. The rate of efavirenz discontinuation was higher than that observed with rilpivirine in both studies, but the rate of viral failure due to rebound or failure to ever suppress was higher in the rilpivirine versus the efavirenz group (9% and 5%, respectively). In summary, rilpivirine 25 mg once daily and efavirenz 600 mg once daily had comparable responses at week 96. Although more virologic failures were observed in the rilpivirine group, the tolerability was better than that observed in efavirenz-treated patients. The majority of virologic failures in the rilpivirine group occurred in the first 48 weeks.

In secondary endpoint analyses of THRIVE and ECHO, mean CD4 cell count increases from baseline were comparable in both treatment arms. A pooled analysis showed that response rates were worse in patients with lower baseline CD4 cell counts, and this effect was more prominent in the rilpivirine group.[29] In THRIVE, 91% of patients with a baseline viral load of <100,000 copies/mL, 80% of those with a baseline viral load of 100,000–500,000 copies/mL, and 77% of those with a baseline viral load >500,000 copies/mL responded in the rilpivirine group, and the proportion of responders in the efavirenz group in each viral load stratum was 84%, 82%, and 69%, respectively. In ECHO, the corresponding numbers of responders in the rilpivirine group were 90%, 79%, and 62% for baseline viral loads of <100,000 copies/mL, 100,000–500,000 copies/mL, and >500,000 copies/mL, respectively, and 83%, 83%, and 81%, respectively, for each viral load stratum in subjects treated with efavirenz (Figure 1). Thus, despite comparable CD4 responses between the two arms, virologic response was reduced in the rilpivirine group when baseline viral load was >100,000 copies/mL. Discontinuation rates due to adverse events were higher in the efavirenz than in the rilpivirine group; grade 2–4 adverse events were more common in the efavirenz than in the rilpivirine group. In THRIVE, the incidence of mild-to-moderate adverse effects was identical between the rilpivirine and efavirenz groups (92%), but incidence of grade 2–4 adverse effects associated with treatment was lower in the rilpivirine than in the efavirenz group. Among common treatment-related (grade 2 or higher) adverse events, the incidence of rash in the rilpivirine group was significantly lower, and the incidence of neuropsychiatric adverse events was higher in the efavirenz group. These findings were similar in ECHO, with a higher incidence of grade 2–4 adverse effects associated with treatment in the efavirenz group. Among common treatment-related (grade 2 or higher) adverse events, the incidence of rash in the rilpivirine and efavirenz groups was 2% and 8%, respectively ($P < 0.001$). Mean changes in lipid parameters, total cholesterol, low-density lipoprotein cholesterol and triglycerides from baseline to week 48 after initiation of treatment were significantly lower in the rilpivirine group in THRIVE. In ECHO, the rate of discontinuation due to adverse events was six patients (2%) in the rilpivirine group and 25 patients (7%) in the efavirenz group. More patients in the efavirenz group had grade 2–4 adverse events than in the rilpivirine group. The change in triglycerides was not significantly different between the two treatment arms.

Patterns of rilpivirine-associated mutations and response to treatment in patients with primary NNRTI resistance

A resistance analysis from THRIVE and ECHO demonstrated that the most common NNRTI-resistant mutation that emerged when subjects failed rilpivirine was E138K (77%), and K103N (57%) in subjects who failed efavirenz. A unique pattern of NRTI-associated mutations that emerged when failing rilpivirine was M184I or M184V/I mixtures. This pattern is also found in etravirine resistance, the M184I that co-emerges with E138K facilitates the replication capacity of resistant viruses.[30] In addition, E138K and M184V/I that emerged in patients who have virologic failure to rilpivirine may confer resistance to other NNRTIs such as efavirenz, nevirapine, and etravirine.[31,32] In patients who failed efavirenz with only the K103N mutation, viruses still maintained susceptibility to etravirine.[17]

Currently, there are concerns over transmitted (primary) HIV drug resistance and virologic response after initiation of ART. The prevalence of primary drug resistance in western countries is approximately 10% and may be higher in particular areas.[33] Many studies have shown a reduced virologic response associated with transmitted drug-resistant viruses.[34] Response to rilpivirine at week 48 in the THRIVE and ECHO studies was not affected by pre-existing NNRTI mutations, due to low prevalence of rilpivirine resistance-associated mutations.[35] This suggests rilpivirine may have a role in treatment-naïve patients in settings with a high or increasing prevalence of primary resistance from first-generation NNRTI-associated mutations.

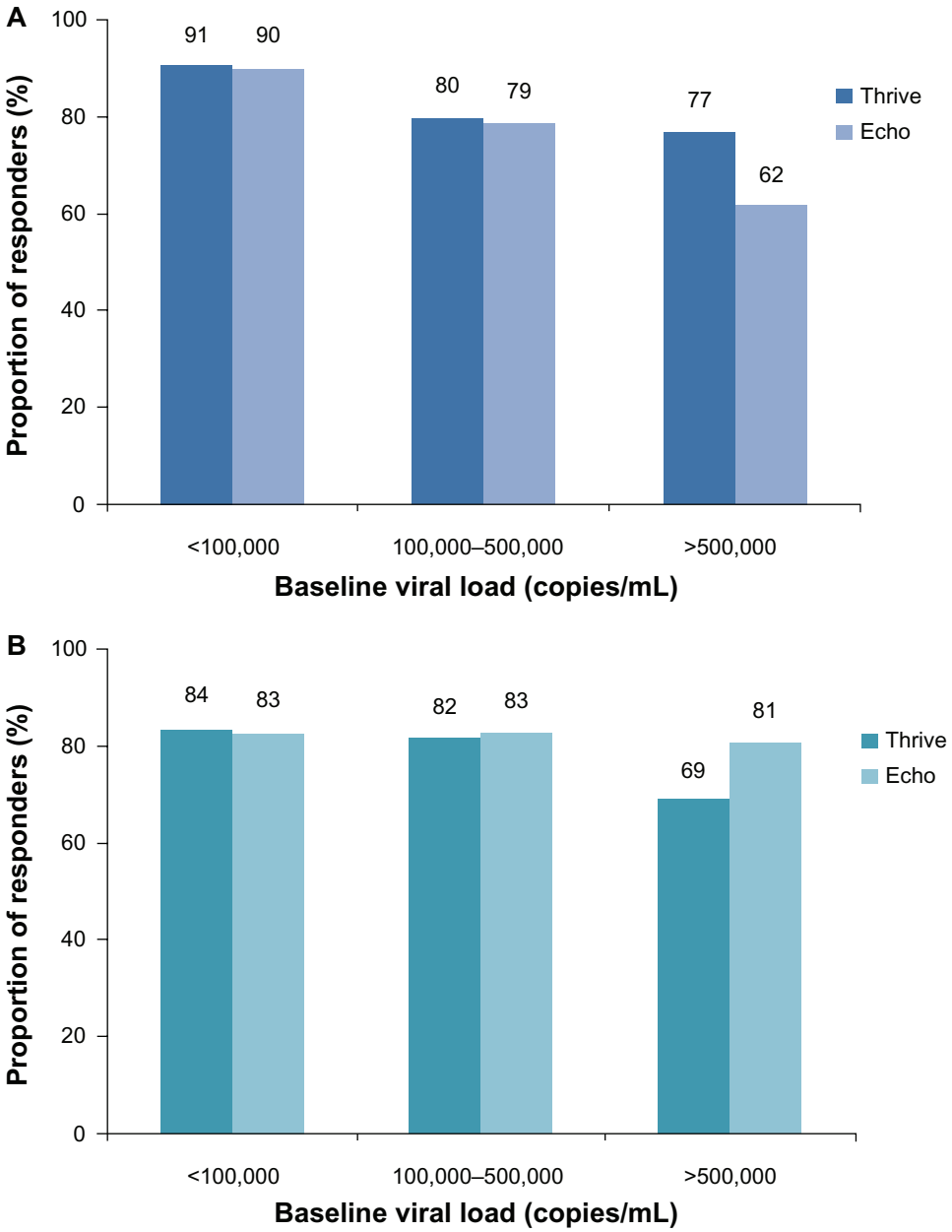

Figure 1 Proportion of responders to rilpivirine (**A**) and efavirenz (**B**) in the THRIVE and ECHO studies. Response rate in subjects in the rilpivirine group was reduced when baseline viral load was >100,000 copies/mL.[26,27]
Abbreviations: THRIVE, TMC278 against HIV, in a once daily Reglmen Versus Efavirenz; ECHO, Early Capture HIV Cohort Study.

Patterns of response and use of rilpivirine among different populations

No differences in response rates for subjects in either group were noted in subjects stratified by backbone regimen, gender, race, and HIV subtypes.[36] However, it appeared that Asian subjects and those infected with HIV-1 CRF01_AE had higher response rates in both treatment arms.[28] A subsequent pharmacodynamic study found that rilpivirine exposure was higher in female and Asian populations.[36] Patients with hepatitis co-infection in both treatment arms had a higher rate of hepatic adverse events.[37]

Although efavirenz causes fetal anomalies in animals and is classified as a US FDA pharmaceutical pregnancy category D drug, rilpivirine has not demonstrated any increased teratogenic risk in animal fetuses at doses 15 and 70 times higher than those recommended in humans. Currently, rilpivirine is classified in pregnancy category B. Rilpivirine might therefore be an alternative option for pregnant women. Nevertheless, recent evidence has confirmed that efavirenz is safe in pregnant women and has

been endorsed in the most recent British HIV Association (BHIVA) and World Health Organization (WHO) guidelines for women after the first trimester.[38,39] Rilpivirine may be preferable for women taking contraceptives, due to a lack of significant drug interactions with norethindrone and ethinyl estradiol.

Switching study of rilpivirine

In the SPIRIT (Switching boosted PI to Rilpivirine In-combination with Truvada as a single tablet regimen) trial, improvement in lipid parameters was demonstrated in 476 subjects, 24 weeks after switching to a rilpivirine-based regimen. Most patients in this study had received a boosted-PI regimen for at least 6 months, with viral load <50 copies/mL before switching. Patients were randomized to receive tenofovir/emtricitabine/rilpivirine (TDF/FTC/RPV) or ritonavir-boosted PI plus two NRTIs for 24 weeks, then patients randomized to the PI-based arm were switched to TDF/FTC/RPV. The primary endpoint of this study was virologic suppression at week 24 after switching, and secondary endpoints were changes in CD4 cell count, safety, and fasting lipid parameters from baseline before switching. After switching, the rate of virologic suppression between the two arms was comparable. In addition, subjects who switched to TDF/FTC/RPV had favorable changes in lipid parameters, particularly in triglyceride levels (Figure 2).[40]

Neuropsychiatric adverse effects were less common in subjects treated with rilpivirine than in those treated with efavirenz in the THRIVE and ECHO studies. Thus, rilpivirine may be an alternative choice for patients with intolerable CNS adverse effects from efavirenz. However, there is a concern over the drug interaction between efavirenz and rilpivirine: a pharmacokinetic study demonstrated that efavirenz decreases the minimum rilpivirine concentration by 25%. This interaction might reduce efficacy when switching from efavirenz to rilpivirine. However, virologic suppression at 12 weeks was maintained in all of 49 subjects who were stable on an efavirenz-based regimen, then switched to rilpivirine.[41] Follow-up data at week 48 will provide additional information on the clinical significance of this interaction.

Summary: the clinical use of rilpivirine for treatment-naïve patients – data from relevant clinical studies

In THRIVE and ECHO, rilpivirine was non-inferior to efavirenz in treatment-naïve patients. However, the primary composite endpoint, combining either virologic failure or treatment discontinuation mandates that results should be interpreted with caution. Although the rate of virologic failure was higher in the rilpivirine group, overall efficacy was balanced by higher discontinuation rates in the efavirenz group. Based on resistance results from these studies, rilpivirine might be a preferred agent in patients with transmitted NNRTI resistance. In addition, the virologic efficacy of rilpivirine was reduced in those with baseline HIV-1 viral loads >100,000 copies/mL. These facts must be considered when starting ART, since the ultimate goal of HIV treatment is maximal viral suppression. Due to the higher rate of virologic failures in subjects

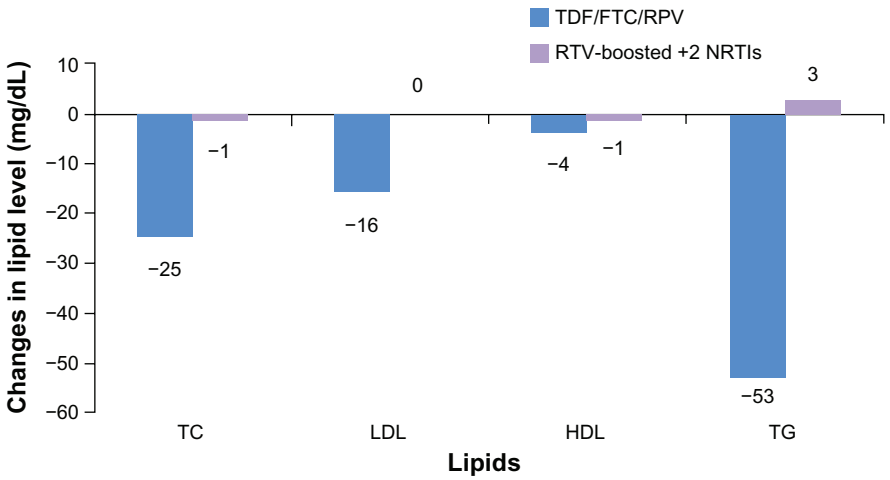

Figure 2 Lipid changes (mg/dL) in TDF/FTC/RPV versus continued ritonavir-boosted plus two NRTIs at week 24 after switching.
Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; NRTIs, nucleoside analog reverse transcriptase inhibitors; TC, total cholesterol; TDF/FTC/RPV, tenofovir/emtricitabine/rilpivirine; TG, triglyceride; RTV, ritonavir.

taking rilpivirine than in those taking efavirenz, current US Department of Health and Human Services (DHHS) ART treatment guidelines for adults and adolescents recommend rilpivirine as an alternative initial regimen for treatment-naïve patients.[10] The overall adverse effect rates and incidence of grade 2–4 events in the THRIVE and ECHO studies were lower in subjects taking rilpivirine than in those taking efavirenz. Adverse events leading to discontinuation of treatment were rash and depression, and these were higher in the efavirenz group; neurological adverse events such as dizziness and abnormal dreams were less common in subjects randomized to rilpivirine. In addition, mean change in lipid levels was lower in the rilpivirine group. This minimal effect on lipid metabolism of rilpivirine makes this agent suitable for patients with cardiovascular risk. Rilpivirine may be useful in patients who experience adverse effects such as hyperlipidemia or neuropsychiatric symptoms.

Since the most common rilpivirine-associated resistance mutations may have cross-resistance to other NNRTIs, including etravirine, patients failing rilpivirine would probably have fewer treatment options than patients who failed efavirenz.[42]

Use of rilpivirine in a single-tablet regimen

Use of once-daily ART is one strategy to improve adherence in HIV patients. Tenofovir/emtricitabine/efavirenz (TDF/FTC/EFV) is a well-tolerated option for single-tablet regimens (STRs). The STaR study aimed to compare two STRs: TDF/FTC/EFV versus TDF/FTC/RPV in treatment-naïve patients for 96 weeks. The primary endpoint was the proportion of subjects with HIV-1 RNA <50 copies/mL at week 48 determined by the FDA snapshot algorithm (12% pre-specified non-inferiority margin). A total of 784 subjects were enrolled and randomized. Baseline characteristics were well balanced in both treatment arms, with a baseline mean CD4 count of 390 cells/mm^3 and HIV-1 RNA of 4.8 $\log_{10}$ copies/mL. The analysis showed that TDF/FTC/RPV was non-inferior to TDF/FTC/EFV (86% versus 81%) at week 48 for HIV RNA <50 copies/mL (difference 4.0%, 95% CI –1.2%–9.2%) per FDA snapshot analysis. Furthermore, superiority in efficacy was demonstrated for baseline HIV-1 RNA ≤100,000 copies/mL (n = 508), 88% FTC/RPV/TDF versus 81% EFV/FTC/TDF (difference 7.2%, 95% CI 0.9%–13.4%), and non-inferiority for >100,000 copies/mL (n = 276), 80% FTC/RPV/TDF versus 82% EFV/FTC/TDF (difference –1.8%, 95% CI –11.2%–7.5%). Overall, virologic failure, defined as HIV RNA ≥50 copies/mL at week 48, discontinuation due to lack of efficacy per investigator or discontinuation of study drug for reasons other than an adverse event with HIV RNA ≥50 copies/mL was 8% for FTC/RPV/TDF versus 6% for EFV/FTC/TDF (difference 2.7%, 95% CI –0.9%–6.3%). There were fewer study drug discontinuations due to adverse events in FTC/RPV/TDF than in EFV/FTC/TDF. The STR FTC/RPV/TDF showed overall non-inferior efficacy and improved tolerability compared with the STR EFV/FTC/TDF, as well as superior efficacy for subjects with a baseline viral load ≤100,000 copies/mL in treatment-naïve HIV-1-infected subjects.[43]

Practical issue: selecting an NNRTI as the third agent in antiretroviral regimens for treatment-naïve patients

Most guidelines recommend NNRTIs, PIs, or integrase inhibitors for use as the third agent in antiretroviral regimens.[9,10] When comparing first- and second-generation NNRTIs, efavirenz is the preferred agent. However, when selecting an NNRTI as part of a treatment regimen, the characteristics of each individual antiretroviral agent should be considered, to tailor the appropriate treatment for a patient. Efavirenz has more CNS adverse events than others, and some patients may discontinue this agent due to this unfavorable effect; efavirenz should be avoided in patients with pre-existing psychiatric conditions. Furthermore, efavirenz has considerable adverse effects on lipid metabolism and leads to cutaneous eruptions. Nevirapine is an alternative to efavirenz in patients who experience adverse effects. Nevirapine also has some limitations, particularly severe hepatitis in patients with high CD4 levels (>250 cells/mm^3 in females and >400 cells/mm^3 in males), and current guidelines recommend initiating ART at higher CD4 cell count levels than in the past.[9] This guideline change may limit the use of nevirapine in patients unless they present with advanced disease. Nevirapine has less effect on lipid parameters than efavirenz, and no CNS adverse effects. Likewise, rilpivirine has a favorable effect on lipid profiles and also has no significant CNS side effects. However, it is clear that in subjects with a previous suboptimal response, and those with baseline viral loads >100,000 copies/mL, rilpivirine should be avoided. Other considerations include the requirement of food for absorption, and the contraindication in patients who are on rifamycins, such as rifampicin, rifabutin, or rifapentine, due to a significant drug interaction.[44] When selecting an NNRTI for treatment-naïve

Table 1 Comparison of characteristics of non-nucleoside analog reverse transcriptase inhibitors that are recommended for treatment-naïve patients

Initial US approval	**Efavirenz** **1998**	**Nevirapine** **1996**	**Rilpivirine** **2011**
Action	Noncompetitive inhibition of HIV-1 RT	Noncompetitive inhibition of HIV-1 RT	Noncompetitive inhibition of HIV-1 RT
Dose	Tablet 600, 200, 50 mg	Tablet 200 mg, 400 mg (od tablet with XR tablet formulation, Nevirapine XR) Oral suspension	Tablet 25 mg
Dose in adult and frequency of dosing	600 mg od	200 mg bid or 400 mg od (NVP XR) Require 14-day lead-in period	25 mg od
$T_{1/2}$	40–55 hours	25–30 hours	50 hours
Protein binding	99.5%	60%	99.7%
Elimination	Metabolized by CYP2B6 and CYP3A4; CYP3A4 mixed inducer/inhibitor (more an inducer than an inhibitor)	Metabolized by CYP substrate, inducer of 3A4 and 2B6	Metabolized by CYP3A4
Major drug and food interactions			
Use with rifamycin (rifampicin or rifabutin)	Increase dose of efavirenz to 800 mg od when used with rifampicin	Rifampicin should not be used*	Contraindicated
Use with antifungal agents	Decrease to 300 mg od, increase voriconazole to 400 mg every 12 hours	Significant drug interaction with itraconazole and ketoconazole	No significant change in voriconazole
Hormonal contraceptives	No significant interaction levonorgestrel (decrease AUC 83%), norelgestromin (decrease AUC 64%) (Consider alternative or additional method)	Significant interaction with ethinyl estradiol, norethindrone (Consider alternative or additional method)	No significant interaction with ethinyl estradiol, levonorgestrel, norelgestromin
Other major drug interactions			Contraindicated when used with PPI Contraindicated when used with systemic steroid Contraindicated when co-administered with carbamazepine, phenobarbital, phenytoin
Food interaction	High-fat and high-calorie meal increases AUC by 22% and 17%	No food effect	Food requirement
Adverse events			
Rash	Any type of rash occurs 8%–26%, discontinue efavirenz due to rash 1.7%	All rash 15% Higher incidence of rash, including fatal hypersensitivity reactions	All rash 1%–3%
Hepatotoxicity	4.5% had any hepatic event Rate of elevated liver enzymes 25% in patients with HBV or HCV co-infection	10% had hepatotoxicity Higher incidence of hepatoxicity than other NNRTIs Contraindicated in moderate or severe hepatic impairment Restriction of use in females with CD4 >250 and males with CD4 >400 cells/mm^3	3.6% had any hepatic event Rate of elevated liver enzymes 27.8% in patients with HBV or HCV co-infection
Lipids	Increase in concentration of total cholesterol, triglyceride	Increase in HDL-C and decreases in TC: HDL-C ratio than an EFV-containing regimen	Minimal increase in TC and TG

(*Continued*)

Table 1 (*Continued*)

Initial US approval	Efavirenz 1998	Nevirapine 1996	Rilpivirine 2011
Neuropsychiatric side effects	35% of patients had any grade of CNS side effects Dizziness, insomnia, impaired concentration, drowsiness, and abnormal dreams Serious psychiatric symptoms including severe depression, suicide attempts, aggressive behavior, delusions, paranoia, and psychosis-like symptoms	None	Dizziness, abnormal dreams and nightmare but significantly lower than with EFV
Use in specific populations			
Use in pregnancy	Pregnancy category D (teratogenic in nonhuman primate)	Pregnancy category B; however, risk of severe hepatic event in CD4 >250 cells/mm^3	Pregnancy category B; lacking data for teratogenicity in animals
Use in renal impairment	No dosage adjustment	No contraindication in renal impairment. Adjust dosage in CL_{CR} <20 cc/mL	No dosage adjustment
Use in liver impairment	Contraindicated in Child-Pugh B or C (moderate to severe hepatic impairment)	Contraindicated in Child-Pugh B or C (moderate to severe hepatic impairment)	No dose adjustment in mild hepatic impairment but (Child-Pugh A and B) Limited data in severe hepatic impairment
Fixed-dose combination	Co-formulated with TDF/FTC/EFV (Atripla®)	AZT/3TC/NVP (200 mg of NVP) D4T/3TC/NVP Available in some countries	Co-formulated with TDF/FTC/RPV (Complera®)
Pricing	Sustiva® $US785.90/month Atripla® $US2,253.88/month	Viramune® $US723.08/month Viramune XR® $US670.63/month	Edurant® $US804.38/month Complera® $US2,195.83/month
Patterns of resistance	K103N/S P225H K101E/Q/R V108I M230I/L G190S/T/A L100I	Y181C K101E G190A/S K103N V106A/M V108I T188C/L A97G F227L M230L	• More likely to develop virologic failure due to resistance than EFV and more likely to have resistance to 3TC or FTC • 14% of patients in THRIVE and ECHO had virologic failure with novel NNRTI-associated mutations E138K/G *K101E/P/T* V90I Y181C/I *V189I* H221Y *V179I/D/L* Emergent NRTI mutations in patients who failed rilpivirine M184I/V 53% K65R 9%

Notes: Pricing of antiretroviral agents was from DHHS guidelines version dated February 12, 2013.[10] *NVP with rifampicin may be co-administered in patients who cannot tolerate EFV.[45]

Abbreviations: AUC, area under the concentration–time curve; AZT/3TC/NVP, zidovudine/lamivudine/nevirapine; bid, twice daily; CL_{CR}, creatinine clearance; CNS, central nervous system; CYP, cytochrome P450; D4T/3TC/NVP, stavudine/lamivudine/nevirapine; EFV, efavirenz; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL-C, high-density lipoprotein cholesterol; NRTI, nucleoside analog reverse transcriptase inhibitor; NNRTI, non-nucleoside analog reverse transcriptase inhibitor; od, once daily; PPI, proton-pump inhibitor; RT, reverse transcriptase; $T_{1/2}$, elimination half-life; TC, total cholesterol; TDF/FTC/EFV, tenofovir/emtricitabine/efavirenz; TDF/FTC/RPV, tenofovir/emtricitabine/rilpivirine; TG, triglyceride; XR, extended release; THRIVE, TMC278 against HIV, in a once daily Reglmen Versus Efavirenz; ECHO, Early Capture HIV Cohort Study.

Table 2 Summary characteristics of rilpivirine (Edurant®)

Class	NNRTI
Action	Rilpivirine acts at hydrophobic position near NNRTI-binding site and causes inactivation of reverse transcriptase enzyme
Dose	25 mg once daily, with food
Formulation	Tablet, fixed-dose combination with TDF/FTC
Time to maximal plasma concentration	4–5 hours
Elimination half-life	Approximately 50 hours
Dose in hepatic impairment	• No dose adjustment in mild and moderate hepatic impairment (Child-Pugh class A and B) • No clinical information in Child-Pugh class A
Dose in renal impairment	• No dose adjustment is required in mild to moderate renal impairment • Require monitoring in severe or end-stage renal disease • Rilpivirine is highly protein-bound and may not be significantly removed by hemodialysis or peritoneal dialysis • Higher risk of hepatitis in patients co-infected with HBV or HCV
Use in pregnancy	Pregnancy category B
Use in patients with tuberculosis	Contraindicated if co-administered with rifampicin and rifabutin, rifapentine
Adverse effects	Rash, depression, insomnia, headache Use with caution when co-administered with drugs that prolong QTc
Major drug interactions	Acid-lowering agents such as antacid and H-receptor antagonists. RPV is contraindicated when co-administered with PPI Contraindicated when co-administered with • Anticonvulsants: carbamazepine, oxcarbamazepine, Phenobarbital, and phenytoin • Glucocorticoid (>one dose) systemic dexamethasone • St John's wort • Rifabutin
Conditions in which it should be used with caution	Patients with baseline HIV-1 viral load >100,000 copies/mL due to possible suboptimal response
Resistance pattern	• E138K/G, *K101E/P/T*, V90I, Y181C/I, *V189I*, H221Y, *V179I/D/L* • M184I/V (emergent NRTI mutations in patients who failed rilpivirine) • 90% of patients who failed rilpivirine had cross-resistance to etravirine and efavirenz
Price in the USA	Edurant® (rilpivirine) 30 tabs $804.38 Complera® (TDF/FTC/RPV) 30 tabs $2,195.83

Note: Data from.[10]

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; NNRTI, non-nucleoside analog reverse transcriptase inhibitor; NRTI, nucleoside analog reverse transcriptase inhibitor; PPI, proton-pump inhibitor; QTc, corrected QT interval; TDF/FTC/RPV, tenofovir/emtricitabine/rilpivirine.

patients, the physician should compare the advantages and disadvantages of each individual agent. Table 1 shows a comparison of characteristics of NNRTIs currently recommended for treatment-naïve patients, and Table 2 shows the clinical characteristics of rilpivirine.

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