INTRODUCTION

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) constitute a class of medications that have contributed significantly to the management of human immunodeficiency virus (HIV) infection. This article reviews the NNRTI class, with an emphasis on efavirenz (Sustiva), nevirapine (Viramune), etravirine (Intellence), and the newest agent, rilpivirine (Edurant), which has recently received FDA approval.

CURRENTLY USED AGENTS
Efavirenz (Sustiva)

**Pharmacokinetics**

Efavirenz (Sustiva, EFV, Bristol-Myers Squibb) is available as 50-mg and 200-mg capsules and as a 600-mg tablet. EFV has also been co-formulated with tenofovir (Viread, Gilead) and emtricitabine (Emtriva, ETC, Gilead) into one tablet (Atripla, Bristol-Myers Squibb/Gilead), which can be taken once daily. The recommended EFV dose is 600 mg at bedtime. Patients should be advised to take EFV on an empty stomach to lessen the likelihood of neuropsychiatric adverse effects (AEs), including vivid dreams. The presence of food increases the peak concentration (C_max) and the area-under-the-curve (AUC) concentration of EFV; therefore, the drug is best taken with the patient in a fasting state.\(^1\)

EFV has good oral bioavailability and is highly protein-bound (99.5%–99.75%). It is metabolized in the liver by cytochrome P450 (CYP) enzymes, specifically CYP 2B6 and CYP 3A4. Of note, EFV is capable of auto-induction; its half-life, therefore, can change from 52 to 76 hours after the first dose to 40 to 55 hours after multiple doses. However, no dosage adjustments are necessary to compensate for auto-induction or for renal insufficiency, including patients on hemodialysis. Furthermore, no dosage adjustments are needed for patients with mild hepatic insufficiency, although clinical experience and data are limited for patients with moderate-to-severe impairment.\(^1\) As a result of AEs, some sources suggest that therapeutic drug monitoring of EFV may be warranted; however, it is rarely used in clinical practice.\(^2,^3\)

**Drug–Drug Interactions**

Numerous drug interactions have been observed with EFV-containing regimens, but many of them can be managed by adjusting the doses of concomitant agents or using therapeutic alternatives. Because EFV is metabolized by CYP 3A4, other drugs that are inducers or inhibitors of this enzyme may increase or decrease EFV concentrations. Because EFV also induces CYP 3A4, agents that are substrates for this enzyme may have lower concentrations when coadministered with EFV. For example, the concomitant use of the protease inhibitor (PI) atazanavir (Reyataz, ATV, Bristol-Myers Squibb) in treatment-naïve patients is not recommended unless it is boosted by ritonavir (RTV, Norvir, Abbott), because ATV’s AUC concentration can decrease significantly when taken with EFV.\(^1,^4\)

Some antifungal agents increase the AUC concentration of EFV, and dosage adjustments are warranted. However, concomitant administration of EFV and voriconazole (Vend, Pfizer) is contraindicated; voriconazole levels are reduced significantly with standard dosing.\(^1,^5\) Administration of antimycobacterial agents with EFV may also cause drug interactions. Coadministration with rifampin (Rifadin, Sanofi-aventis) decreases the AUC concentration of EFV, whereas coadministration with rifabutin (Mycobutin, Pfizer) decreases the AUC concentration of rifabutin. Thus, it is often recommended that the combination of EFV and rifampin be avoided in favor of combining EFV with a higher-than-normal dose of rifabutin.\(^6,^7\)

Some antiepileptic drugs are also affected by EFV. For example, carbamazepine (e.g., Carbatrol, Shire) causes a dual decrease in both EFV and carbamazepine AUC concentrations.\(^8\) Therefore, it may be advisable to avoid this combination of agents when possible. Additional clinically relevant drug–drug interactions with EFV are presented in Table 1.

Safety

Important clinical AEs associated with efavirenz are listed in Table 2 (see page 348). Hepatotoxicity has been reported in patients receiving EFV, but the incidence may be lower in these patients than in those receiving other NNRTIs, including nevirapine (Viramune, NVP, Boehringer Ingelheim).

In a prospective study comparing the incidence of severe hepatic injury, 8% of patients receiving EFV (n = 312) and 15.6% of patients receiving NVP (n = 256) experienced this AE.\(^9\) The incidence of hepatotoxicity with these agents appears to be much higher when pre-existing viral hepatitis is also present. Skin rashes are also common among patients receiving EFV. This reaction is often described as a transient AE, and only a limited number of patients have discontinued therapy. The rash typically appears within the first few months of treatment and often improves within two weeks.\(^10\) Antihistamines or a low-dose, tapering course of corticosteroids can be useful while patients recover from the skin reaction.

Disclosure: The authors report that they have no financial or commercial relationships in regard to this article.
**Table 1  Pertinent Drug Interactions Among Three NNRTIs**

<table>
<thead>
<tr>
<th>Concomitant Drug Class/Name</th>
<th>Nevirapine (Viramune, NVP)</th>
<th>Efavirenz (Sustiva, EFV)</th>
<th>Etravirine (Intolerance, ETV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>NVP concentration increases with coadministration</td>
<td>No significant effect expected</td>
<td>↑ ETV exposure</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>NVP strongly induces metabolism of itraconazole ↑ NVP possible</td>
<td>Itraconazole and OH-itraconazole AUC, C&lt;sub&gt;max&lt;/sub&gt; and C&lt;sub&gt;min&lt;/sub&gt; ↓ 35%–44%</td>
<td>↓ Itraconazole exposure ↑ ETV exposure</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Posaconazole AUC ↓ 50%</td>
<td>↑ ETV possible</td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>↓ Voriconazole possible ↑ NVP possible</td>
<td>Voriconazole AUC ↓ 77%↑ EFV AUC ↑ 44%</td>
<td>↑ Voriconazole possible ↑ ETV possible</td>
</tr>
<tr>
<td>Carbamazepine Phenobarbital Phenytoin</td>
<td>↓ Anticonvulsant and NVP possible</td>
<td>Carbamazepine + EFV: carbamazepine AUC ↓ 27% and EFV AUC ↓ 36% Phenytoin + EFV: ↓ EFV and ↓ phenytoin possible</td>
<td>↓ Anticonvulsanth Decreased levels of ETV</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Clarithromycin AUC ↓ 30% I4-OH-clarithromycin AUC ↑ 27%–58%</td>
<td>Reduces clarithromycin concentration</td>
<td>Decreased clarithromycin exposure Increased ETV exposure</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Rifabutin AUC ↑ 17% and metabolite AUC ↑ 24% NVP C&lt;sub&gt;min&lt;/sub&gt; ↓ 16%</td>
<td>Rifabutin ↓ 38%</td>
<td>Rifabutin and metabolite AUC ↓ 17% ETV AUC ↓ 37%</td>
</tr>
<tr>
<td>Rifampin</td>
<td>NVP ↓ 31%*</td>
<td>EFV AUC ↓ 26%</td>
<td>Significant ↓ ETR possible</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Lorazepam C&lt;sub&gt;max&lt;/sub&gt; ↑ 16%, AUC no significant effect expected</td>
<td>↑ Diazepam possible</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>↑ Diazepam possible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>Significant ↑ midazolam expected‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dihydropyridine CCBs</td>
<td>↓ CCBs possible</td>
<td>↓ CCBs possible</td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>↓ Diltiazem possible</td>
<td>Diltiazem AUC ↓ 69%</td>
<td></td>
</tr>
<tr>
<td>Hormonal contraceptives</td>
<td>Ethinyl estradiol AUC ↓ 29%</td>
<td>Ethinyl estradiol AUC ↑ 37%</td>
<td>Ethinyl estradiol AUC ↑ 22% Norethindrone: no significant effect expected</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Atrovastatin AUC ↓ 32%–43%</td>
<td>Decrease exposure to atorvastatin with increase in active metabolite</td>
<td></td>
</tr>
<tr>
<td>Lovastatin Simvastatin</td>
<td>↓ Lovastatin possible ↓ Simvastatin possible</td>
<td>Simvastatin AUC ↓ 68%</td>
<td>↓ Lovastatin possible ↓ Simvastatin possible</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Pravastatin AUC ↓ 44%</td>
<td>No effect on pravastatin expected</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>Methadone AUC ↓ 41% NVP: no significant effect</td>
<td>Methadone AUC ↓ 52%</td>
<td>No significant effect expected</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Induces warfarin metabolism ↑ or ↓ Warfarin possible</td>
<td>↑ Warfarin possible</td>
<td></td>
</tr>
</tbody>
</table>

*Contraindicated.
† Contraindicated at the standard dose.
‡ Contraindicated with oral midazolam.
Data from references 23, 49–52, 79–95.
The most commonly reported and use-limiting AEs encountered with EFV are neuropsychiatric effects.\textsuperscript{10–14} In one study, 174 patients receiving EFV were given a questionnaire and were observed for three months. Many of the respondents reported the presence of central nervous system (CNS) disturbances such as emotional instability (12.1%), insomnia (17.8%), hallucinations (5.7%), impaired concentration (17.9%), and abnormal dreams (27%).\textsuperscript{10} These particular AEs are common after therapy with EFV is begun, but they usually diminish over time and often disappear entirely after one or two months. However, these AEs sometimes last up to one year or longer, often leading to changes in therapy. Because of the high likelihood of experiencing CNS-related AEs with EFV, it is often recommended that patients with pre-existing neuropsychiatric diagnoses not begin therapy with this agent in order to avoid potential exacerbations.\textsuperscript{1,10}

When candidates are being evaluated for EFV therapy, it is also important to consider the drug’s known potential for teratogenicity. These effects have led to the designation of EFV as a Pregnancy Category D medication that is contraindicated during the first trimester. Women of childbearing age and those who wish to become pregnant should avoid the use of EFV owing to its potential for causing teratogenic effects.\textsuperscript{15,16}

## Clinical Efficacy

Many trials have consistently found efavirenz to be safe and effective as part of a highly active antiretroviral therapy (HAART) regimen.\textsuperscript{17–22} As a result, EFV has become the preferred NNRTI for primary therapy in the U.S. Department of Health and Human Services (DHHS) HIV treatment guidelines.\textsuperscript{23}

One of the initial investigations that established the role of EFV was an open-label, randomized study demonstrating superior efficacy to unboosted indinavir (Crixivan, IDV, Merck).\textsuperscript{20} Nelson et al. compared the rates of virological suppression at the end of 48 weeks using standard doses of each regimen combined with two drugs: lamivudine (Epivir, 3TC, GlaxoSmithKline), zidovudine (Retrovir, ZDV, AZT) (Combivir, GlaxoSmithKline/Shire/ViiV Healthcare). In patients with baseline CD4 counts of 100 cells/mm\(^3\) or more, the rate of virological suppression was 72.5% with EFV and 52.1% with IDV, respectively (\(P \leq 0.05\)). In patients with CD4 counts of 100 cells/mm\(^3\) or less, 69.8% in the EFV group and 50% in the IDV group achieved virological suppression (\(P \leq 0.05\)).\textsuperscript{20} The Nelson trial and others were among the first to demonstrate comparable efficacy between NNRTIs and the PI class when each drug was combined with an optimized nucleoside reverse transcriptase inhibitor (NRTI) background. This study, however, was conducted before the consistent use of PI boosting; thus, the results were considered to be limited.\textsuperscript{20}

The AIDS Clinical Trials Group (ACTG) subsequently conducted a follow-up study to compare the efficacy of EFV with that of a boosted PI regimen. ACTG A5142 was a randomized, open-label study designed primarily to compare the rates of virological suppression of EFV with RTV-boosted lopinavir (LPV/r) in HIV treatment-naive patients.\textsuperscript{21} The proportion of patients achieving virological suppression (a viral load below 50 copies) was 89% in the EFV-containing regimen and 77% in the lopinavir/ritonavir (Kaletra, Abbott)—containing regimen (\(P = 0.003\)).\textsuperscript{21} The results clearly indicated that EFV, when combined with an appropriate background regimen, could provide potent virological efficacy similar to and, at times, greater than that provided by a boosted PI regimen. Moreover, as a result of this investigation and subsequent trials that continue to demonstrate the efficacy of EFV, the agent remains a preferred option for the treatment of HIV infection. Although available efficacy data are limited in treatment-experienced patients, several investigations have studied rates of adherence to EFV therapy. Specifically, simplifying treatment in selected patients with the combination of EFV, tenofovir, and ETC (Atripla) has been found to maintain virological suppression as well as baseline regimens, which can be more complex or can have a greater pill burden. In this prospective, randomized, open-label multicenter study, 91% of the patients receiving Atripla preferred it to other regimens.\textsuperscript{22}

### Resistance

Efavirenz possesses a low genetic barrier to the development of HIV resistance. The most prevalent point mutation observed with EFV is K103N, which has led to significant cross-resistance among other NNRTIs, namely nevirapine (NVP). The mutation causes resistance to NVP and EFV by stabilizing the closed-pocket form of reverse transcriptase and inhibiting the binding of these agents.\textsuperscript{24,25} Other mutations that can affect EFV activity include L100I, K101E, V108I, P225H, K101P, V106M, Y181C/I, Y188L, and G190A/S. These minor NNRTI-resistant variants are more common in treatment-experienced patients and can contribute to treatment failure.\textsuperscript{26}

### Role of Efavirenz in Therapy

In the current DHHS guidelines, efavirenz is the preferred NNRTI recommended in therapy-naive patients, whereas nevirapine (NVP) is recommended as an alternative agent. A multicenter, open-label, randomized trial (2NN) compared the rates of treatment failure (within 10%) for EFV and NVP; both in combination with stavudine (Zerit, d4T, Bristol-Myers Squibb) and lamivudine (Epivir, 3TC, GlaxoSmithKline).\textsuperscript{21} EFV and NVP did not differ significantly in treatment failure, but the study was not adequately powered to prove equivalence within the 10% limit. In addition, besides CNS-related AEs, the side-effect

## Table 2 Incidence Rates of Grade 3 or 4 Clinical Adverse Events with Nevirapine and Efavirenz

<table>
<thead>
<tr>
<th></th>
<th>Nevirapine (Viramune)</th>
<th>Efavirenz (Sustiva)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical hepatitis</td>
<td>2.1%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Rash</td>
<td>3.4%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Insomnia, abnormal dreams</td>
<td>0</td>
<td>1.5%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0</td>
<td>1.0%</td>
</tr>
<tr>
<td>Depression</td>
<td>0.3%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Hepatobiliary laboratory toxicities</td>
<td>8.3%</td>
<td>4.5%</td>
</tr>
</tbody>
</table>

Data from van Leth F, et al. Lancet 2004;363:1253–1263.\textsuperscript{19}
profile for NVP was not favorable when compared with EFV. As a result of this comparison and other investigations demonstrating its safety and efficacy, EFV is currently considered to be the preferred agent in NNRTI-based regimens.

**Nevirapine (Viramune)**

**Pharmacokinetics**

The pharmacokinetic profile of nevirapine (NVP) is similar to that of the other NNRTIs, although differences exist. NVP is available as a 200-mg tablet and as a 50-mg/5-mL suspension. Its oral bioavailability is more than 90%. Similar to the other agents in this class, NVP is metabolized in the liver by CYP 3A4 and CYP 2B6 enzymes. Like efavirenz (EFV), NVP demonstrates auto-induction; unlike EFV, however, NVP necessitates dosing adjustments to compensate for auto-induction—a change from 200 mg once daily to 200 mg twice daily after two weeks of therapy. This change also decreases the potential for adverse drug reactions.

Excretion of NVP is predominantly renal, and the elimination half-life is 20 hours. No dosing adjustments are needed for patients with renal dysfunction. A study published by Cramer et al. in 2010 also found that hemodialysis did not significantly alter NVP steady-state concentrations for patients receiving 200 mg twice daily. Patients with liver dysfunction, particularly those with Child–Pugh Class B or C, should not take NVP.

A distinct disadvantage of NVP is the need for twice-daily dosing. Therefore, in an effort to provide an option for once-daily dosing, some studies have tested the pharmacokinetic profile of several NVP extended-release (XR) formulations. One open-label, multistage, crossover analysis was designed to identify a formulation for further development. All patients (n = 92) were treated with NVP immediate-release (IR) for more than 12 weeks and were then switched to one of four XR formulations given once daily. Following the switch, steady-state plasma concentrations were obtained for a 24-hour period.

The results indicated slow absorption of the XR formulation in addition to a decrease in bioavailability compared with the IR agent. However, compared with the IR formulation, which showed fluctuating plasma concentrations, the XR formulation maintained steady concentrations of NVP during a dosing interval. XR formulations were also considered to be safe. The most commonly reported AE was nasopharyngitis.

The researchers did not observe clinically relevant changes in laboratory values during the study. They concluded that the 400-mg XR formulation would be chosen for further development because it had better bioavailability and less variability than the other formulations. The FDA has not yet approved the XR formulation, but its clinical efficacy has been studied.

**Drug–Drug Interactions**

Like efavirenz, nevirapine (NVP) is also subject to many drug–drug interactions. NVP is a CYP 3A4 and 2B6 inducer. Therefore, drugs metabolized by these enzymes may have lower plasma levels because of increased metabolism. CYP inducers and inhibitors also may affect NVP levels. Clinically relevant drug–drug interactions are listed in Table 1 (see page 347).

**Safety**

A major side effect of nevirapine is hepatotoxicity, resulting in elevated transaminase (AST and ALT) levels. To decrease the potential for hepatotoxicity, CD4 cell counts should be below 250 cells/mm² in women and below 400 cells/mm² in men when NVP is initiated. Other risk factors for hepatotoxicity include elevated AST/ALT levels at baseline and either hepatitis B or hepatitis C infection. Most hepatotoxic events occur within the first six weeks of treatment, and the incidence decreases over time.

Another serious warning regarding NVP is the risk of hypersensitivity reactions, which can lead to Stevens–Johnson syndrome and toxic epidermal necrolysis. Studies comparing EFV and NVP have also noted that AEs, including rash, tend to be more common in patients receiving NVP-containing regimens.

NVP should be initiated with caution in HIV treatment-experienced patients. This recommendation stems from a cohort study of treatment-experienced patients who had low CD4 cell counts (below 250 cells/mm² in women and below 400 cells/mm² in men) before starting therapy and variable CD4 and HIV-RNA levels when they were switched to NVP. Interestingly, patients with high CD4 cell counts and undetectable viral loads safely switched to NVP. However, patients with detectable viral loads and higher CD4 cell counts, when switched to NVP, had higher rates of hypersensitivity. As a result, NVP should not be used as salvage therapy in this situation (Figure 1), and careful attention should be given to the patient’s current viral load prior to a switch to NVP therapy.

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**Figure 1** Algorithm for switching to nevirapine therapy in treatment-experienced patients. (Data from Wit FW, et al. *Clin Infect Dis* 2008;46:933–940.)

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**Clinical Efficacy**

One common reason for choosing nevirapine over efavirenz (EFV) is that NVP can be initiated safely in pregnant women if the CD4 cell count is 250 cells/mm³ or less. NVP therapy should be initiated in women with higher CD4 cell counts only if the benefits outweigh the risks. If a pregnant woman is receiving NVP and if her immune system indicates virological suppression and tolerance of the agent, she may continue with NVP regardless of her current CD4 cell count.²³

NVP is also a cost-effective option that is often used to prevent the transmission of HIV from mother to child during labor in resource-limited settings. The mother receives a single dose of NVP within 48 hours before labor, and the neonate subsequently receives a dose of NVP at 72 hours of age.³⁸ Recent studies indicate that ritonavir-boosted lopinavir (LPV/r), along with tenofovir and emtricitabine (Truvada, Gilead) should be prescribed for patients who have received a single dose of NVP within the previous 24 months or who have evidence of NVP resistance.

**OCTANE (Optimal Combination Therapy After Nevirapine Exposure)** was a randomized, open-label trial that evaluated the efficacy of NVP in women who had previously received single-dose NVP (trial 1) and in those without prior NVP exposure (trial 2).³⁹ Patients in both trials received either LPV/r or NVP, each combined with tenofovir and emtricitabine. Primary endpoints were time to virological failure or death.

Protease inhibitors (PIs) showed superior efficacy in patients with pre-treatment CD4 cell counts of fewer than 200 cells/mm³. PI therapy was also more effective in patients who had been exposed to a single dose of NVP within six months of starting treatment (26% of those in the NVP arm vs. 8% of the LPV/r arm; P = 0.001) but not in patients without prior exposure (14% of the NVP arm and 14% of the LVP/r arm). The hazard ratio (HR) for patients receiving single-dose NVP within different time periods is shown in Table 3.

In addition to women who have received single doses of NVP, PI-based therapy is also recommended for children with prior exposure to the single-dose regimen.⁴⁰ The P1060 study, a randomized, controlled trial, compared NVP with LPV/r, both with Combivir—zidovudine (Retrovir, AZT) and lamivudine (Epivir, 3TC)—in children six to 36 months of age who had received single-dose NVP as prophylaxis (cohort 1). A second cohort included patients without prior NVP exposure. In cohort 1, 164 children from nine sites in Africa were chosen to participate.

The primary objective was to compare the rates of treatment failure in 24 weeks between the two study arms. Treatment failure included death, virological failure, toxic effects, and permanent discontinuation of the drug for any reason. The percentage of children with previous exposure to single-dose NVP who experienced treatment failure was significantly higher in the NVP study arm, especially for children younger than 12 months of age. Virological failure or death was also significantly higher in the NVP arm for this age group. As a result, it is recommended that HIV-positive children younger than 12 months of age who have been treated with single-dose NVP as prophylaxis receive LPV/r with AZT and 3TC as their HIV regimen. However, PIs are known to cause suboptimal growth in children, and an investigation of the long-term effects of these agents is ongoing in the second cohort of this clinical trial.

As mentioned previously, a new extended-release formulation of NVP has been developed for once-daily dosing. VERxVE, an international, randomized, double-blind, double dummy, parallel-group trial, compared the efficacy of NVP XR 400 mg daily with NVP IR 200 mg twice daily.³² Treatment-naïve patients received NVP XR (n = 505) or NVP IR (n = 506), each with Truvada, a combination of tenofovir (Viread) plus emtricitabine (Emtriva). Secondary analyses included both safety and pharmacokinetic parameters.

The efficacy of the once-daily NVP XR formulation was found to be non-inferior to the NVP IR formulation. An undetectable viral load was achieved in 81% of XR patients and in 78% of IR patients. The safety profiles of both formulations were similar, with fewer discontinuations in the NVP XR arm. Symptomatic hepatic events were also lower in the XR study arm (1.6% vs. 2.8%), whereas the incidence of rash in both study arms was similar. Common AEs associated with NVP XR included nasopharyngitis, diarrhea, upper respiratory tract infection, rash, and headache.³¹

**Resistance**

In contrast to the mutations associated with efavirenz, *Y181C* is the most common genetic mutation associated with nevirapine (NVP) resistance, although there is also cross-resistance with K103N. The development of resistance is particularly noteworthy when NVP is used to prevent transmission of HIV infection from mother to child.⁴¹ The pharmacokinetic properties of NVP in pregnant women differ from those in non-pregnant HIV-positive women and may contribute to the incidence of resistance in this population.

The median half-life of NVP is 61.3 hours and 20 hours in HIV-infected pregnant and non-pregnant women, respectively.³² After pregnancy, up to 60.5% of maternal NVP concentrations can be found in breast milk.³³ The NVP breast milk concentration declines from 454 ng/mL at birth to 103
ng/mL seven days thereafter, but low concentrations of NVP can remain in breast milk for two to three weeks.43 In infants, the half-life of the transplazently acquired drug is 54 hours, and the half-life at 72 hours after birth is 46.5 hours.41 These pharmacokinetic factors are important to the development of resistance and for administering NVP correctly in pregnant HIV-positive women and newborn infants.

Of note, resistance to NVP can develop when the drug is administered as monotherapy, in contrast to combination therapy. For pregnant women who are breast-feeding for more than seven days, the risk of resistance is elevated in infants receiving single-dose NVP. The risk of resistance increases in infants and mothers who received a single dose of NVP to prevent mother-to-child HIV transmission.44

Role of Nevirapine in Therapy
One of the unique uses of nevirapine is in HIV-positive pregnant women. NVP can be used as part of a combination regimen with Combivir (AZT/3TC) for this purpose.44 NVP is also used to prevent mother-to-child HIV transmission during labor. To prevent the spread of HIV, the World Health Organization (WHO) has developed international guidelines for preventing the transmission of HIV infection from mother to child. Untreated pregnant patients with HIV should receive AZT starting at 28 weeks of pregnancy.44 During the intrapartum period, they should receive AZT/3TC plus a single dose of NVP.44 For the postpartum period, the mother should receive AZT/3TC for seven additional days; the infant should receive single-dose NVP and AZT for a total of seven days.44

In countries where these regimens cannot be obtained, at least single-dose NVP should be used to prevent transmission;44 however, there are risks to using single-dose NVP, and not all patient populations are eligible. Although the WHO guidelines are not the standard of care in the U.S., they are beneficial in settings with limited resources. For example, WHO recommends using daily NVP for a minimum of four to six weeks for infants who are breast-fed.44 DHHS guidelines do not recommend breast-feeding in women with HIV co-infection, because other options are readily available.23

Etravirine (Intelence) Pharmacokinetics
In January 2008, the FDA approved etravirine (Intelence, ETV, Tibotec), a second-generation NNRTI for treatment-experienced patients for use with other antiretroviral (ARV) agents. ETV is currently available as 100-mg or 200-mg tablets at a recommended dosage of 200 mg twice daily. The tablets are dispersible in water, forming a tasteless liquid for patients who have difficulty swallowing.45

Although ETV possesses some pharmacokinetic parameters that are similar to those of other NNRTI agents, it also has some exceptional characteristics. Its absorption takes place in the small intestine, and the peak concentration (C_{max}) is reached within four to five hours after dosing.45,46 The drug exhibits a long half-life (30–40 hours), which is shorter than that of EFV but longer than that of NVP.45,46 Alterations in gastric pH do not affect the bioavailability of ETV, and elimination is primarily via the fecal route (93.7%) with negligible urinary excretion (1.2%).45 No dosage adjustments are required for patients with hepatic or renal impairment, including those receiving hemodialysis and peritoneal dialysis.45

Unlike EFV, ETV should be taken with food. When ETV is taken in the fasting state, there is a 51% decrease in overall drug exposure.47 It is thought that the increased bioavailability of ETV, when taken with food, is a result of the increased bile content and the drug’s improved solubility. Improved absorption might also be explained by the presence of lipid digestion products within the intestinal lumen and by a prolonged gastric residence time.

ETV is highly bound (99.9%) by plasma proteins, and like EFV and NVP, it is metabolized in the liver.48 Compared with EFV and NVP, which are metabolized by CYP 3A4 and CYP 2B6, ETV is metabolized by CYP 3A4, CYP 2C9, and CYP 2C19.49 Although ETV is a substrate of these isoenzymes, it is also a weak inducer of CYP 3A4 and a mild inhibitor of CYP 2C9, CYP 2C19, and p-glycoprotein.50,51 These characteristics lead to a host of potential drug–drug interactions with ETV.

Drug–Drug Interactions
Coadministration of etravirine with agents that inhibit or induce CYP 3A4, CYP 2C9, or CYP 2C19 has the potential to alter the drug’s therapeutic effect. Substrates for these enzymes or p-glycoprotein may also undergo altered therapeutic effects owing to ETV-associated induction or inhibition. As a result, any medications administered with ETV should be investigated for potential interactions.

A reduction in ETV exposure can occur with several ARV agents, and coadministration should be avoided with atazanavir/ritonavir, fosamprenavir/ritonavir, tipranavir/ritonavir, unboosted PIs, and other NNRTIs.50–52 In phase 3 clinical trials, ritonavir-boosted darunavir (DRV, Prezista, Tibotec) reduced ETV exposure by 37% when it was administered as part of the background regimen. Although ETV exposure was reduced, alterations in efficacy did not occur; therefore, avoiding this combination is not necessary.53–55

When taken with other agents, ETV decreased serum concentrations of maraviroc (Selzentry, Pfizer) by 53%.56 It is therefore recommended that maraviroc 600 mg be administered twice daily when combined with ETV in the absence of a CYP 3A4 inhibitor.

Clarithromycin (Biaxin, Abbott) also undergoes alterations in exposure as a result of ETV coadministration, namely a decrease in clarithromycin concentrations with a corresponding increase in its active metabolite, 14-OH-clarithromycin.44 An adjustment of doses is not warranted, although clarithromycin activity against Mycobacterium avium may be reduced.49

ETV also has the potential to lower plasma concentrations of other medications, including HMG–CoA reductase inhibitors (statins), calcium-channel blockers, and tricyclic antidepressants.49 Additional drug–drug interactions are presented in Table 1 on page 347.

Safety
During phase 3 clinical trials, the most common adverse effects (AEs) reported with etravirine (ETV) were nausea, diarrhea, headache, and rash.33,55 Specifically, 19% of patients receiving ETV experienced a self-limiting rash compared with
Clinical Efficacy
The FDA approved etravirine on the basis of data established in two phase 3 studies. DUET I and II were randomized, double-blind, placebo-controlled, international trials designed to evaluate the safety and efficacy of ETV at 24 and 48 weeks. Treatment-experienced adult patients who were not responding to an ARV regimen with at least one NNRTI mutation, three primary PI mutations, and a viral load of 5,000 copies/mL or more received either ETV or a placebo, each combined with an optimized background regimen. The primary endpoint was the total number of patients achieving a viral load of 50 copies/mL or below after 24 and 48 weeks. The optimized background regimen included darunavir/ritonavir 600/100 mg twice daily, an investigator-selected NRTI, and a second NRTI or optional enfuvirtide (Fuzeon, Roche/Trimeris).

In the pooled analysis of these trials (n = 1,203), 61% of patients receiving ETV achieved the primary endpoint at 48 weeks compared with 40% of placebo patients (P < 0.0001). Virological response was achieved at a median of 15.7 weeks with ETV compared with 32.7 weeks with placebo (P = 0.0001).

Factors contributing to the superior virological response to ETV included the baseline viral load, baseline CD4 count, adherence, background regimen, and use of enfuvirtide. When enfuvirtide was included, 71% of the ETV group reached the primary endpoint compared with 59% of the placebo group (P = 0.0199). Among patients who did not use enfuvirtide, 57% in the ETV group and 33% in the placebo group achieved undetectable viral loads (P < 0.0001). Overall, the results of these studies confirmed an improved response when ETV was included as part of the ARV regimen.

Resistance
The resistance profile of etravirine has been attributed to the agent’s unique diarylpyrimidine structure, which allows for greater flexibility with multiple binding conformations through torsion. The enhanced flexibility enables ETV to retain its binding capacity for reverse transcriptase in the presence of multiple NNRTI mutations, including K103N, which confers resistance to EFV and NVP. When mutations occur within the binding pocket, ETV performs conformational adaptation by reorientation. The ability to withstand multiple NNRTI mutations gives ETV a superior resistance profile when compared with efavirenz (EFV) and nevirapine (NVP).

Currently, 17 resistance-associated mutations (RAMs) affect ETV’s binding capacity: V90I, A98G, L100I, K101E/P/H, V106I, V179D/F/T, Y181C/I/V, G190A/S, E138A, and M230L. Unique to ETV is its ability to retain ARV activity when the high-level cross-class mutation, K103N, is present in the reverse transcriptase enzyme. When K103N is present with Y181C, ETV is 10 times more potent than EFV. In an analysis of pooled clinical isolates for RAMs that caused NNRTI resistance, 60% of the 89,113 isolates expressed ETV RAMs. The most common mutations among these were G190A (21%) and Y181C (28%); V179T was the least frequently detected mutation.

In the DUET trials, RAMs were identified and were assigned weight factors to indicate their impact on ETV activity. RAMs with higher weight factors indicated increased resistance and decreased virological response. If three or more RAMs were found, ETV resulted in a virological response similar to that of placebo. These results and supporting data from additional studies confirm a direct correlation between the number of ETV RAMs present in a patient’s virus and loss of virological response.
The absorption of rilpivirine is highly pH-dependent. In acidic conditions, its bioavailability is increased; therefore, it is recommended that patients take rilpivirine with food. In a study of 12 healthy volunteers, the $C_{\text{max}}$ and AUC concentrations of rilpivirine were 71% and 45%, higher, respectively, when the drug was given with food.\textsuperscript{66} Comparable to other NNRTIs, rilpivirine has a half-life of approximately 38 hours. It is also highly protein-bound, and it is a substrate and inducer of CYP 3A4.\textsuperscript{66}

In addition to the tablet formulation, a parenteral depot designed to lengthen dosing intervals in HIV-positive patients is under development.\textsuperscript{69} Tibotec has announced an effort to combine rilpivirine with Gilead’s Truvada (tenofovir/emtricitabine) into a single-combination, once-daily tablet. In January 2011, however, the FDA declined to approve the NDA for the combination and requested more information on the analytical methodology.\textsuperscript{70}

**Drug–Drug Interactions**

As a substrate and inducer of CYP 3A4, rilpivirine is expected to carry significant drug interactions. In particular, when rilpivirine was combined with darunavir/ritonavir, the AUC concentration, the $C_{\text{max}}$ and the $C_{\text{min}}$ of rilpivirine were increased by 230%, 79%, and 278%, respectively, whereas no clinically significant AEs occurred with darunavir (DRV).\textsuperscript{71} Despite these altered concentrations, there are currently no specific recommendations for dosage adjustments when this combination is administered. Additional studies are necessary to address the potential interactions of rilpivirine with other agents from the PI class.

Aside from the PIs, drug interactions with rilpivirine have been documented with ketoconazole (Nizoral, Janssen) and rifampicin. As a potent CYP 3A4 inducer, rifampicin reduces rilpivirine concentrations by 80% to 89%. As a result, it is recommended that rilpivirine not be given in combination with rifampicin.\textsuperscript{72,73}

Finally, given the pH-dependent absorption of rilpivirine, Van Heeswijk et al. investigated the effects of concomitant administration of famotidine (Pepsid, Merck).\textsuperscript{74} As expected, the coadministration of famotidine 40 mg reduced rilpivirine concentrations, leading to the recommendation that these agents be taken separately. Famotidine can be given 12 hours before or four hours after rilpivirine is administered.

**Safety**

In two phase 3 international randomized clinical trials—ECHO (Early Capture HIV Cohort, TMC-278-C209) and THRIVE (TMC-278-C215)—the safety of rilpivirine in treatment-naïve patients was compared with that of efavirenz (EFV) (Table 4). In the pooled analysis of these trials, rilpivirine was found to be well tolerated. Overall, fewer AEs led to discontinuation of rilpivirine, and the incidence of grade 2–4 events related to the treatment, including rash, dizziness, and abnormal dreams, was also lower. In addition, fewer psychiatric and neurological AEs were reported for rilpivirine than for EFV.\textsuperscript{75}

**Resistance**

Rilpivirine exhibits a chemical structure similar to that of etravirine (ETV). As a result, it possesses conformational flexibility within the allosteric binding pocket of reverse transcriptase that conveys stability against many NNRTI mutations.\textsuperscript{76} Like ETV, rilpivirine also has a high barrier to ARV resistance and remains active in the presence of multiple NNRTI mutations, including $K103N$ and $Y181C$.\textsuperscript{76} Compared with ETV, rilpivirine appears to display greater potency in wild-type HIV as well as in viruses with specific mutations, including $Y181C$ and $K103N$.\textsuperscript{77}

In phase 3 trials, new NNRTI mutations developed in 63% of rilpivirine recipients.\textsuperscript{78} The mutation that occurred most often was $E138K$, a novel NNRTI mutation. Of particular note, 90% of these patients experienced cross-resistance to ETV.

Compared with rilpivirine in the phase 3 clinical trials, 54% of patients receiving efavirenz (EFV) developed new NNRTI resistance-associated mutations (RAMs), most commonly $K103N$. However, compared with EFV, NRTI resistance mutations were more likely to develop in patients receiving rilpivirine (68% vs. 32%, respectively).\textsuperscript{78} The clinical significance of these differences in resistance patterns with rilpivirine and EFV has not yet been determined.

**Clinical Efficacy**

In addition to addressing safety and resistance, the ECHO and THRIVE trials were conducted to compare the efficacy of rilpivirine and efavirenz (EFV).\textsuperscript{75} Both of these international phase 3 randomized, double-blinded, double-dummy, active-control studies were performed in treatment-naïve individuals. In ECHO, patients were assigned to receive either rilpivirine 25 mg once daily or EFV 600 mg once daily with a background regimen of tenofovir/emtricitabine (Truvada).\textsuperscript{75} THRIVE had a similar design. Patients were assigned to the same doses of rilpivirine and EFV, but background regimens could include
one of three combinations: Truvada (tenofovir/emtricitabine), Combivir (zidovudine/lamivudine), or Epzicom (abacavir, Zidovudine) plus lamivudine (Epivir). The only variation in the inclusion and exclusion criteria in THRIVE was that patients had to have a negative human leukocyte antigen (HLA-B*5701); in that case, abacavir (ABC) was included in the treatment regimen.\textsuperscript{75}

Overall, the combined results for these trials demonstrated that the virological efficacy of rilpivirine was non inferior to that of EFV. An undetectable viral load (below 50 copies/mL) was achieved in 84.3\% of those taking rilpivirine compared with 82.3\% in the EFV group; the estimated difference in response was 1.6\% (95\% confidence interval [CI], –2.2 to 5.3).\textsuperscript{75}

Although virological failure rates for EFV and rilpivirine were similar (11.5\% and 11\%, respectively), the reasons for failure between the groups differed. More patients receiving rilpivirine (9\%) experienced virological failure compared with the EFV group (4.8\%), whereas those receiving EFV generally failed to respond to therapy because of treatment-emergent AEs (6.7\%) or toxicities (2\%). The difference in virological efficacy was driven mostly by patients with a high viral load (more than 100,000 copies/mL) when they began therapy.

Another difference between treatment arms involved immunological response. The mean CD4 cell count increase from baseline was slightly higher with rilpivirine than with EFV (192 and 176 cells/mm\(^3\), respectively). Despite these differences, rilpivirine appears to be a safe and effective agent overall for the management of treatment-naive patients with HIV infection.\textsuperscript{75}

Role of Rilpivirine in Therapy

A second-generation NNRTI, rilpivirine has recently received FDA approval for use in combination with other antiretrovirals for the treatment of HIV-1 infection in treatment-naive adults. It is administered as a 25-mg tablet once daily with food, and it appears to be safe and effective, though questions remain regarding differences in virological response, compared with efavirenz in phase 3 clinical trials. As a result of its extensive resistance profile, rilpivirine may also be considered in treatment-experienced patients, particularly in those who have not responded to first-generation agents. However, more studies are necessary to establish this use for rilpivirine, because clinical data are currently limited to treatment-naive patients.

CONCLUSION

NNRTIs are commonly used in the management of HIV infection in the U.S. and throughout the world. Given the recent addition of etravirine (Intelenz) to the U.S. market and the fact that a fourth agent (rilpivirine) has been approved, a review of these agents is warranted. Each agent in this class has specific characteristics and potential benefits when used in appropriate patients.

REFERENCES

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56. Rîlpiuvirine (Edurant), prescribing information. Ritanj, N.J.: Tibotec Therapeutics, Division of Centocor Ortho Biotech Products, L.P.


