

## NEW ANTIRETROVIRAL DRUGS: MARAVIROC, RALTEGRAVIR, ETRAVIRINE, AND RILPIVIRINE

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### Editor's Note:

For comprehensive information regarding the use of antiretroviral agents, see [Antiretroviral Therapy](#).

#### What's New - November 2011 Update

- The FDA has issued new rash and hypersensitivity warnings regarding raltegravir (see Section III)
- The new NNRTI rilpivirine has been approved by the FDA for treatment in ART-naïve patients (see Section V)

### I. INTRODUCTION

#### RECOMMENDATION:

**Prescribers should consult with a clinician with extensive experience with antiretroviral therapy and management before initiating treatment with maraviroc, raltegravir, etravirine, or rilpivirine. These drugs should optimally be used as part of a regimen with at least two fully active agents plus the new agent.**

Four antiretroviral agents have recently been approved by the Food and Drug Administration (FDA) for treatment of HIV-1 infection. Two of these agents, maraviroc (Selzentry) and raltegravir (Isentress), are the first in new classes of antiretroviral therapy (ART) agents: CCR5 co-receptor antagonists and integrase inhibitors, respectively. The third and fourth agents, etravirine (Intelence) and rilpivirine (Edurant), are NNRTIs.

Maraviroc and raltegravir are approved for use in both ART-experienced and ART-naïve patients. Etravirine is approved only for use as a component of a salvage ART regimen for treatment-experienced patients, and rilpivirine is approved only for use in ART-naïve patients.

Maraviroc, raltegravir, etravirine, and rilpivirine have not been studied in pregnant women. Clinicians who are treating HIV-infected pregnant women should report cases of prenatal exposure to ART medications to the [Antiretroviral Pregnancy Registry](#).

## II. MARAVIROC

Updated June 2010

### RECOMMENDATION:

**Maraviroc should be prescribed only for patients with CCR5-tropic virus, as determined by a tropism assay that is performed at the time that therapy is considered. (AII)**

**Maraviroc should not be used outside of clinical trials in patients with dual/mixed- or CXCR4-tropic virus. (AII)**

The CCR5 co-receptor antagonist maraviroc is a potent agent that has been approved by the FDA for therapy in CCR5-tropic, HIV-infected patients. Maraviroc is approved for use in ART-naïve patients and for construction of a potent, fully suppressible regimen for patients with intolerance or resistance to first- or later-line agents. A phase III study showed that maraviroc achieved comparable viral suppression when compared to efavirenz in ART-naïve patients receiving combination treatment. However, more ART-naïve patients treated with maraviroc experienced virologic failure and developed lamivudine resistance compared to efavirenz.<sup>1</sup> Maraviroc has been demonstrated to be effective in ART-experienced adults.<sup>2,3</sup>

Screening with a co-receptor tropism assay should be performed at the time that therapy is considered because previous results may not be valid due to tropism changes. The sensitivity of some co-receptor tropism assays has been enhanced, but treatment with agents in the CCR5 co-receptor antagonist class remains a challenge (see [Diagnostic, Monitoring, and Resistance Laboratory Tests for HIV](#)). In the past, many patients who failed therapy with maraviroc and other investigational CCR5 receptor antagonists were found to have dual- or mixed-tropic HIV-1 that was not detected by the screening assay used.<sup>4</sup> One study found that maraviroc was no more effective than placebo when used with an optimized background regimen in individuals with dual/mixed tropic virus.<sup>5</sup> Therefore, maraviroc should not be used outside of clinical trials in patients with dual/mixed-tropic virus.

### **Key Point:**

Maraviroc may be used as part of a salvage regimen in treatment-experienced, CCR5-tropic patients when resistance or side effects have limited the use of other available agents. Maraviroc is also approved by the FDA for use in initial regimens for treatment-naïve, CCR5-tropic patients.

- *Dosing:* 300 mg PO twice daily, with the following caveats:
  - The metabolism of maraviroc is affected by strong CYP3A inducers and inhibitors; therefore, co-administration of potent CYP3A inducers and potent CYP3A inhibitors may require dosing adjustments (see Table 1 and [HIV Drug-Drug Interactions: Table 2](#)).
  - Maraviroc should not be prescribed for patients with severe renal impairment or ESRD who are receiving potent CYP3A inducers or potent CYP3A inhibitors. Patients with severe renal impairment or ESRD who are not receiving potent CYP3A inducers or inhibitors may require dose adjustments for maraviroc to avoid cardiovascular risks associated with postural hypotension (see [Antiretroviral Therapy, Maraviroc table](#)).

- *Should not be co-administered with the following:*
  - The CYP3A inducer St. John’s wort (*Hypericum perforatum*) or products containing St. John’s wort.
- *Main side effects:* cough, fever, colds, rash, muscle and joint pain, stomach pain, and dizziness; however, it is generally well tolerated.
- *FDA Pregnancy Category:* B

For additional prescribing information, see [Antiretroviral Therapy: Maraviroc table](#), as well as the [manufacturer’s maraviroc label](#).

<b>TABLE 1 ADULT DOSING OF MARAVIROC</b>	
<ul style="list-style-type: none"> <li>○ All NRTIs</li> <li>○ Nevirapine</li> <li>○ Tipranavir/ritonavir</li> <li>○ Enfuvirtide</li> <li>○ Raltegravir</li> </ul>	300 mg twice daily
<ul style="list-style-type: none"> <li>○ Potent CYP3A inhibitors<sup>a,b</sup> <ul style="list-style-type: none"> <li>– PIs (except tipranavir/ritonavir)</li> <li>– Delavirdine</li> <li>– Ketoconazole, itraconazole, clarithromycin</li> <li>– Other potent CYP3A inhibitors (e.g., nefazodone, telithromycin)</li> </ul> </li> </ul>	150 mg twice daily
<ul style="list-style-type: none"> <li>○ Potent CYP3A inducers<sup>a</sup> (without co-administration of a strong CYP3A inhibitor): <ul style="list-style-type: none"> <li>– Efavirenz</li> <li>– Etravirine</li> <li>– Rifampin</li> <li>– Carbamazepine, phenobarbital, and phenytoin</li> </ul> </li> </ul>	600 mg twice daily
<ul style="list-style-type: none"> <li>○ Severe renal impairment<sup>c</sup></li> </ul>	Adjustment may be necessary
<ul style="list-style-type: none"> <li>○ Severe hepatic impairment<sup>d</sup></li> </ul>	Adjustment necessary
<p>From Product Information Selzentry (maraviroc) Pfizer, 2011. Available at: <a href="http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022128s0071bl.pdf">http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022128s0071bl.pdf</a></p> <p><sup>a</sup> Maraviroc is a CYP3A and a P-gp substrate; therefore, interactions are difficult to predict. The dosage of maraviroc must be adjusted if it is taken with other strong CYP3A inhibitors or CYP3A inducers (without a strong CYP3A inhibitor); multiple competing drug interactions can occur. See full package insert for further information on dosage adjustment (also see <a href="#">HIV Drug-Drug Interactions: Table 2</a> and <a href="#">Antiretroviral Therapy: Maraviroc table</a>) or consult with a clinician with extensive experience with ART and management.</p> <p><sup>b</sup> Regardless of whether or not a potent CYP3A inducer is co-administered.</p> <p><sup>c</sup> Postural hypotension may increase the risk for cardiovascular adverse events in patients receiving maraviroc who have severe renal impairment or ESRD (creatinine clearance &lt;30 mL/min). Maraviroc should not be prescribed for patients with severe renal impairment who are receiving CYP3A inhibitors or inducers (see <a href="#">Antiretroviral Therapy: Maraviroc table</a>).</p> <p><sup>d</sup> Dose adjustment is necessary with severe hepatic impairment; no dose adjustment is likely with mild to moderate hepatic impairment. Use with caution in patients receiving a concomitant/potent CYP3A4 inhibitor (see <a href="#">Antiretroviral Therapy: Maraviroc table</a>).</p>	

### III. RALTEGRAVIR

Updated November 2011

#### RECOMMENDATIONS:

**Clinicians should perform resistance testing before changing from a PI-boosted regimen to raltegravir** (see [Antiretroviral Therapy: Section VI. 3. HIV Resistance Assays](#)). (AII)

**Clinicians should discontinue raltegravir in patients who develop signs or symptoms of severe skin reactions or hypersensitivity reactions.**

Raltegravir has been approved by the FDA for use in both ART-naïve and ART-experienced adults for construction of a potent, fully suppressible regimen for patients with intolerance or resistance to first- or later-line agents. In one study, raltegravir was as effective as efavirenz when used in ART-naïve patients receiving combination treatment.<sup>6</sup>

Raltegravir has been demonstrated to be effective in ART-experienced adults with triple-class-resistant HIV-1 infection.<sup>7</sup> Phase III studies have shown that an optimized regimen plus raltegravir is superior to an optimized regimen alone in suppressing HIV RNA below detection and in increasing CD4 counts. Raltegravir has been successfully used as a substitution for enfuvirtide in virally suppressed patients,<sup>8</sup> but was not as effective when substituted for lopinavir/ritonavir in extensively ART-experienced patients.<sup>9</sup> If change from a boosted-PI regimen to raltegravir is under consideration because of treatment failure, evaluation for potential resistance to the background regimen is critical. The use of raltegravir in patients who require a change in ART because of side effects continues to be studied.

#### **Key Point:**

Raltegravir has been recently approved by the FDA for use in initial regimens for treatment-naïve patients. Raltegravir may also be used as part of a salvage regimen in treatment-experienced patients when resistance or side effects have limited the use of other available agents.

- *Dosing:* 400 mg PO twice daily. Dose adjustment is not required for mild to moderate hepatic insufficiency or severe renal insufficiency.<sup>10</sup> Raltegravir should be used with caution in patients with severe hepatic impairment.
- *When used with etravirine:* Monitor for virologic efficacy with co-administration
- *When used with tipranavir/ritonavir:* Monitor closely
- *When used with rifampin:* Recommended dosing of raltegravir is 800 mg PO twice daily, but there are no clinical data. Use of rifabutin should be considered with raltegravir co-administration.
- *Main side effects:* rash and diarrhea
- *Adverse effects:* Severe, potentially life-threatening, and fatal skin reactions have been reported, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Discontinue immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop, including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema.
- *FDA Pregnancy Category:* C – No human data. Animal developmental studies found a higher incidence of supernumerary ribs compared to control.

For additional information regarding prescribing considerations for raltegravir, see [Antiretroviral Therapy: Raltegravir table, as well as the manufacturer's raltegravir label](#).

## IV. ETRAVIRINE

Updated December 2009

### RECOMMENDATIONS:

**Etravirine should be used only as part of a salvage ART regimen in treatment-experienced patients for whom the use of other available agents is limited because of resistance to previously approved NNRTIs. (AII)**

**For regimens that include both etravirine and a protease inhibitor, clinicians should co-administer etravirine with only one of the following ritonavir-boosted protease inhibitors: lopinavir, darunavir, or saquinavir. (AII)**

Phase III studies have shown that the NNRTI etravirine is effective in suppressing HIV RNA levels and increasing CD4 counts in treatment-experienced patients with triple-class resistance, including resistance to NNRTIs.<sup>11</sup> The main side effect was increased risk of rash. Stevens-Johnson syndrome, erythema multiforme, and/or hepatic failure occurred rarely; the development of any of these conditions warrants immediate discontinuation of etravirine.

Etravirine should be used only as part of a combination regimen in patients with documented resistance to previously approved NNRTIs and other agents. Etravirine is recommended for use in NNRTI-experienced patients with no more than two existing NNRTI mutations. Use of a weighted NNRTI mutation score or a < 3-fold decrease in susceptibility by phenotype may improve the likelihood of treatment success with this agent.<sup>12,13</sup> Importantly, K103N does not confer decreased susceptibility to etravirine and, therefore, is not among the mutations that would limit the use of etravirine in a given patient.

Etravirine is best used as part of an optimized regimen consisting of etravirine plus at least two active agents. When etravirine is co-administered with a protease inhibitor, only one of the following ritonavir-boosted protease inhibitors should be used: lopinavir, darunavir, or saquinavir. See below for ART regimens in which etravirine should not be used.

Because etravirine is a substrate of hepatic CYP450 enzymes and an inducer/inhibitor of these enzymes, significant drug interactions can occur with concurrent medications. See the [etravirine package insert](#) for a listing of known interactions.

- *Dosing:* Two 100-mg tablets twice daily with food
- *Should not be co-administered with the following:*
  - Other NNRTIs
  - Any unboosted PI (i.e., administered without ritonavir)
  - Certain boosted PIs: tipranavir/ritonavir (Note: the clinical significance is unknown for fosamprenavir/ritonavir and atazanavir/ritonavir)
- *Main side effects:* Mild to moderate rash, which may resolve with continued treatment
- *FDA Pregnancy Category:* B

## V. RILPIVIRINE

Posted November 2011

### RECOMMENDATIONS:

**Rilpivirine is recommended only for ART-naïve adults in combination therapy when an alternative to the preferred NNRTI, efavirenz, is being considered (AII).**

**Clinicians should use caution when prescribing rilpivirine for patients with HIV RNA levels >100,000 copies/mL because of the increased risk for virologic failure compared with efavirenz (see Table 2). (AII)**

**Rilpivirine should be used with at least two other fully active agents, such as tenofovir plus emtricitabine or abacavir plus lamivudine (for information regarding selection of an initial ART regimen, see [Antiretroviral Therapy: Section V. Selecting an Initial Antiretroviral Regimen](#)). (AII)**

Rilpivirine is an NNRTI that has been approved by the FDA for use in ART-naïve patients. The agent should ideally be prescribed in combination with at least two fully active agents against HIV. Two randomized, double-blind, controlled trials (TMC278-C209: ECHO and TMC278-C215: THRIVE) compared rilpivirine with efavirenz.<sup>14</sup> Rilpivirine had a lower incidence of dizziness and rash compared with efavirenz. Achievement of overall viral suppression to <50 copies/mL was similar between both agents at 96 weeks (rilpivirine, 76%; efavirenz, 71%). However, rilpivirine was inferior to efavirenz on several outcome measures (Table 2). High baseline HIV viral load (>100,000 copies/mL) was a predictor of virologic failure. However, rilpivirine may be considered for some individuals with high viral loads when efavirenz is not preferred or feasible, such as for women of childbearing potential, patients with psychiatric disorders, or those receiving medications that are contraindicated with efavirenz.

**TABLE 2  
KEY DIFFERENCES BETWEEN RILPIVIRINE AND EFAVIRENZ: POOLED DATA FROM  
TMC278-C209 AND TMC278-C215**

<b>Outcome Measure</b>	<b>Rilpivirine</b>	<b>Efavirenz</b>
Overall viral suppression	76%	71%
Overall virologic failure	14%	10%
Virologic failure at high baseline HIV RNA levels		
>100,000 to ≤500,000 copies/mL	20%	11%
>500,000 copies/mL	29%	17%
Treatment resistance among virologic failures	41%	25%
Cross-resistance to NNRTI class among virologic failures	48%	15%
Dizziness	1%	7%
Rash	3%	11%

Data are from phase III and phase IIb analyses of the TMC278-C209: ECHO and TMC278-C215: THRIVE trials. See the manufacturer's EDURANT package insert; 2011 (available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2011/202022s000lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202022s000lbl.pdf)).

The findings in Table 2 are important considerations when deciding whether to prescribe rilpivirine. Additional information regarding rilpivirine is available from Tibotec Therapeutics (see [EDURANT full prescribing information](#)).

**Key Point:**

A fixed-dosed combination pill, Complera, containing rilpivirine, tenofovir, and emtricitabine, is available (see [Complera full prescribing information](#) from Gilead Sciences).\*

\* When prescribing the combination drug Complera, clinicians should be aware that a vitamin preparation has a similar trade name (i.e., Complere); confirmation that the correct prescription is dispensed to patients should be ensured.

- *Dosing:* One 25-mg tablet once daily with a meal ( $\geq 550$  calories)
- *Should not be co-administered with the following:*
  - Other NNRTIs
  - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin
  - Rifabutin, rifampin, rifapentine
  - Esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole
  - The CYP3A inducer St. John's wort (*Hypericum perforatum*) or products containing St. John's wort
  - Dexamethasone (long-term use)
  - Drugs that can significantly prolong QTc interval
- *Should be co-administered with caution:* With a drug with a known risk for Torsade de Pointes
- *Main side effects:* Depression, insomnia, headache, and rash. Dizziness occurred less frequently in rilpivirine-treated patients than in those receiving efavirenz; fat redistribution, immune reconstitution syndrome, and possible prolonged QTc interval are also possible adverse reactions
- *FDA Pregnancy Category:* B (Note: no adequate and well-controlled or pharmacokinetic studies of rilpivirine use in pregnant women have been conducted)

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