

NEW ANTIRETROVIRAL DRUGS: MARAVIROC, RALTEGRAVIR, AND ETRAVIRINE

Editor's Note:

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

What's New - June 2010 Update

- Maraviroc should not be prescribed for patients with severe renal insufficiency or end-stage renal disease (ESRD) who are receiving potent CYP3A inducers or potent CYP3A inhibitors (see Section II: *Maraviroc*).
- For patients with severe renal insufficiency or ESRD who are not receiving potent CYP3A inducers or potent CYP3A inhibitors, dose adjustment with maraviroc may be necessary to avoid cardiovascular risk associated with postural hypotension.

I. INTRODUCTION

RECOMMENDATION:

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

Three new 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 ARV agents: CCR5 co-receptor antagonists and integrase inhibitors, respectively. The third agent, etravirine (Intelence), is an NNRTI.

In addition to previous FDA approval for treatment-experienced patients, maraviroc and raltegravir have recently received approval for use in ARV treatment-naïve patients. Etravirine is approved only for use as a component of a salvage ARV regimen for treatment-experienced patients.

Maraviroc, raltegravir, and etravirine have not been studied in pregnant women. Clinicians who are treating HIV-infected pregnant women should report cases of prenatal exposure to ARV 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 ARV treatment-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 ARV-naïve patients receiving combination treatment. However, more treatment-naïve patients treated with maraviroc experienced virologic failure and developed lamivudine resistance compared to efavirenz.¹ Maraviroc has been demonstrated to be effective in ARV-experienced adults.^{2,3}

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.⁴ 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.⁵ 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 also has been recently approved by the FDA for use in initial regimens for treatment-naïve, CCR5-tropic patients.

- *Dosing:* 300 mg PO, 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 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 information regarding the recent FDA approval for treatment-naïve patients, see the [FDA maraviroc label](#).

TABLE 1 ADULT DOSING OF MARAVIROC	
<ul style="list-style-type: none"> ○ All NRTIs ○ Nevirapine ○ Tipranavir/ritonavir ○ Enfuvirtide ○ Raltegravir 	300 mg bid
<ul style="list-style-type: none"> ○ Potent CYP3A inhibitors^{a,b} <ul style="list-style-type: none"> – PIs (except tipranavir/ritonavir) – Delavirdine – Ketoconazole, itraconazole, clarithromycin – Other potent CYP3A inhibitors (e.g., nefazodone, telithromycin) 	150 mg bid
<ul style="list-style-type: none"> ○ Potent CYP3A inducers^a (without co-administration of a strong CYP3A inhibitor): <ul style="list-style-type: none"> – Efavirenz – Etravirine – Rifampin – Carbamazepine, phenobarbital, and phenytoin 	600 mg bid
<ul style="list-style-type: none"> ○ Severe renal impairment^c 	Adjustment may be necessary
<ul style="list-style-type: none"> ○ Severe hepatic impairment^d 	Adjustment necessary

From Product Information Selzentry (maraviroc) Pfizer, 2007. Available at:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022128s004lbl.pdf

^a 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 [HIV Drug-Drug Interactions: Table 2](#) and [Antiretroviral Therapy: Maraviroc table](#)) or consult with a clinician with extensive experience with ARV treatment and management.

^b Regardless of whether or not a potent CYP3A inducer is co-administered.

^c Postural hypotension may increase the risk for cardiovascular adverse events in patients receiving maraviroc who have severe renal impairment or ESRD (creatinine clearance <30 mL/min). Maraviroc should not be prescribed for patients with severe renal impairment who are receiving CYP3A inhibitors or inducers (see [Antiretroviral Therapy: Maraviroc table](#)).

^d 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 [Antiretroviral Therapy: Maraviroc table](#)).

III. RALTEGRAVIR

RECOMMENDATION:

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

Raltegravir has been approved by the FDA for use in ARV treatment-naïve patients and 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 ARV-naïve patients receiving combination treatment.⁶

Raltegravir has been demonstrated to be effective in ARV-experienced adults with triple-class-resistant HIV-1 infection.⁷ 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,⁸ but was not as effective when substituted for lopinavir/ritonavir in extensively ARV treatment-experienced patients.⁹ 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 bid. Dose adjustment is not required for mild to moderate hepatic insufficiency or severe renal insufficiency.¹⁰
- *When used with rifampin:* Recommended dosing of raltegravir is 800 mg PO bid, but there are no clinical data. Use of rifabutin should be considered with raltegravir co-administration.
- *Main side effects:* rash and diarrhea.
- *FDA Pregnancy Category:* C—No human data. Animal developmental studies found a higher incidence of supernumerary ribs compared to control.

For additional information regarding the recent FDA approval for treatment-naïve patients, see the [FDA raltegravir label](#).

IV. ETRAVIRINE

RECOMMENDATIONS:

Etravirine should be used only as part of a salvage ARV 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.¹¹ 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.^{12,13} 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 ARV 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 bid after eating.
- *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

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