NEW ANTIRETROVIRAL DRUGS: MARAVIROC, RALTEGRAVIR, AND ETRAVIRINE

For comprehensive information regarding the use of antiretroviral agents, see *Antiretroviral Therapy*.

I. INTRODUCTION

RECOMMENDATIONS:

Maraviroc, raltegravir, and etravirine should be used only as part of a new ARV regimen in treatment-experienced patients when resistance or side effects have resulted in an inadequate number of other available approved agents. The new regimen should optimally include at least two fully active agents plus the new agent and should be initiated after consultation with an HIV Specialist.

The CCR5 co-receptor antagonist maraviroc should be prescribed only in patients with CCR5-tropic virus, as determined by a tropism assay that is performed at the time that therapy is considered. Maraviroc should not be used outside of clinical trials in patients with dual/mixed- or CXCR4-tropic virus.

The new NNRTI etravirine should be used only in patients with resistance to previously approved NNRTIs and in combination with one of the following ritonavir-boosted protease inhibitors: lopinavir, darunavir, or saquinavir.

Three new antiretroviral agents have recently been FDA-approved 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. The use of these new drugs should be limited to treatment-experienced patients when resistance or side effects have resulted in an inadequate number of other available approved agents. The new drugs should optimally be used as part of a regimen with at least two fully active agents plus the new agent. Clinicians should consult with an HIV Specialist before initiating these agents.

II. MARAVIROC

The CCR5 co-receptor antagonist maraviroc is a potent agent for therapy in CCR5-tropic ARV-experienced patients whose ARV regimens are failing. In phase III studies, maraviroc, as part of combination ARV therapy in treatment-experienced adults, led to virologic suppression, increased CD4 counts, and was associated with few side effects.[1]

Screening with a co-receptor tropism assay should be performed at the time that therapy is considered because results from previous screening may not be valid. The sensitivity of current co-receptor tropism assays is a challenge to treatment with agents in the CCR5 co-receptor antagonist class. Many patients who fail therapy with maraviroc and other investigational CCR5 receptor antagonists have been found to have dual- or mixed-tropic HIV-1 that was undetected by the screening assay used.[2] One study of maraviroc plus an optimized background regimen in

subjects found to have dual/mixed tropic virus at screening concluded that overall efficacy of maraviroc was not better than placebo.[3] Maraviroc therefore should not be used outside of clinical trials in patients with dual/mixed-tropic virus.

- *Dosing*: 300 mg PO bid; however, its metabolism is affected by strong CYP3A inducers and inhibitors, so dosing may range from 150 to 600 mg bid based on other concurrent medications that the patient is receiving (see Table 1 and *HIV Drug-Drug Interactions*: Table 2).
- *Main side effects*: cough, fever, colds, rash, muscle and joint pain, stomach pain, and dizziness.

TABLE 1
ADULT DOSING OF MARAVIROC

Co-Administered ARV Medications*	Maraviroc Dosage
• All NRTIs • Nevirapine • Tipranavir • Enfuvirtide	300 mg bid
CYP3A inhibitors (with or without a strong CYP3A inducer): • PIs (other than tipranavir) • Delavirdine	150 mg bid
CYP3A inducer (if used without a strong CYP3A inhibitor as listed above): • Efavirenz • Etravirine	600 mg bid

From Product Information Selzentry (maraviroc) Pfizer, 2007. Available at: http://media.pfizer.com/files/products/uspi_maraviroc.pdf

* 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 or consult with an HIV Specialist (also see *HIV Drug-Drug Interactions*: Table 2).

III. RALTEGRAVIR

The integrase inhibitor raltegravir is a potent addition to treatment regimens in ARV-experienced adults with triple-class-resistant HIV-1 infection.[4,5] 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. At this time, raltegravir should only be used in ARV-resistant patients, as described above, until additional clinical trial data become available. Raltegravir is being studied in ARV-naïve patients and in patients who are changing ARV therapy due to side effects. Use in these patient populations should only be in consultation with an HIV Specialist.

- *Dosing*: 400 mg PO bid.
- *Main side effects*: rash and diarrhea.

IV. ETRAVIRINE

The new NNRTI etravirine is effective at suppressing HIV RNA levels and raising CD4 counts in treatment-experienced patients with triple-class (including NNRTI) resistance.[6,7] Side effects were similar to placebo except for an increased risk of rash. Etravirine is best used as part of an optimized regimen consisting of etravirine plus at least two active agents, including one of the following ritonavir-boosted protease inhibitors: lopinavir, darunavir, or saquinavir. See below for HAART regimens in which etravirine should not be used.

Because the drug is a substrate of hepatic CYP enzymes and an inducer/inhibitor of these enzymes, significant drug interactions can occur with concurrent medications. See the package insert for a listing of known interactions. Etravirine should only be used as part of a combination regimen in patients with documented resistance to previously approved NNRTIs and other agents. Etravirine is recommended to be used in NNRTI-experienced patients with two or fewer existing NNRTI mutations, excluding K103N, which does not confer decreased susceptibility to etravirine.

- *Dosing*: Two 100-mg tablets twice daily after eating.
- *Should not be administered*:
    - With other NNRTIs.
    - In a PI-containing regimen without ritonavir or with regimens containing tipranavir, fosamprenavir, or atazanavir.
- *Main side effects*: Mild to moderate rash may resolve with continued treatment, but severe rash, including Stevens-Johnson syndrome and erythema multiforme, have occurred and require immediate discontinuation.

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