DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents
Recommendations for NNRTI use in Antiretroviral Treatment-Naive Patients with HIV-1 Infection (August 16, 2011)

Rilpivirine (RPV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) recently approved by the Food and Drug Administration (FDA) as part of a combination antiretroviral (ARV) regimen for treatment-naive HIV-1-infected patients[1]. The FDA also approved a fixed-dose combination tablet of RPV/tenofovir(TDF)/emtricitabine(FTC) as a one-tablet, once-a day-regimen[2]. This communication includes important information about available NNRTI options that must be carefully considered when choosing an NNRTI-based regimen as initial therapy for treatment-naive patients.

In two large, multinational, randomized, double-blind clinical trials, RPV (25 mg once daily) was compared with efavirenz (EFV) (600 mg once daily), each in combination with two nucleos(t)ide reverse transcriptase inhibitors (NRTIs). In a pooled analysis of the two studies, 83% of RPV-treated subjects and 80% of EFV-treated subjects had plasma HIV RNA <50 copies/mL at 48 weeks[3, 4]. Although RPV demonstrated noninferiority in this analysis, it was noted that for participants with higher pretreatment HIV RNA (>100,000 copies/mL), virologic failure occurred more frequently in participants randomized to receive RPV. Furthermore, subjects receiving RPV who experienced virologic failure were more likely to have failure with genotypic resistance to other NNRTIs (EFV, etravirine [ETR], and nevirapine [NVP]) and to have resistance to their prescribed NRTIs. Drug discontinuations because of adverse effects were more common with EFV than RPV. The frequency of depressive disorders and discontinuations because of depressive disorders were similar between the two arms, whereas dizziness, abnormal dreams, rash, and hyperlipidemia were more frequent with EFV compared with RPV.

RPV must be administered with a meal (preferably high fat). Its oral bioavailability can be significantly reduced in the presence of acid lowering agents. RPV should be used with caution with antacids and H_2-receptor antagonists. RPV use with proton-pump inhibitors (PPIs) is contraindicated.

Based on limited data on durability of treatment responses (48 weeks), the lower virologic response compared with EFV in subjects with pretreatment HIV RNA >100,000 copies/mL, and the greater likelihood of NNRTI resistance with failure, the Panel recommends the following with regard to NNRTI use as part of an initial ARV regimen:

EFV remains the preferred NNRTI[a] **(AI)**
RPV is now classified as an alternative NNRTI[b] **(BI)**
NVP remains an acceptable NNRTI[c] in women with CD4 counts <250 cells/mm^3 and in men with CD4 counts <400 cells/mm^3 **(CI)**

[a] Preferred regimen = regimen with optimal and durable efficacy, favorable tolerability and toxicity profile, and ease of use.
[b] Alternative regimen = regimen that is effective and tolerable but has potential disadvantages compared with preferred regimens. An alternative regimen may be the preferred regimen for some patients.
[c] Acceptable regimen = regimen that may be selected for some patients but is less satisfactory than preferred or alternative regimen.

EFV should not be used during the first trimester of pregnancy or in women of childbearing age who are trying to conceive or who are not using effective and consistent contraception. Data on the pharmacokinetics (PKs) and safety of RPV use in pregnant HIV-infected women are insufficient at this time. RPV is not recommended for adolescents younger than 18 years of age because appropriate dosing information is lacking.

Caution should be exercised when using RPV in patients with plasma HIV RNA >100,000 copies/mL, given the higher RPV virologic failure rates and the greater likelihood of having broad NNRTI resistance at the time of failure observed in this population in clinical trials.

Clinicians should refer to Tables 5a and 5b of the January 10, 2011, Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents[5] for a list of preferred, alternative, and acceptable ARV regimen options for the treatment-naive patient.

1. Food and Drug Administration, Edurant (package insert), 2011. http://www.accessdata.fda.gov/drugsatfda-docs/label/2011/ 202022s000lbl-5.pdf. Accessed Aug 15, 2011.
2. Food and Drug Administration, Complera (package insert), 2011. http://www.accessdata.fda.gov/drugsatfda-docs/label/2011/ 202123s000lbl-1.pdf. Accessed Aug 15, 2011.
3. Cohen CJ, Andrade-Villanueva J, Clotet B, et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomized, non-inferiority trial. *Lancet.* 2011;378:229-37.
4. Molina J-M, Cahn P, Grinsztejn B, et al. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. *Lancet*. 2011;378:238-246.
5. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 10, 2011;1-166. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed Aug 15, 2011 [Tables 5a and 5b].