Update to the "Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents" (July 15, 2005)

The Panel on Clinical Practices for Treatment of HIV Infection is providing the readers with the following supplemental recommendations to the April 7, 2005 guidelines. Please note that these recommendations are in effect immediately. The text and tables of the full document will be updated at a later date.

Below are the supplemental recommendations:

1. **The Panel recommends that a regimen containing "tenofovir + didanosine + NNRTI" should not be used as an initial regimen in antiretroviral treatment naïve patients.**

   This recommendation is based on results from several small observational studies and pilot clinical trials showing a high rate of early virologic failure in treatment-naïve patients who received this combination as their initial regimen. Emergence of resistant mutations to NNRTIs and to tenofovir and/or didanosine (K65R or L74V mutations) was frequently seen in patients who failed to respond to this combination *[1-4]*. Of note, patients with high baseline HIV-RNA (> 100,000 copies/mL) and low $CD4^+$ T-cell counts (< 200 cells/mm^3) were particularly at risk of early virologic failure. There are not enough data for the combination of tenofovir/didanosine with protease inhibitor in treatment-naïve patients to assess virologic responses of this regimen, thus, there is no recommendation for or against the use of this combination at this time.

2. **The Panel recommends that lopinavir/ritonavir can be dosed as one single daily dose (6 capsules or 10 mL – equivalent to 800mg lopinavir/200mg ritonavir) in treatment-naïve patients.**

   Once daily dosing is not recommended in treatment-experiences patients or in patients receiving concomitant efavirenz, nevirapine, amprenavir (or fosamprenavir), or nelfinavir.

   This recommendation is based on 48-week data from two clinical trials comparing once vs. twice daily lopinavir/ritonavir, used in combination with tenofovir + emtricitabine in treatment-naïve patients, demonstrating similar virologic responses in both treatment arms.

   Once daily dosing has not been studied in treatment-experienced patients. In the pharmacokinetic study, the trough concentration of lopinavir at the end of a 24 hour dosing interval was found to be approximately 60% lower than with twice daily dosing. Given the lower trough concentration and no clinical trial data in treatment-experienced patients, once daily dosing is currently not recommended in these patients.

   It is also important to note that moderate to severe diarrhea were reported significantly more frequently in subjects who received once daily lopinavir/ritonavir as compared to twice daily dosing (16% vs. 5% respectively) *[5]*.

References:

1. Podzamczer D, Ferrer E, Gatell JM, et al. Early virological failure with a combination of tenofovir, didanosine and efavirenz. *Antivir Ther*, 2005. 10(1):171-7.
2. Maitland D, Moyle G, Hand J, et al. Early virological failure in HIV-infected subjects on didanosine/tenofovir/efavirenz: 12-week results from a randomized trial. *AIDS,* 2005. 19(11):1183-8.
3. Van Lunzen J, Schewe K, Kuhlmann B, et al. High rate of virological failure during once daily therapy with tenofovir + didanosine 250mg qd + efavirenz in antiretroviral naïve patients – Results of the 12 week interim analysis of the TEDDI trial. To be presented at the 3rd IAS Conference on HIV Pathogenesis and Treatment. Rio de Janeiro, Brazil, July 24-27, 2005.
4. Leon A, Martinez E, Mallolas J, et al. Early virological failure in treatment-naïve HIV-infected adults receiving didanosine and tenofovir plus efavirenz or nevirapine. *AIDS,* 2005. 19(2):213-5.
5. KALETRA (Product Labelling), Abbott Laboratories, 2005.