

## **NRTI Research Project**

**Contact: Christine Hughes (chughes@pharmacy.ualberta.ca)**

### **Background**

High virologic failure rates have been reported recently with several triple nucleoside reverse transcriptase inhibitor (NRTI) combinations including abacavir + lamivudine + tenofovir, didanosine + abacavir + tenofovir, and didanosine + lamivudine + tenofovir. The K65R mutation is frequently observed upon genotypic testing in patients who experienced virologic failure in these studies. This mutation is selected by tenofovir, abacavir, zalcitabine, and didanosine and confers decreased antiviral activity to tenofovir, abacavir, and lamivudine. High failure rates have also been recently noted with didanosine + tenofovir + efavirenz. In addition, declines in absolute CD4 cell counts have been described with the combination of didanosine + tenofovir, even after adjusting the didanosine dose due to the interaction with tenofovir. Several theories have been proposed to explain the high virologic failure rates seen with these combinations, however one of the favored theories is the low genetic barrier to resistance. Little information is available as to whether other NRTI backbones lead to an increased risk of virologic failure (e.g. didanosine + abacavir or tenofovir + abacavir) when used in combination with protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) therapy.

### **Research Design:**

Retrospective chart review to identify patients who received treatment with the following NRTI backbones: abacavir + didanosine, didanosine + tenofovir, or tenofovir + abacavir in combination with either a protease inhibitor or non-nucleoside reverse transcriptase inhibitor. Endpoints would include virologic response, CD4 response, and development of resistance mutations in patients who experience virologic failure. Factors associated with increased risk of virologic failure (e.g. NNRTI or PI, baseline CD4 and VL) will be identified.

Note: Although we are unlikely to find many (any) naïve patients who were treated with these combinations, we could use evidence of resistance to any of the drugs as a basis for exclusion.

### **Commitment from CHAP members:**

Interested CHAP members must have a way to identify patients treated with these combinations as well as be able to perform data collection (either themselves or using a student/research nurse).

**Timelines** (Could be flexible but would be nice to have some results to present poster at International AIDS Conference in Aug 2006: abstract deadline Feb 2006):

Research Proposal Completion: August

Ethics: August/September

Data Collection: October – December

Data analysis: January

**Project: Drug Interaction: inhaled corticosteroid & ritonavir-containing regimen**

**Principal Investigator: Lizanne Béïque (lbeique@ottawahospital.on.ca)**

A number of case reports indicate the potential for a significant drug interaction between inhaled fluticasone and ritonavir. Patients showed signs of a Cushing's syndrome clinical picture accompanied by adrenal suppression. This interaction occurs as a result of a potent inhibition of P450-3A, the cytochrome that metabolizes fluticasone, by ritonavir.

Consequently, the latest DHHS guidelines have listed fluticasone as a drug that should not be used with ritonavir or lopinavir/ritonavir.

A number of patients take inhaled corticosteroids with a ritonavir-containing regimen without any signs of Cushing syndrome.

This research project will consist of measuring cortisol and performing a short ACTH test in patients taking inhaled or intranasal corticosteroids and ritonavir-containing regimens. Should the manufacturer of fluticasone agree, levels of fluticasone will also be measured.

The protocol for this study will be ready for submission to ethics committees by July 8, 2005.

**Project: Clinical experience in the usage of Kaletra in pregnancy**  
**Contact: Jinell MahMing (Jinell.MahMing@CalgaryHealthRegion.ca)**

**Background:**

Antiretroviral therapy is recommended during pregnancy to reduce perinatal transmission of HIV-1 infection, and to improve maternal health (DHHS guidelines Feb, 2005). However, treatment options become limited in HAART experienced patients with documented drug resistance. The greatest challenge is obtaining prompt viral suppression during the gestational period, while considering the toxicity profiles among the currently available antiretrovirals.

Kaletra has demonstrated its efficacy and safety in the PI-experienced population in numerous randomized and controlled trials (GSK Lexiva vs. LPV/RTV, BMS-045 –ATV/RTV and SQV/RTV, vs LPV/RTV, ABBOT studies 888,765,957) and it therefore expected to provide benefit. However, Kaletra is category C under the pregnancy use guidelines. There is very limited data in its usage in pregnancy. Only one abstract has been presented that describes Kaletra usage during pregnancy in 11 patients (London, UK). There are no trials that have been initiated in the developing world to assess the safety of Kaletra in pregnancy according to my correspondence with Abbott pharmaceuticals.

**Objective:** To review Kaletra usage in pregnancy outcome in HIV-1 positive women (a paper written as a CHAP case series)

**Methods:**

1. Retrospective chart review of the following:
  - ARV treatment hx, current viral load and CD4 at pregnancy
  - Time of ARV initiation for pregnancy (newly initiated HAART or switch); time at which Kaletra was started
  - Resistance testing; genotype/virtual phenotype results
  - ADRs and possible drug related complications during pregnancy
  - Maternal and gestational age at delivery
  - Mode of delivery
  - Birth wt
  - Maternal VL and CD4 at delivery
  - Infant HIV-1 status, and 6 month follow up for any complications
2. In addition we could collect prospective data if we want to have a larger “n”
3. Another thought is to also look at prevalence of using Kaletra among all regimens used in pregnancy over a certain time period.
4. Time line is 1-2 years depending on how we want to do this study