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# HIV Resistance Testing Consultation Service Consultation Report

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Consultation is available to California AIDS Drug Assistance Program providers through the California State Office of AIDS Voucher Program by calling the HRSA/ AIDS ETC National HIV Telephone Consultation Service (Warmline) at 1/800/933-3413. The HIV Resistance Testing Consultation Service is supported by a grant from the California State Office of AIDS through the Pacific AIDS Education and Training Center.

**History/Clinical Course**

Question: Would you change the nucleoside backbone or add another “fully active” agent to the regimen?

History: The patient is a 30-year-old pregnant woman who was diagnosed with HIV in 2003. She presented at that time with viral load of 288,000 copies RNA/mL and her CD4 count was 59 cells /mm<sup>3</sup> (nadir). She was started on Combivir® (zidovudine and lamivudine) and nevirapine (Virammune®). Her viral load became undetectable and CD4 cell count increased to 500 cells /mm<sup>3</sup>. To simplify the regimen, the Combivir®/nevirapine was changed to Atripla® (efavirenz, tenofovir, emtricitabine) in 2004. Her viral load and CD4 remained stable on this regimen.

The patient became pregnant (unplanned) in April 2008 and the Atripla® was stopped immediately. Due to concerns about developing resistance to efavirenz during the interruption, a one week nucleoside “tail” was used (Truvada® was continued for seven days after the Sustiva® was stopped). The plan was to hold antiretroviral (ARV) drugs during the first trimester. An ultrasound determined the baby’s due date to be 10-28-08.

On 6-29-08, the patient was started on Truvada® (tenofovir, and emtricitabine) one tablet daily and Kaletra® (lopinavir/ritonavir) (two pills BID, to be increased to three pills BID during the third trimester). Two days before starting this regimen, a genotype was obtained. The patient had been off therapy for two months at that time and had a viral load of 57,885 copies/mL and CD4 cell count of 257 cells/mm<sup>3</sup>. The genotype showed reverse transcriptase inhibitor (RTI) M41L and L210W mutations; there were no nonnucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI) mutations.

DATES	REGIMEN	CD4 (cells/mm <sup>3</sup> )	VL (copies/mL)	RESISTANCE TEST FINDINGS	CLINICAL COURSE
2003 (dx with HIV)	NO ART	59	288,000		
2003	COMBIVIR NEVIRAPINE	500	UNDET		
2004	ATRIPLA	500	UNDET		
4-29-08	ATRIPLA STOPPED				
6-27-08	NO ART	257	57,885	Genotype: M41L, L210W	
6-29-08	TRUVADA KALETRA	PENDING	PENDING		

## Resistance Test Findings

6-27-08 Genotype (on no ART for 2 months, HIV viral load  
57,885 copies/mL)

### Key Mutations

NRT	M41L, L210W
NNRT	None
PI	None

## Interpretation/Implications for Treatment

The panel agreed that the nucleoside analog mutations (NAMS) detected (i.e. M41L and L210W) are not the typical mutations seen after a fully suppressive NNRTI-based regimen is stopped. If mutations were present, one would have expected to see the standard NNRTI mutations such as the K103N and/or the M184V (lamivudine-associated) mutation. Recently, Hare et al demonstrated that after stopping an NNRTI (while maintaining the background drugs for two additional days), 11 of 54 (20%) patients had measurable NNRTI resistance during the interruption period [1].

It is unclear when the M41L and L210W mutations appeared. If these mutations were transmitted at the time of infection, then the two NNRTI-based regimens that the patient used should not have worked. This is particularly true as it seems likely that an M184V mutation was transmitted with 41L and 210W, and then subsequently waned. It is less likely that the NAMS appeared after the fully suppressive Atripla® was stopped. Regardless of the origin of the 41L and 210W mutations, the panel believed that the NRTIs were clearly compromised and that a standard regimen of two NRTIs and an NNRTI would likely not work again.

Antiretroviral therapy (ART) is recommended for all pregnant HIV-infected women to reduce the risk of HIV transmission from mother to baby [2]. The Perinatal Guidelines [2] recommend inclusion of ZDV in any ART regimen regardless of the maternal viral load, unless prohibited by severe drug toxicity or documented resistance. The mechanism of ZDV's protective effect is not entirely clear and may not be solely based on decreasing maternal viral load. Full virologic suppression is critical by week 38 of pregnancy to reduce the risk of vertical transmission. The use of pre- and post-exposure prophylaxis for the mother and infant may also be important.

The pharmacokinetics of some ARV drugs are altered during pregnancy. In general, NRTI and NNRTI do not require a dosage adjustment. Conversely, protease inhibitor levels may be much lower during pregnancy compared to postpartum and non-pregnant women (this has been most clearly shown with the previous capsule formulation of Kaletra®). Although pharmacokinetic evaluation of the Kaletra® tablet formulation is underway, some recommend an empiric increase of the Kaletra® dosage during the third trimester pending the results of these studies.

## Recommendations

Based on the patient's prior response to the two NNRTI-based regimens, any one of the three following regimens should result in full virological suppression and reduce the risk of vertical transmission.

### Regimen Options

**Option 1:** Combivir® + Kaletra®.

There is more experience with zidovudine in pregnancy and despite the presence of the M41L and L210W mutations, zidovudine is a reasonable option. The M184V can phenotypically re-sensitize zidovudine. Boosted protease inhibitors are less dependent on a fully active NRTI "backbone" than are the NNRTIs.

Dose: Combivir® one tablet twice a day + Kaletra® two tablets twice a day (increasing to three tablets twice a day in the third trimester).

Side effects/toxicities: Fatigue, nausea, diarrhea, headaches, insomnia, leukopenia, anemia, chemical hepatitis.

**Option 2:** Continue the Truvada® + Kaletra®.

Based on the genotype, tenofovir probably has slightly more activity than zidovudine. As with zidovudine, the M184V can phenotypically re-sensitize tenofovir, which would result in at least two active agents.

Dose: Truvada® one tablet daily + Kaletra® two tablets twice a day (increasing to three tablets twice a day in the third trimester).

Side effects/toxicities: Fatigue, bloating, renal insufficiency, chemical hepatitis, hypertriglyceridemia, insulin resistance.

**Option 3:** Combivir® + Tenofovir + Kaletra®.

This combination could potentially have three active agents. However, the increase in the number of ARV agents can result in increased side effects/toxicity.

Dose: Combivir® one tablet twice a day + Tenofovir 300mg one tablet daily + Kaletra® two tablets twice a day (increasing to three tablets twice a day in the third trimester).

Side effects/toxicities: See Options 1 and 2.

Plan and Follow-up Recommendations: An HIV viral load and a CD4 cell count will be done after four weeks of treatment. If the viral load is undetectable or if there is a one log 10 decrease in the viral load, the regimen will be continued. If there is not at least a one log 10 decrease in the viral load and the viral load is >1,000 copies/mL, a resistance test will be done.

CASE NUMBER  
PANEL CLINICIAN:

DATE

References:

[1]. Bradley Hare C, Mellors J, Krambrink A, et al. Detection of nonnucleoside reverse transcriptase inhibitor-resistant HIV-1 after discontinuation of virologically suppressive antiretroviral therapy. *CID* 2008; 47:421-424.

[2] Recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. July 8, 2008. <http://AIDSinfo.nih.gov>