

# 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

TS is a 59-year-old male, HIV-infected since 1991, with co-morbidities of diabetes, hypertension, and hyperlipidemia. His antiretroviral history includes zidovudine (AZT), lamivudine (3TC), abacavir (ABC), and didanosine (ddI) in various combinations. He is asymptomatic from his HIV infection and he has no history of opportunistic infections. His pretreatment viral load and CD4+ are 2000-3000 copies/mm<sup>3</sup> and 700cells/mm<sup>3</sup>, respectively and his CD4+ nadir is 467cells/mm<sup>3</sup> (9/04). On Trizivir (abacavir, zidovudine, lamivudine) his viral load became undetectable once in 2003 His most recent (6/3/06) CD4+ was 556 (20%) and viral load was 841copies/mL. His adherence is estimated to be about 95-100%. All other laboratory values are normal except his triglycerides (556 mg/dL). His current medications include Trizivir, vardenafil (Levitra), ezetimibe (Zetia), allopurinol (Zyloprim), triamterene/HCTZ (Dyazide), glyburide (Micronase), propranolol (Inderal), and fenofibrate (Tricor).

DATE	REGIMEN	CD4 range	HIV RNA range	COMMENTS
1/99- 7/99	AZT/3TC	751-773 (29%)	2498- 3869	
7/99- 7/01	CBV/ABC	496 (26%) - 864 (28%)	93- 796	
7/01- 4/02	Trizivir	692 (26%) - 765 (26%)	547-1257	D/C from 4/02-6/02 due to ↑LFTs
6/02- 10/02	CBV/ddI	531 (25%) - 841 (24%)	89- 1138	Off HAART from 10/02-11/02
11/02- 5/03	CBV/ddI	714 (23%) - 757 (21%)	1417- 2055	Off HAART 5/03-6/03 due to ↑LFTs
7/03- current	Trizivir	467 (23%) - 734 (21%)	<75- 3128	<75 on 10/10/03

## Resistance Test Findings

### 7/12/99 Genotype (Quest Diagnostic)

NRTI	184V
NNRTI	
PI	63P

### 6/7/02 genotype (Stanford Virology Laboratory)

NRTI	67N, 70R, 184V, 215F, 219E (60I, 135L, 214L, 248D)
NNRTI	
PI	63P, 77I/V, 93L (37D, 62I/V, 72E, 75I/V)

## Questions for Discussion:

### Interpretation/Implications for Treatment

This is a 59-year-old man with a long-standing history of nucleoside reverse transcriptase inhibitor (NRTI) use. He was infected in 1999 and has been on various combinations of AZT (zidovudine), 3TC (lamivudine), ddI (didanosine), and ABC (abacavir). Although he has only one undetectable viral load since 1999, his HIV RNA levels have remained low (less than 400 copies/mm<sup>3</sup>). Since his pretreatment HIV RNA level ranges between 2000-3000 copies/mm<sup>3</sup>, this may suggest infection with a “less fit” virus or a strong immune system controlling viral replication.

This patient has three major cardiovascular risk factors: hypertension, hyperlipidemia, and diabetes. Therefore, it would be very important to consider the risks from the inflammatory effects of ongoing viral replication if treatment was delayed as well as the cardiovascular adverse effects of antiretrovirals such as lopinavir/ritonavir (Kaletra).

There are two thymidine analog mutation (TAM) pathways for the NRTIs. The most common pathway is the TAM1 pathway, which produces mutations at 41L, 210W, and 215Y. This patient's genotype is consistent with mutations at sites 67N, 70R, and 219E, or the TAM2 pathway. However, the patient has a substitution at position 215, which may indicate that he will soon be acquiring mutations from the TAM1 pathway.

The 184V mutation confers resistance to lamivudine (3TC) and emtricitabine (FTC) and occurs rapidly after virologic failure with regimens that include these medications. M18V reduces viral fitness by affecting the reverse transcriptase function.<sup>1-5</sup> Because the M184 mutation reduces viral fitness, increases sensitization to AZT and TDF,<sup>6</sup> and provides residual activity against susceptible virus, the patient's next regimen should include one of these two well-tolerated agents.

The usual amino acid substitution at the 215 is position Y; however this patient's genotype shows the 215F mutation. The 215Y mutation has faster replication kinetics and better fitness compared to the 215F mutation in the absence or presence of AZT.<sup>7</sup> The 215F mutation, in a TAM2 background, increases viral fitness in the presence of AZT but causes a decrease in fitness in the TAM1 pathway.

A study by Margot et al, found that tenofovir (TDF) can cause a 0.67 log reduction in viral load in patients with the 184V mutation and ≥3 TAMs without the 41L and 210W.<sup>8</sup> Therefore TDF is also a viable antiretroviral agent for this patient.

There was no difference in stopping or continuing antiretrovirals (the benefit of continuing treatment was observed in patients who had viral suppression) in the SMART study in patients who had ongoing viremia on treatment.<sup>9</sup> The SMART study also found that in patients with baseline CD4+ of 450-549 cells/mm<sup>3</sup> or in those with CD4+ nadirs >400 cells/mm<sup>3</sup>, there were no differences in hazard ratio between the “drug conservation” versus the “viral suppression” groups. It should be noted that this study was not powered to answer the question of stopping or continuing ARV in patients with high baseline or nadir CD4+ cell counts.

The panel did not reach consensus regarding therapeutic options in this patient. Options discussed included 1) continuing Trizivir; 2) changing to 3TC monotherapy; or 3) changing to a fully suppressive regimen.

The primary reason for continuing Trizivir is that the patient has maintained a high CD4+ cell count and a low viral load throughout the years on this regimen. In addition, Trizivir does not have a detrimental effect on the patient's cholesterol level. The disadvantage of this strategy is that the patient is likely to acquire additional NRTI mutations and develop future tenofovir resistance.

Lamivudine (3TC) or emtricitabine (FTC) can be used as monotherapy in patients with few options and the M184V mutation by impairing viral fitness. In these patients, 3TC monotherapy has been associated with better immunologic and clinical outcomes as compared to complete treatment interruption.<sup>10</sup> Given this patient's high CD4 cell count, 3TC or FTC monotherapy can be considered. The advantage of this strategy is that the patient will not continue to accumulate NRTI mutations. However, due to increasing viral load, the patient may be at increased risk of non-HIV related morbidity and mortality.

If our goal is viral suppression, there are numerous treatment options that can be considered. These options are 1) combination of Combivir (AZT/3TC) plus tenofovir plus ritonavir-boosted atazanavir (ATV) and 2) Atripla (TDF/FTC/EFV) plus Kaletra (lopinavir/ritonavir).

In a poster by Martinez et al presented at the 12<sup>th</sup> Conference of Retroviruses and Opportunistic infections,<sup>11</sup> changing patients with hyperlipidemia to a ritonavir boosted ATV-based regimen was associated with improvements in total cholesterol, triglycerides, and LDL cholesterol. Therefore, it would be expected that the use of ritonavir and atazanavir in this patient would not significantly exacerbate his plasma cholesterol level.

Conversely, the combination of efavirenz (EFV) and Kaletra has been shown to significantly increase total cholesterol and triglycerides without adversely affecting glucose metabolism.<sup>12</sup> A study by Riddler and colleagues<sup>13</sup> found that an NRTI-sparing regimen consisting of efavirenz plus Kaletra had similar efficacy and safety as an efavirenz plus 2 NRTI regimen.

## Regimen Options

**Option 1:** Stop Trizivir, continue monotherapy with 3TC 150 mg bid or 300 mg once daily

**Pro:** CD4 nadir is >350 cells/mm<sup>3</sup>, so this is a feasible option. Good tolerability. In the SMART study, no difference in "drug conservation" versus "viral suppression" groups with CD4+ nadir >400 or CD4+ of 450-549 cells/mm<sup>3</sup>. Low risk of drug-drug interactions

**Con:** Patient is 59 years old and has three major cardiovascular risk factors, therefore may be at increased risk of non-HIV related morbidity and mortality.

**Option 2:** Change to Combivir one tablet bid po plus tenofovir 300 mg po daily plus ritonavir 100 mg daily plus atazanavir (ATV) 300 mg po daily. (Combivir + TDF + ATV/r).

**Pro:** Two active agents (TDF and ATV), with AZT contributing residual effects.

**Con:** RTV-boosting may affect triglycerides and/or LDL but given that it is low-dose, it may not be very significant. Do not have three fully active medications on board. Risk of drug-drug interactions, including increasing vardenafil levels and drug toxicity.

**Option 3:** Change to Truvada one tablet daily plus Kaletra three tablets bid plus efavirenz 600 mg po daily or Atripla one tablet daily plus Kaletra 3 tablets bid po.

**Pro:** Three fully active agents (TDF, EFV, LPV/r) with high likelihood of viral suppression. Similar virologic efficacy and time to treatment limiting toxicity as EFV-based regimens.

**Con:** EFV/LPV/r may cause significant increases in triglyceride, total cholesterol, and glucose levels. Risk of drug-drug interactions, including increasing vardenafil levels and toxicity.

**Option 4:** Continue Trizivir

**Pro:** Continue to keep CD4 cell count in the 400-700 range. Good tolerability

**Con:** Possibly acquire more drug resistance in the NRTI class (may go down other TAM pathway as well). This option may jeopardize future options. Low risk of drug-drug interactions

## Dosing, Monitoring, and Follow-up Recommendation

Monitor CD4 count every 2-3 months and HIV RNA very frequently (every 1 to 2 months).

Monitor lipid panel, glucose, hemoglobin A1c, and blood pressure.

Monitor side effects of antiretrovirals.

Truvada: monitor serum creatinine and urinalysis for renal insufficiency.

Combivir: monitor for anemia, GI distress.

Ritonavir boosted atazanavir: monitor indirect bilirubin, glucose, lipids, jaundice.

Kaletra: monitor for GI side effects, including diarrhea, lipids, glucose, LFT's.

Efavirenz: monitor for rash, CNS effects, LFT's.

Monitor for drug-drug interactions, PIs can increase vardenafil levels and toxicity.

1- Back NK, Berkhout B. Limiting deoxynucleoside triphosphate concentrations emphasize the processivity defect of lamivudine-resistant variants of human immunodeficiency virus type 1 reverse transcriptase. *Antimicrob Agents Chemother.* 1997; 41: 2484-2491.

2- Back NK, Hijhuis M, Keulen W, et al. Reduced replication of 3TC-resistant HIV-1 variants in primary cells due to a processivity defect of the reverse transcriptase enzyme. *EMBO J.* 1996; 15: 4040-4049.

3- Sharma PL, Crumpacker CS. Decreased processivity of human immunodeficiency virus type 1 reverse transcriptase (RT) containing didanosine-selected mutation Leu74Val: a comparative analysis of RT variants Leu74Val and lamivudine-selected Met184Val. *J Virol.* 1999; 73: 8448-8456.

- 4- Gotte M, Arion D, Pamiak MA, Wainberg MA. The M184V mutation in the reverse transcriptase of human immunodeficiency virus type 1 impairs rescue of chain-terminated DNA synthesis. *J Virol.* 2000; 74: 3579-3585.
- 5- Wainberg MA, Drosopoulos WC, Salomon H, et al. Enhanced fidelity of 3TC-selected mutant HIV-1 reverse transcriptase. *Science.* 1996; 271: 2282-2285.
- 6- Ross L, Parkin N, Chappey C, et al. Phenotypic impact of HIV reverse transcriptase M184I/V mutations in combination with single thymidine analog mutations on nucleoside reverse transcriptase inhibitor resistance. *AIDS.* 2004; 18: 1691-6169.
- 7- Hu Z, et al. Fitness Comparison of Thymidine Analog Resistance Pathways in Human Immunodeficiency Virus Type 1. *Journal of Virology.* 2006; 80 (14): 7020-2027.
- 8- Margot, et al. Expanded Response Analyses of Tenofovir DF Therapy by Baseline Resistance Genotype and Phenotype. International Conference of AIDS. 2002: Abstract No. ThOrB1390.
- 9- El-Sadr et al. CD4+ Count-Guided Interruption of Antiretroviral Treatment. *NEJM.* 2006; 355 (22): 2283-2296.
- 10- Castagna A, Danise A, Menzo S, et al. Lamivudine monotherapy in HIV-1-infected patients harbouring a lamivudine-resistant virus: a randomized pilot study (E-184V study). *AIDS.* 2006; 20: 795-803.
- 11- Martinez E, et al. Effects of Switching to Ritonavir-boosted Atazanavir on HIV-infected Patients Receiving Antiretroviral Therapy with Hyperlipidemia. 12<sup>th</sup> Conference on Retroviruses and Opportunistic Infections. Boston, 2005.
- 12- Tebas P, et al. Switch to a protease inhibitor-containing/nucleoside reverse transcriptase inhibitor-sparing regimen increases appendicular fat and serum lipid levels without affecting glucose metabolism or bone mineral density. The results of a prospective randomized trial, ACTG 5125s. 12th CROI; Feb 22-25, 2005; Boston, MA. Abstract 40.
- 13- Riddler SA, et al. A prospective randomized Phased III Trial of NRTI-, PI-, and NNRTI-sparing Regimens for Initial Therapy of HIV-1, ACTG 5142. XVI International AIDS Conference. Toronto, 2006.