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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

The patient is a 51-year-old male diagnosed with HIV in 1985. His CD4 nadir is 190 cells/mm<sup>3</sup>. He is currently on Trizivir® (zidovudine/lamivudine/abacavir), tenofovir (TDF, Viread®) and lopinavir/ritonavir (LPV/r, Kaletra®) with a current CD4 cell count of 402 cells/mm<sup>3</sup> and an viral load of 302 copies/mL(9/2007). He has a history of oral and esophageal candidiasis but no other opportunistic infections. In June 2005, he had a bout of pneumococcal pneumonia and meningitis. His past antiretroviral therapy have included zidovudine (AZT, Retrovir®), efavirenz (EFV, Sustiva®), stavudine (d4T, Zerit®), lamivudine (3TC, Epivir®), abacavir (Ziagen), atazanavir (Reyataz) and ritonavir boosted amprenavir (Agenerase®). On these regimens, the viral load has never been undetectable, but has been consistently low (~1000 copies/mL). Adherence has been an issue due to depression and financial difficulties. His recent ART history is as follows:

DATE	REGIMEN *	CD4 cells/mm <sup>3</sup>	VL COPIES/ML	RESISTANCE TEST FINDINGS	CLINICAL COURSE
9/04	none	407	138,912		
2/05	none	358	158,954		
8/05	Combivir®, tenofovir, ritonavir boosted atazanavir	327	115		
10/05	as above	327	<75		
12/05	as above	417	<75		
3/06	as above	320	371		
4/06	as above	374	1270		
5/06	as above		2301		6/16/06 Phenosense
8/06	Trizivir®, tenofovir, Kaletra®	348	<75		
10/06	as above	469	<75		

CASE NUMBER  
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1/07	Trizivir®, tenofovir, Kaletra®	313	<75		
7/07	as above	398	<75		
8/07	as above		173		
9/07	as above	440	924		Genotype 9/24/07
9/07	as above		302		Phenosense 10/4/07

## Resistance Test Findings

### Key Mutations

UCSF Resistance Test (Genotype) 9/24/07 (while on Trizivir®, tenofovir, Kaletra®)

NRTI	M41L D67N T69N K70R T215F K219Q Others: K43KE A158S I178M L214F D218E L228H V245E
NNRTI	K101H
PI	L10I V11I K20R L33F M36I I54V I62V L63P A71V G73S T74S I84V L90M I93L Others: Q18H E35D S37D K45R K55R

PhenoSense (Monogram)

Fold-changes

		6/6/06	10/4/07	cut-offs
NRTI:	abacavir (ABC)	5.44	4.23	(4.5-6.5)
	didanosine (ddI)	2.19	1.94	(1.3-2.2)
	emtricitabine (FTC)	7.41	4.45	(3.5)
	lamivudine (3TC)	5.40	4.16	(3.5)
	stavudine (d4T)	3.42	3.41	(1.7)

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	tenofovir (TDF)	7.41	6.65	(1.4-4)
	zidovudine (AZT)	>max	1068	(1.9)
NNRTI:	efavirenz (EFV)	2.66	1.97	(3)
	nevirapine (NFV)	8.98	6.63	(4.5)
PI:	atazanavir/RTV	76	21	(5.2)
	fosamprenavir/RTV	25	12	(4-11)
	indinavir/RTV	9.40	5.61	(10)
	lopinavir/RTV	16	12	(9-55)
	saquinavir/RTV	>max	23	(2.3-12)
	tipranavir	1.70	1.70	(2-8)
	darunavir		4.22	(10-90)
	Replication Capacity	5.1%.		

## **Questions for the Panel**

The patient's primary physician has the following questions:

### 1. Why did his genotype not report 3TC resistance?

One would have expected to see the M184V (the 3TC- and FTC-associated resistant mutations), as this mutation emerges rapidly in nearly all patients failing either 3TC or FTC. Although the lower-level phenotypic resistance to 3TC noted on the phenotype suggests that the virus found a non-M184V pathway to resistance, this does not explain why the virus did not select for M184V, which selects for much higher levels of resistance.

One theoretical barrier preventing the M184V mutation pertains to its impact on viral fitness. It is well known that the M184V mutation significantly decreases viral fitness and perhaps this patient's virus "avoided" the generation of this mutation to prevent further effect on an already compromised ability to replicate from other mutations. An alternative explanation is that the patient was not adherent to the Trizivir®, and that the various mutations noted in the reverse transcriptase gene were due to continued use of tenofovir.

### 2. Is abacavir really still active in this patient (as shown in the phenotype)?

There is clearly high-level resistance to most of the NRTIs. However, based on the genotypic mutations and the phenotypic fold change, abacavir probably has some residual activity. The M41L plus T215F reduces abacavir susceptibility by two- to three-fold [1]. The absence of the M184V mutation may reduce the further loss of susceptibility to abacavir. High-level resistance to the remaining NRTIs is likely.

### 3. Can the unusually low replication capacity be attributed to a particular subset of mutations or selection by a particular subset of drugs?

Viral fitness refers to the ability of HIV to replicate in a specifically-defined environment. Replication capacity (RC) measures the intrinsic ability of HIV to replicate ex vivo in the absence of other pressures. Certain HIV mutations that confer resistance also decrease replication capacity. For

example, the M184V mutation which confers genotypic resistance to 3TC and FTC results in a less fit virus, with some evidence suggesting that this “fitness defect” results in a ~ 0.5 log<sub>10</sub> drop in viral load [2]. The impact of the TAMS on replication capacity/fitness is less clear. [3]. The K103N does not impair replication capacity/fitness [3]. The protease mutations, D30N alone or L90M in combination with mutations at 20, 56, 73, or 88 are associated with a low RC [3].

One study showed a correlation between RC and immunological and clinical outcome [4]. However, at this time the clinical role of RC in making therapeutic decisions is unknown.

4. What are the implications of the 101H mutation for susceptibility to etravirine? In a patient with a history of nonnucleoside reverse transcriptase inhibitor (NNRTI) use without viral suppression, does the 101H make it likely that there are other “hidden” NNRTI mutations which would render etravirine ineffective?

Data from the Duet 1 and 2 studies identified 13 NNRTI mutations associated with etravirine resistance: V90I, A98G, L100I, K101E/P, V106I, V179D/E, Y181C/I/V, and G190S/A [5]. Loss of etravirine efficacy was greatest among patients with three or more of these mutations [5]. There is always the possibility that the K101H is a marker for more archived NNRTI mutations, especially in a patient who was on a prior NNRTI based regimen without virological control and who was not on an NNRTI for many years when the genotype was done.

5. Are there reasons to prefer tipranavir over darunavir?

There is no head-to-head study comparing tipranavir to darunavir in highly experienced patients. It may be possible to determine whether one or more of these drugs is effective based on the phenotype, although how best to interpret the fold-changes to these drugs remains a work in progress. The decision to use either agent would be based on pill burden (tipranavir/ritonavir = 4 pills bid; darunavir/ritonavir = 3 pills bid), tolerability, toxicity (e.g. a patient with an AV malformation or a patient on anti-platelet agents or coumadin should probably not take tipranavir due to the association between this drug and an increased risk of intracranial hemorrhage)[6]. Tipranavir also has significant drug-drug interactions, which may make it difficult to combine this drug with drugs such as etravirine (tipranavir/ritonavir decreased etravirine exposures by 75%)[7].

6. Can the patient be suppressed without raltegravir (e.g. just by switching PI and adding etravirine)?

See discussion below.

## Interpretation/Implications for Treatment

Nucleoside reverse transcriptase inhibitors (NRTIs): Both the genotype and phenotype indicate that there is no fully active NRTI. Of the NRTIs, abacavir, and either 3TC or FTC probably has some activity. Whether resistance to the remaining NRTIs is complete or not can not be determined based on the available data. Several prospective interruption studies have shown that selective removal of NRTIs in patients with high-level genotypic/phenotypic resistance results in some loss of virologic control. For this reason, NRTIs are often continued even in the presence of resistance.

Nonnucleoside reverse transcriptase inhibitors (NNRTIs): The genotype only shows the K101H which does not confer resistance to any of the NNRTIs. The phenotype indicates the virus is sensitive to efavirenz (EFV, Sustiva®); however, the patient has failed an EFV-based regimen in the past. Because of EFV's low genetic barrier to resistance, there is a high probability that significant NNRTI mutations are archived. Thus there is concern that the commercially-available NNRTIs are not active.

Protease inhibitors (pi): There is a discordant response for both tipranavir and darunavir (i.e. the genotype indicates that the virus is resistant to both agents but the phenotype shows that the virus is sensitive to both). Even though genotypic algorithms have been developed to determine whether a virus is sensitive to PIs when there are multiple mutations, it is difficult to assess the overall effect of multiple mutations on susceptibility. Thus, the phenotype may be more accurate in determining susceptibility in this situation.

## Recommendations

Regimen Options: The patient has several options for complete viral suppression. It was the consensus of the panel that the patient switch his regimen to a fully suppressive regimen that contained NRTIs, ritonavir/darunavir, raltegravir, and at least one other potent agent, either enfuvirtide, etravirine, or maraviroc. The optimal choice depends on patient preference and the result of a tropism assay.

### **Option A :**

**Trizivir® one tablet BID plus tenofovir (Viread®) 300 mg po daily OR Combivir® (zidovudine + lamivudine) one tablet BID plus tenofovir or Truvada® (tenofovir + emtricitabine) one tablet daily PLUS enfuvirtide (T-20, Fuzeon®) (90 mg SQ q 12 hours) PLUS darunavir (Prezista®) 300 mg 2 tablets bid PLUS ritonavir 100mg one tablet bid PLUS raltegravir(Isentress®) 400 mg one tablet bid.**

The December 1, 2007 Department of Health and Human Services' Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents recommend that the goal of treatment for patients with prior drug exposure and drug resistance is maximal virologic suppression (i.e. a viral load of <50 copies/mL) using at least two, preferably three active agents. The available data suggest that darunavir, enfuvirtide, and raltegravir will be fully effective.

The Benchmark 1 and 2 study [8,9] showed that at 16 weeks, 98%(intent-to-treat analysis) achieved an HIV viral load of <400 copies/mL if the patient received three active agent consisting of T-20, ritonavir boosted darunavir, and raltegravir. If the patient received two active agents (e.g. T-20 and raltegravir or ritonavir-boosted darunavir and raltegravir), 90% reached a viral load of <400 copies/mL. This response rate was durable out to 48 weeks.[10].

The NRTI backbone is compromised as there is no fully active agent; however, as noted above, several of these drugs should have residual partial activity. Any one of the above three NRTI backbones is reasonable (choice would depend on pill burden, toxicity).

PRO; Meets the recommendations of the December 1, 2007 DHHS guidelines.

Obviates the need for doing a tropism test.

CON: Increased pill burden.

Potential for increased toxicity.

Patient may not take T-20 (patient has refused in the past).

Patient's viral load is not very high while the CD4 cell count is high, and therefore may not need such an aggressive regimen for the viral load to become undetectable. In addition, if there is virologic breakthrough on this option, potentially the only active agents available will be etravirine and maraviroc.

**Option B:** There are two possible options for B, one of which will require a tropism test:

**Trizivir® one tablet BID plus tenofovir (Viread®) 300 mg po daily OR Combivir® (zidovudine + lamivudine) one tablet BID plus tenofovir or Truvada® (tenofovir + emtricitabine) one tablet daily Trizivir® one tablet bid PLUS darunavir (Prezista®) 300 mg 2 tablets bid PLUS ritonavir 100mg one tablet bid PLUS raltegravir(Isentress®) 400 mg one tablet bid**

**PLUS etravirine (investigational on expanded access)**

OR

**Maraviroc (MAV, Selzentry® 150 mg; one tablet bid.**

PRO: Avoids T-20.

Patient's viral load is not very high and the CD4 cell count is high. Two active agents may be sufficiently active for maximal viral suppression.

CON: There is some risk to using etravirine as the clear extent of NNRTI resistance is not known in this patient.

Maraviroc is a CCR5 antagonist which appears to be well tolerated, safe (through 48 weeks of observation), and effective, assuming that the patient lacks a CXCR4 utilizing virus. A tropism test should be ordered before using maraviroc. The majority of heavily pre-treated patients harbor CXCR4-utilizing viruses.

**Option C:** Continue with the current regimen since the patient is doing well from a virological and immunological standpoint

PRO: Patient tolerating the current regimen.

CON: Generation of more PI mutations resulting in phenotypic resistance to both darunavir and tipranavir.

## **Dosing, Monitoring, and Follow-up Recommendations**

Repeat CD4 and viral load approximately four weeks after regimen change.

Monitor for drug related side effects-

T-20: primarily injection site reaction.

darunavir: skin rash(7%), diarrhea, hyperlipidemia.

raltegravir: nausea, headache, diarrhea, CPK elevation.

maraviroc: abdominal pain, dizziness, hepatotoxicity, orthostatic hypotension.

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