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# HIV Resistance Testing Consultation Service

## Consultation Report

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**Disclaimer:** This information has been developed solely as an educational resource for health care professionals interested in HIV care and research. The information presented represents the views of the Panel members only and not necessarily those of the National HIV/AIDS Clinicians' Consultation Center's HIV Telephone Consultation Service (Warmline), the Positive Health Program at San Francisco General Hospital, or sponsoring organizations. Resistance testing can help identify whether certain drugs or classes of drugs might be ineffective, but cannot establish which drugs will be effective. Furthermore, test results can be inaccurate and interpretation of tests is not yet standardized. Because of the many factors involved in treatment decisions when resistant virus is present, the antiretroviral regimens and the therapeutic strategies discussed are not the only possible options and might be different from current Practice Guidelines. Other sources of information on resistance testing, such as clinical HIV websites, can be of help. Health care professionals should consult the HIV Telephone Consultation Service (Warmline) or HIV experts in their community before using any of the recommended therapeutic regimens or strategies in this document.

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

This is a 42-year-old Caucasian male with a history of HIV/AIDS, active substance abuse (methamphetamine, cocaine), prior IV drug use, chronic Hepatitis C, depression, and recurrent HSV-2. He has been on multiple antiretroviral regimens with inconsistent adherence and now has developed triple class drug resistance. He was apparently exposed to nucleoside analogues in the early 1990s. His CD4 declined to 75 cells/mm<sup>3</sup> in 1997, at which point he started Combivir® (CBV, zidovudine plus lamivudine), nelfinavir (NFV, Viracept®) and efavirenz (EFV, Sustiva®). Despite never achieving an undetectable viral load, his CD4 increased steadily, and was nearly 500 cells/mm<sup>3</sup> by 2004. His CD4 cell count has since fallen to 32 cells/mm<sup>3</sup> (in July 2007); his viral load at that time was 39,128 copies/ml.

Despite the persistent viremia and low CD4 counts, he has had no opportunistic infections except for thrush. Because of poor adherence, his HIV medications were stopped in July 2007. In August 2007, he was started on lamivudine (3TC, Epivir®) monotherapy while awaiting further treatment options.

In November 2007, based on a PhenoSense (obtained on lamivudine alone), a new regimen of Trizivir® (zidovudine, abacavir, lamivudine), tenofovir (TDF, Viread®), raltegravir (RAL, Isentress®) and darunavir/ritonavir (DRV/r, Prezista®/Norvir®) was prescribed. However, because of pharmacy errors and other issues, he received only one week of raltegravir, left the drug treatment program, and stopped all his HIV medications.

His antiretroviral therapy is summarized below:

DATE	REGIMEN *	CD4 cells/mm <sup>3</sup>	VL COPIES/ML	RESISTANCE TEST FINDINGS	CLINICAL COURSE
1990's	Unknown ARVs in prison				
10/96	None	96	3,082		Speed and cocaine on methadone
4/97	None	75	6,212		
9/01	CBV/NFV/EFV	169	59,992		More stable on methadone
11/27/01	CBV/NFV/EFV	192			Spotty adherence
5/17/03	"	170			
12/03	"	333			
3/04	"	478	12,562		

CASE NUMBER  
 PANEL CLINICIAN:

DATE

5/04	“	324			
11/04	Stopped meds	93			
2/05	Truvada® (tenofovir emtricitabine) Atazanavir/Ritonavir				Needed once a day
5/05	“	139	37,668		
7/05				GART #1 done	
10/05	Epzicom® (abacavir/lamivudine), Tenofovir/ Atazanavir/Ritonavir  (may have been on Trizivir® bid with missing doses)	138	14,804		Meds at methadone window
1/06	“	116	47,692		
4/06				GART #2 done	
7/06	“	61	74,289		
2/07		58	28,325		
7/07	Stopped meds	32	39,128		
8/07	Epivir®				
9/07	“			Phenotype sent	

## Resistance Test Findings

### Key Mutations

7/18/05	Protease: L101V, K20I, L33I/L, M36L, I54I/V, L63P, A71V, G73S, L90M
	RT: M41L, D67N, K103N, M184V, T215Y

4/17/06	Protease: L10V, K20T/I, L33I, M36L, I54V, L63P, A71V, G73S, L90M
	RT: M41L, D67N, K103N, M184V, L210W/L, T215Y, K219K/R

9/13/07	Phenosense: ABC 1.82 (4.5-6.5), DDI 0.73 (1.3-2.2), FTC 1.00 (3.5), 3TC 1.06 (3.5), D4T 0.73 (1.7), TDF 0.72 (1.4-4), ZDV 1.14 (1.9)
	EFV 0.69 (3), NVP 0.53 (4.5)
	ATZ/Rit 3.16 (5.2), DRV 0.96 (10-90), FOS/Rit 1.77 (4-11), IND/Rit 2.60 (10), LOP/Rit 2.32 (9-52), NEL 4.23 (3.6), RIT 4.13 (2.5), SAQ/Rit 2.63 (2.3-12), TIP/Rit 1.99 (2-8) Reported resistant to ATZ, IND, NEL, RIT, SAQ

### Questions:

1. What medication regimen is now recommended?
2. Does the NRTI resistance pattern make sense with his NRTI exposure history?
3. Would you ever consider lamivudine monotherapy until his substance abuse is under control?

## Interpretation/Implications for Treatment

This is a 42-year-old individual with a long, complicated treatment history. He has ongoing drug addiction and an unstable living situation. He has been in and out of care for years. His ability to adhere to future regimens is not clear.

The panel was asked to interpret the available genotypes and phenotype and recommend a maximally suppressive regimen, assuming an ideal scenario in which this patient might be fully adherent. One genotype (7/05) was performed while on Truvada® and ritonavir boosted atazanavir (ATV/r), and another (4/06) was obtained while on Epzicom®, tenofovir, and ritonavir boosted atazanavir (both in the setting of uncertain adherence). The Phenosense was obtained on lamivudine (3TC) and after being off of his last regimen for at least two to three months. Thus, there may be more archived mutations than

are apparent on the available genotypes and there may be more phenotypic resistance than appears on the phenotype.

There was evidence of high-level NRTI and NNRTI resistance and only moderate protease inhibitor resistance in 2005. There was limited change in the genotype between 2005 and 2006. The genotypes reveal five thymidine-analogue mutations (TAMs): M41L, D67N, L210W, T215Y, and K219R. This pattern is consistent with broad resistance to all the NRTIs (Larder 1989, Whitcomb 2002). Of note, there are two TAM pathways. Pathway 1 (41L, 215Y, 210W) confers higher-level zidovudine (AZT, Retrovir®) and stavudine (d4T, Zerit®) resistance and is associated with greater NRTI cross-resistance. Pathway 2 (67N, 70R, 219Q/E) confers lower-level AZT and d4T and tenofovir resistance, and is associated with less cross-resistance within the class. This patient has a mixed pathway picture, and likely has compromised most if not all of the NRTIs. The M184V mutation is associated with high-level resistance to emtricitabine (FTC) and lamivudine (3TC) but also reduces viral fitness. It also confers low-level resistance to abacavir (ABC, Ziagen®) and didanosine (ddI, Videx EC®). Abacavir sensitivity is significantly reduced (Lanier 2004).

The phenotype was performed while the patient was taking 3TC monotherapy, and shows limited NRTI resistance, presumably because the drug-resistance mutations have waned in the absence of drug-pressure. The number of NRTIs needed in the optimized background is not clear. Given data suggesting that the NRTIs remain partially effective even in the presence of drug-resistance mutations, many clinicians choose to use these drugs in any salvage regimen. Lamivudine or emtricitabine is often one of these drugs, given that these drugs often have partial direct activity, and that the M184V mutation appears to reduce viral fitness. Most would recommend Truvada® (tenofovir plus emtricitabine) as the “nuke backbone” due to good tolerability.

The presence of the K103N mutation confers resistance to efavirenz (EFV, Sustiva®) and nevirapine (NVP, Viramune®) (Antinori et al, AIDS Res Hum Retroviruses 2002), but not to etravirine (ETR, Intelence™). Of note, many of the etravirine mutations were not routinely reported until a few years ago so they may have been present in 2005 or 2006. The absence of these mutations in these older genotypes needs to be confirmed by the laboratory. Most of the panel members believed that etravirine would still be a reasonable alternative for this patient. (Vingerhoets, Azijn et al. 2005).

The patient had some evidence of protease inhibitor resistance. The L90M (and also the D30N) mutation confers resistance to nelfinavir (NFV, Viracept®). Approximately 10% of subtype B patients go down the 90M pathway, and this pathway has more cross resistance implications (as in this case). Similar protease mutations were apparent on genotypes obtained in 2005 and 2006 (L10I/V, K20I, L33 I/L, M36L, I54I/V, G73S) showing eight atazanavir mutations, seven lopinavir mutations, three fosamprenavir mutations, one darunavir mutation, five indinavir mutations, five saquinavir mutations, and four tipranavir mutations. In 2007, the Phenosense (off meds) revealed fold changes lower than susceptibility cut-off (lower limit) with ritonavir boosted atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, and tipranavir (borderline), suggesting that these antiretrovirals would be active against this virus. However, based on mutations noted on previous genotypes one would expect more PI resistance, so under selective PI pressure the fold changes might actually be higher than reported. Since there is only one darunavir-specific mutation present and low fold change on the phenotype, ritonavir-boosted darunavir appears to be the most active PI agent.

The management of drug-resistant HIV has been dramatically altered by the recent approval of several drugs. Maraviroc (MVC, Selzentry®) is an CCR5 inhibitor that would be effective if the virus does not use CXCR4 for cell entry (a Trofile® test is recommended). Raltegravir (RAL, Isentress®) can be considered but resistance to this drug appears to emerge rapidly if used in a suboptimal manner, and this patient has already been exposed to this drug for a brief period. Finally, etravirine, a second generation NNRTI that was recently approved, is likely to be an effective option.

The panel also discussed the role of enfuvirtide (T20, Fuzeon®) in the next regimen. In clinical trials and clinical practice, this drug has proven to be highly effective (when used with at least two other active agents). However, the major barrier to treatment success for this patient is adherence. The use of enfuvirtide administration (injection) and its side effects should be carefully discussed with the patient.

The January 2008 DHHS adult antiretroviral treatment guidelines state that the most effective antiretroviral regimen for highly experienced patients should consist of at least two, and preferably three active agents. However, it is not always possible to find three active drugs in the setting of multi-class drug resistance. Sometimes a regimen containing only two active drugs is all that is available.

The question of whether one should treat with 3TC alone (as a “bridge”) while the substance abuse is being controlled was discussed. The panel believed that with a CD4 of 30 cells/mm<sup>3</sup>, it would be important to offer this patient the best regimen for successful viral suppression. If the CD4 were higher and there were adherence issues, perhaps one could temporize (by weakening the virus) with 3TC or even a regimen to which the virus is resistant (such as Combivir® -nelfinavir).

## Recommendations

### Regimen Options

#### Option 1

Ritonavir 100 mg po BID plus darunavir 600 mg po BID plus raltegravir 400 mg po BID plus etravirine 200 mg po BID plus Truvada® (tenofovir and emtricitabine) once daily orally

Pro: Likely to achieve virologic suppression with optimized background of three active drugs

Con: If the previous genotype showed three etravirine mutations (or if this information is not available), etravirine may not be effective. Also, since resistance to raltegravir emerges quickly (when used in a suboptimal regimen); it is possible that the efficacy of this drug may have already been compromised.

#### Option 2

Ritonavir 100 mg po BID plus darunavir 600 mg po BID plus raltegravir 400 mg po BID plus maraviroc 150 mg po BID (if Trofile® shows R5 tropic virus) plus Truvada® (tenofovir and emtricitabine) once daily orally

Pro: Likely to achieve virologic suppression with optimized background of three active drugs

Con: The long-term safety of maraviroc remains a concern; however, if the patient's virus is R5, then this drug should be strongly considered, given its lack of short-term toxicity and proven anti-viral activity.

### Option 3

Ritonavir 100 mg po BID plus darunavir 600 mg po BID plus raltegravir 400 mg po BID plus enfuvirtide 90mg SQ BID plus Truvada® (tenofovir and emtricitabine) once daily orally

Pro: Likely to achieve virologic suppression with optimized background of three active drugs

Con: Enfuvirtide is an injectable medication, which may further reduce adherence.

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

Monitor CD4 count every 2-3 months and HIV-RNA every month until undetectable

Monitor Cr, LFTs, CBC every month for 3 months, then once stable every 3 mos

Monitor lipids and fasting glucose at baseline and then q 6 months

*Antinori et al. "Cross-resistance among nonnucleoside reverse transcriptase inhibitors limits recycling efavirenz after nevirapine failure." AIDS Res. Human Retroviruses. 2002 Aug 10; 18(12) 835-8*

*Lanier et al (2004). "Antiviral efficacy of abacavir in antiretroviral therapy-experienced adults harbouring HIV-1 with specific patterns of resistance to nucleoside reverse transcriptase inhibitors" Antiretroviral Therapy. 2004 Feb; 9(1) . 37-45.*

*Larder, B. A. and S. D. Kemp (1989). "Multiple mutations in HIV-1 reverse transcriptase confer high-level resistance to zidovudine (AZT)." Science 246(4934): 1155-8.*

*Vingerhoets, J., H. Azijn, et al. (2005). "TMC125 displays a high genetic barrier to the development of resistance: evidence from in vitro selection experiments." J Virol 79(20): 12773-82.*

*Whitcomb J.M., Paxinos E.E., Huang W. The presence of nucleoside analogue mutations (NAMs) is highly correlated with reduced susceptibility to all NRTIs. Program and Abstracts of the 9th Conference on Retroviruses and Opportunistic Infections; Seattle; Washington. 2002;Abstract 569. February 24-8.*