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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

A 45-year-old gay Colombian man was diagnosed with HIV in 1992. His other medical problems include severe depression, intermittent methamphetamine use, Bell's palsy with residual R facial droop, and repeated sexually transmitted diseases (i.e. urethral chlamydia, rectal chlamydia [different episode], giardia, intestinal amebiasis). He denies injection drug use and is HCV-negative. There are no histories of opportunistic infections (OIs) or malignancies. From 11/02, he was enrolled in the SMART study and was randomized to continuous rather than CD4-driven episodic therapy. His adherence is reported as intermittent due to his methamphetamine use. The patient tends to take antiretrovirals (ARVs) that he "likes" and to stop taking those that he doesn't like, regardless of the activity and efficacy of the agents.

His exact early ARV history is not clear, but he reports exposure to lamivudine (3TC), zidovudine (AZT) (nausea), stavudine (d4T), didanosine (ddI), and nevirapine (NVP) (Stevens-Johnsons' syndrome by medical report, undocumented). He has also declined enfuvirtide (T-20) use.

A summary of his selected HIV history is as follows:

DATE	REGIMEN	CD4	VL	COMMENTS
3/26/98		174	26,290	First available data
9/15/98	3TC/d4T/IDV/r	159	<50	
4/2/99	off	92	>500,000	Nadir CD4 on record
8/23/99	3TC/d4T/IDV/r	237	4955	
5/10/00	3TC/d4T/IDV/r	277 (13%)	<50	
12/4/00	off	185	267,713	Start 3TC/ABC/LPV/r
7/9/01	3TC/ABC/LPV/r	546	<50	Stopped LPV/r 12/01 due to Diarrhea
7/29/02	off	109	189,637	Start 3TC/ddI/LPV/r
7/02 – 12/03	3TC/ddI/LPV/r	331-567 (14-24%)	<75 with intermittent rises to 10k	Stopped LPV/r 3/04 due to patient fear it was causing visceral fat accumulation
2/3/04	off	176 (9%)	12,947	Start 3TC/ddI/ATV
3/31/04	3TC/ddI/ATV	406 (13%)	<50	Stop ATV 7/04 due to subjective jaundice (total bilirubin 2.3)
8/11/04	off	187 (14%)	7,687	
10/21/04	3TC/ddI/FPV/r	393 (19%)	<75	Unable to tolerate RTV (capsule or liquid) boosting due to GI

				intolerance
	3TC/ddI/FPV		<75 x6mo	
6/30/05	3TC/ddI/FPV	413 (15%)	585	VL rising over next 3 checks
8/15/05	3TC/ddI/FPV		1504	Resistance testing done
12/19/05	ABC/FTC/TDF/LPV/r	390 (17%)	142	Use of LPV/r tablets
1/23/06	FTC/TDF/LPV/r	458 (22%)	<75	Stopped ABC due to nausea and abdominal pain
3/06 – 10/07	FTC/TDF/LPV/r	265-499 (18-26%)	119-1087 Never <75	Improved adherence; mild diarrhea, but tolerable
10/15/07	FTC/TDF/LPV/r	348 (20%)	376	Fatigue, malaise

AZT = zidovudine (Retrovir®)

d4T= stavudine (Zerit®)

3TC = lamivudine (Epivir®)

ABC= abacavir (Ziagen®)

ddI = didanosine (Videx ®)

FTC= emtricitabine (Emtriva®)

TFV = tenofovir (Viread®)

IDV/r = ritonavir (Norvir®) boosted indinavir (Crixivan®)

LPV/r = lopinavir/ritonavir (Kaletra®)

ATV= atazanavir (Reyataz®)

FPV = fosamprenavir (Lexiva®)

FPV/r = ritonavir (Norvir®) boosted fosamprenavir (Lexiva®)

## Resistance Test Findings

PhenoSense GT, 8/25/05 (on ddI/3TC/FPV)

**RT:** V75V/A/I/T, M184V, T215T/I.

**PI:** L10V, M46I, I50V, L63P, A71A/V.

**RT Fold changes:** ABC (4.89)

	ddl (2.24)
	3TC (MAX)
	FTC (MAX)
	d4T (0.92)
	AZT (0.33)
	TDF (0.53)
<b>NNRTI</b>	DLV (1.22)
	EFV (1.12)
	NVP (0.91)
<b>PI</b>	ATV (1.09)
	FPV (20)
	IDV (1.21)
	LPV (6.37)
	NFV (3.56)
	RTV (4.53)
	SQV (2.27)
	TPV (0.33)

Replication capacity = 70%.

Clade B.

Genotype, Gladstone, 8/25/05

Protease: L10V, M46I, I50V, L63P, A71A/V

RT: A62A/V, V75TIAV, M184V

## Interpretation/Implications for Treatment

**Summary:** This is a patient with intermittent adherence who is also selective about which ARVs he will take. He is triple class-experienced and reports a history of multiple intolerances to meds (mainly GI intolerances). His history is also significant for nevirapine-induced Stevens-Johnsons' syndrome. Resistance testing shows moderate nucleoside reverse transcriptase inhibitor (NRTI) resistance and protease inhibitor (PI) resistance. Currently, he has been taking his PI-based regimen for the last two years with reasonable tolerability and improved adherence, and he remains immunologically stable with stable low-level viremia. The most recent resistance testing data is more than two years old.

### Questions:

1. Can I intensify with Raltegravir? If so, should I make an empiric PI change as well (i.e, change to ritonavir boosted darunavir (DRV/r) or just keep him on what he's tolerating?

The panel strongly cautions against “intensifying” a regimen with a single drug that has a low genetic barrier to resistance – these ARVs include lamivudine (3TC, Epivir®), efavirenz (EFV, Sustiva®), nevirapine (NVP, Virammune®), enfuvirtide (T-20, Fuzeon®), and perhaps raltegravir (RAL, Isentress®). The concern is ongoing viral replication, even at low levels, could make it relatively easy for the virus to generate resistant mutations to these aforementioned agents when compared to other ARVs with higher genetic barriers.

Thus, the Panel believed that if a switch was to occur, it should involve at least two and preferably three fully effective agents. Selecting a new PI might be difficult based on lack of any recent resistance data. Although the genotype shows only one (I50V) of the ten mutations (V11I, V32I, L33F, I 47V, I50V, I54M/L, G73S, L76V, I84V L89V) known to impair darunavir’s activity, some panel members were somewhat less confident in darunavir’s activity, given the similarity between DRV and fosamprenavir (FPV) and the patient’s failure on FPV with associated phenotypic resistance.

2. How important is it to repeat resistance testing now – ie, “let” his viral load (VL) rise to 1,000 copies/mL before acting?

While the lower limit of viral load for sending commercial genotypes, phenotypes, and tropism assays is usually 1,000 copies/mL, results can sometimes be obtained at lower viral loads. At the UCSF Virology Lab, a genotype can be obtained in 85% of cases with VL of 400 copies/mL, which is accurate with replicate trials. Results at lower viral loads are more subject to a “founder effect” whereby only a few single genomes are amplified and may misrepresent the true distribution of resistance present in a population. However, if mutations are found, they should be considered as reliably present.

3. What about the rationale of stopping ARVs for a brief period and then performing resistance testing immediately after achieving a viral load of >1,000 copies/mL?

While there are some potential arguments to be made for this approach, clinical concerns around treatment interruptions as well as lack of data supporting this approach or informing the timing of the resistance testing limit its applicability. The Panel did not recommend this strategy.

4. Is it reasonable to use Efavirenz (EFV) or Etravirine (ETV) with his history of NVP-induced Stevens Johnsons’ syndrome (undocumented)?

Despite the fact that NNRTIs are structurally dissimilar, cross-reactivity of NNRTI toxicity is a concern. While the risks may be acceptable when switching to EFV from non-life threatening hepatotoxicity or hypersensitivity to NVP.<sup>1,2,3</sup> the risks after a potential Stevens-Johnsons’ reaction are unknown and of concern. The Panel believed that a switch to Etravirine may be a safer alternative, although the risks are unknown.

## General Management Considerations:

The Panel supported the strategy that the patient's regimen should be changed as soon as fully-suppressive ARV treatment options were available.

Additional resistance testing could inform options, although it would be difficult at the current viral load. Working in conjunction with the laboratory, a genotype/phenotype, and potentially a tropism assay would be helpful.

## Regimen Options

Several treatment options were considered by the Panel. The recommendations that follow are based on available resistance testing. The Panel recommended obtaining additional resistance testing if feasible, the results of which may affect the Panel's recommendations. Options 1 and 2 were preferred by the majority of the members; least favored was Option 3 given the multiple unknowns with this approach.

**Option 1:** Maintain Truvada® (tenofovir and emtricitabine) one tablet daily orally. Add ritonavir 100 mg bid plus darunavir 600 mg bid (DRV/r) plus etravirine (ETV) 200 mg bid (FO60 formulation) plus raltegravir (RAL) 400 mg bid. Stop lopinavir/r (LPV/r, Kaletra®)

Rationale: Data exist from the DUET trials<sup>6,7</sup> about the efficacy of the DRV/r-ETV combination. This combination would be more protective for RAL, and would most likely achieve complete viral suppression. The Panel acknowledged the complexity and high pill burden of this regimen particularly with his history of poor adherence. Additionally, since he has had poor tolerability of RTV in the past, this regimen may be difficult.

**Option 2:** Maintain Truvada® (tenofovir and emtricitabine) one tablet daily orally. Add ritonavir 100 mg bid plus darunavir 600 mg bid (DRV/r) plus etravirine (ETV) 200 mg bid (FO60 formulation). Stop LPV/r.

Rationale: The group believed that using the regimen in option #2 without RAL would also likely work well, as per the DUET data, and would preserve RAL and perhaps maravroc for future options.

Of note, both options 2 and 3 are based on the patient's virus remaining susceptible to darunavir; if a genotype/phenotype fails to confirm this, then a tipranavir based regimen might be considered, although the high dose of ritonavir and multiple drug interactions make this approach less desirable.

**Option 3:** Intensification with maraviroc (Selzentry®) 150 mg orally twice daily; continue his current ARV regimen.

**Rationale:** As stated above, intensification with a low genetic barrier drug is of concern; however, it appears that Maraviroc may have a higher genetic barrier and be a wiser choice in this regard. Although it would be impossible to obtain a valid tropism assay with the patient's viral load <1,000 copies/mL, the group reasoned that this assay may not be necessary before using Maraviroc in this particular situation. If the patient has R5 virus, Maraviroc would be effective and achieve viral load reduction. If the virus is a dual/mixed virus, it is less likely that an undetectable viral load would result from maraviroc treatment. If an X4 virus is currently present, it is unlikely that harm would be done based on data from the Motivate trial.<sup>4,5</sup> Maraviroc is likely to be well-tolerated; however, one caveat is the potential long-term unknown toxicity of CCR5 inhibitors, including malignancy. Adverse effects of maraviroc include cough, pyrexia, upper respiratory tract infections, rash, musculoskeletal symptoms, abdominal pain, and dizziness. Rarely, hepatotoxicity and cardiovascular events have been reported.

## Monitoring, and Follow-up Recommendation

Regardless of which regimen is chosen, the Panel recommends repeating the CD4 and viral load within four weeks of a change in regimen, with frequent monitoring immediately thereafter to ensure virologic suppression.

Enrollment in adherence support programs and/or substance abuse programs would be helpful in maintaining the patient's adherence.

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