

# 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

Mr. F.L is a 44 y/o HIV-infected Latino male who started zidovudine (AZT), lamivudine (3TC), and nelfinavir (NFV) in 1999 after an AIDS diagnosis by T-Cell counts. Although he has achieved excellent virologic control and a consistently high T-Cell response on his only ARV regimen, he is now showing virological breakthrough. Multiple genotypes have been obtained during the course of his therapy. His adherence is estimated at about 95%. He is tolerating his ARV's and does not identify any criteria as important in choosing a new regimen although he would prefer not to use an injectable medication. His LDL is normal, his clinical course is stable, and he has no comorbidities. His primary provider does not identify any considerations, either medical or psychosocial, that would impact on his future therapeutic options.

In summary, Mr. F.L. is accustomed to and happy with his current regimen and not inspired to change until absolutely necessary. However, he definitely wants to maximize his chances of long-term survival, and would agree with any changes in therapy that are recommended.

DATE	REGIMEN *	CD4 cells/m <sup>3</sup>	VL COPIES/ mL	RESISTANCE TEST FINDINGS	CLINICAL COURSE
5/26/99		180	281k		
7/4/99	AZT/3TC/NFV				
8/16/99		336	281		
11/8/99		440	59		
2/28/00		575	<50		
6/12/00		552	<50		
10/2/00		667	751		
10/30/00			1520		
1/8/00		800	527		
3/21/01		672	4,000		
4/4/01				Test 1  PI: L10I, L63P, A71TIAV, L90M/L	

				RT: M41M/L, A62A/V, M184V	
5/9/01			1,400		
7/11/01		704	1,350		
9/26/01				Test 2  PI: L10I, L63P, L90M  RT: M41L, M184V	
11/27/01		676	1,609		
4/9/02			5,000	Test 3  PI: L10I, L63P, A71T/A, L90M  RT: M41L, D67N, K70R, M184V	
5/6/02		522	3,000		
7/24/02		672	3,500		
11/8/02		450	7,800		
12/0/02				Test 4  PI: L10I, L63P, A71V, L90M  RT: M41L, D67N, K70R, M194V, T215F, T215O, K219E	
3/10/03		616	4,000		
7/103		570	10,000		
10/27/03		546	6,080		
3/04/03		588	8,094		
7/22/04		510	8,851		
8/09/04				Test 5  PI: L10I, M46I/M, L63P,	

				A71V, L90M RT: M41L, D67N, K70R, M184V, T215F, K219Q/E	
11/1/04		643	4,200		
3/3/05		655	23,371		
4/20/05			8,371	Test 6 PI: L10I, M36V, L63P, A71V, L90M RT: M41L, D67N, K70R, M184V, T215F, K219Q/E	

## Resistance Test Findings

### Key Mutations

NRT	M41L, D67N, K70R, M 184 V, L210W, T215F, K 219Q/E
NNRT	
PI	L10L, L 63P, A71I, V77I, L90M.

### Clinical Questions:

- 1) Is there a value to a phenotype?
- 2) How effective will Kaletra or atazanavir or an NNRTI be?
- 3) What changes should be made now and how will this impact on his future treatment options?

## Interpretation/Implications for Treatment

This case is distinguished by the remarkable durability of an incompletely suppressive nelfinavir regimen and the ability to monitor over time the progression of mutation development via multiple genotypes. The panel unanimously agreed that future treatment decisions would greatly benefit from a phenotype. A phenotype would provide information about the likelihood that a boosted PI such as lopinavir/r (Kaletra) could overcome the primary L90 mutation and secondary PI mutations. If the phenotype showed less than a 40 fold change, then it is likely that a lopinavir/r based regimen could successfully control the virus. It was acknowledged that the thymidine analogue mutations (TAMs) were very extensive and likely to confer cross-resistance to all the nucleoside analogues.<sup>1</sup> However, it is now recognized that these thymidine analogue mutations (TAMs) are responsible for "rescuing" chain-terminated primers.<sup>2</sup> Didanosine (ddI) might provide some efficacy and the addition of

<sup>1</sup> Victoria A. Johnson, MD, Françoise Brun-Vézinet, MD, PhD, Bonaventura Clotet, MD, et al. Update of the Drug Resistance Mutations in HIV-1: 2005. Topics in HIV Medicine. 2005 Mar/Apr 13 (1) 2005, 51-56.  
[http://www.iasusa.org/resistance\\_mutations/mutations\\_figures.pdf](http://www.iasusa.org/resistance_mutations/mutations_figures.pdf)

<sup>2</sup> Shafer RW. Genotypic Testing for HIV-1 Drug Resistance. Available at  
<http://hivinsite.ucsf.edu/InSite.jsp?page=kb-03-02-07>.

lamivudine (3TC) might sustain mutational pressure that would compromise viral fitness. Of note, the TAMs, M41L and T210Y, will reduce activity to tenofovir.

There was consensus that it would not be advisable to use the nonnucleosides reverse transcriptase inhibitors (NNRTI) now as the risk of losing this very potent class is too high. Rather, a recommendation was made to preserve this drug until it can be combined with a second drug that has complete activity against this patient's virus (e.g., an integrase inhibitor). The panel did not feel confident that future therapies with novel mechanisms of action were sufficiently developed that could be combined with an NNRTI at this time. . Furthermore, the panel felt that T20 would be difficult to access given the patient's CD4 and that the patient would likely not want to use this drug at this time..

Some consideration was given to dual boosted PIs such as lopinavir/r with saquinavir or lopinavir/r with atazanavir. However, these recommendations were guarded by the negative impact of these regimens on quality of life and side effects, particularly the risks of worsening lipids in a 44 y/o smoker.

The option to remain on the same regimen was not favored by the panel due to 1) evidence of progressive PI mutations; 2) rising viral load during the past years despite the low viral load level, and 3) the risk of developing further PI mutations and compromising future PI options. In addition, at the time of this panel meeting, the tolerability, side effect, resistance profile, and drug interactions of boosted tipranavir were unclear and panel members were not confident that it would be a reasonable option if all other protease inhibitors were ineffective.

The option to stop therapy was not appropriate due to his low CD4 nadir of 180 cells/mm<sup>3</sup>. If the nadir was greater than 400 cells/mm<sup>3</sup>, then there was consensus that stopping all medications might be a reasonable option.

Support for stopping nelfinavir and continuing with two nucleosides was also not an appropriate treatment option. Dual NRTI therapy would likely result in further T-cell loss which might be less forgiving in someone with a low nadir. While this prediction is not yet fully supported in the literature the consequence of its outcome would be to commit the patient to PI, NNRTI, and NRTI therapy, starting from a lower baseline CD4. If the use of the preserved NNRTI class failed then the patient would likely be vulnerable to sequential monotherapy as noted above.

## Recommendations

### Regimen Options

#### 1) Continue Regimen

PRO: The possible advantage to continuing the current regimen is the benefit from the significant CD4 boost and the relatively but not completely suppressed viral load. The regimen is tolerable, he has remained well on this regimen for a very long time, and he will likely retain some PI efficacy towards viral suppression. The disadvantage is the possible development of more PI mutations which would compromise the value of future potent PIs.

#### 2) Stop Regimen

There were few advantages given the lack of side effects, the low CD4 nadir, and the overall success of the therapy.

### 3) Change Regimen

- a) Option 1: Kaletra tablets 2 to 3 tablets bid plus lamivudine (3TC) 300 mg daily with food plus one to two other NRTIs (selected based on tolerability).

Advantage: Possible viral suppression while preserving NNRTI

Disadvantage: Possible lack of viral suppression with loss of PI class, drug intolerance from didanosine

Deciding Factor: Result of Phenotype

- b) Option 2: Kaletra tablets 3 tablets bid plus efavirenz (Sustiva) 600 mg once daily plus lamivudine (3TC) 300 mg once daily with food plus one to two other NRTIS.

Advantage: Very high likelihood of viral suppression given use of an NNRTI.

Disadvantage: Chance of breakthrough and risk of sequential monotherapy, poor tolerability and toxicity from didanosine.

- c) Option 3: Kaletra tablets 2 tablets bid plus Saquinavir 1000 mg bid or Kaletra 2 tablets bid plus atazanavir 300 mg once daily plus lamivudine (3TC) 300 mg once daily with food plus didanosine (Videx EC) 400 mg once daily on empty stomach,

Advantage: Higher chance of viral suppression while preserving NNRTI class

Disadvantage: Higher chance of lipodystrophy and decreased tolerability, large pill burden. Limited data supporting use of dual protease inhibitors.

- d) Option 4: Ritonavir/tipranavir or ritonavir/darunavir (TMC 114) plus lamivudine (3TC) 300 mg once daily with food plus one to two other NRTIs

Advantage: Higher chance of viral suppression while preserving NNRTI class

Disadvantage: Higher chance of lipodystrophy and decreased tolerability, large pill burden.

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

Check Phenotype

Promote patient to stop smoking

Check viral load and CD4 count 4 to 6 weeks after starting new regimen.

Monitor for drug toxicity:

ddl peripheral neuropathy, pancreatitis, lactic acidosis

lopinavir/r hyperlipidemia, lipodystrophy, hepatitis, insulin resistance

atazanavir hyperbilirubinemia