
HIV Resistance Testing Consultation Service

Consultation Report

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History/Clinical Course

A 43 year old Caucasian male was diagnosed HIV+ in 9/92 when he presented Kaposi's sarcoma. Zidovudine (AZT) monotherapy was begun in 9/92 and continued for 2 years. Lamivudine (3TC) was added to AZT in 5/94, and indinavir (IDV) was added in 5/96. In 12/00 the addition of ritonavir (RTV) to his regimen caused a transient VL reduction and an increase in his CD4 count. Because of a detectable viral load and a falling CD4 count, a genotype and phenotype were obtained in 11/02, and his regimen was changed to AZT/3TC (Combivir), tenofovir (TDF), and lopinavir/RTV (Kaletra). On this regimen, his VL became undetectable and his CD4 count remained stable until 12/04 when his viral load became intermittently detectable. The patient remains non-nucleoside (NNRTI) naïve. His adherence is historically excellent. His nadir CD4 count is 163 cells/mm³.

DATE	REGIMEN	CD4 cells /mm ³	VL COPIES/ML	RESISTANCE TEST FINDINGS	CLINICAL COURSE
9/92	AZT	330	NA	NA	KS of tonsilar pillar and left arm (stable)
3/94	AZT/3TC (Combivir®)	294	NA	NA	Neuropathy develops and persists
5/96	AZT/3TC/IDV (indinavir)	163	1800	NA	Sepra added for PCP prophylaxis VL decreases to 1-3K and CD4 rises to 200-300 cells/mm ³
12/00	AZT/3TC IDV/RTV	227	2950	1st Genotype and Phenotype obtained Genotype NRTI: 41L, 67N, 69D, 184V, 210L, 215Y PI: 46M/L, 54I/V, 71A/T, 82V/A, 84I/V (Specialty Lab)	Transient VL decreased to 250 copies/ml CD4 rise to 251 until 8/01 VL 1730 CD4 191

11/02	Combivir, tenofovir, Kaletra	179	2740	2 nd Genotype and Phenotype obtained Genotype NRTI: 41L, 67N, 184V, 215Y PI: 46I, 71T, 84V (Specialty Lab)	VL<50 copies. MI 12/02 CD4 233
9/04	Combivir Tenofovir Kaletra	331 (29 %)	<75 remains undetected until 12/04		Note 12/04 – 6/05 patient with low level viremia
6/05	Combivir Tenofovir Kaletra	270	150	3 rd Genotype obtained Genotype NRTI: 41L, 67N, 69D, 184V, 210W, 211K, 215Y PI 10I, 20I, 33Y, 36I, 46I, 54V, 71T, 84V, 88D	
9/05	Combivir Tenofovir Kaletra	280	<75		

Resistance Test Findings (Phenotypes 12/00 and 11/02)
 (Genotypes from 12/00, 11/02 and 6/05 listed in above table)

ARV	Mean Fold Change in IC50
Test Date 12/00	
AZT	10
3TC	>>>
ddI	1.9
ABC	5.3
D4T	1.5
EFV	0.4
NVP	0.6
IDV	25
RTV	20
NFV	22
SAQ	6.8
APV	3.0

ARV	Mean Fold Change in IC50
Test Date 11/02	
AZT	8.5
3TC	>>>
ddI	1.4
ABC	4.8
D4T	1.2
TVF	1.2
IDV	31
RTV	20
NFV	25
SAQ	17
APV	1.3
LPV	6.5

Interpretation/Implications for Treatment

Interpretation of genotypes:

The 184V mutation confers high level resistance to 3TC and FTC (emtricitabine). The 69D insertion occurs in about 2% of heavily pretreated individuals (1) and in conjunction with the presence of major thymidine analog mutations (M41L, D67N, L210W, 211K, T215Y/F) confers resistance to each of the NRTIs (2). However, despite the presence of multiple resistance mutations, this class of drugs can retain some partial activity against the drug resistant variant. (3) Although the presence of the M184V mutation confers resistance, it retains some virologic activity by impairing "viral fitness". (4)

The patient is non-nucleoside naive and the absence of NNRTI mutations is consistent with the patient's history.

The genotypes shows at least 4 major protease inhibitor mutations (M46I, I54V, I84V, N88D) that confer significant resistance to most protease inhibitors. In addition, there are several "minor" PI mutations (L10I, K20I, L33V, M36L, 71T) that in conjunction with the presence of major mutations contribute to PI resistance.

Specific Issues Addressed by the Resistance Panel:

- 1) **What are the implications of low level viremia for this patient?**
- 2) **Identify if any changes should be made to this patients current ARV regimen.**
- 3) **The patient returns for his clinic visit on 9/05. He clinically remains well. His CD4 count is 270 and is VL is <75 copies/mL. Does this change our treatment recommendations?**

Members of the Resistance Panel discussed the following pertinent issues.

1) **What are the implications of low level viremia for this patient?**

a) What is the difference between low level viremia and a viral blip?

Low level viremia can often be measured in patients doing well using conventional viral load assays (< 50 copies/ml). This low-level viremia may represent residual ongoing replication and/or virus release from stable reservoirs such as resting memory CD4+T cells and other as yet undefined reservoirs. (5). Hence, even, "suppressed" patients can have low-level persistent viremia (1-43 copies/ml) that may be related to the natural viral decay (estimated half-life 88 weeks) (6) and/or the result of random occasional activation of the virus from within these reservoirs and/or ongoing low level viral replication.

The goal of ART therapy is to suppress viral replication to levels below which resistance mutations do not emerge. This "threshold" has not been defined but is likely in the 50 to 200 copies RNA/mL range.

Many patients otherwise doing well on HAART have intermittent episodes of detectable viremia > 50 copies/ml and of low magnitude (viral "blips") (7). Ultra-sensitive genotyping indicates that no new drug resistance mutations appeared in the timeframe surrounding these viral blips. In addition Nettles (8) studied 10 patients on HAART who had transient episodes of low level viremia. These viral loads were measured in two different laboratories three times a week over a 3 month period. 9 out of 10 patients experienced at least one viral blip. The median duration of these blips was 60 hours and the median magnitude was 79 copies/ml. Of the 18 blips observed, only one was

detected by both laboratories raising the possibility that many blips may represent normal assay variation rather than true low level viremia.

b) What is the significance of low level viremia > 50 copies per ml ?

The major concern of ongoing low level plasma HIV RNA levels (> 50 but < 1000) is ongoing viral evolution and the risk of drug resistance accumulation(10).

c) What are the implications of a genotype when the viral load is less than 1000 copies/ml?

Although patients with low level viremia ideally should undergo resistance testing before changing antiretroviral regimens, current resistance assays often fail to yield accurate results when the viral load is less than 1000 copies/ml. Although the value of resistance testing with viral loads less than 1000 copies/ml is unclear, the panel felt that the mutations that do show on resistance testing may be useful in constructing a new antiretroviral regimen. The major concern is that results of a genotype may not be representative of the whole virus population but may represent only a subspecies of the virus present if the sample assayed has a viral load is less than 1000 copies/ml ("founder effect"). Therefore, the mutations that the genotype does identify are useful. However, if a mutation does not appear on the genotype this does not exclude the presence of a particular mutation in the total population of virus in the infected individual.

2) Identify if any changes should be considered to this patients current ARV regimen?

The panel agreed that the risk of evolution of further mutations in this patient is real but believed it less likely to occur in a patient with very low (often undetectable) stable HIV RNA levels and "mature" highly evolved virus.(11, 12). Therefore the panel believed that the best option was to continue the current regimen and closely monitor the patient's clinical status, CD4 count, and viral load. If a significant elevation occurs in the viral load, then a change in antiretroviral regimens is indicated.

Since the patient is NNRTI naïve, the panel agreed not to use (intensify) with NNRTIs and to preserve these agents for future options when a new "salvage" regimen is needed. The panel considered intensifying the regimen with abacavir although the likelihood of a virologic response is unlikely in the presence of 4 TAMS and the 184V mutation (13).

3) The patient returns for his clinic visit on 9/05. He clinically remains well. His CD4 count is 270 cells/mm³ and is VL is <75 copies. Does this change our recommendations?

The more recent undetectable HIV RNA level does not negate the concern of ongoing low level viremia and the possibility of increasing resistance mutations. However, the panel believed that without a significant rise in the viral load, the risk of developing new resistance mutations was less likely and a regimen change is not indicated.

Recommendations

Treatment Options:

Option 1: Continue the current antiretroviral regimen of Combivir one tablet BID, tenofovir 300 mg po QD and Kaletra 3 capsules bid or 2 tablets bid PO with food.

Option 2: None of the panel members would consider stopping therapy in a patient with a low CD4 nadir.

Dosing, Monitoring, and Follow-up Recommendations

- 1) Continue monitoring the clinical status, CD4 count, and viral load, to help further define level of low level viremia
- 2) If low level viremia persists, reconsider pros and cons of continuing current regimen using clinical status, CD4 counts, and rate of viral load increase as useful markers
- 3) If viral load rises above 1000 copies/mL, a repeat genotype/phenotype is recommended
- 4) If low level viremia persists yet remains below 1000 copies/mL, a repeat genotype/phenotype in the future would be helpful with the caveats as discussed in the above text, especially if construction of a new HAART regimen is to be considered.

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