
HIV Resistance Testing Consultation Service

Consultation Report

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Disclaimer:

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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

This is the second resistance panel consultation for this patient. The first consult was done in September 2001 (See Case #009). The reason for this second consult is that on the most recent phenotype, there was less resistance to various antiretroviral agents when compared to a phenotype done 6 months ago. Because of this discrepancy, the provider has not yet changed the patient's regimen and has ordered a third confirmatory phenotypic assay.

Briefly, this is a 44-year old gay white male who was diagnosed with HIV in 1985. Past medical history is significant for esophageal candidiasis, oral Herpes simplex virus (HSV), cryptogenic seizures, Mycobacterium tuberculosis (1966), vacuolar myelopathy, and peripheral neuropathy.

Antiretroviral therapy at the time of the most recent phenotypic resistance assay included saquinavir (SAQ), ritonavir (RTV), efavirenz (EFV), didanosine (ddI), and stavudine (d4T). His CD4+ T cell count was 89 cells/mm³ and the viral load was 75,000 copies RNA/mL. The patient is doing well clinically and is adherent to therapy. His previous antiretroviral history is outlined below.

Date	ART	CD4	Viral load	Resistance test
	AZT monotherapy			
3/96	none	53	1,900,000	
4/96	D4T/3TC			
7/96			54,000	
8/96	D4T/3TC/SQV			
9/96		150		
10/96			213,000	
10/96	AZT/3TC/IDV			
11/97				D67N, M184V, 219
2/98		75	49,000	
8/98				Multiple. PI mutation
2/99	ABC/EFV/RTV/SQV	RTV/SQV intolerance		
3/99	ABC/EFV/NFV	Didn't take meds, ? ABC hypersensitivity		
4/99	DDI/D4T/EFV/NFV			
5/99		75	15,000	
6/99			18,000	D67N, T69D, K70R
				10I, 46L, 54L/V,

64I/V, 71V, 82 A

7/99	DDI/D4T/EFV/RTV/SQV			
	(+/- HU)			
9/99	128	50,000		
10/99				Phenotype 1
11/99	146	35,000		
2/00	121	35,000		
1/01	146	35,000		
6/01	125			Phenotype 2
12/01	89	75,000		Genotype and Phenotype 3 (see below)

Resistance Test Findings

Genotype (12/01)

NRT	35V/A,43K/N,44E/D, 102K,122K/E,135 I/T,142I/V,162A/G/S/T, 207Q/E, 214F/L,286A, 288S,293I
NNRT	L100L/I, K103K/N
PI	L10I, I15V, N37 A/D, I62I/V, L63L/F/P/S, I93I/L

Phenotype 1 (10/29/99)

Nucleoside Reverse Transcriptase Inhibitors (NRTI)	Fold Change in IC50
Abacavir (ABC)	6.7
Didanosine (ddI)	1.3
Lamivudine (3TC)	2.6
Stavudine (d4T)	2.3
Zalcitabine (ddC)	1.1
Zidovudine (AZT)	200
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTI)	
Delavirdine (DLV)	1.3
Efavirenz (EFV)	34.5
Nevirapine (NVP)	150.7
Protease Inhibitors (PI)	

Amprenavir (APV)	0.9
Indinavir (IDV)	2.6
Nelfinavir (NFV)	4.7
Ritonavir (RTV)	11.0
Saquinavir (SAQ)	1.9

Phenotype 2 (6/5/01)

Nucleoside Reverse Transcriptase Inhibitors (NRTI)	Fold Change in IC50
Abacavir	2.6
Didanosine	1.4
Lamivudine	2.2
Stavudine	3.3
Zalcitabine	1.4
Zidovudine	28.0
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTI)	
Delavirdine	0.04
Efavirenz	132
Nevirapine	183
Protease Inhibitors (PI)	
Amprenavir	4.0
Indinavir	14.0
Lopinavir	15.0
Nelfinavir	11.0
Ritonavir	49.0
Saquinavir	29.0

Phenotype 3(12-01)

Nucleoside Reverse Transcriptase Inhibitors (NRTI)	Fold Change in IC50
Abacavir	1.8
Didanosine	1.3
Lamivudine	1.6
Stavudine	1.6
Zalcitabine	1.1
Zidovudine	4.4
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTI)	
Delavirdine	1.2
Efavirenz	1.0
Nevirapine	0.6
Protease Inhibitors (PI)	
Amprenavir	1.4
Indinavir	1.0
Lopinavir	0.9

Nelfinavir	1.2
Ritonavir	1.1
Saquinavir	0.5

Interpretation/Implications for Treatment

The patient has been on saquinavir/ritonavir/efavirenz/DDI/D4T since 7/99 with incomplete viral suppression. A phenotype obtained on 6/5/01 and 12/01 gave conflicting results, with the latter phenotype showing a less resistant virus. There are several possible explanations for this discrepancy, including laboratory error, medication non-adherence, and altered drug metabolism (e.g., malabsorption).

The panel felt that the most common reason for the discordant phenotypes was the presence of a mixture at the time of the December 2001 phenotype. Notably, the genotype performed in December 2001 did show a mixture (for example, the K101K/N mutation indicates that two dominant viruses were present, one containing the 103K wild-type variant and one the 103N resistant variant) (1).

During the initial consultation, the panel concluded that the December 2001 phenotypic assay was most likely due to a laboratory error. Therefore, it was recommended that the genotypic and phenotypic tests be repeated but that the earlier resistance assays should direct future treatment decisions.

Repeat genotype/phenotype results are presented below.

1-15-02 Genotype (Specialty Laboratories)

NRT	K70R, D67N, T69D
NNRT	G190S
PI	L10I, K20M, L24I, M36I, M46L, I54V, L63P, A71V, V82A, I84V

1-17-02 Genotype (Virologic)

NRT	D67N, T69D, K70R, V75M
NNRT	G190C
PI	L10I, K20I/M, L24I, M36I, M46L, I54V, L63P, A71V, V82A, I84V

1-17-02 Phenotype (Virologic)

Nucleoside Reverse Transcriptase Inhibitors (NRTI)	Fold Change in IC50
Abacavir	2.9
Didanosine	1.6
Lamivudine	3.2
Stavudine	3.3
Tenofovir	2.2
Zalcitabine	1.2
Zidovudine	14.0

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTI)	
Delavirdine	0.03
Efavirenz	115
Nevirapine	119
Protease Inhibitors (PI)	
Amprenavir	4.1
Indinavir	6.7
Lopinavir	17.0
Nelfinavir	12.0
Ritonavir	42.0
Saquinavir	17.0

The phenotype repeated January 2002 was similar to the phenotype performed in June 2001. The most recent resistance tests were notable for the presence of a mutation at position 190 of the reverse transcriptase (G190S) gene. This mutation confers high level resistance to both nevirapine and efavirenz while possibly retaining susceptibility to delavirdine. There were several mutations associated with NRTI and protease inhibitor resistance and, as expected, significant levels of phenotypic resistance.

Recommendations

Regimen Options

The first consultation (case 009) discussed the following 2 options for this patient.

Option 1: Continue the partially suppressive dual PI regimen (saquinavir/ritonavir) to avoid immunological decline but replace the ddI and d4T with AZT and 3TC to minimize neuropathy symptoms. Abacavir is likely to contribute to the efficacy of this regimen, but its use is precluded by the history of ABC hypersensitivity in the past.

Efavirenz should be discontinued, since it increases the regimen's complexity and is not likely to be adding benefit. In addition, it may be contributing to this patient's worsening depression.

In addition to discontinuing ddI and d4T, there is preliminary evidence that treatment with L-carnitine 330 mg, 2-3 tablets BID-TID may help with drug-induced peripheral neuropathy. It may be worth considering a trial of this supplement, if symptoms persist after adjusting the antiretroviral regimen.

Advantages

Familiar and likely to maintain partial viral suppression without additional toxicity

Saves drugs with partial activity for future use in combination with new agents

Reduces risk of accumulating additional NNRTI mutations that may limit usefulness of newer agents in this class

Minimizes risk of clinically disadvantageous complex drug-drug interactions

Disadvantages

May miss opportunity to capitalize on DLV hypersusceptibility

Very unlikely to suppress viral load completely

Unlikely to improve immunologic status significantly

Ongoing risk of developing GI intolerance, body habitus changes and/or hyperlipidemia

Option 2: Attempt complete viral suppression with all available drugs likely to have activity.

Based on the current genotype results, it may be difficult to achieve complete viral suppression. For the NRTIs, lamivudine (3TC) and tenofovir may have some activity (although the remote history of the E44D mutation may prevent a significant response to lamivudine). The recent phenotype suggests that tenofovir will have some activity against this virus (the phenotypic thresholds for when tenofovir begins to lose activity and when activity is completely lost appears to be 1.7 fold and 4 fold, respectively). The patient also shows significant resistance to all currently available protease inhibitors. However, as with tenofovir, the level of phenotypic resistance to lopinavir is modest (the phenotypic thresholds are 10 and 40). The use of ritonavir/lopinavir should be considered.

There is some enthusiasm for "triple protease inhibitor" regimens in patients with highly resistant HIV. Although data are limited, many now favor the use of ritonavir/lopinavir and amprenavir. The efficacy, tolerability and long-term safety of regimens containing three protease inhibitors are not known.

Finally, the use of delavirdine might be considered. The most recent phenotype suggests hypersusceptibility, perhaps due to the unique mutational pattern selected for by efavirenz and the NRTIs. However, the history of efavirenz use and the remote history of a K103N mutation make a response less likely. This variant likely persists and could compromise any response to delavirdine.

Advantages:

Most suppressive regimen

May capitalize on DLV hypersusceptibility

Disadvantages:

Unknown risk of dangerous drug-drug interaction

Risk of unfamiliar toxicity

Moderately large pill burden with TID dosing of delavirdine

Moderately high probability of rash, GI intolerance, body habitus changes and/or hyperlipidemia

Dosing, Monitoring, and Follow-up Recommendations

- Increase amprenavir dose from 600 mg BID to 750 mg (5 tablets) BID when co-administered with lopinavir/ritonavir (Kaletra). Preliminary pharmacokinetic interaction studies with amprenavir suggest that lopinavir levels may decrease as much as 40% compared to lopinavir alone (2). Although available data regarding the proper dosing of lopinavir is still investigational, an increase to 4 capsules bid of lopinavir appear sufficient to overcome this interaction with amprenavir. This dosage increase is especially warranted

when considering the higher serum concentrations appropriate for a salvage regimen. Monitor closely for toxicity, especially GI, hepatic, and metabolic (hyperlipidemia, insulin resistance)

- If tenofovir is administered, the dosage is 300 mg po daily. Because didanosine (ddl) levels may be increased, it is recommended that tenofovir be administered 2 hours before or one hour after tenofovir administration. However, clinical toxicity from higher ddl levels has not been reported.

Selected References

1. Parkin NT et al. Incidence and nature of phenotype-genotype discordance: maximizing the utility of resistance testing. Virologic Inc
2. Bertz R, et al. Assessment of the multiple dose pharmacokinetic interaction between Kaletra (Lopinavir/ritonavir) and amprenavir in healthy volunteers. 3rd International Workshop on Clinical Pharmacology of HIV Therapy. Abstract 7.6. Washington, DC. March 2002.