

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

This is a 44-year-old man who was originally diagnosed with HIV in 1985. His HIV history is notable for a questionable history of esophageal candidiasis, a history of thrush (treated with Mycelex troches), fatigue, chronic sinusitis (now responding to Claritin), and recent weight loss (9 lbs in 4 months). He is currently 161 lbs and 6 feet tall. In 1988 he was started on AZT and has been on nearly continuous antiretroviral therapy since that time, with a notable exception four year ago when HIV RNA levels increased to > 100,000 during a brief treatment interruption. His previous ARVs include didanosine (ddi), stavudine (d4T), efavirenz (EFV), and lopinavir/r (Kaletra). He received a T20 based regimen beginning in 2004 and had notable improvement his fatigue although his CD4 count did not change. Of note a CBC with manual differential in 6/05 showed a white count with 13 % bands. Other comorbidities include atrial fibrillation, mitral regurgitation and right ventricular systolic dysfunction. His medications include trimethoprim/sulfamethoxazole, azithromycin, Remeron®, oxandrolone, and mycelex troches. His cholesterol is 168mg/dL, HDL 25 mg/dL, LDL 106 mg/dL and TG 186 mg/dL. Hepatitis serologies are negative and his LFTs are normal. Details regarding his more recent antiretroviral history are shown below.

DATE	REGIMEN *	CD4 cells/mm ³	VL COPIES/ML	RESISTANCE TEST FINDINGS	CLINICAL COURSE
1999		50			
6/04	ABC/3TC/tenofovir/ Delavirdine/T-20	31 (2%)	34k		
7/04		24 (1-2%)	23k		
10/04		11(1-2%)	43k	SEE GART	
11/04	ABC/3TC/TFV/RTV fosamprenavir/T-20				
12/05	ABC/3TC/TFV/fosam prenavir/T-20				
3/05		15(1-2%)	65k		
6/05		23 (1-2%)	161k	GART/Phenotype	

Resistance Test Findings

10/04 – Quest Genotype Key Mutations

NRT	62V, 67E, 69SSS, 184V, 210S, 215Y
NNRT	98G, 103N, 190S
PI	10I, 20I, 36I, 48V, 54V, 63T, 73S, 82C, 90M
Others	NRTI: 4S, 35I, 43Q, 111I, 123E, 137H, 162DGN, 166R, 177E, 179I, 195K, 196E, 200A, 211K, 228Q, 245E, 272P, 277R, 286R, 286A, 297R PI: 11V, 13V, 35D, 37D, 57K, 58E, 62V, 89V

* listed under "other"

6/05 - Virologic Phenosense Phenotype

	Fold Change	Sensitivity
NRTI		
ABC	24	Reduced susc
TDF	3.23	Reduced susc
ddI	2.98	Reduced susc
3TC	>>>	Reduced susc
D4T	5.22	Reduced susc
AZT	65	Reduced susc
ddC	1.8	Reduced susc
NNRTI		
DLV	5.75	Reduced susc
NVP	>Max	Reduced susc
EFV	139	Reduced susc
PI		
fAMP	40	Reduced susc
IDV	46	Reduced susc
LPV	77	Reduced susc
NFV	87	Reduced susc
RTV	170	Reduced susc
SQV	>max	Reduced susc

6/05 - Virologic Genotype Key Mutations

NRT	62V, 69SSS, 184V, 215Y
NNRT	98G, 103S, 190A/S
PI	10F/I, 20I, 33 L/F/V, 36I, 48G/V, 54I/M/V, 58E, 63T, 73S, 89V, 90M

Replication Capacity: 55%

Some discussion questions for the panel:

- 1) How does the 69 insertion mutation affect his antiretroviral therapy?
- 2) What would be feasible ARV treatment options for this patient?

Interpretation/Implications for Treatment

Amongst the nucleoside reverse transcriptase inhibitor (NRTI) resistance mutations noted, the most significant is the 69 insertion mutation (reported as 69SSS). In contrast with most reported mutations that are single amino acid substitutions, this mutation represents an insertion of two or more amino acids at this site. This is a rare mutation that occurs in only about 2% of heavily experienced HIV-infected patients. The presence of the 69 insertion with at least one other nucleoside associated mutation (NAM) at either codons 41L, 210W or 215Y, produces high level resistance to all NRTIs (1). As both the 10/04 and 6/05 genotypes show at least one of these NAMS, the patient can be assumed to have high level resistance to all nucleoside analogues, a conclusion that is also supported by the consistently high fold-changes in IC50 noted on the phenotype (the fold change measured for each of the NRTIs is well above the expected clinical cutoffs to achieve significant antiretroviral activity). Thus, one would not expect significant antiretroviral activity from any of the currently available NRTIs. In addition, Reverset, a NRTI currently under investigation does not appear to have any activity against the 69SSS mutation.

The K103N mutation seen in the 10/04 genotype and the 190A/S mutation found in the 6/05 genotype each impart significant resistance to the entire class of approved nonnucleoside reverse transcriptase inhibitors (NNRTIs). Although only one of these mutations is sufficient to confer resistance to the NNRTI class, the presence of both of these mutations may have significant implications for some of the investigational 2nd generation NNRTIs. Indeed, recent evidence suggests that TMC 125—a novel NNRTI under development—has lower activity in presence of an increasing number of mutations. The phenotype results of 6/05 corroborate the lack of antiretroviral activity within the NNRTI class as the fold changes are well above the clinical cutoffs for significant antiretroviral activity.

The results of the genotype for the protease inhibitors (PIs) show the presence of a number of atypical mutations. These are atypical because they deviate from wild type, but are not currently known to confer significant resistance (e.g., 63T, 82C, 58E, and 89V). The clinical significance of many of these mutations is unknown. Of note, the mutation 89V has recently been reported to predict a diminished response to TMC 114 (duranavir).

Of the PI mutations detected, 5 are known to confer resistance to lopinavir/ritonavir (10I, 33F, 54IMV, 73S, and 90M). If less than 6 lopinavir-associated mutations occur (as is the case here), one usually expects this drug to have significant activity. (2) In contrast, the phenotype test done on the same date, shows very high level resistance with a fold change (77) that is significantly above the usual clinical cut off of 40. This large discordance between the phenotype and the genotype may be explained by the large number of atypical mutations reported.

An alternative explanation for the genotype/phenotype discordance is that the combination of mutations at 48VM, 54VTAS and 82ATFS are known to cause cross resistance to all of the PIs. (3) The 10/04 genotype reports an atypical mutation of 82C along with a 48V and a 54V. It is unknown if this atypical 82C mutation is having the same effect as an 82 A,T,F, or S mutation, thereby causing pan resistance to the entire class of PIs. Regardless, the patient's clinical history (he is currently failing a boosted PI regimen) and the phenotype of 6/05 suggest that the currently approved PIs are unlikely to have significant activity against this virus.

The patient is also failing a regimen containing T-20. Although there are no resistance data on this agent, we can assume that there is significant resistance to T-20 and that a resistance test specific for T-20 would be unlikely to yield additional useful information.

In summary, this patient harbors a virus with significant resistance to most if not all approved antiretroviral agents. Clinical data suggests that this patient will still derive some benefit from agents in the NRTI and perhaps the PI class, with no residual activity expected from the NNRTI class. The residual activity of enfuvirtide is less clear, but recent data suggests that this drug has only modest antiviral activity in face of drug-resistance.

The patient's current CD4 count is very low. Although he has not had an AIDS-related complication despite years of having a low CD4+ T cell count, he should be considered at high risk for disease progression.

As this patient's virus exhibits high level resistance to all US FDA approved antiretrovirals, the best option might be to obtain access to antiretroviral drugs that are currently under investigation. It is unknown if tipranavir would have activity against this virus. A phenotype specific for tipranavir (TPV) is now available. Unfortunately, clinical data suggests that TPV is unlikely to produce durable viral suppression without the use of another active agent (such as T-20). As there is already T-20 resistance in this patient, TPV might be unlikely to significantly benefit this patient.

CCR-5 inhibitors (a new class of antiretrovirals), integrase inhibitors and TMC 114 (a new protease inhibitor with activity against resistant viruses) are new agents now widely available in clinical trials. An attempt to get into a clinical trial with one of these agents is advised.

If a clinical trial is unavailable for this patient, a dual boosted protease inhibitor regimen, although controversial, might be considered. An appropriate regimen might include the combination of lopinavir/r and saquinavir together along with a tolerable number of NRTIs. However, there is a paucity of data to support such an approach and this regimen tends to be difficult to tolerate.

Regimen Options

OPTION 1: Tenofovir 300 mg PO QD plus Trizivir PO one table BID plus Tipranavir/ritonavir BID PO with food plus T20 90 mg SQ BID plus an CCR-5 inhibitor or an integrase inhibitor (investigational)

Pros: Involves a new class of antiretrovirals that this patient is naïve to which provides the greatest likelihood of virologic suppression.

Cons: Risks of unknown drug toxicity, drug interactions, efficacy, and impact on future treatment options with the CCR-5 inhibitors; poor tolerability with a more complex regimen

OPTION 2: Trizivir one tablet PO BID plus Tenofovir 300 mg daily PO plus TMC 114 (expanded access) PO plus T-20 90 mg SQ BID.

Pros: Provides an investigational PI with potential activity against resistant viruses.

Cons: Unknown risks of drug toxicity, drug interactions, efficacy, and impact on future treatment options.

OPTION 3: Trizivir one tablet BID PO plus Tenofovir 300 mg QD PO plus Kaletra 2 tablets BID PO with food plus saquinavir 1 gm BID PO plus T-20 90 mg SQ BID

Pros: Entry into a clinical trial not required; May provide more antiretroviral activity than current ARV regimen.

Cons: – Uses agents to which this virus is known to have significant resistance; poorly tolerable regimen.

Dosing, Monitoring, and Follow-up Recommendation

- Repeat the viral load to ensure that the most recent VL is accurate and not an aberrant result due to concurrent infections. The most recent VL significantly deviates from the previous values
- Monitor the viral load and CD4 count within 4 to 6 weeks after an ARV regimen change and then every 3-4 months.
- Monitor for toxicities specific to each antiretroviral agents

T-20 injection site reactions, increased risk of bacterial pneumonia

Kaletra: GI symptoms, hyperlipidemia, hyperglycemia, hepatitis, lipodystrophy

Tenofovir: renal toxicity, check UA and serum creatinine before starting tenofovir

Trizivir: anemia, lactic acidosis, lipoatrophy

References

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