
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

JE is a 44-year-old man who has been infected with HIV for more than 10 years. He entered into the clinician's care in 2000 on zalcitabine (ddc), abacavir (ABC), lamivudine (3TC), and amprenavir (APV) with a CD4 count of 300cells/mm³ and a viral load (VL) of 118,000 copies/mL. He has a history of taking multiple antiretrovirals (ARV), including Combivir (CBV), didanosine (DDI), tenofovir (TDF), delavirdine (DLV), nelfinavir (NFV), indinavir (IDV) stavudine (d4T) lopinavir/ritonavir (Kaletra), saquinavir (SQV), and enfuvirtide (T20). The patient rarely achieved an undetectable viral load on any given regimen. He also had difficulty with injection site reactions during his prior exposure to enfuvirtide (T-20) but is willing to try it again if absolutely necessary. There is no history of opportunistic infections or concomitant illnesses. The patient is clinically well and adherence is reported to be good. The history is incomplete but is as follows:

DATE	REGIMEN	CD4 (cells/mm ³)	VL(copies/ml)	COMMENTS
5/00	ddC/ABC/3TC/APV	300	423K	
5/02	ddC/ABC/APV	150		
8/02		90		
11/03		150	>500K	Neuropathy Genotype (GART) obtained
11/03	CBV/TDF/ LPV/r/SQV/T-20	289	37K	Injection site rxns
5/04			94K	
2/04		296	74K	
8/04		271	>100K	
9/04		284	146K	GART obtained
12/04		282	478K	
3/05	CBV/TDF/LPV/r/ SQV	233	>100k	
8/05		231	120k	
11/05		176	321k	
12/05		199		

Forsamprenavir (fosAPV)	42.4
Indinavir (IDV)	33.9
Lopinavir/r (LPV/r)	96.2
Nelfinavir (NFV)	39.6
Ritonavir (RTV)	198.1
Saquinavir (SQV)	33.5
Tipranavir (TPV)	9.5

Interpretation/Implications for Treatment

As suggested by the treatment history, the genotypes, and the phenotype, this patient now harbors a highly resistant virus. The only approved drug which may be effective is darunavir. Given the lack of a viable regimen, consideration of not switching while awaiting the emergence of more options was strongly considered by the panel, as discussed below.

This patient has accumulated a significant number of resistant mutations from his years of antiretroviral therapy with a detectable viral load. In the reverse transcriptase gene of his virus, there are four mutations classic nucleoside associated mutations (NAMS; 41L, 67N, 210W and 215Y). Having more than three of these mutations confers high level resistance to many of the nucleoside reverse transcriptase inhibitors (e.g TDF, AZT, d4T, and ABC). In addition, the mutations 44D and 118I may increase resistance to some or all NRTIs. The mutation 74V confers high level resistance to ddI (particularly when present with NAMS) while the mutation at 184V confers high level resistance to 3TC and FTC and low level resistance to abacavir. Thus the results of these two genotypes suggest that this patient's virus has high level resistance to all of the approved nucleoside reverse transcriptase inhibitors. The results of the phenotype corroborate this as all the reported fold changes are above the cutoffs associated with significantly reduced response to these drugs.

It is important that NRTI, especially 3TC or FTC, be continued during salvage therapy even when significant resistance exists. Many of these NRTI resistance mutations reduce the replicative capacity (fitness) of the virus which can reduce the viral load, and these mutations can partially reduce the level of resistance to AZT, tenofovir and perhaps d4T. In addition, the NRTIs often retain partial antiviral activity even in the presence of these mutations.

The mutations K103N, 181C and 190A each confer high level resistance to all approved nonnucleoside reverse transcriptase inhibitors (NNRTI). These mutations do not seem to affect the replicative capacity of the virus so it is not recommended to use these drugs when resistance is present. Of interest, there is a second generation NNRTI, TMC 125 or etravirine, that is available on expanded access. Early data on TMC125 suggests it is less efficacious when more than one NNRTI mutation is present (as in this patient). The mutation 181C may be particularly detrimental to the efficacy of TMC-125. More data needs to be available before the optimal use of this agent is identified but it would appear that TMC-125 would not be very active against this virus.

The genotype and phenotype both show high level resistance to all approved protease inhibitors (PI). All of the fold changes reported on the phenotype are associated with significantly reduced response to protease inhibitors. As with the NRTI, the PI mutations reduce the replicative capacity of the virus and as a consequence may either reduce the viral load or preserve CD4+ T cells (when used in partially suppressive regimens). Therefore, PI therapy is often continued in patients who harbor multi-resistant virus and have few therapeutic options. The fold change to darunavir, a protease inhibitor, is not

reported on the phenotype. It might be useful to ask the laboratory to identify the sensitivity of darunavir as it frequently has some activity against virus resistant to other PI.

This patient has been receiving T-20 for 14 months with a detectable viral load. Resistance to this agent is likely as it tends to develop rapidly in the setting of incomplete viral suppression. Results of resistance testing for T-20 are not available for this patient; they are probably not necessary as resistance to this agent is very predictable.

Of interest is the observation that the patient maintained a CD4 count of 271-289cells/mm³ while receiving T-20. When T-20 was discontinued with no other changes in his ARV regimen, the CD4 count declined to 176-233 cells/mm³ with the two most recent values being less than 200 cells/mm³. In contrast, the viral load did not significantly change when T-20 was discontinued. This is consistent with a number of studies that show that a mutation at 38A in the gp41 gene is associated with an increase in CD4 cell count independent of the viral load (1, 2). This 38A mutation also confers resistance to T-20. Thus it appears that continuing T-20 after resistance has developed *may be* associated with a CD4 cell benefit that is independent of viral load. The mechanism for this effect is not well understood. It may be mediated through a change in viral co-receptor tropism from CXCR4 to CCR5 associated with the appearance of the 38A mutation. CXCR4 viral strains are associated with significantly lower CD4 cell counts but comparable viral loads, when compared with R5 viral strains (3). Thus, restarting T-20 may provide significant immunological benefits. In addition, mutations associated with T-20 may be beneficial by decreasing the replicative capacity of HIV (4).

In this patient with highly resistant virus, it would be important to consider the use of investigational agents. There are currently two CCR5 receptor antagonists and two integrase inhibitors in clinical trials that may be appropriate for this patient. One concern with this approach is that if darunavir is not active against this virus (pending phenotype results), then there would be no active agents to use with the experimental agents. Past experience has shown that adding only one active drug to a failing regimen is not a long term successful approach and frequently leads to resistance to the active agent. As this patient has maintained a good CD4 count when T-20 is used with his present regimen, it may be prudent to wait until at least two fully active agents are available.

Recommendations

Regimen Options:

Recommend obtaining more information about the genotypic and phenotypic sensitivity of darunavir and access to clinical trials. There are two options: attempt to modify the regimen now with a goal of achieving and maintaining an undetectable viral load (Option 1) or identifying a stable, partially suppressive regimen aimed at maintaining immunologic and clinical stability until more fully effective agents are readily available.

OPTION 1: Combivir (CBV), tenofovir (TDF), Enfuvirtide (T-20), ritonavir boosted darunavir (DRV/r), Integrase inhibitor MK-0518 (or other investigational agent). Can also consider adding abacavir (ABC)

PROs 1) Most likely to obtain full viral suppression and/or immunological benefit

- CONS
- 1) Requires entry into clinical trial
 - 2) History of poor tolerance to T-20 (patient is willing to try again)
 - 3) Phenotype may show high level resistance to darunavir/r with risk of virologic failure

OPTION 2: CBV plus TDF plus Kaletra (LPV/r) plus saquinavir (SAQ) with or without T-20. Consider adding ABC.

- PROS:
- 1) History of being on this regimen with no known toxicities
 - 2) History of fairly good immunological status on this regimen in spite of a high viral load
 - 3) May "maintain" good CD4 count until 2 active agents are available for use
- CONS:
- 1) History of increasing viral loads on this regimen and risk of immunological decline
 - 2) Resistance may evolve, compromising future treatment options
 - 3) History of poor tolerance to T-20 (although willing to try again)

Dosing, Monitoring, and Follow-up Recommendations

T-20 90 mg sq q12h

Darunavir/ ritonavir 600 mg po bid / 100 mg po bid

MK-0528 400mg po bid

Combivir (zidovudine 300mg and lamivudine 150mg) 1 pill po bid

Tenofovir 300 mg po qd

Abacavir 600 mg po qd

Kaletra (lopinavir 200 mg/ritonavir 50 mg) 2 tabs po bid

Saquinavir (when used with Kaletra) 1000 mg po bid

Would monitor viral load and CD4 every 1-2 months if no experimental agent is used. Also monitor liver function tests, CBC, lipids q 3-6months. If an experimental agent is used would follow clinical trial protocol.

Footnotes:

1. Aquaro, S. et al, Characterization of Gp41 Evolution in a Large Cohort of HIV-1 infected Patients Receiving Long term T-20 Treatment as a Single Active Drug. Conference on Retroviruses and Opportunistic Infections 2/2006. Abstract 596.
2. Melby, T. et al, Impact of Enfuvirtide Resistance Genotype on CD4 Increase in Patients with Ongoing Viral Replication while Receiving Enfuvirtide. XV International HIV Drug Resistance Workshop, 6/06. Abstract 35
3. Melby, T. et al. HIV -1 Co-receptor Use in Triple Class Treatment Experienced Patients: Baseline Prevalence, Correlates, and Relationship to Enfuvirtide Response. J Infect Dis 2006. 194; 238-246.
4. Marconi,V, et al In vivo Fitness of Enfuvirtide Resistant HIV-1 estimated by allele-specific PCR during partial treatment interruption and Pulse Intensification. Conference on Retroviruses and Opportunistic Infections. 2/2006. Abstract 629.