
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

A 50-year-old GWM was diagnosed with acute HIV seroconversion in November 2003 after failing post-exposure prophylaxis (PEP). His risk factor for HIV infection was anal receptive intercourse with ejaculation after a broken condom occurred on 9/21/03. His partner was known HIV positive, and had by report an undetectable viral load (VL) on an unknown antiretroviral regimen. The patient reportedly received 28 days of PEP with Combivir (CBV) + lopinavir/ritonavir (LPV/r, *Kaletra*). The time after exposure to starting PEP was unclear but was likely within 24 hours. He reported complete adherence with the PEP regimen. In November (11/26/03) the patient experienced night sweats and fatigue with a negative HIV antibody test and a high VL. He was enrolled in the Options research project for recent HIV seroconverters.

He remains treatment naïve and is now prepared to initiate ARVs due to concerns about a falling CD4 count. He is asymptomatic and has no co-morbidities. He is highly educated about HIV and asks if he should include an integrase inhibitor in his first regimen.

His viral load, CD4+ T cell counts and resistance data are outlined below.

Date	Screen Cycle	Extra Week	IL2		CD4	%	CD8	CD4/CD8	Viral Load (bDNA)		Log VL	Detuned
			PC	Cycle Day								
12/02/2003	<input checked="" type="checkbox"/>	<input type="checkbox"/>			706	39	597	1.18	3,858	Chiron 3.0	3.59	0.01
12/12/2003	<input type="checkbox"/>	<input checked="" type="checkbox"/>			604	38	604	1.00	519	Chiron 3.0	2.72	
01/14/2004	1	0			853	36	901	0.95	4,084	Chiron 3.0	3.61	
02/18/2004	1	4			884	34	1,014	0.87	258	Chiron 3.0	2.41	
03/10/2004	1	8							355	Chiron 3.0	2.55	
04/14/2004	1	12			816	35	839	0.97	957	Chiron 3.0	2.98	
05/05/2004	1	16							682	Chiron 3.0	2.83	
06/30/2004	1	24			746	33	836	0.89	1,170	Chiron 3.0	3.07	
08/18/2004	1	32			870	32	1,088	0.80	75	Bayer HIV-1 RNA Assay	1.88	
10/21/2004	1	40			599	35	752	0.80	2,622	Chiron 3.0	3.42	
12/16/2004	1	48			749	24	1,716	0.44	3,365	Chiron 3.0	3.53	
03/15/2005	1	60			829	26	1,723	0.48	1,813	Chiron 3.0	3.26	
06/09/2005	1	72			594	28	1,102	0.54	1,763	Chiron 3.0	3.25	
08/23/2005	1	84			644	28	1,150	0.56	3,168	Chiron 3.0	3.50	
11/17/2005	1	96			708	24	1,534	0.46	1,060	Bayer HIV-1 RNA Assay	3.03	
02/21/2006	1	108			605	24	1,310	0.46	2,085	Bayer HIV-1 RNA Assay	3.32	
05/03/2006	1	120			508	22	1,317	0.39	1,197	Bayer HIV-1 RNA Assay	3.08	
11/13/2006	1	144			418	22	1,159	0.36	2,066	Bayer HIV-1 RNA Assay	3.32	

Resistance Test Findings

Genotype (Gladstone Institute, 12/2/2003)

RT	K70R, V118I, M184V
PRO	L10F, L24I, M46I, I54V, A71V, V82A, N88D

Interpretation/Implications for Treatment

Specific questions:

- (1) Should the patient start medications now?
- (2) What is an appropriate initial regimen for this patient? Should an integrase inhibitor be included?

The panel discussed numerous interesting aspects about this case. First was the issue of possible PEP failure. Complete details about his PEP experience in 2003 are not available, but it would be noteworthy for transmission to occur in the presence of a documented undetectable HIV viral load in the source partner – note that such documentation was not available in this case. Additionally, while PEP failures are reported, it would be surprising for such to occur in this setting as the patient received an aggressive regimen immediately after his exposure. However, resistance to at least some the agents used in this patient's PEP regimen were evident on his genotype of 12/03.

The panel was also interested in his low HIV viral load, both during acute seroconversion and throughout the three years of observation. While recent reports highlight that viral load may contribute less than commonly perceived to CD4 decline over time¹, this patient's CD4 decline in the setting of such a low viral load is interesting. HLA B*5701 haplotype is greatly over-represented among patients controlling HIV compared to those not-controlling HIV (e.g., 85% vs. 9.5% in on study; $P < 0.001$)². Other host factors have been associated with durable viral control. Equally interesting is the relative rapid decrease in CD4+ T cell counts; this is consistent with a recent study indicating that the ability of HIV RNA levels to predict CD4+ T cell counts on an individual level is often limited.

With reference to this patient's particular mutation pattern, Dr. Aranow highlighted the presence of K70R, a component of the TAM-II pathway, and V118I, which has been described to produce thymidine analog resistance in the setting of other mutations. Dr. Tokumoto pointed out that V118I has been removed from the Fall 2006 list of mutations on the IAS-USA guidelines³, as the role of this mutation in the absence of other mutations is unclear.

This patient has no NNRTI-associated resistance mutations and would be expected to respond well to this class of drugs.

Numerous protease (PI) mutations are present on the genotype. Since this genotype was done in 2003, some of the newer protease inhibitors are not included in this interpretation. The group believed that a repeat genotype would likely show continued mutations and would help define susceptibility to newer PIs. The group also felt that a phenotype might help decide among PIs with this complex mutational pattern. The table below highlights protease mutations that correlate with impaired response to tipranavir and/or darunavir⁴. Of these listed mutations, this patient's virus carries only the I54V for tipranavir resistance and no mutations on the darunavir list. Thus, with the currently available information, it is likely that both tipranavir and darunavir will have significant activity against this virus.

Table 1. Mutations correlating with impaired response to tipranavir or darunavir.⁴

<i>Tipranavir only</i>	<i>Both PIs</i>	<i>Darunavir only</i>
L10V		
		V11I
I13V		
K20M/R/V		
		V32I
	L33F	
E35G		
M36I		
K43T		
M46L		
	I47V	
		I50V
I54A/V	I54M	I54L
Q58E		
H69K		
		G73S
T74P		
		L76V
V82L/T		
N83D		
	I84V	
		L89V

Data on the new class of integrase inhibitors in both highly treatment experienced⁵ and naïve⁶ patients are encouraging. The panel points out that although this patient is treatment naïve, he should be considered similar to treatment experienced patients given the acquisition of multi-class resistant virus. Panel members cautioned against over-interpretation of the integrase inhibitor data presented to date, as it involved a relatively small number of patients and only a 24-week follow-up; however, most thought the use of integrase inhibitors in this case was reasonable.

In summary, the panel believed that the most active drugs in this case would be non-nucleoside reverse transcriptase inhibitors (NNRTIs) and integrase inhibitors. Among the NNRTIs, the group generally favored efavirenz, noting that the patient's high CD4 count would put him at higher risk for hepatotoxicity from nevirapine⁷. Enfuvirtide is also likely to be highly active, and resistance testing could be performed to confirm activity. The group believed that with other available and less invasive options, use of injectible enfuvirtide could likely be avoided in this patient's initial regimen. Among PIs, there was consensus that both tipranavir and darunavir would be active, and the panel preferred darunavir based on its safety and tolerability profile. Lopinavir/ritonavir should likely be avoided, as this patient may have been a failure of Kaletra-containing PEP. Most also believed that the nucleotide/nucleoside class would have some residual activity and should be included in his regimen. Combivir + tenofovir would be one preferred combination. Abacavir may also be included; however, with a significant note of caution that based on the discussion above, this patient may have higher chance of carrying the HLA B*5701 allele, putting him at higher risk of abacavir hypersensitivity reaction. Most members of the panel believed that it would be wise to screen this patient for HLA B*5701, if available, before initiating an abacavir-containing regimen.

In terms of the timing of antiretroviral initiation, most panel members believed that the patient could wait until the approval of the integrase inhibitor (anticipated in 2007), with close monitoring of his CD4 count in the interim. In that case, the regimen generally recommended by the panel would be Combivir + tenofovir + efavirenz + integrase inhibitor. Although no comparative data are available, the panel would recommend the Merck integrase inhibitor (MK-0518) in this case – not only because it is likely to be FDA-approved earlier, but also because ritonavir could be avoided. MK-0518 does not require ritonavir boosting but requires BID dosing, whereas the Gilead integrase inhibitor (GS 9137) does require boosting to allow once daily dosing. However, the BID dosing of the Merck integrase integrator is less of a concern since the patient will also be taking BID dosing of Combivir. The group commented that this initial regimen would then leave darunavir + enfuvirtide + nucleoside/nucleotide analogs as a subsequent regimen in case of failure.

If, however, the patient is eager to start medications before integrase inhibitors are available, or if his CD4 declines precipitously, the panel recommends initiation of Combivir + tenofovir + efavirenz + darunavir/r (with or without T20). If this strategy were undertaken, the patient could transition to integrase inhibitor and eliminate either the darunavir/r or T20, depending on tolerability of the prescribed regimen.

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- 1 – Rodriguez B, et al. JAMA 2006;296(12):1498-506.
 - 2 – Migueles SA, et al. PNAS 2000;97(6):2709-14.
 - 3 - http://www.iasusa.org/resistance_mutations/mutations_figures.pdf
 - 4 – Mascolini M. http://natap.org/2006/ResisWksp/ResisWksp_38.htm
 - 5 - Grinsztejn, ICAAC 2006, abstract 159LB.
 - 6 - Markowitz, IAS 2006, abstract THLB0214.
 - 7 – Viramune® package insert.

Recommendations

Regimen Options

Obtain repeat genotype and phenotype if available. [Panel recommendations may be altered based on the results of these tests.]

- 1) Wait for integrase inhibitor approval, anticipated in mid-2007. Then, initiate Combivir one tablet BID + tenofovir (Viread) 300 mg once daily + efavirenz (sustiva) 600 mg once daily on empty stomach + integrase inhibitor (MK018 400 mg BID). Take all with food except for EFV which should be taken with a low fat meal.
- 2) If the patient wishes to start immediately or if CD4 declines further before integrase inhibitor is available, initiate Combivir one tablet BID + tenofovir (Viread) 300 mg once daily + efavirenz (Sustiva) 600 mg daily with low fat meal + darunavir 600 mg bid plus ritonavir 100 mg bid. Take all with food except as noted for EFV. The additional use of enfuvirtide may be considered.

Dosing, Monitoring, and Follow-up Recommendations

Monitor CD4 count every 2-3 months while patient is not on therapy, pending approval of integrase inhibitor.

CASE NUMBER
PANEL CLINICIAN: BRAD HARE, MD

DATE

Use the time to reinforce the importance of adherence and create strategies with patient for medication self-management.

After initiation of treatment, check-in with patient at week-2 to assess compliance, understanding of regimen dosing, and side effects. Repeat CD4 and Viral Load at week-4 after initiation.

Monitor patient carefully for signs of virologic failure and repeat resistance testing immediately if such occurs.