
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.

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History/Clinical Course

The patient is a 39 year old woman who has been HIV positive since 1996. Prior to starting antiretroviral therapy in 1996 her CD4 was less than 100 cells/mm³ and her viral load was approximately 40,000 copies RNA/mL. She started on zidovudine (AZT) and zalcitabine (ddc) in 1996 and subsequently interrupted these drugs due to possible liver toxicity. She eventually resumed AZT and added lamivudine (3TC) and indinavir (IDV). She remained on this regimen until December 2000 but had difficulty with adherence and failed to maintain an undetectable viral load.

In December, 2000 her regimen was changed to didanosine (ddI), stavudine (d4T), and ritonavir (RTV)/saquinavir (SAQ) 400/400 bid. Her viral load decreased at first, but subsequently increased over time (see Table).

In September of 2000, when her viral load was approximately 11,000 copies RNA/mL, a genotypic resistance test revealed no evidence of drug resistance. She was counseled about the need for better adherence and was maintained on the same regimen. Although she subsequently reported excellent adherence, her follow up visits were infrequent and her viral load remained high. A second genotype (June of 2004) showed no nucleoside reverse transcriptase inhibitor (NRTI) or nonnucleoside reverse transcriptase inhibitor (NNRTI) mutations but multiple protease inhibitor (PI) resistance mutations (results detailed below).

Other problems have included cervical dysplasia and mild asthma, but in general, she has felt well. She remains physically active, and works full time. She has had no significant antiretroviral (ARV) toxicity. Her eosinophilic folliculitis has flared over the past several months.

Her primary care provider wonders if her treatment regimen should be changed. He believes that her adherence now is excellent and that she misses almost no doses.

DATE	REGIMEN	CD4 cells/mm ³	VL	COMMENTS
1996	None	<100	41K	
1996	AZT/ddC			Hepatitis
1996	None			Hepatitis resolved (attributed to TMP/SMX)
1996	AZT/3TC			
Late 1996	AZT/3TC/IDV			Adherence difficulties
12/02	d4T/ddI/RTV/SQV			Dapsone and itraconazole
1/02	Same		~600	

9/02	Same	131	11K	Genotype showed no mutations
7/23/03	Same	104	84k	
6/21/04	Same	24	168K	"Excellent" adherence; genotype below

Resistance Test Findings

6/21/04 Key Mutations

NRT	None
NNRT	None
PI	L10I; L63P; A71V; G73S; I84V; L90M

Interpretation/Implications for Treatment

This patient has an extensive antiretroviral treatment history. She has never achieved complete viral suppression, which appears to be due both to the use of sequential suboptimal regimens as well as poor medication adherence. Taken together, these factors suggest that her virus is likely to have developed clinically significant resistance to the 2 ARV classes to which she has been exposed. The failure of her current regimen to achieve complete viral suppression despite excellent adherence, and the progressive increase in her viral load are consistent with this prediction. What is unusual about this case, and what distinguishes it from the typical findings in patients with similar clinical histories, is the unusual pattern of resistance to only protease inhibitors but not to the reverse transcriptase inhibitors.

The genotype shows no mutations in the reverse transcriptase gene. This is surprising in view of the many years of ongoing viral replication in the presence of NRTIs. A more typical resistance test result for a patient with this clinical history would include at least a few mutations associated with 3TC and thymidine analog exposure. It is possible that such mutations are archived and were not detected in June 2004 because drugs which rapidly select for resistance (e.g., 3TC) were no longer being administered. It is harder to invoke this explanation for the absence of other NRTI mutations, since d4T usually provides sufficient selective pressure for these quasi-species to be detected.

Most resistance tests are only capable of detecting quasi-species of HIV that comprise at least 20% of the total virus population. In addition, wild type virus is thought to replicate more efficiently than virus with multiple mutations. As a result, in the absence of drug-related selective pressure, wild type virus would be expected to "overgrow" mutant quasi-species and the genotype would fail to detect NRTI resistance. In this situation, the nucleoside mutations are not truly "lost", but are persist at low levels. The implication for this case is that even though the resistance test shows no NRTI resistance, the clinical history suggests that resistant quasi-species of virus are present. This should be considered in defining the next treatment strategy.

The patient has never been treated with an NNRTI and the absence of NNRTI mutations is consistent with this history. We would expect drugs from this class to be fully active against this patient's virus. Similarly, we would expect the virus to be fully susceptible to T20.

The genotype displays 6 mutations in the protease gene and suggests that significant resistance to most PIs may be present. Three of these six mutations (i.e., those at positions 10, 84, and 90) are “major” mutations. They generally predict broad cross resistance and poor clinical response to PIs in this class. The mutations at positions 63, 71, and 73 are “minor” PI mutations that are not, by themselves, associated with significant phenotypic resistance. However, when these minor mutations occur along with major mutations, they may contribute to PI resistance and/or impair viral fitness. All 6 of these mutations are thought to affect lopinavir/ritonavir susceptibility.¹

The persistence of resistance mutations may differ among ARVs. The M184V mutation can be lost in just 4 months while reversion of protease inhibitor mutations may take 1 year or longer.² Reversion of T-20 mutations can occur within weeks. There is no data on the persistence of NNRTI or non-3TC nucleoside mutations, though data on primary infection with resistant virus show that non-nucleoside mutations may persist for years.

Several options were considered, including: (1) stopping all medications, (2) continuing her partially suppressive regimen or (3) switching to a new salvage regimen with a goal of achieving and maintaining an undetectable viral load.

The panel did not believe that stopping this patient’s antiretroviral medicines was a feasible option given her advanced disease. For the same reason, the panel did not believe that it was reasonable to continue the same regimen because of the progressive immunodeficiency. The panel felt that changing her regimen as soon as possible would be the best option, and that the focus should be placed on constructing a regimen that was both effective and well-tolerated.

The panel believed that the most suppressive regimen should contain as many new classes of ARVs as possible. This does not include the NRTI class as a “new” class of ARVs because the patient has been exposed to them before. Again, as outlined above, resistance to these drugs needs to be assumed, even though it was not present on the genotype. Hence, a regimen of two NRTIs and an NNRTI—which should work in a patient without resistance to these drugs, was not recommended. Any archived NRTI resistance will result in rapid virologic failure and loss of the NNRTI option.

The patient has never been on an NNRTI or a fusion inhibitor, so the likelihood of suppression on a combination of these agents would be very high. However, this option requires the use of a twice daily injection, which may be challenging for a non-motivated patient with a history of non-adherence. If she prefers not to use T20, the third option of a triple class regimen containing NRTIs, an NNRTI, and PIs might still be viable and virologically suppressive.

Recommendations

Treatment Options

OPTION 1: CHANGE REGIMEN: Utilize 2 new classes of ARV regimens to achieve the most potent and suppressive regimen. Consider Combivir™ one bid plus tenofovir 300 mg once daily plus efavirenz 600 mg once daily plus T-20 90 mg SQ bid. Reconstitute T-20 no earlier than 24 hours before injection. T-20 must remain refrigerated or used immediately once reconstituted.

¹ International AIDS Society-USA Drug Resistance Mutations Group. Drug Resistance Mutations. Topics in HIV Medicine 2003; 11(6) Nov/Dec.

² Vasudevachari MB., Zhang YM, Imamichi H, et al. Emergence of Protease Inhibitor Resistance Mutations in Human Immunodeficiency Virus Type 1 Isolates from Patients and Rapid Screening Procedure for Their Detection. Antimicrob Agents Chemother 1996; 40(11): 2536-2540

PROS: Durable viral suppression likely.

CONS: Need to incorporate T-20 subcutaneous injections into patient's lifestyle when she is not feeling ill.

OPTION 2: CHANGE REGIMEN: Utilize as many potentially active drugs as possible. Consider Combivir™ one bid plus tenofovir 300 mg once daily plus efavirenz 600 mg once daily with low fat meal plus Kaletra (lopinavir/ritonavir) 4 capsules bid plus T-20 90 mg SQ bid. Reconstitute T-20 no earlier than 24 hours before injection. T-20 must remain refrigerated or used immediately once reconstituted.

PROS: Durable viral suppression if the patient is able to adhere to this regimen.

CONS: The multiple medications (and multiple side effects) may compromise adherence and lead to loss of both NNRTIs and T-20 activity

OPTION 3: CHANGE REGIMEN: Utilize one new class of ARVs to try to virologically suppress and raise the CD4 counts. Consider Combivir™ one bid plus tenofovir 300 mg once daily plus Kaletra™ (lopinavir/ritonavir) 3 capsules bid (or tipranavir 500 mg bid plus ritonavir 200 mg bid) plus T-20 90 mg SQ bid. Reconstitute T-20 no earlier than 24 hours before injection. T-20 must remain refrigerated or used immediately once reconstituted.

PROS: Patient is already tolerating a boosted PI-based regimen. Possibility of suppression based on RESIST and TORO data. Preserves NNRTI for future regimens.

CONS: Less likely to achieve viral suppression with the addition of only 1 new class of ARVs. It is unknown how active the PI class would be with the existing mutations. Lifestyle changes needed to incorporate T-20 injections. Drug-drug interactions with tipranavir with PIs and NNRTI need to be clarified.

OPTION 4: CHANGE REGIMEN: Utilize one new class of ARVs to attempt viral suppression and raise CD4 counts. Consider Combivir™ one bid plus tenofovir 300 mg once daily plus efavirenz 600 mg once daily plus Kaletra (lopinavir/ritonavir) 4 capsules bid (or tipranavir 500 mg bid plus ritonavir 200 mg bid).

PROS: Does not include T-20 and no need for SQ injections

CONS: Less likely to provide virologic suppression than other treatment options. Unknown durability because not clear how active the PIs are. Potential for drug-drug interactions between NNRTI and PI class. Drug-drug interactions with tipranavir and NNRTI and PI need further clarification.

Dosing, Monitoring, and Follow-up Recommendations

Monitor CD4 counts and VL before initiating regimen and 4-6 weeks after initiation of new regimen. If using options #2 or #3 consider obtaining phenotype to check for PI susceptibilities. If there is a PI more sensitive than Kaletra, could substitute.