
HIV Resistance Testing Consultation Service

Consultation Report

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Disclaimer:

This information has been developed solely as an educational resource for health care professionals interested in HIV care and research. The information presented represents the views of the Panel members only and not necessarily those of the National HIV/AIDS Clinicians' Consultation Center's HIV Telephone Consultation Service (Warmline), the Positive Health Program at San Francisco General Hospital, or sponsoring organizations. Resistance testing can help identify whether certain drugs or classes of drugs might be ineffective, but cannot establish which drugs will be effective. Furthermore, test results can be inaccurate and interpretation of tests is not yet standardized. Because of the many factors involved in treatment decisions when resistant virus is present, the antiretroviral regimens and the therapeutic strategies discussed are not the only possible options and might also be different from current Practice Guidelines. Other sources of information on resistance testing, such as clinical HIV websites, can be of help. Health care professionals should consult the HIV Telephone Consultation Service (Warmline) or HIV experts in their community before using any of the recommended therapeutic regimens or strategies in this document.

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 41 year old Hispanic male who presented in July 1999 with a CD4 count = 180 cells/mm³ (CD4%=15%) and an HIV viral load of 281,000 copies/mL by bDNA assay. This patient was asymptomatic with no prior history of opportunistic infections. He was started on zidovudine (AZT) + lamivudine (3TC) + nelfinavir (NFV) as his first HAART regimen with a good initial response. His plasma viral load was suppressed to <50 copies/mL until 10/2/00 when he experienced viral breakthrough and an increase in HIV viral load to approximately 1000 copies/mL. From March 2001 until May 2002 the patient had viral loads remaining in the range of 1350 to 5000 copies/mL. His last lab values prior to consulting the WARM line were on 5/6/02 and showed the following: CD4=522 (29%) and bDNA HIV viral load = 3,173 copies/mL. The patient has reportedly shown good adherence to his antiretroviral medications and is tolerating his current regimen without notable side effects.

This patient has had three HIV genotypic resistance tests performed on the following dates: 4/4/01, 10/8/02, and 4/9/02 (see below). The viral genotypes have remained fairly stable over this one-year period in spite of ongoing viral replication and detectable plasma viremia. There is some evidence of progressive resistance to the nucleoside analogues (NRTIs) but there has been little change in the protease (PI) mutations. The provider is leaning toward changing the patient's regimen to lopinavir/ritonavir (Kaletra) + tenofovir + 3TC + nevirapine (NVP), but seeks the panel's input. The provider is especially interested in the panel's opinion on the likelihood that tenofovir will still be efficacious in this setting.

Resistance Test Findings

4/4/2001 Key Mutations

NRT	M41M/L, A62A/V, M184V
NNRT	none
PI	L10I, L63P, A71T/IAV, L90M/L

9/26/2001 Key Mutations

NRT	M41L, M184V
NNRT	none
PI	L10I, L63P, L90M

4/9/2002 Key Mutations

NRT	M41L, D67N, K70R, M184V
NNRT	none
PI	L10I, L63P, A71T/A, L90M

Interpretation/Implications for Treatment

Genotype interpretation (Gladstone):

		Sensitive	Partial/Possible	Resistant	Insufficient evidence
4/4/2001	NRTI	d4T , TFV, FOS	AZT, ddl, ddC, ABC	3TC	
Version 2	NNRTI	all			
	PI	LPV	IND, RTV, AMP	NFV, SQV	
9/26/2001	NRTI	d4T	AZT, ddl, ddC, ABC	3TC	TFV, FOS
Version 3	NNRTI	all			
	PI	LPV, AMP	IND, RTV	NFV, SQV	
4/9/2002	NRTI		AZT, ddl, ddC, ABC, d4T		TFV, FOS
Version 4	NNRTI	ass			
	PI	LPV, AMP	IND, RTV	NFV, SQV	

Summary:

First, it is important to realize that the viral genotypic resistance testing listed above for this patient involved three different versions (version 2, 3, and 4) of the software used for interpreting the clinical relevance of these mutation patterns. In some cases, the interpretation changed while the mutations remained the same. This reflects the dynamic nature of this area of HIV research and the advancements made over time in our understanding of HIV resistance. Initially, tenofovir resistance was thought to involve primarily the K65R mutation, and therefore this patient's isolate was read as being sensitive to tenofovir. However, it soon became clear that there was more cross-resistance between NRTIs than expected and additional information was needed before a definitive interpretation of tenofovir resistance patterns could be made.

There is no evidence of resistance to nonnucleoside analogues (NNRTIs), which is consistent with the patient's history of being naïve to this drug class. Switching to a new regimen containing an NNRTI would therefore likely be efficacious and durable as long as there were enough other active drugs in the regimen to safeguard against the rapid development of resistance to the NNRTI class.

The results suggest strong resistance to nelfinavir and saquinavir, possible resistance to indinavir and ritonavir, variable interpretation of susceptibility to amprenavir, and full susceptibility to lopinavir/ritonavir (Kaletra). Therefore, switching to a new regimen that contains lopinavir/ritonavir (Kaletra) as a single (ritonavir-boosted) PI-based regimen or combining lopinavir/ritonavir with another active PI or with an NNRTI should be efficacious. In the Abbott M98-957 study, the combination of lopinavir/ritonavir plus efavirenz exhibited a potent anti-viral effect through 72 weeks in multiple PI-experienced patients (Abstract #1925, 41st ICAAC, 2001)

There appears to be an increasing number of thymidine analog mutations (TAMS) found in this patient's virus suggesting progression toward multi-NRTI resistance. The mutations associated with multi-NRTI resistance include mutations at loci 41, 67, 70, 210, 215, 219. Presence of the A62V mutation (seen earlier in this patient) along with the aforementioned mutations is suggestive of a multi-drug-resistance pathway involving the 69 insertion complex. Although the 69 insertion mutation has not been detected yet in this patient, it should be emphasized that the genotypic resistance test is limited in its ability to detect quasi-species that comprise less than 10 to 20% of the total amount of virus present in the sample.

In vitro data suggest that 4 or more TAMs (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) will lead to a significant degree of resistance to tenofovir. More recent information from Gilead Science presented at the XIV International AIDS Conference in Barcelona (Abstract ThOrB1390) further elucidates the clinical impact of TAMs on tenofovir efficacy. Patients from the 902 and 907 Studies with virus containing 3 or more TAMs including either M41L or L210W had a substantially lower response rate and diminished phenotypic susceptibility to tenofovir. Patients with an accumulation of D67N, K70R, T215Y/K, or K219Q/E in the absence of M41L or L210W had a better response and showed only minor changes in phenotypic susceptibility to tenofovir. The M184V mutation associated with lamivudine resistance resulted in an increased virologic response. Based on these reports, the patient presented in this case might be expected to have a mild reduction in susceptibility to tenofovir due to the presence of the 3 TAMs including M41L. However, the presence of M184V would serve to re-sensitize the virus somewhat.

One strategy would be to switch this patient to a new regimen containing lopinavir/ritonavir, an NNRTI, and tenofovir, +/- additional background agents, to provide maximum potency with at least 3 new drugs. Another strategy, however, would be to switch to a new PI-based regimen, using lopinavir/ritonavir with tenofovir plus optimized background NRTIs, and save the NNRTI class for third-line salvage once other new agents (e.g. T-20, etc) are available. Alternatively, one could save the lopinavir/ritonavir for subsequent salvage and switch to an NNRTI-based regimen using tenofovir and optimized background NRTIs. The latter strategy might be somewhat risky in this patient since the results of resistance testing suggests the efficacy of tenofovir and background NRTIs may be somewhat compromised.

Recommendations

Regimen Options:

The therapeutic options for this patient include (1) changing therapy and (2) continuing the same regimen. The panel believed that full viral suppression is likely with a change of antiretroviral therapy.

1. Option # 1 : Lopinavir/ritonavir (Kaletra) + tenofovir + 3TC +/- Abacavir.

The majority of the panel members favored this potent treatment option.

Advantages:

- Likely to result in full viral suppression.
- Saves the nonnucleosides for future treatment strategies (T-20 tipranavir, etc)
- Minimizes risk for developing additional resistance mutations

Disadvantages:

- May not be quite as potent as a triple class regimen
- Increased pill burden
- Increased risk of drug toxicity

2. Option # 2 : Lopinavir/ritonavir (Kaletra) + nevirapine (Viramune) + tenofovir + lamivudine

Advantage

- This triple class regimen is likely to have greater potency.
- Likely to result in full viral suppression

Disadvantage:

- The treatment options would be very limited if the virus breaks through this regimen.
- Does not preserve NNRTI for future use.
- Greater risk of treatment toxicity, especially nevirapine-induced hepatitis.

3. Option #3: Continue current antiretroviral treatment: Nelfinavir + Combivir

Advantage:

- Tolerating this regimen without problem
- Stable disease based on viral load and CD4 count.

Disadvantage:

- There is increased risk of further accumulation of resistance mutations in the setting of ongoing replication with detectable viral loads.

Dosing, Monitoring, and Follow-up Recommendations

Lopinavir/Ritonavir (Kaletra) 133 mg lopinavir plus 33 mg ritonavir per capsule. Take 3 capsules po bid with meals. If administered with nevirapine (Virammune), the dose of lopinavir/ritonavir should be increased to 533/133 mg (4 capsules) bid with standard dosing of nevirapine.

Tenofovir (Viread) is dosed at 300 mg, one tablet po qd with meals.

Lamivudine (3TC) is dosed at 300 mg, one tablet daily, or 150 mg, one tablet po bid. Lamivudine can be given with food if desired.

Abacavir (Ziagen) is dosed at 300 mg, one tablet po bid. Patients should be counseled about the possibility for a hypersensitivity reaction that occurs in 5 to 6% of patients.

Nevirapine is dosed at 200 mg, one tab qd for the first 14 days, then one tab bid. Patients should be counseled about rash and the risk of hepatitis.

The CD4 count and viral load should be measured approximately 3 to 4 weeks after the regimen change, and then every 3 to 6 months thereafter.