
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 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

A 40 year-old Latino gay male with a negative history for intravenous drug use, no significant comorbidities, and good adherence has the following antiretroviral history.

<u>Date</u>	<u>Antiretroviral</u>	<u>CD4</u>	<u>VL</u>
10/93-95	Zidovudine (AZT)	16	
2/96-3/96	Stavudine (D4T)/Lamivudine (3TC)	0	
3/96-4/97	D4T/3TC/ hard gel saquinavir (HG-SAQ)	25-→160	undetectable
9/96----			→66K (4/97)
4/97—7/97	D4T/3TC/ritonavir (RTV)/HG-SAQ	150-→230	3k
(6/97) ----			→25 K (7/97)
7/97 – 10/97	AZT/nevirapine (NVP)/nelfinavir (NFV)	231	(7/97) <400
(9/97)			160 K
(10/97)			220 K
10/97 –11/99	D4T/3TC/RTV/HG-SAQ	200 – 260	10 K – 60 K
12/99-present	D4T/3TC/RTV/soft gel SAQ (SG-SAQ)	190 – 205	3 – 5 K

Resistance Test Findings

Obtained 4/01 on D4T/3TC/RTV/SAQ

Key Mutations

NRTI	V35T, T39T/A, M41L, K43K/Q, V60V/I/M, D67N,T69D, Q102K,, V118I, K122E, D123E, C162S, V179V/I, M184V, T200T/A, I202I/V, H206H/Y, L210W, R211K, T215Y, A272P, R277P, R277K, V293I E297K
NNRTI	K103K/N
PI	L10I, I13V, L19I, K20R,E35D, M36I,M37D, F53F/L, I54V, Q58Q/E, I62V, L63P, I66I/L, A71V, G73S, L90M

Phenotype Test Obtained 4/01 on D4T/3TC/RTV/SAQ

NRTI Fold Chnge in IC50 (compared to wild type control)

Abacavir (ABC)	5.0
Didanosine (DDI)	1.8
Lamivudine (3TC)	>>>
Stavudine (D4T)	2.0

Zalcitabine (DDC)	1.9
Zidovudine (AZT)	4.0

Nonnucleoside Reverse Transcriptase Inhibitors

Delaviridine (DLV)	0.1
Efavirenz (EFV)	0.2
Nevirapine (NVP)	0.2

Protease Inhibitors

Amprenavir (APV)	2.5
Indinavir (IDV)	15.0
Lopinavir (LPV)	14.0
Nelfinavir (NFV)	47
Ritonavir (RTV)	56
Saquinavir (SAQ)	110

Interpretation/Implications for Treatment

The laboratory that performed the genotypic resistance test reported a large number of mutations. Most of these mutations represent genetic polymorphisms which are of uncertain clinical significance (e.g. L10I, I13V, L19I, K20R).

The most important NRTI mutations are the changes at codons 41, 67, 69, 184, 210, and 215. Of these, M184V is associated with reduced susceptibility to lamivudine (3TC). Reduced susceptibility to thymidine analog drugs (AZT and D4T) are predicted by mutations at codons 41, 67, 210 and 215. However, the presence of the 184 mutation may make a virus with a 215 mutation more susceptible to AZT.

Abacavir (ABC) susceptibility is usually reduced in patients that have resistance to AZT and/or 3TC. Although the important mutations predicting resistance to didanosine (DDI) are missing, cross-resistance within this class is a concern. These results are compatible with the patient's history.

Among the PI mutations reported, the important ones are likely those changes at codons 10, 20, 36, 53, 54, 63, 71, 73, and 90. Of these mutations, L90M is a primary mutation for saquinavir and nelfinavir; the others are secondary mutations for each of the PI's. These results are also consistent with the patient's clinical history.

The patient has a mixture of K103N mutated virus and K103K (no mutation) virus. This K103N mutation is associated with high level resistance to the entire class of available NNRTI's.

There is still uncertainty regarding clinically relevant phenotypic "cut-points" for each of the currently available antiretroviral agents. The phenotypic assays compare the measured IC50 for a patient derived virus and compare this number to a wild-type reference. The fold-difference reflects the relative amount of "resistance" to a drug. The level at which a fold-change becomes clinically relevant is often defined as the "cut-point". There are likely two relevant cut-offs: 1) the point at which response to a given drug begins to diminish, and 2) the point at which no response is likely to occur. Partial activity of a drug could be predicted between these two points. These cut-points have not been defined for most drugs.

The patient's phenotype test in many respects corresponds to the genotype test (with the one exception described below). There is high level resistance to 3TC, which correlates well with the genotype (M184V). There is low to intermediate resistance to the other NRTI's. There is high level resistance to RTV, SAQ, and

NFV, and low to moderate resistance to lopinavir, indinavir and amprenavir. Of interest are the phenotypic test results for the nonnucleoside reverse transcriptase inhibitors (NNRTIs). The phenotype shows that this patient's virus is more susceptible to nonnucleoside agents than the wild type control. This poorly understood phenomenon, termed "hypersusceptibility", is of unknown clinical significance and has been described only in nonnucleoside naïve patients. In one unpublished study, patients with NNRTI "hypersusceptible" phenotypes treated with an EFV based regimen had a 0.5 greater log reduction in plasma HIV-1 RNA at 2 and 4 months compared to patients with wild-type phenotypes (only statistically significant at month 2).

This patient present with results not previously described before. This patient is nonnucleoside experienced and harbors virus with the K103N mutation. This suggests that NNRTI susceptibility may have been restored as a consequence of changes to the virus. For example, multiple AZT-related mutations may restore NNRTI susceptibility in a manner analogous to the impact of M184V on AZT resistance. Alternatively, a mixture of viruses are present and the phenotype is only capturing resistance levels in the dominant virus. There is insufficient understanding of this phenomenon to accurately interpret this finding, however the panel attempted to explain this result with the following hypothesis. The patient has primarily been on a regimen of D4T/3TC/RTV/SAQ with a 3 month interval of AZT/NVP/NFV. His genotypic resistance test results show a mixture of viruses some of which exhibit the K103N mutation and some of which exhibit the K103K (wild type) virus. Three years after discontinuing the NNRTI, the K103N variant has receded to become a minority quasi-species. This K103K virus is apparently hypersusceptible due to certain nucleoside mutations, yielding the hypersusceptibility seen on the phenotype. The K103N minority quasi-species may have some degree of restoration of susceptibility to NNRTI's as well, but we cannot determine this from the data available.

Therefore, an NNRTI is unlikely to be useful in this patient because the patient has previously failed NVP, and harbors the K103N mutation. The use of an NNRTI would therefore be unlikely to be helpful despite the presence of hypersusceptibility on his phenotype test. The panel does not recommend using a nonnucleoside agent in this patient.

This patient has had a good response to his present regimen which he has been on for several years. His viral load has been less than, 5000 copies RNA/mL for a year and his CD4 count seems stable at about 200. There may be some concern that there is a recent downward trend in his CD4 count. Given this scenario, one option would be to continue the patient on his current regimen.

If this option is not chosen, then full viral suppression (<50) should be a feasible goal. One would not want to risk using a new regimen without being reasonably confident that adequate viral suppression will occur. Without the use of nonnucleosides this may be difficult to achieve but 2 new nucleosides and 2-3 PI's would likely be warranted.

One should also be cognizant that new ARV agents may be approved within the next year or two and that those new agents will likely work best if there is a strong regimen to use with them.

Recommendations

OPTION 1: Maintain current antiretroviral regimen

The consensus of the Panel is to maintain his current antiretroviral regimen and monitor the patient closely for significant loss of CD4 cells or rise in viral load.

Pros

- Patient has been fairly stable on this regimen

- Pt tolerates it well
- Saves other available drugs for later use when newer agents can be used with them

Cons:

- Pt. has ongoing viral replication, allowing accumulation of more mutations.
- CD4 count is low and may drop without better viral suppression

OPTION 2: Tenofovir (expanded access) plus lamivudine (3TC) plus ritonavir/lopinavir (Kaletra) plus amprenavir

PROS:

- Resistance tests suggest at least moderate susceptibility to these drugs so viral suppression is possible/likely.
- Tenofovir may retain susceptibility in those with multiple NRTI mutations, including the M184V

CONS

- No data to support efficacy
- Difficult regimen to tolerate due to large number of drugs and toxicities
- If viral suppression doesn't occur, there is a risk of developing new mutations making future options less efficacious.

Dosing, Monitoring, and Follow-up Recommendations

Lopinavir and ritonavir can be given together in a combination tablet named Kaletra. Each pill contains 33 mg of ritonavir and 133 mg of lopinavir. The standard dosage is 3 pills bid. The panel thought that amprenavir, when used with the above dose of ritonavir, should be dosed at 600 mg bid. A dosage of amprenavir 750 mg bid but data is not yet available. Lamivudine should be given at their standard doses of 150 mg bid,. Dosing of tenofovir would be determined by the relevant protocol.

After changing an antiretroviral regimen it is advisable to monitor viral load and CD4 count at 1 month, 2 months, and 4-6 months. The patient should also be monitored closely for changes in blood lipids, blood glucose, and LFTs as PI's (particularly lopinavir/ritonavir with regards to lipids) can adversely affect these values.

If patient is maintained on the present regimen, dosages should remain the same. It is advisable to monitor viral load and CD4 count monthly for significant changes that would necessitate a regimen change.