
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

The patient is a 51-year-old gay white male who has been HIV positive for several years. He has been off antiretroviral therapy since the last week of November 2002 due to lipoatrophy. Clinically, he is doing well with a current CD4 of 616 (9-02) and a viral load of 2,178 copies/ml (off antiretroviral therapy). His nadir CD4 cell count is 175 cell/mm³ (1996) and his highest recorded viral load is 60,000 copies/ml. He has no history of opportunistic infections. His current medications are testosterone supplementation, Ambient ® prn, and Viagra® prn. His antiretroviral history is as follows:

	CD4	Viral load
1990s "pulse" monotherapy with AZT, DDI, DDC	Unknown	Unknown
1994 AZT/D4T/3TC (was on nelfinavir for 2 weeks but stopped due to diarrhea)	Unknown	Unknown
1996 D4T/3TC/nevirapine	No available CD4 and VLI	
3-00 "	598	1,161
6-00 "	345	394
8-00 "	290	123
11-00 "	772	169
3-01 "	738	154
10-01 "	675	400
3-02 "	739	229
5-02 "	650	441
9-02 "	616	
10-02 "	genotype and phenotype (see results below)	
12-02 off antiretrovirals		2,178

The provider wants our opinion about antiretroviral management in this patient.

Resistance Test Findings

Genotype (10-02) Virologic Inc. {on stavudine (d4T) lamivudine (3TC) and NVP (nevirapine)}

NRT	K70R, M184V
NNRT	K103N
PI	L63P

Phenotype 1 (10-02) Virologic Inc. PhenoSense on d4T/3TC/NVP

Nucleoside Reverse Transcriptase Inhibitors (NRTI)	Fold Change in IC50
Abacavir (ABC)	2.9
Didanosine (ddI)	1.8
Lamivudine (3TC)	>max
Stavudine (d4T)	0.7
Zalcitabine (ddC)	1.7
Zidovudine (AZT)	1.3
Tenofovir	0.7
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTI)	
Delavirdine (DLV)	>max
Efavirenz (EFV)	167
Nevirapine (NVP)	>max
Protease Inhibitors (PI)	
Amprenavir (APV)	0.6
Indinavir (IDV)	0.6
Nelfinavir (NFV)	0.9
Ritonavir (RTV)	0.6
Saquinavir (SAQ)	0.6
Lopinavir(kaletra)	0.6

Interpretation/Implications for Treatment

One of the concerns in evaluating the results of this resistance test is that it was performed at a viral load of <1,000 copies/ml. It is generally recommended that commercially available resistance tests be performed on viral loads of at least 1,000 copies/ml. When resistance testing is obtained at viral loads <1000 copies/ml, a risk exists that the measured level of resistance is not representative of the viral population. If a virus population is too low to be detected by the assay, then a resistant quasi-species may be missed. Thus, when a resistance test is done on a viral load of <1,000 copies/ml, the mutations detected are probably real; however other non-detected mutations may also be present.

Although this patient has been on nucleoside analogues for several years, and has had ongoing replication in the presence of these drugs for much of that time, only one nucleoside analogue mutation (NAM) was detected (K70R). As expected given the genotype, the concomitant phenotype indicates that the patient's dominant virus in October of 2002 was sensitive to all nucleoside analogues except lamivudine (3TC) and didanosine (ddI).

The K103N mutation was also observed, and is consistent with this individual's exposure to nevirapine. This mutation confers resistance to all available non-nucleoside analogues.

The patient was on nelfinavir for only two weeks so one does not expect to detect protease inhibitor (PI) mutations. The L63P is a protease polymorphism which can be found in 45% of PI naive patients.

RECOMMENDATIONS

The panel's recommendations for this patient is to balance the patient's desires, minimize medication toxicities, and evaluate the clinical need for therapy.

Regimen Options

Option 1: Continue off antiretroviral therapy.

This was the preferred option of the panel since the patient has already interrupted therapy and apparently feels well off therapy. Although not well defined, his nadir CD4+ T cell count does not appear to be low. Therapy should be restarted when the CD4 falls to between 200-350 cells/mm³. (see option 2 regimen).

Pros: Decrease toxicity

Preservation of remaining agents.

Possible amelioration of the lipoatrophy.

Cons: Department of Health and Human Services guidelines recommend that patients with a

CD4 nadir of 175/mm³ should remain on therapy.

Option 2: Restart therapy

Based on the patient's antiretroviral history, resistance tests, CD4 cell count, and viral load, maximal viral suppression is possible. However, this would involve the use of multiple medications. The most potent combination would include nucleoside analogues and a dual boosted protease inhibitor-containing regimen. The panel did not feel the need to recommend a triple protease inhibitor containing regimen because there is no history of protease inhibitor failure.

The choice of nucleoside analogues is based on balancing potency and side effects, especially the lipoatrophy since this was a major reason for stopping therapy. Although the exact cause of lipoatrophy remains to be clarified, there are convincing reports of a strong association between stavudine (d4T) and lipoatrophy and therefore, the panel recommended against using stavudine (d4T). Lamivudine (3TC) should be considered in order to maintain the M184V mutation. This enhances virus susceptibility to zidovudine, lamivudine and possibly tenofovir. The M184V mutation may have a "fitness" benefit as well. Instead of lamivudine (3TC), abacavir might be reasonable since it also selects for the M184V mutation but it is not known whether abacavir maintains this mutation. Notably, from a side effect perspective, a recent switch study {2} did show improvement in lipoatrophy when abacavir was substituted for stavudine (d4T). The other nucleoside analogue to be considered is tenofovir because it is potent, can be administered once daily, and has limited short-term toxicity.

Pros: Complete suppression will be likely.

Cons: Medication toxicities and side effects.

Exposure to a new therapeutic class (thereby risking loss of this drug class).

Ritonavir's interaction with Viagra. Limit Viagra to 25 mg in 48 hours

Dosing, Monitoring, and Follow-up Recommendations

Recommended regimen and dosing:

Lopinavir/ritonavir (Kaletra®) 3 capsules PO bid + tenofovir (Viread®) 300mg daily + lamuvidine (Epivir®) 300mg po dail (or abacavir (Ziagen®) 300mg po bid). Take with food to minimize GI distress and increase tenofovir absorption

Side effects:

Lopinavir/ritonavir: nausea/vomiting, diarrhea, liver toxicity, hyperlipidemia

Tenofovir: nausea, vomiting, gi upset, Fanconi's syndrome (very rare), flatulence

Abacavir: hypersensitivity reaction, nausea/vomiting

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.

RESEARCH OPTION

The following option falls outside of the current Department of Health and Human Services as well as the International AIDS Society-USA antiretroviral guidelines but was brought up by the panel as a possible option for this patient. This option is not evidence based and is highly theoretical. This option consists of 3TC monotherapy. The rationale behind the use of 3TC monotherapy is to maintain the M184V (which the patient already has) which confers a "less fit" virus which may result in sustained viral suppression. If this option is chosen, it is advisable to enroll this patient into a research study.

References

{1} Lee SY, Sandhu M, Griswold MP, Van Gorder M. Validation of the Ultra sensitive HIV-1 Genotyping Assay (Abstract). 8th Conference on Retroviruses and Opportunistic Infections, Feb 4-8, 2001, Chicago, Illinois.

{2} Switch from d4T to abacavir: Changes in Fat and Mitochondria(Abstract). International Conference on Antimicrobial Agents and Chemotherapy, September 2002, San Diego, California.