
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 36 -year -old man with a history of IVDU presented to his current primary care provider in November 1996 with a CD4 count of 13cells/mm3 and a viral load (VL) of 186,000. The patient initially was treated with indinavir (IDV) plus lamivudine (3TC) and zidovudine (AZT) but subsequently failed therapy and was placed on nevirapine (NVP) plus nelfinavir (NFV) plus stavudine (d4T) plus didanosine (ddl) with the response below. The patient was initially non-adherent. However, he did not show a VL response even during a period of documented good adherence to the treatment. While on this last regimen, he developed elevations in his liver function tests which was associated with nausea, vomiting, and abdominal pain. These symptoms were not associated with ETOH use. This prompted the primary care provider to obtain a genotype and stop all antiretroviral treatment until symptoms resolved. The patient has no history of opportunistic infections or viral hepatitis but he does have peripheral neuropathy.

11/96	Baseline (pre-treatment):	CD4=13	VL=186,000
11/96 – 12/97	AZT, 3TC, IDV (1 st regimen)		
12/97		CD4=20	VL=100,000
12/97 – 10/31/00	d4T, ddl, NFV, NVP (2 nd regimen)		
8/98			VL= 188,000
10/99:			VL=110,000
6/00	patient admitted non-adherence	CD4=84	
8/00	entered adherence study with 98% adherence (pill ct, phone)		
10/31/00	developed increased LFTs with nausea + abdominal pain, stopped all ARVs, got genotype.		
11/00		CD4=77	VL=112K

Current medications: Azithromycin, Bactrim, Ultram, and Marinol

Resistance Test Findings

Key Mutations

NRT I	M41L, A62V, L74V, V75T, L210W, T215Y
NNRTI	K103N, Y181C
PI	M46I, G73S/A, V77I, L90M

Interpretation/Implications for Treatment

This patient is significantly immunocompromised with a CD4 count that has been persistently less than 100 for the last 3 years. He has limited treatment options based on his prior exposure with treatment failures to multiple antiretroviral drugs, including agents from all three major classes of currently available HIV drugs.

Previous antiretroviral exposure by class include the following:

PI: Nelfinavir, Indinavir

NNRTI: Nevirapine

NRTI: AZT, ddl, d4T, 3TC

The genotypic resistance pattern indicates likely reduced sensitivity to the following

1. Protease inhibitors (PI): saquinavir, nelfinavir, indinavir, ritonavir, lopinavir, amprenavir

The mutation L90M is thought to confer fairly broad class resistance to protease inhibitors. The mutation 46 is a major resistance mutation for indinavir and is commonly seen in resistance to other protease inhibitors as well. The mutation 73 is primarily seen in resistance to indinavir, saquinavir, and lopinavir. The mutation at 77 is commonly seen with general protease inhibitor exposure and may represent a polymorphism or contribute to resistance when added to other mutational changes.

The protease inhibitors most likely to be effective based on this genotypic resistance pattern are amprenavir and lopinavir. A phenotype might help to assess whether amprenavir or lopinavir would be more active in this patient.

2. NonNucleoside Reverse Transcriptase Inhibitors (NNRTI): efavirenz, nevirapine, delavirdine

The mutation at site K103N confers high level cross-resistance to all the currently FDA-approved NNRTIs (nevirapine, delavirdine, efavirenz). The mutation at Y181C confers high level resistance to nevirapine and delavirdine plus moderate to high level resistance to efavirenz.

3. Nucleoside Reverse Transcriptase Inhibitors (NRTI): AZT, ddl, ddC, d4T, abacavir

The zidovudine (AZT) or "thymidine analogue" mutations (i.e. M41L, 62, L210W, T215Y) are associated with broad NRTI class resistance. The mutation at L74V is associated with resistance to ddl/ddC/ABC and the mutation at V75T is associated with d4T resistance.

Note: although the patient's HIV genotypic data obtained on his last treatment regimen does not show the 184 mutation associated with 3TC resistance, this mutation was likely present earlier when the patient experienced treatment failure while taking 3TC. Therefore low levels of viral populations resistant to 3TC may remain and may contribute to subsequent resistance to abacavir (ABC).

Recommendations

Regimen Options:

In February 2001, the panel met and discussed potential antiretroviral strategies for salvage therapy for this patient. The consensus opinion of the panel was to treat this patient with a combination of two or more protease inhibitors plus two or more NRTIs (recycled). Use of the currently available NNRTIs (nevirapine, delavirdine, or efavirenz) is not recommended based on the genotypic resistance pattern indicating cross-resistance to all of these drugs. Since this patient has a history of peripheral neuropathy, the panel would be cautious in using d4T and ddl as recycled agents in the next salvage regimen.

The optimistic goal in this case is to reach full and durable viral suppression with future regimens. However attaining partial viral suppression while attempting to prevent further CD4 count loss may be a more realistic goal until newer drugs are available.

For greater durability of antiviral response, one would ideally like to include in the new regimen more than one new drug to which the patient's virus is likely to be sensitive. If the patient and primary provider wished to await the availability of an experimental drug through an expanded access program, the agents currently furthest along in development are tenofovir and T20. Tenofovir is available through an expanded access program from Gilead Sciences and is pending FDA approval.

Treatment options 1: Kaletra (Lopinavir+Ritonavir) + Combivir (AZT+3TC)

Pros: simple regimen, low pill burden, not associated with peripheral neuropathy

Cons: may have insufficient potency without additional agents to sustain complete viral suppression

Treatment options 2: Kaletra (Lopinavir+Ritonavir) + Trizavir (AZT+3TC+Abacavir) With or without Tenofovir +/- T20 (depending on availability)

Pros: simple regimen, low pill burden, may be more effective with additional drugs

Cons: the increased drug toxicity may outweigh the potential increase in potency; T-20 requires bid injections

Treatment options 3: Kaletra (Lopinavir+Ritonavir) + Amprenavir + either Combivir or Trizavir with or without Tenofovir +/- T20 (depending on availability)

Pros: may be more effective with the combination of 2 potent PIs (plus ritonavir as a pharmacokinetic enhancer)

Cons: drug toxicity may be substantial with "MegaHAART". Added costs and toxicity with ABC in Trizavir compared to Combivir.

Dosing, Monitoring, and Follow-up Recommendations

Lopinavir and ritonavir can be given as a fixed combination capsule known as Kaletra. Each Kaletra capsule contains 33 mg of ritonavir and 133 mg of lopinavir. The standard dosage is 3 capsules bid. The panel thought that amprenavir, when used with the above dose of ritonavir, should be dosed at 600 mg bid. The manufacturer recommends 750 mg bid amprenavir when used in combination with Kaletra. The correct dosing of the combination of amprenavir with Kaletra is unknown.

Combivir and Trizavir should be given at their standard doses of one pill bid, respectively. The dosing of T-20 and tenofovir would be determined by the relevant protocols.

After changing the 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 liver function tests (LFTs) as PIs (particularly lopinavir/ritonavir with regards to lipids) can adversely affect these values.

When beginning or restarting abacavir, the patients should be educated to monitor for symptoms suggestive of an abacavir hypersensitivity reaction. Rash, fever, respiratory symptoms, flu-like symptoms of malaise and fatigue, and gastrointestinal symptoms of nausea, vomiting, and abdominal pain should be aggressively evaluated per the package insert. If abacavir hypersensitivity reaction is suspected, rechallenge should be avoided since fatalities can occur.