
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

38 yo AA male began AZT monotherapy in '96 with VL=31,000 copies/mL /CD4=220 cells/mm³ (nadir). In 11/96, changed to AZT/3TC with one undetectable viral load <500 copies/mL in 12/96. For next few years, viral load rebounded to 5,000-10,000 copies/mL with a CD4 stable in 300-400s cells/mm³ range. Eventually VL increased to 30,000 copies/mL /CD4=416 cells/mm³, so on 1/7/00, changed to d4T/ddI/EFV. Viral load in 3/00 <50 copies/mL, but with subsequent rebound to 702 copies/mL in 7/00 and 3,824 copies/mL in 9/00. Despite rebound, CD4 stable at 538 cells/mm³. Patient reportedly adherent, genotype done while patient on d4T/ddI/EFV in 9/00.

Resistance Test Findings

Key Mutations	
NRTI	M41L, L210LW, T215Y
NNRTI	K103N, V108V/I
PI	None

Interpretation/Implications for Treatment

Genotype shows NRTI mutations suggesting AZT resistance. Although patient is no longer taking AZT, d4T may be selecting for these "thymidine analog mutations." These mutational patterns suggest significant resistance to AZT. Moderate cross-resistance to d4T, ddI and abacavir is also likely. Of note, there is no evidence of resistance to 3TC.

The mutation at 103 is a classic NNRTI mutation that confers high level resistance to the currently available NNRTIs (efavirenz, nevirapine, delavirdine). As would be expected of somebody naïve to protease inhibitors, no protease mutations were detected.

Recommendations

Regimen Options

This case presents a challenging dilemma of when and how to change therapy in a patient with an increasing viral load despite good immunologic function, as measured by CD4 count. Determining the patient and provider's goal of therapy is important in order to find a balance between preserving future therapy options and achieving potent, durable viral suppression. The first option below attempts to maximize suppression with a nucleoside only regimen, thus delaying use of PIs for as long as possible. It is difficult to predict how long this period will be and close monitoring of both labs and clinical status are crucial. The second option is a more aggressive protease inhibitor regimen striving for complete and sustained virologic suppression.

- **OPTION ONE:** D/C efavirenz, continue d4T/ddI (either as a dual NRTI regimen or with abacavir intensification):

- This strategy of intensification may help enhance the viral activity of the nucleoside regimen, while sparing addition of other drug classes (protease inhibitors). Discontinuation of efavirenz will prevent development of additional NNRTI resistance mutations. Continuing efavirenz in the setting of viral replication and in the presence of the K103N mutation is unlikely to contribute to viral activity, as this mutation selects for high level NNRTI resistance. Stopping efavirenz may, in theory, preserve future NNRTI options, as drugs in development are being designed to be active against viruses with the K103N NNRTI mutation, but *in vitro* are less active against viruses with multiple NNRTI mutations. While this strategy risks development of further resistance to the NRTI class, this risk is offset by the benefit of preserving future classes of drugs. It is difficult to predict whether susceptibility to abacavir is still present, however there is little to lose as abacavir shares a similar mutation pattern to the AZT/3TC regimen failed previously. If abacavir is used, close attention should be paid to abacavir hypersensitivity, which can occur in up to 5% of patients and is manifested by multi-system involvement with symptoms including rash, fever, nausea/vomiting, malaise, gastrointestinal, and/or pulmonary symptoms. Another related option is to D/C efavirenz and continue d4T/ddI dual-therapy. Although two-drug therapy would not be considered standard-of-care according to published antiretroviral therapy guidelines, in this case it may be possible to maintain partial suppression with two nucleosides. Using a 2 or 3 nucleoside regimen allows delaying use of other antiretroviral agents until new drugs (tenofovir, fusion inhibitors, possibly 2nd generation NNRTIs) are available.

- **PROS:** Adding third NRTI may enhance viral activity, preserves future NNRTI options, does not sacrifice other ARV classes
- **CONS:** Risk of additional development of NRTI resistance, monitor for abacavir hypersensitivity and mitochondrial toxicity

- **OPTION TWO:** Switch to protease inhibitor containing regimen (either immediately or after interruption of d4T, ddI and efavirenz).
- This approach is most consistent with currently published guidelines and is perhaps the most aggressive approach. The major concern is the early use of the patient's one remaining therapeutic class (protease inhibitors). If this aggressive approach is chosen, many panel members would discontinue the current regimen, either simultaneously or in stages (e.g. discontinue the efavirenz first and observe virologic response. If no virologic rebound and viral load is stable, then discontinue the d4T/ddI to observe virologic response) before switching. This allows "re-staging" of the patient to determine baseline viral load and CD4 **off medications**, plus his immune system may be able to partially control virus in the absence of medication. If rapid viral rebound occurs and CD4 count drops to below 300-350 cells/mm³ occurs, a new HAART regimen containing a protease inhibitor should be restarted. Protease inhibitor options include but are not limited to ritonavir/indinavir, ritonavir/saquinavir, or ritonavir/lopinavir (Kaletra™).

- **PROS:** Most aggressive, likely to attain complete viral suppression
- **CONS:** Risks exposing patient to protease inhibitor class, but without new drugs he has not used yet, patient may be able to maintain partial suppression on a nucleoside regimen and delay protease inhibitors, additional protease inhibitor side effects/complexity/pill burden

Dosing, Monitoring, and Follow-up Recommendations

Dosing: Normal dosing of d4T (20-40mg po bid), ddI (200mg bid or 400mg qd on empty stomach), and abacavir (300mg bid) should be used, if option one is chosen. Various protease inhibitor regimens are possible if option two is chosen, including ritonavir/saquinavir (400/400mg bid), ritonavir/indinavir (200/800mg bid) and ritonavir/lopinavir (Kaletra™). 100/400 mg or 3 capsules bid.

Side effects: Side effects should be closely monitored for. If abacavir is started, the patient must be educated on symptoms of abacavir hypersensitivity and how to contact their provider if they experience symptoms. Abacavir hypersensitivity can occur in up to 5% of patients and is manifested by multi-system involvement with symptoms including rash, fever, nausea/vomiting, malaise, gastrointestinal, and/or pulmonary symptoms. Additionally, peripheral neuropathy, pancreatitis, and mitochondrial toxicity (e.g. lactic acidosis) are possible with the combination of d4T and ddI. Heavy alcohol use should be avoided to decrease the risk of pancreatitis. Protease inhibitors are frequently associated with GI side effects, particularly common with ritonavir. Hepatotoxicity, lipid abnormalities, hyperglycemia/insulin resistance, and fat redistribution abnormalities are also associated with protease inhibitors. Indinavir has the potential for causing nephrolithiasis and patients should drink at least 1.5L of fluid per day.

Clinical monitoring: Adherence should be reinforced and addressed at each visit and patient preferences should be considered in the clinical decision. This patient should be followed closely with viral load and CD4 count lab draws at least every 3 months once stable and as frequently as monthly initially. A rapid and sustained drop in CD4 or increase in viral load should prompt reevaluation and consideration of alternate therapy.