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# 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

37 yo white man who first tested HIV positive in 1987. He is an intravenous drug user. He began using antiretrovirals in 1990 and his antiretroviral (ARV) drug history is as follows:

Date	Regimen	CD4	VL
1990	Zidovudine (AZT)		
5/97	d4T/3TC/ IDV	113	
9/97		263	<400
5/98		204	670
10/98		246	485
7/99		141	921
2/00		166	1324
6/00		242	406
9/00		196	2105
9/00			4154
10/00			3238
11/00		146	1836

He is clinically well. He has been on Septra for PCP prophylaxis. There is no history of other antiretrovirals than those listed above. His adherence is believed to be good.

## Resistance Test Findings

Key Mutations

NRT	41, 184, 215
NNRTI	None
PI	10, 46, 54, 71, 77, 90

## Interpretation/Implications for Treatment

This patient had not been heavily pretreated with antiretroviral therapy. Other than his initial course of AZT monotherapy, his only regimen has been stavudine (d4T), lamivudine (3TC), and indinavir (IDV). On this regimen, his viral load initially became undetectable for a few months but then remained at low but detectable levels for the past three years. His CD4 count also responded initially to the present regimen, rising to the mid 200's and then falling to below 200. His CD4 is now approaching his pretreatment level.

This patient's overall clinical course is not unusual. He has had a "smoldering" viral load with some CD4 response (although it unfortunately never became a robust response). Although his immune system and drug regimen were controlling the virus relatively well, mutations were accumulating during this time and his response to his regimen s appears to be weakening.

The genotype test results presented above are consistent with this antiretroviral history. The 184 mutation correlates with 3TC use and confers significant resistance to this drug. The other two nucleoside reverse transcriptase (NRT) mutations (41, 215) are consistent with both AZT and d4T use and probably confer moderate resistance to these thymidine analog drugs. As would be expected of somebody naïve to nonnucleoside reverse transcriptase inhibitors (NNRTI), there is no evidence of resistance to this class of drugs. Therefore, one expects the virus to be completely susceptible to the NNRTIs.

He has a number of important protease inhibitor (PI) mutations. Mutations at positions 90, 46 and 10 are known to be associated with clinical resistance to most of the currently available protease inhibitors. The virus also has several secondary mutations of uncertain significance. This resistance pattern is consistent with partial resistance to each of the currently available protease inhibitors. However, the level of resistance may be low enough that pharmacokinetically enhanced PI treatment strategies may be effective.

## Recommendations

Goal of Therapy: Since this patient has only had low level viral breakthrough on his first HAART regimen, durable viral suppression (e.g. undetectable VL) is a reasonable goal.

There may be other treatment options available but the following recommendations were those addressed by the Panel. The majority of Panel members believed that the sole addition of ritonavir to this patient's regimen may be the only change required to achieve an undetectable viral load. One Panel member felt strongly that follow-up option one with 2 NRTIs, 2 new PI's and a NNRTI is the optimal initial regimen.

### **OPTION 1: TWO MONTH TRIAL OF D4T/3TC/RITONAVIR/INDINAVIR:**

The majority of Panel members recommended adding ritonavir to the current regimen to achieve higher blood levels of indinavir to try to overcome any PI resistance. The patient's current regimen includes indinavir 800mg every eight hours which must be taken on an empty or near empty stomach. His adherence to this regimen may be less than ideal, accounting for the viral breakthrough. When indinavir is combined with ritonavir it can be administered twice daily without regard to dietary restrictions. Thus, it is usually a much easier regimen to adhere to and take correctly. If this initial change achieves viral suppression, then other drugs and drug classes can be reserved for future use.

#### PROS:

- 1) Minimal change to current regimen.
- 2) Improved adherence
- 3) Can evaluate success of regimen in short time (2 months) before significant new mutations are likely to emerge.
- 4) Reserve other drugs and drug classes for future use.

#### CONS:

- 1) Potential for increased toxicity from both the ritonavir and the higher indinavir levels
- 2) The change might be insufficient to overcome viral resistance, thus allowing for the accumulation of more mutations.

### **OPTION 2: TWO MONTH TRIAL OF D4T/DDI/RTV/IDV**

This option is similar to option 1 but 3TC would be changed to ddl (didanosine). This option would add a naïve drug to which no evidence of resistance appears on the genotype.

It has similar advantages and disadvantages as mentioned above with the additional considerations:

#### PROS

- 1) Viral suppression might be more likely to occur.

CONS :

- 1) Side effects and toxicities of DDI are usually greater than those of 3TC.
- 2) DDI must be taken on an empty stomach, making adherence more difficult.
- 3) DDI must be separated from ritonavir/indinavir which optimally should be administered with food to improve ritonavir tolerability.

If viral suppression is not achieved within 2 months of adding ritonavir in either option 1 or 2, it is unlikely that continuing the regimen will eventually result in additional viral suppression. It is also unlikely that more significant PI mutations would accumulate in just 2 months of therapy. At this point, switching to a more aggressive regimen is recommended. (See Follow Up Options).

FOLLOW UP OPTION 1: 2 NRTIs, 2 new PI's and a NNRTI

One Panel member strongly felt that this is the preferred option of choice. The Panel favored changing to ritonavir/lopinavir (Kaletra™) as the new PI combination of choice because of its potency. The NNRTI of choice would be nevirapine since efavirenz should be avoided in this patient with a significant psychiatric history. The choice of NRTIs are more flexible. AZT/3TC (Combivir) may be the easiest to take. D4T may also be appropriate as well. Abacavir is unlikely to offer significant advantages because of crossresistance with thymidine analogs and 3TC.

PROS:

- 1) It is a very potent regimen and thus most likely to achieve viral suppression,.
- 2) Three new agents are being used to increase the potency of the regimen

CONS:

- 1) High pill burden
- 2) It is more likely to cause adverse effects
- 3) It reserves no drug classes for future use.
- 4) Difficult to distinguish a nevirapine rash from abacavir hypersensitivity reaction.

FOLLOW UP OPTION 2: NRTI's, 2 new PI's

This option is similar to follow up option 1 but the NNRTI is not added and thus is unlikely to as potent a regimen as Follow-up option 2.

PROS:

- 1) Saves the NNRTI class for future use.
- 2) Lower pill burden and less adverse effects

CONS:

- 1) Less potent regimen and less likely to achieve viral suppression.

Dosing, Monitoring, and Follow-up Recommendations:

Dosing:

When ritonavir and indinavir are combined for pharmacokinetic enhancement of indinavir, a common dosage regimen is RTV 200 mg bid and indinavir 800 mg bid. Another dosing regimen is ritonavir 400 mg bid and indinavir 400 mg bid which may be associated with a lower incidence of nephrolithiasis. In choosing which doses to use, one should realize that higher indinavir doses are probably more likely to cause nephrolithiasis, however higher ritonavir doses usually cause more GI side effects and are generally less well tolerated.

DDI can be given as 200 mg po bid or 400 mg po qd. It is to be taken on an empty stomach. The manufacturer states that the QD regimen of ddl should be reserved for those patients unable to take or tolerate the preferable BID regimen. Videx EC is a recently developed formulation of ddl. It can be given as a single small capsule (400 mg qd). As there is no buffer present, the drug appears to be associated with less gastrointestinal effects, including diarrhea and fewer drug interactions. Videx EC, however, must also be given in a fasting state one hour before or two hours after meals.

Lopinavir and ritonavir can be given together in a combination capsule named Kaletra. Each capsule contains 33 mg of ritonavir and 133 mg of lopinavir. The standard dosage is 3 capsules bid. When administered with NNRTI such as nevirapine, it is recommended to increase the dosage to 4 capsules bid.

#### Monitoring:

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 maximum viral suppression should be evident within 6 months of therapy. Since all the options mentioned involve enhanced levels of PI's, one should also be monitored closely for changes in blood lipids, blood glucose, and LFTs as PI's can adversely affect these values.

When beginning abacavir, one should educate the patient to monitor for symptoms of a hypersensitivity reaction. Rash, fever, respiratory symptoms, and abdominal pain should be aggressively evaluated per the package insert.