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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

The patient is a 57 year-old white male who has been HIV-positive since the 1980's. His CD4 cell count has consistently been over 400 cells/mm<sup>3</sup> with a nadir of 316 cells/mm<sup>3</sup>. His previous antiretroviral therapy include zidovudine (AZT) monotherapy x 3 years, didanosine (DDI) monotherapy, AZT + DDI, and stavudine (D4T) monotherapy. His first available viral load (VL) obtained on 2-96 was 416K, CD4 of 316 but it is unclear whether he was taking any anti-retroviral therapy at this time. Based on his viral load of 416K, AZT, lamivudine (3TC) and indinavir (IDV) was started in 1996 with a good immunological and virological response (viral load of <25 and CD4 769) on 9-15-00. However, the patient was concerned about the long term risks of antiretroviral medications (lipodystrophy) and a decision was made to stop treatment on 9-16-00 with close follow-up. Medical history is significant for having a major psychiatric condition.

	Regimen	Viral load	CD4
1996	AZT/3TC/IDV	< 25 copies/mL	453-830
9-15-00	ARVs stopped	< 25 copies/mL	769
9-27-00		1,122	686
10-14-00		receives influenza vaccine	
10-23-00		308,995	570
11-6-00	started combivir/ABC/NVP		
11-09-00	D/C NVP	11,496	614
12-20-00	combivir/ABC	11,118	417
12-29-00	D/C combivir, ABC due to fatigue, gas, nausea, constipation/diarrhea		
1-26-01		81,711	582
2-05-01		98,920	502
			feeling better off meds

## Resistance Test Findings

### Key Mutations

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	T215Y L210W M41L M184V
Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	none
Protease Inhibitors (PIs)	L63P

## Interpretation/Implications for Treatment

The genotype is consistent with the patient's antiretroviral therapy history. The mutations T215Y, L210W, and M41L are commonly observed in patients heavily pre-treated with nucleoside analogues. These mutations are often associated with AZT exposure but likely confer broad-cross resistance within the NRTI class. Because these mutations are selected by d4T as well as AZT they are commonly referred to as thymidine analogue mutations (TAMS). The M184V mutation is associated with high level 3TC resistance. These mutations also confer resistance to abacavir (M184V + 3 or more major TAMS mutations). The M184V mutation does confer low-level resistance to DDI.

The only PI mutation is L63P which is an accessory mutation. Accessory mutations contribute to resistance only when present with other PI mutations. These mutations are polymorphic and can occur in individuals who have not received protease inhibitors.

An interesting question is whether these mutations existed when he was on 3TC, D4T and IDV. If these mutations were present, then he was essentially only on monotherapy with IDV despite a suppressed viral load of <25 copies/mL. His excellent virological suppression might be due to a combination of factors, including IDV activity, his good immune system, and a "less fit" virus conferred by the M184V mutation.

Based on his antiretroviral history and genotype results, a regimen providing full viral suppression is feasible, and therefore, full suppression should be the goal of therapy.

## Recommendations

### Regimen Options

#### Option 1: Continue off therapy

His viral load has been slowly increasing (81,711 to 98,920 to 142,000) since he has been off antiretroviral therapy (since 1-26-01). However, this is not a significant VL rise, as defined by a 0.5 log or 3-fold increase. This viral load range may be his "baseline" off therapy "set point". His CD4 cell count remains high but there is a decreasing trend (582 to 502 to 462). If his viral load remains about 80 to 100K, and as long as his CD4 is greater than 350 cells, remaining off therapy would be a reasonable option since he is very concerned about the side effect of antiretroviral therapy, especially lipodystrophy. However, close monitoring of his CD4 and viral load is essential. It would be prudent to have a discussion with the patient to identify immunological and/or virological parameters that would result in restarting his antiretroviral therapy. Based on the most recent Department of Health and Human Services (DHHS) guidelines (2-2001) for use of antiretroviral agents in HIV-infected adults and adolescents, one parameter that might be used to restart antiretroviral therapy is when his CD4 cell count drops to less than 350 cell/mm<sup>3</sup>, but definitely before it decreases to less than 200.

**PROS:** No pill burden nor SE. "Drug holiday" with reversion to more sensitive wild type virus.

**CONS:** Immunologic and virologic deterioration if not closely followed

#### Option 2: Two NRTIs plus dual PI therapy

When the patient is ready to restart antiretroviral therapy or when immunological and/or virological parameters dictate restarting therapy, the goal for this patient would be maximal viral suppression. Therefore, the panel

recommends using two NRTIs and pharmacokinetic enhancement with a dual protease inhibitor regimen using low dose ritonavir. Based on the antiretroviral history and genotype, the optimal nucleoside analogue regimen is not clear. There is evidence of significant resistance to all of the available agents. Given the clear association of 41, 210, and 215 with AZT resistance, and of 184V with 3TC resistance, the use of d4T and ddl seems reasonable. Abacavir should be avoided because of a possible hypersensitivity reaction. The NRTI regimen may be best determined by safety and tolerability.

There are several dual PI regimens that could be implemented in this patient. Possibilities include Kaletra (lopinavir plus ritonavir), indinavir (Crixivan) + ritonavir (Norvir), or amprenavir (Agenerase) + ritonavir.

**PROS:** Most likely to achieve complete viral suppression

No mid-day dose required

BID dosing

No PI dietary restrictions

**CONS:** Large pill burden

Moderately high probability of GI intolerance, body habitus changes and/or hyperlipidemia

ddl fasting requirement

transaminase elevations with PI combinations

potential for peripheral neuropathy from the dual NRTI combination

### Option 3: Two NRTIs plus one NNRTI

Another option that was discussed was the use of 2 NRTI plus an NNRTI. However, the NNRTI as a class may require greater "support" from the "backbone" medications than a PI-based regimen. Thus, the use of recycled NRTIs with a NNRTI may lead to rapid NNRTI failure. The panel believed that non-nucleoside analogues should not be used at this time to avoid exposure to a new class and thus "save" this class for the future. If an NNRTI is used, it should be used in combination with NRTIs and PIs. Due to the patient's psychiatric condition, the provider feels uncomfortable using efavirenz, and therefore, if a non-nucleoside is used, nevirapine would be the agent of choice. Due to a drug interaction, the dosage of PI needs to be increased when co-administered with an NNRTI.

**PROS:** BID dosing

No PI dietary restrictions

No PI related long term toxicities

**CONS:** Resistance to one NNRTI can prevent further NNRTI use

### Dosing, Monitoring, and Follow-up Recommendations

Nucleoside Reverse Transcriptase Inhibitors: Stavudine (d4T) 40 mg bid (lower dosages of 30 mg bid might be as efficacious as 40mg bid but associated with less neuropathy). Side effects: include neuropathy; pancreatitis, association with mitochondrial toxicity and lactic acidosis, and possible association with peripheral wasting.

Didanosine (ddl): enteric coated (Videx EC) 400mg once a day or "standard" ddl 100 mg 2 tablets twice daily on empty stomach (one-half hour before meals or 2 hours after meals). Videx EC is associated with less gastrointestinal side effects and less drug interactions than "standard" DDI. Side effects include neuropathy, diarrhea (less with enteric coated), pancreatitis, and association with mitochondrial toxicity and lactic acidosis.

The dosage of lamivudine (3TC) is 150mg bid. Lamivudine is generally well-tolerated but headaches can occur.

Protease Inhibitors. The dosage of Kaletra is 3 capsules (400 mg lopinavir plus 100 mg ritonavir) bid. Side effects include gastrointestinal intolerance and high incidence of hyperlipidemia (up to 20-30%). If Kaletra is used with nevirapine, the dosage of Kaletra needs to be increased to 4 capsules bid. Kaletra has the lowest pill burden of the dual PI regimens.

The dosage of indinavir is 800 mg bid and ritonavir is 100 to 200 mg bid (another "acceptable" dose is indinavir 400mg bid and ritonavir 400mg bid but there is potential for increased side effects from the higher ritonavir dose). Side effects of IDV include gastrointestinal intolerance, nephrolithiasis and isolated hyperbilirubinemia. Side effects of ritonavir include gastrointestinal intolerance, circumoral and extremity paresthesia, and taste perversion. This dual PI combination can be taken with food if necessary to decrease the gastrointestinal side effects. If taken with food and DDI is used, the DDI needs to be taken one-half hour before or 2 hours after taking the protease inhibitors. Long term class toxicities of PI therapy include fat redistribution syndrome, hyperlipidemia, osteoporosis and hepatic enzyme elevations.

The recommended dosage for 150 mg amprenavir capsules is 4 capsules (600 mg ) bid and ritonavir 100mg bid. Side effects of amprenavir include gastrointestinal intolerance and rash. Amprenavir also contains significant Vitamin E and patients should be advised to avoid additional vitamin E supplements.

Nonnucleoside Reverse Transcriptase Inhibitors. The dose of nevirapine is 200mg once a day for 14 days then 200mg bid. Side effects include rash and hepatotoxicity (especially in the first few weeks of treatment). Nevirapine can be used with one of the nucleoside combinations discussed in option 2. The use of this regimen would offer an easier regimen and potentially avoid the lipodystrophy side effects which the patient is very concerned about.

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.