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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

This 23-year-old young man with measurable HIV RNA (VL) on a salvage highly active anti-retroviral therapy (HAART) regimen was referred to the Resistance Panel for genotype and phenotype interpretation and antiretroviral (ARV) recommendations. His first positive HIV test was in 1996. At presentation, his CD4 count was <50/mm<sup>3</sup>. A HAART regimen was initiated, then followed over subsequent years by other multi-drug regimens including agents from the non-nucleoside reverse transcriptase inhibitor (NRTI) and protease inhibitor (PI) classes. The patient does not recall the details of his ARV history and no medical records before March 2000 are available. His viral load remained measurable on all of these regimens. Failure of viral suppression was attributed to erratic medication adherence.

In March 2000, while on a regimen that included two nucleoside reverse transcriptase inhibitor (NRTIs) and a protease inhibitor (PI) (details unknown) and with a VL of approximately 18,000 copies/ml, a genotypic resistance test was performed (results summarized below). Following the test, the patient was placed on didanosine (ddl), stavudine (d4T), lamivudine (3TC), ritonavir (RTV) 100 mg bid, and amprenavir 600 mg bid (APV). Several months later, the VL had fallen to approx. 5500 copies and efavirenz (EFV) was added. By October 2000, the VL had risen to 58,000 and a phenotypic resistance test (Virologic, Inc.) obtained.

## Resistance Test Findings

### GENOTYPE (3/28/00)

#### Key Mutations

NRT	D67N, K70R, , K219E
NNRT	K101R, Y181C, G190A
Pr	K20M, M46I, L63P, L90M

### PHENOTYPE (10/17/00)

Nucleoside Reverse Transcriptase Inhibitors (NRTI)	Fold Change in IC50
Abacavir	4.9
Didanosine	3.1
Lamivudine	2.1
Stavudine	4.0
Zalcitabine	3.7
Zidovudine	9.2
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTI)	
Delavirdine	23
Efavirenz	247
Nevirapine	>>>
Protease Inhibitors (PI)	Fold Change in IC50
Amprenavir	2.3
Indinavir	4.9
Nelfinavir	12
Ritonavir	6.0
Saquinavir	1.6

Bold type indicates expected retained phenotypic susceptibility.

## Interpretation/Implications for Treatment

The clinical history and resistance test results for this young man with extensive prior ARV use and advanced immunosuppression suggest that although significant resistance has already developed, viable treatment options may remain. The phenotypic resistance test suggests that NRTI choices are extremely limited (probably only 3TC retains full activity against the predominant viral strain), and NNRTI are unlikely to be helpful at all. However, it is still reasonable to expect a significant response to dual protease inhibitors (PI). In particular, pharmacokinetic enhancement of either amprenavir or saquinavir with ritonavir is likely to be effective. The combination of ritonavir/lopinavir (Kaletra™) would be expected to have significant activity against this virus as well.

It should be emphasized that both genotypic and phenotypic resistance tests are limited in their ability to detect HIV quasi-species that comprise less than 10 to 20% of the total amount of virus present in a sample. Therefore, these tests may miss minority populations of virus with clinically meaningful nucleoside reverse transcriptase (RT) or PI gene mutations and/or reduced ARV susceptibility. Reintroduction of particular agents known to be associated with such "resistance" may provide selective pressure that will allow minority populations a survival advantage. The result may be failure of a regimen for which the test would otherwise have predicted success. Given this patient's extensive ARV history, it is likely that nucleoside analog mutations not detected are actually present. In particular, this patient probably harbors a minority population of virus bearing the 184 mutation and reduced susceptibility associated with 3TC resistance even though we don't see it in either the genotype or the phenotype results. We would expect that such resistance would likely emerge if the patient was again treated with 3TC

It is notable that the patient has limited phenotypic resistance to his currently administered protease inhibitors (ritonavir and amprenavir). There are several possible reasons for this. First, the patient may be intermittently adherent. This seems unlikely, however, since he has demonstrated a partial virologic response. Second, the patient may not be receiving sufficient protease inhibitor exposure due to complicated pharmacokinetic interactions. Efavirenz may be reducing overall exposure to ritonavir and amprenavir such that the level of drug exposure is inadequate to generate resistance. Again, this seems less likely since the patient has demonstrated a partial response. Third, the phenotypic assays may not be sensitive enough to measure clinically significant fold-changes in amprenavir. Little is known regarding the clinically relevant phenotypic "cut-offs" for amprenavir resistance; perhaps only a slight increase in amprenavir resistance is necessary to cause drug failure. Fourth, resistance to amprenavir may be slow to emerge because of the complex and poorly understood relationships between viral replication, drug resistance and viral replicative capacity ("fitness"). Subsequent resistance testing would be of interest.

It is difficult to know *a priori* whether combinations of previously used NRTIs will add sufficiently to the potency of the regimen to achieve complete viral suppression, but such a "recycling" strategy offers the best chance of retaining 3TC activity. It may also represent this young man's best chance for a clinically meaningful virologic and immunologic response.

Unfortunately, complex multi-drug regimens of the sort most likely to suppress viral replication are often associated with inconvenience and/or toxicity. While toxicities often are tolerable, they can sometimes lead to significant morbidity and even mortality. The discomfort and disruption that can result may contribute to poor adherence and eventual therapeutic failure. It is important that the patient understands these risks and is willing to take them on, especially since the ultimate benefit of the therapy is uncertain. It is equally important for the patient to know that choosing not to take ARVs now puts him at very high risk for HIV-related disease progression or death.

If your patient decides that the likely benefits of the proposed regimen are insufficient to justify the risks, other options are still worth considering. Even if an ARV regimen achieves only partial viral suppression, it may still benefit an individual (in terms of reduced HIV-related morbidity and mortality). While a less intensive regimen might be less likely to fully suppress viral replication, such an approach may be more acceptable to the patient and may yield some benefit without as much risk.

Clinical studies have confirmed that the effectiveness of an ARV regimen depends directly on adherence to that regimen. Prescribing a new regimen is an ideal context in which to review patient adherence and to discuss individualized strategies for supporting optimal adherence.

## Recommendations

### Regimen Options

- Option 1: 3 PI + 3 NRTI: Amprenavir/Lopinavir/Ritonavir/ddI/AZT (or d4T)/3TC

- **Advantages**

- Most likely to achieve complete viral suppression  
No mid-day dose required

- **Disadvantages**

- Large pill burden  
Moderately high probability of GI intolerance, body habitus changes and/or hyperlipidemia  
ddI fasting requirement

***The combination of ritonavir, amprenavir and lopinavir has not been studied, and should be used with caution. Pharmacokinetic drug interactions are expected to be complex. The tolerability and long-term safety of regimens containing three protease inhibitors are not known.***

- Option 2: 2 PI + 2 NRTI: Amprenavir/Ritonavir(or Saquinavir/Ritonavir or Indinavir/Ritonavir or Lopinavir/Ritonavir)/ AZT(or d4T)/3TC

- **Advantages**

- May achieve complete viral suppression  
BID regimen without food restriction

- **Disadvantages**

- May be less potent than Option 1  
Moderately large pill burden  
Moderately high probability of GI intolerance, body habitus changes, and/or hyperlipidemia

- Option 3: Best tolerated multidrug combination (w/out NNRTI)

➤ **Advantages**

Most likely to be tolerated and adhered to  
May achieve partial viral suppression

➤ **Disadvantages**

Unlikely to achieve complete viral suppression  
May result in accumulation of additional resistance mutations and/or phenotypic resistance

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

- Option 1: Amprenavir/Lopinavir/Ritonavir/ddI/AZT (or d4T)/3TC

➤ **Dosing**

Amprenavir 150 mg, 4 tablets po bid

Lopinavir/Ritonavir (Kaletra™) 333 mg/33 mg/ capsule, 3 capsules po bid

ddI 200 mg tabs, one tablet po bid or 2 tablets po qd **OR** ddI EC 400 mg cap, one capsule po qd  
(All ddI doses must be taken one hour before or two hours after eating)

AZT/3TC (Combivir) 300 mg/150 mg, one tablet po bid **OR**  
d4T 40 mg, one capsule po bid **AND** 3TC 150 mg, one tablet po bid

➤ **Common Toxicities**

Amprenavir: Nausea, vomiting, diarrhea, rash, perioral paresthesias, vitamin E toxicity (if taken with supplements)

Lopinavir/Ritonavir: Nausea, vomiting, diarrhea, increased triglycerides

ddI: Nausea, vomiting, diarrhea, pancreatitis, peripheral neuropathy

AZT: Nausea, anemia, fatigue, hepatitis

3TC: Usually none

d4T: Peripheral neuropathy, pancreatitis

In addition, HAART therapy has been associated with body habitus changes, fat redistribution syndromes, hyperglycemia, hyperlipidemia, lactic acidosis, and hepatic steatosis

- Option 2: Amprenavir/Ritonavir(or Saquinavir/Ritonavir or Indinavir/Ritonavir or Lopinaivr/Ritonavir)/ AZT(or d4T)/3TC

➤ **Dosing**

Amprenavir 150 mg, four tablets po bid **AND** Ritonavir 100 mg, one capsule po bid

**OR**

Saquinavir 200 mg, two capsules po bid **AND** Ritonavir 100 mg, four capsules po bid

**OR**

Indinavir 400 mg, two capsules po bid **AND** Ritonavir 100 mg,, 2 capsules po bid

Others as above

➤ **Common Toxicities**

Saquinavir: Nausea, vomiting, diarrhea

Ritonavir: Nausea, vomiting, diarrhea, perioral paresthesias

Indinavir: Nausea, urolithiasis (advise increased oral fluid intake to reduce risk of latter)

Others as above

- Option 3: Best tolerated multidrug combination (w/out NNRTI)

➤ **Dosing**

As above

➤ **Common Toxicities**

As above