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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 is a case of a 49-year-old gay man, who has been HIV+ since 1992. By report, the patient has been on a variety of antiretroviral drugs. Details regarding medication exposure and virologic responses are not available before 2002. The CD4+ T cell nadir is not known, although the patient's "off therapy" viral load set-point was approximately 200,000 copies RNA/mL. As of March 2002—when details first become available—he was on amprenavir (APV), didanosine (DDI), and lamivudine (3TC). The patient reports missing several doses of his regimen per month. He feels well and is tolerating his antiretroviral medications. He has never had an opportunistic infection. He presented to his current provider in 4/2003 with the following information:

DATE	ARV REGIMEN	CD4	HIV RNA
3/02	APV/ddI/3TC	210	6700
4/02	Same	?	9200
9/02	Same	?	24,000
11/02	Same	371	64,000
5/03	Same	200	160,000

A phenotypic resistance test was ordered, but a virtual phenotype was done by mistake. The clinician is unfamiliar with virtual phenotypes and requests assistance in interpreting the results. Both the patient and the provider's goal are to achieve complete viral suppression.

## Resistance Test Findings

### Mutations Identified (5/19/03, Virco, Quest Diagnostics)

NRTI	69N, 74V, 184V, 215F, 219Q,
NNRTI	103N, 225H
PI	10F, 20T, 30N, 33F, 54M, 71V, 77I, 88D, 90M

### Virtual Phenotype

DRUG	MATCHES IN DATABASE	FOLD CHANGE IN IC50	CUT-OFF FOR NORMAL SUSCEPTIBLE RANGE
Zidovudine	22	2.0	4.0
Lamivudine	94	45.9	4.5
Didanosine	2	Resistance Unlikely*	
Zalcitabine	2	Resistance Unlikely*	

Stavudine	36	0.8	1.8
Abacavir	2	Resistance Unlikely*	
Tenofovir DF	232	0.9	3.0
Nevirapine	574	53.6	8.0
Delavirdine	266	86.3	10.0
Efavirenz	567	64.8	6.0
Indinavir	18	8.7	3.0
Ritonavir	18	25.8	3.5
Nelfinavir	18	59.5	4.0
Saquinavir	18	33.6	2.5
Amprenavir	19	1.9	2.0
Lopinavir	4	Resistance Likely*	

\*Rule based Interpretation

## Interpretation/Implications for Treatment

A virtual phenotype uses a genotype/phenotype database to match a given genotype with a corresponding phenotype. The accuracy of this approach depends in part on the number of genotypes in the database which corresponds to the measured genotype. A limitation of most virtual phenotypes is that the number of matches in the database is very low for many of the antiretroviral drugs; this is particularly true for newly approved drugs.

The virtual phenotype must also be interpreted in the context of little or no information about the patient's antiretroviral history. It is important to note that resistant mutations that developed while on past treatment regimens may no longer be detectable. These archived mutations may affect the response to antiretroviral drugs

Two thymidine analogue mutations or TAMs (215F and 219Q) are detected on this genotype/virtual phenotype. The presence of the 69N mutation with TAMs confers resistance to most nucleoside analogs (NRTI). The 74V frequently develops with didanosine (ddl) therapy and confers significant resistance to ddl and abacavir (ABC). The 184V mutation confers significant resistance to 3TC but also provides virologic benefits by reducing viral fitness and by increasing the susceptibility of the virus to zidovudine and tenofovir. On the basis of this genotype/virtual phenotype, significant antiretroviral activity from the NRTIs would not be expected. In addition, there may be archived mutations, further reducing the activity of this class.

The non-nucleoside reverse transcriptase inhibitor (NNRTI) mutations, 103N and 225H, confer high-level resistance to the entire NNRTI class. Any residual antiretroviral activity from this class is not expected.

The virtual phenotype/genotype shows a significant number of protease inhibitor (PI) mutations. According to one algorithm, the presence of six PI mutations is associated with significant resistance to lopinavir/ritonavir (Kaletra). Although the patient is not receiving a boosted protease inhibitor presently, antiviral activity is not likely due to the number of accumulated mutations and the predicted high fold change in the phenotype. Based on available data, an antiviral response to tipranavir might occur but further clinical data is necessary. At the time of this report, tipranavir was still investigational.

The only fully active drug is T-20 (enfuvirtide). Unfortunately, at the time of this consultation, there was no other very fully active drugs to use in combination with T-20. Exposure to a regimen containing enfuvirtide in this situation risks the rapid emergence of high-level drug resistance.

Interruption antiretroviral therapy is not appropriate since the patient is at high risk of clinical disease progression (current CD4 count less than 200 cells/mL), and since several randomized studies failed to demonstrate any long-term benefit on interrupting therapy in this setting. Maintaining the current regimen increases the risks of continued immunologic progression and the emergence over time of more resistance and cross-resistance.

As outlined below, three major therapeutic strategies can be considered. The first involves the use of a T-20 based salvage regimen. This approach is likely to produce at least a 1 log<sub>10</sub> decrease in plasma HIV RNA levels although a sustained virologic response is unlikely. Another option is a type of "bridge" salvage therapy using single or dual boosted PI's, while awaiting additional active agents to combine with T-20. This option preserves T-20 for future use, but provides less of an immediate virologic response. The final option is continue the current regimen pending the availability of more effective drugs.

## Recommendations

### Regimen Options

**Option 1: Lopinavir/ritonavir 3 capsules bid plus saquinavir 1000 mg bid plus tenofovir 300 mg qd plus Trizivir® one tablet bid plus T-20 90 mg SQ bid**

Advantages – Potent regimen providing the best chance for achieving an undetectable viral load.

Disadvantages- May not achieve durable "complete" viral suppression as the background regimen being used with T-20 is not very active. Also, there are limited data supporting the use of "dual boosted protease inhibitors" in this setting (although a number of small uncontrolled studies suggest that these combinations may be effective in the setting of "deep" salvage therapy). Finally, this combination has a high pill burden, multiple potential drug-drug interactions, and a high risk of drug toxicity

**Option 2 (Reserve): Lopinavir/ritonavir 3 capsules bid (+/-saquinavir) plus tenofovir 300 mg daily plus Trizivir® one tablet bid**

Advantages - Preserves T-20 for future use when newer agents that may be more active are available. Regimen uses boosted PI (or dual boosted PI) which might provide significant potency and impair viral fitness.

Disadvantages - Unlikely to achieve an undetectable viral load. Dual boosted protease inhibitors are difficult to tolerate. Risk of drug-drug interactions and drug toxicity.

**Option 3: Continue current regimen.**

Advantages- Established tolerability and safety in this patient. This regimen likely has some activity (either due to continued activity of the regimen against a partially resistant virus and/or due to the selection of a poorly fit virus population).

Disadvantages – Continued viral evolution and risk of progressive immunological deterioration.

## Dosing, Monitoring, and Follow-up Recommendations

Monitor adherence. If the patient's adherence is poor, it is important to work with the patient to try to improve adherence. This will likely improve the response to antiretrovirals and may delay development of resistance.

Would also begin PCP prophylaxis because his CD4 count is at 200mm<sup>3</sup> currently.

Monitor CD4 and VL 4 to 6 weeks after ARV change