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# HIV Resistance Testing Consultation Service

## Consultation Report

Panel Members:    Richard Aranow, MD  
                          George W. Beatty, MD, MPH  
                          Steven G. Deeks, MD  
                          Betty J. Dong, Pharm.D  
                          Amy V. Kindrick, MD  
                          Jody Lawrence, MD  
                          Michael L. Lim, Pharm.D (11/00-6/01)  
                          John Stansell, MD (3/10-6/01)  
                          Jason Tokumoto, MD  
                          Paul Volberding, MD (11/00-3/01)

Project Director:    Ronald H. Goldschmidt, MD

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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 43-year-old man has been HIV+ at least since 1994. His nadir CD4 was 221 in 1/98. He has had no opportunistic complications other than recurring HSV outbreaks. His antiretroviral treatment history is as follows:

DATE	REGIMEN	CD4	VL	COMMENTS
8/96-10/96	DDI/3TC/SQV-hgc			Diarrhea
10/96-6/97	DDI/3TC/RTV			
6/97-6/98	DDI/3TC/IDV			
11/97		407	4300	
1/98		221		
6/98-8/98	AZT/3TC/IDV/RTV	335	46,000	
7/98		555	1400	
8/98-1/99	D4T/3TC/IDV/RTV			
1/99-3/99	AZT/3TC/ABC	382		
2/99			314,000	
3/99-7/99	ABC/IDV/RTV/EFV	382		Diarrhea
6/99		839	112,000	
7/99-10/99	ABC/IDV/EFV			
9/99		452	163,000	
1/00		400	150,000	
10/99-2/00	D4T/DDI/RTV/EFV	452		Genotypic Assay Performed
2/00-Present	D4T/DDI			
5/00		386	77,000	
10/01		347	294,000	
1/02		277	>75,000	

His adherence has been judged to be "good". He developed glucose intolerance and hyperlipidemia while receiving protease inhibitor therapy. His concomitant medications include carbamazepine and acyclovir.

## Resistance Test Findings

Genotypic Assay 2/10/00 (Unilab)

Key Mutations	
NRT	M41L, D67D/N, L210W, T215Y
NNRT	K103N, G190A
PI	L10I, M36I, I54V, I64M, A71V, V82A, L90M

## Interpretation/Implications for Treatment

The treatment history, clinical course, and genotype resistance test results all suggest that this patient harbors a virus that has significantly diminished susceptibility to all currently available antiretroviral agents. It is highly unlikely that any regimen will achieve complete viral suppression. Consequently, in choosing which antiretroviral agents to use, the benefits of pursuing an aggressive, potentially fully suppressive antiretroviral regimen must be weighed against the potential risks of such a strategy, including inconvenient dosing, significant toxicity and unpredictable drug-drug interactions.

It is unclear whether this patient's past and current ARV treatment are helpful. The CD4 count has trended downward since 2/2000, when the antiretroviral regimen was changed from stavudine (d4T), ddI (didanosine), zalcitabine (ZDV), and zalcitabine (ZDV) to d4T and ddI. However, during this same time the change in HIV RNA levels were not significantly different from those seen with the more intensive regimen. If the patient's HIV disease is indeed progressing, changing back to a more complex combination regimen may stop or slow the declining CD4 count. Maintaining drug pressure may promote the persistence of multiple resistance mutations that have a negative impact on viral replicative capacity. This "less fit" virus may cause less immunologic damage, even though replication probably won't be completely suppressed. Clarification of whether the more complex regimen was providing additional CD4 and HIV benefits compared to the current dual nucleoside regimen would be important to decide whether a more complicated and toxic ARV regimen would be warranted. Therefore, obtaining several more CD4 counts and RNA measurements on the current dual nucleoside regimen might provide useful information. .

If the decision is to change the current regimen to optimize viral suppression, the genotype results suggest that including a nonnucleoside reverse transcriptase inhibitors (NNRTI) would not be helpful. The K103N and G190A mutations predict that all 3 currently available NNRTIs would be ineffective. An additional advantage of omitting this class from a new regimen would be to reduce the risk of accumulating additional NNRTI mutations. Such cumulative NNRTI mutations may impair this patient's response to "second-generation" NNRTIs currently in development.

The multiple nucleoside analogue mutations (NAMS) at positions M41L, D67D/N, L210W, and T215Y predict broad cross-resistance within the nucleoside reverse transcriptase inhibitor (NRTI) class. Moreover, unpublished data suggest that multiple NAMS (particularly M41L or L210W) predict clinically significant resistance to tenofovir.

Although lamivudine (3TC) susceptibility may not be significantly compromised by these NAMS, the patient's prior unsuccessful treatment with 3TC-containing regimens predicts that virus harboring the M184V mutation almost certainly is archived, even though it is not detected in this genotype. Reintroducing this drug would be expected to lead to the rapid re-emergence of high-level 3TC resistance.

The genotype results also indicate that the protease inhibitor (PI) class is likely to have diminished activity against this patient's virus. Mutations at positions V82A and L90M are likely to confer cross-resistance to saquinavir (SQV) and nelfinavir (NFV). Along with mutations at positions L10I, M36I, I54V, and A71V; the V82A and L90M mutations are likely to predict poor response to all currently available PIs. However, since only 5 of the 8 mutations thought to contribute to lopinavir/ritonavir resistance are seen, it is possible that this drug will retain some efficacy. The impact of these mutations on amprenavir activity is not clear, but phenotypic data from other cohorts suggest that amprenavir susceptibility is often retained after failure of other protease inhibitors. Thus, a salvage regimen containing ritonavir/lopinavir (Kaletra), ritonavir/amprenavir or, preferably, ritonavir/lopinavir and amprenavir should be strongly considered.

In summary, complete viral suppression may not be readily achievable with any combination of FDA-approved antiretroviral agents. However, the benefits of maintaining a partially suppressive regimen, including reduced viral "fitness" and risk of HIV disease progression, may be sufficient to justify the risks of a more complex regimen if this patient truly is experiencing immunologic progression. If recent CD4 counts do not represent immunologic progression, then it is unclear that the benefits of continuing a partially suppressive antiretroviral regimen would outweigh the risks.

## Recommendations

### Regimen Options

#### Option 1: Lopinavir/ritonavir +/- Amprenavir with best-tolerated NRTIs

The majority of the Panel would select this option if immunologic decline is confirmed. Although this regimen is unlikely to suppress viral replication completely, it is likely that some partial viral suppression will be achieved, and that this will translated into sustained CD4 T cell gains. There are also some evidence suggesting that CD4 gains may be greater in patients receiving a protease inhibitor-based regimen (note the accelerated loss of CD4 T cells when the patient switched from an NRTI/PI regimen to a NRTI based regimen). While the clinical implications of the pharmacokinetic interactions between lopinavir, ritonavir, and amprenavir, are under investigation, the majority of Panel members would elect to use all three of these together rather than amprenavir alone, or lopinavir/ritonavir alone (see dosing recommendations below). GI intolerance may dictate which of these approaches is possible.

This genotype does not suggest that there is an advantage to using any particular NRTI over another. The panel unanimously recommended choosing the 2 or 3 NRTIs that the patient is most likely to tolerate and to adhere to. Most members would use tenofovir because it is simple and generally well-tolerated, but would not expect it to be more effective than any other NRTI. Some members would include 3TC because the M184V mutation was not present, although all suspected that any benefit from its inclusion would be temporary.

No Panel members recommended including an NNRTI in the regimen.

#### Advantages:

- Most likely to avert disease progression for longest period of time
- May increase CD4 cell count

#### Disadvantages:

- High risk of gastrointestinal toxicity (amprenavir, lopinavir/ritonavir, ddl, AZT)

- High risk of metabolic abnormalities (hyperglycemia, hyperlipidemia, lipodystrophy, abnormal fat redistribution, lactic acidosis, hepatic steatosis)
- Most complex
- High pill burden
- High likelihood of significant drug-drug interactions

### Option 2: Continue ddl/d4T

If repeat CD4 counts indicate that this patient is immunologically stable, it would be reasonable to consider making no changes in the current antiretroviral regimen. However, most Panel members favored stopping altogether, rather than continuing a regimen with uncertain benefit and the potential for cumulative resistance and toxicity (see Option 3 below). Several Panel members would consider a dual NRTI regimen if the CD4 count declined significantly after stopping all drugs and if the patient did not tolerate or otherwise opted against a more complex salvage regimen. It is possible that a dual NRTI regimen might slow down or stave off immunologic decline without increasing complexity and toxicity risk, although the Panel thought that any such effect was not likely to be durable.

#### Advantages:

- Simple, familiar, and well tolerated (so far)

#### Disadvantages:

- Less likely to maintain CD4 cell counts for long periods of time
- Potential for cumulative toxicity
- Potential for engendering additional antiretroviral resistance

### Option 3: Discontinue all antiretrovirals and follow closely

Many members of the Panel preferred this strategy if the patient's CD4 count is truly at the nadir and additional CD4 measurements failed to confirm immunologic decline. In addition to simplifying this patient's daily regimen, removing drug pressure may encourage the dominant viral quasi-species to revert to wild type, perhaps enhancing (at least temporarily) this patient's response to subsequent regimens.

However, even if immunologic decline were not confirmed, several Panel members would elect Option 1 to discontinuing antiretrovirals altogether. They reasoned that immunologic decline on dual nucleoside therapy is probably inevitable, and that changing the regimen now offers the best chance for delaying future decline and for minimizing the emergence of new resistance mutations.

Advantages:

- Minimizes risk for cumulative antiretroviral toxicity
- Minimizes risk for developing additional resistance mutations
- Provides relief from "treatment fatigue"

Disadvantages:

- High risk of disease progression

## Dosing, Monitoring, and Follow-up Recommendations

- Optimize adherence
- Increase amprenavir dose from 600 mg BID to 750 mg (5 tablets) BID when co-administered with lopinavir/ritonavir (Kaletra). Preliminary pharmacokinetic interaction studies with amprenavir suggest that lopinavir levels may decrease as much as 40% compared to lopinavir alone (1). Although available data regarding the proper dosing of lopinavir is still investigational, an increase to 4 capsules bid of lopinavir appear sufficient to overcome this interaction with amprenavir. This dosage increase is especially warranted when considering the higher serum concentrations appropriate for a salvage regimen and the additional reduction of lopinavir levels that would occur from the P450 enzyme inducing activity of carbamazepine. Monitor closely for toxicity, especially GI, hepatic, and metabolic (hyperlipidemia, insulin resistance)
- PIs (especially ritonavir) are cytochrome P450 3A4 inhibitors and are expected to increase carbamazepine AUC to a clinically significant degree. Consider alternative anti-convulsant medications (e.g., gabapentin), if not contraindicated. If carbamazepine is continued, monitor carbamazepine serum levels carefully and follow closely for toxicity (2). Similarly, the P450 3A4 inducing properties of carbamazepine on reducing lopinavir and amprenavir levels may be significant. An increase in lopinavir levels appears warranted.
- If tenofovir is administered, the dosage is 300 mg po daily. Because didanosine (ddl) levels may be increased, it is recommended that tenofovir be administered 2 hours before or one hour after tenofovir administration. However, clinical toxicity from higher ddl levels has not been reported.

## Selected References

- 1) Bertz R, et al. Assessment of the multiple dose pharmacokinetic interaction between Kaletra (Lopinavir/ritonavir) and amprenavir in healthy volunteers. 3<sup>rd</sup> International Workshop on Clinical Pharmacology of HIV Therapy. Abstract 7.6. Washington, DC. March 2002.
- 2) Kato Y, et al. Potential interaction between ritonavir and carbamazepine. *Pharmacotherapy* 2000; 20:851-54.