
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 50 year old Caucasian male who presented in 3/98 with a CD4 count of 70 cells/mm³, and viral load of 390,000 copies/mL. In 6/98 he began nelfinavir (NFV), lamivudine (3TC), and stavudine (d4T), but in 10/98 his viral load had only decreased to 38,000 copies/mL (CD4 unknown). Genotypic analysis performed in 2/99 was significant for the M184V nucleoside reverse transcriptase inhibitor (NRTI) mutation and the following protease inhibitor (PI) mutations: D30N, M36M/I, and I64V. He continued on his current regimen, and in 6/99 his viral load was 7000 copies/mL. Since that time his viral load has ranged from 1000 to 3000 copies/mL. His most recent CD4 count (8/01) was 475 cells/mm³ and his viral load was 2800 copies/mL. A repeat genotype (9/01) was performed and is shown below. His antiretroviral course is summarized below.

Complicating this case is a history of coronary artery disease with myocardial infarctions x 2, hyperlipidemia, diabetes mellitus, and an aortic valve replacement requiring anticoagulation. His history is also significant for hepatitis C infection, congestive heart failure, asthma/COPD, and a remote history of infective endocarditis from injection drug use. He is a former smoker, and no longer uses injection drugs. In addition to his antiretroviral therapy, his medications include: dapson, benazepril, rosiglitazone, coumadin, atorvastatin, metoprolol, digoxin, ASA, and inhaled bronchodilators.

DATE	REGIMEN *	CD4 cells/mm ³	VL COPIES/ML	RESISTANCE TEST FINDINGS	CLINICAL COURSE
3/98	None	70	390,000		
6/98	D4T, 3TC, NFV				
10/98			38,000		
2/99				M184V, D30N, M36M/I, I64V	
6/99			7,000		
8/01		475	2800		

His primary physician specifically wants to know: 1) Whether he should change therapy now, and 2) What is the likelihood of developing resistance to lopinavir if the current regimen is continued. His goal has been to "save" lopinavir, tenofovir, and the nonnucleosides (NNRTI) for future use.

Resistance Test Findings

(2/99) Key Mutations

NRT	M184V
NNRT	none
PI	D30N, M36M/I, I64V

(9/01) Key Mutations

NRT	D67N, K70R, M184V, K219K/Q,
NNRT	none
PI	L10L/F, D30N, M36I, L63L/P/Q, N88D

Interpretation/Implications for Treatment

This case is illustrative of dilemmas commonly encountered in clinical practice in which decisions regarding antiretroviral therapy must involve careful consideration of serious patient co-morbidities. The patient suffers from coronary artery disease, diabetes, and hyperlipidemia, all of which may be exacerbated by an aggressive "salvage" regimen. In addition, his absolute requirement for anticoagulation complicates treatment decisions, since coumadin interacts with both NNRTI and PI. For these reasons, continuing a partially suppressive and well-tolerated regimen can be considered. However, continuation of this regimen in face of ongoing viral replication will likely lead to acquisition of additional resistance mutations, limiting future therapeutic options and possibly precluding complete viral suppression.

The presence of mutations at codons 67, 70, and 219 (so-called thymidine analog mutations, or TAMs) reflect exposure to zidovudine (AZT) and represent reduced susceptibility to this and other thymidine analogs. The presence of M184V confers high-level resistance to lamivudine (3TC). Although this mutation modestly reduces the resistance to zidovudine and stavudine (d4T) conferred by the 219 mutation, this effect is likely to be of moderate benefit in the face of multiple TAMs. Given the presence of the 3 TAMs, efficacy of any combination of nucleosides is likely compromised. However, recent evidence suggests that high level resistance to tenofovir requires either a mutation at codon 65 or at codons 41 or 210 in the presence of the 3 TAMs. Further, the presence of 184 may confer a slight increase in sensitivity to tenofovir.

In the protease gene, the presence of a D30N mutation signifies significant high-level resistance to nelfinavir, and the secondary mutations at codons 10, 36, 63, confer further loss of sensitivity to this drug. Fortunately D30N does not appear to cause high-level cross-resistance to other protease inhibitors, though, in the presence of a D30N mutation, the mutation at codon 88 may confer some cross resistance to indinavir, saquinavir, and ritonavir. The acquisition of this additional mutation in the interval between this patient's two genotypes highlights the risk of continuation of his current regimen, that is, loss of the opportunity to achieve full viral suppression with future regimens.

In choosing an alternative regimen, a concern is the likelihood of increasing this patient's cardiovascular mortality by exacerbating or causing hyperlipidemia, hypertension, and possibly glucose intolerance. Furthermore, there is considerable potential for causing clinically significant or treatment-limiting hepatotoxicity in a patient with chronic hepatitis C who is concurrently taking a HMGCoA reductase inhibitor (atorvastatin) and rosiglitazone. Drug interactions are another concern. Coumadin metabolism is increased by the addition of an NNRTI, necessitating higher dosages to maintain anticoagulation. The overall therapeutic effects of coumadin is further complicated by the inhibitory effects of the PI on coumadin metabolism, which can potentially lower the effective dosage needed. Despite these risks, the panel believed that a ritonavir-enhanced PI regimen should be recommended.

There was consensus that the NNRTIs should be reserved for future use, for two reasons. The low genetic barrier of this class makes it likely that a virus harboring these 3 TAMs would be at risk of acquiring one of the single RT mutations conferring high-level NNRTI resistance if treatment consisted of a single NNRTI and 2 NRTIs. Conversely, a triple-class regimen may result in sufficient viral suppression to prevent viral evolution, but would probably not result in significant hepatotoxicity and metabolic complications. By using a dual PI-based regimen, the NNRTI class could be reserved for future use when novel agents might become available.

The panel believed that the relative risks of toxicity were similar among the remaining PIs, and members were evenly divided between recommending either a lopinavir/ritonavir (Kaletra™) or indinavir/ritonavir based regimen. A third option, amprenavir/ritonavir, is believed to be less desirable given its poorer tolerability and the limited data for this combination

Recommendations

The majority of the panel members believed that continuation of the current regimen would invariably lead to further accumulation of resistance mutations culminating in high-level multi-drug resistant virus, and therefore, would recommend changing antiretroviral therapy immediately.

A minority (2) believed that they would consider continuation of the patient's current regimen in light of his sustained CD4 increase and low-level viremia. Benefits of this strategy include avoidance of increasing cardiovascular and metabolic complications, potential drug interactions, as well as limiting additional hepatotoxicity. The risks of this strategy are the high likelihood of accumulating further resistance and loss of viral suppression.

Tenofovir (Viread™) should be added, with continuation of lamivudine to perpetuate the M184V mutation. A third nucleoside with possible activity against this virus, such as abacavir, can be considered.

There was consensus that the NNRTIs should be reserved for future use when future novel agents might become available.

Options 1: Change antiretroviral regimen immediately. Options include the following:

lopinavir/ritonavir (Kaletra™), tenofovir, lamivudine, and abacavir or

indinavir/ritonavir, tenofovir, lamivudine, and abacavir or

either of the above PI options with Trizivir™ (AZT, 3tC, abacavir) to limit pill burden.

Advantages: Likely to achieve viral suppression
Reduces risk of accumulating additional NNRTI mutations that may limit usefulness of newer drugs in this class.

Minimizes clinically complex drug-drug interactions with the NNRTI

Disadvantages: High pill burden
Increased risk of gastrointestinal toxicity
May worsen hyperlipidemia
May affect anticoagulation control

Option 2: No change in therapy.

Advantages: Avoidance of increasing cardiovascular and metabolic complications

Avoidance of potential drug interactions

Limiting additional hepatotoxicity

Disadvantages: High likelihood of accumulating further resistant mutations and loss of viral suppression.

Dosing, Monitoring, and Follow-up

Lopinavir/ritonavir (Kaletra™) should be dosed at 400 mg/ 100 mg bid (3 tablets bid)

Tenofovir 300 mg tablet (Viread™) should be dosed at one tablet daily

Lamivudine (Epivir™) should be dosed at 150 mg bid.

Abacavir ((Ziagen™) should be dosed at 300 mg bid.

If employed, indinavir/ritonavir should be dosed at 600 mg/200 mg bid, and Trizivir™ at 1 pill bid.

Viral load should be repeated at 4, 8, and 12 weeks after changing therapy, and liver enzymes should be monitored frequently, such as at 2-4 weeks after changing therapy and monthly thereafter for 3 months. The INR should be monitored as the PI may alter anticoagulation control. As always, the patient should be educated about and monitored for signs and symptoms of abacavir hypersensitivity.