
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

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 patient is a 34 year old gay white male who was diagnosed with HIV infection approximately 10 years ago. His antiretroviral treatment history includes approximately 1 year of monotherapy with AZT and a brief exposure (approximately 2 months) to ddl in the distant past. The patient went off all antiretroviral (ARV) medications for several years and had viral loads as high as 268,000 copies/mL and a nadir CD4 of 112 cells/mm³. He was restarted on ARV therapy in 1999 but he has never reached full suppression of his virus to below levels of detection in plasma (see below).

In October 1999, this patient started combination therapy with abacavir (ABC), stavudine (d4T), and lamivudine (3TC). His HIV viral load decreased to 4,900 copies/mL after 6 weeks. Nevirapine (NVP) was added to this regimen shortly thereafter (January 2000) with further decrease in viral loads to low but detectable levels ranging between 27-400 copies/mL for approximately a year.

During the last 6 months the patient has been experiencing increasing viral loads to approximately 1000 copies/mL two months ago and 5,100 copies/mL most recently (November 2001). The patient's CD4 counts were 136 (17%) cells/mm³ in December 2000, 312 (24%) cells/mm³ in January 2001, and 340 (20%) cells/mm³ most recently in September 2001. The patient is tolerating his current regimen well and not anxious to change medications. However the patient's physician is concerned the virus will become progressively drug resistance on current therapy and has therefore obtained a genotypic resistance test to explore the patient's treatment options.

The patient works full time, feels well and is extremely reluctant to use protease inhibitors (PIs). He has friends who have had significant side effects on PIs and he is particularly fearful of developing lipodystrophy. The patient has told his physician that he would not consider taking PIs unless he started feeling ill or it became obvious that his HIV disease was progressing much more rapidly (e.g. with loss of CD4+ T cells). He would however be open to treatment with a different PI-sparing regimen including the use of non-nucleoside reverse transcriptase inhibitors (NNRTI).

The referring physician is asking for input regarding this patient's treatment options in light of the results from resistance testing and considering the patient's feelings about PIs. In particular, the physician wishes the team's opinion about using delavirdine (DLV) in this circumstance.

DATE	REGIMEN *	CD4 cells/mm ³	VL copies/mL	RESISTANCE TEST FINDINGS
Prior to 1999	AZT monotherapy (1 yr)			
"	ddl (2 months)			
"	No tx for years	112	268,000	
10/99 to 1/00	ABC+d4T+3TC		4,900	
1/00 to 1/01	ABC+d4T+3TC+NVP	136	27-400	

1/01	"	312	"	
9/01	"	340	1,000	
11/01	"		5,100	L74V, Y115F, M184V, G190A

Resistance Test Findings

Key Mutations	
NRT	L74V, Y115F, M184V
NNRT	G190A
PI	none

Interpretation/Implications for Treatment

Genotype interpretation from Specialty Labs:

NRTIs: Resistant to: 3TC, ddl, ddC
 Low resistance to: Combivir (AZT+3TC)
 Sensitive to: AZT, d4T, ABC, Trizavir

NNRTIs: Resistant to: NVP, EFV
 Low resistance to: DLV

PI: No mutations (or evidence of resistance) found

This patient has never received treatment with protease inhibitors and has no evidence of resistance to PIs by genotypic resistance testing. Therefore, a PI-based regimen would offer the greatest chance of fully suppressing this patient's virus. However, this patient has said that he would not consider taking PIs in his current state of health because of concerns about PI-related toxicities. For this reason, switching to a new PI-sparing regimen or continuing a partially suppressive and well tolerated regimen are considered.

This patient has been receiving the non-nucleoside reverse transcriptase inhibitor (NNRTI) Nevirapine for approximately 2 years. His virus has developed the G190A mutation which is associated with high level resistance to Nevirapine and Efavirenz, and at least partial resistance to Delavirdine. It is doubtful that the use of Delavirdine without the addition of other potent agents (eg PIs) would lead to a sustained response. And use of any of the currently available NNRTIs in a less than fully suppressive regimen is likely to eventually lead to full resistance within the NNRTI drug class.

This patient's resistance test reveals several mutations associated with NRTI resistance. The M184V mutation confers high level resistance to lamivudine (3TC). The L74V mutation is associated with resistance to didanosine (ddl) and zalcitabine (ddC). The M184V mutation in combination with other mutations including L74V and Y115F also contribute to abacavir resistance. (This association is not reflected in the resistance report from Specialty Labs.) This patient was previously treated with monotherapy AZT and thus low levels of AZT-resistant virus may be present even though this is not apparent by the current resistance test results. Presence of the M184V mutation may partially reverse the effects of mutations associated with AZT resistance and may also confer a slight increase in sensitivity to tenofovir.

Recommendations

This case illustrates the challenge commonly encountered in clinical practice in individualizing antiretroviral therapy based not only on resistance data and prior treatment history but also on the patient's attitudes about potential drug side effects and his/her likelihood of adhering to a particular regimen.

The panel felt that a PI-based regimen would clearly be the first choice for the goal of attaining maximal viral suppression and reducing the likelihood of progressive resistance. We would favor a ritonavir-boosted PI combination [e.g. Kaletra (Lopinavir+Ritonavir)] for enhanced potency and would optimize the NRTI component of the regimen. Tenofovir should be added with continuation of lamivudine to perpetuate the M184V mutation. Additional nucleosides with possible activity against this virus, such as AZT and/or abacavir, can also be considered and can be conveniently given in a combined formulation (Combivir or Trizavir).

However, the primary care physician has indicated use of PIs is not acceptable to the patient at this point and the patient's concern about drug toxicities, particularly those associated PIs, is an overriding factor. Therefore, we would recommend as an alternative that the patient be switched to another simple and well-tolerated PI-sparing regimen consisting of Trizavir+Tenofovir. The hope is that this strategy might provide an improved response over current therapy while new and less toxic agents are developed.

There was consensus of the panel that the Nevirapine should be stopped and that Delavirdine should be reserved for future use when a more potent backbone of other drugs becomes available. The low genetic barrier of the NNRTI class makes it likely that a virus harboring NRTI resistance would be at risk of acquiring one of the single RT mutations conferring high-level NNRTI-class resistance if treatment consisted of a single NNRTI and 2 NRTIs. Further progression of NNRTI resistance may also compromise the use of 2nd generation NNRTIs in development.

Other options include a) continuing the current, well-tolerated regimen in light of his sustained CD4 increase and low-level viremia or b) stopping all ARV therapy until a more potent and acceptable regimen is available. The panel does not favor either of these approaches. The former will likely lead to progressive resistance and reduced treatment options in the future. The latter could lead to decreased CD4 counts during treatment interruption and should only be done in the context of a closely monitored clinical trial until more is known about this strategy.

Option 1: Change antiretroviral regimen immediately to a double-PI based regimen with optimized NRTIs. Options include the following:

lopinavir/ritonavir, tenofovir, lamivudine, zidovudine and/or abacavir (i.e., Combivir or Trizavir) , or
indinavir/ritonavir, tenofovir, lamivudine, zidovudine and/or abacavir (i.e., Combivir or Trizavir)

Advantages: Likely to achieve complete viral suppression

Reduces risk of accumulating additional resistance mutations that may limit usefulness of newer drugs.

Disadvantages: Unlikely to be acceptable to the patient due to patients concerns regarding PI-associated toxicities

Higher pill burden

Increased risk of lipodystrophy and other toxicities

Option 2: Change antiretroviral regimen immediately to a new PI-sparing regimen with optimized NRTIs. Options include the following:

Tenofovir plus lamivudine, plus zidovudine and/or abacavir (e.g. Combivir or Trizavir)

Advantages: Likely more acceptable to patient
better toxicity profile
Simple, low pill burden
Avoidance of potential drug interactions

Disadvantages: Less likelihood of complete suppression and prevention of accumulating further resistant mutations and loss of viral suppression

Dosing, Monitoring, and Follow-up

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

Tenofovir 300 mg tablet should be dosed at one tablet daily

Lamivudine should be dosed at 150 mg bid.

Abacavir should be dosed at 300 mg bid.

If employed, indinavir/ritonavir should be dosed at 600 mg/200 mg bid, combivir at 1 pill 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. As always, the patient should be educated about and monitored for signs and symptoms of abacavir hypersensitivity.