
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 48 year old Caucasian female who became HIV-infected in 1990 through heterosexual sex. Her CD4 nadir was 250 cells/ μ L. She is HCV negative. Previously, her viral load had been undetectable (VL <400 copies/mL) for several years on an antiretroviral regimen presumed to be Combivir and an unknown protease inhibitor (PI). In 12/00, her VL increased to 11K and she was changed to didanosine (ddI), abacavir (ABC), and Kaletra (lopinavir/ritonavir). She tolerated the regimen well with good adherence but the VL remained detectable (usually about 4K). The CD4 remained stable between 400-500 cells/ μ L until 12/01 when her CD4 count dropped to 320 cells/ μ L. A repeat CD4 in 3/02 was 287 cells/mm with a VL between 10 and 26K. Her current complaints include fatigue and arthralgias. Her provider wants to know if her antiretroviral regimen should be changed? Her treatment course is summarized in the table below.

DATE	REGIMEN *	CD4 cells/mm ³	VL COPIES/ML	RESISTANCE TEST FINDINGS	CLINICAL COURSE
1990	? Combivir +PI	250	<400		
12/00			11K		
1/01	ddI/ABC/Kaletra		4K		Tolerated regimen, good adherence
9/01		540			
12/01		320	5400		
3/02		287	26K	Genotyping 3/4/02 (Quest Diagnostics)	Development of fatigue and arthralgias
3/21/02			10K		
4/19/02				Repeat genotyping	

Resistance Test Findings

Key Mutations (GART 3/4/02 and repeated 4/19/02, Quest Diagnostics)

NRT	M184V, K70G, L210M,
NNRT	None
PI	L63P, I64V

Interpretation/Implications for Treatment

The patient in question has clearly experienced loss of virologic control accompanied by a gradual decrease in CD4 count toward her CD4 nadir. Genotypic analysis (3/4/02) failed to demonstrate mutations associated with high-level resistance. This poses an obvious dilemma: whether the genotype is accurate/reliable or whether other factors could be contributing to loss of viral control through alternative mechanisms, such as inadequate drug exposure due to noncompliance. Thus, as with all patients failing HAART, this patient's adherence should be reassessed. The panel felt that interpretation of the current genotype should be undertaken with caution and concurred that this result was of limited utility in managing the patient.

Loss of viral suppression by a potent regimen in the absence of high-level genotypic resistance has been previously described. Havir, et al, reported viral rebound in 17 patients taking indinavir, lamivudine, and zidovudine without demonstrable indinavir-associated mutations detected at the time of rebound. In 14 of these

cases, the primary mutation observed was M184V in the RT sequence (1). The most straightforward explanation for the lack of concurrence of genotypic analysis and virologic outcome is that the patient may not have been actually taking her ARVs as prescribed. Alternatively, other mechanisms of inadequate drug exposure should be considered, such as the presence of a protease inhibitor efflux pump, malabsorption, or drug interactions. Given the patient's constitutional symptoms, it is also possible that some underlying infectious or neoplastic process is driving viral replication.

It is also possible that the current genotype is inaccurate and has underestimated genotypic resistance in this virus. A recent survey of 34 different laboratories performing HIV-1 genotypic analysis reported a 40% false negative rate in detecting resistance mutations in a pure mutant sample (2). This heterogeneity of accuracy across laboratories was thought to be due to poor quality control rather than differences in technology. Correlation with phenotypic analysis would be of value.

Questions that remain unanswered with regard to the specific mutations observed include: 1) Does K70G potentially play a similar role as K70R in nucleoside reverse transcriptase (NRTI) resistance and has simply not yet been described? 2) Is K70G an intermediate mutation before acquisition of K70R which may have subsequently occurred? The lack of further evolution on the repeat genotype (4/19/02) argues against the latter interpretation.

Fatigue and arthralgias in an HIV-infected patient warrants further evaluation. If her symptoms are related to antiretroviral toxicity, such as NRTI induced-mitochondrial damage and lactic acidosis, it would be prudent to discontinue therapy. Serum lactate should be measured. Other possible explanations, including occult chronic hepatitis, psoriatic arthritis, Reiter's syndrome, depression, and malignancy should be entertained.

Recommendations

Regimen Options

In light of the difficulty in interpreting the current genotype, the panel concurred that phenotypic analysis, if available, be performed with the patient on the current regimen. Concurrently, further work-up of her fatigue and arthralgias should be pursued. Subsequently, her ARVs could be continued, changed, or discontinued. A change in her current regimen without further information would not be recommended at this time.

Option 1: There was a concurrence among panel members that a temporary cessation of therapy be considered. The patient's baseline untreated viral load is unknown. Advantages of temporarily stopping therapy include determination of the baseline viral load and minimizing further antiretroviral toxicity. Obviously an improvement in the patient's symptoms off therapy would suggest drug toxicity as an etiology of her constitutional symptoms and would provide valuable insight into her ability to tolerate future regimens. An obvious disadvantage of therapy interruption would be the potential for further loss of virologic control with a more rapid decrease in CD4 cell count. It has been demonstrated that cessation of therapy in the setting of drug resistance results in recurrence of wild-type HIV which precipitates an often rapid decline in CD4 count to pre-treatment nadir. However, her current CD4 of 297 is already approaching her known nadir, so that it is possible that this disadvantage of therapy interruption is of less importance.

Option 2: Alternatively, therapy could be continued, which would have a lower risk of more rapid loss of CD4 count, but potential disadvantage of possible ongoing antiretroviral toxicity.

References:

- 1) Havlir D, Hellman N, Petropoulos C, et al. Drug susceptibility in HIV infection after viral rebound in patients receiving indinavir-containing regimens. *JAMA*. 2000; 283 (2): 229-234.
- 2) Schuurman R, Brambilla D, DeGroot T, et al. Underestimation of HIV type I drug resistance mutations: Results from the ENVA-2 genotyping proficiency program. *AIDS Res Hum Retroviruses*. 2002; 18 (4): 243-248.

Dosing, Monitoring, and Follow-up Recommendations

It is recommended that the patient be re-evaluated in 4 weeks, and undergo follow-up CD4 and VL measurements at 4 week intervals initially. Further recommendations will be made as the above-mentioned data becomes available in 4 – 6 weeks.