
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

XX is a 42 year old gay male who was diagnosed HIV positive in 1987. He has faithfully taken lamivudine (3TC), nelfinavir (NFV) (3 pills TID per patient preference) and stavudine (d4T) since 1997. His baseline CD4 counts were about 1,500 cells/mm³ (34%). Zidovudine/3TC/NFV was started at a CD4 nadir of 550 cells/mm³ (25%) and a viral load of 35,000 copies/ml (bDNA). In 11/97 with an undetectable viral load, zidovudine was changed to stavudine due to anemia and the rest of his antiretroviral regimen was continued. His viral load remained undetectable, and was <50 copies/ml in 7/99, after which it has ranged between 58 to 258 copies/ml until 12/01. His CD4 count remained consistently above 1,000 cells/mm³ (38%) on treatment. There were no issues of non-compliance. On 7/01/02 the viral load increased to 1,221 copies/ml. On 7/30/02 a genotype was performed along with a viral load. Despite a viral load of only 476 copies/ml, the genotype showed various mutations as outlined below, most notably the D30N, M184V, and the K219Q.

His comorbid conditions include: (1) chronic Hepatitis B carrier for which he received 3 months of interferon in 1984; (2) mild hyperlipidemia with fasting LDL 177 and TG 210 (9/01); (3) a family history of two first degree relatives with myocardial infarctions before age 60; and (4) a 20 pack-year history of smoking which was stopped in 9/01.

His antiretroviral history is as follows.

DATE	REGIMEN *	CD4 cells/m ³	VL COPIES/ML	RESISTANCE TEST FINDINGS	CLINICAL COURSE
8/20/97	AZT/3TC/NFV	550 (25%)	35,000		Severe Anemia, Nausea with AZT
10/22/97	"		<500		
11/10/97	D4T/3TC/NFV				Change AZT to D4T
1/19/98	"	837	<500		Stable Clinical Course on D4T/3TC/NFV
6/1/98	"	875	<500		
10/22/98	"	1155	<50		
3/30/99	"	1254	<50		
7/19/99	"	1073	<50		
3/20/00	"	1110	879		
5/17/00	"		58		

8/19/00	"	1258	142		
11/28/00	"	1092	114		
4/3/01	"	1131	230		
12/13/01	"	1064	216		
4/11/02	"		699		
7/01/02	"		1221		
7/30/02	"		476	Genotype: see below	

Resistance Test Findings

Key Mutations

NRT	D67N, K70K/R, M184V, K219Q
NNRT	
PI	D30N, L63P, N88D

Interpretation/Implications for Treatment

Current antiretroviral guidelines do not recommend drug resistance testing when the viral load is less than 1000 copies/ml because of reduced assay reliability. However, even though the genotype was obtained when the viral load was only 476 copies/mL the panel believed that the genotype results were reliable and consistent with his past antiretroviral history.

The presence of thymidine analog mutations (TAMs) at codons 67, 70, and 219 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), this effect is likely to be of moderate benefit in the face of multiple TAMs. Given the presence of the three TAMs, the efficacy of any combination of nucleosides is likely to be compromised. However, tenofovir DF (TDF) may retain some activity since 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. Furthermore, 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 (NFV), the only PI the patient has been on. Most panel members were concerned that if the patient remained on NFV, cross-resistance to other protease inhibitors might occur. However, one study suggested that patients with the D30N mutation do well virologically even if left on nelfinavir but further investigation is needed.¹

This case is particularly interesting because of the concomitant hepatitis B infection. Specifically, interrupting or modifying his anti-HIV therapy could have a dramatic effect on his chronic active hepatitis B infection. However, at the time of the panel discussion, the activity of the hepatitis B infection was unclear. Therefore, the panel

deliberated the various treatment options that would be appropriate based on the following scenarios: (1) HIV therapy without concomitant hepatitis B infection; (2) Concomitant HIV and Hepatitis B co-infection

HIV Therapy without hepatitis B Co-infection. If hepatitis B infection was NOT a consideration, the majority of panel members believed that stopping his antiretroviral medications would be the optimal choice given the consistency of his high CD4 cells counts. His antiretroviral therapy was originally started at a nadir of 550 CD4 cells, a level considered aggressive by today's treatment standards. However, his primary care physician has indicated that it is likely that the patient will have strong objections to discontinuing all antiretroviral therapy. Therefore, several strategies for educating the patient about treatment interruptions were discussed. These education strategies focused on (1) preserving future treatment options, (2) highlighting the current lack of viral suppression on therapy with its inherent risks of metabolic and cardiovascular toxicity, and lastly (3) the possibility that the patient's own immune status may be sufficient to control ongoing viremia. It would be important to address the patient's apparent need to "do something" to control the virus and explain that not taking meds may be beneficial by allowing his own immune system to control the virus. If therapy were stopped, disease progression, CD4 cell count, and viral load would be carefully monitored and therapy could be restarted at any time in the future if the patient so desired.

Concomitant HIV and Hepatitis B co-infection. However, HIV co-infection with hepatitis B makes treatment much more complex as there are many different issues to consider. Among the issues deliberated by the panel were the impact of single vs. combination antiretroviral therapy on the hepatitis B infection, the likelihood of 3TC resistance in the presence of sustained low-level hepatitis B viremia and the implications for sequencing antiretroviral medications, the potential toxicities of the different therapies on the patient's co-morbidities, and the natural course of the HIV and the hepatitis B free of medications.

The patient converted to e antigen positive in 9/02 from e antigen negative in 4/01 while receiving 3TC, indicating a high likelihood of emergence of a drug resistant strain of HBV. This strain has a mutation in a nucleoside binding site designated the YMDD mutation. Approximately 90% of non-HIV patients with hepatitis B infection develop resistance to 3TC after 4 years of lamivudine monotherapy.² This is consistent with our patient's experience who developed 3TC resistance after receiving several years of therapy. Despite 3TC resistance, there was concern about stopping the 3TC. All patients (not just HIV+) infected with hepatitis B could sustain a "flare" reaction (reactivation) of their hepatitis B when 3TC is stopped --- a common occurrence. In general, the panel decided that 3TC, irregardless of the presence of the M184V and possibly YMDD mutation, should be considered a valuable component of any regimen primarily, for its viral fitness benefits and to prevent the likely possibility of a hepatitis B flare. Therefore, in this patient any treatment interruption would not be a complete interruption but would continue 3TC monotherapy for the reasons stated above. However, most clinicians believed that if a combination of antiretroviral agents with hepatitis B activity (i.e. 3TC+TDF) were given, it would be appropriate to aim for full HIV viral suppression as well.

Currently, there is no published data comparing the advantages and disadvantages of 3TC monotherapy with the combination of 3TC and TDF for the treatment of hepatitis B infection. One abstract suggests that tenofovir has efficacy against hepatitis B in the presence of the YMDD mutation. Therefore, the combination of tenofovir and 3TC in the presence of the YMDD mutation could theoretically, be considered tenofovir monotherapy. Indeed, it should be recognized that given our limited knowledge of the treatment of hepatitis B infection that we might be exposing the patient to sequential monotherapy.

Adefovir 10 mg daily was FDA approved on 9/20/02 for the treatment of hepatitis B based on favorable laboratory parameters. The efficacy of tenofovir for HIV/hepatitis B co-infected patients has shown comparable virologic efficacy to adefovir against hepatitis B but the numbers are too small to be conclusive. To date, the most powerful hepatitis B regimen would be 3TC, tenofovir, and adefovir (which would involve patient assistance applications for non-insured patients). It is important to clarify that the approved lower doses of adefovir have no activity against HIV but appear to have a much lower risk of renal toxicity.

If the patient chooses to treat the hepatitis B with 3TC plus adefovir, or tenofovir, then the preferred regimen of the author is to choose a triple nucleoside HIV regimen. The patient's previous negative experiences and development of anemia would prohibit further administration of zidovudine. However, didanosine (ddI),

stavudine (d4T), and abacavir (ABC) might possibly achieve excellent virologic control. The M184V mutation may still provide hypersusceptibility to d4T and tenofovir. It should be noted that this therapeutic option is possible in this patient because of his overall excellent control of the virus. We would anticipate that even if he did not achieve complete viral suppression, he would derive benefit from containing the virus while preserving future therapeutic options.^{3, 4}

It is worth noting the limitations of our knowledge in making the decisions to “do no harm.” First, we must acknowledge that there appears to be no real “cure” for hepatitis B. Gilead is studying patients who cleared the hepatitis B surface antigen, the e antigen, developed the e antibody and had an undetectable hepatitis viral load. Such patients may still relapse in the setting of corticosteroid therapy.² The duration of therapy remains unknown. Our patient’s clinical course is further complicated by prior treatment with interferon and 3TC and there are some who suggest doing a liver biopsy to assess treatment efficacy. However, unlike treatment for hepatitis C, the relatively benign side effects of the available therapies would lower the threshold for initiating therapy and mitigate against requiring a biopsy. Finally, it should also be noted that unlike hepatitis C, there is no evidence to suggest that the course of hepatitis B is accelerated by HIV or vice versa. More specifically, we do know that there is an overall lower rate of cirrhosis in all hepatitis B patients (with and without HIV). We also know that those who develop cirrhosis have a much greater chance of developing hepatocellular carcinoma but it is unclear if HIV patients tend to develop cirrhosis more often.

Recommendations

Regimen Options: The various treatment options depends on the activity of hepatitis B infection and the need for treatment

If the hepatitis B co-infection is inactive:

Option 1: Stop all ARV medications; or stop all ARV medications and continue 3TC monotherapy

Advantages:

- Preserves ARV treatment options for future use (patient is unlikely to develop additional NRTI-related mutations if 3TC monotherapy is used to control Hepatitis B)
- Reduces exposure to protease inhibitors with their negative cardiovascular effects
- May prevent flare-up of Hepatitis B.

Disadvantages:

- Due to the patient’s bias for ARV treatment, he may not believe that he is receiving appropriate ARV therapy.
- Rebound of VL above baseline and risk of acute antiretroviral syndrome
- Reduction of CD4 cell count below baseline

If treatment of the hepatitis B is a consideration, then several different regimens are viable options

Option 1: Treat the hepatitis B but do not treat the HIV. (e.g. 3TC plus TDF or adefovir)

Advantages:

- Provides effective treatment for hepatitis B
- Well tolerated with minimal side effects

Disadvantages:

- Unlikely to achieve durable suppression of HIV replication
- High potential for the development of additional NRTI-related mutations

Option 2: Treat both the hepatitis B and HIV with a protease-inhibitor based regimen (e.g. TDF + 3TC or other nucleoside plus ritonavir/saquinavir OR lopinavir/ritonavir)

Advantages:

- Likely to achieve complete suppression of HIV replication
- Patient will feel like he's "doing something", about his HIV infection

Disadvantages:

- Exposure to ritonavir will adversely affect lipids
- Using up future options early in treatment for patient who may not yet need it.

Option 3: Treat Hepatitis B and HIV with a nucleoside only based regimen (e.g. 3TC plus d4T plus abacavir, or tenofovir)

Advantages:

- May achieve complete viral suppression
- Preserves other antiretroviral classes (e.g. PI and NNRTI) for future use.

Disadvantages

- May not achieve viral suppression of HIV
- Preserves other antiretroviral classes (PI and NNRTI) for future use
- May not be sufficiently potent

Option 4: Treat hepatitis B and HIV with a NNRTI based regimen (e.g. 3TC plus abacavir, tenofovir, or stavudine plus efavirenz)

Advantages:

- Likely to achieve complete viral suppression

- Patient will feel like he's "doing something", about his HIV infection

Disadvantages:

- Development of rapid resistance to the NNRTIs and loss of future NNRTI use
- Does not preserve NNRTI class for future use with T-20. (the best combination therapeutic regimen to sequence in the future).

Dosing, Monitoring, and Follow-up Recommendations:

Viral load should be repeated at 4, 8, and 12 weeks after stopping or changing therapy. A fasting lipid panel should be repeated and treated if necessary. The hyperlipidemia should be treated with a statin, either pravastatin or atorvastatin. Simvastatin and lovastatin should be avoided in combination with protease inhibitors due to the risk of myalgias and rhabdomyolysis. A fasting lipid panel should be monitored three to six months after beginning a statin. The patient should be re-evaluated for cardiovascular risk factors, including smoking.

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1. Sugiura W, Matsuda Z, Yokomaku Y et al. Interference between D30N and L90M in selection and development of protease inhibitor resistant human immunodeficiency virus type 1. *Antimicrob Agents Chemother* 2002 March; 46:708-15.
 2. Personal communication with Dr. Bradley Hare, MD, SFGH
 3. Hammer S et al. Dual vs Single Protease Inhibitor Therapy Following Antiretroviral Treatment Failure. *JAMA* 2002 (July 10);288: 169-180
 4. Tebas P, Patrick AK, Kane EM et al. Virologic response to a ritonavir-saquinavir containing regimen in patients who had previously failed nelfinavir. *AIDS* 1999;13:F23-F28.