
HIV Resistance Testing Consultation Service

Consultation Report

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Disclaimer:

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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 38 year-old male who was diagnosed with HIV infection in Brazil. His pre-treatment CD4 nadir is unknown. In Brazill, he was started on zidovudine (AZT) and zalcitabine (ddC), later switched to AZT and lamivudine (3TC), and eventually changed to a protease inhibitor-based regimen. He remains naïve to non-nucleoside reverse transcriptase inhibitors. Despite incomplete viral suppression with most of his regimens, his CD4+ T cell counts have remained stable in the 200-350 range. He underwent a brief treatment interruption in 2000 and had a rapid increase in viremia (to > 100,000 copies/mL) and a rapid decrease in CD4 cell counts. His past medical history includes a history of hepatitis B infection, sinusitis X 9 year, syphilis, depression, intermittent diarrhea, knee pain, and viral meningitis. His antiretroviral history is summarized below.

DATE	REGIMEN	CD4 cells/mm3	VL	COMMENTS
8/13/96	AZT/ddC	332 (20%)	8603	C/o fatigue and aphthous ulcers
9/30/96		285(19%)	18,130	C/o insomnia, fatigue, nausea, aphthous ulcers
10/15/96	Stop ddC, change to AZT + 3TC			
2/14/97		256 (21%)	12,520	
5/2/97		264 (21%)	22150	
8/13/97	Stop AZT/3TC due to nausea	221 (12%)	16,860	
9/15/97	Start ddl 200 bid, d4T 20 mg bid, nelfinavir (NVF) 750 TID	285	7550	Resolution of nausea, feels well on testosterone injections
12/30/97		311 (23%)	47,250	
3/398	ddl/d4T/NFV 1250 mg bid		47260	Missed 3-4 pills/wk; diarrhea due to campylobacter
4/14/98		282 (22%)	15,710	
5/22/98		272 (24%)	20,700	
9/22/98		283	10,657	

12/07/98			28228	
3/16/99		189 (17%)	45,672	Diarrhea 6-7X/day on immodium, (+) Entamoeba. coli
5/26/99				St. John's wort, forgets to take ddl
7/19/99		214 (16%)	34793	
10/8/99		201 (16%)	81002	
1/7/00	STOPPED ARV	189	59,435	
3/6/00		181 (11%)	109,675	
3/21/00	Start abacavir (ABC), d4T, indinavir 800 mg bid and ritonavir 200 mg bid			Tolerating new regimen, missed one dose in one month
7/17/00		359 (17%)	6336	Start effexlor for depression
1/23/01		215 (15%)		C/o diarrhea
4/25/01		354	12,429	? lipoatrophy
11/28/01		399	45,077	
4/22/02		328 (18%)	79,232	↑ LFTs (t.bili 1.5/303/729/173)

Resistance Test Findings

(Gladstone 5/10/02) Key Mutations

NRT	M41L, D67N, V118I, T215Y
NNRT	None detected
PI	L10V/F, M36I, I54V, L63P, A71V, V82T, L90M

Interpretation/Implications for Treatment

This patient has been on multiple antiretroviral regimens during the last six years without ever achieving complete viral suppression. The history of incomplete viral suppression could be attributed to several factors, including sequential "monotherapy", intermittent non-adherence, malabsorption due to multiple episodes of

infectious and non-infectious diarrhea, and drug interactions with St. John's wort. He also complains intermittently of fatigue, depression, peripheral neuropathy, and most recently, had asymptomatic elevations in his transaminases that are resolving. Despite virologic failure, he has remained immunologically stable with CD4 counts in the mid 300's and has had no opportunistic infections

Although therapy has clearly failed to achieve an optimal virologic response, the patient appears to maintain some degree of partial viral suppression while on therapy. The optimal management of patients with persistent viral replication and stable CD4 T cell gains (often referred to as "discordant" responses) remains controversial. Although both immunologic and virologic benefit may persist for years in such individuals, ongoing viral replication in the presence of drugs will likely result in the accumulations of additional mutations, thus limiting future treatment options.

The patient's genotype is consistent with his antiretroviral history. The genotypic resistance assay reveals the presence of three nucleoside analogue mutations (NAM's), M41L, D67N, and T215Y. This pattern is consistent with significant resistance to most if not all non-3TC nucleoside analogues, with the possible exception of tenofovir. Clinical trials indicate that tenofovir's activity would be impaired in patients who exhibit three or more NAMS, including either the M41L or L210W.

The presence of the V118I mutation confers low-level resistance to lamivudine (3TC) when accompanied by several NAMS. 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 reveals multiple protease inhibitor (PI)-associated mutations, Mutations at positions V82T and L90M are likely to confer cross-resistance to saquinavir (SQV), nelfinavir (NFV) and—to a lesser extent—all other protease inhibitors.. The presence of multiple mutations (L10V/F, M36I, I54V, I63P, A71V; V82T and L90M mutations) suggests that high level resistance exist to all currently available PI, including ritonavir/lopinavir (Kaletra). High level resistance to ritonavir/lopinavir (Kaletra) has been reported with as few as 4 mutations (Prado et al. AIDS 2002)

As expected, there are no mutations detected to the non-nucleoside reverse transcriptase inhibitors (NNRTI)

The treatment history, clinical course, and genotype resistance test results all suggest that this patient harbors a virus that has significantly diminished susceptibility to currently available NRTI and PI agents. Combining NRTIs and PIs with an NNRTI might result in durable suppression, but the likelihood that such a regimen will achieve durable viral suppression is low. 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, unpredictable drug-drug interactions and the risk of losing the NNRTI class.

Recommendations

Regimen Options:

The following discussion assumes that enfuvirtide (t-20) is either not available, or that the patient would prefer not to use this drug at this time. If T-20 were an option, then combining T-20 with an NNRTI (e.g., efavirenz or nevirapine) and recycled NRTIs and PIs would be a reasonable option.

In the absence of T-20 as an option, the likelihood of complete viral suppression with a new regimen is low. The therapeutic options include (1) continuing the same regimen; (2) stopping therapy; and (3) changing therapy.

OPTION 1: Continue the current regimen pending the availability of enfuvirtide (T-20). The majority of the panel members believed that the most appropriate option at this time would be to maintain his current antiretroviral regimen of abacavir, stavudine, ritonavir, and indinavir. This regimen is affording some clinical benefit without increasing toxicity and is well tolerated. It is unlikely that his elevated transaminases are due to his current regimen since the transaminases are resolving on its own without a therapy change. Repeat hepatitis serology for hepatitis B and C may be helpful. If lipoatrophy is documented, then changing the stavudine to another NRTI should be considered.

ADVANTAGES

- Tolerable regimen
- Avoids additional toxicities and side effects of a new regimen
- Maintenance of immunologic function for the past 2 years
- Preserve effective agents (e.g. NNRTI, tenofovir) for use with newer agents (e.g. T-20)

DISADVANTAGES

- Ongoing virologic and immunologic failure
- Less likely to maintain CD4 cell counts for long periods of time
- Potential for engendering additional antiretroviral resistance

OPTION 2: Stop all antiretroviral therapy, follow closely, and restarting antiretroviral agents (e.g. tenofovir, lamivudine, efavirenz, and T-20) when there is a significant decline in CD4 cell counts (e.g. below 300 cells/mm³). A minority of the panel considered this to be a reasonable option. Stopping all antiretrovirals would allow a shift to wild type virus and potentially enhance his sensitivity (at least temporarily) to existing antiretroviral agents. An treatment interruption may also allow time for newer agents to become available (e.g. T-20).

ADVANTAGES:

- Avoids medication toxicity and side effects
- Improved quality of life and reduced pill burden
- Repopulation of sensitive wild type virus and enhance potential for viral suppression
- Restoration of CD4 count and reduction of viral load back to pre-treatment interruption levels likely when new antiretroviral agent started.

DISADVANTAGES

- Loss of immune restoration
- Viral rebound
- HIV viral syndrome

- No guarantee that CD4 and VL will return to on-therapy levels

OPTION 3: Change regimen with a goal of reducing drug exposure and its associated toxicity. This was the option least favored by the panel members. If lipoatrophy is documented, then changing d4T or stopping the NRTI class may be considered to maintain sensitivity for future treatment options and reduce toxicity. Most would not favor the addition of a NNRTI at this time in order to preserve the NNRTI for use with T-20 or other newer agents that become available.

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

No special dosing requirements are needed with these treatment options. If therapy is interrupted, then close monitoring (e.g q 3-4 weeks) of CD4 count and viral load measurements are recommended

Lamivudine and efavirenz should be given at their standard doses of 300 mg once daily and 600 mg qd respectively. Tenofovir is administered as 300 mg, one tablet daily. All the ARV should be administered with food. If available, T-20 or enfuvirtide is dosed at 90 mg SQ BID.