
HIV Resistance Testing Consultation Service

Consultation Report

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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

This is a 38-year-old HCV-infected man who was diagnosed with HIV infection in Brazil. His pre-treatment CD4 nadir is unknown. In Brazil, he was started on sequential mono- and dual-nucleoside analogues in the 1990s, and switched to a nelfinavir-based regimen in 1997 and a ritonavir-based protease inhibitor regimen in 2000 (see Table). Due to persistent drug-resistant viremia, he switched to a dual-protease inhibitor-based regimen in 2004 and remained on this regimen until 2007, when he stopped all drugs. He remains naïve to non-nucleoside reverse transcriptase inhibitors (NNRTI). Although he has never achieved complete virologic suppression, his CD4+ T cell counts have remained in the 200-350 cells/mm³ range, with a most recent CD4 cell count of 234 (one month after stopping drugs). . Of note, he had one extended treatment interruption in the late 1990s, at which point his off-therapy viral load was > 100,000 and his CD4 was 181 cells/mm.

His transaminases have been elevated since 2000 and he had an episode of jaundice in June 2007 due to anabolic steroids. His antiretroviral drugs (ARVs) were stopped 8/25/07 due to slightly worsening liver function tests (LFTs). He is clinically asymptomatic and has never had an opportunistic infection.

His past medical history includes a history of untreated hepatitis C infection diagnosed in Nov 2002, sinusitis X 9 year, syphilis, depression, intermittent diarrhea, knee pain, and viral meningitis.

His adherence is currently good, although he was noncompliant early in his antiretroviral therapy. He would like to avoid using enfuvirtide (T-20) if possible.

DATE	REGIMEN	CD4 cells/mm ³	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	
3/3/98	ddl/d4T/NFV 1250 mg		47260	Missed 3-4 pills/wk; diarrhea

	bid			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 effexor 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 GART done 5/17/02
11/14/02		331	67,751	HCV AB+
5/23/03		225	166,417	
11/19/03		243	121,702	

3/30/04		201	65,936	GART 3/3/04
4/6/04	Start tenofovir/trizivir/ saquinavir 200 mg 5 tabs bid, lopinavir/r 3 bid			
6/8/04		287	15,480	
8/03/04		317	18,195	
3/28/05	Change Invirase® to 500 mg, 2 bid	243	8,291	
11/30/05		245	10,920	
4/11/06		295	14,666	
4/05/07		333	3697	
6/11/07		284	7303	↑ LFTs Tbili 1.2 (D 0.7) AST 98, ALT 144 Alkphos 164 HCV VL =8,518,119 c/mL AFP 7.2% Albumin 4.1
7/13/07	Stop all ARVs	221		GART 7/13/07
8/24/07		234	11,025	↑ LFTs Tbili 2.5 (D 1.8) AST 421, ALT 375 GGT 326 Alkphos 162

Resistance Test Findings

(Gladstone 5/17/02) Key Mutations

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

Gladstone 3/3/04

NRTI	M41L, D67N, V118I, T215Y
NNRTI	None detected
PI	L10V/F, M36I, M46I/M, I54V, L63P, A71V, V82T, L90M

Gladstone 7/13/07

NRTI	M41L, D67N, V75M, F77L, V118I, M184V, T215Y, K219R, K101Q
	None detected
	L10F, I13V, I15V, K20T, M36I, K43KT, M46I, F53LF, I54V, I62V, L63P, A71V, T74S, V82T, L89IL, L90M, I93L

Phenosense 8/20/07

Nucleosides	Cut-off	Fold-Change	Assessment
Abacavir	4.5-6.5	10	Resistant (R)
Didanosine	1.3-2.2	2.5	R
Emtricitabine	3.5	> max	R
Lamivudine	3.5	>max	R
Stavudine	1.7	5.06	R
Tenofovir	1.4-4	2.57	Partially sensitive
Zidovudine	1.9	165	R

NNRTIS Sensitive

Protease Inhibitors

Atazanavir	2.2	332	R
ATV/r	5.2	332	R
Darunavir/r	10-90	4.31	Sensitive
Fosamprenavir/r	4-11	18	R
Indinavir/r	10	121	R
Lopinavir/r	9-55	166	R
Nelfinavir	3.6	>max	R
Ritonavir	2.5	>max	R
Saquinavir/r	2.3-12	>max	R
Tipranavir/r	2-8	12	R

Viral replication capacity = 22% (range 14-36%)

Panel Questions:

- 1) Since he is NNRTI naive, is ritonavir-boosted DRV plus an NNRTI sufficient? Should two or three fully-active agents be used? Should one of the newer classes of agents (CCR5 inhibitor, integrase inhibitor) be added to improve antiviral activity?
- 2) What are the risks of NNRTI toxicity in this untreated HCV-HIV co-infected patient?

Interpretation/Implications for Treatment

This HCV- and HIV-co-infected patient has been on multiple antiretroviral regimens during the last eleven years without ever achieving complete viral suppression. His CD4 nadir is unknown, but he has had several documented CD4s below 200 cells/mm. His history of incomplete viral suppression is likely due to the use of suboptimal regimens as well as intermittent non-adherence. Other possible factors include malabsorption due to multiple episodes of infectious and non-infectious diarrhea, and previous drug interactions with St. John's wort. Despite virologic failure on his previous ARV regimen of tenofovir (TDF, Trizivir® (zidovudine, lamivudine, abacavir), ritonavir boosted lopinavir (LPV/r, Kaletra®) and saquinavir (SQV, Invirase®), he has remained immunologically stable with CD4 counts in the mid 300s. He currently feels well and his adherence has been excellent during the past few years.

Although therapy has clearly failed to achieve an optimal virologic response, this patient appears to maintain some degree of partial viral suppression while on a dual-boosted protease inhibitor (PI) regimen. 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 status may remain stable 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 three genotypes and phenotype are consistent with his ARV history. Of interest, the genotypic mutation patterns were similar in 2002 and 2004, showing further accumulations of mutations in 2007. The genotypes are notable for the presence of several nucleoside analogue mutations (NAMs), including M41L, D67N, T215Y, and K219R. This pattern is consistent with significant resistance to most if not all non-3TC nucleoside analogues. Tenofovir's activity would be impaired in patients who exhibit three or more NAMS, including either the M41L or L210W. The M184V mutation is also present and is consistent with high-level resistance to lamivudine (3TC, Epivir®) and emtricitabine (FTC, Emtriva®). Overall, these genotypes and phenotype show high-level resistance to all of the FDA-approved NRTIs. Of note, this does not rule out residual partial activity of these drugs, as has been discussed in prior cases.

The absence of nonnucleoside reverse transcriptase mutations (NNRTI) is consistent with his treatment exposure.

The resistance tests also revealed several significant protease inhibitor (PI)-associated mutations, (L10F, M36I, M46I, I54V, L63P, A71V, V82T, L90M). These data, as well as the

recent phenotypic data, suggest that high level resistance to most of the currently available PI, with the notable exception of ritonavir-boosted darunavir (DRV/r, Prezista®). His genotype show none of the 10 mutations (V11I, V32I, L33F, I47V, I50V, I54M/L, G73S, L76V, I84V L89V) known to impair DRV/r's activity, and the recent phenotype is consistent with measurable but limited changes in the fold-change in IC50. Based on our current understanding regarding the cutoffs for the PhenoSense, ritonavir-boosted darunavir remains a fully-active protease inhibitor for this patient.

The tropism assay or Trofile®, shows a CCR5-tropic virus and indicates that maraviroc (MAV, Selzentry®) should be fully active. The MOTIVATE 1 and 2 trials found that maraviroc, when combined with other effective agents, resulted in sustained viral suppression.^{1,2}

Raltegravir (Isentress®, RAL), the first FDA approved integrase inhibitor, is another fully-active drug for this patient. BENCHMRK 1 and 2 showed that a raltegravir-based regimen achieved viral load reduction to < 50 copies/ml at 16 weeks in approximately 60% of treatment experienced patients (as compared to 30% of those receiving placebo).^{3,4} Raltegravir is particularly attractive due to its favorable tolerability, minimum risk of drug interactions, and BID dosing.

In summary, the treatment history, clinical course, and genotype resistance test results all suggest that this patient harbors a virus that has significantly diminished susceptibility to most currently available NRTI and PI agents. Combining NRTIs and PIs with an NNRTI might result in durable suppression, but durable viral suppression can not be assured, so another agent such as raltegarvir would likely be needed.

As always, in choosing which ARV 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 (especially hepatotoxicity), unpredictable drug-drug interactions, and the risk of losing the NNRTI class. Despite these concerns, the panel believed that the optimal approach would be to switch as soon as possible to a fully-suppressive regimen, which for this patient would likely include at least two tolerable NRTIs and at least three fully active ARVs. Fully active agents would include enfuvirtide, efavirenz and nevirapine, maraviroc, and raltegravir (investigational at the time of this report). Since the patient has several viable ARV options, enfuvirtide could be preserved for future use.

Although his HCV infection is untreated and his liver function tests (LFTs) are mildly elevated, the panel believed that an NNRTI should still be tried and his LFTs closely monitored. The risk of efavirenz-induced hepatotoxicity in patients with HCV coinfection is about 11%, and is less than observed with nevirapine.^{5,6} In some HCV-co-infected patients, interferon/ribavarin treatment might be necessary before starting ARVs to reduce the risk of ARV hepatotoxicity.⁷ Maraviroc also carries a black box warning on hepatotoxicity but this risk appears less than with the NNRTIs..

Recommendations

Regimen Options:

All three options include NRTIs, ritonavir/darunavir, an NNRTI, and one additional active agent. At the time of the report, raltegravir was still investigational. There is no consensus on how to use NRTIs in patients with extensive resistance to these drugs; however, based on clinical experience and small pathogenesis-oriented studies, most would recommend that between 2 and 4 NRTIs be used in this patient. The most aggressive approach is outlined below.

OPTION 1: Trizivir® one tablet twice daily plus tenofovir (Viread®) 300 mg po once daily plus efavirenz (Sustiva®) 600 mg orally once at bedtime plus maraviroc (Selzentry®) 150 mg po bid plus darunavir (Prezista®) 300 mg; 2 tablets twice daily plus ritonavir (Norvir®) 100 mg one tablet bid orally.

OPTION 2: Trizivir® one tablet twice daily plus tenofovir (Viread®) 300 mg po once daily plus raltegravir (Isentress®) 400 mg po bid plus maraviroc (Selzentry®) 150 mg po bid plus darunavir (Prezista®) 300 mg; 2 tablets twice daily plus ritonavir (Norvir®) 100 mg one tablet bid orally.

OPTION 3: Trizivir® one tablet twice daily plus tenofovir (Viread®) 300 mg po once daily plus raltegravir (Isentress®) 400 mg po bid plus T-20 (Fuzeon®) 90 mg SQ bid (if patient willing) plus either efavirenz (Sustiva®) 600 mg po daily OR maraviroc (Selzentry®) 300 mg bid po

ADVANTAGES OF ALL TREATMENT OPTIONS

- High likelihood of complete viral suppression and immunologic benefits
- Contains at least three fully active agents

DISADVANTAGES

- High pill burden
- Risks of hepatotoxicity and other drug toxicities
- Potential for engendering additional PI or raltegravir resistance
- Potential for emergence of dual mixed or X4 virus with maraviroc
- Option 3: requires T-20 subcutaneous injections twice daily which patient would like to avoid

Monitoring, and Follow-up Recommendations

Monitor CD4 count every 2-3 months and HIV RNA very frequently (every 1 month) until undetectable.

Monitor adverse effects of antiretrovirals, including complete blood count, lipid panel, blood glucose, serum creatinine, liver function tests, potential for drug interactions

Trizivir®: GI side effects

Tenofovir: serum creatinine, urinalysis

Darunavir: GI side effects, dyslipidemia, hyperglycemia, hepatitis

Enfuvirtide: subcutaneous nodules

Maraviroc: jaundice, LFT, rash

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