
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

A 53-year-old Latina woman was diagnosed HIV in 1985. Her risk factors include heterosexual sex and a blood transfusion. Her self-reported CD4 nadir is 193 cells/mm² (date unknown). She has never had an AIDS-defining complication. Her adherence to medications is believed to be excellent. Her current physician has been following her since 2/02.

The patient's medical history is complicated by diabetes and hyperlipidemia (untreated, with total cholesterol 300s in 2002). She has had a history of elevated creatine kinase (CK) levels and myopathy; these were sometimes coincident with prescriptions of statins but also occurred when she was not taking statins. Due to a recent string of elevated CK levels, zidovudine (AZT, Retrovir®) she was removed from her current regimen of Trizivir® (abacavir, zidovudine, lamivudine) + nelfinavir (NFV, Viracept®). Without the AZT, her CK normalized. Recently, a spot urine sample was sent and she was noted to have near-nephrotic range proteinuria and was referred for a renal consult.

The details of her treatment exposure and response are outlined below. Of note, she received sequential suboptimal regimens in the pre-HAART era, and then received a series of partially suppressive protease inhibitor-based regimens between 1996 and 2007. Her viral load during this time was generally detectable but very low (< 1000 copies RNA/mL). Her CD4 has been greater than 400 cells/mm³ for several years. Although she has no known exposure to the nonnucleoside reverse transcriptase inhibitor (NNRTIs), her prior treatment history is not well documented and she has had evidence of NNRTI resistance on her resistance tests.

DATES	REGIMEN	CD4	VL	RESISTANCE TEST FINDINGS	CLINICAL COURSE
late 1980s	AZT monotherapy				
Unk 1990s	DDI/AZT				
1990s	DDI/AZT/SQV/r				Only brief course – d/c SQV d/t adv fx
1990s	DDI/AZT/RTV				x 1 yr
5/01	AZT/3TC/ABC/NFV				
2/13/02		473	86		Patient joined current practice
5/20/02		434	732		
11/02	AZT/3TC/ABC/NFV/TDF				Intensification with TDF for low level viremia
2/03		427	328		LDL: 202 HDL: 31 Total chol: 300
8/13/03	AZT/3TC/ABC/NFV	513	879		TDF d/c no virologic improvement

3/24/04	AZT/3TC/ABC/NFV	559	271		
9/29/04	AZT/3TC/ABC/NFV	572	853	PT/GT drawn: RT: M41L, D67N, K70R, M184V, T215F, K219Q, G190A, PR: L10I, G16E, K20I, G48V, L63H, A71I, T74S, V77I, V82A, L90M	
3/22/05	AZT/3TC/ABC/NFV	679	1207		
9/20/06	AZT/3TC/ABC/NFV	433	903		
8/20/07	AZT/3TC/ABC/NFV	443	958		
9/26/07	AZT/3TC/ABC/NFV				Random urine Albumin <u>2493</u> CK, total <u>470</u> ; (pt not on statin)
10/10/07	AZT/3TC/ABC/NFV				CK, total 1010 U/L (39-189)
10/24/07	3TC/ABC/NFV			Trofile completed: CCR5+ PT/GT drawn: - essentially unchanged, minor evolution in PR (will bring copy). PT shows sens to darunavir, tipranavir, and partial sens to fosamprenavir	Attempted to remove AZT to see if CK drop
1/30/08					Urine protein *100, renal consult
2/12/08		475	996		Cr: 0.44 mg/dL (0.42-1.06) CK, TOTAL 157

AZT = zidovudine (Retrovir®)
 3TC = lamivudine (Epivir®)
 ABC = abacavir (Ziagen®)
 ddl = didanosine (Videx EC®)
 TDF = tenofovir (Viread®)
 NFV = nelfinavir (Viracept®)
 SAQ/r = ritonavir boosted saquinavir (Invirase®)
 RTV = ritonavir (Norvir®)

Resistance Test Findings

2004 Key Mutations

NRT	M41L, D67N, K70R, M184V, T215F, K219Q
NNRT	G190A,
PI	L10I, G16E, K20I, G48V, L63H, A71I, T74S, V77I, V82A, L90M

2007 Key Mutations

NRT	M41L, D67N, K70R, M184V, T215F, K219Q
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NNRTI	G190A,
PI	L10I, I13V, G16E, K20I, G48V, L63H, A71I, T74S, V77I, V82A, L90M

Phenotype: 9/29/04: Virologic

	Fold Change	Sensitivity		Fold Change	Sensitivity
NRTI			NNRTI		
ABC	5.13	Reduced susc	DLV	0.11	Sens
ddI	1.49	Sens	EFV	0.90	Sens
FTC	>MAX	Reduced susc	NVP	12	Reduced susc
3TC	>MAX	Reduced susc	PI		
D4T	1.88	Reduced susc	ATZ	71	Reduced susc
AZT	14	Reduced susc	FAPV	6.33	Reduced susc
TFV	1.12	Sens	LPV	8.30	Sens
			NFV	78	Reduced susc
			RTV	60	Reduced susc
			SQV	>MAX	Reduced susc

Phenotype: 10/4/07 Virologic

	Fold Change	Sensitivity		Fold Change	Sensitivity
NRTI			PI		
ABC	7.46	Resistant	ATZ/r	94	Resistant
ddI	1.53	Resistant	DRV/r	1.40	Sens
FTC	>MAX	Resistant	FAPV/r	4.43	Partially Sens
3TC	>MAX	Resistant	IDV/r	39	Resistant
D4T	1.59	Sens	LPV/r	5.32	Sens
AZT	30	Resistant	NFV	77	Resistant
TFV	1.34	Sens	RTV	68	Resistant
			SQV/r	>MAX	Resistant
NNRTI			TPV/r	0.78	Sens
DLV	0.16	Sens			
EFV	1.31	Sens			
NVP	25	Resistant			

Interpretation/Implications for Treatment

This case features a pan-resistant HIV virus in a patient who is immunologically stable with persistent low level viremia. The most surprising aspect of her resistance data is the presence of the G190A mutation, which confers high level resistance to nevirapine (NVP, Virammune®) and perhaps hypersusceptibility to delavirdine (DLV, Rescriptor®).¹ The question is how did this patient acquire this mutation? It was retained in the 2007 genotype, so it is unlikely to be a mistake. As G190A rarely occurs as a polymorphism it likely emerged at one point due to exposure to an NNRTI. However, this

patient states that she has never been treated with an NNRTI. It is unlikely it occurred via transmitted resistance because this patient was diagnosed long before these drugs became available. Superinfection with an NNRTI-resistant also seems unlikely, as this is an exceedingly rare chronic disease and has not been reported in patients who are receiving treatment. A Swiss cohort examined a number of patients with chronic HIV infection after loss of control or low level viremia and found that they had divergent viruses.² However, this cohort did not have access to HIV-positive partners to prove the divergent strains were due to superinfection. Other research teams also have reported examples of chronically HIV-infected patients who had low level superinfection.³ The panel believed that the patient likely received an NNRTI before but simply forgot or an NNRTI could have been given her via a medication error where nevirapine was given erroneously for nelfinavir. The panel noted that a medication error such as nelfinavir/nevirapine substitution is particularly dangerous due to the ease with which NNRTI resistance is created.⁴ The panel also agreed that although the G190A does not result in high level phenotypic resistance to efavirenz, there are no data suggesting efavirenz can work after nevirapine failure, so alternatives to efavirenz would be needed.

This virus has acquired a large number of protease inhibitor (PI) mutations. G48V is somewhat unusual in that it generally occurs during treatment with high dose unboosted saquinavir, or saquinavir-soft-gel. L90M likely emerged during the patient's treatment with ritonavir-boosted saquinavir (SAQ/r).¹ Evolution in protease (PR) mutations from the 2004-2007 genotypes has been minor. The only new PR mutation the virus has acquired since 2004 is I13V. Despite the apparent lack of potency with her most recent regimens, the patient's CD4 counts have remained stable and her viremia has remained low-level. The mechanism for the persistent benefit in face of high level drug resistance is likely multifactorial, and includes reduced fitness and/or higher HIV-specific T cell responses.

This patient is technically only two ARV class-experienced (PI and NRTI) but carries a single NNRTI mutation. She is naïve to enfuvirtide (T20, Fuzeon®) and raltegravir (RAL, Isentress®), and her co-receptor tropism test demonstrates sensitivity to maraviroc (MAV, Selzentry®).

The patient has many options for full suppression. Because of these ample options, the current Department of Health and Human Service (DHHS) HIV guidelines would suggest that she should switch to a new regimen rather than maintain the same non-suppressive regimen.⁵ However, there is not much guidance on the optimal construction of this regimen, and it is not clear how to balance the potential benefits associated with viral suppression versus the risk for toxicity in this patient with multiple co-morbidities.

One approach in constructing a regimen for a patient with pan-resistance and co-morbidities would be to first consider constructing regimens which would optimally treat the virus, then modify the regimens based on patient specific characteristics and potential toxicities. Studies in salvage patients recommend utilizing an optimized background which contains a boosted protease inhibitor. The patient's virus is nearly suppressed on an unboosted PI, therefore, it is likely that any boosted PI will be effective. Based on the patient's phenotype, potential protease inhibitor options include tipranavir/ritonavir, lopinavir/ritonavir, and darunavir/ritonavir. 48-week data from the phase 3 TITAN study compared lopinavir/r and darunavir/r in treatment naïve and experienced patients, and found that darunavir generally performed better than lopinavir.⁶

Although a boosted-PI based regimen alone may suppress the patient's virus, most panel members would add one to two more fully active drugs to improve regimen durability. There are no head-to-head studies of maraviroc, raltegravir, etravirine, or T20. Though the studies are not directly comparable, raltegravir appears to be the most potent of those options. Analyses from the BENCHMARK 1 and 2 trials at 48 weeks demonstrated sustained HIV viral suppression < 50 copies/mL in 45-50% of patients even when there were no active agents (by genotype and phenotype sensitivity scores) in the optimized background therapy⁷. Etravirine (ETR, Intelence®) also demonstrated favorable responses in treatment-experienced patients with 56% in the etravirine group achieving undetectable VL at 24

weeks compared to 39% in the placebo group.^{8,9} Though G190A was one of 13 identified etravirine resistance mutations, the drug is still likely to be active because substantial benefit was seen in patients harboring less than three NNRTI mutations.¹

Maraviroc is another potent "second" line option for this patient. The patient's Trofile® test was performed when the viral load was less than 1000 copies/mL, increasing concern if the assay was sensitive enough to pick up CXCR4-using HIV virus. If maraviroc is desired, it may be reasonable to wait for the ultrasensitive Trofile® assay which is scheduled to be released in Summer 2008. The current assay will pick up 50% of the strains if CXCR4 is present at 10% while a new ultrasensitive test will pick up the strains 50% of the time if they are present at a level of 1% (this latter test may become available in the summer of 2008). Although T20 remains a potent salvage option, it is often undesired by patients, despite studies demonstrating that satisfaction with subcutaneous injection does not impair quality of life.¹⁰

In addition to the boosted PI and second fully active agent, there is the question of whether a third fully active agent should be added to the regimen. This additional medication would likely increase the durability and effectiveness of the regimen but would also increase pill burden and (potentially) toxicity.

The optimal regimen to treat the HIV virus must consider the patient's many co-morbidities to minimize toxicity. Of particular concern is her cardiovascular status. Her last cholesterol tests were performed in 2002 – the panel recommended rechecking fasting lipid tests and agreed that she still required aggressive statin therapy. The patient is currently on an abacavir-containing regimen, and the panel discussed whether she should continue it due to the potential association between cumulative plus recent abacavir use and MI in the DAD study.¹¹ Although the overall prevalence of MI was low in the cohort (1.6%), the relative risk of having an MI was 1.9 (p=0.0001) for those taking abacavir. The panel commented that it would be more concerned about maintaining abacavir in the regimen if the patient had had a previous MI, and suggested calculating her Framingham 10-year risk score. If she is in the high risk group, abacavir discontinuation should be considered. This does not leave many options for an NRTI backbone given the patient's intolerance to AZT and concerns about tenofovir use with her proteinuria.

In previous findings, the DAD study group found that protease inhibitor use increased the risk of MI 16% for every year of treatment.¹² The panel discussed whether a PI-sparing regimen should be considered for someone with significant CV risk. One example would be a combination of NRTI, etravirine, maraviroc, and raltegravir. Theoretically, there is no reason that a regimen such as this should not be effective; however, only few studies have evaluated PI-sparing regimens in salvage therapy. Earlier studies of the integrase inhibitor elvitegravir (which did not allow a PI due to potential for drug interactions), did not fare well.

Recommendations

Regimen Options

OPTION 1: Darunavir/ritonavir plus etravirine plus lamivudine (DUET)

- PROS: Likely to achieve viral suppression
- CONS: Associated PI toxicities such as hyperlipidemia; may not be as durable as 3 active agents

OPTION 2: Darunavir/ritonavir plus etravirine (DUET) + raltegravir + lamivudine

- PROS: More likely to be effective and durable compared to above regimen
 - CONS: Increased pill burden and potentially increased side effects due to administration of additional agents
- OPTION 3: Etravirine plus maraviroc plus raltegravir plus lamivudine
- PROS: Likely will achieve viral suppression, PI sparing regimen
 - CONS: No evidence to support this regimen

Dosing, Monitoring, and Follow-up Recommendations

- Dosing
 - Regimen 1: Darunavir one 600mg tablet orally twice daily + one 100mg ritonavir capsule orally twice daily + etravirine two 100mg tablets twice daily + lamivudine 300mg tablet once daily. Take with food. Monitor: LFTs, BUN, CR, lipids, glucose, rash
 - Regimen 2: Darunavir one 600mg tablet orally twice daily + one 100mg ritonavir capsule orally twice daily + raltegravir one 400mg tablet twice daily + lamivudine 300mg tablet once daily. Take with food. Monitor: LFTs, BUN, CR, lipids, rash
 - Regimen 3: raltegravir one 400mg tablet twice daily + etravirine two 100mg tablets twice daily + maraviroc one 300mg twice daily + lamivudine 300mg tablet once daily. Monitor: LFTs, BUN, CR, lipids, glucose, rash
- Lipid recommendations: Obtain new fasting lipid profile. Establish plan to monitor lipids. Continue pravastatin regimen titration to achieve LDL goals < 100 and monitor for toxicity. Consider titrating statin and achieving significant lipid control prior to initiating new ARV therapy.

¹ Johnson VA, Brun-Vézinet F, Clotet B, et al. Update of the Drug Resistance Mutations in HIV-1: 2007 Topics in HIV Med 2007 (15);4: 119-125

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³ Koelsch K, Smith DM, Little SJ et al. Clade B HIV-1 superinfection with wild-type virus after primary infection with drug-resistant clade B virus. *AIDS* 17(7):F11- F16, 2003.

⁴ [Bangsberg DR, Acosta EP, Gupta R, Guzman D, Riley ED, Harrigan PR, Parkin N, Deeks SG.](#) Adherence-resistance relationships for protease and non-nucleoside reverse transcriptase inhibitors explained by virological fitness. *AIDS* 2006 20:223-231

⁵ Panel on Antiretroviral Guidelines for Adult and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 29, 2008; 1-128. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed March 9, 2008

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- ⁶ Madruga JV, Berger D, McMurchie M, Suter F, Banhegyi D, Ruxrungtham K, Norris D, Lefebvre E, de Béthune MP, Tomaka F, De Pauw M, Vangeneugden T, Spinosa-Guzman S; TITAN study group. Efficacy and safety of darunavir-ritonavir compared with that of lopinavir-ritonavir at 48 weeks in treatment-experienced, HIV-infected patients in TITAN: a randomised controlled phase III trial. *Lancet*. 2007 Jul 7;370(9581):49-58
- ⁷ Cooper D, Gatell J, Rockstroh J, et al. 48-Week results from BENCHMRK-1, a phase III study of raltegravir in patients failing ART with triple-class resistant HIV-1. 15th Conference on Retroviruses and Opportunistic Infections. February 3-6, 2008. Boston.
- ⁸ Lazzarin A, Campbell T, Clotet B, Johnson M, Katlama C, Moll A, Towner W, Trottier B, Peeters M, Vingerhoets J, de Smedt G, Baeten B, Beets G, Sinha R, Woodfall B; DUET-2 study group. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomised, double-blind, placebo-controlled trial. *Lancet*. 2007 Jul 7;370(9581):39-48.
- ⁹ Madruga JV, Cahn P, Grinsztejn B, Haubrich R, Lalezari J, Mills A, Pialoux G, Wilkin T, Peeters M, Vingerhoets J, de Smedt G, Leopold L, Trefiglio R, Woodfall B; DUET-1 study group. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomised, double-blind, placebo-controlled trial. *Lancet*. 2007 Jul 7;370(9581):29-38.
- ¹⁰ Green J, Klienman L, Ciesla G, Huang H, Wintfeld N, Revicki D. Subcutaneous injection survey: psychometric evaluation of a treatment satisfaction instrument associated with a novel HIV medication. *HIV Clin Trials*. 2002 Sep-Oct;3(5):387-95.
- ¹¹ Sabin C, Worm S, Weber R, et al. Do thymidine analogues, abacavir, didanosine and lamivudine contribute to the risk of myocardial infarction? The D:A:D study. 15th Conference on Retroviruses and Opportunistic Infections. February 3-6, 2008. Boston. Abstract 957c
- ¹² D:A:D Study Group. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med*. 2007;356:1723-1735.