
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

The patient is a clinically well HIV-infected 12-year-old boy with a dropping CD4 and poorly suppressed virus.

The patient was born in 1996 to a mother who received zidovudine (AZT) monotherapy throughout pregnancy and who had a viral load of 43,000 copies/mL at the time delivery. He has been on antiretroviral therapy most of his life. Prior regimens include AZT and didanosine (ddl) monotherapy, dual nucleoside therapy, and eventually a series of standard combination regimens, as described below. His viral load has been detectable on most of these regimens. Of note, he had one very low viral load in 1/07 that occurred six weeks after adherence counseling and the initiation of directly observed dosing; the virologic response was short-lived, however.

The patient was off all medications between 3/04-7/06. During this time, his viral load was stable in the 20-30,000 copies/mL range, but his CD4 count dropped from 1100 to 394cells/mm³. Antiretrovirals were restarted in 2006 and a recent call to the pharmacy showed a very consistent pattern of refills every 60 days as expected.

In 2/07, the clinician contacted the HIV Warmline for advice. Based on the data available at that time, and based on a consultation and discussions with the family, the patient was placed on tenofovir (TDF), Trizivir (TZV), and ritonavir-boosted darunavir. He has remained clinically stable and has been very close to 100% adherent (he misses 1-2 doses/month). However his CD4 count has continued to drop and his viral load is now rising to a current value of 48,700 copies/mL

The family is now open to trying raltegravir (RAL), maraviroc (MVC), or enfuvirtide (T20). A Trofile test was performed, but was not able to be interpreted by the lab.

DATE	REGIMEN *	CD4 cells/mL	VL c/mL	RESISTANCE TEST FINDINGS	CLINICAL COURSE
1996	Neonatal AZT	5372 (30-40%)	592K		
4/96- 6/97	ddl	1800 - 4673 (28-38%)	72K - 622K		
6/97 - 3/99	d4T/3TC	1300-2500 (24-38%)	<400x1 - 318K	GART 4/98	
3/99 - 12/03	d4T/3TC/NFV	1100-1900 (30-35%)	2580 - 26K	Virtual phenotype 6/03	
12/03-3/04	d4T/ddl				

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3/04 - 7/06	Off all meds	394-1100 (11-25%)	7100-53K	PART 5/04	
7/06 – 4/08	TDF/EFV/LPVr	263-525 (9-14%)	2200-63K	Phenosense GT 7/07	
4/08 – present	TDF/TZV/DRVr	249 - 9% 249 - 8% 181 - 6% 119 - 5%	7,580 (before new regimen) 17,658- 12,528 48,767	Phenosense GT 8/08	

3TC =lamivudine (Epivir®)
AZT = zidovudine

d4T= stavudine (Zerit®)

ddl= didanosine (Videx®)

DRV/r = darunavir (Prezista®)

EFV = efavirenz (Sustiva®)

LPV/r = lopinavir/ritonavir (Kaletra®)

NFV= nelfinavir (Viracept®)

TDF= tenofovir (Viread®)

TZV = zidovudine/lamivudine/abacavir
(Trizivir®)

Resistance Test Findings

Key Mutations

GART 4/98 (on d4T/3TC)

NRTI	70, 135, 184 (specific amino acid substitutions not noted in report)
NNRTI	103
PI	71

Virtual Phenotype 6/03 (on d4T/ddI/nelfinavir)

NRTI	69ins, 70R, 118I, 219Q (interpretation: resistant to AZT)
NNRTI	103R
PI	10I, 20I, 36I, 46I, 58E, 71T, 74S, 88S (interpretation: resistant to indinavir, ritonavir, nelfinavir)

Phenotype 5/04 (off meds for one year – fold changes noted)

NRTI	ABC 0.96, ddl 0.83, FTC 1.83, 3TC 1.49, d4T 1.00, TDF 0.88, ZDV 1.33 (interpretation: pan-sensitive)
NNRTI	DLV 0.30, EFV 0.25, NVP 0.28 (interpretation: pan-sensitive)
PI	ATV 11 (reduced sensitivity), f-APV 0.47, IDV 8.63 (reduced sensitivity), LPVr 2.51, NFV 38 (reduced sensitivity), RTV 1.28, SQV 1.89 (reduced sensitivity)

Phenosense GT 7/07 (on TDF, EFV, Kaletra)

NRTI	67G, 69TN, 118I, 219Q ABC 0.94, ddl 0.98, FTC 2.02, 3TC 1.40, d4T 1.07, TDF 0.87, ZDV 1.37 (Net assessment: pan-resistant)
NNRTI	103R, 106V/I/M, 179V/D, 190A DLV 0.26, EFV >max, NVP >max (Net assessment: pan-resistant)
PI	10I, 13V, 20I, 36I, 46M/I, 63L/P, 71T, 74T/S, 88N/S ATV 1.16 (resistant), DRV 0.73, f-APV 1.14, IDV 1.43 (resistant), LPVr 1.38, NFV 3.62 (resistant)), RTV 1.76, SQV 1.48, TPV 0.66

Phenosense GT 8/08 (on TDF, TZV, DRV, RTV)

NRTI	67G, 69TN, 118I, 219Q ABC 0.84, ddl 0.95, FTC 1.38, 3TC 1.03, d4T 0.92, TDF 0.71, ZDV 0.71
NNRTI	103R, 106/I/M, 179V/D, 190A DLV 0.68, EFV >max, ETV 0.33, NVP >max
PI	10I, 13V, 20I, 36I, 71T ATV 0.71, DRV 0.42, f-APV 0.31, IDV 0.95, LPVr 0.89, NFV 2.18 , RTV 1.03, SQV 0.74, TPV 0.59

Interpretation/Implications for Treatment

The patient has extensive drug resistance, which is common in many young people who were perinatally infected in the 80's and 90's, and who received sequential suboptimal treatment regimens. He has no activity in the NRTI or NNRTI classes and limited options in the PI class.¹ He remains naïve to newer drug classes such as the entry inhibitors (T20, maraviroc) and integrase inhibitors (raltegravir). Given the lack of ongoing drug development, his next regimen will likely be his last chance to achieve durable viral suppression. The clinician, patient and family

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will need to balance the need to quickly and durably suppress the virus using a multi-drug regimen with adherence and tolerability issues, including those specific to adolescence.

The composite genotypes show multiple mutations in the NRTI class, including the 69 insertion complex, which, together with the thymidine analogue mutations (TAMS, i.e. 67, 70, 219) confer high-level resistance to all NRTIs. The M184V mutation confers high-level resistance to 3TC and FTC; however one of these drugs is often continued in "salvage" regimens as (1) the drugs have residual direct activity even if M184V is present, (2) the M184V mutation increases susceptibility to AZT and TDF and (3) the M184V mutation reduces viral fitness.²⁻⁴

The patient has multiple NNRTI mutations including the K103N mutation which confers resistance to the older generation of NNRTI drugs (NVP, EFV). Unfortunately, he also has the 179 and 190 mutations, which would reduce the efficacy of the new NNRTI, etravirine (ETR).⁵ However, in the Duet study, which placed patients with at least one NNRTI mutation on a regimen of ETR and DRVr with an optimized background regimen, patients had a 56-62% chance of achieving an undetectable viral load at 24 weeks.⁶

The PI class is affected by the multiple mutations, though both genotype and phenotype analyses show that some options (including darunavir, which he failed) may still work.

This case brings to light a number of interesting points as it pertains to when and how to switch therapy. First, the tropism assay failed to yield an interpretable result. This is seen sometimes, even with a high viral load. It may be due to loss of sample viability during shipping, or it may be due to unusual virus sequences that prevent PCR amplification. The panel recommended repeating the test.

Second, the patient has been recently experiencing an acute drop in CD4 count despite having a viral load in the same range for a long time. It suggests that there may have been a tropism switch (i.e. R5 to X4, the more virulent strain), or he may have a concurrent illness. The panel recommends evaluating the patient for subclinical herpes or other infections that may be causing his CD4 to drop.

Third, the most recent resistance tests indicate that darunavir is fully active. Such a potent drug might be expected to suppress HIV in absence of drug-resistance, and yet in this presumably adherent patient the virus remained consistently high. This raises the question of whether the patient is achieving adequate blood darunavir levels, which might explain the discordance between the in vitro and in vivo results. The panel recommended obtaining darunavir trough levels before any changes to the regimen. If drug levels are low, they should be addressed before a new regimen is started.

After assessing these considerations, the panel suggested a new regimen consisting of 2-3 fully active drugs with an NRTI backbone that included at least 3TC (or FTC) with one other drug from this class (i.e. Trizivir, Epzicom, or Truvada). If a tropism assay were obtained that showed exclusive R5 tropism, then MVC could be exchanged for another drug in the regimen, such as T20.

Recommendations

Regimen Options

Option 1: NRTI backbone (Truvada, Epzicom, Trizivir) and DRVr, RAL, ETR (etravirine) and T20.

Pros – If all drugs are used (including T20), then this regimen includes at least 2 new agents (RAL, T20), one partially effective agent (ETR) and one agent that should be effective based on the drug resistance data (DRV), although it needs to be emphasized that the DRV failed for unclear reasons in the past. This regimen also includes nucleoside analogues, which are known to have activity even in presence of some drug resistance.

Cons – This regimen includes 3 active agents only if one assumes that ETR or DRV are fully active. This would be expected based on the resistance tests, however the panel is concerned that drug levels may be low given the lack of viral suppression when the patient was on DRV before. The regimen includes T20 which is an injectable agent. Use of multiple agents may impact adherence.

Option 1: NRTI backbone (Trizivir, Epzicom, Truvada) and DRVr, RAL and ETR.

Pros – This regimen is the same as the prior one without the addition of T20, which may make the regimen easier to tolerate.

Cons – The regimen may not have sufficient potency to fully suppress viral replication.

Dosing, Monitoring, and Follow-up Recommendations

1. SHAFER R. Genotypic testing for HIV-1 drug resistance (HIV InSite Knowledge Base Chapter). Available at: <http://www.hivinsite.com/InSite?page=kb-03&doc=kb-03-02-07>. Accessed 2/2/09.
2. BACK NK, NIJHUIS M, KEULEN W, et al. Reduced replication of 3TC-resistant HIV-1 variants in primary cells due to a processivity defect of the reverse transcriptase enzyme. *Embo J* 1996;15:4040-9.
3. GOTTE M, ARION D, PARNIAK MA, WAINBERG MA. The M184V mutation in the reverse transcriptase of human immunodeficiency virus type 1 impairs rescue of chain-terminated DNA synthesis. *J Virol* 2000;74:3579-85.
4. ROSS L, PARKIN N, CHAPPEY C, et al. Phenotypic impact of HIV reverse transcriptase M184I/V mutations in combination with single thymidine analog mutations on nucleoside reverse transcriptase inhibitor resistance. *Aids* 2004;18:1691-6.
5. VINGERHOETS J, AZIJN H, FRANSEN E, et al. TMC125 displays a high genetic barrier to the development of resistance: evidence from in vitro selection experiments. *J Virol* 2005;79:12773-82.
6. MADRUGA JV, CAHN P, GRINSZTEJN B, et al. Efficacy and safety of TMC125 (etravirine) in treatment experienced HIV-1 infected patients in DUET-1: 24 week results from a randomized, double-blind, placebo-controlled trial. *Lancet* 2007; 370: 29-38.