

---

# HIV Resistance Testing Consultation Service

## Consultation Report

Co-Chairs: Steven G. Deeks, MD  
Betty J. Dong, Pharm.D

Panel Members: Richard Aranow, MD  
Lawrence Boly, MD  
Brad Hare, MD  
Amy Kindrick, MD, MPH  
Jason Tokumoto, MD

Project Director: Ronald H. Goldschmidt, MD

---

**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

The patient is a 15-year-old male who was vertically infected in 1991. Records are available only from 1996, at which time the patient was diagnosed with AIDS based on lymphoid interstitial pneumonia (LIP). The patient has had no other opportunistic infections. His CD4 nadir is 18 cells/mm<sup>3</sup>. Clinically, the patient is currently doing well while receiving zidovudine (AZT), stavudine (D4T), and ritonavir boosted fos-amprenavir (fos-APV/r). His most recent CD4 cell count was 881cells/mm<sup>3</sup> and his most recent HIV viral load was 61,000 copies/mL. He reportedly has had a hypersensitivity reaction to abacavir (ABC). He also has developed some evidence of lipodystrophy. Of note, there have been problems with adherence in the past. The patient is under the care of his mother (released from prison one year ago) and grandfather. In November of 2005, there was a case conference discussion about making a CPS referral. The caller indicated that since the case conference, adherence has improved. The antiretroviral history is as follows:

DATE	REGIMEN *	CD4 cells/mm <sup>3</sup>	VL COPIES/ML	RESISTANCE TEST FINDINGS	CLINICAL COURSE
1996-1997	3TC, ritonavir (RTV)	18 to 454	38000 to <400		CD4 454 and HIV RNA<400 c/mLwhen switched to 3TC, ddl, RTV
1997-2001	3TC, ddl, RTV	514 up to 1000 to 422	10000 to <400	Genotype—see below	CD4 422 and HIV RNA <400 c/mL when switched to ddl, efavirenz (EFV),RTV
2001-2004	ddl, RTV, EFV	262-825	<50 to 1500	Genotype –see below	Initially on ABC, EFV, RTV but had hypersensitivity reaction. CD4 390 and HIV RNA 330 c/m when switched to AZT, d4T, fos-APV/r
11/04	AZT, d4T, fos-APV/r	356	1200	Phenosense GT-see below	
1/05	same	552	2800		
3/05	same	910	110		
6/05	same	575	5300		
11/05	same	598	?	Phenosense GT-see below	

2/06	Same	310	490		
3/06	Same	881	1500	Genotype: below	see
5/06	Same	not done	61000		

Caller's questions:

- (1) What antiretroviral therapy to administer to achieve complete viral suppression?
- (2) Is this patient "really" sensitive to nucleoside reverse transcriptase inhibitors (NRTIs)?

## Resistance Test Findings

**Oct 2001**—genotype (Specialty Labs) on ? 3TC, ddI, RTV with a low HIV RNA (?):

NRTI: **M184V**

NNRTI: **none**

PI: **L10V, K20R, M36I, I54V, V82A**

**July 2004**—genotype (Specialty Labs) on ddI, EFV, RTV with HIV RNA 19,000 c/m:

NRTI: **none**

NNRTI: **K103N**

PI: **L10V, K20R**

**Dec 2004**—Phenosense GT(Virologic) on AZT, d4T, fos-APV/r with HIV RNA 1200 c/m:

NRTI: **none**

NNRTI: **K103N**

PI: **L10V, K20R, M36I, I54V, L63P, V82A**

Fold change: ddl 0.99 3TC 0.81 d4T 0.73 AZT 0.40 TDF (tenofovir) 0.54  
ATZ 3.79 Fos-APV 2.16 Kaletra 21 Saquinavir 1.98

**Nov 2005**—Phenosense GT (Monogram) on AZT, d4T, fos-APV/r with HIV RNA 2000 c/m.

Results similar to Dec 2004 Phenosense GT

**May 2006**-genotype (Specialty Labs) on AZT, d4T, fos-APV/r with HIV RNA 61,000 c/m

NRTI: **none**

NNRTI: **K103N**

PI: **L10V, K20R, M36I, I54V, L63P, V82A**

## Interpretation/Implications for Treatment

**Is the virus sensitive to the nucleoside analogues (NRTIs)?** Despite poor virologic control on several NRTIs, the only NRTI mutation observed was on a genotype performed in 2001 while on lamivudine (3TC). As expected, this resistance test demonstrated the presence of the M184V mutation, which confers genotypic resistance to 3TC and emtricitabine (FTC). Since this first genotype, 3TC has been stopped and subsequent genotypes and phenotypes have shown disappearance of the M184V mutation. Nevertheless, the M184V mutation is likely archived and the patient is therefore unlikely to get a full response to either 3TC or FTC. An advantage of the M184V mutation is the existence of a “less fit virus”. The panel believed that the “dominant” plasma virus is likely sensitive to other NRTIs but low levels of NRTI mutations might exist (resistance testing can not routinely identify resistance that exist on less than 10 to 30% of the population).

**NNRTIs.** Due to the patient’s incomplete response to an EFV-based regimen, the patient’s virus has a K103N mutation and is therefore highly resistant to all currently available NNRTIs.

**Protease inhibitors.** The genotype and phenotype suggest partial or high level resistance to several protease inhibitors, including lopinavir. It is less clear if the virus is susceptible to either tipranavir or darunavir, the protease inhibitors now most commonly used in highly experienced patients (see below).

## Recommendations

Antiretroviral strategy suggestions:

**(1) Avoid the combination of zidovudine(AZT) and stavudine(d4T).**

The co-administration of the nucleoside combination of AZT and d4T (both thymidine analogues) should be avoided due to poor immunologic and virologic response. The Department of Health and Human Service Guideline for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents” (10/10/06, [www.aidsinfo.gov](http://www.aidsinfo.gov)) state that the combination of zidovudine and stavudine “should not be offered at any time—no exceptions.” Because both drugs require intracellular phosphorylation by the

cellular enzyme thymidine kinase, competition for this enzyme could occur. In-vitro, AZT has a >100-fold higher affinity for this enzyme than d4T and therefore, there is a theoretical risk for antagonism. Clinically, in one study, patients receiving the combination nucleoside backbone of d4T and AZT showed a progressive decline in their CD4 cell count (median of 22 cells/mm<sup>3</sup> below baseline after 16 weeks of administration).<sup>1</sup> Of note, it is possible that the co-administration of these two drugs may have led to reduced exposure and loss of NRTI-associated mutations.

**(2) Obtain phenotype for tipranavir (TPV) and darunavir (DRV)**

There are several genotypic algorithms to determine resistance to these two protease inhibitors (PI), none of which are easy to interpret. The phenotype results can better clarify resistance or sensitivity to these two agents.

Monogram's PhenoSense lower and upper cutoffs for these PI are as follows:

Tipranavir: 2 – 8 fold

Darunavir: 10 – 40 fold

Virco's VircoTYPE HIV-1 (Virtual Phenotype) ranges are as follows:

Tipranavir: 141.8 – 204.5 fold

Darunavir: 5.8 – 8.1 fold

Significant resistance mutations for these drugs are outlined below. The genotype suggests that the patient's virus remains at least partially susceptible to these drugs.

<i>Tipranavir only</i>	<i>Both PIs</i>	<i>Darunavir only</i>
L10V		
		V11I
I13V		
K20M/R/V		
		V32I
	<b>L33F</b>	
E35G		
M36I		
K43T		
M46L		
	<b>I47V</b>	
		I50V
I54A/V	<b>I54M</b>	I54L
Q58E		
H69K		
		G73S
T74P		
		L76V
V82L/T		
N83D		
	<b>I84V</b>	
		L89V

## Regimen Options

### 1. **Lamivudine monotherapy (pending the availability of other therapeutic drug options)**

Because the current CD4 cell count is high, the patient is young, and there are concerns about poor adherence, the panel considered the possibility of 3TC monotherapy as a potential treatment option. In selected patients, 3TC monotherapy has been shown to maintain clinical and immunological status while avoiding the development of further resistance in non-adherent patients. Viral rebound is also lower when compared to structured treatment interruption.<sup>2</sup> In addition, lamivudine is well tolerated.

**Pros:** Provide a respite from taking medications and avoiding potential side effects. Lack of ongoing viral evolution and loss of future drug options.

**Cons:** With a nadir CD4 count of 18 cell/mm<sup>3</sup>, there is a possibility that removal of some drug pressure may lead to rapid fall in CD4+ T cell counts. Lamivudine monotherapy is not considered "standard of care."

**Follow-up:** Lamivudine monotherapy will require close monitoring of the patient's CD4 cell count and clinical status. In addition, specific CD4 and/or HIV viral load parameters that would trigger restarting antiretroviral therapy should be pre-determined.

**2. Three nucleoside analogues + a boosted protease inhibitor (possibly fully suppressive without using all available options)**

(a) AZT+ 3TC (Combivir™) 1 bid + tenofovir (Viread™) 300mg once daily + darunavir (Prezista™) 600mg bid /ritonavir 100mg bid or tipranavir (Aptivus™) 500mg bid /ritonavir 200mg bid (depending on phenotype results). The rationale for including 3TC in the nucleoside backbone is that lamivudine is generally well tolerated and the M184V mutation confers a "less fit virus" that can phenotypically increase sensitivity to zidovudine and tenofovir.<sup>3</sup>

Side effects: fatigue, gastrointestinal side effects, headache, rash

Toxicities: bone marrow suppression, renal toxicity, hepatotoxicity, hyperlipidemia, lipodystrophy

**Pros:** Avoids the use of enfuvirtide (T-20). Reasonable chance for complete and durable viral suppression.

**Cons:** Assumes there is no low level nucleoside genotypic resistance. Increased likelihood of drug toxicities, high pill burden. Possible virologic failure and loss of future drug options.

**Follow-up:** Monitor HIV viral load and CD4 cell count about one month after starting the above antiretroviral regimen. Monitor also for drug toxicities

**3. Three nucleoside analogues + enfuvirtide(T-20) + either an integrase inhibitor(MK-0518) or etravirine (TMC-125) (with or without a boosted PI) (most likely to achieve full suppression, but leaves no future drug options and is not well tolerated)**

(a) Combivir 1 bid + tenofovir 300mg daily + enfuvirtide (T-20) + either MK-0518 (integrase inhibitor) or etravirine (2<sup>nd</sup> generation NNRTI). This combination will ensure that the regimen contains two active agents irrespective of the concern for low level nucleoside genotypic resistance. In addition, this combination is preferable if it is not possible to determine tipranavir or darunavir resistance through phenotype testing. Both MK-0518 and etravirine are available through expanded access programs. For MK-0518, the phone number is 1-877-327-6751 and for etravirine the phone number is 1-866-889-2074.

Side effect of enfuvirtide (T-20): injection site reaction

Side effects of MK-0518: nausea, headache, diarrhea, fatigue, dizziness, ↑bilirubin and amylase

Side effects of etravirine: nausea, diarrhea, rash

**Pros:** High likelihood of viral suppression due to two new ARV classes if fully adherent.

**Cons:** There will be a significant delay before all of these options are readily available. Enfuvirtide (T-20) is an injection bid and this could be an issue in this young patient with a history of non-adherence. There are limited safety and efficacy data on MK-0518 and etravirine in this age group

**Follow-up:** Monitor HIV viral load and CD4 cell count about one month after starting the antiretroviral regimen. Monitor for drug toxicity.

- 
- 1 Havlir DV, Tierney C, Friedland GH et al. Concise Communication: In vivo antagonism with zidovudine plus stavudine combination therapy. *J Infect Dis* 2000;182:321-5.
  - 2 Castagna A, Danise A, Menzo S. et al. Lamivudine monotherapy in HIV-1 infected patients harboring a lamivudine-resistant virus: a randomized pilot study (E-184V Study). *AIDS* 2006;20:795-803.
  3. Deeks SG, Wrin T, Liegler T, et al. Virologic and Immunologic Consequences of Discontinuing Combination Antiretroviral-Drug Therapy in HIV-Infected Patients with Detectable Viremia. *N Engl J Med*. February 15, 2001 2001;344(7):472-480.