

---

# HIV Resistance Testing Consultation Service

## Consultation Report

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

Panel Members: Richard Aranow, MD  
Teri Liegler, PhD  
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 41-year-old man with HIV who was diagnosed in 1991 after an evaluation for lymphadenopathy. He was previously on HAART as well as interleukin-2 (IL-2), but has been off HAART since 2006. His most recent CD4 was 1019 cells/mm<sup>3</sup> and his most recent viral load was 4477 copies/mL (in 2/08). He is interested in restarting HAART in order to meet criteria for clinical trials requiring him to be on a suppressive antiretroviral (ARV) regimen.

The patient states he was initially treated with a regimen of stavudine (d4T) + interleukin-2 as part of a clinical trial; lamivudine (3TC) was added six months later, and nevirapine (NVP) one year after that. He was changed from NVP to efavirenz (EFV) in 1999, but did not tolerate it, and resumed nevirapine. Zidovudine (ZDV) was substituted for stavudine at that time. He arrived to his current clinic in 7/00 on a regimen of Combivir® (ZDV3TC)/nevirapine and IL-2 (which was being cycled q12-18 months). He maintained a high CD4 count on IL2 despite a persistently detectable viral load.

Because of his low-level viremia, in 3/06 the patient's regimen was changed to a once-daily regimen of Truvada® (tenofovir/emtricitabine) plus ritonavir/atazanavir, and he achieved an undetectable viral load. Shortly after the medication change he developed a pruritic, diffuse papulopustular rash that was attributed to his use of atazanavir and anabolic steroids. Kaletra® (lopinavir/ritonavir) was substituted for the boosted atazanavir in 5/06, but no follow-up labs were obtained before the patient began to have problems with medication adherence due to GI intolerance.

The patient has had no opportunistic infections. His past medical history is notable for prehypertension, asthma, chronic low back pain, hypogonadism, anxiety, hiatal hernia, ventral hernia, upper GI bleed in 2000 with peptic ulcer seen on EGD. He also has carpal tunnel syndrome. There is no history of viral hepatitis. He has mild hypertriglyceridemia off antiretroviral drugs (fasting cholesterol 242 mg/dl, HDL 49 mg/dl, LDL 143 mg/dl, triglycerides 251 mg/dl); fasting glucose was 103 mg/dl.

The patient had previously complained of chronic abdominal pain and bloating, with intermittent diarrhea and constipation (2005-2006). This was worked up extensively with a negative barium swallow, abdominal ultrasound, CT scan, EGD and colonoscopy; antispasmodics were not tolerated and/or not effective. He was diagnosed with likely Irritable Bowel Syndrome, although it was noted that several other medications (including ARVs) may be contributing to poor bowel motility. A trial of tegaserod (Zelnorm®) in 8/06 gave little improvement. The patient's symptoms improved after stopping antiretroviral drugs. Over the next several months, the patient took his antiretroviral drugs sporadically.

In 6/07, because of persistent viremia, as well as a high-nadir CD4 count, the patient's antiretroviral drugs were stopped, with a plan for close follow-up of his CD4 and viral load.

His current medications are omeprazole, celecoxib, carisoprodol (Soma), gabapentin, fluoxetine, alprazolam at bedtime, albuterol MDI, salmeterol, testosterone cypionate IM, acetaminophen/hydrocodone PRN.

ARV history is as follows:

CASE NUMBER  
 PANEL CLINICIAN:

DATE

DATE	REGIMEN *	CD4 cells/mm <sup>3</sup>	VL COPIES/ML	RESISTANCE TEST FINDINGS	CLINICAL COURSE
1992	d4T + IL2, then 3TC, then NVP added				
7/00	CBV/NVP	1488	50		first labs available
11/00 – 1/05	CBV/NVP	866 -- 1708	83 – 12,019 (mostly 100-800)		
3/05	CBV/NVP	956	3870		6/05: last IL-2 cycle
9/05	CBV/NVP	1060	147		
2/06	CBV/NVP	1281	111		3/06: changed to TRV/RTV/ATV (no genotype available)
4/06	TRV/RTV/ATV	823	<75		5/06: changed to TRV/Kaletra
					10/06: self-DC'd meds, then sporadic use
2/07	No ARVs	657	1024		Sporadic ARVs
6/07		968	1982		ARVs were stopped
9/07		867	2005		
10/07		643	856		
12/07		455	1831		Nadir CD4
2/08		1019	4477		
3/08	No ARVs			Genotype (see below)	HLA B57-01: negative. Co-receptor tropism assay: R5-tropic

**Questions:**

The patient understands that his HIV does not need treatment urgently given his high current CD4+ T cell count, but he strongly wishes to enroll in a clinical trial for which he needs to be on a suppressive regimen. He understands the risks and benefits of the trial medication and of resuming HAART. Given his past intolerance to even low-dose ritonavir, it would be preferable to avoid boosted protease inhibitors if possible. He does not wish to resume atazanavir or efavirenz.

- 1) What Efavirenz- and protease (PI) -sparing regimen(s) would be recommended?
- 2) What is the role of the newer antiretroviral drugs in this patient?

## Resistance Test Findings

Monogram GeneSeq (3/27/08) Key Mutations

nRTI	None
NNRTI	None
PI	M36M/I/V
Polymorphisms	RT: K22K/R, K32K/R, V60V/I, Q102K, C162S, L210L/M, V245E/K, K249K/R, A272A/P, T286A, E297K PI: I15I/V, E35D, N37N/S, R41K

## Interpretation/Implications for Treatment

The clinical question this patient presented was **what is the role of the newer antiretroviral drugs in non-salvage situations?**

This patient has generally done well in the absence of combination therapy, and may have met a definition of a “long-term non-progressor” had he not received antiretroviral drugs and IL-2 in the past. Despite his long history of being HIV-positive, he has maintained a high CD4 count and has been fairly well-controlled virologically in the absence of therapy. Given his non-suppressive regimens in the past, it is believed that he likely has some archived NNRTI (non-nucleoside reverse transcriptase inhibitor) resistance mutations as well as perhaps some thymidine-analog mutations.

The panel noted that the patient does not urgently need treatment from a clinical basis, given his high CD4 count and no prior history of opportunistic infections. However, the recent IAS guidelines<sup>1</sup> have expanded the criteria for starting antiretroviral drugs to those patients who may not previously have been considered candidates. This is because of improved tolerability of current regimens and data suggesting decreased incidence of non-AIDS conditions in patients if HAART is started at CD4 counts >350 cells/mm<sup>3</sup><sup>2, 3</sup>. Specifically, the IAS Guidelines state that for asymptomatic individuals with CD4 >350, “antiretroviral therapy should be individualized.” The panel reiterated that he should clearly understand the risks and benefits of restarting a long-term treatment such as HAART.

Given their long track record of tolerability, the panel believed that a **Protease Inhibitor (PI) -based regimen** would be preferred in this patient, who would likely need antiretrovirals for many years. As

noted above, the patient and his clinicians believed that atazanavir caused his acneiform rash; and he is intolerant of Kaletra® because of its GI side effects.

One option discussed was to consider two nucleoside analogues (either tenofovir/FTC or abacavir/3TC) plus darunavir/ritonavir. Darunavir/ritonavir (DRV/r) has been FDA approved as a once-daily regimen only in treatment-naïve patients; but it was believed that the patient was unlikely to have acquired any PI mutations in the short time he was on atazanavir or Kaletra®. Significantly, ritonavir-boosted darunavir was better tolerated than Kaletra® in the ARTEMIS trial (grade 2-4 GI side effects were seen in 7% vs 14%, respectively; moderate-to-severe diarrhea was seen in 4% vs 10% of patients).<sup>4</sup>

It was also believed that two nucleoside analogues plus unboosted fosamprenavir would be an acceptable regimen. Removing ritonavir could potentially limit its GI side-effects but bid dosing would be needed. Alternatively, a regimen of two nucleoside analogues plus ritonavir-boosted fosamprenavir could also be considered.

Regarding the PI-sparing regimens, one option would be to use a **Maraviroc-based regimen**. Given that this patient has a high CD4+ T cell count, it is not surprising that he has an R5-tropic virus. The MERIT study compared Efavirenz vs Maraviroc plus Combivir® (zidovudine plus lamivudine) in ARV-naïve patients.<sup>5</sup> The initial results showed that more treatment failures developed in patients on Maraviroc (using the more stringent endpoint of HIV RNA level <50, but not for <400 copies/mL). Subsequently, if patients in the MERIT study were screened for R5-tropic virus at baseline using the more sensitive tropism assay, and if only patients who were considered "R5-tropic" by the enhanced assay had been analyzed in the trial, virologic endpoints would have been similar between maraviroc and efavirenz.<sup>6</sup> This analysis found that the enhanced tropism assay resulted in reclassification of 15% of patients from R5 to Dual/Mixed at screening, and that non-inferiority criteria (with endpoint of HIV-RNA <50 copies/mL) were met when these Dual/Mixed patients were excluded.

Another less optimal treatment option would be to use an **Etravirine-based regimen**. In a phase II randomized, controlled, open-label trial (TMC125-C227), patients who were PI-naïve but NNRTI-resistant were randomized to receive etravirine or an investigator-selected PI.<sup>7</sup> In an unplanned interim analysis initiated because of efficacy concerns, it was found that fewer etravirine-treated patients achieved undetectable viral loads than did PI-treated patients (approximately 25% vs approximately 55% at week 12, data extracted from Figure in reference<sup>8</sup>). Although the proportion of virologically suppressed patients (with viral load <50 copies per mL) was comparable up until week eight, after that the curves diverged (at week 12, the inter-group difference was -27.8% [95% CI -46.8%, -8.8%]). In post hoc analyses, the poor response to etravirine was attributed to the high rate of NRTI and NNRTI resistance.

It was noted by the Panel that this patient's genotype was performed while off antiretroviral drugs, so he may have archived mutations that were not detectable, but could emerge under selective pressure after starting antiretrovirals. Thus, the Panel believed that an Etravirine-based regimen plus two nucleosides in this patient would have a high risk of treatment failure.

Another option would be to use a **Raltegravir-based regimen**. In the Phase III STARTMRK trial, Raltegravir was compared with Efavirenz in treatment-naïve patients; the nucleoside backbone consisted of Tenofovir and Emtricitabine.<sup>9</sup> The primary endpoint was viral load <50 copies/mL at 48 weeks. In this study, Raltegravir was found to be noninferior to Efavirenz, with virologic suppression seen in 86% and 82% of patients, respectively (inter-group difference was 4 [95% CI -2, 10], p<0.001 for noninferiority). Interestingly, the investigators found that patients on Raltegravir had a significantly shorter time to virologic response (though the clinical significance of this is unclear). In addition, there was a significantly greater CD4 count increase of +189 versus +163 cells/mL (inter-group difference 26 [95% CI 4, 47]).

Regarding tolerability, Raltegravir may be preferred over Efavirenz. In the STARTMRK trial, moderate/severe clinical adverse events were seen less frequently with Raltegravir (16% vs 32%,  $p < 0.001$ ); as expected, fewer patients on Raltegravir experienced central nervous system side effects (10.3% vs 17.7%,  $p = 0.015$ ). Raltegravir was also associated with lower increases in most lipid parameters (and a decrease in triglyceride levels), and fewer patients on Raltegravir required lipid-lowering medications.

However, the panel did not believe that a simple regimen of raltegravir plus two nucleoside analogues could be used in this patient given the potential “low genetic barrier” associated with raltegravir (i. e., raltegravir may not be robust enough to suppress HIV when used in combination with a potentially compromised nucleoside analogue “backbone”). Of note, in a randomized clinical study that was presented after the panel discussion, it was found that raltegravir did not perform as well as a boosted protease inhibitor in a population of treatment-experienced patients although lipid levels improved.<sup>10</sup> If raltegravir were to be used in this patient, it would need to be combined with a boosted protease inhibitor or some other potent drugs beyond the usual dual nucleoside analogue backbone.

## Recommendations

### Regimen Options

**1) Preferred Option: Two nucleoside analogues + ritonavir 100 mg daily + darunavir 800 mg daily**

- Pros – once daily regimen, well tolerated, effective
- Cons – if patient is nonadherent, he may lose darunavir as a viable salvage agent., side effects of rash if sulfa allergic

**2) Second-line Options: Two nucleoside analogues once daily + fosamprenavir 1400mg bid (unboosted) or ritonavir 100mg daily + fosamprenavir 1400mg daily**

- Pros- preserves darunavir as a future treatment option.
- Cons – unboosted fosamprenavir would require bid dosing, side effects of rash if sulfa allergic

**3) Third Option: Epzicom® once daily + tenofovir 300mg daily + raltegravir 400mg bid**

Pros – well-tolerated, few lipid-related side effects in this patient early in his treatment.

- Cons – twice-daily regimen; limited experience with this regimen; risk of failing raltegravir with rapid loss of this therapeutic option

## Follow-up

The patient was ultimately started on a regimen of Epzicom® plus Ritonavir/Darunavir in mid-6/08.

On 7/14/08, CD4 count was stable at 789, viral load was 88 copies/mL.

On 9/8/08, CD4 count was 554 and viral load was  $\leq 40$  copies/mL.

He is tolerating the regimen well.

- 
1. Hammer, JAMA 2008; 300:555
  2. Kitahata MM, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med. 2009;360:[Epub ahead of print
  3. When to Start Consortium. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. Lancet. 2009;373:1352–63
  4. Ortiz, AIDS 2008, 22: 1389
  
  5. Saag, IAS 2007, Sydney, Abstract WESS104
  - 6 Saag, ICAAC/IDSA 2008, Abstract 1232a
  - 7 Ruxrungtham, HIV Med 2008, 9:883.
  - 8 Ruxrungtham, HIV Med 2008, 9:883.
  9. Lennox, ICAAC/IDSA 2008, Washington, Abstract 896a.
  10. Eron J et al. *Switching from stable lopinavir/ritonavir-based to raltegravir-based combination ART resulted in a superior lipid profile at week 12 but did not demonstrate non-inferior virologic efficacy at week 24.* Sixteenth Conference on Retroviruses and Opportunistic Infections, Montreal. Abstract 70aLB, 2009.