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# HIV Resistance Testing Consultation Service

## Consultation Report

Panel Members: Richard Aranow, MD  
George W. Beatty, MD, MPH  
Steven G. Deeks, MD  
Betty J. Dong, Pharm.D  
Amy V. Kindrick, MD  
Jody Lawrence, MD  
Michael L. Lim, Pharm.D (11/00-6/01)  
John Stansell, MD (3/10-6/01)  
Jason Tokumoto, MD  
Paul Volberding, MD (11/00-3/01)

Project Director: Ronald H. Goldschmidt, MD

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**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 an athletic male (MSM) who was first seen 8/19/93. He became HIV-positive around 1992 with a CD4 count of approximately 500 cells/mm<sup>3</sup>. A work-up at that time revealed well-differentiated squamous cell carcinoma of the anus. He underwent local resection. He was started on Combivir and indinavir (IDV) 800mg tid in 1995. On 6/25/98 his CD4 count was 250 cells/mm<sup>3</sup> and his viral load was 990 copies/ml. The patient admitted to missing his afternoon doses of indinavir, but believed that he could be compliant with his medicines. Based on a genotype (12/29/98), his regimen was changed to Combivir, indinavir 800/ritonavir(RTV) 200 bid in early 1999. He was much more compliant with this regimen. However, he developed scleral icterus, renal calculus, and subsequently became non-adherent. His CD4 count was 309 cells/mm<sup>3</sup> and his VL was 4600 copies/mL. He continued to have difficulty with compliance, and admitted to feeling "depressed". After a second renal calculus, his regimen was changed to Combivir plus indinavir 400/RTV 400 Bid. His CD4 count was 340 cells/mm<sup>3</sup> and his VL was 4960 copies/mL. He tolerated the new regimen well but developed hypertriglyceridemia. On his return visit, his CD4 count was 276 with a VL of 11,400. He had his second genotype obtained 4/30/01. He again admitted to missing his medications particularly over the past 5-6 months. The patient was hesitant to modify therapy at this time, and remained on Combivir, ritonavir and indinavir. He had another genotype 2/4/02, at which time his CD4 count was 211 (11%) cell/mm<sup>3</sup> with a VL of 19100 copies/mL. He has remained in excellent health. However, he has developed recurrence of his anal squamous cell CA and will be scheduled for surgical resection when he returns from his trip. The patient's only request is that he does not develop lipodystrophy.

His antiretroviral history is as follows.

DATE	REGIMEN	CD4 cells/m m <sup>3</sup>	VL COPIES/M L	RESISTANCE TEST FINDINGS	CLINICAL COURSE
8/19/93		500			Squamous cell CA of the anus
		792			
1995	Combivir + IDV 800 tid				
6/25/98		250	990		Missing IDV
12/29/98		250	4800	GART 12/29/98	
	Combivir, IDV 800, RTV 200, BID	309	4600		Hyperbilirubinemia, renal calculi X2, noncompliance, depression
	Combivir, IDV 400, RTV 400, BID	340	4960		Diarrhea,  TG 501, chol 176, HDL22

		276	11,400	GART 4/30/01 GART (VA 2/13/01)	Noncompliance X 5-6 months TG 1275, chol 218, HDL 26, started on Tricor
		211 (11%)	19100	GART 2/4/02	Excellent health but recurrence of squamous cell CA

## Resistance Test Findings

### Key Mutations

#### 12/29/98 (Specialty Laboratory) Key Mutations

NRT	M41M/L, D67N, K70R, M184V, T215Y
NNRT	none
PI	M36I, M46I, I54V, I64M, A71V, V82A

#### 4/30/2001 (Specialty Laboratory) Key Mutations

NRT	M41L, M184V, T215F
NNRT	none
PI	L10I, K20R, L24I, M36I, M46I, A71V, V82A

#### 2/13/01 (VA) Key Mutations

NRT	M41L, M184V, R211K, T215F, T215Y
NNRT	none
PI	L10I, K20R, L24I, M36I, M46I, I54V, A71V, V82A, V82S

#### 2/4/02 (Specialty Labs) Key Mutations

NRT	M41, M184V, L210L/W, T215Y
NNRTI	none
PI	L10I, K20R, L24I, M36I, M46I, I54V, A71V, V82A/S

## Interpretation/Implications for Treatment

### **Interpretation of the resistance tests:**

The panel discussed the evolution of drug-resistance over time, focusing on the gradual loss of mutations at codons 67 and 70 and the emergence of resistance mutations at codon 210. The evolution of resistance during nucleoside analogue treatment has been well-described for zidovudine (AZT). The K70R mutation often emerges early and is subsequently replaced as the reverse transcriptase continues to evolve and remodel itself such that it functions efficiently in the presence of drug. As clearly shown in this case, continued viral evolution leads to the sequential development of a larger number of mutations, with the change at codons 41, 210 and 215 emerging. The only way to prevent such evolution is to modify therapy with a goal of achieving complete or near-complete viral suppression.

The emergence of a mutation at M41L and L210W is of particular concern here because these mutations have been associated with high-level cross-resistance to tenofovir. Given this pattern (and the M184V mutation), there appears to be limited options within the nucleoside analogue class (multiple thymidine analogue mutations, or TAMS, confers cross-resistance to all other nucleoside analogues).

The patient has acquired a surprising number of protease inhibitor mutations as well, which is to be expected given the prolonged duration of viral evolution in the presence of indinavir and ritonavir. The remaining protease inhibitors will have weaker activity due to cross-resistance.

This patient has never been on a non-nucleoside reverse transcriptase inhibitor and likely has a virus population which has normal (if not hyper-) susceptibility to this therapeutic class.

### **Patient considerations**

The patient's one primary request is the avoidance of lipodystrophy. His high TG is a confounding problem. Another consideration is the patient's history of variable adherence. The patient's clinicians believed, however, that adherence would not be a problem because he is newly motivated, and now dedicated to his health.

The panel also considered the patient's anal carcinoma. One panel member recalled a recent study which concluded that HAART therapy did not reduce the incidence of anal intraepithelial neoplasia-3 (AIN3)<sup>1</sup>. However, this patient has already progressed to cancer and the panel felt it was appropriate to design the most potent treatment strategy possible.

### **Implications for treatment**

Given the high-level resistance to both NRTIs and protease inhibitors, the panel believed that this patient was a candidate for enfurvitide or T-20 (Fuzeon®) which is commercially available on a very limited basis. The TORO<sup>2,3</sup> trials looked at highly experienced, motivated patients on T-20 plus other agents. The strongest predictors of T-20 success were being naïve to ritonavir/lopinavir (Kaletra), and using this drug in a salvage regimen. Some panel members believed that Kaletra® should be added because there was no existing L90M mutation, and because there is no data to support T-20 *without* the use of a protease inhibitor. Other panel members argued that addition of a protease inhibitor (ritonavir/lopinavir + efavirenz) could exacerbate the patient's hypertriglyceridemia and increase the risk of lipodystrophy. Other T-20 issues discussed included adverse effects (mainly injection site reactions, *rare* allergic reactions), and the difficulty of storage, administration, and reconstitution. T-20 should be reconstituted a few hours before administration, and must be kept in the refrigerator.

The possibility of using atazanavir was discussed due to its minimal lipid abnormalities. The panel believed that atazanavir would not be very active against this virus due to its cross-resistance with other protease inhibitors. The combination of atazanavir plus saquinavir was considered since it would provide dual protease inhibitor therapy with potentially lesser negative effects on lipids. Cons to this regimen included potential lipodystrophy and pill burden if combination with ritonavir was contraindicated.

The panel recommended a phenotype to evaluate the efficacy of adding a protease inhibitor. It would provide additional information on viral susceptibility to Kaletra and atazanavir and possibly assist in the selection of the NRTI back-bone.

## **Recommendations**

### Regimen Options

Option 1: PANEL'S CHOICE: Changing the regimen -- T-20 + non-nucleoside (efavirenz) + nucleosides (3TC + tenofovir) ± Kaletra®

- Pros: Most potent choice available for this patient, also good for suppression of his anal carcinoma, nucleosides have minimal pill burden
- Cons: Potential lipodystrophy, triglyceride effects, T-20 side effects. If lose this regimen, then no other options left.

#### Option 2: Stopping regimen – no medications

- Pros: Preserves non-nucleoside as future option, no lipodystrophy, or triglyceride effects, nadir never below 200
- Cons: Patient has anal carcinoma and CD4 cells are trending ↓ approaching 200 – may need treatment anyway. Panel would be more comfortable with this option if he did not have cancer.

#### Option 3: Continuing same regimen – AZT + 3TC + Indinavir + Ritonavir

- Pros: Preserve non-nucleoside, patient familiar with regimen, may help with anal carcinoma.
- Cons: Continued viremia could produce more drug-resistance mutations, history of diarrhea & kidney stones on this regimen, risk of lipodystrophy, triglyceride problems

## Dosing, Monitoring, and Follow-up Recommendations

- **Monitor CD4 count and viral load 3 to 4 weeks after changing the regimen.**
- **Dosing issues:** T-20 will be dosed as a 90mg SQ injection BID. The dose of Kaletra® in combination with efavirenz should be 4 pills BID. Efavirenz can be administered as 600mg PO QD. Tenofovir and lamivudine (3TC) can both be given as 300mg PO QD.
- **Triglycerides:** This patient may require combination therapy with a statin + a fibrate to lower triglyceride levels. Beware of drug interactions with lipid lowering agents (e.g. simvastatin and lovastatin) and Kaletra®. The patient should be monitored for signs of myositis, hepatitis, and rhabdomyolysis. If the metabolic issues become exacerbated while the patient is on Kaletra®, the panel would consider substituting atazanavir, saquinavir, or amprenavir (at the expense of adding pill burden).

<sup>1</sup> Palefsky J, Holly E, Ralston M, Jay N, Berry M, Darragh T. Effect of HAART on incidence of anal intraepithelial neoplasia grade 3 among HIV-positive men who have sex with men. *Abstract*. Presented at the XIV International AIDS Conference, Barcelona, Spain. July 7-12, 2002.

<sup>2</sup> Clotet B, Lazzarin A, Cooper D, Reynes J, Arasteh K, Nelson M, et al. Enfuvirtide (T-20) in combination with an optimized background (OB) regimen vs. OB alone in patients with prior experience or resistance to each of the three classes of approved antiretrovirals (ARVs) in Europe and Australia. *Abstract*. Presented at the XIV International AIDS Conference, Barcelona, Spain. July 7-12, 2002.

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<sup>3</sup> Henry K, Lalezari J, Ohearn M, Trottier B, Montaner J, Piliero P, et al. Enfuvirtide (T-20) in combination with an optimized background (OB) regimen vs. OB alone in patients with prior experience or resistance to each of the three classes of approved antiretrovirals (ARVs) in North America and Brazil. *Abstract*. Presented at the XIV International AIDS Conference, Barcelona, Spain. July 7-12, 2002.