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# HIV Resistance Testing Consultation Service

## Consultation Report

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## History/Clinical Course

The patient is a 44-year-old woman whose first positive HIV test was in 2001. Her pretreatment CD4 and viral load (VL) were 270 cells/mm<sup>3</sup> and 75,000 copies/mL, respectively. Not long thereafter she started Combivir (CBV) and nelfinavir (NFV). By June 2003 her CD4 and VL were 371 cells/mm<sup>3</sup> and 19,000 copies/mL. For the past year, due to insurance problems, she did not have regular follow up. She was able to continue taking CBV, but couldn't refill the NFV. She reports no problems taking CBV and has never missed a dose. She was first seen by her current provider on 2/1/06, at which point her CD4 and VL were 304 cells/mm<sup>3</sup> and 38,000 copies/mL. She felt well and her physical exam was unremarkable. She takes rosiglitazone, metformin and glipizide for type 2 diabetes that was diagnosed about a year ago. HbA1C is pending. She also takes epinastine ophthalmic solution for allergic conjunctivitis. She is S/P surgery for renal stones, smokes seven cigarettes a day, and has a family history of HTN, DM, and MI.

DATE	REGIMEN	CD4 (cells/mm <sup>3</sup> )	VL (copies/mL)	COMMENTS
2001	None	270	75,000	Pre-treatment
2003	CBV/NFV	371	19,000	
2/1/06	CBV	304	38,000	Excellent CBV adherence; GART/vphenotype obtained

## Resistance Test Findings

### 2/1/06 vircoTYPE Mutations

NRT	184V, 211K
NNRT	None
PI	46I, 63A/P, 77I, 90M, 93L

2/1/06 vircoTYPE Virtual Phenotype

	Matches in DB	Fold Change	CCO1	CCO2	BCO	Interpretation
<b>NRTI</b>						
ABC	3,613	1.5			2.1	Susceptible
TDF	1,857	0.6	1.0	2.0		Maximal Response
ddI	3,917	1.2	1.3	3.0		Maximal Response
3TC	4,010	45.8	1.1	3.7		Minimal Response
FTC	555	47.5			3.7	Resistant
D4T	3,857	0.7	1.1	2.2		Maximal Response
AZT	3,615	0.8	1.9	14.4		Maximal Response
ddC	3,619	1.5			3.0	Susceptible
<b>NNRTI</b>						
DLV	7,543	1.3			7.7	Susceptible
NVP	7,663	1.2			5.2	Susceptible
EFV	14,972	1.0			3.4	Susceptible
<b>PI</b>						
AMP	222	1.2	0.7	1.4		Reduced Response
AMP/r	222	1.2	0.9	6.5		Reduced Response
fAMP	908	1.2			1.8	Susceptible
ATV	--	Rules-Based Interpretation				Susceptible
IDV	128	2.9	0.8	2.2		Minimal Response
IDV/r	128	2.9	4.1	21.2		Maximal Response
LPV/r	186	1.8	10.0	61.6		Maximal Response
NFV	124	8.2	1.0	1.5		Minimal Response
RTV	56	2.9			2.4	Resistant
SQV	565	1.2	0.7	1.0		Minimal Response
SQV/r	565	1.2	1.1	12.0		Reduced Response
TPV	193	0.9			1.6	Susceptible

## Interpretation/Implications for Treatment

This 44-year-old woman has documented failure involving two ARV classes after five years on her first ARV regimen (CBV/NFV). Her HIV treatment course has recently been complicated by limited access to NFV leading to use of CBV alone for the past year. Although data points are few, a CD4 and VL obtained when she was on a HAART regimen showed a good immunologic and partial virologic response. Her CD4 and VL now are not appreciably different than they were at diagnosis despite suboptimal ARV treatment for the past year. She has never had an HIV-associated complication and currently feels well.

With regard to the nucleoside reverse transcriptase inhibitors (NRTIs), the genotype and “virtual” phenotype obtained while on CBV only demonstrates a M184V mutations (which is consistent with high level resistance to 3TC and FTC, and perhaps partial resistance to ABC and ddI). There were no classic thymidine analog mutations, which is surprising given her prolonged history of viral replication on zidovudine (AZT). It is possible, however, that additional NRTI mutations may have been previously “archived” in the face of ongoing viral replication while on CBV.

Regarding the PI class, the recent resistance test suggests that prior treatment with NFV did select for several important PI mutations, including those at positions 46I, 77I, and 90M. The 63A/P mutation usually does not confer clinically significant resistance by itself but it can contribute to LPV/r resistance in the presence of other key PI mutations. All of these mutations are consistent with the treatment history and have persisted over a year in the absence of ongoing drug pressure. Although reversion of mutant virus to wild type occurs in most patients who discontinue all ARVs, persistence of mutant virus in those discontinuing only part of a regimen has been well described<sup>1</sup>.

It is reasonable to assume that the PI mutations seen in this patient’s recent GART are real, but the absence of PI pressure when this test was done also raises concern that the current test might be understating PI resistance. If this is the case, additional resistance might emerge when PI pressure is reapplied<sup>2</sup>, enhancing the risk that a new PI-based regimen might fail. Close monitoring after starting a new PI-based regimen would help to detect such archived resistance, if there is any, so that adjustments can be made before other active drugs in the regimen are threatened.

Both the ARV history and the resistance test findings indicate that the non-nucleoside reverse transcriptase inhibitor (NNRTI) class is likely to be fully active. Even so, panel members were reluctant to suggest that an NNRTI be included in a next regimen because there is a significant risk that high-level NNRTI resistance could rapidly emerge if archived NRTI and PI resistance are uncovered. Such a scenario would seriously limit options for subsequent regimens, in which the greatest chance of long-term success is with at least two fully active drugs from classes to which the virus never has been exposed<sup>3</sup>.

Combining an NNRTI with enfuvirtide and as many NRTIs that are tolerated might have a high probability of achieving full suppression but panel members were concerned about how vulnerable this regimen would be to minor adherence lapses and how burdensome an BID injectable drug would be for a patient already on a complex medical regimen. Given her stable clinical status and the anticipated arrival of new drugs that are likely to be at least as effective and better tolerated, the panel considered whether it made more sense to wait for other effective drugs to become available.

The panel was similarly unenthusiastic about continuing the current ARV regimen, even though this patient is clinically stable. They cited a recent study of patients on incompletely suppressive regimens, which documented the emergence of additional resistance mutations that were likely to be clinically significant (i.e., to impair response to subsequent regimens)<sup>4</sup>.

Any choice of ARV regimen requires an assessment of likely benefits and likely risks. There is reason to be concerned that this patient might be especially vulnerable to some of the drug toxicities that are known to be associated with specific ARVs. Of the NRTIs, tenofovir (TDF) has been associated with renal toxicity, characterized by proteinuria and a Fanconi-type distal renal tubular acidosis. The risk for developing renal toxicity has been shown to be significantly increased in patients with underlying renal disease<sup>5</sup>. This patient's history of diabetes raises concern that she might be at higher than average risk for this complication, especially if her diabetes is poorly controlled. A baseline assessment of creatinine clearance and careful monitoring of BUN, creatinine, electrolytes (including phosphate) and proteinuria are recommended if this patient is prescribed a TDF-containing regimen. Data to support a specific creatinine clearance cut off above which TDF should be avoided are few, but expert opinion suggests that it should be used with caution in patients with GFRs between 60 and 90 mL/min and not at all (unless the benefits clearly outweigh the risks) when GFR is below 60 mL/min.

Additionally, an association has been established between PI use and a spectrum of metabolic abnormalities, including insulin resistance and hyperlipidemia<sup>6,7</sup>. LPV/r might be more likely than other PIs to be associated with these adverse effects. A series of small studies have suggested that these toxicities might be associated with an increased lifetime risk for cardiovascular disease. Subsequently, a large observational study has confirmed these preliminary findings. This patient already has several CV risk factors (family history, diabetes, tobacco use), raising special concern about the potential for PIs to further enhance her risk<sup>8</sup>. A notable exception among the PIs is atazanavir (ATV), which has been associated with a lower occurrence of metabolic toxicity than average for the class as a whole, even when it is boosted with low dose ritonavir. This lower risk for metabolic toxicity associated with ATV/r must be balanced against the higher risk of virologic failure compared to LPV/r when >3 PI mutations are present<sup>9</sup>.

## Regimen Options

The following options were considered in February, 2006, prior to the availability of darunavir/ritonavir. In general, the panel felt that an attempt could be made to achieve complete viral suppression using drugs from the classes the patient had already seen (NRTIs and protease inhibitors), preserving the NNRTIs for a future integrase-inhibitor based regimen.

Option 1: Trizivir one tablet BID plus tenofovir (Viread) 300 mg once daily plus lopinavir/ritonavir (LPV/r, Kaletra) 2 tablets BID. Once-daily Kaletra (LPV/r) is not recommended in treatment - experienced patients. Take all with food.

### Pros

Most likely to optimize activity of NRTI class, even if additional resistance is archived

LPV/r is PI most likely to be active for virus with PI mutations seen in recent GART

Avoids risk of rapidly acquiring NNRTI resistance that would limit future treatment options

Preserves fully active NNRTI for use with new drugs coming soon (e.g., integrase inhibitor, PIs likely to be active against resistant virus); such a regimen is likely to achieve full virologic suppression

Reasonable pill burden

#### Cons

May not be fully suppressive

Risk of ABC-associated hypersensitivity reaction<sup>10-12</sup>; (especially if HLA B5701 haplotype is mutant)

Risk of worsening diabetes control and hyperlipidemia

Possibility of increasing cardiovascular disease risk for pt already at higher risk

**Option 2: Combivir one tablet BID plus tenofovir 300 mg daily plus lopinavir/ritonavir 2 tablets BID. Once-daily Kaletra (LPV/r) not recommended in treatment-experienced patients. Take all with food.**

#### Pros

Avoids ABC hypersensitivity risk if wild type HLA B5701 haplotype can't be obtained

2 NRTIs probably are sufficient if no resistant quasispecies are archived

BMS 045 => LPV/r better than ATV/r for patients with >3 PI mutations

Preserves NNRTI for future use as above

Reasonable pill burden

#### Cons

Might not optimize activity of NRTI class if additional resistance is archived

Risk of worsening diabetes control and hyperlipidemia

Possibility of increasing cardiovascular disease risk for pt already at higher risk

**Option 3: Trizivir one tablet BID plus tenofovir (Viread) 300 mg daily plus atazanavir (Reyataz) 300 mg once daily plus ritonavir 100 mg once daily. Take all with food.**

#### Pros

Optimizes NRTI activity as above

ATV/r less likely than LPV/r to be associated with hyperlipidemia and insulin resistance

Preserves NNRTI for future use as above

Reasonable pill burden

#### Cons

ABC-associated hypersensitivity risk

ATV-associated hyperbilirubinemia risk

TDF-associated renal toxicity risk

BMS 045 => LPV/r better than ATV/r for patients with >3 PI mutations

**Option 4: Trizivir one tablet BID plus atazanavir 300 mg once daily plus ritonavir 100 mg once daily. Take all with food.**

#### Pros

Avoids TDF renal toxicity concern

Preserves NNRTI for future use as above

Reasonable pill burden

#### Cons

ATV-associated hyperbilirubinemia risk

Mitigates metabolic and cardiovascular risks as above

Might not optimize activity of NRTI class if additional resistance is archived

BMS 045 => LPV/r better than ATV/r for patients with >3 PI mutations

## Monitoring, and Follow-up Recommendation

Baseline evaluation of renal function and close monitoring for any renal disease (ScR, Urinalysis, serum Phosphate, Creatinine clearance)

Follow glucose and full lipid panel. Institute aggressive medical management and/or consider regimen change if abnormalities develop<sup>13</sup>.

Monitor VL and CD4 4 to 6 weeks after starting the new ARV regimen.

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