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# HIV Resistance Testing Consultation Service Consultation Report

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## History/Clinical Course

The patient is a 62-year-old white man diagnosed with HIV in 7/96. His other medical conditions include chronic kidney disease, low grade anemia, and cachexia (50kg, 5'10", on Megace). He initiated treatment with lamivudine/stavudine/ritonavir (3TC/d4T/RTV) in 10/96 with a CD4 count of 24 cells/mm<sup>3</sup> and a viral load (VL) of 61,500 copies/mL. The VL quickly fell below 500 copies/mL within two months, but the patient subsequently was lost to follow up and likely discontinued his antiretroviral regimen. He returned to care in 6/97 with a CD4 count of 6 cells/mm<sup>3</sup> and a VL of 43,900 copies/mL. He was started on lamivudine/stavudine/indinavir (3TC/d4T/IDV) in 7/97. His VL again became undetectable (<500 copies/mL) and the CD4 count increased to approximately 100 cells/mm<sup>3</sup>. Between 1999 and 2002, his CD4 continued to improve, stabilizing at about 180 cells/mm<sup>3</sup> (12-14%) but the VL remained persistently detectable. Interestingly, the VL fell to <400 copies/ml from 2003 to mid-2005 (without a change in his regimen). He remained stable on the same regimen and tolerated it well for years. Self-reported adherence was always excellent. His only adverse effect was lipoatrophy.

In January 2005, d4T was switched to ABC (abacavir) in an attempt to reverse the lipoatrophy. Unfortunately, the patient complained of decreased appetite on the ABC. His renal function also declined in 4/05, and the caller was under the misunderstanding that ABC should be avoided if the CLCR < 50mL/min. Therefore, ABC was replaced by TDF (tenofovir), and 3TC and TDF were renally dosed. His first viral breakthrough occurred in July, and in September, with persistently detectable virus, a genotype was obtained.

DATES	REGIMEN	CD4 (cells/mm <sup>3</sup> )	VL (copies/mL)	RESISTANCE TEST FINDINGS	CLINICAL COURSE
10/96	3TC/d4T/RTV	24	61,500		
12/96		12	<500		
6/97		6	43,900		Stopped meds?
7/97	3TC/d4T/IDV				
8/97		25	<500		
9/97		60	<500		
12/97		91	<500		
2/99		135	2,221		
5/99		84	409		
8/99		119	576		
12/99		105	524		
1/00		114	275		

DATES	REGIMEN	CD4 (cells/mm <sup>3</sup> )	VL (copies/mL)	RESISTANCE TEST FINDINGS	CLINICAL COURSE
6/00		75	222		
8/00		175	1,148		
11/00		153	818		
3/01		171	789		
6/01		198	931		
9/01		180	969		
1/02		190	<400		
6/02		165	724		
8/02		170	455		
2/03		204	<400		
4/03		165	<400		
10/03		182	<400		
4/04		181	<400		
6/04		181	<400		
1/05	3TC/ABC/IDV	174	<400		Switched off d4T due to lipoatrophy. 10/04 Scr 1.2mg/dL
4/05	3TC 150mg qd/ TDF 300mg q48h/ IDV	174	<400		Scr increased to 1.6mg/dL, CLcr ~34mL/min. Pt c/o anorexia on ABC, ABC switched to TDF.
7/05		257 (15%)	1,984		
9/05		206 (10%)	3,628	RT: K65R, M184V PR: L10I, M36M/I, M46M/I, I54A, L63P, A71V, V82F, L90M	Clinically well Scr 1.2mg/dL, CLcr ~45mL/min.

## Resistance Test Findings

Key Mutations

NRT	K65R, M184V
NNRT	
PI	L10I, M36M/I, M46M/I, I54A, L63P, A71V, V82F, L90M

Questions for the panel:

1. Is zidovudine (AZT) + a non-nucleoside reverse transcriptase inhibitor (NNRTI) a reasonable treatment option, or does this patient need a more aggressive regimen?
2. Is it reasonable to start T-20 (enfuvirtide) now?

## Interpretation/Implications for Treatment

Interpretation of genotype

The K65R mutation causes intermediate resistance to didanosine (ddI), abacavir (ABC), lamivudine (3TC), emtricitabine (FTC), and tenofovir (TDF), and possibly low-level resistance to d4T. It causes AZT hypersusceptibility. The presence of M184V confers high-level resistance to 3TC and FTC and possible low level resistance to ABC and ddI. The M184V mutation may also confer some benefit to the patient by impairing the virus's replicative fitness and by partially restoring AZT, d4T (stavudine) and possibly tenofovir (TDF) susceptibility.

The M46I, V82F, and L90M are major mutations in the protease gene that reduce susceptibility to most protease inhibitors (PI). V82F and L90M are likely to confer cross-resistance to saquinavir (SQV) and nelfinavir (NFV). However, since only five of the eight mutations thought to contribute to lopinavir/ritonavir resistance are seen, it is possible that this drug will retain some efficacy. Similarly, virologic response is likely to occur with boosted tipranavir (TPV) and darunavir (DRV).

Regarding the non-nucleoside reverse transcriptase inhibitors (NNRTIs), this patient has never been treated with this class of drugs. The resistance test results are consistent with this history and indicate that any drug in the class should be active.

Specific issues addressed by the panel

The panel discussed the unusual development of extensive PI resistance in a patient with viral load <400 copies/mL. It is possible that some of the mutations may have evolved in the past when the patient's viral load was detectable (2-3 logs), and the recent dose adjustment of the NRTI backbone allowed this archived virus to emerge. Another possibility includes the development of mutations during very low level viremia, with slow accumulation of mutations over the years eventually leading to virologic breakthrough. One recent study suggested that the acquisition of new resistance mutations is associated with either no baseline mutations or >3 baseline mutations; viral loads in the 3-4 log range; and a viral load slope of >0.2 log copies/mL per month<sup>1</sup>. Based on these factors, it seems most likely

that the first scenario occurred, where the patient rapidly accumulated his current mutations after virologic breakthrough in July 2005.

A question arose whether the patient may have archived thymidine analog mutations (TAMs) that developed during the prolonged period of viremia from 1999 to 2002. The panel pointed out that the patient was always on an NRTI-based regimen while failing a protease inhibitor; it is therefore likely that such TAMs would have co-evolved with the emerging protease inhibitor-associated mutations. One possible scenario is that tenofovir selected for a K65R variant over a variant that had few TAMs and therefore limited tenofovir-resistance.

The evolution of the K65R mutation was discussed. This mutation likely confers only partial resistance to TDF, ABC, and/or ddI, suggesting that these drugs could be used in a subsequent regimen. Most panel members strongly believed that AZT should in subsequent regimens given the impact which K65R has on susceptibility to this drug.

The panel believed that treatment interruption would not appropriate due to his low CD4 nadir. They also did not favor continuing the same regimen since there are reasonable options to achieve an undetectable viral load. Continuing the current regimen increases the risk of developing more resistance. The panel also felt that since the K65R mutation confers hypersusceptibility to AZT, a potent and durable regimen may be constructed without inclusion of T-20.

The idea of using once daily AZT to simplify the regimen was explored. The panel discussed the possibility of using AZT once daily to facilitate adherence. An abstract presented at CROI in 2004 studied the outcomes of once-daily Trizivir and TDF in naïve patients<sup>2</sup>. Although 24 week results were promising, with 78% and 67% of patients reaching VL < 400 copies/mL and <50 copies/mL, respectively, the 48 week results were disappointing<sup>3</sup>.

## Recommendations

1. The panel recommended against a regimen containing an NNRTI and NRTIs. The panel was concerned about the ease of developing NNRTI resistance when combining an NNRTI with a compromised NRTI backbone.
2. Since K65R confers hypersusceptibility to AZT, a strong nucleoside backbone may still be constructed with a single boosted PI regimen to achieve a potent, durable response. AZT should definitely be included in the new regimen. 3TC should also be added as this drug has many potential benefits: (1) maintenance of M184V, which enhanced susceptibility to TNF and AZT, (2) maintenance of M184V, which reduces viral fitness, and (3) continued partial activity. A 3<sup>rd</sup> nucleoside might be necessary to strengthen the nucleoside backbone. Options would include ABC, TDF (if renal function is appropriate), and ddI.
3. The patient's estimated CLCr is about 45mL/min using a Scr of 1.2 mg/dl, which is just below the threshold for renal dosing. Renal dosing of NRTI is recommended when the CrCl is less than 50 mL/min.
4. The panel suggesting getting a phenotype, if possible. The phenotype would allow careful assessment of lopinavir's, tipranavir's, and darunavir's potential in a salvage regimen. It is difficult to accurately determine the potential activity of these drugs with a genotype. However, algorithms are available; these suggest that all three drugs will likely have some activity. The panel did not believe a genotype could define which of these protease inhibitors would be most effective.

## Regimen Options

**Option 1:** Trizivir (AZT 300mg/3TC 150mg/ABC 300mg) 1 tab po bid plus Kaletra 2 tabs po bid (or TPV 500mg po bid/RTV 200mg po bid or darunavir 600mg po bid/RTV 100mg po bid, depending on phenotype results)

Pros: Likely to be effective. Preservation of NNRTIs for future co-administration with integrase inhibitors and/or R5 inhibitors, if needed.

Cons: Past intolerance of ABC, high pill burden. Side effects and drug interactions from boosted regimens.

**Option 2:** Combivir (AZT 300mg/3TC 150mg) 1 tab po bid + TDF 300mg po qd + Kaletra 2 tabs po bid (or TPV 500mg po bid/RTV 200mg po bid or darunavir 600mg po bid/RTV 100mg po bid, depending on phenotype results)

Pros: Likely to be effective. Preservation of NNRTIs for future co-administration with integrase inhibitors and/or R5 inhibitors, if needed.

Cons: Risk of renal disease from tenofovir (in a patient with pre-existing renal dysfunction), high pill burden, side effects and drug interactions from boosted regimens

**Option 3:** Combivir (AZT 300mg/3TC 150mg) 1 tab po bid + ddl EC 400mg qd + Kaletra 2 tabs po bid (or TPV 500mg po bid/RTV 200mg po bid or darunavir 600mg po bid/RTV 100mg po bid, depending on phenotype results)

Pros: Avoids NRTIs that patient did not tolerate in the past. Preservation of NNRTIs for future co-administration with integrase inhibitors and/or R5 inhibitors, if needed.

Cons: ddl side effect (peripheral neuropathy, pancreatitis), food restraints, high pill burden, side effects and drug interactions from boosted regimens

**Option 4:** One of NRTI backbones above + EFV 600mg po qd + one of PI options above

Pros: Potent, triple class regimen to ensure sustained virologic response

Cons: High pill burden, uses NNRTI option rather than saving for salvage, potential CNS side effects with EFV, and drug interactions from boosted regimens

## Dosing, Monitoring, and Follow-up Recommendations

- Use standard, full doses of NRTIs instead of renal doses as long as CL<sub>cr</sub> remains at or above 50 mL/min. Reduce doses only if renal function worsens significantly.

- Monitor CD4 count and viral load at 4-6 weeks after changing therapy and then every 3 months
  - Monitor for specific toxicities associated with each drug
  - Zidovudine: GI symptoms, anemia, hepatotoxicity, lactic acidosis
- Abacavir: hypersensitivity reaction
- Tenofovir: renal toxicity
- Didanosine: peripheral neuropathy, pancreatitis
- Kaletra: GI symptoms, hepatotoxicity, hyperlipidemia, glucose intolerance
- Tipranavir: GI symptoms, hepatotoxicity, intracranial bleeding, rash
- Darunavir: rash, GI symptoms

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<sup>1</sup> Napravnik S, Edwards D, Stewart P, Stalzer B, Matteson E, Eron J. HIV-1 Drug Resistance Evolution Among Patients on Potent Combination Antiretroviral Therapy With Detectable Viremia. *J Acquir Immune Defic Syndr* 2005;40(1):34-40.

<sup>2</sup> Elion R, Cohen C, DeJesus E, Redfield R, Gathe J, Hsu R, et al. COL40263: Resistance and Efficacy of Once-daily Trizivir and Tenofovir DF in Antiretroviral Naïve Subjects [Abstract]. In: 11<sup>th</sup> Conference on Retroviruses and Opportunistic Infections, San Francisco, California, February 8-11, 2004. Oral abstract no. 53.

<sup>3</sup> S Deeks, personal communication, 2006.