
HIV Resistance Testing Consultation Service

Consultation Report

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History/Clinical Course

The patient is a 24 year old HIV positive man. His medical history states that he was vertically infected, though the details behind this are unclear as the child was adopted. His initial antiretroviral drug exposure is also unclear. It is likely he was taking various mono and dual NRTI regimens while in care at a pediatric infectious disease clinic. The patient transitioned care to his current physician in 2001, while receiving a failing PI-based regimen. Soon thereafter he was switched to an NNRTI-based regimen supported by a quad-NRTI backbone. In retrospect, the treating clinician notes that this had not been the wisest decision considering the amount of NRTI resistance the virus had already acquired. On this NNRTI regimen the viral load briefly went below the level of detection before rising again. This is the patient's only recorded undetectable viral load. Since then the patient has been maintained on various salvage therapies with CD4 counts ranging from 102-183 cells/mm³ and a viral load between 2261-8590 copies/mL. The patient has had no known opportunistic infections. He was admitted earlier this month (June 2005) for appendicitis.

The patient's co-morbidities include fatigue and depression, for which he is receiving testosterone and Paxil®. He has been maintained on Septra DS® prophylaxis since his CD4 count remained below 200 cells/mm³ during the past 3 years. His adherence is thought to be excellent. He is currently in college, feels well, and has not had any overt side effects to medications. The patient is reluctant to perform self-injections of medications but will do so if advised by his provider.

DATE	REGIMEN *	CD4 cells/mm ³	VL COPIES/ML	RESISTANCE TEST FINDINGS	CLINICAL COURSE
10/91	Unknown	340 (16%)			
5/92		390 (26%)			
6/93		230 (25%)			
1/94		140 (16%)			
5/94		157 (16%)			
8/94		57 (7%)			CD4 nadir
1995		133-177 (14-16%)			
1996		124-192 (12-15%)			
1/97	Unknown	230 (19%)			
10/97		342 (13%)			

1998		291-344 (16-18%)			
1/99		272 (15%)			
4/99		315 (15%)	59322		
8/99		289 (21%)	38138		
11/99	unknown	252 (18%)	104125		
4/00		367 (18%)	21891		
9/00		353 (14%)	6944		
12/00		279 (15%)	13922		
1/01	ddl/ABC/SAQ	254 (15%)	18209		Transferred care to adult provider, GART sent
4/01		219 (23%)	21300		
6/01		229 (16%)	31432		
10/01		147 (13%)	34879	Phenosense sent 11/01	
2/02	ddl/d4T/3TC/TDF/ EFV				
3/02		157 (18%)	55		No missed doses
5/02		166 (24%)	<50		
8/02		166 (26%)	356		d/c all except 3TC
9/02	3TC monotherapy?	150 (20%)	2261	GART sent	Felt more fatigued off HAART
4/03	D4T/3TC	102 (11%)	8590		No side effects
7/03		163 (16%)	7148		Was to change to D4T/3TC/LOP/RIT
8/03	D4T/3TC/LOP/RIT? (unclear if Kaletra was actually added)				Changed PIs 8/03, d/t side effects (?) Wt loss, low energy, depression.

					Remeron started
11/03	D4T/3TC/ATV/RIT	183 (21%)	3943		
4/04		180 (20%)	5033		Good adherence
7/04		175 (17%)	2326		
10/04		162 (17%)	3355		
2/14/05		127 (12%)	3135		
2/28/05		182 (15%)	4610	Phenosense GT sent	

Resistance Test Findings

1/31/01 - Quest Genotype Key Mutations

NRT	D67N*, K70R*, T69D, M184V, T215F, K219Q*
NNRT	None
PI	L10I, I54V, L63P, A71V, V82A, I84V, L90M,
Others	L74I/L, A98S, F53L

* listed under "other"

11/27/01 - Virologic Phenosense Phenotype

	Fold Change	Sensitivity
NRTI		
ABC	5.4	Reduced susc
TDF	0.8	Sensitive
ddI	1.8	Reduced susc
3TC	>>>	Reduced susc
D4T	1.6	Sensitive
AZT	7.0	Reduced susc
ddC	1.8	Reduced susc
NNRTI		
DLV	0.9	Sensitive
NVP	0.6	Sensitive
EFV	0.4	Sensitive
PI		
AMP	7.9	Reduced susc
IDV	23	Reduced susc
LPV	30	Reduced susc
NFV	23	Reduced susc
RTV	>>>	Reduced susc
SQV	197	Reduced susc

10/7/02 - Gladstone Genotype Key Mutations

NRT	D67N, T69D, K70R, M184V, T215F, K219Q
NNRT	K103N
PI	L10I, I54V, L63P, A71V, V82A, I84V, L90M
Others	Y188H, F53L

2/28/05 - Virologic Phenosense GT Key Mutations

NRT	D67N, T69D, K70R, M184V, T215F, K219Q
NNRT	None
PI	L10I, V32I, L33F, M46I, I54V, L63P, A71V, V82A, I84V, L90M
Others	E6D, A98S, Q102K, K122K/E, I135T, C162S, D177E, T200T/I, I202V, E203E/Q, Q207D, R211R/K, L228H, R277K, R284K, T286A, A288E/G, V293I, E297E/A, I13V, N37D, F53L, K55K/R, I66F, I72I/V, P79A, V82T, L89V

	Fold Change	Sensitivity
NRTI		
ABC	5.44	Reduced susc
TFV	1.21	Sensitive
ddI	1.69	Sensitive
3TC/FTC	> MAX	Reduced susc
D4T	2.00	Reduced susc
AZT	14	Reduced susc
NNRTI		
DLV	1.55	Sensitive
NVP	0.79	Sensitive
EFV	0.64	Sensitive
PI		
f-AMP	40	Reduced susc
Ataz	> MAX	Reduced susc
IDV/r	94	Reduced susc
LPV/r	110	Reduced susc
NFV	109	Reduced susc
RTV	> MAX	Reduced susc
SQV	> MAX	Reduced susc

Replication Capacity: 52%

CASE DISCUSSIONS

The following questions were considered by the committee:

1. What are the available treatment options now and the impact of such changes, if any, on his HIV infection?

2. Should T-20 be used now or should it be reserved for use when newer agents become available?
3. Is it reasonable to start T-20 and tipranavir or wait to use T-20 plus TMC-114, a second generation NNRTI, or a CCR5 inhibitor?
4. Is there any experience using T-20 in combination with CCR5 inhibitors?

Interpretation/Implications for Treatment

If this patient truly acquired HIV via vertical transmission, then perhaps the most striking element of this resistance case is that he is a long-term survivor of HIV/AIDS with an excellent clinical but suboptimal virologic response to antiretroviral therapy. The patient has survived the 1980s and 1990s without detrimental consequences (e.g. opportunistic infections) from his disease. This patient's course is difficult to predict as there is little information regarding the natural history of slow progressors in the presence of partially suppressive antiretroviral therapy.

The results of the genotypes have been consistent over the last four years. There has been no evidence of evolution in the patient's resistance to NRTIs. This is perhaps due to the high level of genotypic resistance at the time of presentation to his current health care provider.

Interestingly, the mutations D67N, K70R, and T215F were not expected to contribute to NRTI resistance in 2001 when his first genotype was obtained and were therefore listed under the "other" category. However, it is now recognized that these thymidine analogue mutations (TAMs) are responsible for "rescuing" chain-terminated primers.¹

Most TAMs confer cross-resistance to all the nucleoside analogues.² Of note, the TAMs M41L and T210Y are missing from the patient's genotypes. This suggests that tenofovir may retain somewhat greater activity than other NRTIs. This is corroborated by the two phenotypes.

The patient was exposed to NNRTI therapy in 2002. The brief time on that regimen lead to the surfacing of either a new or archived K103N mutation. In either case, the K103N mutation confers broad resistance to the NNRTI class.

There are several mutations in the protease gene that have persisted from the first two genotypes. However, evidence of genotypic evolution is present. In addition to the seven protease mutations that were originally present (L10I, I54V, L63P, A71V, V82A, I84V, L90M), three new mutations (V32I, L33F and M46I) eventually emerged. Based on these genotypes and phenotypes, reduced activity would be expected to all the listed PI. Several mutations may also contribute to tipranavir resistance, including I13V (listed under "other"), L33F, V82A, V82T (listed under "other") and I84V.²

The patient has never been exposed to enfuvirtide, and therefore, resistance is not expected.

The panel agreed that a structured treatment interruption (STI) of his ARV therapy would not be a reasonable option, considering his low CD4 cell count of less than 200 cells/mm³ and the increased risk of opportunistic infections. His current ARV regimen, although not potent enough to achieve

¹ Shafer RW. Genotypic Testing for HIV-1 Drug Resistance. Available at <http://hivinsite.ucsf.edu/InSite.jsp?page=kb-03-02-07>.

² Victoria A. Johnson, MD, Françoise Brun-Vézinet, MD, PhD, Bonaventura Clotet, MD, et al. Update of the Drug Resistance Mutations in HIV-1: 2005. Topics in HIV Medicine. 2005 Mar/Apr 13 (1) 2005, 51-56. http://www.iasusa.org/resistance_mutations/mutations_figures.pdf

complete virologic suppression, is likely still providing some immunologic benefits. The most reasonable options would be to continue his current regimen (or some version of it) or to try an enfuvirtide-based salvage regimen.

The primary clinician states that the patient is just beginning to understand the gravity of his virus's resistance to ARV medications. Tolerability and quality of life are important to the patient, though remaining healthy is also a priority. If a new regimen were to be initiated, the provider would prefer a more durable regimen.

Based on the clinical history (stable CD4, viral load, no OI) and the need to preserve at least 2 fully active agents for a more durable future regimen, the panel concluded that the most reasonable option would be to maintain his current regimen, or a comparable version of his current regimen. His current ARVs have maintained his CD4 cells in the 170-180 range and his viral load less than 5000 copies/mL. It is likely that the patient might be able to continue on this regimen until a potent ARV combination could be constructed.

Minor modifications of his current ARV regimen were discussed by the panel. Due to concerns about the patient's slight stature and the possibility of lipoatrophy, substituting the stavudine component with zidovudine/lamivudine/abacavir (Trizivir™) might be a reasonable alternative. Additional concerns were raised about the accumulations of more NRTI mutations that might impair the activity of tenofovir by continuing a non-suppressive regimen. However, this type of evolution would be inconsistent with the concept of general NRTI mutation "pathways". Once the virus has evolved down the 67, 70, and 215 pathways, it is unlikely that the virus will then change directions and evolve down the 41, 210, and 215 pathways.³

Salvage therapy would be recommended if the patient was symptomatic and ill. An appropriate salvage regimen would include tenofovir, T-20, and tipranavir. However, the magnitude of viral response to tipranavir is unclear given the presence of many tipranavir-associated mutations. In a study presented at the 12th CROI, 44.2% or 40.9% of patients achieved a 1-log decrease in baseline viral load with 1 or 2 key mutations (33, 82, 84, 90), respectively.⁴ If tipranavir therapy is used, a phenotype demonstrating less than a 4- fold change to tipranavir would be helpful.

Another future salvage regimen would incorporate an investigational PI, TMC-114, by Tibotec. Three-class treatment experienced patients achieved viral load reductions from 1.28 to 1.85 logs with various doses of TMC-114 compared to 0.27 logs after comparator protease inhibitors.⁵ Forty-seven percent of salvage regimens in this analysis also contained T-20. Predictors of response to TMC-114 have not yet been identified since the drug is still in phase II clinical trials. In addition, there are no head to head comparisons between tipranavir and TMC 114. Because the clinical status of the patient has been stable, the panel recommended to defer use of TMC114 until further information is available.

³ Flandre P, Descamps D, Joly V, Meiffredy V, Tamalet C, Izopet J, Aboulker JP, Brun-Vezinet F. Predictive factors and selection of thymidine analogue mutations by nucleoside reverse transcriptase inhibitors according to initial regimen received. *Antivir Ther*. 2003 Feb;8(1):65-72.

⁴ Schapiro J, Cahn P, Trottier B, et al. Effect of Baseline Genotype on Response to Tipranavir/ritonavir (TPV/r) Compared with Standard-of-care Comparator (CPI/r) in Treatment-experienced Patients: The Phase 3 RESIST-1 and -2 Trials. 12th Conference on Retroviruses and Opportunistic Infections. Boston, MA. February 2005. Abstract 104.

⁵ Katlama C, Berger D, Bellos N., et al. Efficacy of TMC114/r in 3-Class Experienced Patients with Limited Treatment Options: 24-Week Planned Interim Analysis of 2 96-week Multinational Dose-finding Trials. 12th Conference on Retroviruses and Opportunistic Infections. Boston, MA. February 2005. Abstract L164B.

Recommendations

Regimen Options

Option 1: Maintain current regimen with increased NRTI backbone (stop stavudine)

Trizivir (zidovudine plus lamivudine plus abacavir) one bid plus ritonavir 100 mg plus atazanavir 300 mg daily (or other boosted protease inhibitor)

Pros: Well-tolerated, maintains CD4 and VL, quality of life

Cons: Not suppressive, possibility of developing further PI mutations, risk of abacavir hypersensitivity reaction during the first 6 weeks of therapy.

Option 2: Salvage therapy (preferred if patient develops clinical illness):

Tenofovir 300 mg daily, Trizivir® one tablet bid, tipranavir 500 mg bid, ritonavir 200 mg bid, and T-20 90 mcg SQ bid

Pros: Possibility of viral suppression

Cons: High pill burden, impaired antiviral activity of tipranavir, drug interactions, drug toxicity, poor quality of life

Option 3: Salvage therapy with an experiment medication such as an R5 inhibitor.(assuming a screening test showed presence of an R5 virus)

Pros: Access to a potentially effective agent

Cons: R5 inhibitors are only available in placebo-controlled studies. Also, these drugs can not be administered with tipranavir due to potential drug-drug interactions. The use of the remaining effective agent (T20) in such a study risks exposure to a placebo without other effective agents.

Dosing, Monitoring, and Follow-up Recommendation

- Obtain new phenotype which includes tipranavir fold change for future use
- Monitor closely for clinical illness and progression of CD4 decline and viral load.
- Check viral load, CD4 cell count 4 to 6 weeks after any ARV change
- Monitor for resolution of lipodystrophy