

HIV Resistance Testing Consultation Service Consultation Report

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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

AG is a 46 year old woman who has been HIV-infected for more than a decade. She has been on multiple regimens in the past including zidovudine (AZT), lamivudine (3TC), and indinavir (IDV). She began her care at the caller's clinic in 9/02. In 2003, she was diagnosed with anal and vulvar cancer, both HPV-related, and since then, she has undergone multiple surgeries. According to the caller, she is not a candidate for chemotherapy. She also has a history of peripheral neuropathy and weighs only 90 lbs. She is tolerating her current regimen of tenofovir/emtricitabine (Truvada), lopinavir/ritonavir (Kaletra), and efavirenz (Sustiva). Her adherence is believed to be excellent. Her CD4 nadir is unknown and there are no resistance tests prior to 7/05. Her antiretroviral history is outlined below. Question: "Should I change or continue her current ARV regimen? If it should be changed, what regimen should she be changed to?"

	REGIMEN *	CD4 cells/mm ³	VL COPIES/ML	RESISTANCE TEST FINDINGS	CLINICAL COURSE
10/02	Saquinavir/r, stavudine (d4T), 3TC		3910		Developed peripheral neuropathy; poor adherence
12/02	Abacavir, 3TC, Kaletra (4 tabs), Sustiva	149	10,000		Developed nausea and vomiting believed secondary to abacavir
1/03	Truvada, Kaletra (4tabs), Sustiva		112		Well tolerated
10/03	"		<75		
5/04	"		<75		
9/04	"	437	<75		
2/05	"	375	621		
6/05	"	236	33,700		Had vulvectomy during this time
7/05	"		29,200	GART: see below	
9/05	"	437	2360	Phenotype: below	

Resistance Test Findings

Key Mutations 7/05

NRTI	D67N, K70R, T215, K219E
NNRT	K103N, V118I
PI	L10F, K20R, V32I, M36I, M46I, I47V, A71V, V82A, I90M

Phenotype 9/05

Drug	Fold Change	Assessment
ABC	2.67	S
DDI	1.16	S
FTC	3.46	S
3TC	2.14	S
D4T	2.06	R
TDF	3.12	R
ZDV	205	R
EFV	52	R
ATV	26	R
Fos-APV	15	R
IDV	54	R
LPV/r	90	R
NLV	90	R
RTV	155	R
SQV	4.23	R
TPV/r	3.10	S

Interpretation/Implications for Treatment

There are some minor inconsistencies between the genotype, phenotype, and history. For example, the phenotype shows TDF resistance, while the NRTI mutations seen on the genotype suggest no TDF resistance (Gilead's data show that in the absence of the 41L and 210W mutations, there is not a fold change in TDF susceptibility.¹) Of note, the genotype was done in July 2005 and the phenotype was obtained in September of 2005 (2 months later), making it difficult to predict if an additional genotype done at the time of the phenotype would have been more concordant. It is thus unclear if TDF resistance developed between the time of the genotype and the phenotype.

There is a notable absence of M184V which implies that the patient is nonadherent with Truvada. This might explain the lack of resistance mutations for TDF and FTC on the genotype. The panel wondered if the patient was actually taking only lopinavir/r and efavirenz at the time of the genotype, but started taking tenofovir/emtricitabine before the phenotype, leading to a 4 fold change in FTC and resistance to TDF on the phenotype.

There is a clinical discordance as well. Despite all these mutations, she has done fairly well immunologically. It is possible that she acquired many of these mutations while on previous regimens, and had full viral suppression when she started lopinavir/r and EFV (10/03-2/05). Later, poor adherence led to additional mutations, which lead to viral breakthrough in 2/05. It was assumed that during the time of her multiple surgeries there was poor adherence, which would explain the viral load spike during the summer of 2005. Another explanation for her clinical success is supra-therapeutic levels of lopinavir/r due to her small body size. It is possible that higher lopinavir/r levels are overcoming the phenotypic resistance (90 fold change for lopinavir/r).² The panel discussed the utility of therapeutic drug monitoring for this patient, and it was concluded that the results would not likely alter treatment decisions.³

11/9/05

Recommendations

Regimen Options

- STOP: No one would stop HAART with the history of the low CD4 nadir.
- CONTINUE Truvada and Kaletra: This is the preferred option. It would be important to see if improved adherence on her current regimen would actually lead to full virologic suppression. Minor modifications were also suggested, such as removing EFV given the resistance present in the phenotype and genotype. If the next VL is less than 200 copies/mL, most panel members

¹ <http://www.viread.com/pdf/pi.pdf>

² R Bertz, et al. Lopinavir Inhibitory Quotient Predicts Virologic Response in Highly Antiretroviral-experienced Patients Receiving High-dose Lopinavir/Ritonavir. In. Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, Calif. Abstract 134.

³ ACTG A5146: A Randomized Controlled Trial Evaluating the Impact of Therapeutic Drug Monitoring (TDM) on Virologic Response to a Salvage Regimen in Subjects with a normalized Inhibitory Quotient (NIQ) <1 to one or more Protease Inhibitors. AACTG Pharmacology Committee Scientific Research Agenda March 16, 2004

would suggest continuing the current modified regimen (stopping the EFV, and adjusting the Kaletra to 2 tablets (or 3 capsules) BID) with significant adherence counseling, and monitoring for virologic failure. If the viral load is high, obtain simultaneous phenotype and genotype, and consider future treatment options (see under CHANGE).

- CHANGE: This is the second option. Trizivir™, TDF, TPV/r and T20 would be the ideal regimen virologically, but she probably will not qualify for ADAP coverage of T20..
- Another proposed option is a dual boosted PI-based regimen. Pharmacokinetic data is encouraging for the combination of Kaletra and atazanavir.⁴ Because of her small body weight however, she might be at a higher risk for jaundice. Another proposed combination was Kaletra and saquinavir as the patient's virus is susceptible to SQV. There are issues of tolerability with this combination. Dual boosted PIs with TPV/r are contraindicated due to the potential for a bidirectional drug - drug interaction that could reduce effective PI levels.
- Other options include using NRTIs alone to bridge to the next HAART regimen. The rationale of this approach is to prevent further accumulation of PI mutations and to preserve TPV as a future option, while altering viral fitness.
- Finally, the option of enrolling the patient into a TMC 125 or TMC 114 study was discussed.

Dosing, Monitoring, and Follow-up Recommendations

- If Kaletra is continued without EFV, dose adjust to 3 cap BID or 2 tablets BID
- Check VL and CD4 now and 4 to 6 weeks after a regimen change
- Reinforce adherence

⁴ Duvivier C et al. Dual boosted atazanavir/lopinavir/ritonavir containing regimen in HIV-1 infected pretreated patients: plasma trough concentrations and efficacy results. Abstract presented at International AIDS Society, July 27, 2005.