
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

The patient is a 44 year old man whose first positive HIV test was approximately 15 years ago. He has had no opportunistic complications. His current provider assumed his care in 7/05 (about a year after his last visit). His treatment history has been characterized by 3-class exposure and very poor adherence. When he presented to his current provider he was taking only lamivudine (3TC) and trimethoprim/sulfamethoxazole (TMP/SMX) and he felt well. His CD4 was 26 cells/mm³ (3%) and his viral load was 20,600 copies/mL. Other laboratory values were normal except for a mildly elevated SGOT.

The antiretroviral regimen was changed to abacavir/zidovudine/lamivudine (Trizivir), tenofovir (TDF) and lopinavir/ritonavir (Kaletra; LPV/r). Two months later his CD4 count was 38 cells/mm³ and his viral load was 18,000 copies/mL. His adherence was described as "pretty good". A resistance test and repeat CD4/viral load were ordered but the patient did not follow up. Although he was lost to follow up for about 8 months his pharmacy records showed regular refills.

He presented to clinic again in 5/06, at which point his CD4 count was 32 cells/mm³ and his viral load was 25,000 copies/mL. He said he had missed only "a few" antiretroviral doses since his last visit. His weight was stable and he felt generally well, except for transient episodes of lightheadedness and feeling "itchy all over".

Phenotype (PART) and genotype (GART) resistance tests were obtained in 7/06 (results are below). His provider is asking for ARV regimen advice.

DATE	REGIMEN	CD4 (cells/mm3)	VL (copies/mL)	COMMENTS
1991 – 7/2005	Various 3-class exposure (details N/A)		20, 000 to 40,000	Poor adherence
7/2005	3TC => ABC/3TC/ZDV, TDF, LPV/r	26	20,000	Clinically well
5/2006	TRZ/TDF/LPV/r	32	25,000	Only "a few" missed doses
7/2006	TRZ/TDF/LPV/r			No missed doses GART/PART Obtained

Resistance Test Findings

7/19/06 Trugene HIV-1 GART

NRT	D67N; T69N; K70R; M184V; T215F; K219E
NNRT	None
PI	L10I; I13V; K20M; M36I; F53L; I54L; Q58E; L63P, A71I; V82A; L90M

7/19/06 Monogram Phenotype

	Fold Change	Clinical Cut-off (lower)	Clinical Cut-off (upper)	Biologic Cut-off	Interpretation
NRTI					
ABC	6.84	4.5	6.5	6.84	Resistant
TDF	1.15	1.4	4.0		Sensitive
ddI	2.15	1.3	2.2		Partially Sensitive
3TC	> MAX	3.5			Resistant
FTC	> MAX			3.5	Resistant
D4T	1.9	1.7			Resistant
AZT	18			1.9	Resistant
NNRTI					
DLV	0.47			6.2	Susceptible
NVP	0.54			4.5	Susceptible
EFV	0.48			3	Susceptible
PI					
fAPV	114			2.0	Resistant
fAMP/r	114	4.0	11		Resistant
ATV	266	2.2			Resistant
ATV/r	266	5.2			Resistant
DRV	33	10	40		Partially Sensitive
IDV	135			2.1	Resistant
IDV/r	135	10			Resistant
LPV/r	207	9	55		Resistant
NFV	137			3.6	Resistant
RTV	> MAX			2.5	Resistant
SQV	109			1.7	Resistant
SQV/r	109	2.3	12		Resistant
TPV	2.77	2	8	1.6	Partially Sensitive

Interpretation/Implications for Treatment

This 44 year old man with longstanding HIV infection and advanced immunosuppression has high level multi-class resistance and is unlikely to achieve full virologic suppression with approved antiretroviral agents at the time of the consultation. His relatively modest viral load suggests that his current regimen is having some beneficial effect but his very low CD4 count places him at significant risk for HIV-associated disease progression. Importantly, he has not experienced any obvious toxicity from any of his prior treatment regimens.

The panel felt strongly that therapy should not be discontinued. Observational studies have consistently demonstrated that continued therapy is preferred to no therapy even when highly resistant HIV is present. Also, several randomized studies have failed to show a benefit from interrupting therapy with a goal of allowing the drug-susceptible "wild-type" HIV to emerge.

The recent genotype and phenotype tests demonstrate high level resistance to the nucleoside reverse transcriptase inhibitor (NRTI) class. Although it is unlikely that any drug from this class will be fully active, recent studies from several groups indicate that NRTIs often have persistent anti-HIV activity against highly resistant variants. As the fold-changes for tenofovir and abacavir were relatively low, and as the patient was clearly benefiting virologically from his regimen, it was suggested that these drugs be continued. It was also strongly recommended that 3TC (or FTC) be continued as this drug often has persistent direct activity against drug-resistant variants (~ 0.5 log). Also, the 3TC-associated M184V mutation reduces viral fitness and enhances the viral susceptibility to zidovudine and tenofovir.

Although both geno- and phenotype results suggest that the non-nucleoside reverse transcriptase inhibitor (NNRTI) class should be fully active (and even "hypersusceptible"), given the history of NNRTI-failure, it is almost certain that re-introducing NNRTIs will result in the rapid emergence of archived resistance. In contrast to the NRTIs, there is no data suggesting that NNRTIs have residual benefit once drug-resistance has emerged. Several studies have shown an association between multiple NRTI mutations and apparent NNRTI hypersusceptibility[1] but more recent studies have demonstrated that, while NNRTI naïve persons might benefit from this strategy, there is no long-term virologic advantage for NNRTI experienced patients[2, 3].

It is difficult to predict whether this virus would be susceptible to etravirine (TMC-125), an investigational NNRTI agent[4]. Early reports suggest that the number of NNRTI mutations, particularly if the 181 mutation is present, predicts a significantly diminished response to this drug[5], whereas viruses that harbor only 1 or 2 NNRTI mutations, including K103N, are likely to retain susceptibility[1]. The only way to determine this is to obtain another genotype while taking nevirapine (NVP) or efavirenz (EFV). The panel felt that no NNRTI should be used until etravirine was available.

There is significant resistance to the protease inhibitor class, with only ritonavir boosted darunavir (DRV/r) and tipranavir (TPV/r) likely to retain any activity. Data regarding the resistance profiles of these drugs are limited.

Reduced darunavir activity has been associated with the number of protease mutations present, particularly with cumulative mutations at positions 50, 54, 76, and 84. Analysis of pooled data from the POWER 1, 2, and 3 studies demonstrate a correlation between the number of PI-associated mutations, darunavir fold change, and virologic outcome. Fold changes < 10 are highly correlated with 10 or fewer PI mutations and indicate a high probability of achieving a VL < 50 copies/ml. In addition, >12 mutations was associated with high level phenotypic resistance (fold change > 40) and a low

likelihood of full viral suppression. These authors concluded that phenotypic fold change < 10 was the single best predictor of darunavir activity[6]. This virus shows a darunavir phenotypic fold-change of 33, suggesting that this drug would not be expected to contribute much to his next regimen. However, the genotype shows 11 mutations associated with PI resistance; of these, only the 54V mutation is present from the key mutations associated with DRV resistance, suggesting that this drug should be quite active. The panel felt that the phenotypic assay was a more reliable predictor of outcome than the genotypic assay.

Mutations associated with diminished response to TPV/r include 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D, and 84V[7]; with 10I/V/S, 13V, 33V/I/F, 36V/I/L, 82T/L, and 84V contributing disproportionately[8]. This virus shows mutations at 5 of these sites (unlike the A, M, and V substitutions at position 54, the L substitution has not been associated with diminished TPV activity, nor has the A substitution at position 82). These results would predict substantially diminished clinical response to TPV and would give DRV a clear advantage. However, the phenotypic fold change to TPV for this patient's virus is only 2.7, which is above the lower clinical cut-off but well below the upper clinical cut-off.

Treatment regimens that contain at least 2 fully active ARVs have been shown to offer the best chance of achieving complete and durable virologic suppression and optimal immunologic recovery. Among currently-approved ARV agents, the only agent likely to be fully active for this patient's virus is the fusion inhibitor, enfuvirtide (T-20). Combining enfuvirtide with tipranavir/r, and with as many partially-active NRTIs as tolerated, probably represents a reasonable option and his best immediate chance for viral suppression.

However, there are risks involved with switching to an enfuvirtide-based regimen when the NRTI class is heavily compromised and the degree of residual protease activity is uncertain. Resistance to enfuvirtide has been shown to occur very rapidly when enfuvirtide is not combined with at least one other fully effective agent. If tipranavir is not a strong contributor to an enfuvirtide-containing regimen, there is a good chance that significant enfuvirtide resistance will develop that will preclude its future use (and might also compromise the effectiveness of investigational fusion inhibitors).

Another possible treatment option is to continue the patient's current regimen until new active agents are available. The first novel integrase inhibitor, MK-0518, is currently available via expanded access and FDA approval is expected in late 2008. Data from phase II and III trials suggest that MK-0518 is well-tolerated and very active against virus with high level 3-class resistance[9]. Combining the integrase inhibitor with enfuvirtide and/or boosted tipranavir, and with partially-active NRTIs, would be very likely to achieve complete and durable viral suppression, even in this extensive multi-class resistance virus. Arguments against waiting for the integrase inhibitor rather than switching now is an unquantifiable risk of disease progression or death, even in this generally well patient over a short time interval. An immediate regimen change would be indicated if the current neurologic symptoms worsen or if any new HIV-related symptoms develop.

Since this patient is clinically well, and tolerating his current regimen, panel members were generally in favor of staying the course until the new integrase inhibitor is available. The panel also favored aggressively pursuing access to the integrase inhibitor through manufacturer-sponsored compassionate use program[10]. Review of the eligibility requirements for this program suggests that this patient would qualify for enrollment. More information about eligibility and enrollment is available at the following website: <http://www.benchmark.com/secure/earmrk/earmrk.html>.

Another possible option to consider was accessing maraviroc via expanded access. Maraviroc is an CCR5 inhibitor which may have activity against the patient's virus; however, recent epidemiologic data from a number of groups suggests that this patient has a very high likelihood of harboring measurable

X4-virus (both a low CD4 and extensive treatment exposure are highly associated with having X4 or dual/mixed virus).

The panel also recommends additional evaluation of his non-specific neurologic symptoms, specifically ruling out the possibility of syphilis. If serum RPR is not reactive, CNS imaging and CSF studies should be considered. A thorough medication review looking for potentially unfavorable drug-drug interactions, especially between protease inhibitors and some psychoactive agents, is also indicated.

Poor adherence has been an important barrier to treatment success in the past. Optimizing adherence support now needs to be a very high priority for the success of any new ARV regimen.

Regimen Options

Option 1: Continue the current regimen until an integrase inhibitor is available

Pro: Tolerability and adherence; clinically stable over extended period despite very low CD4

Con: Potential for selection of more PI mutations that could threaten future response to DRV/r or TPV/r; high risk for disease progression unless CD4 improves

Option 2/3: Ritonavir 200 mg bid plus tipranavir 500 mg bid plus enfuvirtide 90 mg SQ bid plus Trizivir one tablet bid plus tenofovir 300 mg po daily +/- Etravirine (TMC-125)

Pro: Contains 2 active drugs. The potential addition of etravirine (TMC-125) by expanded access might provide additional virologic activity

Con: Unclear if TPV/r will have sufficient activity to avoid rapid emergence of enfuvirtide and TPV resistance, high pill burden, complicated drug regimen

Option 2/3: Ritonavir 100 mg bid plus darunavir 600 mg bid plus enfuvirtide 90 mg SQ bid plus Trizivir one tablet bid plus tenofovir 300 mg po daily +/- etravirine (TMC-125)

Pro: Possible incremental benefit from TMC-125 without risk of unfavorable interactions with DRV/r

Con: Complicated regimen with potential for new unexpected toxicity, high pill burden, unclear how active TMC-125 or DRV/r will be; if not fully active, enfuvirtide will be lost

Option 4: 3TC (lamivudine) monotherapy

Pro: Minimizes the risk for accumulating additional PI and NRTI mutations if selective pressure is removed; regimen is simple and well-tolerated

Con: High risk of disease progression in the likely event that the CD4 does not increase

Dosing, Monitoring, and Follow-up Recommendation

- Monitor VL, CD4 one month after regimen change
- Monitor adherence, side effects, and drug toxicity

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