
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 16-year-old Hispanic female who was perinatally infected with HIV infection. Her history is incomplete due to lost records. The patient lives with her grandmother and aunt. According to the family, she takes her pills regularly. This has been confirmed by a review of her pharmacy refill records. The patient has not had any opportunistic infections, but has a history of severe necrotizing sinusitis (currently under control). Currently the patient is clinically well, but she has had two bouts of shingles in the past four months with the last episode involving multiple dermatomes.

Despite extensive antiretroviral therapy use in the past, the patient has never achieved an undetectable viral load (see Table). Her most recent CD4 and viral load were 60 cells/mm and > 500,000 copies/mL, respectively (while receiving tenofovir, FTC and darunavir/ritonavir) The patient's clinician has tried to enroll her in the raltegravir expanded access program (integrase inhibitor), but she was declined because of her age. She refuses to take enfuvirtide (T-20) due to concerns about injection site reactions and the pain of injection. The patient is also unable to take abacavir due to a prior possible hypersensitivity reaction.

DATE	REGIMEN *	CD4 cells/mm ³	VL COPIES/mL	RESISTANCE TEST FINDINGS	CLINICAL COURSE
4/01	CBV/APV/EFV	586	340k		
9/01	CBV/LPV/r/APV/EFV				
11/01		740	58k		
10/02	CBV/TDF/LPV/r				
9/04	unknown	159	180k		
10/04	AZT/TDF/ATV/r				
6/05	unknown	173	323k		
1/06	CBV/TPV/r/T-20	100	100k		Probably not taking T-20
10/06	TDF/FTC/DRV/r /T-20	50	>750k		Undetermined lung disease - resolved

CBV = Combivir™ (zidovudine plus lamivudine)

APV= amprenavir (Agenerase®)

AZT = zidovudine (Retrovir®)

EFV = efavirenz (Sustiva®)

LPV/r = lopinavir/ritonavir (Kaletra®)

TFV = tenofovir (Viread®)

ATV/r= ritonavir (Norvir®) boosted atazanavir (Reyataz®)

TPV/r = ritonavir (Norvir®) boosted tipranavir (Aptivus®)

DRV/r = ritonavir (Norvir®) darunavir (Prezista®)

T 20 = enfuvirtide (Fuzeon®)

Resistance Test Findings

Key Mutations

12/03 unknown regimen unknown labs

NRT	41L, 44D, 118I, 210W, 215Y
NNRT	
PI	10I, 46I, 63P, 82A, 90M

8/04

NRT	41L, 67N, 69N, 70R, 75M, 184V, 210W, 215F, 219Q, 333E,
NNRT	101E, 181C, 190A
PI	10I, 20R, 32I, 33F, 36I, 46I, 47V, 54M, 63P, 71V, 84V, 90M

2/07

NRT	41L, 67N, 69N, 70R, 75M, 184V, 208Y, 210W, 215F, 219Q
NNRT	101E, 181C, 190A
PI	10I, 32I, 33F, 36I, 46I, 47V, 54M, 58E, 60E, 63P, 71V, 84V, 90M

Interpretation/Implications for Treatment

In summary, this perinatally-infected adolescent has a highly resistant virus and is currently exhibiting significant virologic failure on a reasonably potent regimen. She has advanced immunodeficiency and is clinically unwell. Without access to investigational agents, there are no therapeutic antiretroviral options that are expected to provide a satisfactory immunologic and virologic response.

The panel first acknowledged the challenge of treating perinatally-infected adolescents. These patients frequently have multi-drug resistant viruses from prolonged administration of multiple non-suppressive antiretroviral regimens. The promising investigational agents, including those in expanded access programs, are not usually available to those less than 18 years of age. The psychosocial stressors of adolescence frequently make medication adherence particularly difficult.

It is interesting to compare the results of the different genotypes. Between 8/04 and 2/07, there was minor evolution of the virus. In the reverse transcriptase gene, the virus lost the 333E and gained the 208Y mutations. Both of these mutations are uncommon mutations that facilitate some zidovudine (AZT) resistance. In the protease gene, the virus gained the 58E and the 60E mutations that are associated with tipranavir (TPV, Aptivus®) and atazanavir (ATV, Reyataz®) resistance, respectively. These mutations are consistent with the patient's treatment history and demonstrate minor but measurable evolution of the virus under selective pressure.

Six nucleoside associated mutations (41L, 67N, 69N, 70R, 210W, 215F and 219Q), are present in the reverse transcriptase gene.¹ The presence of three or more of these mutations confer high-level resistance to many of the nucleoside reverse transcriptase inhibitors (NRTIs), including AZT, tenofovir (TDF, Viread®), stavudine (d4T, Zerit®) and abacavir (ABC, Ziagen®). The 75M mutation contributes to d4T resistance, while the M184V mutation confers high level resistance to lamivudine (3TC, Epivir®) and emtricitabine (FTC, Emtriva®). Overall, these genotypes show high-level resistance to all of the FDA-approved NRTIs. Despite the presence of highly resistant virus, it is likely that these drugs still exhibit some residual antiviral activity and/or select for a virus that is poorly fit. The continued use of NRTIs in salvage regimens remains the standard approach, although which drugs to use and how many remains undefined. Most clinicians will continue 3TC or FTC given that these drugs often have partial activity and select for a mutation (M184V) that both reduces fitness and enhances the activity of AZT and/or tenofovir.

The 181C and 190A mutations each confer high-level resistance to all FDA-approved nonnucleoside reverse transcriptase inhibitors (NNRTIs) (as of March 2007). The 101E mutation also confers low-level resistance to these drugs. Unlike the NRTIs, none of the NNRTI mutations reduce viral fitness, so there is no advantage to maintaining these agents when resistance is present. Of interest, etravirine (TMC 125) is a second generation NNRTI that should be active against this patient's virus, although the presence of two mutations in RT gene may be associated with reduced activity of this drug.

It is notable that this patient has received both a TPV- and darunavir- (DRV, Prezista®) containing regimen without achieving significant immunologic or virological benefits. Other protease inhibitor failing regimens include ritonavir boosted lopinavir (LPV/r, Kaletra®), atazanavir and amprenavir. The genotype shows at least five DRV-associated mutations, eight TPV-associated mutations, and 11 LPV-associated mutations.¹ The presence of multiple PI mutations on the genotype suggest that none of the currently FDA-approved PI would provide significant antiviral activity. Nevertheless, a phenotype might be helpful in identifying any active PIs; although the likelihood of encouraging results is low.

Although a T-20 genotype is not available, the history of virologic failure on this agent for 10 months strongly suggests that T-20 resistance is present. In some patients continuing T-20 in the face of resistance can still lead to a rise in CD4 count.³ However, no CD4 benefit was observed in this patient, possibly due to non-adherence.

Access to investigational agents is crucial in this patient. The panel suggested aggressively petitioning the drug companies to allow her investigational agents in spite of her age. She is of adult size and likely can take adult doses of the drugs. This patient is not clinically well with a very low CD4 count and a very high viral load. She presents with multi-dermatomal shingles, a recent undetermined lung disease, and a history of severe necrotizing sinusitis. Without access to these investigational drugs, it is unlikely that her immunologic status will improve and her prognosis is poor.

Etravirine has already been discussed in this report. As of March 2007 (when this case was presented) there were two other investigational agents in expanded access programs: maraviroc and raltegravir. Maraviroc can inhibit HIV entry for viruses using the CCR5 co-receptor to enter. Clinical trials show that maraviroc has no antiviral activity against viruses that use the CXCR4 receptor for cell entry. Before prescribing maraviroc, a special lab test known as a tropism assay (Trofile®) is required to determine the viral co-receptor status. Patients infected with HIV for many years (such as this patient) are more likely to harbor viruses that use the CXCR4 receptors and therefore, not respond to maraviroc.

Raltegravir is an integrase inhibitor and appears to be safe, well-tolerated and highly effective when used with other active drugs. Failure of this drug is associated with rapid emergence of high-level drug resistance, suggesting that the drug like the NNRTIs has a low “genetic” barrier. For this reason, at least one and preferably two other active agents should be combined with raltegravir. Although suboptimal, the best chance for success in this patient would be a regimen containing raltegravir, etravirine and perhaps maraviroc (assuming that the virus is R5-tropic). This regimen should be combined with at least two NRTIs (e.g., tenofovir and FTC). A protease inhibitor is also often used in “deep” salvage, although given the level of resistance it must be admitted that the continued use of these drugs is based primarily on the lack of any evidence constructing a protease-inhibitor-sparing regimen.

Because of the seriousness of the patient’s current immunological status, the panel believed that starting raltegravir with an optimized background regimen as soon as other fully active agent is available. The Benchmark study showed that 61% of patients receiving raltegravir with no active agents still achieved viral suppression at 16 weeks.⁴ Although less than ideal, such an approach would offer the patient a reasonable chance of virologic, immunological, and clinical success. Adding etravirine may offer some additional activity.

Recommendations

Regimen Options

Option 1: Tenofovir / Combivir / Rilonavir / Darunavir / Raltegravir and either Etravirine .or Maraviroc or both, depending on the results of the tropism assay.

Benefits – Most likely to achieve durable viral suppression and thus immunological and clinical benefits

Risks –

1. Failure of raltegravir if used with no optimized background
2. Multiple agents causing poor adherence
3. High pill burden
4. Risk of drug toxicity

Dosing, Monitoring, and Follow-up Recommendations

Take all antiretroviral agents with food for optimal tolerability

Tenofovir 300 mg; one tablet po daily

Combivir 1 tablet po bid

Ritonovir 100mg; one capsule po bid

Darunavir 300 mg; two tablets po bid

Raltegravir 400 mg po bid (investigational, expected FDA approval October 2007)

Maraviroc 150mg po bid (when used in combination with ritonavir)

T-20 90 mg sq bid

Etravirine 800 mg po bid (investigational)

Monitor CD4 count every 2-3 months and HIV RNA very frequently (every 1 to 2 months).

Monitor CBC, lipid and hepatic panel, renal function, glucose, hemoglobin A1c, and blood pressure

Monitor side effects of antiretrovirals

Tenofovir: monitor serum creatinine and urinalysis for renal insufficiency.

Combivir: monitor for anemia, gi distress

Ritonavir boosted darunavir: monitor for gi distress, glucose, lipids, hepatitis

Maraviroc: Monitor for hepatitis and allergic reactions of rash, fever, hypotension

Enfuvirtide: monitor for pain at injection and injection site reactions, upper respiratory infections

Etravirine: monitor for rash, fever, hepatitis

Monitor for drug-drug interactions with PI

References

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4. Cooper, D. et al , CROI, 2007. abstr 105 LB