
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 case is a 10-year-old Asian boy who acquired HIV infection through vertical transmission. He is clinically stable and asymptomatic from his HIV infection. His medical problems include seasonal allergies. Previous infections are largely unremarkable. The patient has been on various antiretroviral regimens (see below) since he was approximately 8 months of age. The patient's care is complicated by the fact that he lives in Japan. In addition to the primary care he receives there, he is seen by a U.S. based pediatrician with expertise in HIV disease approximately twice a year. Laboratory tests are mostly drawn in Japan to minimize expenses to the family and results are sent with him during his visits to the US with his mother. Medications are obtained from Japan and the United States (when the medicines are not available in Japan). His adherence, according to his mother, is said to be good

This patient is not yet aware of his HIV diagnosis. The pediatric HIV team has been working on this issue with the mother. However, the mother has been recently diagnosed with breast cancer and this has been extremely stressful on the family lately. Given this added stress, she does not feel that this is the right time to disclose to the child his HIV status.

ARV history is as follows.

DATE	REGIMEN *	CD4 cells/mm ³	VL COPIES/ML	RESISTANCE DATA
12/4/96	ZDV	617 (18%)	720,000	
1/8/97	ZDV + ddl	905 (18%)		
4/9/97	"	1512 (30%)	24000	
9/10/97	Start ZDV + 3TC + NFV	954 (29%)	120000	
10/8/97	ZDV + 3TC + NFV	615 (34%)	4100	
11/11/98		1473 (34%)	110000	
2/15/99				Genotype drawn under research protocol: D67N, K70R, M184V
5/12/99		1180 (30%)	9600	
11/10/99		724 (24%)	110000	
2/9/00		253 (15%)	150000	Start d4T+ddl+EFV
5/17/00	D4T+ddl+EFV	651 (25%)	12000	

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3/12/02		1254 (29%)	2100	
2/18/03		920 (26%)	6900	
2/17/04		682 (22%)	16000	
3/30/05				Genotype: RT: M41L, D67N, K70R, L74V, L100I, K103N, , H208Y, T215F, K219Q Protease: K20M, L10V, M36I, L63P, A71V, L90M
4/19/05		456 (21%)	18000	
6/21/05	Start d4T+ABC+LPV/r	619 (20%)	610	
8/23/05	D4T+ABC+LPV/r	595 (22%)	<400	
10/25/05		826 (25%)	< 400	Genotype obtained – patient switched to FTC + 3TC + LPV/r
11/29/05	FTC + 3TC + LPV/r	652 (27%)	< 400	
2/21/06	Pt changed to TDF + 3TC + LPV/r	580 (19%)	4200	Pt with mumps infection.
3/14/06	TDF + 3TC + LPV/r	596 (25%)	8800	
5/16/06		607 (24%)	4300	
8/8/06		716 (24%)	5100	
10/4/06				Genotype: RT: M41L, D67N, K70R, L74V, L100I, K103N, , H208Y, R211K, T215F, K219Q Protease: L10V, K20M, M36I, I54V, L63P, A71V, L76V, V82A, L90M

Resistance Test Findings

2/99 Gladstone Virology Key Mutations

NRT	D67N, K70R, M184V
NNRT	
PI	L63P

3/06 Quest Diagnostics Key Mutations

NRT	M41L, D67N, K70R, L74V, H208Y, T215F, K219Q
NNRT	K103 N, L100I
PI	L10V, K20M, M36I, L63P, A71V, L90M

10/06 Quest Diagnostics Key Mutations

NRT	M41L, K70R, L74V, H208Y, R211K, T215F, K219Q,
NNRT	K103 N, L100I
PI	L10V, K20M, M36I, M46I, I54V, L63P, A71V, L76V, V82A, L90M

Questions for Discussion:

1. Given this child's age and need for long term planning of therapy, what is the best regimen that can be offered to him?
2. Given the limitations of the family's residence in Japan (expenses, distance, monitoring, etc.), what are the best ARV treatment options?

Interpretation/Implications for Treatment

This patient early antiretroviral drug history is notable for sequential exposure to nucleoside analogues, followed in 1997 by a nelfinavir-based regimen and then in 2000 by an efavirenz based regimen. In retrospect, each regimen was suboptimal and as a consequence the patient developed extensive three class resistance. The patient finally achieved a "complete" virologic response in 2005 when he was switched to a boosted protease inhibitor-based regimen. This treatment history is generally consistent with how adults were managed during this time.

Due to a medication error, the patient in 2005 received emtricitabine (FTC), lamivudine (3TC), and LPV/r, and subsequently developed virologic rebound. At that time, the FTC was changed to tenofovir (TDF) and he continued on his 3TC and LPV/r. He remains on this regimen at the time of the consultation.

During the past 10 years, the patient's CD4 percentage has remained high (~25 to 30%). His most current viral load in August 2006 was 5100 copies/mL with a CD4 count of 716 cells/mm³ (24%). Although adherence by report is good, children typically have less than optimal adherence due to difficulty in swallowing, problems with taste, adverse effects, and interference with life style.¹

The goal of antiretroviral therapy, if feasible, is to achieve maximal virologic suppression. With the availability of several drugs designed to treat drug-resistant HIV (e.g., enfuvirtide, darunavir, tipranavir, raltegravir, maraviroc and etravirine) complete viral suppression may now be achievable in the majority of highly treatment-experienced adults. The primary challenge in this case pertains to the lack of evidence in how best to manage children and adolescents. An equally important challenge pertains to the lack of access to these new drugs in Japan.

How then should this patient be managed? In certain cases such as non-adherence, intolerance, or severe resistance there is clear immunologic and clinical evidence for maintaining a partially suppressive regimen (as compared to no therapy).^{2, 3} This approach may be preferred to switching given that most of the potentially effective drugs are not readily available for children, and any switch now to an incompletely suppressive regimen might result in rapid virologic failure and the loss of even more future drug options. The primary risk of maintaining a non-suppressive regimen is the development of new antiretroviral resistant mutations. The patient's recent history clearly illustrates this

risk, given the accumulation of extensive resistance during approximately 9 years of partially suppressive antiretroviral therapy.

The patient's most recent genotype contains multiple nucleoside analogue mutations (e.g., M41L, D67N, K70R, L74V, T215F, and K219Q). Indeed, of the major mutations associated with the drugs which the patient has received, only K65R, M184V and perhaps L210W are lacking. The patient's current genotype suggests broad cross-resistance to most nucleoside analogues. In addition to the established mutations within reverse transcriptase, the patient's virus has developed R211K (which may simply be polymorphism and the H208Y (which may be a compensatory mutation).⁴

The patient's most recent genotype shows five primary resistance mutations in the protease gene (M36I, M46I, I54V, V82A, and L90M) and a few secondary or minor mutations (L10V, K20M, L63P, A71V, and L76V). In total, 7 mutations to LPV/r are evident and the accumulation of 7 or 8 mutations is likely to confer resistance to LPV/r.⁴ Reduced darunavir activity has been associated with the number of protease mutations present, particularly with cumulative mutations at positions 50, 54, 76, and 84 (the patient has two of these mutations).⁵ 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 with 10I/V/S, 13V, 33V/I/F, 36V/I/L 82T/L, and 84V contributing disproportionately.⁶ This virus shows mutations at 4 of these sites. Predicting which of the novel protease inhibitors to use is challenging. A phenotype may be useful.

The patient also has evidence of significant NNRTI resistance. The presence of the K103N mutation confers resistance to all of the FDA-approved nonnucleosides (NNRTIs), but may spare etravirine (TMC125), a second generation NNRTI.⁷

In summary, this patient has developed triple class ARV resistance. In addition to enfuvirtide and the various experimental medications available in expanded access, the patient's virus may be susceptible to some of the more recently developed protease inhibitors (e.g, darunavir and tipranavir). It is also likely that many of the nucleoside analogues will have residual activity. Constructing a fully suppressive regimen would be easy if the various drugs were available and if the proper dosing for this child was defined.

Despite these therapeutic possibilities, clinical data and dosing recommendations in children is very limited or nonexistent and its availability thru expanded access may not be possible in children. Fortunately, the high CD4 counts allow some time before a new antiretroviral regimen must be started. In addition, continued adherence monitoring would be critical to the success of any new regimen.

Recommendations

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. The panel discussed several options for this child.

One option includes treating the patient with the most aggressive antiretroviral therapy when his CD4 cell counts warrant starting a new ARV regimen. This strategy has the benefit of maximal virologic suppression and immunologic restoration. One such regimen that could be constructed include an integrase inhibitor such as raltegravir plus a protease inhibitor for multi-PI resistant viruses (ritonavir boosted darunavir or tipranavir) in combination with as many partially active nucleosides as tolerated. Lamivudine or emtricitabine might be included in the regimen given (1) these drugs have persistent activity even in the face of resistance, (2) these drugs select for M184V, which reduces fitness and enhance the activity of other nucleoside analogues. The largest challenge is deciding which protease inhibitor to use. The panel felt that a phenotype would be particularly helpful in this regard. Other fully active ARV options include use of a fusion inhibitor (T-20, enfuvirtide) or etravirine (TMC-125) a

second-generation NNRTI manufactured by Tibotec available on expanded access. Etravirine has also been studied safely in combination with darunavir without drug interactions.

Another option favored by the majority of the panel is to make no changes at this time and continue the patient on his current non-suppressive ARV regimen with the goal of immunologic boosting/maintenance. Risks of this strategy include accumulation of further mutations which could negatively affect future strategies. Despite these risks, the panel members were in favor of this approach as how best to use the various drugs which is not yet clear (for children).

Regimen Options

- 1) Ritonavir boosted darunavir (or possibly tipranavir) plus raltegravir (integrase inhibitor) plus multiple NRTIs (ZDV+ ABC+3TC/FTC ±tenofovir)

Pros: best chance of providing viral suppression if phenotype shows susceptibility to darunavir or tipranavir; integrase inhibitors are well tolerated with few adverse effects

Cons: high pill burden, insufficient data on integrase inhibitor in children, twice daily dosing may reduce adherence

- 2) Observe and continue the current regimen of tenofovir, lamivudine, and lopinavir/ritonavir

Pros: will likely result in stable immunologic and clinical status for the next few years

Cons: risk of increasing mutations to NRTIs and PIs with ongoing viral replication

- 3) Etravirine plus enfuvirtide plus multiple NRTIs as identified above in #1

Pros: etravirine is active against the K103N mutation

Cons: subcutaneous injections, twice daily administration, risk of rash/drug toxicities with etravirine and enfuvirtide; data for integrase inhibitors lacking in children

Dosing, Monitoring, and Follow-up Recommendations

- 1) Obtain phenotype to determine susceptibility to darunavir and tipranavir
- 2) Viral load and CD4 count within 3 to 4 weeks after ARV change
- 3) Monitor adherence and anticipate drug toxicities

Dosing (this patient weighs 45 kg)

- 1) Darunavir/ritonavir: Ongoing trial evaluating the dosing of darunavir in children given the adult dose vs doses 20-33% higher. Adult dose of darunavir is 600 mg (2 capsules) po bid plus ritonavir 100 mg bid po; take with food
(<http://clinicaltrials.gov/ct/show/NCT00355524;jsessionid=257A0CBC7BC31354AB66CF7BA93D3779?order=4>)
- 2) A trial in children using tipranavir/ritonavir has completed enrollment and study completion is expected June 2007. California sites include Childrens' Hospital in Los Angeles and USC Medical Center in Los Angeles. (<http://clinicaltrials.gov/show/NCT00076999>)
- 3) NRTIs: take all with food for improved tolerability
 - a. Zidovudine 180 to 240 mg/m² po bid (maximum 300 mg po bid)
 - b. Lamivudine 4 mg/kg bid po (maximum 150 mg po bid)
 - c. Abacavir 8 mg/kg bid po (maximum 300 mg po bid)
 - d. Tenofovir (Viread) not approved in children; the investigational dose is 210 mg/m² BSA up to a maximum of 300 mg po daily
- 4) Etravirine 200 mg bid PO for children > 18 years of age. Available by expanded access by calling **1-866-889-2074**, or by emailing **TMC125EAP@i3research.com**
- 5) Raltegravir is available by expanded access
(<http://www.benchmark.com/secure/earmrk/earmrk.html>) Clinical trials with raltegravir is enrolling for patients >16 years of age.
<http://clinicaltrials.gov/ct/show/NCT00377065?order=1>
- 7) Enfuvirtide 2mg/kg bid SQ into upper arm, anterior thigh, or abdomen (maximum of 90 mg SQ bid) provides levels comparable to adult levels

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