
HIV Resistance Testing Consultation Service

Consultation Report

Co-Chairs: Steven G. Deeks, MD
Betty J. Dong, Pharm.D

Panel Members: Richard Aranow, MD
Teri Liegler, PhD
Brad Hare, MD
Amy Kindrick, MD, MPH
Parya Saberi, PharmD
Jason Tokumoto, MD

Project Director: Ronald H. Goldschmidt, MD

Disclaimer. This information has been developed solely as an educational resource for health care professionals interested in HIV care and research. The information presented represents the views of the Panel members only and not necessarily those of the National HIV/AIDS Clinicians' Consultation Center's HIV Telephone Consultation Service (Warmline), the Positive Health Program at San Francisco General Hospital, or sponsoring organizations. Resistance testing can help identify whether certain drugs or classes of drugs might be ineffective, but cannot establish which drugs will be effective. Furthermore, test results can be inaccurate and interpretation of tests is not yet standardized. Because of the many factors involved in treatment decisions when resistant virus is present, the antiretroviral regimens and the therapeutic strategies discussed are not the only possible options and might be different from current Practice Guidelines. Other sources of information on resistance testing, such as clinical HIV websites, can be of help. Health care professionals should consult the HIV Telephone Consultation Service (Warmline) or HIV experts in their community before using any of the recommended therapeutic regimens or strategies in this document.

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 19-year-old perinatally HIV-infected girl who is now about 28 weeks pregnant. In addition to HIV, she acquired HCV infection at birth (genotype 2b, treated in 1999 with no response, Fibrosure test 6/08 F0,A0, ALT 17). She has a history of Hodgkin's lymphoma which was treated in 2004 and is in remission. She also has a mild developmental delay with decreased verbal skills and learning difficulties.

After a lapse in care for almost a year, she re-entered care at 22 weeks of pregnancy. Her pregnancy has been complicated by *Klebsiella* pyelonephritis and sepsis and anemia requiring a blood transfusion (likely due to combination of anemia of pregnancy, anemia of chronic disease and hemoglobin C trait). Her current hemoglobin is 9.3 mg/dL

She is living with her brother and has her grandmother for social support. Although her adherence has previously been erratic, she is currently motivated to take antiretroviral medications (ARV) because of her pregnancy.

Her medications at present are magnesium, folic acid, and prenatal vitamins. She is supposed to be taking penicillin 250mg BID for lifelong prophylaxis following a splenectomy.

Her HLA B5701 test is negative and her HIV is X4 tropic.

DATE	REGIMEN *	CD4 cells/mL	VL c/mL	RESISTANCE TESTs	CLINICAL COURSE
1/95 – 10/95	AZT				
10-95 – 10/97	AZT/ddC				
8/96 – 10/97	HIVIG				ACTG 273 x 6 doses
10/97 – 1/98	d4T/3TC				
1/98 – 8/98	d4T/3TC/NVP				
8/98 – 4/04	AZT/ddI/NFV/RTV	412 (6/03) drifting down to 268 (3/04)	8/98 – 9/01 UD 9/01 50,000 6 /03: < 400 9/03: 483K 3/04: 150K	GART 9/01 GART 11/01 (Quest and Virologic) GART 9/03 GART 3/04	Admitted poor adherence with high VL levels. Cancer dx 4/04,

4/04 – 2/07	AZT/3TC/TDF/LPVr	57 after chemo up to 700 2/07	5/04: 360 10/04: 6,700 5/05: < 400 4/06: 17,000 2/07: 5,000	GART 5/05	Chemo, XRT and splenectomy 2004. CD4 nadir on chemo. Poor adherence; HAART stopped by patient 2/07.
2/07 – 1/08	Off meds	12/07: 393	7, 144		Mostly out of care. Off meds.
3/08	Off meds	273	3140	GART 3/08	
6/08	TRV/RAL/ETR	271	2950		One month only
6/08 – 4/09	Off meds				Out of care
4/09	Off meds	150, 7%	4370	GART 4/09	Pregnant, urosepsis, anemia
5/09	Off meds	235, 9.4%			

3TC =lamivudine (Epivir®)

LPV/r = lopinavir/ritonavir (Kaletra®)

AZT = zidovudine

NVP= nevirapine (Viramune®)

d4T= stavudine (Zerit®)

NFV= nelfinavir (Viracept®)

ddC= zalcitabine (Hivid®)

TDF= tenofovir (Viread®)

ddl= didanosine (Videx®)

RAL= raltegravir (Isentress®)

ETR= etravavine (Intelence®)

RTV= ritonavir (Norvir®)

HIVIG= HIV immunoglobulin

Resistance Test Findings

Key Mutations

GART 9/01 (on AZT/ddI/NFV/RTV)

:

NRTI	215Y
NNRTI	
PI	36I

GART 11/01 *Quest* (on AZT/ddI/NFV/RTV)

NRTI	41L, 215Y, 184V, 333E
NNRTI	103N
PI	36I

GART 11/01 *Virologic* (on AZT/ddI/NFV/RTV)

NRTI	67D, 70R, 210W, 215T/N/S/Y
NNRTI	
PI	36M/I 77V/I

GART 9/03 (on AZT/ddI/NFV/RTV, VL 483,000)

NRTI	215T/S, 333E
NNRTI	
PI	36I

GART 3/04 (on AZT/ddI/NFV/RTV, VL 150,000)

NRTI	333E
NNRTI	
PI	36I

GART 5/05 (on AZT/3TC/TDF/LPVr, VL < 400)

NRTI	333E
NNRTI	
PI	36I

:

GART 3/08 (on no meds)

NRTI	333E
NNRTI	
PI	36I

GART 4/09 (on no meds)

NRTI	333E
NNRTI	
PI	36I

Interpretation/Implications for Treatment

The most challenging issue in managing this patient's disease is her history of poor adherence to medications. Although she states that her motivation is high now that she is pregnant, adherence support will be the most important intervention. Designing a simple, well tolerated regimen is a priority. Directly observed therapy while admitted to the hospital for the last month or two of pregnancy has been shown to be cost effective.^{1,2}

The panel observed that the patient's viral load set-point since 2007 appears to be consistently less than 10,000 copies/mL, whereas previously she had much higher values. These earlier, very high viral load values may have been surges in viremia after discontinuing her medications. Another explanation is that her virus may have transitioned during this time to pure X4 tropic, which has been shown to achieve a lower viral steady state than dual/mixed virus.

Another point of interest is the patient's splenectomy in 2004, which will cause her CD4 counts to be artificially high. Her CD4 percentage may be a better representation of her immunologic state.

The majority of the genotype tests show only the 333E and 36I mutations, even on treatment. This lack of mutations likely reflects non-adherence, or complete interruptions of her regimen.

The two genotypes with the most resistance mutations were both performed in November of 2001 (at two different laboratories). For unclear reasons, the laboratories reported inconsistent results. The test from Quest Diagnostics shows the more common 41, 210, 215 thymidine analogues mutations (TAMS), while the test from Virologic (now Monogram) showed the less common 67, 70, 215 TAM pathway.^{3,4} The reasons for these discordant results are not clear. However, it is reasonable to assume that there exists an archive of high levels of NRTI-resistant variants, and that the NRTIs will have limited activity. 3TC (lamivudine) or FTC (emtricitabine) may have residual activity against these variants, and often is maintained in subsequent salvage regimens.^{5,6,7} Tenofovir and perhaps other NRTIs may also have some residual activity that is difficult to quantify. Although zidovudine (AZT) is usually a preferred drug during pregnancy,⁸ the mutation pattern suggests that it may not be effective, and the patient's recent severe anemia makes this drug less appealing.

The K103N is present on a single genotype test. Hence, the first generation NNRTIs (efavirenz and nevirapine) should be avoided. K103N does not appear to confer any measurable cross-resistance to

:

etravirine, making this drug potentially useful for this patient. There are, however, no data regarding the safety of this drug in pregnancy.

The only mutations in protease were 36I and 77V/I. Both may be polymorphisms and not true resistance-associated mutations. Although it is possible the resistance tests did not fully reveal the true extent of PI resistance, the panel did not suspect a clinically significant compromise to any of the PIs. As such, ritonavir/lopinavir (Kaletra), the recommended PI in pregnancy, should be fully active and would be the first choice. Atazanavir with low-dose ritonavir is an alternate PI for use in pregnancy and is taken only once daily; however, it may not be as effective as ritonavir/lopinavir in the setting of covert PI resistance. Ritonavir/darunavir would be expected to be potent and effective against this patient's virus, but there are few data in pregnancy to evaluate its potential toxicity.

T20 (enfuvirtide) should be fully active as the patient has never taken the drug. Raltegravir is probably fully active, although she received this drug for one month in 2008 and it is possible she may have developed resistance. Maraviroc is not an option as the patient's virus is X4 tropic.

Recommendations

Regimen Options

Option 1: Truvada one daily with Kaletra 2 tablets bid. Consider increasing Kaletra to 3 bid during the 2nd trimester of pregnancy

Pros: Includes Kaletra, which is a preferred agent in pregnancy. Kaletra should be potent enough to maintain viral suppression for the next few months, even with a compromised NRTI backbone. Low pill burden. Well tolerated.

Cons: Does not contain 2-3 fully active agents for durable viral suppression. BID dosing for Kaletra needed in pregnancy.

Option 2: Truvada one daily with Atazanavir 300 mg daily with Ritonavir 100 mg daily with food

Pros: Once-a-day dosing. Atazanavir with ritonavir is an alternative agent for use in pregnancy.

Cons: Atazanavir less robust than Kaletra in the setting of resistance.

Option 3: Truvada one daily with Darunavir 600 mg bid with Ritonavir 100 mg bid with food

Pros: Darunavir is very potent against PI-resistant virus.

Cons: Few data about darunavir in pregnancy. No pK data about once-daily dosing of darunavir in pregnancy

:

Option 4: Truvada one daily with choice of PI *and* either Etravirine 200 mg bid with food–or- T20 90 mcg SQ bid–or- Raltegravir 400 mg bid

Pros: Regimen has 2 active agents, a PI and a new agent. It will be more durable than above regimens.

Cons: Raltegravir may or may not be fully active. There are very few data about the newer agents in pregnancy.

Dosing, Monitoring, and Follow-up Recommendations

Monitor viral load within 3 weeks of starting the regimen

Monitor for known toxicity of the agents:

Truvada: renal dysfunction, lactic acidosis

PI: nausea, vomiting, diarrhea, hyperlipidemia, hyperglycemia, yellowing of skin and eyes (atazanavir only)

Raltegravir: nausea, vomiting, diarrhea

Etravirine: rash, elevated liver function tests

Enfuvirtide: injection site reactions, hypersensitivity reactions

References:

1. Grobman W A , G., P M The cost effectiveness of directly observed therapy late in pregnancy for HIV-infected women . Poster Exhibition: The XIV International AIDS Conference: Abstract no. TuPeC4863.
2. Fisman D., Perencevich E., et al. The cost effectiveness of directly observed highly active antiretroviral therapy in pregnant women with asymptomatic HIV infection. Poster Presentation: The 1st. IAS Conference on HIV Pathogenesis and Treatment : Abstract no. 745.
3. SHAFER R. Genotypic testing for HIV-1 drug resistance (HIV InSite Knowledge Base Chapter). Available at: <http://www.hivinsite.com/InSite?page=kb-03&doc=kb-03-02-07> . Accessed 2/2/09.
4. Wainberg, M. A., B. G. Brenner, et al. (2005). "Changing patterns in the selection of viral mutations among patients receiving nucleoside and nucleotide drug combinations directed against human immunodeficiency virus type 1 reverse transcriptase." *Antimicrob Agents Chemother* **49**(5): 1671-8.
5. BACK NK, NUHUIS M, KEULEN W, et al. Reduced replication of 3TC-resistant HIV-1 variants in primary cells due to a processivity defect of the reverse transcriptase enzyme. *Embo J* 1996;15:4040-9.
6. GOTTE M, ARION D, PARNIAK MA, WAINBERG MA. The M184V mutation in the reverse transcriptase of human immunodeficiency virus type 1 impairs rescue of chain-terminated DNA synthesis. *J Virol* 2000;74:3579-85.
7. ROSS L, PARKIN N, CHAPPEY C, et al. Phenotypic impact of HIV reverse transcriptase M184I/V mutations in combination with single thymidine analog mutations on nucleoside reverse transcriptase inhibitor resistance. *Aids* 2004;18:1691-6.
8. "Perinatal HIV Guidelines Working Group. Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. March 26, 2009 1-96. Available at <http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf>.