
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 25-year-old woman who is currently 16 weeks pregnant (LMP 3/22/07; EDD 12/30/07; G1P0). She has a CD4 nadir of approximately 75 but has never had an AIDS-defining complication. The patient is currently doing well clinically with a recent CD4 cell count of 202 and viral load of approximately 37,000 (on a partially suppressive regimen; see table).

The patient began antiretroviral drugs in 2003 (see table). Her non-nucleoside reverse transcriptase inhibitor (NNRTI) exposure is not clear; by report, she did receive but did not tolerate efavirenz (EFV, Sustiva®). Ritonavir (RTV, Norvir®) causes some nausea.

The patient has been in and out of care and often becomes lost to follow-up for prolonged periods of time. She reports poor tolerance and adherence to various medications. Despite multiple regimens, she has never achieved an undetectable viral load.

The patient wants very much to keep the pregnancy and is asking about a cesarean section to decrease the risk of perinatal HIV transmission. She denies use of recreational drugs or alcohol or a history of depression. The father of the child is not currently present in her life. She lives alone but her mother is available to help. She seems motivated to adhere to a new antiretroviral regimen and is receptive to using T-20 injections (enfuvirtide, Fuzeon®).

Her other medications include dapsone for *Pneumocystis jirovecii* prophylaxis and prenatal vitamins.

DATE	REGIMEN *	CD4 cells/mm ³	VL c/mL	RESISTANCE TEST FINDINGS	CLINICAL COURSE
7/2003	?	208	350,000		Pre-treatment or on failing meds
?? to 1/2004	d4t /ABC/NFV		Not UD	See GART	
	d4t/ddI/3TC/ LPV/r	74			CD4 nadir
	ddi/3TC/TDF/ LPV/r				
2005 - 1/2007	ddi/3TC/TDF/Fos -APV/r	309	113,826	See GART	
1/2007 - 5/2007	ddi/3TC/TDF /TPV/r	245			Regimen chosen based on based on GART 1/07. Partial adherence only

5/2007		202	VL 37000		Stopped meds 5/29 after pregnancy diagnosed
6/2007-now	3TC				Awaiting RT panel recommendations

d4T= stavudine (Zerit®) ABC= abacavir (Ziagen®)
 NFV= nelfinavir (Viracept®) ddl= didanosine (Videx®)
 3TC =lamivudine (Epivir®) LPV/r = lopinavir/ritonavir (Kaletra®)
 TDF= tenofovir (Viread®) Truvada® = tenofovir plus emtricitabine
 FTC = emtricitabine (Emtriva) ATZ= atazanavir (Reyataz®)
 Fos-APV/r=fosamprenavir (Lexiva®)/ritonavir(Norvir®)
 TPV/r = tipranavir (Aptivus®)
 DRV/r = darunavir (Prezista®)

Resistance Test Findings

Key Mutations

2004

NRTI	20R, 41L, 67N, 70wt/R, 74wt/I, 184V, 196E, 214wt/F, 215Y, 219Q
NNRTI	K103N
PI	90M, 77I, 71V

January 2007

NRTI	20R, 41L, 67N, 70wt/R, 74wt/I, 184V, 196E, 214wt/F, 215Y, 219Q
NNRTI	225H
PI	10F, 30N, 33F, 35D, 36I, 46I, 50V, 63P, 88D

Interpretation/Implications for Treatment

Perinatal human immunodeficiency virus (HIV) transmission can be reduced from 25% to less than 1% with optimal medical and obstetrical management.^{1, 2} Antiretroviral treatment recommendations for HIV-infected pregnant women are the same as for non-pregnant adults,

taking into consideration the potential impact of therapy on the fetus and infant.³ Most antiretroviral agents can be used during pregnancy (FDA pregnancy category B or C), although many of the newer drugs have insufficient data to recommend their use as first line agents. Expanded access programs for investigational agents generally exclude pregnant women, although exceptions can be made if the company is petitioned.

HIV-1 RNA viral load is correlated with the risk of perinatal HIV transmission.⁴⁻⁶ Achieving undetectable viral load suppression in pregnancy minimizes the chance of transmission to the infant and prevents emergence of drug resistance to preserve a woman's future antiretroviral options.

In non-breastfeeding women, about two-thirds of perinatal HIV transmission is believed to occur during labor and delivery, with the remaining one-third occurring during the third trimester of pregnancy.⁷⁻⁹ As such, attaining complete viral load suppression later in pregnancy and especially at the time of labor and delivery is of primary importance. The USPHS recommends starting antiretroviral therapy during the second trimester and the UK BHIVA recommends starting early in the third trimester in order to achieve this goal.^{3, 10}

This patient has a history of poor adherence, leading to triple class antiretroviral drug resistance. Of interest, the change in her protease inhibitor (PI) resistance pattern between the 2003 and 2007 genotype is unusual with the loss of previous mutations and the acquisition of new ones. Although this might be explained by the NFV drug pressure in the first genotype and the LPV/r and Fos-APV/r pressure in the second genotype, there are strikingly different polymorphisms (e.g., 63P, 88D) between the two that are usually not affected by drug pressure. However, her nucleoside reverse transcriptase inhibitor (NRTI) mutations remain almost identical in the two genotypes. This change could be due to superinfection with a second strain of HIV followed by a recombination event that produced the virus seen in the second genotype. This event would be extremely uncommon, but has been reported in the literature.¹¹ For this analysis, it was assumed that the mutations not present in the second genotype were archived and would impact on the choice of future regimens.

This patient has extensive viral mutations that will preclude the use of standard regimens in pregnancy. In order to achieve complete viral suppression, the use of investigational antiretroviral agents available through expanded access will likely be necessary. However, data on the efficacy and safety of these agents in pregnancy are limited.¹² The risk of these unknown future effects must be carefully balanced against the risk of perinatal HIV transmission and a fully informed decision needs to be made by the mother if these experimental treatments are accepted.

In the NRTI class, the presence of the M41L, D67N and T215Y mutations confer a significant degree of resistance to AZT and d4T and a lesser degree of resistance to ddI, ABC, and TDF. AZT and d4T are further compromised by the K70R and K219Q mutations. ABC and ddI are affected by the L74I mutation. The M184V mutation confers high-level resistance to 3TC and FTC, low-level resistance to ABC and ddI, but enhances susceptibility of AZT, d4T and TDF.¹³ In summary, all the NRTIs are expected to have some degree of reduced susceptibility although each may retain some partial activity (this is likely to be particularly true for tenofovir). 3TC/FTC is often continued in "salvage" regimens as (1) these drugs have residual direct activity even if M184V is present, (2) the M184V mutation increases susceptibility to AZT and TNF and (3) the M184V mutation reduces viral fitness.¹⁴⁻¹⁶ During pregnancy, AZT is usually included because it crosses the placenta well and has been shown to help prevent transmission, even in women with extensive prior AZT experience.¹⁷ A nucleoside backbone of fixed-dose Combivir® (zidovudine/lamivudine) or Trizivir® (zidovudine/lamivudine/abacavir) plus TDF was therefore suggested by the panel.

The presence of the K103N mutation confers high-level resistance to all the current nonnucleoside reverse transcriptase inhibitors (NNRTIs) but does not appear to cause any reduced susceptibility to the investigational NNRTI etravirine (TMC-125).¹⁸

The PI class is also affected by the multiple mutations. The L10F, M46I, A71V and L90M will compromise most of the PIs.¹³ She has many NFV, LPV and fos-APV mutations, consistent with her medication history. At the time of her 2007 genotype she had intermediate or high-level resistance to all of the PIs; however, her clinical response may not be accurately predicted from a genotype since genotypic resistance data for the newer drugs are preliminary. Of some concern is the prolonged exposure to fosamprenavir; which may result in emergence of cross-resistance to darunavir.¹⁹

A phenotype test would be helpful to determine the susceptibility of newer PIs such as DRV/r. Even though the patient has been off her ARVs since late May 2007, she has been maintained on 3TC monotherapy that may slow the loss of mutations, making a new genotype/phenotype potentially helpful. Alternatively, her previous TPV/r-based antiretroviral regimen could be restarted and a genotype/phenotype test obtained after a month of selective drug pressure to identify clinical response and any archived mutations, although this was not recommended by several experts on the panel.

Since the patient is naïve to enfuvirtide (T-20, Fuzeon®) and the investigational integrase inhibitor, raltegravir, these ARVs are expected to be fully active. Although, susceptibility to the CCR5 inhibitor, maraviroc is possible, this agent was not favored by the panel because of theoretical concerns about using a drug which specifically targets the host (CCR5) rather than the virus. The impact of CCR5 inhibition on fetal and infant development is not known.

Given the patient's long history of poor adherence, starting a fully suppressive regimen without full adherence for the next five months could lead to viral rebound and further resistance, increasing her chances of vertical transmission and compromising her future treatment options. The panel discussed a treatment strategy of starting her on a non-fully-suppressive "holding" regimen now, to keep her virologically and immunologically stable,²⁰ while preserving the most active agents for later in pregnancy. This would shorten the time of administration of newer and investigational ARVs which might limit the potential for toxicity to the infant and reduce the emergence of further mutations if non-adherent. The optimal time to introduce these new ARVs would be around the middle of the third trimester to achieve an undetectable viral load during the last few weeks of pregnancy and delivery. *Given the possibility of an early delivery, this regimen would need to be started between 30-32 weeks gestational age.*

The "holding" regimen should include as many NRTIs as tolerated. The presence of the M184V mutation has been shown to keep the viral load lower than the set point and reduce viral fitness.¹⁴⁻¹⁶ One option would be 3TC monotherapy; another would be multiple NRTIs, which could be coupled with a PI (see below). Eventually, this partially suppressive regimen would need to be switched to a fully suppressive one, which would likely require the use of raltegravir with or without etravirine and/or enfuvirtide, assuming that the former drugs can be accessed via expanded access. Constructing a fully effective regimen with currently approved drugs may not be feasible.

Recommendations

Addressing adherence with this patient will be an important first step. Many women, when educated about the risk of transmission of HIV to their infant and about the efficacy of antiretroviral therapy in reducing this risk, are able to adhere to regimens for the duration of their pregnancy even if they have

had adherence issues before. Exploring the specific reasons for lack of adherence and finding avenues for support can be helpful. Several studies have shown that admitting pregnant women to the hospital in third trimester for directly- observed therapy is cost-effective. This strategy can be considered and may allow for more effective, yet complicated regimens to be used.

Regimen Options

Start now with one of the “holding” regimen options

Option 1: Lamivudine (3TC, Epivir®) monotherapy

Pros – minimizes maternal and fetal toxicity; easier to adhere to; avoids accumulation of new mutations, reduces viral fitness

Cons – no viral suppression expected; may not protect against immunological decline as well as a PI containing regimen

Option 2: Combivir® plus tenofovir (Viread®) plus nelfinavir (Viracept®) or atazanavir (Reyataz®)

Pros – regimen expected to achieve better viral suppression than 3TC alone. Addition of a PI may help support immunological status

Cons – not expected to achieve complete viral suppression. Some additional resistance accumulation might occur.

Option 3: No holding regimen. Start immediately with full regimen as below

Pros – Viral suppression likely – will minimize risk of mother-to-child HIV transmission

Cons – Adherence may be difficult, and without excellent adherence the patient may develop resistance to new agents that she needs for her future care

Followed by a more potent regimen starting at 30-32 weeks gestational age

Option 1: Darunavir (Prezista®) plus ritonavir plus Etravirine plus Raltegravir plus Combivir® plus tenofovir (Viread®)

Pros – regimen expected to achieve complete viral suppression

Cons – regimen includes many drugs with little or no experience in pregnancy; includes drugs in expanded access programs which may not allow participation of a pregnant patient; if adherence not assured, may develop resistance to agents that she needs for her future care. Unknown if drug interaction between etravirine and raltegravir.

Option 2: Darunavir (Prezista®) plus ritonavir plus enfuvirtide (Fuzeon®) plus Raltegravir plus Combivir® plus tenofovir (Viread®)

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Pros – regimen expected to achieve complete viral suppression. Compared to Option 1, has one less investigational agent included. Enfuvirtide does not appear to cross the placenta so would likely not have an impact on the fetus.

Cons – regimen includes self-administered injections; includes drugs with little or no experience in pregnancy; includes one drug in expanded access program which may not allow participation of a pregnant patient; if adherence not assured, may develop resistance to agents that she needs for her future care.

Dosing, Monitoring, and Follow-up Recommendations

Holding Regimens

1) 3TC: 300 mg tablets, one tablet once daily; or 150 mg tablets, one tablet bid.

Take with food to reduce gi distress

2) Combivir® one tablet bid with food to reduce gi distress.

Monitor for gi distress, fatigue, headache, anemia, and rarely hepatotoxicity

Tenofovir (Viread®) one tablet daily with food to reduce gi distress

Monitor for renal failure (BUN, Scr, proteinuria)

Nelfinavir (Viracept®) 1250 mg bid with food

Monitor for diarrhea, give antimotility agents empirically. Monitor glucose, LFT's, lipids

Boosted Atazanavir (Reyataz®) 300 mg (one capsule once daily) or 150 mg caps (2 caps once daily) plus ritonavir (Norvir®) 100 mg, one capsule once daily. Take with food to reduce gi distress. Avoid any proton pump inhibitors. If using H2 blockers or antacids, separate by 10 hours from ATZ.

Monitor for jaundice, bilirubin, LFT's.

Fully suppressive regimens

Darunavir (Prezista®) 300 mg capsules, 2 capsules (600 mg) bid plus ritonavir 100 mg capsules, one bid. Take with food to improve tolerability and bioavailability

Etravirine (available by expanded access from Tibotec 1-866-889-2074

Raltegravir (available via expanded access from Merck Pharmaceuticals)

Combivir® plus tenofovir (Viread®) dosing as above

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Enfuvirtide (Fuzeon®) 90 mg SQ bid

Monitor for subcutaneous nodules, pain at injection site.

MONITORING

Monitor VL and CD4 within 4 weeks after starting regimen

Undetectable VL by 38th week of pregnancy or consider C-section

Adherence and drug toxicity

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