
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

A 39 year-old African American woman was diagnosed with HIV-1 in 1988 while in Africa. She is currently receiving Trizivir® (zidovudine, lamivudine, and abacavir) bid and atazanavir (ATV) 300 mg/ritonavir (RTV) 100 mg daily. Despite adherence to this regimen, her current CD4 cell count is 2 cells /mm³ and her viral load is >100,000 copies RNA/ml. She is receiving doxorubicin (Doxil) for treatment of recurrent cutaneous Kaposi's sarcoma. She is otherwise currently doing well.

Her antiretroviral history is unclear although she has previously received zidovudine (AZT) monotherapy and didanosine (ddI) monotherapy.

Details regarding her antiretroviral exposure are only available beginning in 2003:

Date	Regimen	CD4	Viral load
2003	ddl, d4T, SAQ/RTV	20	40,000
1/2004	tenofovir (TDF), abacavir (ABC), LPV/r	0	unk
2/2004	IL-2 added to above		
4/2004	IL-2, TDF, ABC, LPV/r	34	34,800
4/2004	FTC, ABC, LPV/r	unk	unk
6/2004	ddl-EC, TDV, ABC, LPV/r		
7/2004	"	<10	>100,000
7/2004	Trizivir, ATZ/RTV		
10/2004	"	12	>100,000
10/2004	TDF added to above		
Current	Trizivir, TDF, ATV/RTV	2	>100,000

Resistance Test Findings

Key Mutations-LabCorp (3/16/2005)

NRT	41L, 44D, 67N, 70R, 118I, 184V, 210W, 215Y, 219E
NNRT	103S
PI	10F, 36I, 46I, 54V, 82A, 84V, 90M

Phenosense(ViroLogic, Inc)—3/16/2005

	Patient IC 50	Fold change
NRTI		
Abacavir	11.13	7.85
Didanosine(DDI)	8.99	1.89
Emtricitabine(FTC)	>100	>max
Lamivudine(3TC)	>300	>max
Stavudine(D4T)	1.5	2.23
Tenofovir	1.316	1.83
Zidovudine(AZT)	1.223	33
NNRTI		
Delavirdine	0.3318	12
Efavirenz	0.0891	49
Nevirapine	5.437	56
PI		
Atazanavir	0.04683	38
Forsamprenavir	0.3009	24
Indinavir	0.1151	16
Lopinavir	0.1879	53
Nelfinavir	0.36645	69
Ritonavir	1.2901	128
Saquinavir	0.174	86

CASE DISCUSSION;

1. Is this patient a candidate for a CCR5 antagonist ("R5 inhibitor")?
2. What antiretroviral regimen could be recommended for this patient?
3. Is there an untoward interaction between tipranavir and CCR5 antagonists?

Interpretation/Implications for Treatment

Based on both the genotype and phenotype, the patient harbors a virus that is partially or perhaps completely resistant to all nucleoside reverse transcriptase inhibitors (NRTI). The presence of all the major thymidine analog mutations (41, 67, 70, 210, 215, and 219) confers resistance to all NRTIs except lamivudine. The 44D and 118I are other NRTI mutations that occur in 10-15% of those receiving NRTI, particularly in isolates containing multiple TAMS. Although, the presence of the M184V mutation confers resistance to lamivudine, it can also retain some virologic activity [1] by impairing "viral fitness" Recently, didanosine was found to retain some antiviral activity despite the presence of 5 NAMs [2]. Although both the genotype and phenotype suggest high level resistance, resistance studies in which single NRTIs were removed despite the presence of multiple resistance mutations demonstrated that this class of drugs can often retain some partial activity against the drug-resistant variant.

The K103S mutation, observed in 0.9% of Virco isolates (60,772 clinical isolates) [3], is associated with high level resistance to nevirapine and intermediate resistance to efavirenz and delavirdine. Therefore, broad class resistance would be expected to occur to the currently available nonnucleoside reverse transcriptase inhibitors (NNRTI). This was confirmed by the phenotype.

Three major mutations (82, 84, 90), in addition to multiple other mutations in the protease inhibitor (PI) gene would suggest a virus that would be resistant to this class of agents. Broad resistance to existing PI is also documented by the phenotype. For example, a fold-change in IC50 of > 40 suggests high-level resistance to lopinavir.

Recommendations

Regimen Options

Although the low CD4 cell count is concerning, the patient has been doing relatively well over the past 2 years. However, the low CD4 cell count increases the risk for HIV disease progression and therefore, HAART is recommended. The current ARV regimen is sub-optimal and a regimen change is indicated.

The patient has never been on T20 (enfuvirtide), a fusion inhibitor. Therefore, the virus can be assumed to be fully susceptible to this drug. However, use of T20 without other effective agents invariably leads to rapid virologic failure. Use of this drug with "recycled" antiretroviral agents would likely result in only a transient clinical benefit. More importantly, failure of such a regimen would change this "three-class failure" to a "four class-failure", thereby significantly reducing future options for "complete" viral suppression.

Given the presence of high-level resistance to all available drugs, the committee discussed which investigational agents to pursue. Several concerns were discussed regarding the use of a CCR5 antagonist, including the following:

- (1) While the initial Phase II data on CCR5 antagonists look promising, there is no clinical data regarding the safety and efficacy of these drugs in a patient with advanced insufficiency.

- (2) Since this patient has advanced disease, there is a high likelihood that the virus would have a CXCR4 receptor (either dual tropic or mixed) which would exclude this patient from any clinical trials.
- (3) If tipranavir was being considered as a protease inhibitor, it is a potent inhibitor and inducer of the cytochrome P450 system and could decrease or increase CCR5 antagonist's blood levels. Current drug interaction studies are not available.
- (4) R5 inhibitors are only available in placebo-controlled studies. The use of the remaining effective agent (T20) in such a study risks exposure to a placebo and effective sequential "monotherapy". This is particularly true because the R5 inhibitor studies do not currently allow the use of tipranavir.

OPTION 1: Based on the antiretroviral history, resistance data, and low CD4 cell count, the panel suggested that the most effective regimen might be:

Trizivir™ one bid, tenofovir 300 mg daily, tipranavir 500 mg bid /ritonavir 200 mg bid, and enfuvirtide (T-20) 90 mg SQ bid.

The rationale for Trizivir™ and tenofovir is that the presence of the M184V mutation can increase susceptibility to zidovudine and tenofovir. In addition, the M184V mutation confers a less fit virus and retains some susceptibility to lamivudine. The panel would discourage the combination of didanosine and tenofovir because this combination (even when the lower dose of ddI 250 mg is used) can have a detrimental effect on CD4 cell count increase [4].

The results of the RESIST -1 and -2 studies [5,6] suggest that ritonavir boosted tipranavir and T-20 might be active in highly treatment experienced patients with multiple PI mutations who had been exposed to all three ARV classes (NRTIs, NNRTIs, PIs). Tipranavir/ritonavir had superior virologic outcomes at 24 weeks when compared to other ritonavir-boosted PIs. In addition, 70% of patients who were T-20 naïve and started T-20 with tipranavir/ritonavir had a 1-log drop in viral load at 24 weeks compared to 30% of subjects receiving T-20 with other ritonavir-boosted PIs.

The RESIST studies also demonstrated genotypic predictors of response to tipranavir/ritonavir. There were 21 mutations (10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D, 84V) associated with tipranavir resistance. The median viral load decrease was -2.1 log₁₀ copies/mL if none of the above mutations were identified, compared to -1.4 log₁₀ copies/mL with 2 mutations, and -0.7 log₁₀ copies/mL with 3 or more mutations. Even with 12 mutations, there was some virologic response.

Option 2: Another plausible combination is Trizivir™, tenofovir, T-20 and boosted TMC 114. TMC 114 is an investigational protease inhibitor that is currently in phase II trials. Preliminary data [7] on TMC 114 in patients with PI resistance appears promising. However, the concern about using TMC 114 is that the patient could potentially be enrolled to the placebo arm of the trial.

Dosing, Monitoring, and Follow-up Recommendations

Option 1: Trizivir™ 1 bid, tenofovir 300mg daily, tipranavir 500mg bid, ritonavir 200mg bid, and T-20 90mg subcutaneously every 12 hours..

Pros: Potentially maintain CD4 and viral load

Cons: May not be fully suppressive, leading to the possibility of developing further PI mutations and rapid loss of T20. This regimen also has the risk of abacavir hypersensitivity reaction during the first 6 weeks of therapy, a high pill burden, and a risk of drug-drug interactions with tipranavir/ritonavir.

Monitoring: Check viral load and CD4 cell count 4 to 6 weeks after any ARV change

The main side effects/toxicity to monitor is as follows:

Zidovudine(AZT) – Bone marrow depression (leukopenia and anemia) and hepatotoxicity. Monitor complete blood count + differential and liver function tests.

Abacavir – Hypersensitivity reaction. Recent data suggest that it can occur in up to 8% of patients [8]. The most common signs and symptoms are fever, rash, nausea, vomiting, abdominal pain, diarrhea, and fatigue. These signs and symptoms worsen if abacavir is continued. More than 90% of abacavir hypersensitivity reactions occur within the first 6 weeks of starting abacavir. Patients developing the hypersensitivity reaction should NEVER be rechallenged because of the risk of fatal reactions.

Tenofovir – Deterioration of renal function tends to be gradual, mild, and generally reversible. There are no specific guidelines as to how to monitor renal toxicity but some general guidelines have been proposed [9]:

1. Determine baseline creatinine clearance and degree of proteinuria
2. Monitor serum creatinine routinely
3. Adjust tenofovir dose in renal dysfunction. Stop therapy if new or worsening renal dysfunction occurs/

Tipranavir/ritonavir – Hepatotoxicity and hyperlipidemia. Monitor liver function tests and lipid levels routinely. Use cautiously in patients with concomitant hepatitis B or C infection.

T-20 – Injection site reaction, hypersensitivity reactions, increased rate of bacterial pneumonia

References:

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