
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 43 year-old Latino man who has been HIV positive for “several” years. He has lost 25 lbs. during the last six months and reports persistent fatigue. He is currently on didanosine (ddl) (dose not clear), tenofovir (TDF), and Kaletra (LPV/r). His most recent CD4 is <20 cells/mm³ and his most recent viral load is >100,000 copies RNA/mL. He is highly treatment-experienced and has taken zidovudine (AZT), stavudine (d4T), abacavir (ABC), lamivudine (3TC), zalcitabine (ddC), nevirapine (NVP), efavirenz (EFV), nelfinavir (NFV), indinavir (IDV), ritonavir (RTV), and tipranavir (TPV) in the past; however, the combinations are unclear. The immunological and virological responses to these combinations are also unknown. It is unclear if he has ever had an undetectable viral load on any prior regimen. Adherence has been poor.

His past medical history is significant for *Pneumocystis jiroveci* (PCP), PML, and HCV.

The caller does not have access to tropism testing or HLAB5701 testing. The patient probably will not take T-20.

DATE	REGIMEN *	CD4 cells/mm ³	VL COPIES/ML	RESISTANCE TEST FINDINGS	CLINICAL COURSE
5/03/05	AZT, ddl, tenofovir, Sustiva and Kaletra	Unknown	unknown	Trugene genotype 5/05	
7/07	Tenofovir, ddl, Kaletra	<20	>100K	8/5/08 Trugene genotype	

Resistance Test Findings

Key Mutations

5/13/05 Trugene genotype

NRTI	K70R, V118I, T215F, K219E
NNRTI	A98G, K103N, V108I, Y181C, G190A
PI	L10F, M46I, I47V, I54L, L63P, I84V

8/5/08 Trugene Genotype

NRTI	T69N, K70R, V118I, K219E
NNRTI	A98G, Y181C
PI	I13V, V32I, M36I/L, M46I, I47V, L63P, N83D, I84V, L89I

Interpretation/Implications for Treatment

Nucleoside Reverse Transcriptase Inhibitors (NRTI): There are three major nucleoside analogue mutations (NAMs): K70R, T215F, and K219E. Each confers some degree of resistance to most of the the NRTIs. Tenofovir may have somewhat better activity than the other NRTIs, as none of the key mutations are present (e.g., K65R or M41L with L201W). Although there are three reported NAMs, there is always the possibility that the other NAMs – M41L, D67N, and L210W – may have been generated in the past and persist at low undetectable levels. This is particularly true with regard to M184V, which presumably merged with prior lamivudine/emtricitabine (3TC/FTC)-based regimens. As a class, the NRTIs are clearly compromised, but it is likely that some or all drugs in this class retain some residual activity.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI): There are multiple NNRTI mutations: A98G, K103N, V108I, Y181C, and G190A. The K103N, Y101C, and G190A mutations each cause high-level resistance to efavirenz (EFV) and nevirapine (NVP). The DUET 1 and 2 studies [1, 2] identified 13 mutations that were associated with etravirine (ETR) resistance: V90I, A98G, L100I, K101E/P, and V106I. V179D/F, Y181C/I/V, G190A/S. The presence of ≥ 3 of these mutations was associated with a decreased response to etravirine [1,2]. Other methods for determining etravirine activity include using Monogram's phenotypic fold change cut-off of <2.9 [3] and/or an etravirine weighted mutation score [4]. With regard to this latter genotypic score, this patient has a score of > 4 and hence potentially harbors a virus with high-level resistance to etravirine (in the DUET studies, a weighted score >4 corresponded to a 38% virological response rates). This patient has three etravirine mutations, and, based on the weighted mutation score, etravirine has limited activity. A phenotype would be helpful in further defining the activity of etravirine.

Protease inhibitor (PI): Combining both genotypes, there are a total of eleven PI mutations. One important theoretical question is whether these mutations appear separately on different virus populations or are linked together on one virus, which could have an impact on whether an antiretroviral agent is active or not. Most clinicians assume that these mutations are linked to one or more virus populations. There are six atazanavir mutations, six lopinavir mutations, six fosamprenavir mutations, five tipranavir mutations, and at least three or possibly four darunavir mutations. Based on various genotypic algorithms, the patient harbors a virus that is highly resistant to each of the protease inhibitors. A phenotype is probably more helpful in determining the activity of the PIs than a genotype.

Recommendations

Dosing, Monitoring, and Follow-up Recommendations

1. It was recommended that a phenotype be obtained to help determine the activity of etravirine and the PIs. The results of the phenotype would help to determine the most effective regimen for this patient.
2. The patient has a very low CD4 cell count and therefore the goal is to have the patient on three fully active agents.
3. If a phenotype is not obtainable, the following are possible regimen options:

- A. Truvada (tenofovir/emtricitabine), enfuvirtide (T-20), raltegravir, darunavir/ritonavir. This combination would be the most effective regimen because there are two fully active agents (T-20 and raltegravir). Darunavir has some activity but it is difficult to determine if it is a fully active agent. For the NRTI backbone, Truvada is a reasonable option since it would maintain the M184V mutation (if it is archived) and the M184V could resensitize the virus to tenofovir. However, the patient indicated that he is not enthusiastic about taking T-20 so this option may not be feasible.

Dose: Truvada 1 tablet daily po; T-20 (fuzeon) 90 mcg bid subcutaneously; raltegravir 400 mg bid po; darunavir 600mg bid po; ritonavir 100mg bid po.

Major side effects to monitor for: tenofovir: renal toxicity, nausea, flatulence; raltegravir: nausea, headache, CPK elevation; T-20: injection site reactions; darunavir-rash (darunavir has a sulfonamide moiety), hyperlipidemia, and elevated transaminases.

- B. Truvada, etravirine, raltegravir, darunavir/ritonavir. This regimen contains one fully active agent (raltegravir) and several compromised agents. Etravirine and darunavir are both potentially compromised due to the number of drug-associated mutations detected on resistance testing. The potential problem of having raltegravir as the only fully active agent is that raltegravir has a low genetic barrier to resistance and incomplete viral suppression could result in raltegravir resistance. Despite this theoretical concern, the Benchmark studies [5] found that when raltegravir was the only active agent in the regimen, 51% still achieved a viral load of <50 copies/mL at 48 weeks [6].

Dose: Truvada 1 daily po; etravirine 200mg (2 X100 mg tablets) bid po; raltegravir 400mg bid po; darunavir 600mg bid po; ritonavir 100mg bid po.

Note: Etravirine cannot be administered with fosamprenavir, atazanavir, tipranavir, or nelfinavir.

Major side effects to monitor for: etravirine: rash, drug interactions, hepatitis

- C. Truvada, maraviroc, raltegravir, darunavir/ritonavir. This regimen contains one fully active agent (raltegravir). It is very likely that this patient has either X4 or dual/mixed virus. In the HOMER and SCOPE cohorts, 60% of treatment-experienced patients

with a CD4 cell count of <134 cells/mm³ had X4 or dual/mixed virus [7]. The rationale for using maraviroc without a tropism test is based on the fact that a pure R5 population may be present (although this is unlikely). Even if a dual-tropic virus is present, maraviroc may still have some benefit [7]. In a 24 week study of patients who lacked pure CCR5 utilizing HIV, maraviroc was safe and potentially associated with a CD4 benefit.

Dose: Truvada 1 daily po; maraviroc 150mg bid po; raltegravir 400mg bid po; darunavir 600mg bid po, ritonavir 100mg bid po.

Major side effects to monitor: maraviroc: abdominal discomfort, dizziness; orthostatic hypotension, hepatotoxicity.

4. Follow-up:

- A. Check HIV viral load and CD4 cell count about four weeks after starting one of the above regimens.

References:

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