
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 50-year-old woman with pulmonary hypertension on bosentan IV therapy. As she is new to this practitioner, much of the medical information is missing. She has been on many antiretroviral drugs (ARVs) in the past and is uncertain of the specific details. In 2006-2007, she experienced virologic failure on Trizivir (TRV), ritonavir/darunavir and T20 (as part of the DUET study where she also may have received etravirine, although details on this are lacking). She was then placed on 3TC monotherapy as a “waiting” strategy. A genotype and virtual phenotype was obtained on 1/07 while on 3TC (see below). She also has a history of diabetes, anemia, bedsores, and is currently in the hospital for aspiration pneumonia. Her creatinine is 2.0 mg/dl. A Trofile® test showed dual/ mixed (DM) virus.

DATES	REGIMEN	CD4 (cells/mm ³)	VL (copies/mL)	RESISTANCE TEST FINDINGS	CLINICAL COURSE
	MANY ARVS				
4/06 – 4/07	TRV/RTV/DRV/T-20/ETV				
6/06	SAME		700		
11/06	SAME	186	>100K		
4/07	TRV/RTV/DRV/T-20				
7/07	3TC				
12/07	3TC	27	500K	Virtual Phenotype	
3/08	3TC	10	>100K		

Resistance Test Findings

Genotype 1/08 Key Mutations

NRT	41L, 67N, 70R, 74V, 184V, 211, 215C, 219E,
NNRT	103N, 108I
PI	10I, 13V, 20R, 32I, 33F, 35D, 36I, 41K, 46I, 53L, 54V, 63P, 71V, 74P, 77I, 82F, 84V, 90M, 93L

Virtual phenotype results (limited) 1/08

PI	FC
Darunavir	131
Tipranavir	30
Kaletra	375
Atazanavir	216

Interpretation/Implications for Treatment

Questions: Should patient get HAART while acutely ill? What HAART regimen is best?

This case illustrates many important clinical issues. Although there is much missing data that the practitioner should try to obtain, the panel made its recommendations based on the available data. The patient was in the DUET study, a study designed for highly experienced patients (1). It was unique among HIV clinical trials since it included two previously investigational non-FDA approved agents. All participants in the study received ritonavir-boosted darunavir (TMC 114, Prezista®). The patients were randomized to receive either etravirine (TMC125 -a second generation NNRTI, Intelence®) or placebo plus an optimized background ARV regimen based on the results of resistance testing. This patient said she was told she received the study drug etravirine. If this is true, it would mean that she failed both etravirine and ritonavir boosted darunavir in this trial. Since she also received T-20 (enfuvirtide, Fuzeon®) in DUET, the antiviral activity of T-20 might be limited. Since her virus uses a dual /mixed coreceptor for viral entry, it is unlikely that the new R5 inhibitor maraviroc (Selzentry®) will be active (2). Thus, even in this era of new ARV agents and classes, this patient has very limited ARV options.

The results of the genotype and virtual phenotype test are consistent with her treatment history. There are five thymidine analogue-associated mutations (M41L, D67N, K70R, T215C, and K219E), which indicates high-level cross-resistance to most of the drugs within this class. In addition, the M184V mutation causes high-level resistance to 3TC and FTC (emtricitabine, Emtriva®) and modest resistance to abacavir and didanosine (Videx EC®). The L74V mutation also imparts some resistance to abacavir and didanosine.

The nonnucleoside reverse transcriptase inhibitor (NNRTI) mutations K103N and V108I cause high-level resistance to the first generation NNRTIs (efavirenz, nevirapine, and delavirdine). Of note, there is not much etravirine resistance exhibited on this genotype (see below).

There are many protease (PI) mutations (3 darunavir (Prezista®), 12 Kaletra®, and 8 tipranavir (Aptivus®) mutations) present on the genotype, which corresponds to high-level resistance to the entire PI class (3). The virtual phenotype is in accord with the genotype. All of the fold changes reported for the protease inhibitors are above the cutoffs, making it highly unlikely that any of these drugs will have significant activity.

After the patient failed the DUET study with a viral load of >100K copies/mL, the practitioner chose to discontinue her ARVs and place the patient on 3TC monotherapy. The rationale for this strategy was that treatment experienced patients receiving 3TC monotherapy experience a 0.5 log lower viral load compared to patients on no ARVs (4). The presence of the M184V mutation, the signature mutation for 3TC and FTC, reduces the replicative capacity of the virus. 3TC may also retain activity in the presence of the 184V mutation. Most experts agree that 3TC monotherapy may have a role in "waiting", particularly among patients who lack the ability to adhere to more effective regimens and as long as patients have reasonable CD4+ T cell counts. The declining CD4+ T cell counts in this paper clearly argues for a rapid change in the treatment approach.

The resistance test showing triple class mutations was obtained when the patient was off all ARVs except 3TC for five months. In general, wild-type virus is more fit than resistant virus so it replicates more vigorously and thus outgrows the resistant virus when drug pressure is removed. An exception to this occurs when some treatment is continued; in this case, wild-type virus is prevented from rebounding by the drugs. Mutations which are no longer under drug pressure may persist in this case as they are linked on the same genome to those mutations conferring resistance to the contemporaneous regimen. This likely explains the persistence of NRTI, NNRTI and PI mutations in the face of continued 3TC monotherapy.

Although it makes sense that a pre-existing wild-type variant is prevented from rebounding by the continued use of 3TC, it is less clear as to why certain mutations do not revert via "back-mutation". With regard to the PI mutations, it has been argued that "fitness valleys" prevent evolutions of the virus to a more fit genotype. During PI failure, primary mutations emerge that increase resistance but reduce "fitness"; this fitness defect is corrected by emergence of compensatory mutations. Theoretically, for back mutation to occur, these compensatory mutations must first be lost, which would entail an initial drop in fitness. Thus, there is an obstacle to the virus mutating back to wild-type called a "fitness valley" (6).

The patient's NNRTI resistance test results suggest that she received placebo in the DUET trial and not etravirine. At the time of this resistance test, etravirine susceptibility was not routinely reported on phenotypes. However, no genotypic mutations are seen that are associated with etravirine resistance. Although the genotype was performed eight months after the study stopped, one would have expected some etravirine mutations to be present since NNRTI mutations tend to persist after stopping NNRTIs. It might be prudent for the practitioner to contact the DUET study investigators and determine the patient's true drug history. If she received placebo, it is very likely that her virus is still susceptible to etravirine.

The integrase inhibitor, raltegravir (Isentress®), is the only ARV agent with full activity against her virus. The most recent DHHS ARV guidelines state that a salvage regimen should contain at least two and preferably three active agents. Only one active ARV in a regimen is concerning, as it frequently results in resistance to the active agent and virologic failure. Most HIV experts are very reluctant to use regimens with only one active agent. The data on raltegravir as a single active agent in a regimen is somewhat contradictory. Resistance is common among those who fail with signature mutations at Q148H/K/R and N155H. However, the BENCHMARK study found that almost 50% of those patients with no other active drugs except raltegravir in their background regimen had undetectable viral loads at 96 weeks (7). The explanation for this phenomenon is not well understood but suggests that raltegravir may be useful in patients with no other active agents.

Based on the available data, the next regimen should include raltegravir, probably etravirine (depending on information obtained from the DUET study investigators), a PI, and some NRTIs as most patients in BENCHMARK received these drug classes. Ritonavir-boosted darunavir (DRV/r) seems a reasonable choice as it is relatively well tolerated and may be more active than other PI. The patient's creatinine precludes the use of tenofovir. Abacavir, 3TC, and AZT are reasonable NRTIs to use.

Additional consideration in this patient is her current hospitalization for aspiration pneumonia and her history of pulmonary hypertension. Pulmonary hypertension has an uncommon but well established association with HIV (8). Treating her HIV and lowering her viral load (hopefully to undetectable levels) may have beneficial effects on this difficult-to-treat and often fatal condition.

There is considerable debate about the merits of starting ARVs during her acute aspiration pneumonia rather than waiting for it to be successfully treated. Some believe that the boost to the immune system from ARVs as well as the decrease in HIV viral load will help resolve the acute illness. Others are

concerned about sorting out adverse drug effects, possible drug interactions, and the possible complications of an immune reconstitution syndrome. A recent study suggested that treating with ARVs during an acute opportunistic infection was beneficial (9). It may be hard to extrapolate these findings to this case as aspiration pneumonia was not a common illness in that study. In spite of this controversy, given the critical nature of this patient, it may be most prudent to start ARVs immediately rather than waiting for the aspiration pneumonia to resolve.

Regimen Options

- If HLA B 5701 negative and if etravirine is active, Epzicom® one tablet po daily plus ritonavir 100 mg po BID with food plus darunavir 600 mg po BID with food plus etravirine 200 mg po BID with food plus Raltegravir 400 mg po BID. If etravirine is indeed active (this information should be available by contacting the DUET investigators) then this regimen includes two active agents and is may result in a durable suppressive regimen
- If HLA B 5701 negative and if etravirine is inactive, Epzicom® one tablet po daily plus zidovudine 300 mg po BID with food plus ritonavir 100 mg BID with food plus darunavir 600 mg BID with food plus Raltegravir 400 mg BID. Take all with food. If Etravirine is inactive then the patient has a 50% chance of achieving an undetectable viral load on this regimen.

Monitoring, and Follow-up Recommendations

- Check HLA B5701 allele. If negative, then risk of abacavir hypersensitivity reaction is nil.

Monitor LFTs and lipids every three months. Monitor CD4 and viral loads monthly until viral load becomes undetectable or plateaus.

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CASE NUMBER
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