

# HIV Resistance Testing Consultation Service

## Consultation Report

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## History/Clinical Course

The patient is a 53 year old man who has newly transferred to the care of the calling clinician. No old records are available, as the patient's previous provider's office was destroyed.

The patient has AIDS with a current CD4 count of 6 cell/mm<sup>3</sup> and viral load of 169,000 copies/mL. He was diagnosed with HIV in 1994 and in the past, has been on multiple antiretrovirals but he is unable to name them. His current regimen is Truvada® (emtricitabine or FTC + tenofovir or TDF) and efavirenz (EFV, Sustiva). His level of adherence to this regimen is unclear.

On his initial visit with this provider, his only complaint was flank pain and hematuria. His BP was 150/100 mmHg. His initial labs were notable for elevated transaminases (AST 53, ALT 65); serologies for viral hepatitis are pending. He was also found to have an enterococcal urinary tract infection.

The patient has a medical history notable for Type 2 diabetes mellitus (on an oral hypoglycemic agent; glycosylated hemoglobin was 7.7% in 12/06), hypertriglyceridemia (triglycerides 507 mg/dL), mild anemia (hematocrit 35, MCV 106), vitiligo, and recurrent herpetic outbreaks. There is a family history of cardio- and cerebrovascular disease, and "kidney failure."

His current medications are Truvada®, efavirenz, trimethoprim/sulfamethoxazole DS, acyclovir, rosiglitazone, zolpidem, and doxazosin.

ARV history is as follows.

DATE	REGIMEN *	CD4 cells/mm <sup>3</sup>	VL COPIES/ML	CLINICAL COURSE
1994				Diagnosed HIV+
1994-2005				Took multiple antiretrovirals, details unclear
December 2005	FTC/TDF/EFV (for at least several months)	6	169,000	No complaints other than flank pain and hematuria
January 2006	FTC/TDF/EFV			Genotype sent

## Resistance Test Findings

LabCorp HIV GenoSURE Key Mutations (1/11/06)

NRT	41L, 44D, 74I, 75S, 118I, 184V, 215Y
NNRT	103N, 108I, 190A
PI	10I/V, 20R, 32I, 33F, 36I, 46L, 47V, 54L/V, 71V, 84V, 90M

## Interpretation/Implications for Treatment

This patient demonstrates a surprising amount of genotypic resistance despite currently being on a regimen that is typically used fairly early in patients' sequence of antiretroviral regimens. In particular, the accumulation of multiple protease inhibitor (PI) resistance mutations suggests that he may have had prior exposure to several agents of this class, perhaps even to some of the newer investigational agents. If so, then perhaps his regimen was simplified in an effort to maintain virus that had decreased viral fitness despite a lack of complete viral suppression. Unfortunately, little history is available to support or negate this potential explanation for the level of resistance present on his recent genotype.

We will interpret the patient's genotypic resistance mutations and discuss his potential treatment options by class.

In the **nucleoside reverse transcriptase inhibitor (nRTI) class**, the patient has extensive class resistance. The M184V mutation confers high-level resistance to lamivudine and emtricitabine, and contributes to resistance to abacavir. The 41L and 215Y nucleoside analog mutations (NAMs) lead to decreased susceptibility against zidovudine (AZT) and stavudine (d4T) and perhaps most other NRTIs, including tenofovir [Johnson 2005]. The 44D and 118I mutations by themselves do not lead to significant resistance, but in combination with other NAMs they may lead to increased AZT and d4T resistance [Shafer 2004].

The L74I mutation is less commonly seen than the other allele at this locus, L74V. They both lead to 2- to 5-fold decreases in activity against didanosine (ddI); but they differ in that the L74I mutation is not known to confer reduced activity against abacavir [Shafer 2004]. However, in this patient, abacavir activity may be reduced anyway: M184V plus two to three NAMs contributes to decreased susceptibility to abacavir [Johnson 2005].

The significance of the V75S mutation is unclear. One panel member noted that a different allele at the same codon (V75I) may be part of the Q151 complex leading to broad nRTI class resistance (except tenofovir), but V75S is not known to be part of this complex.

- **Treatment options: nRTIs.** Despite the reduced effectiveness of the NRTIs against this patient's virus, the panel agreed that multiple nRTIs (e.g., Trizivir® [zidovudine + lamivudine + abacavir] and tenofovir) should be included in his regimen. Preliminary studies have shown that some residual nRTI activity may remain despite the presence of multiple mutations against this class [Eron 2004, Deeks 2005].

A concern was raised by one member of the panel that tenofovir may lead to nephrotoxicity, given this patient's family history and his concurrent diabetes mellitus and hypertension. Other panel members acknowledged that while this was a possibility, it needed to be weighed against the very real risk of administering a less potent regimen.

Regarding mutations for the **nonnucleoside reverse transcriptase inhibitor (NNRTI) class**, the patient's resistance profile (103N, 108I and 190A) demonstrates high level resistance against all currently available agents in this class.

- **Treatment option: NNRTI.** The patient might derive some benefit if he were treated with the investigational agent TMC-125 (etravirine), which has been studied because of its effectiveness against virus with the common NNRTI mutations 103N, 106A, 181C and 190A/S. A phase 2 study reported at CROI 2006 suggested there was a decreased response to TMC-125 with accumulation of the baseline mutations 101P, 179E/F, 181I/V, 190S and 230L [Vingerhoets 2006]. One panel member noted that these data suggested a threshold effect, with a markedly decreased response as viral populations go from having two of these mutations to having ≥ 3 of these mutations, though even with ≥ 3 mutations, there was a mean

0.66 log viral load reduction compared to the active control group. The consensus of the panel was that "if this patient were able to get access to TMC-125, he probably has a reasonable shot" that this agent would be effective, if used with another active agent (e.g., enfuvirtide). This agent is currently available in study protocols only in conjunction with the experimental PI TMC-114.

The **protease inhibitor mutations** seen with this patient's virus suggest that he may have had extensive prior exposure to this class of medications. The patient's virus is likely resistant to lopinavir/ritonavir (LPV/RTV, Kaletra®). The genotype shows the presence of two primary mutations for this agent (32I, 47V) and seven minor mutations (10I/V, 20R, 33F, 46L, 54L/V, 71V, 84V, 90M). Studies have shown reduced response with the accumulation of six or more mutations [Johnson 2005]

- **Treatment options: PIs.** Regarding the experimental PI TMC-114 (darunavir), data are still sparse on exactly which mutations are clinically significant. A recent presentation at CROI 2006 suggested that response was reduced in patients with  $\geq 10$  baseline PI mutations; this patient had eleven [De Meyer 2006]. Furthermore, five (32I, 33F, 47V, 54L and 89V) were identified as baseline "key mutations"; this patient had four of these. Interestingly, these key mutations were also noted to emerge in  $>10\%$  of patients who failed treatment with TMC-114 [De Meyer 2006], which raised the question of whether this patient may have been previously enrolled in a clinical trial with this agent at the site where he previously received medical care. However, most of these key mutations have also been noted to develop with indinavir, ritonavir and amprenavir, so potentially their presence could simply reflect prior treatment with PIs [Shafer 2004]. Overall, given the available data, the panel believed that this patient would be unlikely to derive much durable benefit from being treated with TMC-114.
- Regarding the use of boosted tipranavir (TPV, Aptivus®), the patient's virus has eight of the 21 mutations in the Tipranavir (TPV) Resistance Score, suggesting that he already has significant resistance to this agent [Valdez 2005]. A proposed modification of the Tipranavir Resistance score presented at CROI 2006 shows that this patient has five mutations associated with a higher-than-expected TPV fold change and five other mutations associated with a lower-than-expected fold change; the extent of how this decreases TPV susceptibility is unclear [Parkin 2006].

Tipranavir/r would be most likely to exert a durable virologic response if the patient has not had prior treatment with (and resistance to) enfuvirtide. Results from the Phase 3 studies, 1182.12 and 1182.48, show that use of TPV/r + enfuvirtide increased durable virologic response from 28% to 64%; by comparison, only 19% of subjects with a comparator PI plus enfuvirtide achieved a durable virologic response [Tipranavir package insert].

Overall, the panel believed that the use of TPV/r plus enfuvirtide would represent this patient's second-best chance at durable virologic suppression. A phenotype was believed to be important in determining whether this PI would provide a strong enough virologic response to use in conjunction with enfuvirtide, as well as to determine whether there was any resistance to enfuvirtide.

**In summary**, the panel believed that this patient harbors extensive resistance to currently available antiretrovirals of at least three classes (it is still unclear whether he also has resistance to the fusion inhibitor enfuvirtide). The goal of treatment for this patient with a CD4 count of 6 should be to give as potent a regimen as possible. The panel believed that the best chance at achieving a durable virologic response would be with an investigational agent from a new class (e.g., an integrase inhibitor) if it could be combined with a second active agent (e.g., enfuvirtide).

Another investigational agent from a new class, the R5 inhibitor maraviroc, was also considered. However, the panel believed that with this patient's advanced AIDS, his virus was likely to be mixed or dual tropic (i.e., both X4- and R5-tropic), and therefore, an R5 inhibitor would be unlikely to lead to a

lasting virologic response. Furthermore, one panel member commented that most trials for the R5 inhibitors are now closed to enrollment.

## Recommendations

### Regimen Options

#### Preferred Option: Trizivir® + tenofovir + tipranavir/ritonavir +/- enfuvirtide

- Pros – may be easier to access these FDA-approved medications if he is not close to a clinical trial site.
- Cons – A preferred regimen would include the above drugs with an investigational agent (see below). High pill burden and need for injections

#### Second Option: Trizivir® + tenofovir + tipranavir/ritonavir+ investigational agent of a new class +/- enfuvirtide

- Pros – greatest chance of viral suppression if randomized to a potent new drug class (e.g., an R5 inhibitor or an integrase inhibitor. Randomization to a placebo may risk exposing this virus to “sequential” enfuvirtide monotherapy (particularly if the study does not allow tipranavir or darunavir).
- Cons – most studies of investigational new drugs are placebo controlled and several studies do not currently allow co-administration of either ritonavir/tipranavir or ritonavir/darunavir. Patient’s virus may already be resistant to enfuvirtide. May be difficult to access if not near clinical trial site.

#### Third Option: Trizivir® + tenofovir + dual-boosted PIs +/- enfuvirtide

- Pros – as for Option #1.
- Cons – compared to Regimens #1 and 2, this regimen is likely to be even less effective given his genotypic results. With dual PIs, achieving therapeutic levels may be difficult so the panel would recommend therapeutic drug monitoring with this regimen.

### Dosing, Monitoring, and Follow-up Recommendations

- Most importantly, the panel recommended **temporarily continuing his current regimen of Truvada + efavirenz**, while trying to determine whether he is eligible to enroll in a clinical trial (since many trials require that a patient be on a stable ARV regimen). If he does not qualify, or is unable to access any clinical trials, then the panel agreed that efavirenz should be stopped to prevent the selection of further NNRTI mutations. If there is a choice of which investigational agent to try, an integrase inhibitor would be recommended first, followed by an R5 inhibitor, followed by TMC-125.
- Secondly, a **phenotypic resistance assay** should be sent now. If this were to show only a 1-2 fold-change in resistance to TPV and no significant enfuvirtide resistance, then members of the panel concurred that using these

two agents (along with multiple nucleosides) would provide a reasonable chance at suppression. On the other hand, if a phenotypic test were to show significant TPV resistance (or significant enfuvirtide resistance), the panel would even more strongly recommend that the patient be enrolled in a clinical trial for an investigational agent from a new class, even if it required moving to a new city to access a clinical trial.

- Thirdly, the **patient should be questioned** specifically whether he recalls ever having to give himself twice-daily injections (i.e., enfuvirtide) as part of his HIV regimen in the past. He should also be asked whether he recalls having been enrolled in any clinical studies previously (which might explain the presence of four primary TMC-114 resistance mutations). He should also be queried about adherence, and receive repeated counseling on ways to minimize missed doses.
- Fourth, it would be important to **get expanded information about the current genotype**. Specifically, ask the performing laboratory if other resistance mutations for NNRTIs or enfuvirtide may have been detected but not reported (e.g., because they have as-yet-uncertain clinical significance). This would help to determine the usefulness of these medications.
- Fifth, the patient's **concomitant disease states need to be addressed**, including optimization of his blood pressure, hypertriglyceridemia and diabetes mellitus (especially if the regimen is changed to include PIs again). His elevated transaminases should be investigated. If his flank pain and hematuria did not resolve with treatment of his urinary tract infection, a more extensive urologic evaluation may be needed.
- **Dosing:** Trizivir® 1 tab bid; Tenofovir 300mg daily; enfuvirtide 90mcg SQ bid; tipranavir 500mg/ritonavir 200mg bid.

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