
HIV Resistance Testing Consultation Service

Consultation Report

Co-Chairs: Steven G. Deeks, MD
Betty J. Dong, Pharm.D

Panel Members: Richard Aranow, MD
Lawrence Boly, MD
Brad Hare, MD
Amy Kindrick, MD, MPH
Parya Saberi, PharmD (secretary)
Jason Tokumoto, MD

Project Director: Ronald H. Goldschmidt, MD

Disclaimer: This information has been developed solely as an educational resource for health care professionals interested in HIV care and research. The information presented represents the views of the Panel members only and not necessarily those of the National HIV/AIDS Clinicians' Consultation Center's HIV Telephone Consultation Service (Warmline), the Positive Health Program at San Francisco General Hospital, or sponsoring organizations. Resistance testing can help identify whether certain drugs or classes of drugs might be ineffective, but cannot establish which drugs will be effective. Furthermore, test results can be inaccurate and interpretation of tests is not yet standardized. Because of the many factors involved in treatment decisions when resistant virus is present, the antiretroviral regimens and the therapeutic strategies discussed are not the only possible options and might be different from current Practice Guidelines. Other sources of information on resistance testing, such as clinical HIV websites, can be of help. Health care professionals should consult the HIV Telephone Consultation Service (Warmline) or HIV experts in their community before using any of the recommended therapeutic regimens or strategies in this document.

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 man who was admitted with pancytopenia and fever of unknown origin (FUO) and subsequently found to be HIV positive. His CD4 count is 75 cells/mm³ and viral load is 11,700 copies/mL. The patient denies previous tests for HIV infection. He is married and denies risk factors for HIV infection, including intravenous drug use or sex with men. His wife is HIV negative. He is taking no medications. There is no history of any medical illnesses and no chronic diseases. He is allergic to sulfonamides.

Work-up of FUO and pancytopenia included the following:

- Viruses: Hepatitis A, B & C serology negative. EBV IgG positive and IgM negative, CMV negative, Dengue fever Ab negative, Parvovirus IgG positive and IgM negative. EBV IgM negative; IgG positive. BK virus negative.
- Bacteria: RPR negative but EIA positive, Leptospirosis Ab negative, Q fever Ab negative, Bartonella Ab negative, Salmonella Ab negative, Rickettsial serology negative. Dengue serology negative. RPR negative. Urine, blood and CSF cultures negative. AFB and MAC culture of blood and bone marrow negative at 60 days.
- Fungal: Blood, CSF and bone marrow cultures negative. Coccxy, Histoplasmosis and Blastomycosis Ab negative.
- Parasites: Schistosomiasis Ab negative, Strongyloides Ab negative, Toxo Ab negative. Babesia serology negative
- LDH normal. ANA negative, RF negative
- Lumbar Puncture: 5 WBC (28L, 72M), glucose 61, protein 41, VDRL negative, JCV virus negative.
- CT scan of abdomen reveals adenopathy. Pet scan reported as normal.

Caller calls to ask what HAART recommendations could be made based on the results of his resistance testing (see Table). The caller also wants to know whether a one pill once daily regimen would be possible.

Resistance Test Findings

Key Mutation	
NRT	T69I, V118I, Q151M
NNRT	none
PI	L10V, I54V, L63P, A71V, V77I, L90M

A phenotype showed resistance to zidovudine (FC 3.38, upper cut off 1.9), and stavudine (FC 5.08, cutoff 1.7). The virus was reported to be sensitive to abacavir, lamivudine, emtricitabine, and tenofovir.

Interpretation/Implications for Treatment

This is an interesting case of a transmitted multi-resistant virus in a patient who is naïve to antiretroviral drugs.

The Q151M mutation is an uncommon mutation (the reported frequency varies from 2.4 to 7.9% among highly treatment experienced individuals^{1,2}). The Q151 mutation usually is part of a complex with A62V, V75I, F77L and F116Y. It is rare to have a lone Q 151M mutation. Patients who develop the lone Q151 mutation often go on to develop the other mutations in the complex within one year, but the natural history of this mutation is not well described.

The Q151M mutation confers partial resistance to zidovudine (AZT, Retrovir®), didanosine (ddl, Videx®), and stavudine (d4T, Zerit®). Subsequent mutations at V75K, F77L and F116Y do not confer increased resistance by themselves but when combined with the Q151M the resulting complex confers high-level resistance to AZT, ddl, d4T and possibly cross-resistance to lamivudine (3TC, Epivr®)³.

Panel members hypothesized that in this case there may have been a back mutation from the Q151 complex to the single Q151M mutation or perhaps there was incomplete transmission of the Q151M complex. A third explanation could be that the patient had yet to involve the subsequent mutations in the Q151M complex because there was no drug pressure on the virus. Given the single Q151M mutation one might expect better susceptibility to NRTIs compared to the Q151M complex which confers resistance to all NRTIs except (TDF, Viread®).

The genotype also identifies several protease inhibitor (PI) mutations that affect the regimen selection. The presence of five lopinavir (LPV/r, Kaletra®) mutations: L10V, I54V, L63P, A71V and L90M; suggest that this virus is partially susceptible to LPV/r. Similarly, the presence of the L10V, I54V, A71V, and L90M mutations would also indicate resistance to fosamprenavir (fos-APV, Lexiva®) and atazanavir (ATV, Reyataz®)

Ritonavir boosted darunavir (DRV/r) is likely to be effective since the major mutations for this PI are not present. The presence of the I54M, L 76V, I84V, and the I50V mutations are associated with a three-to-four-fold diminished response to DRV/r.⁴

The absence of any nonnucleoside reverse transcriptase (NNRTI) mutations indicates full susceptibility to this class of agents.

Recommendations

Regimen Options:

Despite the caller's request for a once-a-day regimen of Atripla® or a simplified regimen of Truvada® plus a boosted PI, these regimens would likely produce resistance and virologic failure. Other options might include raltegravir-based regimens or maraviroc-based regimens; however, these drugs are not readily available in many areas.

The optimal regimen for this virus is Atripla® (efavirenz, tenofovir, emtricitbine) and ritonavir-boosted darunavir (DRV/r)

Pro: Regimen likely to be fully active based on the genotype, relatively low pill burden, bid dosing interval.

Con: EFV can reduce darunavir AUC by 13% which may reduce efficacy

Dosing, Monitoring, and Follow-up Recommendations

Darunavir 300 mg: 2 capsules (600mg) bid plus ritonavir 100mg bid, and Atripla one tablet daily. Take all with food to reduce gi intolerance

f/u weekly CBC

f/u electrolytes, BUN, Cr. and LFTs at 2, 4 and 6 weeks.

Viral load and CD4 at 4-6 weeks after any regimen change.

Addendum:

Atripla® and ritonavir boosted darunavir was started with good tolerability. After 10 days of therapy, his viral load became undetectable and his CD4 count was 64 cells/mm³.

He subsequently developed a fever and was started on empiric MAC therapy with rifabutin 150mg qod, ethambutol and ciprofloxacin. His MAC blood, bone marrow, and CSF cultures have remained negative to date. His WBC improved to 6.0 gm/dL, hemoglobin to 13 gm/dL and platelets remained normal at 278,000/mm³

¹ Paolucci S, Baldanati F, et al. Gln 145Met/Leu Changes in Human Immunodeficiency Virus Type 1 Reverse Transcriptase Confer Resistance to Nucleoside and Nonnucleoside Analogs and Impair Virus Replication. *J Antimicrob. Chemother.* 48:4611-4617

² Iler MM, Masuhr AM, Zwingers TZ, Arasteh KA. Frequency of the multidrug resistance mutation Q151M, results of the Berlin cohort. *Int. Conf AIDS, 2002 July 7-12: abstract # B10419*

³ Iversen A, Shafer R, et al. Multidrug-Resistant Human Immunodeficiency Virus type 1 Strains Resulting from Combination Antiretroviral Therapy. *J virology* 1996;70:1086-1090.

⁴ DeMeyer S et al. Weighing the mutations associated with a diminished response to TMC114/r. 15th Intl HIV Drug Resistance Workshop June 13-17th, 2006. Sitges, Spain