
HIV Resistance Testing Consultation Service

Consultation Report

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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 38 year old gay man who has been HIV + since 1992. His CD4 nadir was ~350 cell/mm₃ and he has had no HIV-related opportunistic complications. Zidovudine (AZT) was started in 1992 and lamivudine (3TC) and indinavir (IDV) 800 mg po q 8h were added in 1995, and he has remained on this regimen since that time. The patient feels well, likes his regimen, and has no problems with adherence. His CD4 and HIV RNA history are as follows:

| DATE | CD4 | HIV RNA | COMMENTS |
|-------|------|---------------|------------------------------------|
| 1992 | ~350 | | |
| 1998 | 562 | 1700 | |
| 4/99 | 445 | 26,000 (bDNA) | |
| 8/99 | 526 | 6,800 | |
| 11/99 | | | |
| 1/00 | 554 | 11,000 | Pneumovax |
| 4/00 | | | Viral meningitis |
| 6/00 | 477 | 6,040 | |
| 10/00 | 399 | 4,390 | |
| 11/00 | | | HAV and HBV vaccines |
| 2/01 | 561 | 15,000 | |
| 6/01 | 566 | 11,700 (PCR) | |
| 12/01 | 397 | 7,710 | |
| 6/02 | 705 | 40,200 (bDNA) | 1+ proteinuria |
| 10/02 | 558 | 75,000 (PCR) | |
| 11/02 | | | GART |
| 12/02 | 576 | 6,820 (bDNA) | PART |
| 2/03 | 626 | 10,900 (PCR) | 2+ proteinuria; generalized LAN |

Resistance Test Findings

GART (11/19/02, Quest Diagnostics)

| | |
|------|--|
| NRT | M41L, M184V, L210W, T215Y |
| NNRT | NONE |
| PI | L10I, G48V, I54T, L63P, A71V, V77I/V, V82A |

Virtual Phenotype (12/13/02, Virco, Quest Diagnostics)

| DRUG | FOLD CHANGE IN IC50 |
|--------------|---------------------|
| NRTI | |
| Zidovudine | 7.6 |
| Lamivudine | 45.8 |
| Didanosine | 1.6 |
| Zalcitabine | 1.8 |
| Stavudine | 1.3 |
| Abacavir | 3.3 |
| Tenofovir DF | 1.4 |
| NNRTI | |
| Nevirapine | 1.4 |
| Delavirdine | 1.6 |
| Efavirenz | 1.1 |
| PI | |
| Indinavir | 29.7 |
| Ritonavir | 41.7 |
| Nelfinavir | 34.2 |
| Saquinavir | 40.7 |
| Amprenavir | 2.0 |
| Lopinavir | 18.1 |

Interpretation/Implications for Treatment

This case represents an example of a patient who has had a stable treatment-mediated increase in CD4+ T cell counts despite incomplete viral suppression with combination therapy. This case also illustrates the challenges posed by incomplete histories and the use of different assays (HIV RNA-PCR and HIV b-DNA) for measuring HIV viral load, as well as the potential impact of co-morbid conditions when selecting a therapeutic strategy.

It would be useful to know what this patient's pre-treatment and pre-protease viral and CD4 "set points" were. Without this information it is difficult to judge the magnitude of his response to the treatment he's received.

However, the patient's stable average CD4 count of approximately 500, (which is substantially higher than his nadir of ~350), argues that treatment is providing some benefit.

This patient had a genotype test done in November 2002 and a virtual phenotype test done one month later in December 2002. Both tests use PCR amplification technology to identify specific mutations in the viral genome. The 2 testing approaches differ in that the virtual phenotype compares the patient's mutation pattern with a large database of clinical and laboratory isolates with known genotypic mutations and phenotypic resistance patterns. A computer algorithm then predicts the phenotypic resistance pattern based on phenotype results from all isolates in the database bearing similar mutation patterns. This approach allows inferences to be made about the phenotypic behavior of a patient's virus without performing a phenotype test directly.

Unsurprisingly and reassuringly, the genotype and virtual phenotype tests for this patient delivered the same results. The only genotypic difference was the absence in the December test for the L63P mutation seen in the November test. L63P is a polymorphism which may be seen in viruses from patients whose protease inhibitor therapy has failed.¹ Its disappearance in the later resistance test would not be expected to have a clinically significant impact on this virus's susceptibility to protease inhibitors.

This patient's virus has accumulated multiple major nucleoside analog mutations (NAMS), including M41L, L210W, and T215Y, making it unlikely that any drug in this class will have significant antiviral activity. The M184V mutation also suggests that high level 3TC resistance is present. This M184V mutation may also confer some benefit to the patient by impairing the virus's replicative fitness and by partially restoring AZT, d4T (stavudine) and possibly tenofovir (TDF) activity.

The test results also reveal several major mutations in the viral protease gene (L10I, I54T, and V82A). Together, these mutations suggest broad cross-class protease inhibitor (PI) resistance.^{2,3} However, this mutation pattern does not rule out the possibility that some members of the class have retained at least partial activity. It is possible that if pharmacokinetic exposure to some combination of PIs is optimized, these drugs may still have some benefit for this patient.

Regarding the non-nucleoside reverse transcriptase inhibitors (NNRTIs), this patient has never been treated with this class of drugs. The resistance test results are consistent with this history and indicate that any drug in the class should be fully potent.

The patient feels well, likes his regimen, and has no problems with adherence. His provider is reluctant to switch therapy because the patient is familiar with the regimen and seems to be tolerating it well. However, the regimen is not completely suppressive, and the patient has recently expressed interest in doing "anything to get [his] viral load down." In addition, his persistent proteinuria raises concern about possible cumulative drug toxicity (indinavir).

The panel agreed on the importance of better characterizing this patient's renal disease. His ethnicity (Caucasian) and high CD4 count make HIV-associated nephropathy (HIVAN) less likely. However, none of these factors rule out HIVAN, and if it were to be diagnosed, achieving complete viral suppression would become a high priority. Although indinavir toxicity does not usually present with proteinuria alone,⁴ the panel felt that because of its potential for inducing crystal nephropathy and interstitial nephritis, the risks of continuing

¹ Kozal MJ, Shah N, Shen N, Yang R, Fucini R, Merigan TC, Richman DD, Morris D, Hubbell E, Chee M, Gingeras TR. Extensive polymorphisms observed in HIV-1 clade B protease gene using high-density oligonucleotide arrays. *Nat Med.* 1996 Jul;2(7):753-9

² Palmer S, Shafer RW, Merigan TC. Highly drug-resistant HIV-1 clinical isolates are cross-resistant to many antiretroviral compounds in current clinical development. *AIDS* 13(6): 661-667; Apr 1999

³ Shafer RW, Winters MA, Palmer S, Merigan TC. Multiple concurrent reverse transcriptase and protease mutations and multidrug resistance of HIV-1 isolates from heavily treated patients. *Ann Intern Med.* 1998 Jun 1;128(11):906-11.

⁴ Olyaei AJ, deMattos AM, Bennett WM. Renal toxicity of protease inhibitors. *Curr Opin Nephrol Hypertens.* 2000 Sep;9(5):473-6.

the drug outweighed its benefits. The panel was also cautious about using tenofovir, given its recent association with renal tubule damage and Fanconi's syndrome, especially in individuals with underlying renal disease.⁵

The panel agreed that this patient's best HIV treatment options would be either to stop ARV therapy altogether or to change to a different regimen. The advantages of stopping therapy include removing the risk of any drug toxicity as well as preventing additional resistance mutations from accumulating. However, stopping drugs also carries the risk of virologic and immunologic progression. Overall, the panel believed that given this patient's high nadir CD4 count, stopping his ARVs would be reasonable if he could be closely monitored. The panel thought it likely that his CD4 count would remain greater than 200 for some time off ARVs.

The panel also agreed that it might still be possible to achieve complete viral suppression with drugs from classes to which this patient's virus had already been exposed. Although not guaranteed to be successful, such a strategy would still preserve the NNRTIs for the future. A future regimen containing fully active drugs from at least 2 different classes would be highly likely to completely suppress this patient's virus and, assuming adherence, would be expected to help keep him healthy for a long time. Changing therapy certainly would minimize possible indinavir-related toxicity but it would come at the cost of a more complicated regimen that may jeopardize adherence and may result in additional toxicity.

If the patient were to change therapy, the regimen most likely to suppress his viral load would include two nucleosides, a dual-boosted protease inhibitor, and a non-nucleoside. However, the panel agreed that in an asymptomatic patient with a high CD4 count, the risk of losing the non-nucleoside class by using it with other only partially active drugs greatly outweighed the virologic benefit of using it now. An alternative regimen most likely to suppress without an NNRTI would include two nucleosides and a dual-boosted protease inhibitor combination such as Kaletra and amprenavir.

In patients without the I50V mutation, the combination of Kaletra and amprenavir would be expected to have significant activity.⁶ However, recent data regarding pharmacokinetic interactions between lopinavir, ritonavir, and amprenavir have raised questions about the proper dosing of this combination.^{7,8} Raguin et. al., suggested that an additional 100 mg "boost" of ritonavir would offset the expected reduction in lopinavir AUC by amprenavir P450 induction, and might result in improved virologic outcomes.⁹ In this small study, the "extra boosted" arm experienced a viral load drop of 2.4 logs as compared to the 1.4 log reduction seen in the standard dose arm. The panel noted the heavy pill burden already associated with the Kaletra/amprenavir combination (7 pills twice daily) even without additional ritonavir and agreed that a detailed discussion with the patient about the demands of such a complex regimen, as well as strategies for optimizing adherence, would be important prior to instituting it.

⁵ Reynes J, Peyriere H, de Boever CM, Moing VL. **Renal Tubular Injury and Severe Hypophosphoremia (Fanconi Syndrome) Associated with Tenofovir Therapy.** Program and abstracts from the 10th Conference on Retroviruses and Opportunistic Infections; February 10-14, 2003; Boston, Massachusetts. Poster 717.

⁶ Pazhanisamy, S., J. A. Partaledis, B. G. Rao, and D. J. Livingston. 1998. In vitro selection and characterization of VX-478 resistant HIV-1 variants. *Adv. Exp. Med. Biol.* 436:75-83.

⁷ Solas C, Quinson AM, Couprie C, Ravaux I, Poizot-Martin I, Durand A, Lacarelle B. Pharmacokinetic Interaction between Lopinavir/r and Amprenavir in Salvage Therapy. Program and abstracts from the 9th Conference on Retroviruses and Opportunistic Infections; February 24-28, 2002; Seattle, Washington. Poster 440-W

⁸ Baldini F, Rizzo MGR, Hoetelmans R, Murri R, Di Giambenedetto S, Cingolani A, Cauda R, De Luca A. A Prospective Study of Deep Salvage Therapy with Lopinavir/r, Amprenavir, and NRTIs: Final 24-Week Data, Pharmacokinetics, and Association of Drug Levels/Drug Susceptibility with Virologic Response. Program and abstracts from the 9th Conference on Retroviruses and Opportunistic Infections; February 24-28, 2002; Seattle, Washington. Poster 423-W

⁹ Raguin G, Chene G, Morand-Joubert L, et al. Salvage therapy with lopinavir/ritonavir (LPV/r), amprenavir (APV) +/- an additional boost with ritonavir (RTV) in HIV infected patients (pts) with multiple treatment failure: Final 26-week results of Puzzle 1 - ANRS104 study. Program and abstracts of the 42nd Interscience Congress on Antimicrobial Agents and Chemotherapy; September 27-30, 2002; San Diego, California. Abstract H-1078

Recommendations

Regimen Options

STOP THERAPY (First Choice): Preserve therapy until it is feasible to combine a non-nucleoside with T-20 (Fuzeon®, enfuvirtide) for maximally suppressive regimen or until the CD4 counts deem treatment is necessary (CD4-guided).

Pros: Preserve NNRTI class, spare current protease inhibitor toxicities

Cons: Potential for viral rebound, unsure how long interruption will last

CHANGE THERAPY (Second Choice): didanosine + other nucleoside + Kaletra (with or without the addition of amprenavir and ritonavir)

Pros: Fairly good chance at viral suppression, spares non-nucleoside class

Cons: High pill burden, potential for other protease inhibitor toxicities, especially with added ritonavir

CHANGE THERAPY (Third Choice): didanosine + other nucleoside + Kaletra + efavirenz

Pros: Excellent likelihood of achieving complete suppression

Cons: Risk of losing the remaining NNRTI treatment class; high pill burden; high risk for short term and long-term toxicity.

Dosing, Monitoring, and Follow-up Recommendations

- Monitor CD4 counts Q1-2 months and re-initiate treatment if CD4 falls between 200-350. After restarting ARV therapy, recheck viral load and CD4 counts after 3 to 4 weeks of therapy. Continue work-up of renal disease and proteinuria.

DOSING for salvage regimens would be as follows:

Second Choice Didanosine Enteric Coated 400mg PO QD (if >60 kg) on empty stomach; if necessary, adjust for renal dysfunction)

Plus other tolerable nucleoside with food

Plus Kaletra (lopinavir/ritonavir) 3 capsules PO BID with food

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PANEL CLINICIAN: AMY KINDRICK, MD, MPH

DATE: MARCH 2003

± Amprenavir 600mg PO BID plus Ritonavir 100mg PO BID with food

Third Choice Didanosine Enteric Coated 400mg PO QD (if >60 kg) on empty stomach; if necessary, adjust for renal dysfunction)

Plus other tolerable nucleoside with food

Plus Kaletra (lopinavir/ritonavir) 4 capsules PO BID with food (if given with efavirenz)

Efavirenz 600 mg PO HS