
HIV Resistance Testing Consultation Service

Consultation Report

Panel Members: Richard Aranow, MD
George W. Beatty, MD, MPH
Steven G. Deeks, MD
Betty J. Dong, Pharm.D
Amy V. Kindrick, MD
Jody Lawrence, MD
Michael L. Lim, Pharm.D (11/00-6/01)
John Stansell, MD (3/10-6/01)
Jason Tokumoto, MD
Paul Volberding, MD (11/00-3/01)

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

This is a 45 yo HIV+ woman with an HIV positive partner (partner has an undetectable viral load). This patient has had no opportunistic infections other than recurrent cervical dysplasia and genital warts which appear to be better controlled when her CD4 count is higher. She also has peripheral neuropathy, lipoatrophy and lipoaccumulation. Her cholesterol and triglycerides are within normal limits. She has diabetes mellitus for which she takes metformin.

The patient's CD4 nadir is 47. She has had a long-complicated antiretroviral treatment history (see Table), and is currently on lamivudine (3TC), tenofovir (TFV) and efavirenz (EFV). Her most recent CD4 count was 141 and viral load was 22,000. Sequential genotypes and phenotypes were performed (see below).

Her ARV history is as follows.

| DATE | REGIMEN * | CD4 cells/mm ³ | VL COPIES/ ML | RESISTANCE TEST FINDINGS | CLINICAL COURSE |
|------|------------------------|------------------------------|---------------------|-----------------------------|--------------------|
| 1/94 | | 164 | 48k | | |
| 1994 | AZT/ddC | | | | |
| 5/94 | | 215 | 6300 | | |
| 9/94 | | 185 | | | |
| 9/95 | | 47 (repeated x 2) | | | |
| 9/96 | AZT/3TC/SQV/ IDV | | | | |
| 3/97 | | 106 | 2500 | | |
| 8/97 | | 207 | 22k | | |
| 9/97 | ddl/HU/DLV/NFV | 215 | 6300 | | |
| 4/98 | | 135 | 24k | | |
| 6/98 | D4T/ddl/HU/RTV/S QV | | | | |
| 7/98 | | 59 | 8400 | | |
| 9/98 | Stopped HU | 88 | 21k | | |

| | | | | | |
|-------|-------------------------|-----|------|-------------------------------------|--|
| 4/99 | | 149 | 27k | | |
| 6/99 | | 117 | 21k | | |
| 8/99 | | 79 | 19k | | |
| 10/99 | | 64 | 28k | GART obtained See results | |
| 12/99 | Ddl/d4T/RTV/APV/ EFV | | | | |
| 6/00 | | 114 | 50 | | |
| 12/00 | | 141 | 170 | | |
| 3/01 | | 244 | 400 | | |
| 9/01 | | 182 | 4400 | | |
| 11/01 | | 155 | 9500 | | |
| 12/01 | | 84 | 2400 | | |
| 12/01 | TFV/3TC/EFV | | | | Regimen Changed because of pill burden |
| 1/02 | | 78 | 2300 | | |
| 2/02 | | 150 | 21k | | |
| 3/02 | | 168 | 6500 | | |
| 4/02 | | 144 | 15k | | |
| 5/02 | | 254 | 14k | GART and Phenotype test obtained | |
| 9/02 | | 141 | 22k | | |

Resistance Test Findings

12/99 results
 Key Mutations

| | |
|------|---|
| NRT | 41L, 67N, 208Y, 210W, 215Y, |
| NNRT | Y181C |
| PI | 10I, 46I, 54V, 63P, 71V, 73S, 77I, 84V, 90M |

5/02 GART results

| | |
|------|-----------------------------------|
| NRT | 67N, 184V, 210W, 215Y |
| NNRT | 103N |
| PI | 10I, 46I, 54M, 63P, 71V, 84V, 90M |

5/02 Phenotype Results

NRTI

AZT - 13 FC, d4T - 2.7 FC, ddl - 1.9 FC, ABC - 5.2 FC, 3TC - >>> FC

NNRTI

EFV - 44 FC, NVP - 146 FC

PI

RTV - 32 FC, SQV - 16 FC, IDV - 7.5 FC, NFV - 21 FC, APV - 35 FC

Interpretation/Implications for Treatment

The panel agreed that this patient's most pressing issue was a lack of sufficient immunologic reconstitution, which is likely related to ongoing viral replication. There have been a few times during her history where effective therapy achieved an undetectable viral load (12/99 and 6/00), however this was never sustained. The patient has admitted difficulty in taking high-pill burden regimens (e.g. ritonavir/ amprenavir). Therefore, the panel agreed that the most pressing goals for this patient included consideration of overall pill burden, hopefully improving adherence and thus, hopefully increasing her peripheral CD4+ T cell counts.

This patient's first genotype was obtained while on treatment with didanosine (ddl), stavudine, (d4T) ritonavir (RTV) and saquinavir (SQV). Based on the results following that genotype, therapy was intensified with a change to ritonavir (RTV)/amprenavir (APV) and addition of efavirenz (EFV). At that time she had a Y181C mutation, presumably as a consequence of prior delavirdine (DLV) exposure. The panel commented that these changes were consistent with the standard of care at that time since the 181C mutation was more associated with reduced susceptibility to nevirapine (as opposed to efavirenz). It is now believed that the Y181C mutation causes decreased susceptibility to all non-nucleoside reverse transcriptase inhibitors.¹

Overall, the patient's genotypes and phenotypes are fairly consistent. Her virus contains 4-5 NAMs, the K103N mutation, and several major protease inhibitor mutations (10, 46, 71, 84, 90). The second genotype is very similar to the first, with the only differences being the loss of the 41 NAM and loss of some of the minor protease inhibitor mutations. The panel thought it was interesting that the patient continued to exhibit PI mutations in the second genotype even though she was off protease inhibitor therapy for approximately five months.

Of note, no lopinavir results were included with the phenotype reported in May. Although the clinical "cutoffs" for reduced susceptibility to many antiretroviral agents is not well defined, the panel reviewed the most recent data associated with phenotype interpretation:

| Antiretroviral agent | Fold change after which reduced phenotypic susceptibility is observed | References |
|--|---|------------|
| Zidovudine Lamivudine | ? | |
| Abacavir | 4-8 | 2 |
| Stavudine Didanosine | 1.4 – 1.7 | 3 |
| Tenofovir | 1.3 – 4 | 4 |
| Efavirenz Nevirapine Delavirdine | > 10 | |
| Lopinavir Indinavir | 10-40 | 5 |
| Indinavir/Ritonavir | 2.5 - 25 | 6, 7 |
| | | |

In discussing future choices for this patient, the panel believed that stopping therapy was not a reasonable option for this patient as her nadir CD4 T cell count was low. The panel also believed that continuing an NNRTI –based regimen (efavirenz) would not be beneficial. It is unlikely that a NNRTI adds much antiviral activity in the face of the K103N mutation. There is also a concern that without full viral suppression, continuing an NNRTI could lead to more NNRTI mutations. This may compromise the activity of second and third generation NNRTIs that are currently in development. For example, it was noted that the new NNRTI drug TMC-125 may still be effective in the presence of a K103N mutation.⁸

The possibility of T-20 was discussed for this patient. Unfortunately, recent data from the TORO studies indicate that T-20 rarely achieves a durable virologic response when combined with a regimen containing no active agents. Thus, it is possible that in this patient T-20 would result in only a transient virologic response. The possibility of including Kaletra or other dual-boosted protease inhibitors was also discussed. The panel debated whether or not to initiate Kaletra (plus or minus another protease inhibitor) in this patient. Many panel members believed that Kaletra should be initiated only when T-20 became available. As demonstrated in the TORO-1^{9,10} and TORO-2¹¹ trials, being Kaletra naïve was a strong predictor of success with the T-20 regimen. Furthermore, the patient already has lipodystrophy, lipoatrophy, glucose intolerance, possibly due to her previous protease inhibitor therapy and will be further compromised by the addition of a PI.

In summary, both the genotype and phenotype resistance testing indicate that this patient has a highly resistant virus that is unlikely to be fully suppressed with currently available agents. The best chance for viral suppression may be with a regimen including T-20 and Kaletra. As T-20 is not yet available to this patient, one option is to use a partially suppressive regimen that will not cause more PI mutations to accumulate. Such a regimen could include 3-4 NRTI's and may "tide her over" until T-20 becomes commercially available.

Recommendations

Regimen Options (assuming T-20 is not yet available)

Preferred Option: Nucleoside based therapy with Trizivir® (AZT/3TC/ABC) ± tenofovi pending T-20.

- Pros -- Easy dosing, avoids protease inhibitor toxicities, possibility of reversion to WT protease virus, preserves protease inhibitor options for later use with T-20, preserves options for second generation NNRTIs.
- Cons -- Unlikely to suppress virologically, questionable immunologic benefits, possibility of accumulation of more NAMS

Second Option: Use of Kaletra® alone or in a dual boosted protease inhibitor regimen (Kaletra/SAQ or Kaletra/AMP) + 2 nucleosides of choice

- Pros – Possibility of immediate virologic/immunologic benefit
- Cons -- Protease inhibitor toxicities, pill burden and adherence issues, using “last resort” agents (if this regimen does not work, no effective agents left to combine with T-20)

Dosing, Monitoring, and Follow-up Recommendations

- Continue to monitor the CD4 and VL every 3 to 4 weeks
- Consider doing another GART/PT when initiation of T-20 or other new agent are possible.
- When using Kaletra and Saquinavir together, usual dosing is 3 pills of Kaletra and 1000 mg of Invirase bid.
- When using Kaletra and amprenavir together, the proper dosage is controversial. One option is 3 capsules of Kaletra bid, 100mg of ritonavir bid, and 600 mg of amprenavir bid. Another option is 3-4 capsules of Kaletra with 750mg of Amprenavir bid. Kaletra and amprenavir both have the ability to reduce effective drug concentrations of each other. The optimal dosing is unclear although there is better evidence with the addition of small doses of ritonavir to the regimen.

References:

1. Antinori A, Zaccarelli M, Cingolani A, Forbici F, Rizzo MG, Trotta MP, et al. Cross-resistance among nonnucleoside reverse transcriptase inhibitors limits recycling efavirenz after nevirapine failure. *AIDS Res Hum Retroviruses* 2002 Aug 10;18(12):835-8.
2. Lanier ER, Hellman N, Scott J, Ait-Khaled M, Melby T, Carsanaro J, et al. Determination of a clinically relevant phenotypic “cutoff” for abacavir using the phenosense assay. 8th Retrovirus Conference. Chicago, IL, February 4-8, 2001
3. Shulman NS, Hughes MD, Winters MA, Shafer RW, Zolopa AR, Hellmann NS, Bates M, Whitcomb JM, Katzenstein DA. Subtle decreases in stavudine phenotypic susceptibility predict poor virologic response to stavudine monotherapy in zidovudine-experienced patients. *J Acquir Immune Defic Syndr* 2002 Oct 1;31(2):121-7.
4. Harrigan PR, McKenna P, Larder BA, Miller MD. Phenotypic Analysis of Tenofovir Susceptibility among 5000 Clinical HIV-1 Isolates. 41st International Conference on Antimicrobial Agents and Chemotherapy. Chicago, IL, December 2001.

5. Kempf DJ, Isaacson J, King M, Rode R, Brun S, Xu Y, Real K, Hsu A, Granneman GR, Bernstein BR, Sun E. Interpretation of Phenotypic and Genotypic Resistance to Kaletra (ABT-378/ritonavir) in Protease Inhibitor Experienced Patients. 5TH International Congress on Drug Therapy in HIV Infection. Glasgow, Scotland, October 22-26, 2000
6. Rice H, Zolopa A, Coram M, Murlidharan U, Shulman N, Vaamonde C, et al. Correlation of Phenotypic Resistance and Virologic Response to Indinavir/Ritonavir Boosted Regimens. 9th Conference on Retroviruses and Opportunistic Infections. Seattle, WA, February 24-28, 2002
7. Szumiloski J, Wilson H, Jensen E, Campo R, Rice H, Zolopa A. Relationship between Phenotypic Susceptibility to Indinavir and Virologic Response to Indinavir-Ritonavir-Containing Regimens Following Failure of a Previous Protease Inhibitor. XI International HIV Drug Resistance Workshop. Seville, Spain, July 2 - 5, 2002
8. TMC125, A Next-Generation NNRTI, Demonstrates High Potency After 7 Days Therapy in Treatment-Experienced HIV-1-Infected Individuals with Phenotypic NNRTI Resistance. Gazzard B, Pozniak A, Arasteh K, Staszewski S, Rozenbaum W, Yeni P, et al. 9th Conference on Retroviruses and Opportunistic Infections. Seattle, Washington, 2002
9. ALazzarin, BClotet, DCooper, JReynes, KArasteh, MNelson, CKatlama, JChung, LFang, JDelehanty, M Salgo. Enfuvirtide (T-20) in combination with an optimized background (OB) regimen vs. OB alone in patients with prior experience or resistance to each of the three classes of approved antiretrovirals (ARVs) in Europe and Australia. XIV International AIDS Conference. Barcelona, Spain, July 7-12, 2002.
10. Lalezari J et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. N Engl J Med 2003 (May 29) (<http://www.nejm.org>)
11. KHenry, JLalezari, MOHearn, BTrottier, JMontaner, PPilero, SWalmsley, JChung, LFang, JDelehanty, Msalgo. Enfuvirtide (T-20) in combination with an optimized background (OB) regimen vs. OB alone in patients with prior experience or resistance to each of the three classes of approved antiretrovirals (ARVs) in North America and Brazil. XIV International AIDS Conference. Barcelona, Spain, July 7-12, 2002