
HIV Resistance Testing Consultation Service

Consultation Report

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Disclaimer:

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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

In January, the caller inherited care of a 39-year-old man who was diagnosed with HIV in 1991. The patient has had extensive antiretroviral exposure, including all nucleoside reverse transcriptase inhibitors (NRTI's), all non-nucleoside reverse transcriptase inhibitors (NNRTIs) except delavirdine, and all protease inhibitors (PIs) except ritonavir/lopinavir (Kaletra). Information regarding the timing and sequencing of therapy, and response to therapy is not available. The patient has a history of anemia attributed to AZT, and "won't ever take AZT again." His most recent regimen consisted of stavudine (d4T) plus lamivudine (3TC) plus ritonavir (RTV) and saquinavir {SC-SQV (Fortovase)}, begun in summer 2000. Over the last several months, he experienced ongoing weight loss down to 98 lbs, anorexia, and diarrhea, all attributed to antiretroviral agents (ARVs), though the patient reports a history of Crohn's disease. The patient underwent phenotyping on 12/19/00, the results of which were unavailable to the provider but reportedly demonstrated pan-resistance, including "maximal resistance" to lamivudine (3TC), nevirapine (NVP), and ritonavir (RTV). In January the patient had a CD4 of 56 and on-treatment viral load (VL) of 458K. Genotyping was obtained on 1/24/01. Therapy was discontinued on 1/31/01, with improvement in gastrointestinal symptoms and slight weight gain. The patient remains off therapy.

Concomitant medications include trimethoprim/sulfamethoxazole (TMP/SMX), azithromycin, multivitamins, and omeprazole.

The patient does not use drugs and his adherence is thought to be excellent. He is well informed and is interested in T-20.

Resistance Test Findings

GENOTYPE (3/28/00)

Key Mutations

NRT	M41L, T69DN, L74V, V118L, M184V, L210W, T215Y, K219R
NNRT	K101E, V108I/V, V179I, Y181C, G190A
PI	L10I, V32I, M36I, M46I, I47V, F63L, I64V, L63P, A71A/I/T/V, G73C, L90M, I93L

Interpretation/Implications for Treatment

This patient's extensive exposure to multiple antiretroviral agents is reflected in the large number of mutations detected in the reverse transcriptase and protease genes of the virus that was predominant at the time of genotyping. Based on the high viral load and low CD4 count seen with his most recent antiretroviral regimen, it is unlikely that this last regimen provided any important antiretroviral activity. The most significant implication of the presence of this number of mutations is that full viral suppression is highly unlikely to be achieved with any combination of antiretrovirals, and it may not be a reasonable goal of therapy. A more realistic goal of therapy would be to achieve partial suppression of viral replication. Theoretically, this partial suppression would be associated with a durable and clinically relevant CD4 benefit. This approach would use as many drugs as the patient could tolerate, with an understanding that suppression would likely be incomplete.

Considered broadly, the multiple mutations in reverse transcriptase gene suggest multi-NRTI resistance. Specifically, the presence of several "zidovudine (AZT)" or "thymidine analogue" mutations (i.e., M41L, L210W, T215Y, K219R) are thought to be associated with broad class resistance within the class. The mutation T69D/N, along with L74V and M184V indicates resistance to didanosine. The M184V mutation was probably selected for by lamivudine, and confers high-level resistance to this drug, and moderate resistance to abacavir. It may, however, potentiate the antiviral effect of zidovudine and perhaps the nucleotide tenofovir, or at least mitigate the effect of some resistance associated mutations. The presence of Y181C indicates high level resistance to delavirdine and nevirapine, and moderate to high level resistance to efavirenz. Higher level resistance to efavirenz is conferred by the G190A mutation, and the mutations at codons 108 and 179 confer additional resistance to all of the NNRTI's. It is unlikely that the addition of a NNRTI to the patient's next regimen would add any significant antiviral activity.

Similar to the NRTIs, the presence of multiple mutations within the protease genes suggest broad PI cross-resistance. The L90M mutation is particularly concerning and associated with resistance to each of the currently available antiretroviral agents. More specifically, the patient's resistance to saquinavir is caused by the L90M mutation, along with the accumulation of mutations at codons 10, 36, 63, 71, 73, and 93. The L90M mutation also confers resistance to nelfinavir. Though the primary ritonavir and indinavir-associated mutations at codons 82 and 84 are absent, resistance to these agents is expected from the accumulation of mutations at 10, 32, 46, 47, 63, 73, and 90. Likewise, the key mutations associated with amprenavir resistance at codons 50 and 84 were not detected. However, decreased susceptibility to amprenavir is conferred by the accumulation of mutations at codons 10, 32, 46, 47, and 90. Finally, the presence of mutations at 10, 46, 63, 71, and 90 suggests partial or possible resistance to lopinavir/ritonavir (Kaletra). Among the different PIs, amprenavir and ritonavir/lopinavir might offer the most potency against this highly resistant virus.

Thus, no combination of the currently approved antiretroviral agents is expected to have a potent antiviral effect. Access to investigational agents with alternate resistance profiles and/or different mechanisms of action should be explored. Specifically, the patient may benefit from the fusion inhibitor, T20, and possibly, the nucleotide RT inhibitor, tenofovir, though benefit from this agent is less likely given the number of RT mutations present.

A significant concern in this patient is how he came to harbor such a number of mutations. Though his adherence is thought to be good, vigorous exploration of any barriers to adherence, such as psychiatric illness, depression, and substance abuse should be undertaken. Similarly, given his history of Crohn's disease, malabsorption of antiretroviral agents may have contributed to suboptimal levels of antiretroviral agents and fostered the emergence of viral resistance. Any malabsorption should be thoroughly evaluated, and corrected if possible before starting a new regimen. A final concern is this patient's weight loss that appeared to improve with cessation of antiretroviral therapy. Decisions regarding therapy should include consideration of possible cumulative drug toxicity (i.e. mitochondrial toxicity from NRTIs).

Recommendations

The first decision before starting antiretroviral therapy should be to decide the goal of therapy based on the patient's willingness to adhere and the impact of such a regimen on his quality of life. Based on the number of mutations seen, no combinations of antiretroviral agents would be expected to produce complete viral suppression. A less aggressive approach would be to aim for a goal of partial suppression using with a regimen with a lower pill burden such as ritonavir/lopinavir (Kaletra) plus abacavir with or without the addition of 3TC.

Listed below are the most aggressive approaches for therapy as recommended by the Panel. It is highly likely that drug intolerance will be a primary limitation of the following treatment regimens.

Regimen Options

- OPTION 1: Ritonavir/lopinavir(Kaletra) 3 capsules bid + amprenavir 600 mg (4 capsules) bid+ lamivudine 150 mg (one tablet) bid + abacavir 300 mg (one tablet) bid along with as many additional NRTs as tolerated, (i.e. "mega-HAART")

PROS: Maximizes any remaining activity of currently approved PI's, minimizes nucleoside toxicity, maintains pool of highly resistant (and thus less virulent) virus.

CONS: Pill burden, GI intolerance (e.g. nausea, vomiting, diarrhea) with ritonavir/lopinavir and amprenavir, minimal likelihood of significant long term suppression

- OPTION 2: Ritonavir/lopinavir + amprenavir + lamivudine + abacavir + T-20

PROS: As above plus efficacy of novel agent with different mechanism of action, close follow-up provided by experimental protocol

CONS: As above plus the need for bid injections of T-20, toxicity of T-20 (primarily injection-site reactions), unknown efficacy of T-20 in this setting

- OPTION 3: Ritonavir/lopinavir + amprenavir + lamivudine + abacavir + T20 + tenofovir

PROS: As above + possible added efficacy of tenofovir, possible attenuation of tenofovir resistance by maintaining M184V mutation with lamivudine

CONS: As above + added nucleotide toxicity

Dosing, Monitoring, and Follow-up Recommendations

Lopinavir and ritonavir can be given as a fixed combination capsule known as Kaletra. Each Kaletra capsule contains 33 mg of ritonavir and 133 mg of lopinavir. The standard dosage is 3 capsules bid. The panel thought that amprenavir, when used with the above dose of ritonavir, should be dosed at 600 mg bid. Lamivudine and abacavir should be given at their standard doses of 150 mg and 300 mg bid, respectively. The dosing of T-20 and tenofovir would be determined by the relevant protocols.

After changing the antiretroviral regimen, it is advisable to monitor viral load and CD4 count at 1 month, 2 months, and 4-6 months. The patient should also be monitored closely for changes in blood lipids, blood glucose, and liver function tests (LFTs) as PI's (particularly lopinavir/ritonavir with regards to lipids) can adversely affect these values.

When beginning or restarting abacavir, the patients should be educated to monitor for symptoms suggestive of an abacavir hypersensitivity reaction. Rash, fever, respiratory symptoms, flu-like symptoms of malaise and fatigue, and gastrointestinal symptoms of nausea, vomiting, and abdominal pain should be aggressively evaluated per the package insert. If abacavir hypersensitivity reaction is suspected, rechallenge should be avoided since fatalities can occur.