

Perspective

HIV Drug Resistance: Implications for Management

Selection of antiretroviral treatment based on drug resistance profile is a crucial element in maintaining optimal response to therapy in individual patients. Interpretation of results from resistance testing continues to increase in complexity with increasing numbers of resistance mutations and resistance mutational interactions identified, increasing numbers of drugs used, and increasing prevalence of resistance in patients with recent infection and those taking antiretroviral therapy. At the International AIDS Society–USA course in San Francisco in June 2002, Scott M. Hammer, MD, presented cases to illustrate issues related to HIV resistance that are encountered in clinical practice, and he discussed management responses for these situations.

Underlying Concepts in HIV Resistance

Genetic variants of HIV are continuously produced in the absence of drug pressure as a result of high viral turnover and the inherent error rate of the HIV-1 reverse transcriptase enzyme. Mutations at each codon site are produced daily, and the viability of resultant mutant virus depends on replication competence and the presence of selective pressure exerted by antiretroviral drugs or the immune system. In the absence of drug pressure, double mutations in the same viral genome can occur, although simultaneous occurrence of 3 or more mutations in the same genome is a rare event. Further, numerous natural polymorphisms exist. Thus, mutations that confer resistance to antiretroviral drugs can be present before a patient begins drug treatment and can evolve rapidly with drug use. High-level resistance emerges with a single mutation in the presence of certain drugs, and use of

these drugs confers the greatest risk for emergence of resistance if they are not used in maximally suppressive regimens. These include lamivudine (eg, M184V mutation) and nonnucleoside reverse transcriptase inhibitors (NNRTIs), including efavirenz (eg, K103N mutation) and nevirapine (eg, Y181C mutation). Resistance to agents that require multiple mutations evolves more slowly. Use of partially suppressive antiretroviral regimens inevitably leads to development of resistance. Thus, a goal of treatment is to set a high genetic barrier to resistance through the use of potent combination regimens.

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particular importance

The number of identified antiretroviral drug resistance mutations (including those identified for investigational agents) increased from 42 in 1994 to 144 in 1997 and 236 in 2000. Please see page 21 for the current list of resistance mutations as maintained by the International AIDS Society–USA Drug Resistance Mutations Group, showing mutations in the reverse transcriptase and protease genes associated with antiretroviral resistance. Of particular importance among the identified mutations are those that confer cross-resistance to other drugs in the same class. Thus, among nucleoside reverse transcriptase inhibitors (nRTIs), the codon 151-associated complex of mutations and the codon 69 insertion complex confer cross-resistance. In addition, the classic zidovudine-associated resistance mutations at codons 41, 67, 70, 210, 215, and

219, which are now called NAMs (nRTI-associated mutations), confer cross-resistance to nRTIs except lamivudine. Among NNRTIs, there is considerable clustering of resistance mutations in 2 sections of reverse transcriptase, and mutations at codons 103 and 188 confer class cross-resistance. Protease inhibitor (PI) resistance mutations are classified as major and minor. Major mutations are those that tend to be selected first by the drug and cause a decrease in phenotypic susceptibility by themselves (usually occurring in the enzyme active site). Minor mutations are those that tend to appear subsequently and to cause changes in phenotypic sensitivity in the presence of major mutations rather than by themselves. Frequently, these mutations are compensatory, permitting the virus to replicate more efficiently in the presence of major resistance mutations. Mutations at codons 46, 82, 84, and 90 confer cross-PI resistance. It is a striking finding regarding PI resistance mutations that approximately one quarter to one third of the amino acids in protease can be altered with the enzyme remaining functional.

The following clinical cases illustrate some of the complexities in the emergence of HIV resistance and resistance testing.

Case 1: Acute HIV Infection

Case Presentation and Decision Point 1

A 20-year-old woman presents with complaints of fever, malaise, headache, mild neck stiffness, sore throat, lymphadenopathy, and rash 2 weeks after returning from a vacation during which she had unprotected sex with a new male partner. Differential diagnosis is broad and may include nonspecific viral syndrome, mononucleosis associated with cytomegalovirus (CMV) and Epstein-Barr virus, acute toxoplasmosis, and acute HIV infection. Physical examination shows temperature of 101°F, maculopapular rash on the torso, oral ulcers, mild neck stiffness, and cervical

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lymphadenopathy. The initial laboratory evaluation shows hemoglobin of 13.5 g/dL; somewhat low white blood cell (WBC) count at $3.1 \times 10^3/\mu\text{L}$ with 56% polymorphonuclear cells, 35% lymphocytes, and 9% atypical lymphocytes; and minimally elevated aspartate aminotransferase of 47 U/L and alanine aminotransferase of 50 U/L. Cerebrospinal fluid (CSF) tap shows WBC of $30/\mu\text{L}$ with 99% lymphocytes, mildly elevated protein at 50 mg/dL, and normal glucose level. Should subsequent laboratory evaluation consist of Monospot, CMV IgG and IgM, *Toxoplasma* IgG and IgM, hepatitis serologies, HIV antibody, plasma HIV-1 RNA level, CSF HIV-1 RNA level, or all of these?

Discussion

It is reasonable to consider performing all of these laboratory assessments, except for the CSF HIV-1 RNA assay, since diagnostic efforts should be focused on the practical and standard assays to start. Although suspicion may be high for acute HIV infection, the mononucleosis-like symptoms call for wider evaluation, and hepatitis serology is indicated even if HIV infection is suspected because simultaneous coinfection may have occurred. Both the HIV antibody test and plasma HIV-1 RNA assay should be performed, since the antibody test may be negative if the patient has acute infection.

Decision Point 2

Laboratory results indicate negative Monospot and serologies for CMV, toxoplasmosis, and hepatitis A, B, and C virus infections. The HIV antibody test is negative, but plasma HIV-1 RNA assay indicates a viral load of 15,000,000 copies/mL. The patient has a CD4+ cell count of $450/\mu\text{L}$. Should treatment be started—for example, with a regimen including 2 nRTIs in combination with efavirenz, abacavir, or lopinavir/ritonavir—or should the patient be referred to a clinical trial? Should a resistance test be performed, and should treatment be delayed until results of the resistance test are available?

Discussion

Reasonable options to consider to begin therapy include any of the regimens list-

ed or, preferably, referral to a clinical trial. Deferring therapy in the case of acute infection is not recommended, since there is the potential for the intervention to maintain or restore HIV-specific immunity during primary infection. Although therapy or enrollment in a clinical trial should not be deferred until results of resistance testing are available, resistance testing should be performed. As shown in Table 1, a 9-city study of prevalence of antiretroviral drug resistance in 377 cases of recent HIV infection demonstrated a significant increase in prevalence of resistance to any drug in all drug classes and to multiple classes, with 12.4% of cases from 1999 to 2000 having resistance to 1 or more drugs and 6.2% having resistance to 2 or more drug classes (Little et al, *N Engl J Med*, 2002).

Decision Point 3

The patient refused enrollment in a clinical trial and started a regimen of lopinavir/ritonavir/zidovudine/lamivudine, for which she reported 100% adherence. Her plasma HIV-1 RNA level was 15,000 copies/mL after 2 weeks and 1500 copies/mL after 4 weeks. Results of the genotypic test became available at this point and showed the presence of a single T215D zidovudine resistance mutation. Should the regimen be changed by substituting stavudine for zidovudine or stavudine/didanosine for

lamivudine/zidovudine, or by adding abacavir or tenofovir; or should the current regimen be continued?

Discussion

The best course in this instance is likely to continue the patient on the current regimen. The T215D mutation is not associated with high-level zidovudine resistance and has not been associated with treatment failure unless further mutational evolution occurs. This mutant appears to be a revertant from previously harbored virus with a T215F/Y mutation. The finding suggests that virus in this patient has reverted to the T215D mutant after infection with the T215F/Y form or that the revertant had emerged in the individual from whom she acquired HIV infection.

Decision Point 4

The patient's plasma HIV-1 RNA level increases to 5000 copies/mL at 8 weeks and to 10,000 copies/mL at 12 weeks. Genotypic analysis from week 4 shows K70R, T215Y, and M184V resistance mutations. Based on this information, should the same regimen be continued, should treatment be changed by substituting stavudine for zidovudine or by switching treatment to lopinavir/ritonavir/efavirenz/abacavir/tenofovir, or should the patient undergo a structured treatment interruption?

Table 1. Change in Prevalance of Drug Resistance at Baseline in Clinical Isolates in a 9-City Study

High-Level* Drug Resistance By Phenotypic Assay	Patients With Drug-Resistant Virus		
	1995-1998	1999-2000	P Value
Any 1 or more antiretroviral drug	3.4%	12.4%	.002
Nucleoside reverse transcriptase inhibitor	2.3%	6.2%	.07
Nonnucleoside reverse transcriptase inhibitor	1.9%	7.1%	.03
Protease inhibitor	0.4%	8.0%	<.001
≥ 2 drug classes (multidrug resistance)	1.1%	6.2%	.01

*High-level resistance was defined as >10-fold decrease in susceptibility. Adapted with permission from Little et al, *N Engl J Med*, 2002.

Discussion

The K70R and T215Y mutations are classic zidovudine-associated resistance mutations, and the M184V mutation is a classic lamivudine-associated resistance mutation. No PI resistance mutations were detected at this visit. The current regimen should be changed to a regimen that will result in optimal viral suppression, and the likelihood of cross-resistance for zidovudine and stavudine argues against substitution of the latter for the former. The addition of efavirenz, abacavir, and tenofovir to lopinavir/ritonavir is reasonable, since (1) there are no NNRTI resistance mutations; (2) abacavir can still be effective in the presence of the M184V mutation and relatively few zidovudine-associated mutations; and (3) tenofovir can be expected to remain active in the context of the observed mutations.

Outcome

The patient was switched to the lopinavir/ritonavir/efavirenz/abacavir/tenofovir regimen. Plasma HIV-1 RNA level was below the assay detection limit (<50 copies/mL) at weeks 16, 20, and 24.

Case 2: Asymptomatic Established Infection

Case Presentation and Decision Point 1

A 35-year-old man with HIV infection has been observed for 8 years and has had a slowly declining CD4+ cell count. At the current visit, the CD4+ cell count is 275/μL, plasma HIV-1 RNA level is 50,000 copies/mL, and the patient wishes to begin treatment. Should treatment be started with a PI-based regimen such as indinavir/ritonavir, lopinavir/ritonavir, or nelfinavir plus 2 nRTIs; an NNRTI-based regimen such as efavirenz plus 2 nRTIs; or a triple nRTI regimen such as abacavir/zidovudine/lamivudine?

Discussion

The NNRTI-based and triple-nRTI regimens are reasonable choices for beginning treatment. At this level of CD4+ cell count and plasma HIV-1 RNA, these reg-

imens should be successful, assuming good drug adherence. In Dr Hammer's opinion, this permits patients and clinicians to defer use of a PI-based regimen and avoid the potential metabolic toxicities.

Decision Point 2

Treatment is initiated with an efavirenz-based regimen. There are a number of possible nRTI "backbone" options for this patient; zidovudine/lamivudine is chosen. The patient reports full adherence to the new regimen. At 12 weeks, the patient's plasma HIV-1 RNA level is less than 50 copies/mL and CD4+ cell count has increased to 350/μL. However, at 24 weeks, plasma HIV-1 RNA is 500

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copies/mL and a repeat test indicates a level of 1000 copies/mL. A sample is sent for genotypic analysis. Are the results most likely to show wild-type virus, the lamivudine-associated M184V mutation, the K103N efavirenz-associated mutation, both M184V and K103N, or zidovudine-associated mutations (eg, M41L, K70R, T215Y)?

Discussion

Breakthrough resistance in this situation is most likely to be caused by mutations to drugs to which high-level resistance occurs with a single-step mutation—in other words, those with a low genetic barrier to resistance. Thus, in this case, resistance is likely due to the efavirenz-associated mutation or the

lamivudine-associated mutation. One or both mutations are observed in patients receiving both drugs, with no apparent preferred order of appearance and with both mutations sometimes emerging nearly simultaneously.

Decision Point 3

Genotypic assay results indicate the presence of the efavirenz-associated K103N mutation. Given that the patient's plasma HIV-1 RNA level is 1000 copies/mL, which of the following constitute reasonable approaches to management: continuing the same regimen, efavirenz/lamivudine/zidovudine, until plasma HIV-1 RNA level rises above 10,000 copies/mL; substituting nevirapine, abacavir, or lopinavir for efavirenz; switching the entire regimen to lopinavir/ritonavir/stavudine/didanosine; substituting lopinavir/ritonavir for efavirenz and substituting abacavir for zidovudine; or adding tenofovir?

Discussion

Changing the regimen by substituting lopinavir/ritonavir or abacavir for efavirenz makes the most sense in this case. Substitution of nevirapine is not an option given the NNRTI class cross-resistance conferred by the K103N mutation. Substitution of nRTIs may be considered unnecessary since no NAMS were detected. However, it is possible that minority populations of nRTI-resistant mutants (eg, M184V mutants) were not detected by the genotypic test; thus the switch from efavirenz to abacavir, resulting in an nRTI-only regimen, may be riskier than the switch to lopinavir/ritonavir. Although waiting to make a change in regimen until a plasma HIV-1 RNA level of 10,000 copies/mL may be reasonable in some settings, it is predictable in this case that additional resistance mutations will appear with inadequate suppression, and it is highly likely that the M184V resistance mutation will emerge. The accumulating data concerning the efficacy of tenofovir in treatment-experienced and treatment-naive patients makes use of this drug in this situation an alternative option. There is, however, a dearth of published experience with use of tenofovir in the specific situation described here.

Outcome

The patient's regimen was changed by substituting lopinavir/ritonavir for efavirenz. Plasma HIV-1 RNA level decreased to less than 50 copies/mL and remained at this level.

Case 3: The Treatment-Experienced Patient

Case Presentation and Decision Point 1

A 45-year-old man makes his first visit to the office. He has a 15-year history of HIV infection and prior exposure to stavudine, didanosine, zidovudine, lamivudine, nevirapine, nelfinavir, and indinavir. His regimen for the past year has been indinavir/ritonavir/stavudine/abacavir. His CD4+ cell count is 300/ μ L (nadir count of 100/ μ L) and plasma HIV-1 RNA level is 12,000 copies/mL. Phenotypic assay results show the following changes in susceptibility: 70-fold to zidovudine, greater than 100-fold to lamivudine, 5-fold to didanosine and stavudine, 10-fold to abacavir, 5-fold to efavirenz, 10-fold to lopinavir, 12-fold to amprenavir, and 6-fold to tenofovir. Is this patient best managed by continuing the current regimen, recommending a structured treatment interruption, instituting a mega-combination regimen of zidovudine/lamivudine/didanosine/abacavir/efavirenz/nevirapine/lopinavir/ritonavir/amprenavir/hydroxyurea, instituting a regimen of abacavir/tenofovir/efavirenz/lopinavir/ritonavir/amprenavir, or seeking out a clinical trial or expanded access program for new agents?

Discussion

The patient's susceptibility profile shows multiple drug resistance with high-level zidovudine and NNRTI resistance. In a patient with moderately depressed CD4+ cell count and moderately elevated viral load, maintaining the current regimen and seeking out investigational options are reasonable choices. Use of the abacavir/tenofovir/efavirenz/lopinavir/ritonavir/amprenavir regimen is also a reasonable option. If the latter regimen is chosen, one would be most reliant on the ritonavir-enhanced dual-PI component and

potentially the efavirenz, if higher-level NNRTI resistance is not harbored in a reservoir. The abacavir and tenofovir may provide minimal to no activity, given the fold-changes in resistance, but subpopulations that may retain susceptibility to one or both of these agents may not be detected with the standard method of resistance testing. Further, even minimal additional antiretroviral activity may help protect the "core" of the new regimen. The mega-combination option is a viable one, but issues of tolerance and adherence are substantial with this approach.

This case represents a common scenario in clinical practice. There is a high prevalence of drug resistance in patients receiving potent antiretroviral therapy. The HIV Cost and Services Utilization Study (Richman et al, 41st ICAAC, 2001) found that 63% (132,442) of HIV-1-infected Americans who had survived the first 2 years of the potent antiretroviral therapy era had plasma HIV-1 RNA levels greater than 500 copies/mL and that 78% had resistance to at least 1 drug and 51% had resistance to multiple drug classes. Robust treatment options are lacking for many of these patients. The option of watching and waiting for new treatment options is supported by data indicating a prolonged time to return of CD4+ cell count to baseline levels after virologic failure on potent antiretroviral therapy. A study by Deeks and colleagues (AIDS, 2002) indicated that the time to such immunologic failure after virologic failure was 36.4 months. This delay of immunologic failure appears to be associated with reduced replicative fitness or capacity of HIV with PI-associated resistance mutations, resulting in reduced cytopathic effect on CD4+ cells.

Decision Point 2

How might management differ, given the same options as above, if the patient discussed in case 3 had a CD4+ cell count of 100/ μ L instead of 300/ μ L and plasma HIV-1 RNA level of 100,000 copies/mL instead of 12,000 copies/mL at the current presentation?

Discussion

Use of the abacavir/tenofovir/efavirenz/lopinavir/ritonavir/amprenavir regimen is a reasonable option in this scenario. A

change of 8-fold or greater in susceptibility to abacavir indicates that the drug will have little effectiveness. Similarly, the 6-fold change in susceptibility to tenofovir suggests that this drug will have little effectiveness, since a greater than 4-fold change is associated with loss of the likelihood of any response. On the other hand, changes in susceptibility to efavirenz such as the 5-fold

In multi-regimen failure, the option of watching and waiting for new treatments is supported by data indicating a prolonged delay of immunologic failure after virologic failure

decrease seen in this case are common among wild-type isolates, representing naturally occurring polymorphisms, and might not of themselves indicate loss of effectiveness of the drug. The combination of lopinavir/ritonavir and amprenavir may be expected to further boost the effects of the PIs in this case. Thus, use of this regimen is essentially based on the hope that a dual enhanced PI/efavirenz-based regimen will be effective in the patient and the possibility that abacavir and tenofovir will add some additional activity.

At this point, structured treatment interruptions should not be attempted outside the setting of a clinical trial. As shown in studies by Deeks and colleagues (*N Engl J Med*, 2001), interruption of treatment in patients harboring virus resistant to multiple drugs generally results in reversion of virus to wild-type susceptibilities at periods ranging from 2 to 12 weeks after stopping treatment. However, this switch in phenotypic susceptibility is accompanied by inflections in the slopes of plasma HIV-1

RNA level increases (eg, rapid increases of 0.8-1 log₁₀ HIV-1 RNA copies/mL) and CD4+ cell decreases (eg, rapid decreases of 100/μL). These decreases may place patients at risk for opportunistic diseases. Any potential application of this approach to resensitize virus awaits additional examination in clinical studies.

Additional Considerations in Management

Common questions and issues in the management of HIV drug resistance are summarized below.

In evaluating a patient with virologic failure on the first regimen, which tests from among genotype, phenotype, and virtual phenotype should be ordered?

Many practitioners would order a genotypic test, since such testing allows detection of mutations that may be emerging prior to any marked change in phenotypic susceptibility. The virtual phenotype test is essentially a genotypic test with an interpretation system that is linked to a large relational database of genotypes and phenotypes.

Of the currently available types of tests, which should be ordered in the case of a patient with a history of numerous regimen failures?

Given the likelihood of numerous resistance mutations to multiple drugs in such a patient, and the likelihood of complex resistance interactions, phenotyping to determine which drugs might still be active may be of greater assistance in making decisions about managing treatment than genotyping.

Is stavudine active against zidovudine-resistant virus?

Zidovudine resistance mutations confer cross-resistance to stavudine, even though phenotyping may not demonstrate this resistance unless a low cutoff is set.

Does hypersusceptibility to NNRTIs improve response to efavirenz?

Hypersusceptibility to NNRTIs in the presence of multiple nRTI mutations has

been observed in a number of studies. Patients with virus that is hypersusceptible to efavirenz exhibit a better virologic response to treatment with the drug.

Which mutations are associated with tenofovir resistance?

Tenofovir resistance has been shown to be mediated by the K65R and T69S insertion mutations, and multiple nRTI mutations, especially M41L and L210W (Miller et al, 9th CROI, 2002) and T215Y/F. As noted above, a change in susceptibility of more than 4-fold is associated with a probable loss of any response to the drug.

In addition to the observation that NAMs confer considerable cross-class resistance in HIV, there have been a number of other recent findings regarding nRTI resistance. One is that the mechanism of zidovudine resistance has been demonstrated to be that of pyrophosphorolysis (Arion et al, *Biochemistry*, 1998; Arion et al, *J Biol Chem*, 2000). Another is that stavudine and stavudine/didanosine select for zidovudine resistance mutations and the Q151M complex (Coakley et al, *AIDS*, 2000); thus, care is required in interpreting resistance testing results for stavudine and didanosine.

In which clinical scenarios should resistance testing routinely be performed?

Resistance testing is clearly warranted in the following settings: primary (acute) infection, simultaneously with initiation of treatment; first-regimen failure; multiple-regimen failure; and pregnancy. With regard to primary infection, treatment should not be delayed until resistance results are known. In cases of established infection (up to 2 years) in drug-naïve patients, baseline resistance testing is reasonable to perform, given the prevalence of drug resistance in patients with recent infection (Little et al, *N Engl J Med*, 2002). In cases of longer established (>2 years) HIV infection, whether resistance testing is performed as part of baseline evaluation in antiretroviral-naïve patients depends on prevalence of drug resistance in the patient's locale and on clinician index of suspicion of likelihood of drug resistance.

Presented in June 2002. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Hammer in September 2002.

Financial Disclosure: Dr Hammer has served as site investigator for or consultant to Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, Roche-Trimeris, Shionogi, Shire BioChem, Tibotec-Virco, and Triangle.

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