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IMPROVING THE MANAGEMENT OF HIV DISEASE

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IN THIS ISSUE

Reprints:

Antiretroviral Drug Resistance
Testing in Adults With HIV Infection:
Implications for Clinical Management

And

ABOUT THIS ISSUE...

This issue of Improving the Management of HIV Disease contains reprints of updated recommendations for antiretroviral therapy and recommendations for the use of HIV drug resistance testing in HIV disease. Both of these papers, developed by panels convened by the International AIDS Society–USA, were recently published in the Journal of the American Medical Association (JAMA).

The International AIDS Society–USA Panel on Antiretroviral Therapy published its first report in JAMA in 1996, and has since continued to meet regularly to evaluate new results of clinical trials and basic science investigations in order to keep its recommendations for the clinical use of antiretroviral drugs current. The recommendations for the use of HIV drug resistance testing in HIV disease is the first report by the International AIDS Society–USA Panel to discuss this relatively new aspect of clinical management. The report reviews biology of HIV drug resistance and outlines potential applications of resistance testing for individual patient management.

Both articles can be accessed from the Internet on the JAMA HIV page (http://www.ama-assn.org). A future issue of Improving the Management of HIV Disease will feature responses to questions posed to both International AIDS Society–USA panels in an effort to address specific clinical concerns.

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Antiretroviral Drug Resistance Testing in Adults With HIV Infection

Implications for Clinical Management

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Objectives.—To review current knowledge of the biology and clinical implications of human immunodeficiency virus (HIV) resistance to antiretroviral drugs, describe assays for measuring resistance, and assess their use in clinical practice.

Participants.—The International AIDS Society—USA assembled a panel of 13 physicians with expertise in basic science, clinical research, and patient care relevant to HIV resistance to antiretroviral drugs.

Evidence.—We reviewed available data from published reports and presented at national and international research conferences. Basic science research, clinical trial results, and expert opinions were used to form the basis of this report. Data on methods for and characteristics of specific genotypic and phenotypic assays were obtained from manufacturers and service providers.

Consensus Process.—The panel met regularly between October 1997 and April 1998. Panel subgroups developed and discussed different sections of the report before discussing them with the entire panel. Conclusions and suggested approaches to the use of resistance testing were determined by group consensus.

Conclusions.—Plasma HIV RNA level and CD4+ cell count are the primary values that should be used to guide the initiation of antiretroviral therapy and subsequent changes in therapy. Possible causes of treatment failure other than development of drug resistance that should be considered are adherence, drug potency, and pharmacokinetic issues. Genotypic and phenotypic testing for HIV resistance to antiretroviral drugs may prove useful for individual patient management. Assays under development need validation, standardization, and a clearer definition of their clinical roles. Possible current roles of resistance testing for choosing an initial regimen or changing antiretroviral therapy, as well as possible implications of the presence or absence of phenotypic resistance and genotypic changes, are discussed.

DEVELOPMENT of viral resistance to antiretroviral drugs used for treatment of human immunodeficiency virus (HIV) infection is an important cause of treatment failure4 and limits options for alternative antiretroviral regimens. Prevention, characterization, and clinical management of such resistance is receiving increasing attention. The International AIDS Society—USA assembled a panel to review for clinicians the biologic principles underlying HIV drug resistance, phenotypic and genotypic resistance assays either available or under development, and approaches using viral resistance testing for patient care. The panel consists of persons with expertise in HIV antiretroviral drug resistance and in care of patients with HIV infection. Panel members reviewed relevant clinical and basic science data and evaluated expert opinion. Recommendations were developed by consensus.

BACKGROUND

The virus population in a person infected with an RNA virus (eg, HIV-1, hepatitis C virus) has been termed a quasi species,6 which refers to the existence of genetically distinct viral variants that evolve from the initial virus inoculum. The variants are generated because DNA proofreading mechanisms that preserve the genetic composition of organisms with double-stranded DNA genomes do not exist for RNA viruses.
Thus, as single-stranded RNA viruses replicate, each newly copied genome differs from the parental virus on average by a single nucleotide.13-18

Viral polymorphisms (genetic variants with apparently equivalent fitness [replication capacity]) are commonly seen in virus populations in infected persons. Nucleotide differences may be "neutral" (no impact on fitness), be deleterious (variants replicating less well or not at all), or confer replicative advantage if selective pressures such as immune responses or drug treatments change. These possibilities illustrate the survival strategy of organisms with high mutation rates that provides a large pool of genetic variants able to adapt rapidly to changing selective pressures.13-18

An estimated 10 billion (109) HIV-1 virions are produced daily in established HIV infection.19 If each contains on average 1 mutation per 2500 nucleotide genome, replication-competent virus with every possible single drug–resistance mutation is likely to be generated daily. Double mutants are less likely, and the probability of 3 or more drug-resistance mutations in the same genome is very low.19

These estimates are supported by observations in infected persons. Virus or HIV-1 RNA with single drug–resistance mutations have been isolated from treatment-naïve patients or those infected before antiretroviral drug availability.13-18 Mathematical modeling of rate of resistance emergence after nevirapine treatment in previously untreated persons permitted estimates of plasma prevalence of HIV-1 variants with nevirapine-resistance mutations before treatment. About 1 in 1000 copies/mL of plasma HIV-1 RNA contains the tyrosine-to-cysteine mutation at amino acid residue 181 (le, the Y181C mutation) of the reverse transcriptase conferring nevirapine resistance.20

When antiviral drug selective pressures are applied to viral quasi species in an infected person, preexisting minor viral species resistant to that drug rapidly become predominant and are selected as the most fit species in the presence of drug. For some antiretroviral drugs such as lamivudine and certain non-nucleoside reverse transcriptase inhibitors (NNRTIs; eg, nevirapine), a single mutation can confer high-level resistance. When these drugs are given in combination only partially suppressing virus replication, drug-resistant mutants predominate within weeks.21,22

For some other drugs, such as didovudine and certain protease inhibitors, high-level resistance requires accumulation of 3 or more resistance mutations in a single viral genome.23-25 These highly resistant variants emerge more slowly, requiring months to predominate during less than maximum viral suppression,26,27 supporting the prediction that genetic variants with multiple mutations are present at much lower levels than those with single mutations in untreated patients. Development of high-level resistance to these drugs requires persistent viral replication and selective drug pressure. Persistent viral replication permits further viral evolution leading to high-level drug resistance by cumulative mutation acquisition.

What is known about development of resistance with potent combination therapy? First, the higher the trough plasma concentrations of a protease inhibitor (eg, ritonavir), the more slowly resistance mutations emerge.26 Second, the lower the naldix of plasma HIV-1 RNA levels, the longer it takes for drug failure to occur.28 In patients with suppressions of plasma HIV-1 RNA to below 50 copies/mL for 1 year, no resistance mutations or other evidence of virus evolution were discerned, even though HIV-1 RNA and DNA and replication-competent virus persisted.29-31 Conversely, patients with detectable HIV-1 RNA levels had ongoing virus replication and evidence of evolution.

Several practical inferences can be derived from these principles (Table 1). First, drugs for which only a single mutation is required for high-level resistance, eg, lamivudine and nevirapine, should be reserved for use with other drugs in regimen designed to maximally suppress virus replication. Use in less suppressive regimens will select for high-level resistance more quickly.28 Second, combination regimens should be designed to confer potency needed to suppress maximally preexisting genetic variants and prevent replication. Regimens must establish a "genetic barrier" by suppressing minor populations with 1 or 2 mutations that could emerge with individual regimen components, permitting cumulative mutation acquisition. This requirement is more formidable in previously treatment patients because prior treatment may have established a genetic archive of drug-resistant virus in peripheral blood mononuclear cells (PBMCs) and other tissue reservoirs.4

### Table 1—Practical Implications of the Biology of HIV-1 Drug Resistance

<table>
<thead>
<tr>
<th>Practical Implications</th>
<th>Implications for Drug Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic variants of HIV with any single and probably many double mutations (albeit less likely) present in all patients before treatment is started.30</td>
<td>Partially suppressive regimens containing lamivudine and ritonavir rapidly fail because of breakthrough replication of preexisting resistant variants.</td>
</tr>
<tr>
<td>Genetic variants with 3 or more resistance mutations probably exist rarely, if at all, in untreated patients. Thus, potent combination regimens are required to suppress resistance mutations for viral escape to be achieved.31</td>
<td>Preventing cumulative acquisition of resistance mutations requires potent combination regimens that suppress virus replication to below levels of detection of the most sensitive assays available (about 50 copies/mL).</td>
</tr>
<tr>
<td>Complex mixture of genetic variants exist in all patients. Assays for drug resistance, both genotypic and phenotypic, may provide information only on the predominant deselecting variants and many minor variants.</td>
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<td>Prior treatment may select for resistant mutants that persist in lymphoid tissues but are not longer present in blood detectable in the absence of drug pressure. Resistance to the same drug may be not effective because of rapid selection of these mutants.</td>
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</table>

*HIV indicates human immunodeficiency virus; NNRTI, non-nucleoside reverse transcriptase inhibitor.*

There is good concordance between mutations seen in laboratory selection experiments and those in clinical isolates from patients with failing treatment. However, mutations in vitro are not found in patients in whom that particular drug has failed, eg, the stavudine-selected V757M mutation and delavirdine-selected P236L mutation32 observed resistance during in vitro virus passage experiments, but were rarely identified in patients in whom the drugs failed.33,34

Some mutations selected by antiretroviral drugs directly affect viral enzymes and cause resistance via decreased drug binding; whereas others have indirect effects.35,40 It is useful to categorize resistance mutations as primary or secondary (Figure 1). Primary mutations are genetically selected early in the process of resistance mutation accumulation, are relatively inhibitor specific, and may have a discernible effect on virus drug susceptibility. Secondary mutations accumulate in virus genomes already containing 1 or more primary mutations. Many secondary mutations alone have little or no discernible effect on resistance magnitude but may be selected because they improve viral fitness rather than decrease drug binding to target enzymes.

The distinction between primary and secondary mutations depicted in Figure 1, A, may help explain protease inhibitor cross-resistance. There seems to be little overlap in primary mutations selected by different protease inhibitors (eg, saquinavir-selected L80I M and G48V; ritonavir-selected D80N; and amprenavir-selected I50V). By themselves, these primary mu-
A. Mutations in the Protease Gene Selected by Protease Inhibitors

<table>
<thead>
<tr>
<th>Indinavir</th>
<th>L</th>
<th>K</th>
<th>L</th>
<th>V</th>
<th>M</th>
<th>I</th>
<th>L</th>
<th>AG</th>
<th>V</th>
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<th>L</th>
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<tbody>
<tr>
<td>Ritonavir</td>
<td>F</td>
<td>I</td>
<td>G</td>
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<td>Nelfinavir</td>
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<td>Amprenavir</td>
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</table>

B. Mutations in the Reverse Transcriptase (RT) Gene Selected by RT Inhibitors

<table>
<thead>
<tr>
<th>Nucleoside RT Inhibitors</th>
<th>Zidovudine</th>
<th>Didanosine</th>
<th>Zalcitabine</th>
<th>Lamivudine</th>
<th>Stavudine</th>
<th>Abacavir</th>
<th>Multinucleoside Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>D</td>
<td>K</td>
<td>L</td>
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<td>A</td>
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Figure 1.—The most common human immunodeficiency virus 1 mutations selected by protease inhibitors (A) and nucleoside and nonnucleoside reverse transcriptase inhibitors (B). For each amino acid residue listed, the letter above the listing indicates the amino acid associated with the wild-type virus. The italicized letter below the residue indicates the substitution that confers drug resistance. The drug-selected mutations are categorized as “primary” (black bars) or “secondary” (white bars). (The black-and-white bar indicates a mutation selected in vitro, but rarely seen in specimens from patients in whom therapy fails.) Primary mutations generally decrease inhibitor binding and are the first mutations selected. For indinavir, the mutations listed as primary may not be the first mutations selected, but they are selected in most patients’ isolates in combination with other mutations. For zidovudine, all mutations are listed as secondary because of inadequate clinical data to determine a common initial mutation. For nevirapine and delavirdine, each mutation can occur after an initial or subsequent mutation and affect inhibitor binding. The asterisk indicates that the mutation has been reported in vitro, but relevance for clinical drug failure is uncertain. Amino acid abbreviations are as follows: A, alanine; C, cysteine; D, aspartate; E, glutamate; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine. Multinucleoside resistance viruses have phenotypic resistance to most nucleoside reverse transcriptase inhibitors. Current listings are also available at http://www.aidsinfo.nih.gov or at http://www.viral-resistance.com.

Mutations may not cause cross-resistance to other protease inhibitors. However, there is an overlapping spectrum of secondary mutations in the protease gene selected by all protease inhibitors (Figure 1, A). Many of the secondary changes are compensatory, improving fitness of virus containing primary mutations without actually increasing inhibitor resistance. The mutations may improve enzymatic function by altering protease catalytic activity or by affecting protease substrates (eg, making sites in gag or other viral protein more easily cleavable).

The NNRTIs can select for a single primary mutation (eg, lamivudine), any one of a few primary mutations (eg, didanosine and zalcitabine), or an accumulation of primary and secondary mutations (eg, zidovudine) (Figure 1, B). Secondary mutations that compensate for replication impairment caused by primary resistance mutations are also selected by reverse transcriptase inhibitors. Cross-resistance among NNRTIs can be mediated by inhibitor-specific mutations and less specific secondary mutations, especially among drugs that bind to similar or adjacent viral target residues (evident for didanosine and zalcitabine, which select for similar mutations [Figure 1, B]). Similarly, the primary mutation commonly selected by lamivudine confers high-level phenotypic resistance to this drug as well as low-level phenotypic resistance to didanosine, zalcitabine, and abacavir in vitro. The clinical significance of cross-resistance among these drugs has not been determined.

Mutations selected by drug combinations may differ from those expected based on monotherapy experience. A unique mutation pattern in the reverse transcriptase gene that confers broad cross-resistance to all NNRTIs includes the Q151M mutation associated with 3 or 4 additional mutations (Figure 1, B), occasionally seen in patients with long-term exposure to NNRTIs and first described in association with exposure to zidovudine-didanosine combination therapy or weekly alternating zidovudine-zalcitabine monotherapy supplemented briefly with didanosine.

The NNRTIs (nevirapine, delavirdine, and efavirenz) select for mutations in 2 different reverse transcriptase regions (codons 98 to 108 and 179 to 190). None of the mutations overlaps with mutations conferring resistance to NNRTIs (Figure 1, B). However, some of the mutations cause broad cross-resistance among all members of the NNRTI drug class (eg, K103N).

Interactive Effects of Mutations on Drug Susceptibility

Some mutations selected by one drug suppress phenotypic effects of another mutation, eg, suppression of zidovudine resistance by didanosine-selected L74V, NRTI-selected Y181C, and lamivudine-selected M184V. Molecular mechanisms for these interactions are not well understood.

Lamivudine primarily selects for reverse transcriptase codon 184 mutations whether it is given as monotherapy or in combination. Suppression of the zidovudine resistance phenotype or delay in its emergence due to M184V is common during zidovudine-lamivudine combination therapy. Nevertheless, additional reverse transcriptase mutations emerge with combination zidovudine-lamivudine therapy and eventually overcome the suppressive effect, resulting in high-
level resistance to both drugs. The M184V mutation effect is thus likely to be transient and its induction less useful than maximizing HIV suppression. Presence of this mutation should prompt reconsideration of change in therapy, unless no satisfactory therapeutic options remain.

**Techniques for Genotyping**

Assays for detecting HIV-1 genome mutations are based on polymerase chain reaction (PCR) as the first methodological step. The PCR amplifies an RNA fragment (after a reverse transcription step) or DNA to quantities large enough for genotyping (the second step). Most laboratories now analyze protease and reverse transcriptase gene DNA sequences but may not investigate other genome regions relevant for drug resistance (e.g., gag cleavage sites). It is still a technical challenge to amplify and genotype all gene regions implicated in protease and reverse transcriptase inhibitor resistance.

Generally, plasma samples with more than 1000 copies/mL of HIV RNA are needed to generate results. Resistance testing is not as likely to be useful when values are below this level. With current methods, species constituting 20% or more of amplified product can usually be detected. False positivity for mutations is possible from carryover from other HIV-1 samples in the laboratory or from random polymerase errors in vitro during in vitro nucleic acid synthesis. Also, unless molecular clones of PCR products are studied (not routinely done), it is impossible to be certain whether multiple positions in the sequence are physically linked together on the same genome; i.e., it is impossible to differentiate a mixture of singly mutant genomes from a mixture having some genomes with accumulated different mutations.

Crucial issues for analysis of genotypic results include laboratory quality assurance, use of appropriate controls, and laboratory report clarity and comprehensiveness. Importantly, expert clinical interpretation is needed to assess likelihood that a given mutation pattern confers cross-resistance to related antiretroviral drugs and to define expected impact of mutation combinations on resistance phenotype. Other factors, e.g., treatment history and plasma HIV-1 RNA levels, must also be considered when interpreting resistance data.

Two methods of sequencing the amplified HIV-1 DNA fragment are used: one is based on in vitro copying of amplified DNA templates (dideoxynucleotide terminator cycle sequencing), and the other is based on hybridization of the amplified nucleic acid (sequencing by hybridization). Other methods do not involve sequencing all PCR product positions but interrogate only certain codons.

Dideoxynucleotide terminator cycle sequencing using automated fluorescent dye-based sequencers is the most common approach. Human immunodeficiency virus protease and reverse transcriptase can also be sequenced by hybridization using high-density oligonucleotide arrays, chips with thousands of immobilized oligonucleotides are used to interrogate labeled, fragmented nucleic acid molecules derived from circulating HIV. The hybridization and computerized data analyses are highly automated, minimizing human input after template RNA preparation. Compared with cycle sequencing using automated sequencers, the chip hybridization-based method has yielded virtually identical results. However, it is not currently designed to identify genetic mixtures of mutant and wild-type viruses.

A more targeted genotyping method now commercially available is the line probe assay that interrogates only certain codons. This method involves detecting a nonradioactive colorimetric signal from hybridization of HIV-1 PCR product to oligonucleotide probes immobilized in lines on a paper strip. Data analysis is simple and fast with this method; however, it is now available only for genotyping selected reverse transcriptase codons associated with nucleoside, nucleotide, and lamivudine resistance (reverse transcriptase codons 41, 69, 70, 74, 194, 214, and 215). This assay may have greater sensitivity for detecting minority species in a genetic mixture in some samples but may sometimes give no results because nearby polymorphisms impair hybridization.

**Antiretroviral Resistance Phenotypes**

Drug-resistant virus phenotypes are detected by measuring the 50% or 90% inhibitory concentration (IC50 or IC90) of a drug in vitro. In standardized drug susceptibility assays, cells are infected with a fixed amount of viral inoculum, and various drug concentrations are tested to quantitate drug concentration required to inhibit viral replication (i.e., determine dose-response curve) compared with untreated infected control cells. The precise IC50 or IC90 values obtained depend on the assay used, cell type used, antiretroviral drug tested, input viral inoculum, marker of viral replication selected (e.g., measurement of HIV p24 antigen or reverse transcriptase activity), and time in culture. Therefore, IC50 or IC90 values from one type of assay should not be compared with those obtained by another method.

Drug susceptibility testing measures HIV ability to grow at different drug concentrations vs a drug-susceptible laboratory strain of virus or previous isolate from the same patient. In general, a 4-fold increase is the minimum change reliably detectable in the laboratory. Changes in IC50 or IC90 values that are clinically important are usually drug activity have not been defined. High-level HIV-1 resistance to zidovudine (i.e., isolates for which IC50 values are ≥1.0 μmol/L) predicted more rapid clinical progression and death in analyses adjusting for other risk factors in patients with advanced HIV disease receiving zidovudine monotherapy. The clinical relevance of IC50 or IC90 values for each multidrug regimen component has not been defined. Also, sustained virus suppression may be seen in patients in whom drug-resistant virus has been detected. This may result from achieving plasma drug levels in vivo that exceed IC50 or IC90 values for resistant virus in vitro.

Phenotypic assays may fail to detect evolving resistance that has not yet led to measurable increases in IC50 values, e.g., the K70R zidovudine resistance-conferring mutation emerges within 12 weeks in nearly half of patients receiving zidovudine monotherapy, yet its presence alone is not associated with measurable increases in zidovudine IC50. Thus, detection of a mutant genotype may be expected to precede detection of an increased IC50 value. Moreover, a limitation of all drug susceptibility assays described to date is that only predominant circulating viral populations are sampled to yield IC50 or IC90 values. Thus, minority drug-resistant virus contributing to drug failure or transmission of resistant virus may not be detected.

One method for detecting viral drug resistance involves drug susceptibility testing in PBMCs using clinical isolates derived from HIV-1-infected PBMCs or plasma. A high-titer viral stock is grown, followed by end point dilution to yield an infectivity titr. An appropriate drug concentration is then used in a subsequent susceptibility assay in PBMCs. The multistage procedure is time-consuming and expensive, and requires expertise beyond the capability of most clinical virology laboratories. The requirement to grow virus stocks from infected PBMCs in long-term culture and need to perform the assays over at least 7 days, may result in selection of viral subpopulations in vitro that do not reflect the majority species in vivo.

More rapid viral phenotypic assays based on recombinant DNA technology (Figure 2) are under development and may soon be available commercially. An advantage of recombinant virus susceptibility assays is use of un-
validation before routine use can be recommended.

**IMPLICATIONS FOR CLINICAL MANAGEMENT**

**Role of Resistance Testing in Selecting an Initial Regimen**

Transmission of HIV-1 mutants resistant to zidovudine was initially described in 1992. Since then, several cross-sectional surveys to detect primary infection involving drug-resistant virus have been done (Table 3). In Europe and North America, prevalence of primary zidovudine resistance is variable, from 0% to 10% of isolates. Transmission of lamivudine, or nevirapine-resistant virus has also been reported. Primary infection with virus resistant to protease inhibitors has not yet been reported but is expected.

Epidemiologic surveys of HIV isolates from newly infected patients in representative populations are needed to assess whether prevalence of primary infection with resistant virus is increasing, particularly in adults with primary HIV infection and pregnant women and their newborn children. In our opinion, drug-resistance testing should be considered for use in the design of initial antiretroviral regimens if there is an increased prevalence of resistance in a particular population.

Genotypic or phenotypic testing for drug resistance before antiretroviral therapy initiation in treatment-naive persons cannot be recommended for routine use at this time. Decisions concerning therapy initiation should be made on the basis of plasma HIV RNA level, CD4+ cell count, and clinical status. However, transmission of drug-resistant variants is likely to increase with widespread use of antiretroviral drugs. In absence of therapy, isolates with primary drug resistance may only be detectable early in infection, as wild-type strains may have a replication advantage that dominates over time in absence of drug selection. Drug-resistant variants that persist as minority species may be difficult to detect yet would quickly reemerge under drug-selective pressure.

For high-risk occupational, and possibly nonoccupational, HIV exposures, treatment with postexposure prophylactic antiretrovirals should be started as soon as possible and should not be delayed for results of resistance testing of virus from the source patient, whose antiretroviral treatment history should be carefully considered when choosing the prophylactic regimen for the exposed person.

**Use of Resistance Testing When Changing Therapy**

Resistance is only one possible cause of therapy failure (Figure 3). Increasing evidence, however, indicates that viral resistance and treatment failure are closely linked. In recent reports, a minority of those taking complex antiretroviral therapy regimens in whom virologic drug failure was observed appeared to have predominantly wild-type HIV isolates from peripheral blood. Although these findings could be attributed in part to lack of assay sensitivity, other factors may be operative. First, adherence to increasingly complex drug regimens is often difficult, and some patients discontinue therapy intermittently. The removal of drug pressure leads to repletion of wild-type virus and apparent loss of drug efficacy. In this setting, drug resistance may not have developed, but an alternative antiretroviral treatment regimen to which these persons would more likely adhere is advised. Other causes of drug failure may include widely divergent plasma trough drug levels among patients, limited drug potency, inadequate intracellular phosphorylation to active drug in the case of nucleosides, or ongoing viral replication in sanctuary sites relatively inaccessible to inhibitory drug concentrations. Suboptimal drug levels, whatever the cause, will permit ongoing viral replication and favor emergence of resistant virus over time (Figure 5). A confirmed increase in plasma HIV-1 RNA level should be the main trigger for
considering change in therapy. 1., 2, 3, 4 Resistance testing, therefore, should not be the primary assay used to decide when to change therapy. One issue of adherence (or related factors) are excluded, it may be reasonable to conduct resistance testing to help guide the choice of alternate antiretroviral regimens. When patients have received complex regimens, however, a search for known mutations conferring resistance to an individual drug may yield results that are difficult to interpret. There is no substitute for a thorough treatment history in guiding choice of appropriate regimens in such patients. Mutants selected by a drug from a previous regimen may not be currently detected by available resistance assays, and may rapidly reemerge within days to weeks of "recycling" the drug. Similar considerations would apply to initiating a drug known to share cross-resistance with the first. A longitudinal record of resistance test results from time of initial presentation (including formal evaluation prior to therapy) may ultimately prove useful, but would be costly and require validation in controlled clinical studies.

If a person in whom therapy is failing never received a given antiretroviral drug or one inducing cross-resistant mutants, it can be assumed that absence of mutations known to confer resistance will lead to acceptable drug activity when used as part of a potent regimen.

The presence of resistance-conferring mutations in a patient in whom therapy is failing, however, indicates that the drug in question may not be sufficiently active, and that other antiretroviral drugs should be considered. This has been shown for zidovudine or didanosine, for which resistance is associated with lack of clinical efficacy. 5, 6, 7, 8 These drugs should be replaced when resistance is seen in the setting of confirmed detectable plasma HIV RNA levels. Similar predictive data are emerging for other antiretroviral drugs, e.g., phenotypic resistance to abacavir in vitro (ie, >8-fold increase in IC50) appears to be associated with poor virologic response to abacavir therapy in vivo. 9, 10, 11 Protease inhibitor failure has also been associated with demonstrable resistance in vitro, and identification of mutations associated with decreased susceptibility to these drugs should prompt a change in therapy. 12 Although cross-resistance to all other protease inhibitors may not be present, development of broad cross-resistance under drug selective pressure may be rapid. 13 Further research is needed to determine the best strategies for serial use of protease inhibitors when resistance emerges to one member. If resistance to any given drug has ever been detected, that drug should probably not be used again, even if current test results suggest viral susceptibility, unless no other options are available. The safest approach is to change all members of a failing regimen, regardless of resistance-testing results. Prevention of perinatal transmission is a special situation in which many, although not all, experts believe that zidovudine should be included in the antiretroviral regimen, regardless of history of zidovudine use, because it is the only drug shown to date to reduce HIV transmission to neonates. 14

**SUMMARY**

Drug-resistant HIV strains emerge readily in the setting of ongoing viral replication during antiretroviral therapy. In patients receiving sequential multidrug regimens, complex interactions involving multiple mutations can occur. In such settings, results of susceptibility testing and mutational analyses require clinical interpretation that also considers drug history and plasma viral load information. However, emerging evidence suggests that in drug-experienced patients, genotypic or phenotypic evidence of resistance to a drug in vivo is associated with poor virologic response to the drug in vivo. Thus, resistance testing will likely be useful for identifying drugs that will not be optimally active in a treatment regimen. The absence of phenotypic or genotypic evidence of resistance in the setting of previous therapy, however, does not necessarily predict a good response, since minor variants may not be detected by current assays. Thus, a confirmed increase in plasma HIV RNA level should remain the main trigger for considering a change in therapy.

Epidemiologic research is needed to track drug resistance prevalence in populations. In our opinion, routine testing for certain patients, eg, antiretroviral drug-naive pregnant women or persons with primary HIV infection, should be considered when prevalence of drug resistance testing is high.

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**Table 3.—Resistance Testing in Clinical Management**

<table>
<thead>
<tr>
<th>Drug-Resistant Variants</th>
<th>Subinhibitory Drug Levels</th>
<th>Host Immune Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preexisting</td>
<td>Limited Potency or Distribution</td>
<td>CD4+ Cell Function</td>
</tr>
<tr>
<td>Selected</td>
<td>Incomplete Adherence</td>
<td>CTLs</td>
</tr>
<tr>
<td></td>
<td>Poor Absorption</td>
<td>Chemokines</td>
</tr>
<tr>
<td></td>
<td>Rapid Clearance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonactivation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Protein Binding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug-Drug Interactions</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 3.—Factors that contribute to antiretroviral drug failure due to resistance. Ongoing viral replication leads to the emergence of resistant virus, and ultimately to drug failure. The emergence or absence of resistant virus, the lack of drug levels adequate to inhibit viral replication, and host immune function each play a role. CTLs indicates cytotoxic T lymphocytes.**
resistance in that population is increased. As sequential data are generated about patterns of resistance in drug-naive patients starting therapy, such information may also guide selection of initial antiretroviral regimens.

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References
Drug Resistance Testing in HIV-Infected Adults—Hirsch et al. 1991
Antiretroviral Therapy for HIV Infection in 1998

Updated Recommendations of the International AIDS Society–USA Panel

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Objective.—To provide recommendations for antiretroviral therapy based on information available in mid-1998.

Participants.—An international panel of physicians with expertise in antiretroviral research and care of patients with human immunodeficiency virus (HIV) infection, first convened by the International AIDS Society–USA in December 1995.

Evidence.—The panel reviewed available clinical and basic science study results (including phase 3 controlled trials; clinical, virologic, and immunologic end point data; data presented at research conferences; and studies of HIV pathophysiology); opinions of panel members were also considered. Recommendations were limited to drugs available in mid-1998.

Consensus Process.—Panel members monitor new clinical research reports and interim results. The full panel meets regularly to discuss how the new information may change treatment recommendations. Updated recommendations are developed through consensus of the entire panel at each stage of development.

Conclusions.—Accumulating data from clinical and pathogenesis studies continue to support early institution of potent antiretroviral therapy in patients with HIV infection. A variety of combination regimens show potency, expanding choices for initial regimens for individual patients. Plasma HIV RNA assays with increased sensitivity are important in monitoring therapeutic response; however, more data are needed to determine precisely the HIV RNA levels that define treatment failure. Long-term adverse drug effects are beginning to emerge, requiring ongoing attention. Some issues regarding optimal long-term approaches to antiretroviral management are unresolved. The increased complexity in HIV management requires ongoing monitoring of new data for optimal treatment of HIV infection.

JAMA. 1998;280:78-86

THE INTERNATIONAL AIDS Society–USA panel, which has previously evaluated data on antiretroviral therapy, continues to provide updates of its earlier recommendations with the goal of providing clinicians with a practical synthesis of the therapeutic implications of human immunodeficiency virus (HIV) disease pathogenesis and clinical research. The panel consists of an international group of physicians experienced in antiretroviral drug–related research and care of patients with HIV infection. In preparing these recommendations, which were developed by consensus, available clinical and basic science data as well as expert opinion were considered. The rapidly evolving knowledge base, increasing level of sophistication of patient monitoring, and complexity of therapeutic options dictate the need for updated recommendations.

SCIENTIFIC RATIONALE FOR UPDATED RECOMMENDATIONS

Seminal observations reported in 1995 continue to provide the pathogenetic basis for current therapeutic recommendations. The high viral turnover rate and the error-prone nature of RNA virus replication support the use of potent antiretroviral combination regimens to achieve long-term control of HIV replication. Original calculations describing HIV dynamics were based on observations of the initial phase of plasma HIV-1 decline observed following antiretroviral treatment initiation. A second phase of decline was then ob-
Table 1.—Pharmacokinetic Interactions Among Protease Inhibitors and Nonnucleoside Reverse Transcriptase Inhibitors*  

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>Indinavir</th>
<th>Ritonavir</th>
<th>Saquinavir Soft Gel</th>
<th>Nelfinavir</th>
<th>Amprenavir</th>
<th>Nevirapine</th>
<th>Delavirdine</th>
<th>Efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indinavir</td>
<td>No effect (24)†</td>
<td>TAUC 120% 800 mg; 36% 1200 mg (25, 26)</td>
<td>No effect (27)</td>
<td>TAUC 10%; single dose (28)</td>
<td>No dose change</td>
<td>No effect (30)</td>
<td>No effect (31, 32)</td>
<td>No effect</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>TAUC 48% (24)†</td>
<td>TAUC 121% (26)</td>
<td>TAUC 152% (28)</td>
<td>Pending</td>
<td>No effect (30)</td>
<td>No effect (31-33)</td>
<td>TAUC 21%</td>
<td></td>
</tr>
<tr>
<td>Seque/lavir soft gel</td>
<td>Pending</td>
<td>No effect (26)</td>
<td>TAUC 14% (24)†</td>
<td>Pending</td>
<td>No effect (36)</td>
<td>Pending</td>
<td>TAUC 10%</td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>No effect (27)</td>
<td>TAUC 61%; single dose (28)</td>
<td>TAUC 38% (34)†</td>
<td>Pending</td>
<td>No effect (36)</td>
<td>TAUC 60% (37)</td>
<td>No effect (38, 39)</td>
<td>No effect</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>No effect (29)</td>
<td>Pending</td>
<td>Pending</td>
<td>Pending</td>
<td>No data</td>
<td>Pending</td>
<td>Pending</td>
<td>TAUC 15% (29)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>JAU G 28% (30)</td>
<td>No effect (30)</td>
<td>JAU G 24% of HCQ (28); 27% (36)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Delavirdine</td>
<td>TAUC 2-fold (31, 32)†</td>
<td>No effect (31, 32)</td>
<td>TAUC 10% 5-fold (31, 32)</td>
<td>TAUC 113% Imatinib, AUC 50% (37, 40)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>JAU G 30%†</td>
<td>TAUC 15%</td>
<td>TAUC 20% Imatinib, AUC 3% (38, 39)</td>
<td>No dose change</td>
<td>No data</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Drugs in the vertical column are interacting drugs; those listed horizontally are the drugs affected by the interaction. Ellipses indicate data not applicable; arrows, the direction of the change of area under the curve (AUC): ↓, decrease; ↑, increase, and the numbers in parentheses, the reference citations. The possible dose changes are as follows: 1) AUC 120%—TAUC 10%: Indinavir 400 mg twice daily, with ritonavir 400 mg twice daily, based on pharmacokinetic study only. Nelfinavir 750 mg 3 times daily, with saquinavir soft gel 1000 mg twice daily. 2) Nelfinavir 750 or 1000 mg, with indinavir 1000 mg twice daily. 3) Ritonavir, 400 mg twice daily, with saquinavir soft gel capsule (SSG) or hard-gel capsule (HGC), 400 mg twice daily. 4) Ritonavir, 400 mg twice daily with Nelfinavir, 750 mg twice daily. 5) Delavirdine, 400 mg 3 times daily with Indinavir, 400 mg or 600 mg 3 times daily. 6) Efavirenz, 600 mg daily, with indinavir, 1000 mg 3 times daily. Efavirenz, 600 mg daily, with saquinavir SSG, 400 mg twice daily, with ritonavir, 400 mg twice daily. 7) Pending dose change may be necessary due to the interaction.  

† For these combinations, only data for the HGC formulation of saquinavir are available.

...
INITIATING ANTIRETROVIRAL THERAPY

When to Initiate Therapy

There is no decisive new information regarding the optimal time to begin treatment. The point at which theoretical benefits of preventing immunologic damage are offset by realities of nonadherence or adverse effects is unknown. There is, however, growing consensus, as represented by recommendations of a Department of Health and Human Services (DHHS)-appointed panel, that early treatment initiation is associated with virologic, immunologic, and clinical benefits. The International AIDS Society–USA panel continues to recommend antiretroviral therapy for any patient with established HIV infection and a confirmed plasma HIV-1 RNA level greater than 5000 to 10,000 copies/mL who is committed to the complex, long-term therapy. Accumulating data show that viral load is a strong, independent predictor of clinical outcome. Degree and durability of virologic response correlate directly with plasma HIV RNA level and CD4+ cell count at baseline. Treatment options should be discussed with all patients with HIV infection.

 Pretreatment plasma HIV RNA level and CD4+ cell count are important for evaluation of response to treatment. In general, prior to therapy initiation, 2 plasma viral load levels using the same technology and 2 CD4+ cell counts should be obtained at 2 separate visits, at which time drug therapy options, implications, and requirements are discussed and reviewed. A baseline plasma HIV RNA level obtained using the more sensitive assays is not generally needed as more routinely available standard assays will suffice.

The first therapeutic intervention is the most important in achieving a maximum and durable virologic response as emergence of resistance may severely limit future treatment options. Although there are many reasons for drug failure, resistance secondary to poor adherence and suboptimal regimens may have the most serious long-term consequences. Therapy should not be initiated until treatment goals and need for close adherence to a regimen are understood and endorsed by the patient. Factors leading to rebound adherence may include drug adverse effects, inconvenience of dosing schedules, high pill burden, interference with normal lifestyle, including food restrictions and hydration requirements, and competition from activities of daily living (eg, full-time employment or alcohol use).

For asymptomatic patients with low plasma HIV RNA level (eg, <5000-10,000 copies/mL) and high CD4+ cell count (eg, >35-0.50 x 10^9/L [350-500/µL]), deferral of therapy with close follow-up may be appropriate given treatment complexities, risk of adverse effects, consequences of resistance, and the possibility that such persons may fall into the category broadly described as long-term nonprogressor. For those with low HIV RNA level (eg, <5000-10,000 copies/mL) and low CD4+ cell count (eg, <0.50 x 10^9/L) and particularly <0.35 x 10^9/L, therapy initiation is recommended, given independent prognostic significance of CD4+ cell count and clinical trial data support.

Initial Antiretroviral Regimens

The goal of antiretroviral therapy is to improve survival and decrease morbidity via continuous maximum suppression of HIV replication. Choice of a regimen should also take into consideration preservation of future treatment options. The initial regimen failure of regimens that will durably reduce plasma HIV RNA below levels of detection of the most sensitive assays available is recommended with the expectation that such suppression will limit or prevent the development of resistance and provide durable clinical benefit. Although even modest reductions in viral load (eg, 0.5 to 1 log reductions) provide clinical benefit, an approach that does not maximally suppress viral replication may lead to resistance and treatment failure, limiting treatment options.

Numerous clinical trials have been and are being conducted with combination antiretroviral regimens in treatment-naïve patients. Most are designed with primary virologic not clinical endpoints, and many potentially effective combinations have not been directly compared or evaluated long term. However, an increasing number of drug combinations appear to have similar short-term potency. Thus, potential choices for a potent initial regimen are expanding. Examples of combinations in current use or under investigation for initial therapy include the following: (1) PI and 2 NRTIs; (2) 1 NRTI and 2 NRTIs; (3) 2 PIs with or without 1 or 2 NRTIs; (4) 1 PI and 1 NRTI with or without 1 or 2 NRTIs; and (5) 3 NRTIs (Table 2).

These regimens result in virologic success rates from 60% to 90% in antiretroviral-naïve patients, as judged by achievement of a plasma HIV-1 RNA level less than 500 copies/mL at 24 weeks or beyond. The absence of data from randomized, comparative clinical trials makes it impossible to be certain of long-term superiority of one approach vs another. Considerations in this choice include strength of clinical trial data, potential for drug interactions with other necessary medications or exacerbation of underlying medical conditions (eg, nephropathy), likelihood of adherence, potential for long-term adverse effects, and preservation of future treatment options. Necessary commitment to years of therapy, cost, and availability of drugs, and clinician familiarity with drugs and combinations are also important considerations in the choice of an initial regimen.

An increasing concern has been whether disease stage should dictate the approach. The panel cautions against any strictly "staged" approach to treatment; however, response rates decrease as HIV disease advances. For example, zidovudine-lamivudine-indinavir resulted in 45% to 88% of zidovudine-experienced subjects achieving viral loads below 500 copies/mL at 24 weeks, with lower response rates associated with low CD4+ cell count and high viral load level at baseline.

At this time, initiation of a potent PI and 2 NRTIs should remain the primary consideration, given the clinical trial data support for the durability of these combinations, and population-based data documenting reduced morbidity and mortality. The place of dual PI-based combinations (typically combined with 2 NRTIs) as initial therapy is yet to be fully defined, but may be most appropriate for those with advanced
HIV disease. If deferral of a PI-containing regimen is desired, combination of an NNRTI with 2 nRTIs is an alternative approach. Regimens combining a PI with an NNRTI (with or without an nRTI) hold promise based on durable responses reported for the combination of indinavir and the experimental drug efavirenz through 60 weeks. One concern with employing representatives of each of the 3 drug classes in an initial regimen is potential for multidrug-class resistance should the initial regimen fail. Data concerning initial potency of triple-nRTI-based regimens with the approved drugs (eg, zidovudine-didanosine-lamivudine) or with zidovudine-lamivudine-abacavir are limited and durability of responses is uncertain.

Constructing a potent combination from among the 3 current classes of drugs, nRTIs, NNRTIs, and PIs, requires thorough knowledge of their activities, adverse effects, and potential drug interactions.

Nucleoside Reverse Transcriptase Inhibitors

Although single nRTIs can be used as part of 3-drug and 4-drug combinations, dual nRTI combinations are most commonly used as components of such regimens. In antiretroviral-naive patients, there are several reasonable dual nRTI combinations for consideration as regimen components: zidovudine-lamivudine, stavudine-lamivudine, stavudine-didanosine, zidovudine-didanosine, didanosine-lamivudine, and zidovudine-zalcitabine. The first 3 combinations are the most commonly used. Lamivudine should be used only in regimens designed to be fully suppressive to prevent emergence of the lamivudine-associated M184V mutation and loss of its antiretroviral effect. The report of zidovudine exposure can limit cell ability to phosphorylate stavudine on subsequent exposure needs confirmation; there are no data on ability of stavudine to affect subsequent zidovudine phosphorylation. Such data might influence the decision concerning which dual nRTI component to use initially. Combining zidovudine and stavudine should be avoided because of antagonism shown with this combination.

Nonnucleoside Reverse Transcriptase Inhibitors

Nevirapine was the first available compound in this class. Its activity in combination with zidovudine-didanosine in antiretroviral-naive patients led to the recommendation that an NNRTI–nRTI combination is a reasonable alternative to a PI–nRTI regimen in selected situations. Delavirdine has been shown to result in reasonable virologic responses when given in combination with zidovudine-lamivudine. The investigational NNRTI efavirenz holds promise because of potency and potential for once-daily dosing (see http://www.ama-assn.org/special/hiv/library/library.htm). Potential for high-level resistance as a result of a single reverse transcriptase mutation suggests that drugs in this class should be used only in regimens designed to be maximally suppressive. Also, drug-drug interactions must be considered when NNRTIs are given with PIs (Table 1).

Protease Inhibitors

The major requirement for choice of PI is in vivo potency. Indinavir, ritonavir, and nelfinavir were each previously recommended as combination regimen elements. The new soft-gel capsule formulation of saquinavir (saquinavir-SGC) has enhanced bioavailability and, when given at recommended dosage in combination with zidovudine-lamivudine, produced virologic response comparable to that of indinavir-zidovudine-lamivudine through 24 weeks. Saquinavir-SGC can thus be an additional consideration as a potent PI component, although experience with it is still limited. With respect to dual PI–nRTI-based regimens, most data exist for ritonavir-saquinavir; durable virologic suppression has been reported through 60 weeks. However, except with indinavir-saquinavir, in which in vitro antagonism has been shown, most dual PI combinations involving indinavir, ritonavir, nelfinavir, saquinavir, and ritonavir have been or will be investigated. Data are too preliminary for specific recommendations concerning these other dual PI combinations as initial therapy.

Strategies to enhance adherence are being addressed in several ways, eg, combining drugs in a single formulation (zidovudine-lamivudine). More convenient drug schedules are being explored, eg, studies of indinavir or nelfinavir, each administered in a twice-daily regimen in combination with zidovudine-lamivudine, report activity comparable to that of standard 3-times-daily regimens through 32 and 24 weeks, respectively.

CHANGING ANTIRETROVIRAL THERAPY

Considerations for Changing or Modifying Therapy

The basic indications for changing therapy, treatment failure, drug adverse effects, intolerance, and nonadherence, have not changed. However, there are refinements in monitoring tools, increased complexity of the treatment failure definition, new considerations of treatment modification in absence of an adverse effect or drug failure, and increased recognition of the potential for long-term adverse effects.

Monitoring Response to Therapy

A major advance in monitoring has been development of plasma HIV RNA assays of increased sensitivity, which have a dynamic range of about 50 to 50 to about 50,000 copies/mL of plasma and are suitable for monitoring for the majority of patients on treatment. Assay precision at lower limits is yet to be defined, but assay results are generally reproducible when viewed as a detection tool at the 50- to 500-copies/mL lower limit. Assays will likely improve even further regarding lower limits of sensitivity. Small but careful studies involving potent regimens provide evidence for ongoing replication in patients with viral load consistently between 50 and 500 copies/mL. In those with levels below 50 copies/mL, evolution of resistance is restricted, although low levels of viral replication may persist. In other studies, durability of virologic response at 18 to 24 months was much greater when viral load was below a 20- to 500-copies/mL level of assay detection than when it was in the 20 to 500 copies/mL range.

The most sensitive assays available are thus recommended for continued monitoring of response to therapy. Frequency of viral load monitoring may need to be increased (eg, every 2 months) when using more sensitive assays to detect early viral rebound when re-establishment of control of viral replication is more likely possible. However, nontoxic data exist to guide optimal monitoring frequency. Assay variation at low levels (eg, 50-200 copies/mL) will result in some patients having intermittently detectable virus. After treatment initiation, it may take longer (eg, >24 weeks) to reach a 50-copies/mL cutoff than it would a 500-copies/mL cutoff.

Other monitoring tools are entering the clinical arena or being developed. Although technologies to report codon alterations and phenotypic susceptibilities are being commercialized, there are unanswered questions concerning the role of resistance testing in routine clinical practice. The complex issues surrounding possible clinical application of resistance testing are described elsewhere. CD4+ cell subset determinations to enumerate memory and naive cells are being studied in clinical trials and may have a role in better defining degree of immune reconstitution. Therapeutic drug level monitoring is becoming available to clinicians, but its utility as a monitoring tool is a subject of considerable debate and cannot be recommended at this time.
Definition of Treatment Failure

The predicted use of plasma HIV RNA assays of increased sensitivity has focused more attention on defining treatment failure and its management. Treatment failure is a biologic continuum and has many variations. The strictest definition is that of confirmed detectable plasma HIV RNA (≥ 50 copies/mL) in an adherent patient who had achieved a viral load level below the detection limit and has not experienced a recent acute infectious illness or vaccination. Many such patients, however, are asymptomatic, have maintained good CD4+ cell responses, and may have a favorable clinical prognosis (at least short term). The question arises as to whether treatment failure by this definition should mandate change in therapy. Continuing a regimen with low but detectable plasma viremia will be associated with viral evolution and gradual emergence of resistance, but this must be balanced against concern that premature treatment changes will constrain future options. There are no available prospective, comparative clinical trial data to assist clinicians with the issue of whether to change treatment at all, except for 50, 500, or 5,000 copies/mL, and thus, the decision should be individualized via discussion between patient and physician. However, evolution of resistance mutations continues when HIV is not maximally suppressed, and the greater possibility of success when treatment changes are made at lower HIV RNA levels suggest that an increasingly rigorous approach is warranted. This may be of most practical value for those experiencing their first confirmed drug failure. For those with their second or third regimen failure, the fewer options dictate a more conservative stance, with deferral of treatment changes until evidence of further increases in HIV RNA level or decreases in CD4+ cell count. In these cases, patients should generally remain on the antecedent regimen until they can begin a new regimen. Accumulating data show that many patients continue to have immunologic and clinical benefit from potent regimens even after rebound viremia; for them, stopping therapy may result in further viral load increase, rendering re-establishment of adequate viral suppression more difficult.

Other considerations regarding treatment failure are as follows: (1) the lack of initial virologic response that may result from poor adherence, inadequate drug absorption, or primary viral resistance; and (2) a falling CD4+ cell count. When CD4+ cell count decline occurs in concert with a rising HIV RNA level in an adherent patient, there is no question that treatment failure has occurred. The more difficult issue is a discordant response (e.g., CD4+ cell count decreases and HIV RNA level remains below the detection limit). The pathogenic causes for this are uncertain, although drug adverse effect must be considered. For those with a confirmed CD4 cell decrease to below 0.10 x 10^9/L, or a confirmed rapid decrease, treatment changes may be useful. Although clinical disease progression remains an indication for treatment change, occurrence of an opportunistic infection must be considered in relation to the time of treatment initiation and virologic and immunologic status of the patient. New or recurrent opportunistic infections occurring during immune reconstitution and after potent therapy do not automatically mean treatment failure if occurring with a rising CD4+ cell count or a low viral load or both.

Modifications of Therapy in Absence of Treatment Failure or Adverse Effect

There has been increasing interest in considering treatment alterations not dictated by overt treatment failure or adverse effects, such as maintaining viral suppression with induction-maintenance regimens or enhancing regimens that appear effective without achieving maximal viral suppression (intensification). In composite data from 2 trials of induction-maintenance strategies, 3 to 6 months of induction with indinavir-zidovudine-lamivudine followed by randomization to zidovudine-lamivudine, zidovudine-indinavir, or indinavir monotherapy when the plasma HIV RNA level was below 200 to 500 copies/mL was inferior to continuing the 3-drug regimen.32 These results, together with the observation that replication-competent virus was recovered from latent CD4+ cell reservoirs for up to 2 years following potent therapy initiation,25,29 suggest that longer duration of induction regimens, more potent maintenance regimens, or both may be needed.

For regimens achieving substantial early HIV RNA declines, but not below the limits of the most sensitive assay available, close monitoring in the first few months of treatment may permit addition of drug(s) to intensify the regimen and maximize long-term treatment benefit. The rationale for intensification is based on data suggesting that the HIV RNA nadir following initiation of an antiretroviral regimen is predictive of subsequent virus suppression and response durability.11 However, the new drugs must be added before viral rebound occurs; otherwise, addition of a single new drug can be viewed as incremental therapy, which may promote resistance. There are no prospective, randomized, controlled clinical trials comparing intensification of an existing regimen with changing a regimen entirely if optimal early response is not achieved, but this is under study.

Although dual NNRTI therapy alone is generally considered suboptimal, clinicians may face the dilemma of how to manage patients on dual NNRTI regimens alone with HIV RNA levels below 500 copies/mL. In this situation, more sensitive assays may provide important information. If the HIV RNA concentration is in the 50 to 500 copies/mL range, treatment changes should be considered, and the strategies outlined for selecting a new regimen in the setting of virologic failure should be employed. If the level is below 50 copies/mL, regimen continuation and close monitoring are reasonable.

Implications of Long-term Adverse Effects

There is increasing recognition of, and concern for, complications of long-term exposure to antiretroviral therapies, including hyperglycemia, hyperlipidemia, peripheral fat redistribution (lipodystrophy), and visceral fat accumulation.30-37 Precise incidence, underlying pathogenic mechanisms, and long-term implications of these derangements need defining. In general, their occurrence does not mandate change in therapy when a good therapeutic response is achieved. Their potential occurrence needs to be discussed with each patient prior to treatment initiation.

What to Change to

When the decision is made to change therapy, the approach should be driven by the underlying reason for the change. For adverse effects, intolerance, or suboptimal adherence to an otherwise successful regimen (i.e., HIV RNA level below detection limits), selective substitution of individual, identifiable offending components is reasonable. When a change in therapy is indicated due to drug failure, the same principles and considerations apply as described previously.5 Efforts should be made to change the regimen in its entirety, using drugs with least potential for cross-resistance to current drugs. Cross-resistance among drugs within a class may be due to overlapping genotypic alterations conferred by individual drugs, unique pathways of multidrug resistance, intracellular pharmacologic interference (e.g., zidovudine's potentially negative effect on stavudine phosphorylation), or less well-understood mechanisms, whereby one drug within a class may blunt subsequent response to other drugs in the
class. The role of resistance testing in choosing alternative drugs is not fully defined. Absence of genotypic or phenotypic resistance in a given sample may simply mean that the resistant minor virus subpopulation is present at a frequency below detection limits of the assay.

Given the increasing number of potential drug combinations, it is not possible to outline herein alternative regimens for every possible initial regimen. Table 2 illustrates general principles to be used in such decision making.

A most pressing clinical question in 1989 is how to manage patients in whom PI-containing regimens have failed. Prospective, randomized clinical trials to address this are ongoing or planned. Available data suggest that successful virologic suppression following failure on an initial regimen is more likely if a treatment alteration is made at a lower vs higher HIV RNA level. However, data are lacking regarding durability of responses beyond 48 weeks. Use of dual PI-based regimens in combination with new nRTI(s) and an NNRTI (if not previously used) is the preferred approach currently, but more data to support this are necessary. The role of investigational drugs as components of alternative regimens is being defined via ongoing clinical trials; however, cross-resistance to currently approved drugs may prove limiting in many instances. Other approaches may include adjunctive modalities such as hydroxyurea. Hydroxyurea enhances didanosine by altering normal nucleotide pool size, but its efficacy and safety in this setting are not established.

When to Stop Therapy

Eradication of HIV with maximally suppressive therapy alone for 2 years is unlikely given the present understanding of HIV pathogenesis; thus, therapy should be continued as long as possible. Even with virologic failure, many patients maintain clinical and immunologic benefit. After attempts to adjust the drug regimen to suppress replication are made, therapy should be continued in the face of virologic failure, if evidence of clinical and immunologic stability exists. In general, stopping all antiretroviral therapy is reasonable when the patient, after discussion with the physician, believes that the adverse effects outweigh potential benefits of therapy.

SPECIAL CONSIDERATIONS

Primary Infection

Immediate initiation of potent therapy appears warranted when primary HIV infection is identified. Recent data indicating immunologic benefit of such therapy when initiated before seroconversion support antiretroviral intervention in primary infection. Selection of the regimen must balance potential benefits with the possible difficulties in adherence. While viral eradication in established HIV infection may not be possible with available antiretroviral drugs, the possibility of eradication in early primary infection remains. Patients with primary HIV infection should be referred to clinical trials if possible so these strategies can be systematically investigated. Strategies that seek to limit cellular activation and cellular targets for HIV infection are being investigated.

HIV Infection in Pregnancy

This topic has been reviewed extensively by a US Public Health Service task force. In most respects, HIV infection in pregnant women should be treated as in infection in nonpregnant patients. There are situations, however, in which therapy may be altered in the pregnancy setting. If HIV infection and pregnancy are simultaneously identified during the first trimester or if the pregnant woman has early-stage HIV disease, it may be preferable to defer therapy to the second trimester, at which time potent combination treatment can be initiated. For asymptomatic pregnant women with low HIV RNA levels and high CD4+ cell counts, the goals of antiretroviral therapy are to prevent perinatal transmission and avoid compromising subsequent response to therapy for the woman. Although the US Public Health Service guidelines recommend zidovudine alone as a possible option, many physicians prescribe potent combination therapy to minimize the possibility that resistance will develop in the mother as a result of suboptimal therapy during pregnancy. However, given available data, zidovudine should probably be included in any regimen intended to prevent perinatal transmission.

Clinical trials are exploring new strategies for the timing of therapy for mother and child and for specific therapeutic options for maximally effective transmission prevention. Since experience in several regions indicated that antiretroviral therapy can reduce risk of perinatal transmission to about 4%, there is hope that more effective interventions will prevent it entirely. Women taking antiretrovirals during pregnancy should be encouraged to enroll in the Antiretroviral Pregnancy Registry (telephone number: [800] 722-9232, ext 38466).

Table 3.—Clinical Management Issues Regarding Antiretroviral Therapy for Which Existing Data Are Incomplete

<table>
<thead>
<tr>
<th>Question</th>
<th>Potential Answers</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the optimal initial antiretroviral regimen?</td>
<td>Is a protease inhibitor-containing regimen always preferable?</td>
</tr>
<tr>
<td>Is there a role for therapy with a protease inhibitor in a 3-drug regimen?</td>
<td>Should the complexity and potency of the starting regimen be adjusted according to the patient’s disease stage?</td>
</tr>
<tr>
<td>Are regimens that use potent combinations directed at a single viral target beneficial in the long term if multiple target regimens are less effective?</td>
<td>Is the use of a protease inhibitor an adequate substitution for a nonnucleoside reverse transcriptase inhibitor in a 3-drug regimen?</td>
</tr>
<tr>
<td>Are patients with drug-resistant virus likely to be cured?</td>
<td>Is the durability of immunologic response even with relative virologic failure, when is the optimal time to abandon a drug or drugs when plasma virus load becomes detectable?</td>
</tr>
</tbody>
</table>

Postexposure Prophylaxis

Risk of HIV infection associated with unintended sexual or needle exposure to HIV is probably comparable to occupational risk in medical personnel who have accidental puncture wounds. Benefits of postexposure prophylaxis have been established in occupational settings, and immediate initiation of potent combination antiretroviral therapy consisting of 2 or more drugs is recommended for high-risk occupational exposures. If exposure to resistant virus is suspected, a maximally suppressive regimen of drugs to which the virus is likely susceptible should be chosen. According to the Centers for Disease Control and Prevention guidelines, therapy should continue for 4 weeks. Laboratory evaluations for antiretroviral adverse effects after 2 weeks should be considered. Health care workers who receive chemotherapy for HIV exposure should be encouraged to enroll in the Centers for Disease Control and Prevention registry (telephone number: [888] HIV-4EP, or [888] 787-4449).

Concerns have been raised regarding routine provision of postexposure prophylaxis for sexual and needle-sharing HIV exposures, eg, the risk of exposing many people to therapy and associated adverse effects, especially when index case HIV status is unknown and there is the possibility that treatment availability might result in an increase in less safe behaviors. Other issues include the likelihood that sexual and needle-sharing exposures are often repeated and would require repeated treatment courses, and cost implications of provid-
ing widespread postexposure treatment to persons with low risk of infection when financial constraints already exist for providing therapy to persons known to be infected. Because the risk/benefit ratio for prophylaxis in these settings is not known, it is premature to make general recommendations at this time. Pilot investigations are under way to explore these issues. Meanwhile, if the decision is made to initiate prophylaxis, the principles regarding use of potent combination therapy for occupational exposures should be followed. Any such initiation of prophylaxis should be coupled with education designed to decrease the probability of repeated exposure. Recommendations for postexposure prophylaxis should be made by or in consultation with physicians experienced in antiretroviral drug management.

SUMMARY

The above recommendations are intended to provide a summary of current information about management of HIV infection with potent antiretroviral regimens. There are clinical settings for which definitive data are not yet available (Table 3). The panel will continue to monitor research findings in the field and provide updated recommendations as necessary.

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Upcoming International AIDS Society–USA Activities

Antiretroviral Therapy and HIV Drug Resistance Testing in 1998: Answers to Questions Posed to the IAS-USA Panels

The International AIDS Society–USA recently convened its international panels on antiretroviral therapy and resistance testing at the 12th International Conference on AIDS in Geneva, Switzerland, where their respective recommendations were presented and discussed. Questions posed to the Panels were collected and will be addressed in an upcoming issue of Improving the Management of HIV Disease in an effort to clarify specific concerns and address the day-to-day clinical implications for patient management.

Topics

- HIV Pathogenesis
- Clinical Aspects of Resistance Testing
- Antiretroviral Therapy: When to Start/
  What to Start With
- Antiretroviral Therapy: When to Change/
  What to Change to

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Current Challenges in HIV Disease:
A Case-based, Advanced Course in Clinical HIV Management

The annual fall CME courses are under development. New data will be presented in didactic formats as well as within the context of clinical case presentations, blending advanced-level understanding of HIV treatment with the realities of patient care. Faculty will include experts from the various disciplines in the field of HIV medicine. The following sites and dates have been scheduled for these upcoming courses, and brochures and registration materials will be available shortly.

New York, October 9, 1998
Chair: Douglas T. Dieterich, MD
Vice Chair: Michael L. Tapper, MD

Chicago, October 15, 1998
Chair: John P. Phair, MD
Vice Chair: Harold A. Kessler, MD

San Francisco, October 28, 1998
Chair: Molly Cooke, MD
Vice Chair: Kathryn M. Kocurek, MD

For further information about these and other IAS-USA activities, contact:
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Invitational brochures and complete symposia information will be available shortly.

A webcast of the symposium can be viewed at www.webcast.aids98.org