Topics in
HIV Medicine®

Perspectives

Special Contribution

The International AIDS Society–USA

About This Issue

This issue presents 4 *Perspectives* articles adapted from presentations given at the International AIDS Society–USA conferences "An Advanced Course in HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management," held earlier this year throughout the United States. Richard B. Kim, MD, discusses the effect of drug transporters on protease inhibitor levels in the body, with particular emphasis on P-glycoprotein. Carlos del Rio, MD, highlights the importance of risk reduction counseling in the HIV-infected population. And Diane V. Havlir, MD, offers a strategic framework for approaching antiretroviral treatment at four distinct periods of therapy.

Also included in this issue is a special section of questions posed to the International AIDS Society–USA Resistance Testing Guidelines Panel on a host of clinical issues relating to resistance testing. Topics covered include the clinical situations in which resistance testing may be useful, treatment implications and strategies, and therapeutic drug monitoring. The updated recommendations of the IAS–USA Resistance Testing Guidelines Panel appear in the July 1 issue of *Clinical Infectious Diseases.*

Topics in HIV Medicine®

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Perspective
Drug Transporters in HIV Therapy

Drug transporter proteins play a crucial role in drug disposition. The P-glycoprotein drug efflux transporter is a determinant of oral bioavailability and central nervous system (CNS) penetration of protease inhibitors (PIs), and may affect drug penetration to other tissue compartments that can serve as sanctuaries for HIV. Potent and selective inhibitors of P-glycoprotein can dramatically increase PI CNS penetration. Polymorphisms in the MDR1 gene regulating P-glycoprotein expression are associated with differences in drug disposition, with some data indicating that different genotypes are associated with differences in plasma PI levels and magnitudes of CD4+ cell count recovery under therapy. The activity of drug transporters in modulating antiretroviral drug effects and the potential for exploiting this activity to maximize therapeutic benefit and minimize drug toxicity are the subjects of ongoing study. In addition, inhibition of transporter proteins may increase the risk of hepatotoxicity and other adverse drug effects and is being investigated. This article summarizes a presentation given by Richard B. Kim, MD, at the March 2003 International AIDS Society–USA course in Atlanta.

Drug disposition and drug interactions are important components of the activity of and response to antiretroviral drugs. Determinants of drug disposition include the transporter proteins active in cellular uptake and efflux of drug molecules. Considerable attention has recently been given to understanding the role of the P-glycoprotein (P-gp), or *MDR* (multidrug resistance)*-1*, efflux transporter in modulating drug levels in cells and tissues and to delineating the genetic variation in this transporter that may account for differences in individual responses to drug therapy.

Characteristics of the P-gp Transporter

The P-gp transporter was initially studied in the setting of anticancer treatment and was identified as the means by which a number of drugs were removed from cells, resulting in what has been termed multidrug resistance in tumor cells. This transporter is expressed in cells in a number of locations in the body that are important to drug absorption and disposition, including the same cells in the intestine, liver, and kidney that express cytochrome P450 3A enzymes. They are also present at the level of the blood-brain barrier and act to limit central nervous system (CNS) penetration of many drugs and toxins. The transporters exhibit a broad substrate specificity, including hormones, plant-derived chemicals, and many drugs in clinical use. In the gastrointestinal tract, P-gp is exclusively expressed on the brush border, or apical domain, of the intestinal enterocyte. Its activity there limits intestinal absorption and thus oral bioavailability of a number of drugs. Expression of the transporter in the liver and kidney enhances elimination of drugs. The transporters are exclusively expressed in the liver on the canalicular membrane domain of hepatocytes and in the kidney on the luminal side of the proximal tubular cells, where they act to increase excretion of drugs into the bile and urine, respectively. Drugs cross the blood-brain barrier via either passive diffusion or active transport from capillary endothelial cells. The P-gp transporter is expressed on the luminal side of these endothelial cells and acts to pump drug molecules back into the blood. Given the great variability of CNS penetration of many drugs and the fact that the CNS may act as a sanctuary for HIV in the absence of drug activity in this compartment, the role of the P-gp transporter in limiting antiretroviral drug CNS penetration has attracted particular attention.

Effects of the P-gp Transporter on PI Concentrations

HIV protease inhibitors (PIs) are substrates for the P-gp transporter. In initial studies of the interaction of P-gp expression and PI disposition, Dr Kim's group assessed plasma and brain concentrations of nelfinavir in P-gp *(mdr1a)* wild-type mice. Plasma drug levels were
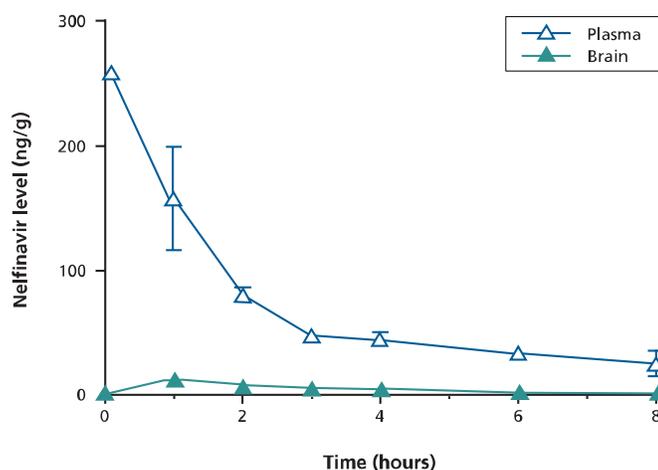
Figure 1. Nelfinavir concentrations in plasma and brain tissue of *mdr1a* wild-type mice after intravenous administration. Adapted with permission from Choo et al, *Drug Metab Dispos,* 2000.

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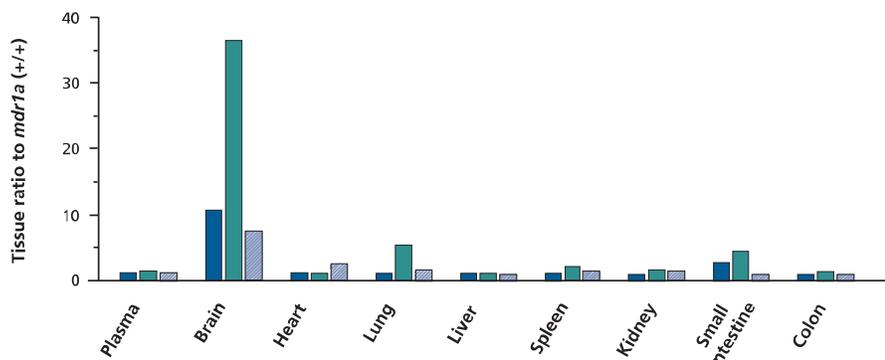
Figure **2.** Ratio of plasma and tissue levels of indinavir (blue bar), nelfinavir (green bar), and saquinavir (striped bar), in *mdr1a*-knockout mice to levels in *mdr1a* wild-type mice after intravenus drug administration. Adapted with permission from Kim et al, *J Clin Invest,* 1998.

Polymorphisms Affecting P-gp Function

Dr Kim's group and others have identified a number of polymorphisms in the *MDR1* gene (Kim, *Clin Pharmacol Ther,* 2001). One of the most common haplotypes is the *MDR1*2* haplotype (ie, 2 synonymous mutations in exons 12 and 26 that do not change the encoded amino acid flanking a mutation in exon 21 that does change the amino acid [ie, non-synonymous]) involving an Ala 893Ser substitution (Kim, *Clin Pharmacol Ther*, 2001). Work is ongoing to identify polymorphisms that have functional consequences in humans. Hoffmeyer and colleagues (*Proc Natl Acad Sci U S A,* 2000) have reported that some individuals naturally express low amounts of duodenal P-gp. This low expression phenotype is determined by natural polymorphisms within the P-gp gene (those with a TT genotype have low levels of P-gp while those with a CC or CT genotype have higher levels). Fexofenadine is a terminal metabolite of terfenadine that is a high-affinity substrate of P-gp and that can be used safely as a probe drug to study transporter function in humans. Studies using fexofenadine have found that there are marked differences in plasma drug concentrations according to *MDR1* haplotypes (Figure 4). With regard to HIV PI activity, Fellay and colleagues (*Lancet,* 2002) reported marked differences in

markedly higher than brain levels, which had a minimal peak and were virtually negligible from 2 hours after an intravenous (IV) dose (Figure 1). Comparison of tissue levels of indinavir, saquinavir, and nelfinavir after IV dosing in *mdr1a* wild-type mice and in *mdr1a*-knockout mice in which the gene regulating transporter expression is deleted, showed that brain levels of the drugs were dramatically increased (approximately 7- to 40-fold) in the *mdr1a*-knockout mice (Figure 2). In subsequent studies, Dr Kim's group sought to determine whether CNS entry of PIs could be selectively increased by pharmacologic inhibition of the transporter. Use of the potent P-gp inhibitor LY335979 in mice resulted in an approximate doubling of plasma nelfinavir levels but a dramatic increase in brain drug levels after IV nelfinavir dosing (Figure 3), with the increase in brain-to-plasma drug ratio being LY335979 dose-dependent. Cells in the testes are also known to express P-gp, and these studies likewise showed a dose-dependent increase in testes-to-plasma nelfinavir concentration ratio. Testing of other compounds and drugs selected on the basis of known effects on transporter inhibition showed markedly reduced ability to increase nelfinavir brain-to-plasma ratios compared with LY335979. These studies have suggested that there may be a number of tissue compartments protected from adequate PI levels by function of the transporter, and that potency and selectivity of P-gp inhibition are

necessary for adequate reduction of activity at blood-tissue barriers.

These issues of drug disposition and adequate penetration to tissue compartments are not limited to PIs. The P-gp transporter may be the most important transporter identified to date in terms of clinically relevant effects on drug disposition. Table 1 provides a list of drugs known to be substrates, inhibitors, or inducers of the transporter, a list that is similar to that of drugs known to affect CYP3A4 metabolism. In some cases, drug interactions are known to be completely accounted for on the basis of P-gp activity—eg, in the case of interaction of digoxin (a transporter substrate that is not metabolized) and quinidine (a transporter inhibitor).

Figure **3.** Plasma and brain levels of nelfinavir in control animals and after administration of P-glycoprotein inhibitor LY335979. Adapted with permission from Choo et al, *Drug Metab Dispos,* 2000.

Table 1. P-glycoprotein Substrates, Inhibitors, and Inducers

Substrates

- Cyclosporine
- Digoxin
- Erythromycin
- Fexofenadine
- HIV protease inhibitors
- Mibefradil
- Paclitaxel
- Quinidine
- Tacrolimus
- Terfenadine
- Verapamil (but not nifedipine or felodipine)

Inhibitors

- Clarithromycin
- Cyclosporine
- Erythromycin
- HIV protease inhibitors
- Itraconazole
- Ketoconazole
- Mibefradil
- Quinidine
- Terfenadine
- Verapamil

Inducers

- Rifampin
- St John's wort

Figure 4. Fexofenadine concentrations in healthy humans according to type of *MDR1* polymorphisms. Subjects with *MDR1*1*1*, *1*2*, and *2*2* were given a single dose of fexofenadine, and plasma levels for the drug were determined. Those with the *MDR1*2* alleles tended to have lower fexofenadine levels. Adapted with permission from Kim et al, *Clin Pharmacol Ther,* 2001.

nelfinavir plasma concentrations according to genotype in patients with *MDR1* exon 26 3435C/T polymorphisms (Figure 5, left). The finding of genetic differences that affect plasma drug levels suggests the possibility that these differences can alter drug effectiveness. Indeed, these investigators found that the TT genotype was associated with a significantly greater CD4 + cell count recovery under antiretroviral therapy including nelfinavir (Figure 5, right). Analysis of a number of factors associated with CD4 + cell count recovery showed that the TT genotype was among the best predictors (odds ratio, 3.0) of cell count, after baseline plasma HIV-1 RNA level. A subset of CD4 + cells expresses P-gp. It is thus possible that the transporter could affect levels of CD4 + cells, the cellular targets of HIV, by altering the amount of drug within these cells that is available for intracellular antiviral effect. It should be noted that the study by Fellay et al also observed an *MDR1* genotype-dependent effect for efavirenz, a drug which has not been shown to be a substrate of this transporter. Accordingly, many aspects of the Fellay et al study remain controversial.

Despite the promising findings indicating an association of particular *MDR1* polymorphisms with alterations in P-gp function, a significant amount of debate remains regarding the actual impact of these mutations. A number of groups, including HIV researchers, are currently attempting to better define the relevance of *MDR1* polymorphisms to effects of drug therapies.

Drug Transporters and Drug Toxicity

The prospect of maximizing therapeutic effectiveness of drug therapy by modulating activity of drug transporters is an attractive one. It should also be recognized that modulation of transporter function can result in drug toxicity and drug-drug interactions. The endothelial receptor antagonist bosentan furnishes one example of drug inhibition of transport function that appears to account for toxic effects. Initial trials of bosentan in the settings of chronic heart failure and hypertension showed an increasing frequency of elevated liver transaminases with increasing bosentan doses. Bosentan is an inhibitor of the bile salt export pump (BSEP) transporter located on the canalicular membrane of hepatocytes (Fattinger et al, *Clin Pharmacol Ther,* 2001). Since inhibition of this transporter may result in cholestasis and hepatocellular damage, it is possible that the drug produces liver toxicity via this mechanism. Similar considerations apply to the drug troglitazone, which was withdrawn from the market on the basis of hepatotoxicity in 2000. Although it was initially unclear why some patients appeared to be more susceptible to liver toxicity associated with troglitazone use, it has been shown that the sulfate metabolite of troglitazone is a particularly potent inhibitor of the BSEP transporter (Funk et al, *Mol Pharmacol,* 2001) and may also cause hepatotoxicity through this mechanism. These and other findings suggest that this transporter may be susceptible to inhibition by many drugs that cause hepatotoxicity. Indeed, it may turn out to be the case that a substantial proportion of otherwise unexplained liver toxicity and toxicity in other organs is explained by inhibition of drug transporters. A number of groups currently are investigating the potential role of drug transporters in hepatotoxicity associated with antiretroviral drugs.

Figure 5. Effect of genotype in patients with *MDR1* 3435C/T polymorphism on nelfinavir plasma concentrations (left) and CD4+ cell count recovery during antiretroviral therapy including nelfinavir (right). Adapted with permission from Fellay et al, *Lancet,* 2002.

Conclusions

Drug transporter proteins play a significant role in drug disposition and tissue penetration. The P-gp transporter is a key determinant of oral bioavailability and CNS penetration of PIs and also appears to affect drug penetration of other tissues that could act as sanctuaries for HIV. Specific inhibitors of P-gp can dramatically increase PI penetration of the CNS. Available data indicate *MDR1* polymorphisms can significantly alter drug disposition. In the case of PIs, mutations affecting transporter expression may also affect HIV infectivity in CD4 + cells by modulating intracellular drug levels. Inhibition of drug transporters may increase risk of hepatotoxicity and other adverse drug effects. Investigation is ongoing into the activity of transporters in modulating antiretroviral drug effects and into the possibility of exploiting this activity to maximize therapeutic benefit and minimize drug toxicity.

Presented in March 2003. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Kim in June 2003.

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Suggested Reading

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Transporter Terminology

CYP3A4: A drug-metabolizing enzyme in the cytochrome P450 superfamily. This CYP enzyme is involved in the metabolism of nearly 50% of all the drugs in clinical use. It is involved in the metabolism of nearly all the HIV protease inhibitors.

Efflux pumps: Family of cell membrane expressed transporters which pump drugs from intracellular to extracellular compartment.

MDR efflux system: This typically refers to the P-glycoprotein transporter. However, there are other transporters capable of mediating MDR (multidrug resistance) phenomena.

MDR1: This is the gene encoding for human P-glycoprotein.

P-glycoprotein (P-gp): This is a transmembrane protein found on many cell types; it mediates transport of certain molecules out of cells.

Polymorphisms: Refers to naturally occurring nucleotide substitutions in the genomic DNA.

Perspective
New Challenges in HIV Care: Prevention Among HIV-Infected Patients

The HIV-infected population has been understudied and underserved with respect to risk reduction and prevention interventions. Increases in high-risk sex practices and sexually transmitted diseases (STDs) have prompted considerable concern and have led to initiatives to implement routine STD screening and risk reduction counseling among the HIV-infected population. Available evidence indicates that risk reduction counseling can be effective. Improved attention to risk reduction counseling in the HIV medical care setting is needed, and efforts to improve access and maintain linkage to care must be increased. This article summarizes a presentation given by Carlos del Rio, MD, at the March 2003 International AIDS Society–USA course in Atlanta.

HIV prevention to date has focused almost entirely on encouraging risk reduction behaviors among at-risk HIV-seronegative populations. In general, these programs are theory-driven and emphasize the development of cognitive, social, and technical competencies and skills associated with lower-risk sex and drug use practices. However, a population that has been understudied and underserved with respect to risk reduction and prevention interventions is people living with HIV disease. It is now recognized that this is a crucial population to target for such interventions, for the sake of these individuals themselves and as an important public health measure.

The success of potent antiretroviral therapy in reducing HIV disease morbidity and mortality over the last 6 years has resulted in more people with HIV disease living longer—and living with improved health status, sense of well-being, and energy. These benefits have allowed many to continue to pursue normal life activities, including sex. A variety of recent data indicate that there has been an upsurge in high-risk sex practices. For example, Chen et al reported (XIV Int AIDS Conf, 2002) steady

increases in unprotected anal sex in general and with multiple partners among men who have sex with men (MSM) over the past several years in San Francisco. This high-risk sexual behavior has been accompanied by an increase in rectal gonorrhea and early syphilis rates (Figure 1). Indeed, syphilis epidemics are now being seen in numerous cities. Colfax et al (14th Int AIDS Conf, 2002) reported that predic-

tors of high-risk behavior among HIV-infected individuals included having the belief that an "undetectable" plasma HIV-1 RNA reduces the risk of transmission (odds ratio, 5.9) as well as actually having a plasma HIV-1 RNA level below assay detection limits on the most recent clinic visit (odds ratio, 9.3).

Increasing attention is thus now being called for prevention measures among the HIV-infected population. Two public health initiatives that include a framework for HIV prevention in this population are the Centers for Disease Control and Prevention (CDC) document, "HIV Prevention Strategic Plan Through 2005" (available at www.cdc.gov/nchstp/od/hiv_plan/default.htm), and the Institute of Medicine's *No Time to Lose: Getting More Out of HIV Prevention* (available at www.nap.edu/books/0309071372/html). Two impor-

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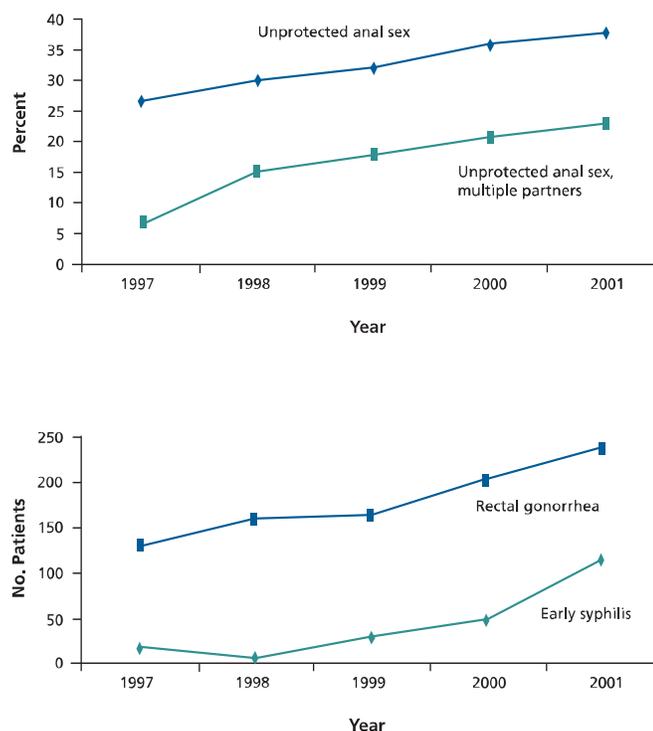
Figure **1.** Rates of high-risk sex (top) and cases of sexually transmitted diseases (ie, rectal gonorrhea and early syphilis) (bottom) in men who have sex with men in San Francisco. Adapted with permission from Chen et al, XIV Int AIDS Conf, 2002.

tant goals specified by the CDC that bear upon prevention strategies in HIV-infected populations are: (1) to increase the proportion of those who know they are infected from the current 70% to 95% by 2005 through voluntary counseling and testing, and (2) to increase the proportion of infected individuals who are linked to appropriate care, prevention services, and treatment services from the current 50% to 80% by 2005. As part of its strategic plan, the CDC has developed the SAFE (Serostatus Approach to Fighting the HIV Epidemic) strategy (Janssen, *Am J Public Health,* 2001). This strategy calls for efforts to (1) increase availability of prevention services for people with HIV; (2) teach health care practitioners to perform HIV and sexually transmitted disease (STD) risk assessments in HIV-infected patients; and (3) increase delivery of prevention messages to HIV-infected patients by health care workers.

Does Risk Reduction Counseling Work?

There is evidence that risk reduction counseling works. For example, in a meta-analysis reported by Johnson et al (*J Acquir Immune Defic Syndr,* 2002), counseling resulted in a 26% decrease in unprotected anal sex among MSM. Prendergast et al (*J Consult Clin Psychol,* 2001) reported that counseling produced a 30% increase in risk reduction skills among injection drug users and a 16% decrease in sexual risk behaviors. Kamb et al (*JAMA*, 1998) and Shain et al (*N Engl J Med,* 1999) reported that didactic counseling significantly reduced rates of gonorrhea and chlamydial infection, but that degrading of the intervention effects between 6 and 12 months after initial counseling suggested the need for "booster" counseling for many individuals. The National Institute of Mental Health (NIMH) Multisite HIV Prevention Trial (*Science,* 1998) showed that patients with high-risk behaviors who were in a behavioral counseling intervention group had fewer unprotected sexual encounters and reported higher levels of condom use and more consistent condom use than those who did not receive such counseling over 12 months of follow-up. The Project Respect study reported by Kamb et al

showed that counseling at STD clinics resulted in increased condom use and decreased frequency of STDs over 6 months of follow-up. The problems with many studies in this area, however, are that they employ specialized risk reduction counselors for counseling, rather than general health care practitioners, and that the interventions used are fairly intensive processes. It would be better for general health care practitioners, who have the most frequent contact with patients, to incorporate an effective form of counseling into the regular patient visit framework.

Barriers to Prevention Measures

A major problem in effecting risk reduction is that many health care practitioners do not make prevention a priority. Marks et al (*AIDS,* 2002) reported findings of a cross-sectional survey in which 839 HIV-infected men and women from 6 public HIV clinics in California were asked if practitioners had discussed lower-risk sex or the need to disclose HIV status to sex partners. Discussion of disclosure was reported by 50% of respondents, and discussion of lower-risk sex was reported by 71%. MSM were half as likely as heterosexual men to report discussion of lower-risk sex; a potential explanation was that many practitioners believed that MSM already knew risk reduction practices and therefore needed no counseling.

Barriers to delivery of prevention interventions by clinicians include lack of training or knowledge regarding sex- and drug-related risk behaviors; lack of skills or reluctance in discussing sex and drug use issues; absence of perception that patients are at risk; lack of standardized tools to assess patient risk or conduct interventions; belief that prevention attempts will not be successful; and constraints of time and resources. In addition, many clinicians feel that they are too busy discussing issues of treatment adherence, drug toxicities, laboratory monitoring, and health maintenance with HIV-seropositive patients and that there is little time left to discuss issues of prevention. However, a considerable amount of research shows that patients view clinicians as a trusted source of prevention information—eg,

in the settings of exercise promotion, smoking cessation, and coronary disease risk reduction, and thus clinicians must make prevention a priority and part of their patient encounter time.

The CDC-sponsored Antiretroviral Treatment and Access Studies (ARTAS) project is a multicenter controlled intervention study evaluating use of a case management approach to improve linkage to care after HIV diagnosis. As part of the study, a survey that included questions regarding prevention counseling practices was sent to HIV medical care practitioners in Atlanta, Baltimore, Los Angeles, and Miami. Findings in this survey point out many of the problems to be confronted in improving prevention interventions. Risk reduction counseling such as that around condom use, safe injection practices, and HIV disclosure were more commonly discussed with newly diagnosed rather than with established patients. However, risk reduction counseling was routinely provided by less than two-thirds of providers (Metsch L, XIV Int AIDS Conf, 2002). Furthermore, risk reduction counseling was more likely to be provided if the HIV practitioner was a physician assistant, nurse practitioner, or other non-physician personnel; if the practitioner was Hispanic or black; and if the practitioner spent at least 31 minutes with an established patient. Overall, the perceived percentage of patients practicing low-risk sex by practitioners was low (0% to 25% for 18.4% of practitioners, 25% to 75% for 16.3%, and 76% to 100% for 29.8%). A substudy looking at the impact of subspecialty training in prevention counseling showed that board-certified infectious diseases specialists were significantly less likely to provide condom use, risk reduction, and drug use counseling than were practitioners who were not infectious diseases specialists (Duffus et al, *Clin Infect Dis,* 2003; Figure 2).

Role of HIV Care Practitioners in Prevention

There is a clear role for HIV care practitioners in preventing HIV and other STD transmission by assessing patients for presence of STDs and risk behaviors and providing risk reduction/counseling. STDs exhibit what has been termed epi-
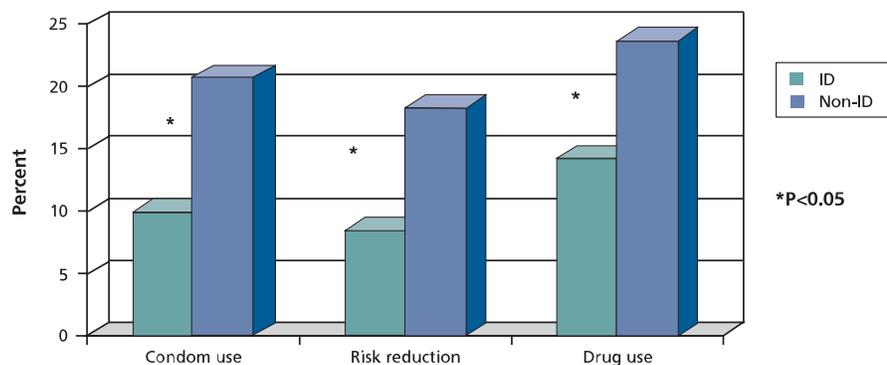
Figure 2. Rates of risk reduction counseling among infectious diseases specialists (ID) and nonspecialists (Non-ID) in the Centers for Disease Control and Prevention–sponsored Antiretroviral Treatment and Access Studies (ARTAS) clinician population. Adapted in part from Duffus et al, *Clin Infect Dis,* 2003.

demiologic synergy with HIV, meaning that the presence of an STD increases the risk of both acquiring and transmitting HIV infection. The CDC 2002 STD Treatment Guidelines (*MMWR,* 2002) recommend that all newly diagnosed HIV-infected patients undergo screening for gonorrhea, chlamydial infection, hepatitis B and C virus infections, and syphilis. Screening for curable STDs (gonorrhea, chlamydial infection, and syphilis) should be performed at least annually in sexually active patients. The CDC, Health Resources and Services Administration, National Institutes of Health, and Infectious Diseases Society of America currently are finalizing joint recommendations for incorporating HIV prevention into the HIV medical care setting. These guidelines reflect four basic priorities: (1) screening for risky behaviors and STDs; (2) providing general and tailored risk reduction messages to patients; (3) when indicated, referring patients for additional risk reduction services and other services that may affect risk reduction (eg, substance abuse treatment); and (4) ensuring that patients are provided with partner counseling and referral services.

To fully appreciate the role that the HIV health care practitioner must assume in prevention, it needs to be emphasized that the clinic or office visit may be the only time when the patient will have contact with someone who can provide education about HIV trans-

mission prevention. Although it remains unclear precisely what type of intervention strategy is optimal, it is desirable that counseling be supportive, nonpunitive, individualized, goal-oriented, and repeated at regular intervals. An attractive and promising approach based on motivational interview techniques is being assessed in the NIMH-Options Project. In this approach, clinicians in the intervention group use motivational interviewing at each clinic visit, consisting of statements such as, *"Now that we have finished discussing your medications, I'd like to ask you some questions about your sex and drug use behaviors.... How important is reducing risk behavior to you and how confident are you that you can do this?"* Patients can indicate their answers to these questions on a numeric scale. The clinician may then respond with a statement such as, *"Well, let's try to move that from a 5 to a 7."* The approach also involves use of "prevention prescriptions" in which the clinician uses the prescription pad to furnish the patient with instructions such as *Pick up condoms at the pharmacy.* Although full results of this study will not be available until next year, preliminary data are encouraging (Schreibman and Friedland, *Clin Infect Dis,* 2003).

Other priorities in reducing risk behaviors in HIV-infected individuals include bringing more of these individuals into settings in which risk reduction education can be provided, for example,

by enhancing access to HIV testing and medical care. In this regard, alternative models for getting patients into care and keeping them there are needed. One such effort has been undertaken in the Atlanta-based Grady Memorial Hospital Infectious Disease Program with the development of a "transition center." This center provides a location at which people who cannot or do not maintain regular health care contact can access care in a relatively unstructured way that tends to mesh with the unstructured nature of their lives. Preliminary data from this program suggest that this approach may be useful in keeping patients linked to care. The availability of an oral HIV test also promises to have some impact on the ability to rapidly determine infection status of new patients and their partners and to facilitate on-the-spot linkage to care.

Challenges to improving access to care and keeping patients in care have been documented in a variety of studies. The difficulty of keeping patients in care, for example, is illustrated by a 1994 study showing that 27% of HIV-infected patients delayed seeking medical care for more than 1 year and 12% for more than 2 years after initially testing as seropositive (Samet et al, *Am J Med, 1994*). Once in care, many patients use the emergency department rather than a clinic as their care setting. For example, it has been shown that African-American and Hispanic patients, the poor, and patients with lower psychologic well-being are more likely to use the emergency department than a clinic for visits associated with common HIV disease symptoms (Gifford et al, *J Gen Intern Med,* 2000). In addition, many patients in care are not on antiretroviral therapy, with 1 study indicating that women and injection drug users are less likely than other patients to be prescribed antiretroviral treatment (Strathdee et al, *JAMA,* 1998). Once prescribed antiretroviral treatment, most patients at urban clinics do not have the desired virologic response, with missed clinic appointments being the most important risk factor for virologic failure (Lucas, *Ann Intern Med,* 1999).

Some of the risks of inadequate linkage to medical care are indicated by preliminary findings of a study under way in Atlanta. Comparison of HIV-infected

individuals in care (regular attenders) with those not in care (nonattenders) shows that nonattenders have a higher frequency of crack cocaine use in the past 6 months (53% vs 13%), lower rates of regular condom use for vaginal sex (7% vs 60%) and anal sex (7% vs 20%), and higher rates of sex and drug contacts who are HIV-infected (64% vs 19%). Among nonattenders, 27% had been prescribed antiretroviral therapy in the past and were no longer receiving therapy, raising concerns about transmission of resistant virus.

Issues in Antiretroviral Therapy

By decreasing plasma HIV-1 RNA level, potent antiretroviral therapy may be the most effective medical intervention available for reducing HIV transmission. Maintenance of optimal suppression of plasma HIV-1 RNA level requires strict adherence to treatment. Higher rates of risky behavior have been reported among patients with lower adherence to antiretroviral therapy, suggesting increased potential for transmission of resistant virus. Indeed, the prevalence of high-level antiretroviral resistance in recently infected individuals increased from 3.4% in 1995-1998 to 12.4% in 1999-2000 (Little, *N Engl J Med,* 2002; Grant, *JAMA,* 2002). Further, it is now known that HIV superinfection is possible in humans (Jost, *N Engl J Med,* 2002; Goulder, *N Engl J Med,* 2002), raising additional concerns regarding transmission of drug-resistant virus between those already infected.

Conclusions

The overall prevention message for HIV-infected patients is clear: HIV-infected persons must practice safe sex and other risk-reduction measures to protect themselves and others from new infections, and they must adhere to antiretroviral therapy both to benefit themselves and to prevent development of resistant virus that can be transmitted to others. HIV care settings provide an ideal location for risk assessment and prevention counseling. Additional work is needed to define optimal strategies for delivering risk reduction counseling in these settings. However, a number of basic recommendations can be made:

1) Training in risk reduction counseling should be made more available to physicians and other health care workers; 2) More time should be allocated in the typical office/clinic visit to discuss prevention measures with patients; and 3) Use of referrals and other strategies for providing prevention counseling to patients should be optimized in clinical practice.

Suggested Reading

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Perspective
Strategic Approaches to Antiretroviral Treatment

A useful clinical framework for decision making in antiretroviral treatment is to consider treatment options and goals at 4 decision points: initial therapy, early treatment failure, late treatment failure with high CD4+ cell count, and late treatment failure with low CD4+ cell count. Basic principles appropriate to these decision points are discussed. For initial treatment, the goal is to suppress viral replication for as long as possible. In early failure, the aim is to achieve resuppression of viral replication. For late treatment failure in patients with high CD4+ cell counts with limited treatment options, a reasonable approach is to be cautious in making treatment changes, since sustained incomplete suppression is not associated with immunologic collapse. In patients with late treatment failure and lower CD4+ cell counts, a reasonable strategy is to maintain some form of antiretroviral therapy until new drug classes become available. These basic approaches are reviewed in this article, with findings reported at the recent 10th Conference on Retroviruses and Opportunistic Infections discussed in light of this strategic framework. This article summarizes a presentation given by Diane V. Havlir, MD, at the March 2003 International AIDS Society–USA course in Los Angeles.

Selection of an antiretroviral treatment regimen requires consideration of a variety of factors, including potency, safety, and tolerability of regimens; resistance patterns; and the clinical and immunologic condition of the patient. A useful clinical framework for decision making is to consider treatment options and goals at 4 decision points: initial therapy; early treatment failure, with treatment failure defined as loss of viral suppression; late treatment failure with high CD4+ cell count; and late treatment failure with low CD4+ cell count (see Table 1). Decisions and recommendations regarding which regimens to use at these points should be continuously reexamined on the basis of emerging data. Several studies reported at the recent 10th Conference on Retroviruses and Opportunistic Infections (CROI) add to the body of data that needs to be considered in formulating optimal treatment strategies.

Initial Treatment

The guiding principle for selection of an initial antiretroviral regimen may be best formulated as *choose a regimen to avoid treatment failure.* Thus, the initial regimen should provide optimal antiviral potency, facilitate adherence, and minimize toxicity. Currently, optimal potency is regarded as reduction in plasma HIV-1 RNA levels to less than 50 copies/mL. Although this cut-off point initially reflected assay detection limits, it has since been found that reaching this level has real biologic significance in terms of producing durable suppression.

Among the many possible combinations of antiretroviral drugs, Dr Havlir noted that in her opinion a few have emerged as leading candidates for initial therapy based on available data. For triple-drug regimens, these include efavirenz or lopinavir/ritonavir plus a backbone of lamivudine with either zidovudine or tenofovir. Although some 4-drug regimens may achieve optimal viral suppression more rapidly than do 3-drug regimens, the overall superiority of a 4-drug approach remains unproven, and the associated increase in toxicity is an important consideration. Although potent antiretroviral therapy has traditionally involved 3-drug regimens, some current or future 2-drug combinations may achieve optimal viral suppression. One ongoing large comparative trial (ACTG 5142) is evaluating potency, toxicity, and tolerability of initial treatment with an efavirenz-based 3-drug regimen, a lopinavir/ritonavir-based 3-drug regimen, and the dual combination of efavirenz plus lopinavir/ritonavir.

The 96-week follow-up of a tenofovir trial reported at the 10th CROI provides some important information regarding use of tenofovir-including regimens in initial therapy. Two primary concerns with using tenofovir in an initial regimen were the modest CD4+ cell count increases observed with single-drug treatment in initial studies in treatment-experienced patients and the adverse effects that occurred when the drug was used in long-term combination treat-

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Table **1.** Treatment Principles at Major Decision Points in Antiretroviral Therapy

Decision Point	Treatment Principle
Initial Treatment	Choose a regimen to avoid treatment failure and suppress viral replication for as long as possible
Early Treatment Failure	Treat aggressively to achieve resuppression of viral replication
Late Treatment Failure*, High CD4+ Cell Count	Continue treatment with monitoring
Late Treatment Failure, Low CD4+ Cell Count	Maintain antiretroviral therapy until new drugs become available

*No suppressive antiretroviral regimen available

ment. In the trial reported by Staszewski et al, 600 treatment-naive patients received efavirenz/lamivudine plus either tenofovir once daily or stavudine twice daily for 144 weeks. Data at 96 weeks indicate comparable virologic response to the 2 regimens, with intent-to-treat analysis showing plasma HIV-1 RNA reduction to less than 50 copies/mL in 78% of the tenofovir arm and 74% of the stavudine arm. CD4+ cell count responses were robust in both arms, with increases of 261 and 266 cells/µL for the tenofovir and stavudine arms, respectively. A lower frequency of toxicities associated with mitochondrial dysfunction was observed in the tenofovir arm, with peripheral neuritis/neuropathy occurring in 3% of patients on tenofovir versus 10% of patients on stavudine (P < .001), investigator-defined lipodystrophy in 1% versus 12% (P < .001), and investigator-defined lactic acidosis in 0% versus 1%. No pancreatitis was observed. The relative risk of these combined adverse events was 5.5 (95% confidence interval, 3.0-10.3) in the stavudine arm. Total limb fat as measured by dual x–ray absorptiometry was significantly greater in the tenofovir group at 96 weeks; although no longitudinal analysis was performed, these data suggest less peripheral fat loss in the tenofovir group. Adverse lipid changes were also less common in tenofovir-treated patients. Increases from baseline in fasting triglyceride and total cholesterol levels were lower at 96 weeks in the tenofovir arm than in the stavudine arm (5 mg/dL vs 103 mg/dL and 30 mg/dL vs 51 mg/dL, respectively; both P < .001). New lipid-lowering therapy was prescribed in fewer patients in the tenofovir arm than in the stavudine arm (2% vs 10%, P < .001). The findings in this trial thus alleviate some of the concerns regarding up-front use of tenofovir on the basis of antiviral potency and reductions in some important long-term toxicities compared with the other regimen in the study.

The 48-week findings of a large international study presented at the 10th CROI also highlight the need to take tolerability and toxicity into account in overall assessment of antiviral effectiveness (van Leth, 2003). In this trial, 1216 treatment-naive patients received a dual nucleoside reverse tran-

scriptase inhibitor (nRTI) backbone plus efavirenz, plus nevirapine once daily, plus nevirapine twice daily, or plus efavirenz and nevirapine. Antiretroviral potency was not higher in the patients receiving both efavirenz and nevirapine and was comparable across the 4 arms in terms of proportions of patients achieving viral suppression. Toxicity and treatment discontinuations were significantly higher in the nevirapine plus efavirenz arm, resulting in a significantly higher treatment failure rate in this arm compared with the other 3 arms. Liver-associated adverse events were also higher in the nevirapine once-daily (13.2%) and twice-daily (7.8%) arms compared with the efavirenz arm (4.5%). Reduced tolerability or increased toxicity may require withdrawal of a drug or regimen, and the ability to remain on suppressive treatment is an important measure of the effectiveness of the treatment.

Early Treatment Failure

Precisely what level of viral rebound should be considered indicative of virologic failure meriting a treatment switch appears to differ among practitioners, with many feeling that a plasma HIV-1 RNA level in the thousands of copies/mL constitutes the threshold for failure. To make things more complex, it is possible that with different treatment regimens, thresholds of virologic failure that should trigger treatment switches could differ among regimens. Some guidance in this regard is provided by studies of intermittent viremia (viral "blips") during therapy, which can be observed in up to 40% of patients receiving treatment. Studies performed with an ultra-sensitive assay with limits of detection of 2 HIV-1 RNA copies/mL have shown that patients with blips reaching hundreds of copies/mL generally have higher overall plasma HIV-1 RNA levels than those without blips, although the HIV-1 RNA level remains below 50 copies/mL at all times and the blips are not associated with subsequent loss of viral suppression (Figure 1) (Havlir et al, *JAMA,* 2001). In contrast, a Swiss study has shown that patients exhibiting blips with zeniths between 1000 and 10,000 copies/mL have a higher chance of virologic failure than do patients without

blips. It is clear that achieving a nadir of HIV-1 RNA level below 50 copies/mL is important for treatment success. However, single blips in HIV-1 RNA level should not trigger therapy switches, but sustained low-level viremia in the range of 100 to 1000 copies/mL of HIV-1 RNA signals virologic failure.

It has become clear that initial viral breakthrough under treatment with some regimens is not due to viral resistance to all drugs in the regimen. This is an encouraging finding, since it suggests that not all drugs in a previously successful regimen need to be replaced, permitting a more judicious approach to treatment change and drug substitution. For example, many studies have now shown that virus resistant to lamivudine is the first to emerge in patients receiving regimens including this drug in combination with a protease inhibitor (PI) and another nRTI such as zidovudine. Thus, in many cases it may be possible to substitute another active drug for lamivudine instead of changing the entire regimen, although the validity of this approach has not yet been verified.

These and other factors suggest that approaches to early treatment failure should include careful monitoring to permit initial detection of viral breakthrough and increase chances for a successful change in treatment. The most important part of the initial response to treatment failure is to determine the reason for failure, such as emergence of resistance, inadequate adherence, toxicity, or preexistance of resistance (eg, through recent infection with drug-resistant virus). Resistance testing is of clear value in this setting to guide selection of salvage treatment. In effect, the guiding principle in this setting is to *treat early virologic failure aggressively.* Reestablishing viral suppression will optimize immune responses, limit broad cross-resistance, and preserve subsequent treatment options. With the many treatment options currently available, resuppression should be achievable in most cases. Examining examples of sequencing therapy involving popular candidates for first-line treatment, the drug mutation most likely to first emerge under an efavirenz/lamivudine/zidovudine regimen is the K103N efavirenz-associated mutation or the M184V lamivudine-associated mutation (or

both). Replacement of the affected drug only may preserve future options but risk the possibility that resistant sub-populations not detectable on drug resistance testing will emerge. On the other hand, replacement of both the nonnucleoside reverse transcriptase inhibitor (NNRTI) and lamivudine may be unnecessary if detectable resistance to only a single drug is present. Since resistance to efavirenz confers broad cross-resistance to other NNRTIs, this drug should be replaced with a PI. If resistance is due to the single M184V lamivudine mutation, activity of most other nRTIs is retained, and substitution of tenofovir or abacavir for lamivudine is a reasonable option. In the case of the lopinavir/ritonavir/lamivudine/zidovu-dine regimen, early resistant isolates almost invariably have only the lamivu-dine M184V mutation. Thus, substitu-tion of tenofovir or abacavir is a reason-able option that also permits sparing of the NNRTI class for later use.

A recent trial comparing lopinavir/ritonavir-based and nelfinavir-based regimens provides an instructive exam-ple of both the importance of antiviral potency in limiting resistance and the rapidity with which resistant viral popu-lations can become majority popula-tions and result in treatment failure. In this study, the regimen of lopinavir/ritonavir/lamivudine/stavudine produc-ed a greater rate of virologic suppres-sion than did nelfinavir/lamivudine/stavudine. Lamivudine resistance was much higher in the nelfinavir arm than in the lopinavir/ritonavir arm (29% vs 7%) over 96 weeks of treatment (Kempf, 10th CROI, 2003). In the nelfi-navir arm, lamivudine resistance was observed in significant proportions of isolates within 3 to 6 months after the last measurement of plasma HIV-1 RNA level showing suppression to below assay detection limits, highlighting the need for frequent monitoring to detect resistance in a timely manner.

Late Treatment Failure with High CD4+ Cell Count

The guiding principle in treatment in patients with virologic failure of 2 or 3 drug classes who have an elevated CD4+ cell count and no available regi-men that could achieve virologic sup-pression may be to *continue treatment with monitoring*. The treatment regimen may be optimized, but there should be no unnecessary increases in toxicity and adding single new drug classes should be avoided. It is important to note that recent data suggest that there is no benefit of a 4-month structured treatment interruption (STI) in this pop-ulation of patients.

This approach of continuing treat-ment while monitoring is based in part on data showing that immunologic col-lapse is not necessarily accompanied by persistent viremia at certain levels. One analysis has shown that maintaining partial suppression of plasma HIV-1 RNA level to between 10,000 and 20,000 copies/mL is associated with sta-ble increases in CD4+ cell count through 4 years of such incomplete viro-logic suppression (Deeks et al, *AIDS,* 2002). The downside to such an approach is that incomplete viral sup-pression is associated with increasing viral resistance to the drugs used. Thus, continued treatment with a regimen that provides incomplete viral suppres-sion is reasonable if CD4+ cell count declines are not observed, with benefits including the prevention of a greater, "wild-type" viral rebound and mainte-nance of a viral population that has less replicative fitness and, perhaps, less vir-ulence. The primary risk associated with continuing such treatment is the evolution of resistant virus that may result in loss of future treatment options.

The recently reported findings on STI from the Community Programs for Clinical Research on AIDS (CPCRA) study 064 have dampened enthusiasm for this strategy in treatment-experi-enced patients. Prior studies have sug-gested that STI is associated with rever-sion of virus to wild-type and thus return of susceptibility to previously used drug classes. In the CPCRA study,
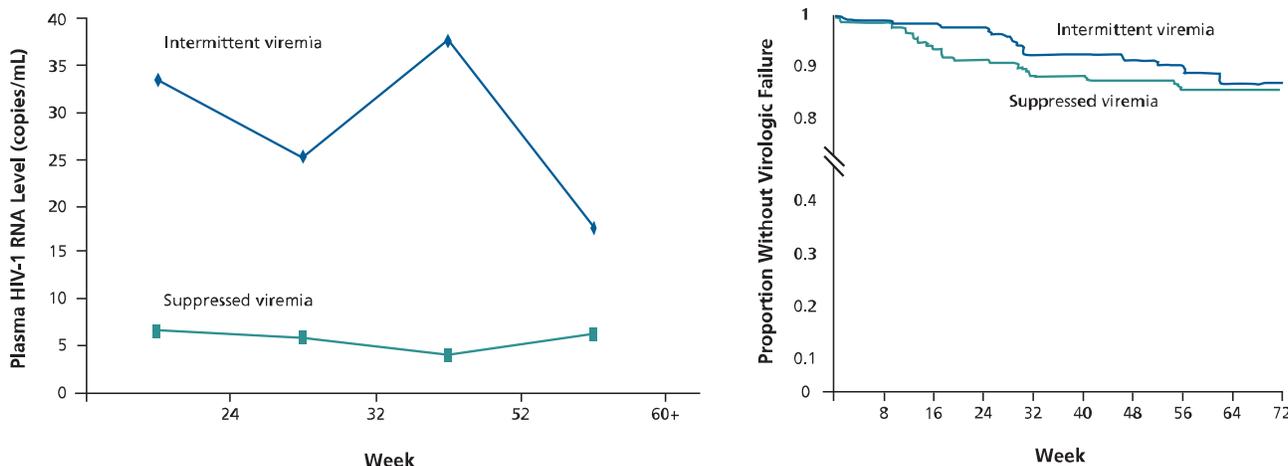

Figure **1.** Plasma HIV-1 RNA level in patients with and without intermittent viremia (left) and proportions of patients remaining free of viro-logic failure (right). Adapted with permission from Havlir et al, *JAMA,* 2001.

270 patients with multidrug-resistant virus were randomized to a 4-month STI or no interruption and treatment with an optimized salvage regimen selected on the basis of phenotypic and genotypic evaluation (Lawrence, 10th CROI, 2003). Patients had a mean CD4+ count of 180 cells/µL and mean plasma HIV-1 RNA level of 5.0 $\log_{10}$ copies/mL, and 48% had triple-class drug resistance. Salvage regimens consisted of a mean of 3.6 to 3.8 drugs, including 2.7 to 2.8 active drugs, with an "active drug" defined as one to which virus was susceptible or had intermediate susceptibility on the basis of either phenotypic or genotypic assays. There was no difference between groups with regard to change in plasma HIV-1 RNA level, with changes of +0.31 $\log_{10}$ in the STI group and –0.75 $\log_{10}$ in the no-STI group at 4 months and –0.76 and –0.66 $\log_{10}$, respectively, at 12 months. Mean changes in CD4+ cell count were better in the no-STI group, with changes of –53 cells/µL in the STI group versus +37 cells/µL in the no-STI group at 4 months and +7 cells/µL versus +42 cells/µL, respectively, at 12 months. Most disconcerting was the observation of 22 clinical endpoints (opportunistic disease or death) in the STI group versus 12 in the no-STI group (hazard ratio, 2.6; $P = .01$) over mean follow-up of 11.6 months. Although most of these events consisted of candidal esophagitis, there were also cases of *Pneumocystis carinii* pneumonia (also now known as *Pneumocystis jiroveci* pneumonia) and cryptosporidiosis; 8 patients in each group died. These results suggest that STI poses significant risk of clinical disease progression in patients at this stage of HIV infection.

Although enthusiasm for STI has thus been dampened, there are encouraging data on the possibility of a strategy of partial treatment interruption, in which 1 or 2 drugs in a multidrug regimen are discontinued and partial viral suppression is maintained. The rationale for this strategy is that control of wild-type virus can be maintained with the remaining drugs in the regimen, thereby preserving immune function and reducing cumulative resistance. As reported by Deeks at the 10th CROI, although 3 of 15 patients discontinuing PI treatment but remaining on nRTI
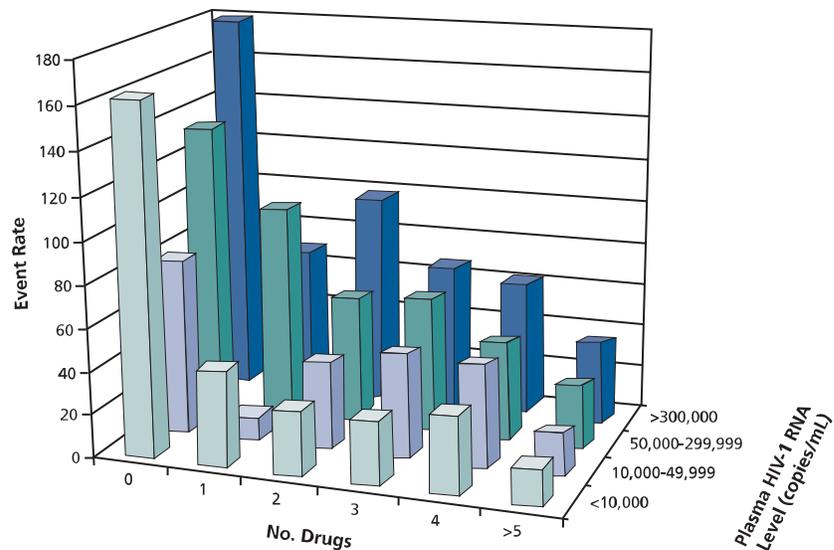
Figure 2. Clinical event rate according to number of drugs used and plasma HIV-1 RNA level (copies/mL) in EuroSIDA study. Adapted with permission from Miller et al, *J Infect Dis,* 2002.

treatment exhibited a consistent increase in viremia of greater than 0.5 $\log_{10}$ copies/mL over 24 weeks, the overall mean change in plasma HIV-1 RNA level following PI interruption in the 15 patients was only 0.005 $\log_{10}$ copies/mL per week. Conversely, 5 of 5 patients in whom nRTI treatment was interrupted while PI treatment was maintained exhibited an immediate and persistent increase in viremia of greater than 0.5 $\log_{10}$ copies/mL, with the mean change being an increase of 0.05 $\log_{10}$ copies/mL per week. Systematic studies are needed to determine if a partial treatment interruption strategy can be incorporated into clinical practice.

Late Treatment Failure with Low CD4+ Cell Count

Based on currently available data, a principle of treatment in patients with late treatment failure and low CD4+ cell count is to *continue antiretroviral therapy*. It has been shown in numerous settings that continuation of some therapy is better than stopping therapy in terms of delaying clinical disease, and continued treatment can be used as a temporizing measure until new antiretroviral drugs become available. The EuroSIDA study, for example, has shown that use of 1 or more antiretroviral drugs protects against clinical progression to AIDS or death, even in

patients with CD4+ counts less than 50 cells/µL and very high plasma HIV-1 RNA levels (Figure 2) (Miller, *J Infect Dis,* 2002). There is hope in this approach, since data from initial studies on new antiretroviral classes have been encouraging.

The use of STI in this setting remains controversial. A study by Katlama et al presented at the 10th CROI indicates a pronounced benefit of STI and use of a multidrug regimen consisting of 3 or 4 nRTIs, an NNRTI, and 2 PIs plus ritonavir. Hydroxyurea was included in 71% of the patients. In this trial, 68 patients with median plasma HIV-1 RNA level of 5.3 $\log_{10}$ copies/mL and median CD4+ count of 27 cells/µL underwent either an 8-week STI or no STI and received the multidrug regimen. Median reductions in plasma HIV-1 RNA level were 0.29 $\log_{10}$ copies/mL in the no-STI group versus 1.1 $\log_{10}$ copies/mL in the STI group at 24 weeks ($P = .01$) and 0.37 $\log_{10}$ copies/mL versus 0.80 $\log_{10}$ copies/mL, respectively, at 48 weeks. CD4+ cell count increases were markedly better in the STI group than in the no-STI group, increasing by 51 versus 7 cells/µL, respectively, at 24 weeks and by 69 versus 7 cells/µL, respectively, at 48 weeks. Predictors of virologic success in the study were reversion to wild-type virus after STI (relative hazard, 12.4), optimization of drug blood concentrations (relative hazard, 5.6), and use of

lopinavir/ritonavir (relative hazard, 6.0). There were clinical events in 10 patients in the STI group and in 6 patients in the no-STI group. It is unclear why STI appeared beneficial in this study but not in the CPCRA study in less-advanced patients. Differences between the 2 studies include the lower CD4+ cell count in the Katlama et al study; potential differences in the number of active drugs used; use of hydroxyurea differentially among treatment arms in the Katlama et al study; and the difference in STI duration (8 weeks in the Katlama study vs 16 weeks in the CPCRA study). It also appeared that in the GIGHAART study, more patients in the STI arm stayed on 6 or more drugs (47%) compared with the no-STI arm (22%). Further data on STI in this setting are needed before it can be adopted as a routine treatment strategy.

Presented by Dr Havlir in March 2003. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Havlir in June 2003.

Suggested Reading

Deeks SG. When to switch antiretroviral therapy. [Abstract 188.] 10th Conference on Retroviruses and Opportunistic Infections. February 10-14, 2003; Boston, Mass.

Deeks SG, Barbour JD, Grant RM, Martin JN. Duration and predictors of CD4 T-cell gains in patients who continue combination therapy despite detectable plasma viremia. *AIDS.* 2002;16:201-207.

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Kempf D, King M, Bauer E, et al. Comparative incidence and temporal accumulation of PI and NRTI resistance in HIV-infected subjects receiving lopinavir/ritonavir or nelfinavir as initial therapy. [Abstract 600.] 10th Conference on Retroviruses and Opportunistic Infections. February 10-14, 2003; Boston, Mass.

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Van Leth F, Hassink E, Phanuphak P, et al. Results of the 2NN study: A randomized comparative trial of first-line antiretroviral therapy with regimens containing either nevirapine alone, efavirenz alone or both drugs combined, together with stavudine and lamivudine. [Abstract 176.] 10th Conference on Retroviruses and Opportunistic Infections. February 10-14, 2003; Boston, Mass.

Special Contribution

Questions to and Answers from the International AIDS Society–USA Resistance Testing Guidelines Panel

In 1996 the International AIDS Society–USA convened an international panel of experts in HIV drug resistance and clinical management to develop guidelines for the clinical use and limitations of resistance testing. Since then the International AIDS Society–USA Resistance Testing Guidelines Panel has developed and regularly published its recommendations. The latest panel recommendations appear in the July 1 issue of Clinical Infectious Diseases.

We periodically pose questions to the panel relating to clinical elements of resistance testing that have been collected from HIV practitioners across the nation. We are happy to feature the latest edition in this issue of Topics in HIV Medicine. *It is our hope that addressing these issues will help guide your treatment strategy decisions regarding resistance testing.*

The International AIDS Society–USA Resistance Testing Guidelines Panel consists of Martin S. Hirsch, MD; Françoise Brun-Vézinet, MD, PhD; Bonaventura Clotet, MD, PhD; Brian Conway, MD; Daniel R. Kuritzkes, MD; Richard T. D'Aquila, MD; Lisa M. Demeter, MD; Scott M. Hammer, MD; Victoria A. Johnson, MD; Clive Loveday, MD, PhD; John W. Mellors, MD; and Douglas D. Richman, MD.

On a related note, the International AIDS Society–USA Drug Resistance Mutations Group will publish its update later this year in Topics in HIV Medicine. *The current version is available at www.iasusa.org.*

Question 1: Are there some patient populations for whom you would not perform resistance testing (eg, substance users, nonadherent patients) and rely only on clinical indicator as a screening measure?

Dr D'Aquila: No. Resistance testing is an adjunct that can help to choose which antiretroviral drugs to use. The decision to start or change therapy must be based on other factors (CD4 + cell count, viral load, or clinical manifestations). In any situation when antiretroviral therapy is going to be changed, and in many situations when therapy is to be started, I would order a resistance test. There is no other way in which to know whether a patient has a fully wild-type drug-susceptible virus or to gauge the magnitude and type of drug-resistant virus predominating in that patient at that time. We no longer prescribe what should work best for most patients who are in certain circumstances. We can now prescribe the best choices for each individual patient at any point in the course of his or her disease. Resistance testing is one of the tools that can help us to do that, and I use it whenever a patient has access to it.

Question 2: In the setting of genotypic testing showing only minor mutations, would you change the drug regimen?

Dr Conway: No, if the level of viremia and CD4 + cell count suggests continuing therapy, I would not change only on the basis of minor mutations being present. I would follow the level of virologic suppression that is being maintained, ensure adherence to the regimen is optimal, and have a low threshold for repeating resistance testing if progressive virologic breakthrough is observed. If changes in viral load or CD4 + cell count suggest a change in the regimen is indicated, I would select the most effective combination that would also favor patient adherence, taking all the resistance mutations into consideration (even the minor ones) that are present at that time.

Question 3: A patient's 3-drug regimen is starting to fail. Resistance testing results show mutations associated with resistance to only 1 of the 3 drugs. Would you replace just the 1 drug?

Dr Mellors: I would not change just one drug in a failing regimen as the only

alteration in patient management. I would try to determine why the regimen failed. Without this understanding, the next regimen might fail also. Was the reason inadequate regimen potency, advanced disease (low CD4 + cell count and high HIV-1 RNA levels), incomplete regimen adherence, drug intolerance, pre-existing resistance, or inadequate drug exposure from malabsorption or negative drug-drug interactions? I would probably increase the potency of the regimen as well as its convenience. There is no set formula for managing drug failure, and therapy changes must be individualized.

Question 4: Is there a point in time after which resistance testing in drug-naive patients may not be useful (ie, time after seroconversion)?

Dr Conway: Probably after 18 to 24 months. After this time, it is likely that resistance mutations that may have been present initially have been outcompeted by wild-type isolates in the absence of drug pressure. In such patients, I would favor performing a resistance test if appropriate virologic suppression is not achieved in the first 4 to 6 weeks of therapy. This is enough

time to allow for the selection of a minority species of resistant viruses that could have been present in the baseline viral swarm.

Question 5: Can therapeutic drug monitoring combined with genotypic and phenotypic testing improve care outcomes? If so, why is it taking so long to incorporate therapeutic drug monitoring (TDM) into practice in the United States, compared with in Europe?

Dr Demeter: TDM has been proposed as potentially useful, primarily to optimize levels of protease inhibitors (PIs). Retrospective data suggest that having higher trough levels of PIs is associated with improved virologic outcome. In addition, retrospective data correlating inhibitory quotient (IQ = trough level/IC_{50}) with plasma HIV-1 RNA suppression indicate that IQ may be a better predictor of outcome than trough level or IC_{50} alone. However, it is still not clear whether TDM to increase PI dose and optimize IQ is a useful prospective strategy for managing treatment-experienced patients. One problem is the variable quality of current TDM laboratories and insufficiently rigorous standards to evaluate their performance in measuring antiretroviral drug levels. The second problem is that the VIRADAPT trial, the one prospective study that has evaluated TDM in treatment-experienced patients, showed no benefit of TDM. A weakness of this trial is that PI drug levels, rather than IQs, were used to adjust dosing (ie, the targeted drug levels were not chosen to exceed the IC_{50}). TDM strategies are being evaluated in a number of clinical trials currently, but cannot be recommended at this time for routine clinical use.

Question 6: Should lamivudine be used even if the M184V mutation is present, based on the assumption that this mutation makes the virus less "fit"?

Dr Kuritzkes: To date this remains a hypothetical rationale for maintaining lamivudine in a failing regimen. There are, as yet, no compelling data for or against this strategy.

Question 7: What is the current practice in antiretroviral cycling to decrease the emergence of drug resistance?

Dr Clotet: Cycling of drugs is not currently used as a strategy outside of clinical trials. However, many patients on highly active antiretroviral therapy (HAART) who undergo a simplification or switch for intolerance or side effects while having plasma HIV-1 RNA levels below detection limits are in fact experiencing preemptive switching. This antiretroviral cycling might decrease the risk of emergence of resistance. The SWATCH study[1] showed that the virologic outcome was better with preemptive switching and drug alternating than with the current standard of care. In addition, this approach had similar adverse events and adherence to that observed with currently prescribed fixed HAART. Preemptive switching and alternating of antiretroviral regimens with different drug-resistance profiles theoretically might extend the overall long-term effectiveness of the first- and second-line drug options without adversely affecting either patients' adherence or quality of life, assuming tolerance and toxicity do not adversely affect outcome.

Question 8: For a pregnant woman who emigrated from Africa to the United States and is infected with HIV-2, which resistance and HIV-2 quantitative tests should be used and what is the availability of such tests in the United States?

Dr Loveday: HIV-2 originated in West Africa and is found predominantly in patients in this region and in countries that have colonial links to it. Clinically, HIV-2 appears to be less pathogenic than HIV-1, with slower progression to symptomatic disease and death; overall its numerical contribution to the AIDS pandemic is minor. Nevertheless, it does contribute to morbidity and mortality. At present there are approximately 100 reported cases of HIV-2 in the United States. Genetically, HIV-2 has approximately 40% homology with HIV-1, and this can lead to difficulties in interpretation of laboratory diagnostic tests. This is further confounded by the increasing prevalence of dual HIV-1/HIV-2 infections in patients originating from West Africa.

In the case described, the clinical diagnosis of HIV-2 should first be reviewed, as the local diagnostic tools may not be reliable. This is best carried out using a commercial dual-screening enzyme immunoassay (EIA) to assess reactivity and confirmed using an HIV-2–specific EIA or HIV-2 Western blot assay and polymerase chain reaction (PCR). The goal is not only to confirm the diagnosis but also to confirm the exclusion of dual infection with HIV-1 and HIV-2. The confirmation of dual infection has major implications for future management of the patient and her offspring. For example, dual infection requires a more aggressive strategy, selective use of nonnucleoside reverse transcriptase inhibitors (NNRTIs, which are not effective against HIV-2), and cautious diagnosis of mother-to-child transmission that may theoretically include both or either virus. HIV-1 is more readily transmitted from mother to child than is HIV-2.

I know of no US Food and Drug Administration–approved assays for PCR-based diagnosis, or for quantification of HIV-2 viral load and resistance determination. In the United Kingdom, the Public Health Laboratory Service (soon to be renamed the Health Protection Agency: www.phls.co.uk) can furnish advice and some "home brew" PCR assays for diagnosis, quantification, and genotypic analysis of reverse transcriptase and protease genes on an ad hoc basis. However, these are not clinically routine tests.

Question 9: Is there any research being conducted into ways to "reverse" drug resistance (eg, the association between the M184V mutation and enhanced sensitivity to zidovudine, and "hypersensitive" viral strains)? Are there any novel molecules that may be able to cause similar results?

Dr Kuritzkes: Although some drugs select resistance mutations that sensitize HIV to other drugs, when confronted with both drugs simultaneously the virus inevitably finds an alternative pathway, leading to evolution of dual- (or

multi-) drug resistance.

Question 10: When the M184V mutation is present in a patient who is receiving lamivudine and zidovudine, are both drugs effective? Does zidovudine reverse resistance to lamivudine caused by M184V? In addition, given the rapid emergence of resistance to lamivudine, should lamivudine be reserved as a "booster" for other nucleoside reverse transcriptase inhibitors (nRTIs) for which the M184V mutation increases viral sensitivity?

Dr Kuritzkes: Zidovudine resistance does not reverse lamivudine resistance. When zidovudine and lamivudine are used together in the setting of treatment failure, eventually dually resistant viruses are selected by emergence of additional nRTI-associated mutations (NAMs). The goal of therapy is complete virus suppression, not selection of particular mutations. There are no data at present to favor a strategy that defers use of lamivudine for later regimens.

Question 11: For patients who discontinue antiretroviral therapy independently, is there any advantage in reinstituting therapy before sampling for genotypic resistance?

Dr Brun-Vézinet: The question of whether treatment interruptions, either in patients with controlled viremia or in patients in whom therapy is failing, lead to virologic or immunologic benefit remains controversial. The optimized use of resistance assays during treatment interruptions, either structured or self-directed, is unknown. In patients interrupting treatment when HIV-1 RNA level is below detection, it could be appropriate to reintroduce the same antiretroviral treatment without performing resistance testing. If this regimen contained NNRTIs (nonnucleoside reverse transcriptase inhibitors), it is recommended to temporarily replace NNRTIs with other agents prior to complete discontinuation of the therapy, as drug resistance could emerge when NNRTI levels are subtherapeutic.

In highly experienced patients in whom antiretroviral therapy is failing, the treatment interruption may lead to

reversion from resistant viruses to a dominant plasma drug-sensitive wild-type virus population with an improved response to the subsequent reinstitution of salvage therapy. This concept of improving outcomes with treatment interruption before salvage therapy is controversial.[2,3] In patients interrupting therapy while in virologic failure, the resistance profile should be evaluated just before stopping treatment. In a small number of patients, a durable response to salvage therapy was observed among those who initiated a subsequent regimen containing at least a single agent to which their virus was fully susceptible before interruption.[4]

Question 12: It has been suggested that resistance testing is useful in primary infection. What is the prevalence cutoff to make this prediction? The studies by Richman[5] and Little[6] show the cutoff as greater than 20%, but one study showed 11% in 10 US cities. Is 11% high enough? If prevalence decreases in later years, do you stop conducting resistance tests in primary infection?

Dr Richman: There is no precise criterion to define what prevalence of transmitted drug resistance is an indication for testing of recently infected patients. Little et al[6] documented the adverse impact of transmitted drug resistance on treatment efficacy. Various studies in Europe and North America have reported rates between 5% and 20% over the past several years. Although the rates vary by location and year, the recent IAS–USA Resistance Guidelines Panel[7] concluded that any rate in this range indicated resistance testing for recently infected patients. If treatment is selected, then the components of the regimen can be optimized. If treatment is deferred, then documentation of whether resistant virus was transmitted is available for future use. Accumulating data suggest that transmitted drug resistance persists for months to years. Thus the rapid reversion of resistant virus is not likely to provide misleading information; however, drug-resistant virus could be archived but no longer circulating in the blood of a patient who defers treatment for years. A significant

decline in transmitted drug resistance might diminish the indications for obtaining drug-resistance testing in the future, but unfortunately this is an unlikely prospect.

Question 13: In a drug-naive patient diagnosed last year, resistance testing showed M41L and L210W without other mutations and with no evidence of phenotypic resistance. Could these mutations indicate that the patient was actually infected with a strain fully resistant to zidovudine or stavudine, but that additional mutations are in the "archived" strain and cannot be detected? Should this possibility be taken into account in choosing the first regimen?

Dr Demeter: It is certainly possible that more highly resistant minority variants are present and not detectable by the resistance test. It is reasonable to take this consideration into account when designing an initial regimen for this patient.

Question 14: With more reports on the persistence of NNRTI mutations, should resistance testing be done for chronically infected patients?

Dr Johnson: The IAS–USA panel has recommended resistance testing be done on patients with established HIV infection of up to 2 years' duration and perhaps longer, as some mutations conferring resistance may persist for prolonged periods of time (ie, more than 12 months).[7] We also recommend resistance testing in subjects initiating therapy who have chronic HIV infection of more than 2 years if regional data are available showing genotypic or phenotypic drug-resistance prevalence is greater than 5%. My own clinical experience (and that of other practitioners) is that some patients can indeed harbor NNRTI resistance mutations in their blood while not on any therapy, based on both genotypic and phenotypic assay results. In some instances, the patients are reportedly drug-naive, suggesting that they were infected with drug-resis-

tant viral variants. In other cases, NNRTI-resistant viral variants have been found in chronically infected patients who have been off NNRTI therapy for many months to years, suggesting that persistence of these mutant viruses can occur and may impact the success of subsequent therapeutic regimens. This suggests that HIV drug-resistance testing may be increasingly important to consider in subjects with chronic HIV infection who are either drug-naive or drug-experienced, particularly in regions where patient populations are heavily exposed to antiretroviral agents (including NNRTIs) and when planning HAART therapy that includes a drug from the NNRTI class.

Question 15: Can replication capacity be helpful in judging when to start HIV therapy?

Dr Richman: The measurement of replication capacity has been shown to be a predictor of the benefits conferred by drug-resistant virus on the discordant response.[8] Discordance is defined as a sustained CD4+ cell count elevation despite incomplete suppression of HIV-1 RNA levels with chemotherapy. It is likely that changes in replication capacity may impact pathogenesis and natural history in other settings; however, the utility of the measurement of this parameter for clinical management at present requires further investigation.

Question 16: If virus in a patient is resistant to all currently available antiretroviral drugs, is it better to stay on a suboptimal regimen or to discontinue drug therapy completely until a better treatment comes along?

Dr Hammer: It is difficult to provide an answer to this question that fits all patient circumstances. The data available suggest that ongoing benefit may be provided by regimens to which multidrug resistance has developed. The drop in CD4+ cell count and rise in plasma HIV-1 RNA levels that occur after drug discontinuation in this setting reflect the fact that antiviral activity may still be present or that a viral replicative defect may be conferred by some of the drug-

resistance mutations. Conflicting data were presented at the recent 10th Conference on Retroviruses and Opportunistic Infections in Boston concerning the efficacy of drug interruptions in the setting of multidrug resistance. The CPCRA 064[2] study did not demonstrate a benefit but the ANRS GIGHAART[3] study did. These contrasting results may be explained by the patient populations studied and the lengths of treatment interruptions, which differed in the 2 studies. Although there might not be a consensus in the field, in general, treatment interruptions should not be a routine clinical strategy in the management of the treatment-experienced patient with multidrug resistance at the present time.

Question 17: Given the increasing transmission of resistant virus as reported by Little and colleagues[6], which regimen would you recommend for initial treatment in the setting of very limited resources and the inability to genotype newly diagnosed patients?

Dr Clotet: The most frequently transmitted drug-resistant viruses are those resistant to NNRTIs. Thus recently infected patients should not be started on a regimen including that class of drugs without a drug-resistance test. Since the most common mutations to the other drug classes found in recently infected patients are at codons 118, 184, 215, and 103 of the reverse transcriptase gene and codons 82 and 90 of the protease gene[6], I might recommend starting with lopinavir/ritonavir plus tenofovir plus abacavir. This approach may be active enough to control viral replication even if the patient's virus harbors all the above-mentioned mutations.

Dr D'Aquila: This might not be a feasible strategy over a long term. Today, viruses resistant to a relatively new drug might be less common among recently infected subjects. However, this may change over an unpredictable time span as resistant virus emerges after wider use of that new drug. Resistance testing may also prove less costly than frequent viral load/CD4+ cell count monitoring that might be an alternative strategy to

ensure an adequate response. My first line choices, however, if resistance testing is not available for technical reasons (for example, the laboratory fails to get a result) or due to unavoidable lack of access would be based on ease of adherence and tolerability. Options that I would suggest include lamivudine along with either stavudine, zidovudine, or tenofovir and either efavirenz, nevirapine, nelfinavir, or lopinovir/ritonavir. I would monitor viral load at least monthly over the first 6 months.

Question 18: How useful is resistance testing in a patient almost certainly infected more than 6 to 12 months previously who is treatment-naive? Is it possible to reliably detect archived virus or is testing in this case a waste of money?

Dr Loveday: The initiation of antiretroviral therapy is a crucial decision made between patient and physician, as it currently involves a life-long commitment by the patient to daily drug therapy. Failure of such treatment due to viral resistance to the drug(s) can have disastrous effects on the patient, both physically in terms of limiting future treatment options and psychologically in terms of the patient's future confidence in his or her clinical management. Resistance tests have a limited sensitivity, and because resistance prevalence in specific communities remained very low, the benefits (in terms of cost-effectiveness) were limited.

Evidence now exists that drug resistance is increasing in patients who are naive to therapy. For example, in 2002 in our United Kingdom (UK) group (undertaking the clinical molecular virology care for 7000 UK patients), of 91 drug-naive patients tested, 24 (26.4%) had 2 or more mutations (according to the IAS–USA Drug Resistance Mutations in HIV-1 summary, available at www.iasusa.org) associated with resistance, a marked increase in number and distribution from our survey in 2000.[9] Further, 48% had major mutations including all drug classes. These data have since been confirmed (but not yet published) by the Medical Research Council UK Collaborative Group in HIV Resistance, which describes an overall prevalence

of 17% (n = 2000 patients) with no differences between acute or recent and nonacute naive infections. In other geographic areas where antiretroviral therapy is in use, similar results have been reported.

These data provide evidence that resistance testing will benefit a significant proportion of the population and should be part of our standard of care for management of patients infected with HIV-1 prior to initiating therapy. In circumstances in which this testing cannot be performed, a sample should be stored as soon as possible after infection for later review and support of patient care.

Data regarding the persistence of transmitted drug-resistant virus are sketchy; however, several cases describing the detectability of drug-resistant virus to both NNRTIs and PIs as long as 2 to 3 years after infection without treatment have recently been reported.[10]

Question 19: Resistance testing is indicated in primary HIV infection, but what is the recommendation for patients who had a negative resistance test 3 months, 6 months, or 1 year ago? If you are not going to treat such patients now, do you order the resistance test anyway and use the results years later when treatment is started?

Dr Demeter: Resistance testing is currently indicated for use in guiding initiation of therapy in the setting of primary HIV infection. Resistance testing could be ordered for a patient who has been infected for up to 2 years, or even longer, even if treatment is not planned immediately, so as to have a history of prior possible resistance. Resistance testing of this patient population in the absence of planned therapy may also be appropriate as part of a larger surveillance effort.

Question 20: How large an impact does "ideal" use of resistance test results have on outcome (ie, plasma HIV-1 RNA levels in the short term, percent below detection levels, and patient survival)? Is there a measurable benefit in the fine-tuning of antiretroviral regimens now becoming standard?

Dr D'Aquila: This is difficult to quantify, and clinicians need to consider this issue for an individual patient, not an idealized population of research subjects. It is the help provided by a resistance test result in choosing more active drugs and minimizing toxicity from ineffective drugs that benefits the patient. In clinical trials in which subjects are randomized to receive resistance testing or not, there was about a one-half to 1 log copies/mL greater drop in HIV-1 RNA level for the group randomized to testing. However, in our practices, there will be a large difference in response with testing in a patient with a very resistant virus (or one with an unexpected resistance pattern), but testing may make little difference in others who have an anticipated, fully wild-type virus. The clinical reality is that we cannot differentiate which individual will benefit greatly or not from resistance testing. In my opinion, the lesser benefit in some is balanced by the great benefit in a few and warrants testing for all.

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Richard H. Haubrich, MD
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University of Medicine and Dentistry of New Jersey

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Friday, October 17, 2003
Chairs: Roy M. Gulick, MD, MPH, and Douglas T. Dieterich, MD
The course will include updates from the 2003 IAS and ICAAC conferences.

Sacramento, California
Monday, November 3, 2003
Chairs: Judith S. Currier, MD, and Neil M. Flynn, MD, MPH
The course will include updates from the 2003 ICAAC and IDSA conferences.

Cases on the Web - www.iasusa.org/cow

Cases on the Web is an ongoing series of case-based, advanced online CME activities produced by the International AIDS Society–USA. Editor in Chief of the series is Michael S. Saag, MD, of the University of Alabama at Birmingham, and Co-Editor is Meg D. Newman, MD, of the University of California San Francisco.

CURRENT PRESENTATIONS

Screening for and Management of Anal Squamous Intraepithelial Lesions
Timothy J. Wilkin, MD, MPH

Current Applications of Drug Resistance Testing
Richard H. Haubrich, MD

HIV Therapy in "Triple-Diagnosed" Patients: HIV Infection, Drug Use, and Mental Illness
Gerald H. Friedland, MD

COMING SOON

Issues in Perinatal HIV
Deborah Cohan, MD

Considerations in Resistance Testing
Eoin Coakley, MD

For information about any of these and additional programs, please contact the International AIDS Society–USA.
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