Perspectives

Will Pharmacogenomic Discoveries Improve HIV Therapeutics? 90
David W. Haas, MD

Can Genetics Predict Efavirenz Central Nervous System Side Effects and Drug Levels? • Can Genetics Predict Risk for Efavirenz Resistance During Treatment Interruption? • Can Genetics Predict Liver Toxicity Associated With Nevirapine? • Can Genetics Predict Long-Term Response to Efavirenz? • Can Genetics Predict Nelfinavir Drug Levels and Treatment Response?

Scientific Rationale for Antiretroviral Therapy in 2005: Viral Reservoirs and Resistance Evolution 96
Robert F. Siliciano, MD, PhD

Establishment of Stable Latent Reservoir • Role of the Latent Reservoir in Archiving Viral Strains • Studies of Residual Viremia in Effective Antiretroviral Therapy

HIV in Adolescents and Young Adults: Half of All New Infections in the United States 101
Donna C. Futterman, MD

Youth Susceptibility to HIV • Sexual Transmission Among the Young • Challenges in Adolescent HIV and Other STD Care • Identifying HIV-Infected Youth • Barriers to HIV Prevention
About This Issue

This issue of *Topics in HIV Medicine* includes 3 Perspectives articles based on presentations at recent International AIDS Society-USA (IAS-USA) continuing medical education (CME) courses. At the 13th annual IAS-USA CME course in Atlanta in March 2005, Dr. David W. Haas discussed how pharmacogenomics studies may contribute to understanding interindividual differences in responses to antiretroviral drugs. Better knowledge about the associations between human genetics and effects of therapy may allow for individualization of antiretroviral therapy based on genotyping. Dr. Robert F. Siliciano presented a review of HIV reservoirs and the evolution of viral resistance at the 15th annual course in New York in February, 2005. He described the 2 distinct sources of viremia, and the impact of each on antiretroviral decision making. Dr. Donna C. Futterman presented an overview of HIV infection in adolescents and young adults, at the 7th annual CME conference for Ryan White Care Act clinicians in Washington, DC, in August 2004. She described the unique challenges facing this patient population, which now shoulders half of all new HIV infections in the United States.
Perspectives

Will Pharmacogenomic Discoveries Improve HIV Therapeutics?
David W. Haas, MD

Scientific Rationale for Antiretroviral Therapy in 2005: Viral Reservoirs and Resistance Evolution
Robert F. Siliciano, MD, PhD

HIV in Adolescents and Young Adults: Half of All New Infections in the United States
Donna C. Futterman, MD

Announcements

Guidelines for Authors and Contributors
106

Subscription Request
107

Educational Programs of the International AIDS Society–USA
109
**Perspective**

**Will Pharmacogenomic Discoveries Improve HIV Therapeutics?**

Pharmacogenomic studies are contributing to our understanding of interindividual differences in response to antiretroviral drugs. Genetic polymorphisms in major histocompatibility complex genes predict likelihood of hypersensitivity reactions in persons prescribed abacavir, and perhaps nevirapine. Recent studies have shown that a polymorphism in the CYP2B6 gene is associated with higher plasma efavirenz concentrations and increased efavirenz central nervous system side effects. Polymorphisms in the MDR1 gene encoding the drug pump, P-glycoprotein, may predict nevirapine-associated hepatotoxicity and long-term virologic response to efavirenz. CYP2C19 polymorphisms predict nelfinavir plasma levels and, possibly, risk of virologic failure on this drug. A European mitochondrial haplogroup may predict increased risk of peripheral neuropathy associated with nucleoside reverse transcriptase inhibitors. Expansion and refinement of knowledge regarding associations between human genetics and response to antiretroviral drugs may ultimately permit individualization of therapy based on genotyping. This article summarizes a presentation on HIV therapeutics and pharmacogenomics by David W. Haas, MD, at the International AIDS Society–USA course in Atlanta in March 2005.

Genetic differences among individuals can affect ways in which drugs are metabolized, distributed to cells and tissues, and eliminated from the body, and how the body responds to these drugs. Pharmacogenomic studies involving HIV-infected patients have begun to identify genetic differences and profiles that affect responses to antiretroviral drugs. However, there is much work to be done in this area before application of such knowledge can help to guide therapy. Ongoing studies need to determine the extent to which treatment efficacy and toxicities can be predicted by human genetic differences, and the underlying mechanisms involved. Furthermore, genetic analysis for use in clinical practice is somewhat expensive. The human genome consists of about 3 billion nucleotide base pairs that include approximately 1 single nucleotide polymorphism (SNP; a single nucleotide substitution that has the potential to affect gene expression or protein function) per 1000 base pairs. There are thus about 3 million SNPs in each individual. Currently, at the lowest possible assay cost of $.05 to $.10 per SNP, whole genome SNP scanning would theoretically cost about $150,000 to $300,000 per person. Cost reductions are being realized through advances in technology and also through such strategies as scanning only coding regions of genes, scanning only non-synonymous SNPs (ie, those that alter the amino acids), and taking advantage of linkage disequilibrium (ie, the tendency of groups of SNPs to be inherited together).

Selected associations between genetic profiles and responses to antiretroviral drugs that have been reported in the literature include those between abacavir hypersensitivity and HLA-B*5701 and hsp70-hom (Mallal et al, *Lancet*, 2002; Martin et al, *Proc Natl Acad Sci*, 2004); indinavir- and atazanavir-associated hyperbilirubinemia and UGT-1A1 (Gilbert’s syndrome gene; Zucker et al, *Proc Natl Acad Sci*, 2001 and O’Mara et al, 42nd ICAAC, 2002); nucleoside reverse transcriptase inhibitor (nRTI)-associated lipoatrophy and a TNF-α gene promoter polymorphism (Maher, *AIDS*,

---

**Figure 1.** Relationship between efavirenz area under the concentration-time curve (AUC) and the CYP2B6 G516T single nucleotide polymorphisms in AIDS Clinical Trials Group A5095 and A5097s study participants. The T allele was associated with significantly greater plasma AUC values in all subjects (left panel), and in European-American (middle panel) and African-American (right panel) populations analyzed separately. Adapted with permission from Haas et al, *AIDS*, 2004.

---

Dr Haas is an Associate Professor of Medicine and Director of the AIDS Clinical Trials Center at Vanderbilt University in Nashville, TN.
forms, with the greatest proportion of these being metabolized by CYP3A isoenzymes. In contrast, efavirenz is one of a much smaller group of drugs, including the antiretroviral drug nevirapine, that are metabolized primarily via CYP2B6. An initial study examining the potential influence of genetic factors in CNS toxicity and drug clearance of efavirenz therefore included analysis of polymorphisms in CYP2B6 and several other candidate genes.

This analysis involved antiretroviral-naive patients who had been randomized to receive efavirenz in ACTG study A5095 and its substudy A5097s. In study A5095, patients had received efavirenz 600 mg once daily, abacavir, or both, in combination with zidovudine and lamivudine. The efavirenz and abacavir were double-blinded. The A5097s substudy focused on characterizing efavirenz CNS adverse effects and pharmacokinetics, and 202 of the 303 subjects were randomized to efavirenz. Data from the pharmacokinetics study showed that efavirenz plasma levels were greater in both Hispanic patients and black patients than in white patients, although there were relative-ly few Hispanics in this study (Ribaudo et al, 11th CROI, 2004). The median values for area under the concentration-time curve from 0 to 24 hours (AUC_{0-24}) were 66, 58, and 46 μg·hr/mL, respectively (P≤.001 for all), although there was considerable overlap in pharmacokinetic parameters among the groups.

A CYP2B6 G-to-T polymorphism at position 516 was strongly associated with efavirenz plasma levels. As shown in Figure 1, the TT genotype predicted greater efavirenz AUC values among all subjects, as well as in white patients and in black patients separately (Haas et al, AIDS, 2004). This polymorphism was significantly more frequent in black patients (20% TT homozygotes) than in white patients (3% TT homozygotes), which may explain the finding of higher plasma efavirenz concentrations in the black patient population. Other genetic analysis from this study suggested that CYP3A4 and CYP3A5 SNPs may also be weakly associated with efavirenz levels. This association between CYP2B6 G516T and plasma efavirenz exposure was subsequently validated in a larger group of patients.

Can Genetics Predict Efavirenz Central Nervous System Side Effects and Drug Levels?

Efavirenz is a commonly prescribed drug used in initial therapy for HIV infection in the United States. Central nervous system (CNS) side effects are common during the initial days of efavirenz treatment. Several studies have shown that efavirenz plasma clearance is slower in black patients than in white patients (Barrett et al, Int J Clin Pharmacol Ther, 2002; Pfister et al, Antimicrob Agents Chemother, 2003). Although one report suggested earlier virologic failure on efavirenz in blacks than in whites (Wegner et al, 9th CROI, 2002), this was not confirmed in a subsequent study (Lupo, 6th Int Congr Drug Ther HIV Infect, 2002). Many drugs are metabolized by cytochrome P450 (CYP450) iso-

---

2002; Nolan, AIDS, 2003); and nevirapine-related rash/fever/hepatitis and HLA-DRB1*01 (Martin, AIDS, 2005). The finding of a correlation between HLA type HLA-B*5701 and the likelihood of hypersensitivity reaction to abacavir is the best example of the potential utility of pharmacogenomic analysis thus far. Approximately 3% of patients receiving abacavir have a hypersensitivity reaction to the drug, which can be life threatening. Since identifying the very strong association between HLA type and risk for this reaction, Mallal and colleagues routinely assess patients for HLA type prior to using abacavir in treatment, a practice that has markedly decreased abacavir hypersensitivity in their patient population (Mallal, personal communication).

To improve the pharmacogenomic database in HIV therapeutics, the Adult AIDS Clinical Trials Group (ACTG) instituted a program in which patients participating in ACTG clinical trials are offered the opportunity to contribute a DNA specimen to a repository for use in pharmacogenomic studies. Findings from initial studies in this program are summarized below.

---

**Figure 2.** Relationship between CYP2B6 position 516 genotypes and risk of central nervous system adverse experiences in the AIDS Clinical Trials Group A5097s study population. Adapted with permission from Haas et al, AIDS, 2004.
from ACTG study 384, including in Hispanic, black, and white patients analyzed separately (Haas et al, 12th CROI, 2005).

Careful assessment of CNS side effects by questionnaires in study A5097s showed that the T allele at CYP2B6 position 516 was associated with significantly greater adverse CNS experiences during the first week of efavirenz therapy, although this difference disappeared at later time points (Figure 2; Haas et al, AIDS, 2004). Thus the CYP2B6 T516T variant, which is more common in black than in white individuals, is associated with higher efavirenz plasma levels and greater frequency of CNS adverse events. It must be emphasized that black patients did not have more CNS side effects in the ACTG substudy.

Can Genetics Predict Risk for Efavirenz Resistance During Treatment Interruption?

Efavirenz has a relatively long half-life and a low genetic barrier to viral drug resistance. These factors have raised concern that when a regimen containing efavirenz is completely interrupted, the persistence of the drug beyond clearance of the other drugs in the regimen may pose the risk of developing efavirenz resistance—that is, through exposure of virus to what is essentially efavirenz monotherapy. Researchers used modeled data from the study described above to predict how long efavirenz concentrations would persist above the protein-adjusted 95% inhibitory concentration (IC95) according to genotype in patients stopping therapy will need to be determined to confirm this prediction.

Can Genetics Predict Liver Toxicity Associated With Nevirapine?

Nevirapine can cause hepatotoxicity. As noted above, a recent report suggested an association between HLA-DRB1*01 and nevirapine-associated hypersensitivity, which included hepatitis, in many patients (Martin, AIDS, 2005). Additional studies were conducted to assess the potential role of drug metabolism and transporter genes. As with efavirenz, nevirapine is primarily metabolized by CYP2B6; it has not been recognized as a substrate for P-glycoprotein. In a study performed in South Africa (FTC-302), grade 3 or 4 liver enzyme elevations occurred in 17% of nevirapine recipients. Researchers thus explored the potential association of MDR1, CYP2B6, CYP3A4, and CYP3A5 SNPs and nevirapine hepatotoxicity in a case-control study using data and specimens from this study (Haas et al, 12th CROI, 2005). Cases and controls were matched for age, race, sex, pretreatment CD4+ cell count, and pretreatment plasma viral load. Patients with the MDR1 position 3435 CT or TT genotypes were significantly less likely to have liver toxicity than those with the CC genotype, suggesting a potential protective effect of the T allele at this position.

The researchers examined this potential association with nonnucleoside reverse transcriptase inhibitor (NNRTI) hepatotoxicity in their own clinical population at Vanderbilt University and observed a similar pro-
other drugs (e.g., protease inhibitors, digoxin) known to be P-glycoprotein substrates. These findings suggest that SNPs in the MDRI gene may indeed affect the risk for nevirapine liver toxicity and suggest a possible mechanism.

**Can Genetics Predict Long-term Response to Efavirenz?**

Haas and colleagues subsequently examined the potential genetic correlates of long-term response to efavirenz in patients enrolled in ACTG study 384 (Haas et al, 12th CROI, 2005). In this study, treatment-naive patients were randomized to receive either efavirenz 600 mg once daily, nelfinavir 1250 mg twice daily, or both, in combination with either zidovudine/lamivudine or didanosine/stavudine. The efavirenz and nelfinavir were double-blinded. Data from patients followed up for as long as 3 years were available from this study. Somewhat surprisingly, no associations were observed between CYP2B6 SNPs and long-term responses to efavirenz. In contrast, as shown in Figure 4, MDRI position 3435 TT genotype was associated with significantly less virologic failure on efavirenz. No differences among genotypes were observed for treatment failure due to toxicity or all-cause treatment failure. The MDRI T allele at position 3435 was also a significant predictor of decreased likelihood of virologic failure with emergence of efavirenz resistance ($P = 0.05$), with an odds ratio (OR) of 0.6 per T allele, whereas age, race, sex, baseline CD4+ cell count, and baseline plasma viral load were not significant predictors. This provocative finding needs to be validated in other studies.

**Can Genetics Predict Nelfinavir Drug Levels and Treatment Response?**

Nelfinavir is metabolized via CYP2C19, and it is known that genetic variants of the CYP2C19 gene can result in a poor drug metabolism phenotype. This is most frequent among Asian populations. Analysis of nelfinavir levels among participants from ACTG 384 showed that those with GA or AA genotypes at CYP2C19 position 681 had higher AUC values than GG homozygotes (Figure 5, left; Haas et al, 12th CROI, 2005). There was also a trend toward more favorable virologic responses on nelfinavir in subjects with the GA genotype (Figure 5, right).
Can Genetics Predict nRTI-Associated Peripheral Neuropathy?

In the ACTG 384 study, peripheral neuropathy was much more common among patients randomized to receive didanosine/stavudine than among those who received zidovudine/lamivudine. Peripheral neuropathy associated with nRTIs is the result of toxicity to mitochondria. Mitochondrial DNA from different individuals can be classified according to distinct haplogroups, which are specific heritable patterns of polymorphisms in the mitochondrial genome. There are 9 mitochondrial haplogroups that have been identified in persons of European ancestry. Analysis of risk for peripheral neuropathy by mitochondrial haplogroup among 137 white (European ancestry) patients in the ACTG 384 study who received didanosine/stavudine showed that patients with haplogroup T, who constituted 9% of study participants of European ancestry, had a significantly increased risk of developing neuropathy (Figure 6; Hulgan et al, 12th CROI, 2005). By multivariate analysis, independent predictors of peripheral neuropathy were randomization to didanosine/stavudine (OR, 2.57; P = 0.003), age at randomization (OR, 1.05 per year; P = 0.005), and haplogroup T (OR, 2.89; P = 0.02).

**Conclusion**

Associations between human genetics and HIV treatment responses are increasingly being described. Refining and expanding our knowledge of genotypes and their interaction with drug therapies will ultimately enable us to tailor drug treatments to individuals, whether the treatment be antiretroviral, antihypertensive, antidepressant, or otherwise. Since an individual’s genetic profile does not change over time, genetic testing performed at one point time may help inform both current and future choices of pharmacologic agents for the individual. On a global level, the pharmacogenomic knowledge base is likely to be of considerable importance in helping to anticipate complications of antiretroviral drug treatment in ethnic populations that may not have been well represented in drug registration trials.

**Financial Disclosure:** Dr Haas has received grant and research support from Boehringer Ingelheim, Bristol-Myers Squibb, and Tanox.

**Suggested Reading**


Ribaudo H, Clifford D, Gultic R, et al. Relationships between efavirenz pharmacokinetics, side effects, drug discontinuation, virologic response, and race: results from ACTG A5095/A5097s. [Abstract 132.] 11th Conference...
The 14th Annual IAS–USA Course Series, Improving the Management of HIV Disease®

Mark Your Calendar!

HIV PATHOGENESIS, ANTIRETROVIRALS, AND OTHER SELECTED ISSUES IN HIV DISEASE MANAGEMENT

2006 will be the 14th year of the IAS–USA advanced CME courses designed for HIV specialists. These activities have been approved for AMA PRA credit. Topics are tailored to the needs of each regional audience and may include:

- Strategies for antiretroviral management
- New insights into HIV disease pathogenesis
- New antiretroviral drugs and combinations
- Complications and toxicities of antiretroviral therapy
- Hepatitis C virus and other coinfections

CME 2006 Spring Courses

LOS ANGELES, CA
Friday February 24, 2006
Hilton Los Angeles/Universal City
Chair: Ronald T. Mitsuyasu, MD
Registration is open.

ATLANTA, GA
Monday, March 6, 2006
Westin Peachtree Plaza
Chair: Michael S. Saag, MD
Vice-Chair: Jeffrey L. Lennox, MD
Registration is open.

NEW YORK, NY
Wednesday, March 15, 2006
New York Marriott Marquis
Chair: Gerald H. Friedland, MD
Vice-Chair: Paul A. Volberding, MD
Registration is open.

SAN FRANCISCO, CA
Tuesday, April 4, 2006
San Francisco Grand Hyatt
Chair: Robert T. Schooley, MD
Vice-Chair: Stephen E. Follansbee, MD
Registration is open.

CHICAGO, IL
Monday, May 8, 2006
Marriott Chicago Downtown
Chair: John P. Phair, MD
Vice-Chair: Harold A. Kessler, MD
Registration is open.

WASHINGTON, DC
Friday, May 19, 2006
JW Marriott on Pennsylvania Avenue
Chair: Henry Masur, MD
Vice-Chair: Michael S. Saag, MD
Registration is open.

Visit www.iassusa.org for online registration and current course schedules.

Office: (415) 544-9400
Fax: (415) 544-9402
E-mail: info2006@iassusa.org
(as of January 1, 2006, info2006@iassusa.org)

The International AIDS Society–USA is a 501(c)(3) not-for-profit organization. Our activities are intended to bridge clinical research and patient care.

Sponsored by the International AIDS Society–USA
**Perspective**

**Scientific Rationale for Antiretroviral Therapy in 2005: Viral Reservoirs and Resistance Evolution**

Hope for a cure for HIV-1 infection was dampened by the discovery of a latent form of the virus that persists in resting CD4+ cells. This reservoir of latently HIV-infected resting memory T cells represents an archive of viral genotypes produced in an individual from the onset of infection. Entry into the reservoir is stopped with suppressive antiretroviral therapy, but the archived viruses are capable of reinitiating active infections, are released continuously from this reservoir, and can cause viral rebound if antiretroviral therapy is stopped. Studies of residual low-level viremia (<50 HIV RNA copies/mL of plasma) in the setting of effective antiretroviral therapy indicate that such viremia is largely caused by activation of the latently infected cells and the release of virus from this and other stable reservoirs. These studies support the notion that the stability of the latent reservoir is consistent with the long life span of resting memory T cells, rather than reflecting rounds of active replication under suppressive antiretroviral therapy that replenish the reservoir. There may be other stable reservoirs in addition to the resting T-cell pool, further complicating the problem of eradication. This article summarizes a presentation on viral reservoirs and viral evolution by Robert F. Siliciano, MD, PhD, at the International AIDS Society–USA course in New York in March 2005.

It has become clear that there are 2 distinct sources of viremia in HIV-infected individuals and that understanding the differences between them is important for making correct decisions about antiretroviral therapy. In an untreated patient, most of the plasma virus is produced by active rounds of replication in permissive cells, such as activated CD4+ cells; this is an extremely dynamic process, with many new cells being infected each day, replacing those killed by infection. In each newly infected cell, the error-prone process of reverse transcription of the HIV genome is occurring, generating mutations that can lead to drug resistance. Indeed, in a patient with a plasma HIV RNA level of 30,000 copies/mL, every possible mutation in the entire HIV genome arises on a daily basis. In the presence of a selective advantage—for example, suboptimal antiretroviral therapy—preferential replication of resistant mutants will result in an outgrowth of a drug-resistant viral population.

Whereas active cycles of replication produce most of the steady-state viremia in an untreated patient, some of the virus in plasma is released by stable reservoirs of HIV. One of these stable reservoirs consists of CD4+ cells infected at some time in the past that carry a latent form of the virus. With appropriate immune stimulation, these cells can subsequently become activated and produce virus. Although the amount of virus produced by the activation of these latently infected cells is quantitatively insignificant, this latent reservoir is nevertheless clinically important for 3 reasons: first, it renders HIV infection intrinsically incurable with current antiretroviral therapy alone; second, it helps explain what is happening virologically in patients who are doing well on antiretroviral therapy; and third, it helps explain the unique mode of evolution of HIV in which all of the major variants that have arisen during the course of an infection persist indefinitely.

**Establishment of Stable Latent Reservoir**

The establishment of a reservoir of latently infected CD4+ cells is a result of the normal physiology of the immune system. Most of the T cells in the body are in a resting state; approximately half are naive cells (cells that have not yet responded to any foreign antigen), and the remainder are memory cells (cells that have previously responded to some antigen). The cells circulate throughout the lymphoid tissues until they encounter an antigen that they recognize, after which they undergo blast transformation, proliferate, and carry out their functions. Some of the cells survive and revert back to a resting state as long-lived memory T cells, cells that allow the host to respond to the same antigen again in the future.

In HIV infection, the virus replicates preferentially in activated CD4+ cells and tends to kill them very quickly. However, some of the activated cells can become infected as they are in the process of reverting back to a resting state, resulting in a stably integrated viral genome in a long-lived memory T cell. Conditions for HIV gene expression are unfavorable in resting cells; for example, host transcription factors such as nuclear factor-κB and nuclear factor of activated T cells, which are necessary for high-level HIV gene expression, are excluded from the nucleus in resting CD4+ cells. The result of infection in this case is a stably integrated but transcriptionally silent form of the virus.
virus in a cell that is designed to live a long time: a perfect recipe for viral persistence. If these cells are reactivated in the future, they can begin to produce virus.

Latently infected cells are present in all infected individuals, at a frequency of approximately 1 per million resting CD4+ cells. Virus in these cells is not eradicated during antiretroviral therapy. This latent reservoir appears to be extremely stable. The best estimates of the decay of the viral population in this latent reservoir, based on studies in patients in whom antiretroviral therapy has reduced plasma HIV RNA levels to below 50 copies/mL for as long as 7 years, indicate a half-life of 44.2 months. Based on these estimates, eradication of HIV from the latent reservoir would require 73.4 years of suppressive therapy.

Role of the Latent Reservoir in Archiving Viral Strains

Actively replicating viruses in the plasma of viremic patients are a complex mixture of majority and minority variants that can be seen as participants in replicative competition. In the latent reservoir, there is a broader group of variants that persist in a manner that does not allow them to engage in such competition. In essence, this reservoir allows viruses to drop out of the competition and persist in a latent form, only to reemerge at a later time. In viremic patients, there is constant entry of viruses of a wide variety of genotypes—including viruses with drug-resistance mutations, if they have arisen—into the reservoir. There is no marked change in reservoir size because the high level of immune activation that occurs with viremia also results in increased emergence of virus from the reservoir as the host cells become activated. With initiation of antiretroviral therapy, entry into the reservoir is reduced. Exit from the reservoir is also reduced, owing to the decreased immune activation that occurs in the setting of effective antiretroviral therapy. Nevertheless, a small number of latently infected cells become activated each day and release virus, which can result in viral rebound if antiretroviral therapy is stopped.

Thus the latent reservoir is an archive of the viral genotypes that have been produced in an individual from the onset of infection. Figure 1 provides an example of the complex mixture of genotypes present in the reservoir. The patient represented received zidovudine beginning in the early 1990s, followed by the addition and substitution of a number of other drugs. After breakthrough viremia occurred in 1998, all drugs then being used were switched to a new 4-drug regimen, and the patient has been doing well on this regimen. The bottom portion of Figure 1 shows results of genotypic analysis of HIV isolates from the resting memory T-cell reservoir in this patient, organized according to presence of resistance mutations. Each horizontal entry represents an independent viral clone.

This picture of the types of virus present in the individual differs from that of a routine clinical genotyping of plasma virus, which shows a population average of circulating genotypes. Analysis of individual clones of virus in the latent reservoir reveals a wide variety of genotypes. Wild-type virus is present, and likely represents virus sequestered very early in the patient’s infection, since these strains are at a large competitive disadvantage in the context of antiretroviral therapy. Also present are viruses with resistance mutations that reflect exposure to various drugs in the patient’s treatment history. All of the viruses in the latent reservoir have the potential to reemerge at some point in the future. Wild-type virus, which in the absence of antiretroviral therapy has a competitive advantage against many strains with resistance mutations, reemerges as the dominant plasma virus when patients are taken off failing antiretroviral therapy. The latent reservoir appears to be the source of this reemergence.

The latent reservoir allows the virus in an individual to evolve in a unique way. With HIV, what occurs is not survival of the fittest, but survival of all major forms that have been generated, and active replication of the forms that are the most fit under the current conditions. This situation needs to be taken into account in strategies for antiretroviral treatment. For example, the use of nevirapine to prevent mother-to-child transmission of HIV in developing countries results in emergence of nevirapine-resistant virus in most mothers after the single dose of nevirapine, with the resistant variants appearing to disappear over time. However, they are likely to be archived in the latent reservoir and will have the potential to reemerge if nevirapine, or other nonnucleoside reverse transcriptase inhibitors with similar resistance profiles, are subsequently used in an antiretroviral regimen. Similarly, the observation that wild-type virus may reemerge as the dominant plasma virus when antiretroviral therapy is stopped in patients in whom therapy is failing contributed to the notion of strategic treatment interruptions to regain viral susceptibility to antiretroviral drugs. However, the resistant strains are likely to have been archived and to reemerge when drugs are restarted. Patients in whom this strategy has been attempted did not have better outcomes as a result of treatment interruption.

Studies of Residual Viremia in Effective Antiretroviral Therapy

With the initiation of antiretroviral therapy, viremia is reduced from the original setpoint of replication in an individual to some point below the assay detection limit of 50 RNA copies/mL. Whether there is residual active viral replication under such therapy remains controversial. However, even if it were possible for antiretroviral therapy to be 100 percent effective in preventing new infection of susceptible cells from the moment treatment was initiated, there would still be residual low-level viremia, detectable
**Figure 1.** Right: Antiretroviral treatment and plasma HIV RNA level over time in one patient. Arrow indicates period of breakthrough. Bottom: Results of recent clonal genotypic analysis of HIV in the latent reservoir of the same patient showing persistence of archival wild-type viruses (Wt) and viruses with drug resistance mutations (indicated as colored boxes: purple, nelfinavir; red, zidovudine; dark blue, lamivudine).
only with special research assays. This residual viremia results from the release of virus from latent reservoirs. This level of viremia can be termed the “release point,” representing the amount of virus released from the reservoir without any additional cycles of replication. This point represents the best that can ever be expected from antiretroviral therapy in terms of reduction in viremia. Determining how close current antiretroviral therapy is to achieving reduction to this release point is important because any residual replication can generate drug-resistant variants and replenish the latent reservoirs. In a recent study, phylogenetic analyses of plasma virus and virus from resting memory T cells were performed in patients who had been doing well on antiretroviral therapy for an average of 3 years (Nettles et al, *JAMA*, 2005) Plasma and reservoir samples were taken at baseline; plasma samples were then taken every other day for 3 months and follow-up samples from the latent reservoir were obtained at regular intervals. As shown in Figure 2, the genetic sequences of the plasma and reservoir viruses are intermingled and often identical, consistent with the idea that the source of the plasma virus in the residual viremia observed in the patient is predominantly the infected resting T-cell pool. No resistance mutations to the drugs in the patient’s antiretroviral regimen were observed, despite the fact that a single mutation could produce high-level resistance for 2 of the drugs in the regimen.

Such findings suggest that residual viremia in patients on potent antiretroviral therapy may be due to the release of virus from the latent reservoir and that such viremia can occur for prolonged periods without viral evolution (including resistance mutations). In addition, such findings support the notion that lifelong control of HIV infection is possible if highly active regimens can be maintained, and if suboptimal treatment—and consequent emergence of resistant virus—can be avoided.

Although the above results suggest
that there can be residual viremia without viral evolution in patients on potent antiretroviral therapy who have viral loads reduced to below assay detection limits, many patients experience transient elevations of viremia into the detectable range (blips). The source of virus in the blips remains unclear. Blips are common, having been detected in 10% to 40% of patients doing well on antiretroviral therapy, and available evidence has suggested that they do not necessarily predict treatment failure. However, there has been concern that these blips may represent viral evolution through active replication and may thus result in the increased emergence of resistance to ongoing regimens. Much of the data on these transient elevations are from studies using relatively infrequent sampling. The frequent sampling performed as part of the above-mentioned study provided an opportunity to more closely evaluate characteristics of the viral blips. Blips were detected in the majority of patients examined; they were low in magnitude, typically at an HIV RNA level below 200 copies/mL, and brief in duration, generally resolving within 2 to 3 days. These increases were more common in some patients than in others but showed no correlation with concurrently measured plasma levels of antiretroviral drugs or with intercurrent illness or vaccinations.

Genotyping showed that no new resistance mutations appeared during or after the blips, with any resistance mutations found in the samples having been present in patients at baseline. These findings are consistent with the notion that viral blips represent normal biologic variation or statistical variation around a mean setpoint value that is below 50 copies/mL. However, blips that are greater than 200 copies/mL or that are reproducible on sequential testing are a greater cause for concern in terms of the potential for ongoing active replication and generation of resistant mutants.

With regard to stable viral reservoirs, it is possible that reservoirs other than the resting T-cells exist. Such other stable reservoirs would further complicate the problem of HIV eradication.

**Conclusion**

Both ongoing replication and viral release from stable reservoirs contribute to viremia in infected individuals. Antiretroviral therapy largely stops ongoing replication. The low-level viremia that continues despite antiretroviral therapy and the (smaller-magnitude) viral blips that occur in many patients do not depend on the presence of new drug resistance mutations, resulting from rounds of active replication; they may instead largely reflect viral release from stable reservoirs. Most blips may represent normal biologic and statistical variation around mean HIV RNA levels of below 50 copies/mL, rather than clinically significant elevations in viremia. However, blips that are greater than 200 copies/mL or reproducible on independent or sequential testing are a greater cause for concern.

Findings in the studies of viremia in patients with plasma HIV RNA levels below 50 copies/mL indicate that there can be viremia without viral evolution and thus suggest that lifelong control of viral replication is possible.


Financial Disclosure: Dr Siliciano has no affiliations with commercial organizations that may have interests related to the content of this article

**Suggested Reading**


Perspective

HIV in Adolescents and Young Adults: Half of all New Infections in the United States

Half of new HIV infections in the United States are in individuals aged 13 to 24 years, accounting for 20,000 new infections annually, or 1 every hour. Two thirds of infected youth contract HIV sexually, and more than 60% of new infections are in young women. Approximately 75% of infected youth are in racial or ethnic minority groups. More than one third of HIV-infected young people have not been tested for HIV infection, and the majority of homosexual HIV-infected youth are unaware of their infection status. Increased efforts are needed in comprehensive sex education, including safer sex practices, bringing young people into health care networks, increasing health care provider awareness of risk, and extending counseling and testing to young people. This article summarizes a presentation by Donna Futterman, MD, at the 7th Annual Clinical Conference for Ryan White CARE Act Title I, II, III, and IV Grantees, held in August 2004 in Washington, DC.

In the United States, 50% of new HIV infections occur among 13- to 24-year-olds. This group accounts for 20,000 new infections annually, or on average, 1 every hour. Two thirds of these youth contract HIV sexually, and more than 60% of new infections are in young women. Approximately 75% of HIV-infected youth are in racial or ethnic minority groups. More than one third have not been tested for HIV infection. Approximately 80% of homosexual HIV-infected youth are unaware of their infection status (Centers for Disease Control and Prevention [CDC] 2004; Valleroy et al, JAMA, 2002).

In addition to the new infections in America’s youth, a growing number of perinatally infected children are surviving into adolescence. In the early 1980s, it was thought that perinatally acquired HIV infection was a disease of infants and that children did not exhibit the same protracted course of disease without clinical symptoms that adults exhibited. However, it is now known that the course of HIV infection can be asymptomatic in children for many years. With the use of antiretroviral therapy, many perinatally infected children are now well into adolescence. Indeed, half of the HIV-infected children in some of the cohorts that formed the original pediatric programs are now adolescents. Clinically, these adolescents may be sicker, but present with many of the same issues regarding sexual relationships and drug treatment adherence as do others their age.

Youth Susceptibility to HIV

Factors affecting youth susceptibility to acquiring HIV infection include behavioral, biologic, and socioeconomic factors. One behavioral factor is that a large proportion of young people in the United States are sexually active. According to the CDC, half of US high school students (including those in grades 9 through 12) have had sex (CDC, MMWR, 2004). By the time they are in 12th grade, 70% of teens have had sex. Another behavioral factor is that relationships between young people are often marked by a gender power imbalance, wherein it is more difficult for young women to insist on condom use or other safer sex practices, particularly when they are involved with older men.

There are several biologic factors contributing to youth susceptibility to HIV. The immature cervix of a young woman is lined with single-layer columnar cells that increase vulnerability to infection compared with the multilayer squamous cell structure in the cervix of an older woman. Sexually transmitted diseases (STDs) in the young are also more likely to be asymptomatic—for example, inflammatory diseases, such as chlamydial infection, can often go undetected in young women—and both ulcerative and inflammatory STDs can facilitate HIV transmission. HIV is more efficiently transmitted from men to women. It is thought that the majority of cases of HIV transmission in women occur through the cervix, but the percentage that results from invasion of the vaginal wall remains unclear. With regard to female-to-male transmission, the urethral opening in the penis is the main site of acquisition, and this location obviously presents a much smaller vulnerable surface area than that found in women. The higher rate of transmission to uncircumcised men indicates that the lining of the foreskin may be comparable to the cervix in terms of vulnerability to infection.

Socioeconomic factors putting youth at risk include the fact that they are the least-insured segment of the population and are thus liable to receive less than adequate health care and support. In addition, much of the youth sex education is inadequate. From a public health standpoint alone, it is crucial that young people learn the methods of safer sex. Further, the lack of confidentiality in health care is a problem for younger people. Many rely on confidentiality in the health

Dr Futterman is Director of the Adolescent AIDS Program and Professor of Clinical Pediatrics at Albert Einstein College of Medicine in Bronx, NY.
care setting in order to access health care, and confidential care is an important component of adolescent medicine with regard to sensitive issues such as sexuality, pregnancy, and substance abuse. Confidentiality is not inviolable in situations in which individuals are endangering themselves or others, and every effort should be made to involve parents or other caretakers when necessary. However, confidentiality is a starting point for bringing young patients in to receive the care that they need.

**Sexual Transmission Among Youth**

Epidemiologic characteristics of HIV transmission in youth include a wide variation in the number of sexual partners among those infected. Half of the infected young women in the Adolescent AIDS Program at Children’s Hospital at Montefiore in Bronx, New York, over the last 15 years reported having only 1 sexual partner. Thus, one of the commonly disseminated messages about reducing risk—reduce the number of partners—turns out not to be protective in some settings. In fact, it has been reported that being married is one of the leading risk factors for HIV acquisition in women in some areas in Africa. Thus, women can be at risk for HIV infection even if they have only 1 sexual partner. Overall, three quarters of HIV-infected young women were unaware that the partner from whom they acquired the infection was at risk.

Among young men, male-to-male sex remains the leading risk behavior. In this regard, it is important to recognize that sexual orientation does not necessarily equal sexual behavior. Many young men who ultimately will be heterosexual experiment sexually with other men; others may experiment with other men long before they self-identify as homosexual; and others confidently identify themselves as gay but have not yet had sex with another man. These distinctions are important for discussion and counseling, which should focus on behaviors as well as orientation.

Figure 1 shows a sexual transmission network from a small town in upstate New York, where an outbreak of HIV infection was not expected. The blue square in the center represents a young man with HIV infection, and every circle to which the square is connected represents a woman with whom he had sex. The blue circles indicate those contacts who acquired HIV infection; the sexual contacts of those women and their HIV infection status are also shown. The young man at the center of this network was a drug dealer, who also offered the women gifts and clothing. Most of the women did not know that the man might be putting them at risk, and they may have been unaware that he was also having sex with many other women.

Most HIV transmission does not occur as in this example, featuring 1 “supertransmitter” with a large number of sexual partners. However, there is reason to suspect the existence of numerous transmission networks that are similar (although smaller) to this in inner cities and elsewhere. For example, the presentation at one clinic of numerous HIV-seropositive young women from the same ZIP code may indicate that sexual networks are involved. Years ago, many clinicians would hesitate to think about partner notification when seeing a new patient, because it seemed in some way contrary to the patient’s best interest. This type of thinking must be eschewed for the sake of preventing new cases, and the tried—and-true public health techniques of identifying cases and contacts should be adopted when appropriate. A recent report from North Carolina of a group of young African-American men acquiring HIV infection through college sexual networks emphasizes the need for vigilance in this regard (CDC, MMWR, 2004)

With regard to men who have sex with men, the landmark study conducted by the CDC from 1994 to 1998 showed that of a random sampling of 3449 males aged 15 to 22 years who
reported having sex with men, 7% were HIV seropositive. (Valleroy et al, *JAMA*, 2002) This HIV seroprevalence rate is higher than that in Haiti, for example, which has been declared a focus country for the President’s Emergency Plan for AIDS Relief. Among African American men in the CDC sample, the seroprevalence rate was 14%, higher than the estimated seroprevalence in Kenya. Among 15- to 19-year-old men in the CDC study, 6% were HIV seropositive. Among all infected individuals in this study, 82% were unaware of their infection status. Of those infected, 87% reported having anal sex with a man and 31% reported unprotected receptive anal sex. The fact that 61% reported having sex with a woman emphasizes that both opposite-sex and same-sex sexual experimentation is common among youth who ultimately identify themselves as homosexual. Homosexual youth today live with psychosocial pressure that adds to the pressures posed by adolescence per se. Societal prejudice against homosexuality, coupled with challenges in accessing comprehensive sex education and prevention information, discourages the development of the self-love and self-motivation that can form the basis of safer-sex practices.

Dr. Futterman and colleagues at the Adolescent AIDS Program have identified history of sexual abuse and having a parent with HIV infection as risk factors for infection in young people. There is a high frequency of history of sexual abuse among young people of both sexes infected with HIV. At the Adolescent AIDS Program, rates of sexual abuse range from 25% to 40%. Safer-sex behavior depends on some degree of self-motivation and self-love, and unless young people (or adults) have worked through the consequences of sexual abuse, it is difficult for them to successfully maintain safer-sex practices in later life.

In a study conducted at the Adolescent AIDS Program, 20% of HIV-infected young people who were infected sexually knew that at least 1 parent had HIV infection. Identification of this risk group emphasizes that vulnerable youth are vulnerable to acquiring HIV infection. Young people growing up with a parent who is sick, who uses drugs, or who is otherwise “absent” are vulnerable because they lack a supportive and involved parent. In addition, geography is destiny in the sense that adolescents growing up in a neighborhood with high rates of HIV infection are generally more vulnerable because their sexual involvement with partners from their neighborhood puts them at greater risk than would the same behaviors in a location with low HIV infection rates. There is no doubt that there is a heightened vulnerability among young people growing up in neighborhoods that are poor and without resources and that have high rates of substance abuse.

After identifying the rate of HIV-infected young people in the above-mentioned study who were aware of their parents’ HIV-seropositive status, the interviewers found that less than half of patients in the adult HIV clinic who had teenage children had told their children of their HIV status. Thus, the 20% figure cited for the proportion of young patients knowing that a parent was infected very likely reflects a low estimate of the number of HIV-infected youth with at least 1 HIV-infected patient.

**Challenges in Adolescent HIV and Other STD Care**

**Risk Awareness and Retention in Care**

A primary challenge in care for at-risk youth is increasing risk awareness among health care practitioners. Every STD program should provide or have a link to HIV counseling and testing services. Unfortunately, many do not, which results in missed opportunities for diagnosis (Burstein et al, *Pediatrics*, 2003). If linkage to health care can be accomplished, the challenges are to retain the patients in care, including guiding the transition of patients from pediatric to adolescent programs and from adolescent to adult programs, and to provide support regarding drug treatment adherence. Success in these areas frequently involves collaboration with schools and community-based organizations and health programs.

**Treatment and Treatment Adherence**

The course of HIV disease in adolescents is similar to that in adults, largely because most adolescents are infected after the immune system has matured. Adolescents appear to have more resilient immune systems, and thus constitute an ideal target for early antiretroviral intervention (Rudy et al, *J Adolesc Health*, 2001). Treatment is based on adult treatment guidelines, depending on the Tanner stage of the individual, (Working Group of Antiretroviral Therapy and Medical Management of HIV-infected children. [http://aidsinfo.nih.gov/], 2005). In the Adolescent AIDS Program, the preferred approach to antiretroviral treatment is to provide the best regimen with the highest chance of adherence, an approach termed “Keep It Simple and Safe,” or “KISS.” The manner of coping with disease and treatment varies by stage of development; in general, maturity enhances adherence. One cognitive barrier to adherence in young people is concrete, rather than abstract, thinking: Although concrete thought, which encourages following rules, can actually aid adherence, for the most part it is difficult for younger patients to imagine the virus multiplying in their bodies, to attach meaning to the numbers used in assessing and monitoring disease, and to feel the need to keep taking medication while they do not feel sick, especially if the medication makes them feel unwell. Other cognitive barriers include decreased future orientation and a limited understanding of medicines. In addition, many young people do not disclose their HIV serostatus to their family and are therefore deprived of potential support that may improve adherence (Schietinger et al, 2005).
Identifying HIV-Infected Youth

Health care providers provide a key role in identifying HIV-infected young people. They occupy a unique position at the intersection of case finding and care, and the respect that they typically garner from young people and parents can facilitate their activities in this regard. Although the CDC, the American Academy of Pediatrics, and other bodies recommend routine testing or offering of HIV testing to young people, testing is still not standard practice in many health care settings.

The Adolescent AIDS Program has designed an HIV testing program that is intended to facilitate the adoption of HIV-related assessment into routine practice in high-HIV-prevalence areas. The initial step in the development of the program was to determine the degree to which HIV testing was not linked to other STD care. Providers were interviewed and data obtained from 9 community health centers in Bronx, New York. The majority of providers performed HIV testing in 10% or less of their clients; they performed Chlamydia testing in 20% to 50% (Figure 2). Based on the contention that every person receiving a Chlamydia test should also be tested for HIV, interviews were then conducted with providers and key staff to identify barriers to offering HIV testing. These barriers included the feeling of a lack of skills, time constraints, lack of appropriate staff training, and the belief that their patients were not at risk for HIV infection.

In response to provider and patient needs, a simple, rapid protocol was designed for HIV counseling and testing for use in high-prevalence areas, called Assess, Consent, Test, Support (ACTS). The program is concise and comprehensive; its components include a laminated pocket guide, a manual for instruction and reference (including keyed discussion of talking points listed on the pocket guide), and a tool kit containing screening and consent forms and patient materials. The program includes meeting with key staff to discuss challenges and solutions and an academic detailing session to train providers to use the program. The front of the laminated pocket guide is reproduced in Table 1. New York State has among the strictest counseling and testing regulations, and the ACTS system allows them to be met in 5 minutes. The time-constraint barrier was minimized by removing preven-

Table 1. ACTS—A Rapid System for HIV Counseling and Testing

<table>
<thead>
<tr>
<th>Assess for HIV Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Note it is now standard practice to discuss HIV with all patients</td>
</tr>
<tr>
<td>– Explain benefits of testing for patient’s health and prevention</td>
</tr>
<tr>
<td>– Describe HIV transmission: sex/needles/perinatal</td>
</tr>
<tr>
<td>• Review risk screen or explain that HIV testing is advisable if:</td>
</tr>
<tr>
<td>– You have ever had sex (esp. if condoms are not always used)</td>
</tr>
<tr>
<td>– You have ever used injection drugs (especially if sharing needles)</td>
</tr>
<tr>
<td>• If yes, recommend testing and assess testing readiness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consent</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Review DOH consent form: meaning of positive and negative results, confidential vs anonymous testing, names reporting, partner notification and domestic violence screening</td>
</tr>
<tr>
<td>• Obtain consent</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Describe/provide HIV test (blood, oral, urine, or rapid)</td>
</tr>
<tr>
<td>• Make a plan to deliver results or have patient wait for rapid results</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Support During Testing and Afterward</th>
</tr>
</thead>
<tbody>
<tr>
<td>• HIV-seronegative</td>
</tr>
<tr>
<td>– HIV testing by itself is not prevention: provide prevention strategies and referrals</td>
</tr>
<tr>
<td>– Clarify if need to retest in 3 months (window period)</td>
</tr>
<tr>
<td>• HIV-seropositive</td>
</tr>
<tr>
<td>– Provide support and link to care and prevention</td>
</tr>
<tr>
<td>– Review HIV reporting, partner notification and domestic/partner violence issues</td>
</tr>
</tbody>
</table>

Adapted from the pocket guide for the Assess, Consent, Test, Support (ACTS) project of the Adolescent AIDS Program at Montefiore Medical Center (See www.adolescentaids.org).
tion and risk assessment from the pretest counseling and testing program. This is a controversial strategy. If an individual site has time to fit risk assessment and prevention counseling into its counseling and testing program, it should do so; however, the time constraint posed by offering all of these components should not stand in the way of the primary objective of pretest counseling and testing.

**Barriers to HIV Prevention**

A barrier to HIV prevention among adolescents is how they think about the need for prevention. “I don’t think I have anything to worry about. I assume they are negative. If they were positive, they wouldn’t put you at risk. You can tell a lot by appearance” is a typical thought among adolescents in regard to the HIV serostatus of a sexual partner. This way of thinking is often supported by society and current American culture. Sex is commonly portrayed in the entertainment media, but it is rarely accompanied by the depiction of safer-sex practices. There is almost no social marketing regarding HIV and its prevention. In addition, physicians in many areas are still unaware of the risk to young people and are resistant to offering testing.

Still, some progress has been made. As shown in Figure 3, the proportion of sexually active high-school students reporting condom use during their most recent sexual intercourse decreased from 46% in 1991 to 33% in 2003. Reality-based prevention programs that go beyond “abstinence only” are needed to maintain and improve the gains that have been made. Safer-sex practice needs to be discussed as a continuum, starting with issues of communication regarding readiness for sex and decision-making for oneself and with one’s partner. The possibility of abstinence should be discussed, along with ways to be sexually active without exchanging body fluids (ie, heterosexual). Condom use needs to be discussed realistically, acknowledging that although it is not easy and certainly not always convenient, it is nonetheless necessary. Issues arising for youth with older sexual partners need to be addressed. Information on the links among sex, STDs, and HIV and the link between prevention and testing needs to be delivered to young people in ways that they can easily access and understand. The Adolescent AIDS Program has attempted to convey these messages through the intermittently published magazine “The Deal,” which talks to kids about sexuality in language they use and understand and does so in the context of other lifestyle issues. (See www.adolescentaids.org.) Other public health initiatives have included social marketing campaigns using radio, outdoor media, and handouts to reach young people.

**Conclusion**

Currently there is a sense of complacency about the HIV/AIDS epidemic in the United States, but the epidemic is not over. It is now, officially, the worst epidemic in human history. Here in the United States, more than half of the 40,000 new infections each year are among the youth population, and most of the young people who are infected do not know it and are not in treatment. Safer sexual practice is the key to preventing HIV infection and protecting America’s youth.

**Figure 3.** Proportion of currently sexually active high-school students reporting condom use at most recent sexual intercourse. *Significant linear increase, P<.05. Adapted from the Centers for Disease Control and Prevention, National Youth Risk Behavior Surveys, 1991-2003

**Suggested Reading**


Guidelines for Authors and Contributors

The International AIDS Society–USA publishes *Topics in HIV Medicine* as a resource for physicians and other health care practitioners who are actively involved in HIV and AIDS care. The journal is indexed in *Index Medicus*/MEDLINE and is distributed to approximately 12,000 national and international subscribers.

The following guidelines describe the types of articles and contributions published in the journal, outline its policies, and provide instructions for authors. For further information, contact *Topics in HIV Medicine* at topics2005@iasusa.org.

Categories of Articles

**Perspectives.** Perspectives articles are summaries of selected talks given at International AIDS Society–USA continuing medical education courses. An International AIDS Society–USA medical writer prepares a summary manuscript from a transcript of the talk. The manuscript is reviewed and edited by the specific course presenter and the journal’s appointed peer reviewers.

**Reviews.** *Topics in HIV Medicine* welcomes original review articles on current issues in HIV and AIDS for consideration. *Topics in HIV Medicine* does not publish original research. Manuscripts should be 3000 to 6000 words (excluding references, tables, and figures) and should include numbered references and a brief introductory abstract of approximately 100 to 200 words. Original, adapted, or reprinted figures and tables may be included and should be cited in the text and accompanied by a brief title. Adapted and reprinted work requires proof of permission obtained from the original publishers and authors. Authors interested in submitting unsolicited manuscripts are encouraged to submit an outline or abstract of the proposed manuscript first; please contact the editor for further information.

**Editorials.** *Topics in HIV Medicine* and its editors invite submission of editorials. Editorials should be approximately 500 to 1500 words (excluding references) and should include numbered references.

Special Contributions. A special contribution article often represents the unique contribution (such as a consensus statement) of an author or group of authors and is invited by the editors.

**Stories.** Stories for the “Telling Stories” column share the experiences of those involved in HIV and AIDS care. Stories may be approximately 800 to 3500 words; unsolicited submissions are welcome.

**Letters to the Editor.** Letters to the editor are welcome and should be sent to the address listed below.

**Submission of Manuscripts**

Manuscripts should be submitted via e-mail or PC-compatible floppy disk with a double-spaced hard copy to the address below. Each manuscript should include a separate Authorship Form, which is available online at http://www.iasusa.org/ pub or may be obtained by contacting the editor at the address below. Outlines or abstracts of proposed manuscripts are welcome and may be sent via mail or e-mail.

Editor, *Topics in HIV Medicine*
International AIDS Society–USA
425 California Street, Suite 1450
San Francisco, CA  94104-2120
E-mail: topics2005@iasusa.org

Receipt of submitted manuscripts will be acknowledged by editorial staff, and submissions will be reviewed by peer reviewers. Acceptance for publication is based on the quality and relevance of the work.

Copyright

Copyright to manuscripts published in *Topics in HIV Medicine* is owned by the International AIDS Society–USA. All authors and contributors of manuscripts accepted for publication, with the exception of US federal government employees, must sign a copyright transfer form as a condition of publication.

Authorship Requirements

*Topics in HIV Medicine* uses the definition of authorship formulated by the International Committee of Medical Journal Editors and published in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals. This definition states: “Authorship credit should be based only on (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Conditions 1, 2, and 3 must all be met. Acquisition of funding, the collection of data, or general supervision of the research group, by themselves, do not justify authorship.”

Financial Disclosure

It is the policy of the International AIDS Society–USA to ensure balance, independence, objectivity, and scientific rigor in all of its educational programs. To that end, all authors and contributors of articles published in *Topics in HIV Medicine* are expected to disclose to readers any significant financial interest or other relationship with any organization having financial interest in the content of the manuscript. Financial interests include employment, consultancy, honorarium, grant/research support, major stock ownership, and membership in a speakers bureau. The complete financial disclosure statements for all authors and contributors are published with the articles.

---

Topics in HIV Medicine® Subscription Request
Address Change

Topics in HIV Medicine is published 4 to 6 times per year. Please complete this form if you would like to obtain a complimentary subscription or notify the International AIDS Society–USA of a change in address. Subscribers will also receive information about upcoming International AIDS Society–USA continuing medical education courses.

Please mark the appropriate box:

- [ ] I would like to subscribe to Topics in HIV Medicine. Please send my subscription to the address below.
- [ ] I am a current subscriber. Please note my change of address below.

IAS–USA ID Number ___________ Please see upper left corner of mailing address as shown in sample.

First Name ___________________________ M I Last Name ___________________________

Degree or License (MD, RN, PA, none, etc) ___________________________ Title ___________________________

Institution or Organization ___________________________

Specialty / Primary Field of Interest ___________________________

Address ( _Home Address _Work Address ) ___________________________

City ___________________________ State / Province ___________________________

Postal Code ___________________________ Country ___________________________

Telephone ___________________________ Facsimile ___________________________

E-mail Address ___________________________

Currently, for how many HIV-infected patients are you providing care? ___________

What percentage of your patients are HIV-infected? _______%

Do you work for a commercial company? Yes [ ] No [ ]
(eg, pharmaceutical, diagnostic, medical product, advertising, insurance, investment, communications)

If yes, please indicate company: ___________________________

Fax or mail this form to: International AIDS Society–USA
425 California Street, Suite 1450
San Francisco, CA 94104-2120
Fax: (415) 544-9401

FOR INTERNAL USE ONLY
DATE _______________ INITIALS ____________ CHANGES ___________________________

107
Established in 1992, the International AIDS Society–USA is a not-for-profit physician education organization. The mission of the International AIDS Society–USA is to improve the treatment, care, and quality of life of persons with HIV and AIDS through balanced, relevant, innovative, and state-of-the-art education and information for practitioners who are actively involved in HIV and AIDS care. The organization’s educational activities are particularly intended to bridge clinical research and patient care.

**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. Michael S. Saag, MD, of the University of Alabama at Birmingham, is editor in chief of the series, and Meg D. Newman, MD, of the University of California San Francisco, is co-editor.

**NEW!**

Management of Virologic Failure in Treatment-Experienced Patients
Carlos Zala, MD, and Pedro Cahn, MD, PhD

Diagnosis and Management of Immune Reconstitution Syndrome in HIV-Infected Patients
Jaime C. Robertson, MD, and Carl J. Fichtenbaum, MD

**UPDATED!**

Perinatal HIV: Special Considerations
Deborah Cohan, MD, MPH

The Importance of Viral Fitness and Drug Resistance in Chronic and Recent HIV Infection
Mark A. Wainberg, PhD, and Dan Turner, MD

**2005/2006 CME Courses**

*Improving the Management of HIV Disease®* continues to focus on cutting-edge, scientifically rigorous agendas presented by leading experts in the field. The one-day, advanced level CME courses scheduled for the remainder of 2005 through early 2006 are as follows:

**New York, NY**
Monday, October 17, 2005
New York Marriott Marquis
Chair: Douglas D. Dieterich, MD, Vice-Chair: Roy M. Gulick, MD, MPH

**Los Angeles, CA**
Friday, February 24, 2006
Hilton Los Angeles/Universal City
Chair: Ronald T. Mitsuyasu, MD

**Atlanta, GA**
Monday, March 6, 2006
Westin Peachtree Plaza
Chair: Michael S. Saag, MD, Vice-Chair: Jeffrey L. Lennox, MD

**New York, NY**
Wednesday, March 15, 2006
New York Marriott Marquis
Chair: Gerald H. Friedland, MD, Vice-Chair: Paul A. Volberding, MD

**San Francisco, CA**
Tuesday, April 4, 2006
San Francisco Grand Hyatt
Chair: Robert T. Schooley, MD, Vice-Chair: Stephen E. Follansbee, MD

**Chicago, IL**
Monday, May 8, 2006
Marriott Chicago Downtown
Chair: John P. Phair, MD, Vice-Chair: Harold A. Kessler, MD

**Washington, DC**
Friday, May 19, 2006
JW Marriott on Pennsylvania Avenue
Chair: Henry Masur, MD, Vice-Chair: Michael S. Saag, MD

**Co-Organized Sessions at Scientific Meetings**

The International AIDS Society–USA co-sponsors sessions at the annual Infectious Diseases Society of America (IDSA) meeting and at the annual *Interscience Conference on Antimicrobial Agents and Chemotherapy* (ICAAC). The agendas feature current clinical issues and controversies presented in interactive formats, with expert faculty using clinical decision points as springboards for discussion of new data and updates in diagnostic and therapeutic issues in HIV management.

**ICAAC 2005**
Washington, DC

The Interactive Session has been rescheduled
*Current Issues and Controversies in HIV Infection Management*
Chairs: Judith S. Currier, MD, and Diane V. Havlir, MD
Due to Hurricane Katrina and its devastating effect on New Orleans, the ICAAC organizers have rescheduled the conference for December 16-19, 2005, in Washington DC. Please visit www.icaac.org or www.iasusa.org for updated information about this interactive session.

**IDSA 2005 Interactive Session**
San Francisco, CA

Friday, October 7, 2005, 4:15 pm-6:15 pm
*Clinical Management of HIV Infection*
Chairs: Paul A. Volberding, MD, and Valerie E. Stone, MD

For information about any of these programs, please contact the International AIDS Society–USA.
Phone: (415) 544-9400 • Fax: (415) 544-9401 • E-mail: info2005 “at” iasusa.org • Web Site: www.iasusa.org
Visit our Web site at www.iasusa.org for...

• New Cases on the Web presentations, including “Clinical Management of Treatment-Experienced Patients Presenting with Virologic Failure”

• Recent Issues of *Topics in HIV Medicine*

• Continuing Medical Education Courses: Schedules and Agendas

• Treatment Guidelines