Perspectives

Sustaining HIV Prevention: HIV Testing in Health Care Settings

Kevin A. Fenton, MD

Epidemiology of HIV and AIDS and HIV Testing Trends • Routine Testing: Reaching Those at Risk and the Undiagnosed • Revised Centers for Disease Control and Prevention Recommendations on Testing • Moving Forward

HIV Resistance: Frequency, Testing, Mechanisms

Daniel R. Kuritzkes, MD

Prevalence of Antiretroviral Resistance • Testing Methods • Resistance to Newer Drugs

Cardiovascular Risk and Management in HIV-infected Patients

Oluwatoyin Adeyemi, MD

Cardiovascular Risk in HIV-infected Persons • Management of Cardiovascular Risk • Case History

Diagnosis and Management of Hepatitis B Virus and HIV Coinfection

Marion G. Peters, MD

Characteristics of Coinfection • Initial Evaluation • Management
About This Issue

This issue features 4 Perspective articles taken from presentations given at recent International AIDS Society–USA Continuing Medical Education courses. One Perspective article reviews the recent recommendations for routine HIV testing in the general population by the Centers for Disease Control and Prevention, based on a presentation by Kevin A. Fenton, MD, PhD, at the 10th Annual Ryan White HIV/AIDS Program Clinical Update in June 2007 in Phoenix, Arizona. A second Perspective article summarizes a presentation on the frequency, testing, and mechanisms of HIV resistance given by Daniel R. Kuritzkes, MD, in San Francisco in May 2007. Dr Oluwa-toyin Adeyemi offered a discussion of cardiovascular risk and risk management in HIV-infected persons at a course in Chicago in May 2007, which is summarized here. A fourth Perspective article is based on a presentation made by Dr Marion G. Peters in San Francisco in May 2007 on the characteristics, evaluation, and management of hepatitis B virus in HIV-infected persons.

Topics in HIV Medicine®

Topics in HIV Medicine (formerly Improving the Management of HIV Disease) is published by the International AIDS Society–USA. This journal is intended to be a resource for physicians and other health care practitioners who are actively involved in HIV and AIDS care.

Editorial Policy

The views and opinions expressed in this journal are those of the contributors and do not necessarily reflect the views or recommendations of the International AIDS Society–USA. Topics in HIV Medicine is supported through educational grants from several commercial companies that are committed to supporting CME in the field of HIV and AIDS. In the interest of an objective, balanced, and scientifically rigorous publication, the International AIDS Society–USA seeks funding from companies with competing products; these companies have no input or control over the journal content or the selection of contributors.

All authors and contributors provide disclosures of financial interests, and this information is available at the end of each article.

This journal may contain information about the investigational uses of drugs or products that are not approved by the US Food and Drug Administration. Please consult full prescribing information before using any medication or product mentioned in Topics in HIV Medicine.

Copyrights and Reprints

The contents of Topics in HIV Medicine are protected by copyright. We welcome reference to and use of portions of this journal; however, we do require that permission to reproduce or use any part of the journal be obtained from the International AIDS Society–USA. In the case of reprinted or adapted materials where the International AIDS Society–USA does not own the copyright, permission to reproduce these materials must be obtained directly from the original source. For more information about reprints, please send an e-mail to topics2007@iasusa.org.

Subscription Information

Topics in HIV Medicine is published 4 to 6 times a year. To obtain a complimentary subscription or notify the International AIDS Society–USA of a change in address, please contact the International AIDS Society–USA at the address listed below or use the Subscription Request/Address Change form at the back of this issue.

Correspondence

Topics in HIV Medicine welcomes editorial correspondence. Address letters to:

Editor, Topics in HIV Medicine
International AIDS Society–USA
425 California Street, Suite 1450
San Francisco, CA 94104-2120
Phone: (415) 544-9400
Fax: (415) 544-9401
Website: http://www.iasusa.org
E-mail: topics2007@iasusa.org

On the Web

Current and previous issues of Topics in HIV Medicine are available online at www.iasusa.org.

ISSN 1542-8826
Printed in USA on acid-free paper
December 2007

©2007 International AIDS Society–USA
CONTENTS

Perspectives
Sustaining HIV Prevention: HIV Testing in Health Care Settings
Kevin A. Fenton, MD

HIV Resistance: Frequency, Testing, Mechanisms
Daniel R. Kuritzkes, MD

Cardiovascular Risk and Management in HIV-Infected Patients
Oluwatoyin Adeyemi, MD

Diagnosis and Management of Hepatitis B Virus and HIV Coinfection
Marion G. Peters, MD

Announcements
Educational Programs of the International AIDS Society–USA
2008 CME Course Schedule and Registration Form
Subscription Request/Address Change Form
Guidelines for Authors and Contributors
Perspective

Sustaining HIV Prevention: HIV Testing in Health Care Settings

The Centers for Disease Control and Prevention (CDC) recently issued revised HIV testing recommendations, including a recommendation for routine, voluntary screening for all persons aged 13 years to 64 years in health care settings. Screening is not based on risk, and prevention counseling in conjunction with HIV testing in health care settings is not required. The revisions were motivated in part by concerns regarding the substantial undiagnosed fraction of prevalent HIV infections in the United States and evidence awareness of HIV infection leads to substantial reductions in high-risk sexual behavior. It is hoped that implementation of these recommendations, which will require coordination and education initiatives, will increase identification of the large number of HIV-infected individuals unaware of their infection status and facilitate their linkage to care. This article summarizes a presentation on HIV prevention and HIV testing in health care settings made by Kevin A. Fenton, MD, PhD, at the 10th Annual Ryan White HIV/AIDS Program Clinical Update in June 2007 in Phoenix, AZ. The original presentation is available as a Webcast at www.iasusa.org.

Epidemiology of HIV and AIDS and HIV Testing Trends

The prevalence of AIDS in the United States continues to increase in the setting of a steady rate of new cases per year and longer survival associated with the use of potent antiretroviral therapy. However, the post-potent antiretroviral therapy era is marked not only by improved survival among patients receiving high-quality treatment, but by increasing evolution of the HIV epidemic among individuals who are socially disadvantaged or have poor access to medical services. This includes an increasing concentration of the epidemic among individuals with high rates of sex partner change and involvement in sexual and social networks largely unlinked to such services. New AIDS cases occur disproportionately among blacks and Hispanics. Among 40,733 new cases of AIDS reported in 2005, nearly 50% were in blacks, who account for 13% of the population of the United States, and 18% were in Hispanics, who account for 14% of the population (see Figure 1).

A 2006 survey by the Kaiser Family Foundation found that of non-elderly adults, 55% had been tested for HIV, including 21% within the prior 12 months (Kaiser Family Foundation Survey of Americans on HIV/AIDS, conducted March 24 to April 18, 2006). Percentages of individuals ever tested and tested within the prior 12 months were 48% and 16%, respectively, among whites; 70% and 41%, respectively, among blacks; and 56% and 28%, respectively, among Hispanics. Data from 2002 indicate that whereas 44% of all HIV tests are performed in the private physician or Health Maintenance Organization setting, positive tests in this setting account for only 17% of all positive tests. Reflecting the fact that poor, uninsured, or socioeconomically disadvantaged individuals in the United States typically use hospital and emergency department (ED) settings for primary care, testing in this setting accounts for 22% of all tests but 27% of all positive tests. Similar high yields of positive tests occur in community clinics (9% of all tests, 21% of positive tests), HIV counseling and testing settings, corrections facilities, sexually transmitted disease (STD) clinics, and drug treatment clinics (see Figure 2).

Routine Testing: Reaching Those at Risk and the Undiagnosed

Americans have a generally positive view on routine HIV testing. The Kaiser Family Foundation survey showed that 65% of respondents agreed with the statement “HIV testing should be

---

Dr Fenton is Director of the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention at the Centers for Disease Control and Prevention in Atlanta, GA.
treated just like routine screening for any other disease, and should be included as part of regular check-ups and exams.” In contrast, 27% agreed with the statement “HIV testing is different from screening for other diseases, and should require special procedures, such as written permission from the patient in order to perform the test.”

It is currently estimated that of the approximately 1.2 million individuals living with HIV and AIDS in the US, 25% are undiagnosed and 25% are diagnosed but not receiving care. The undiagnosed are disproportionately people of color, and estimates from 2003 indicate that of undiagnosed individuals, blacks account for approximately 50%, whites for approximately 30%, and Hispanics for approximately 20% (see Figure 3, left). The undiagnosed are also somewhat more likely to have been infected via sexual contact, with transmission via heterosexual sex or sex among men who have sex with men (MSM) being estimated to account for approximately 80% of undiagnosed cases (see Figure 3, right). A 2004 to 2005 study of HIV testing among MSM in Baltimore, Los Angeles, Miami, New York, and San Francisco showed that 48% of HIV-seropositive individuals were unaware of their infection status, including 67% of blacks, 18% of whites, and 48% of Hispanics (MMWR, 2005). These findings are not inconsistent with the Kaiser Family Foundation survey on prevalence of testing. First, the high rate of undiagnosed infection despite the fairly high rates of reported testing may suggest that both prevalence and incidence of infection is high and exposure is frequent in risk groups, with the testing rates being insufficient to keep pace with incidence. Second, failure to return for test results is common. For example, a 2000 study indicated that among individuals at high risk for infection, 10% of MSM, 20% of high-risk heterosexuals, and 27% of injection drug users did not return for test results (Sullivan, JAIDS, 2004).

Revised Centers for Disease Control and Prevention Recommendations on Testing

The Centers for Disease Control and Prevention (CDC) issued revised recommendations for HIV testing of adults, adolescents, and pregnant women in health care settings in September 2006 (Centers for Disease Control and Pre-
vention, *MMWR Recomm Rep*, 2006). In part, the revisions were motivated by evidence gained in continued experience in HIV testing, including evidence indicating that awareness of HIV infection leads to substantial reductions in high-risk sexual behavior and evidence from numerous studies indicating that HIV screening is cost-effective, even in populations with HIV prevalence as low as 0.01%. There is an additional element of urgency to improving testing, since late testing is now common and the full benefit of effective treatments is not being realized.

**Adults and Adolescents**

The revised recommendations call for routine, voluntary HIV screening for all persons aged 13 years to 64 years in health care settings. This screening is not based on risk, although screening should be repeated at least annually in persons with known risk. It is recommended that screening be opt-out screening with the opportunity to ask questions and the option to decline testing, and that HIV testing consent be included in the general consent for health care.

Prevention counseling in conjunction with HIV testing in health care settings is not required. Instead, patients with positive test results are to be linked to clinical care, counseling, support, and prevention services. Those with negative results who are known to be at high risk should be advised of the need for periodic retesting and offered or referred for prevention counseling. The prevention counseling recommendations are intended for all health care settings but are not intended for nonclinical settings; thus, for example, in community outreach programs (eg, community-based organizations and nongovernmental organizations), prevention counseling should remain linked with HIV testing.

Recommendations on referral to care remain unchanged; that is, all HIV-seropositive persons should be referred or linked to care. Recommendations for persons in low-prevalence settings call for initiation of screening, with screening no longer being warranted if HIV prevalence is shown to be less than 1 case per 1000 population.

**Pregnant Women**

The recommendations call for universal opt-out screening for pregnant women, with inclusion of HIV testing in the panel of prenatal screening tests and inclusion of HIV testing consent in consent for prenatal care. A second HIV test should be performed in the third trimester of pregnancy for women (1) known to be at risk of infection; (2) in high-incidence and high-prevalence jurisdictions; or (3) in high-prevalence health care facilities. Opt-out rapid testing is recommended for women presenting in labor and delivery with undocumented HIV serostatus. Antiretroviral prophylaxis should be initiated on the basis of rapid test results, and newborns should be tested if the mother’s infection status is unknown.

**Moving Forward**

The initiative to routinize HIV testing is already yielding results in terms of increasing testing, identifying greater numbers of HIV-infected individuals, and linking those individuals to care. The New York City Health and Hospitals Corporation, which serves approximately 1.3 million New Yorkers and is the largest municipal hospital system in the country, has undertaken an HIV testing expansion initiative. The goals are to (1) increase the number of patients who know their HIV serostatus, with an objective of testing 100,000 patients per year; and (2) increase the proportion of HIV-infected patients who enter care early (ie, reduce the number of concurrent HIV and AIDS diagnoses). During the first year of the initiative, the number of patients tested increased by 57%, from 58,785 in fiscal year 2005 to 92,123 in fiscal year 2006. The number of new HIV diagnoses nearly doubled to 1514. Of newly diagnosed patients, 76% (589 of 774) received and kept their first appointment for primary HIV care. A report from the San Francisco Department of Public Health (Zetola et al, *JAMA*, 2007) shows a marked increase in number of tests performed and an increase in number of positive tests per month from 20.6 to 30.6 as a result of measures to streamline HIV testing, including removing the requirement for written consent for testing (see Figure 4). Consent was instead obtained by the physicians, a separate test form for the HIV test was eliminated, and the test was included as part of other diagnostic test requirements.

To support expansion of routine HIV testing, the CDC has formed planning
groups to address issues in domains where gain from testing activities can be maximized (Table 1). Numerous partnerships with national organizations are being strengthened to support implementation of recommendations through training and technical assistance, including partnerships with the National Medical Association, American Medical Association, American Academy of Pediatrics, Society of General Internal Medicine, HIV Medicine Association, American Academy of HIV Medicine, Health Research and Educational Trust of the American Hospital Association, and the National Association of Community Health Centers.

As an example of current initiatives, the CDC and partners are formulating implementation guidance for various settings in collaboration with key stakeholders, including specific guidance for hospitals (ED, inpatient, labor and delivery), STD clinics, substance abuse treatment centers, community health centers, correctional health facilities, primary care settings, urgent care clinics, and prenatal care clinics. Over the past year, steps in fostering implementation have included regional workshops held by the CDC for high-priority EDs in 5 cities, a close partnership with the National Medical Association and its primary care providers in select cities with high rates of disease in blacks, and a partnership with one pharmaceutical company in acute care testing in 8 cities.

The CDC also has been working with sister federal agencies and health insurers on reimbursement for screening. Work is ongoing with the Centers for Medicare and Medicaid Services and state Medicaid directors to enable HIV testing to be considered part of the Early Periodic Screening, Diagnosis, and Treatment Program. Another set of problems being addressed is that of HIV testing in the large numbers of uninsured persons in this country. Implementation of expanded testing also requires working with state and local jurisdictions to implement policies to support the current recommendations. At the time of preparing this report, 26 states and the District of Columbia require written consent for HIV testing, 24 states require specific pretest counseling, 7 have specific training and certification requirements for individuals providing pretest counseling, and 5 require test results to be given face-to-face by trained individuals. Despite apparent conflict of such policies with CDC recommendations, screening can still be implemented in these locales with education and collaboration.

To support the HIV testing initiative during fiscal year 2007, the CDC realigned $35 million in agency funds to foster implementation of testing in 23 jurisdictions with the highest incidence of reported AIDS cases. The majority of these funds will be given to health departments for testing in clinical settings.

**Summary**

HIV testing is an important HIV prevention strategy that serves as a component of a comprehensive prevention strategy. The CDC has issued revised recommendations for HIV screening in adults, adolescents, and pregnant women in health care settings. HIV screening in health care settings is feasible. Implementation of these recommendations will require new partnerships and strategies in a variety of domains, and a number of initiatives are under way to build and support these partnerships and strategies.


Dr Fenton had no relevant financial affiliations to disclose.

**Suggested Reading**


Prevalence of Antiretroviral Resistance

The prevalence of antiretroviral-resistant virus in patients with newly diagnosed HIV infection according to Centers for Disease Control and Prevention (CDC) surveys is shown in Table 1. In the most recent survey, covering 2003 to 2006, 10.9% of patients exhibited resistance to any drug, with the majority having resistance to nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs) and 1.9% having resistance to at least 1 drug in numerous drug classes. At one point, data for this latter period indicated a prevalence rate of approximately 15% for resistance to any drug, and it is unclear whether a peak and decline in prevalence occurred or whether prevalence has indeed been stable at around 10% for the past 4 or 5 years. It should also be noted that very few of the patients with multiclass resistance exhibit resistance to multiple drugs or all drugs within multiple classes.

Data on long-term risk of developing resistance from the UK Collaborative HIV Cohort (CHIC) study in 4306 patients beginning antiretroviral therapy with 2 nucleoside analogue reverse transcriptase inhibitors (nRTIs) and a third agent show that risk of accumulating resistance mutations to any drug over 6 years was 27%, in the context of an overall treatment failure rate of 38% (Phillips et al, AIDS, 2005). As shown in Figure 1, resistance to 2 and 3 drug classes occurred in approximately 20% and 5% of patients, respectively, after 6 years. However, these data were first reported in 2004 and may reflect antiretroviral therapy practices from as early as 1998. With use of newer, better-tolerated, and more potent regimens in recent years (including fixed-dose nRTI combinations, once-daily regimens, ritonavir-boosted protease inhibitors [PIs], and efavirenz-based regimens), virologic failure rates and resistance rates are likely lower than those reflected in this study. This impression is supported by some data, including those from a chart review study in the University of North Carolina HIV Cohort Study (n = 1466; Napravnik et al, Antivir Ther, 2006). Overall, 8% of patients had triple-class resistance, with independent predictors of such resistance consisting of prior use of antiretrovirals (odds ratio [OR] 1.7) and use of a nonantiretroviral regimen as the first treatment regimen (OR, 1.7). Of 24 patients with triple-class resistance whose first regimen was potent antiretroviral therapy, the regimen included an unboosted PI in 21 (87.5%) and nelfinavir in 15. These findings suggest that triple-class resistance is indeed likely to become less common in patients initiating antiretroviral therapy as currently practiced.

Based in part on evidence that resistance testing before treatment is cost-effective when the prevalence of resistance in untreated patients is greater than a threshold, the importance of using resistance testing for treatment selection has been emphasized. Initial resistance testing is most useful when resistance mutations are likely to be present at baseline. Data on resistance patterns for new drugs and new drug classes are beginning to emerge. This article summarizes a presentation on HIV resistance made by Daniel R. Kuritzkes, MD, at an International AIDS Society–USA Continuing Medical Education course in San Francisco in May 2007. The original presentation is available as a Webcast at www.iasusa.org

Table 1. Centers for Disease Control and Prevention Surveys: Drug-resistant HIV Among Newly Diagnosed Patients

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Any drug</td>
<td>5.5</td>
<td>8.8</td>
<td>10.7</td>
<td>10.4</td>
</tr>
<tr>
<td>nRTI</td>
<td>5.1</td>
<td>7.1</td>
<td>7.7</td>
<td>3.6</td>
</tr>
<tr>
<td>NNRTI</td>
<td>0.4</td>
<td>2.1</td>
<td>1.7</td>
<td>6.9</td>
</tr>
<tr>
<td>PI</td>
<td>0</td>
<td>0.8</td>
<td>3.0</td>
<td>2.4</td>
</tr>
<tr>
<td>≥2 drug classes</td>
<td>0</td>
<td>1.3</td>
<td>1.3</td>
<td>1.9</td>
</tr>
</tbody>
</table>

nRTI indicates nucleoside analogue reverse transcriptase inhibitor; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor. Adapted from Bennett et al, 9th CROI, 2002; Bennett et al, 12th CROI 2005; Wheeler et al, 14th CROI, 2007.

Dr Kuritzkes is Professor of Medicine at Harvard Medical School and Director of AIDS Research at Brigham and Women’s Hospital in Boston, MA.
than 1%, pretreatment testing is recommended by Department of Health and Human Services and International AIDS Society–USA guidelines (Hammer et al, J Infect Dis, 2003; Hirsch et al, Clin Infect Dis, 2003). Genotypic testing is preferred for initial testing, because it at least identifies minority variants that constitute more than 20% of the viral pool in a patient, whereas reduced susceptibility might not yet be evident on phenotypic testing. Resistance testing should be performed at the first evaluation after diagnosis of infection.

Whether repeat testing should be performed in patients for whom there is a considerable duration between initial testing and the start of antiretroviral therapy is unresolved. There is a small chance that an individual might acquire superinfection with a resistant strain after initial testing. However, given the low likelihood of this occurrence, it is rational to begin antiretroviral therapy selected on the basis of the initial resistance test, assess HIV RNA level at 2 and 4 weeks, and perform resistance testing again if the expected viral response is not observed.

Dr Kuritzkes and colleagues recently performed a case-cohort study in the population of AIDS Clinical Trial Group (ACTG) 5095 study that provides information on risk of treatment failure in patients with pre-existing antiretroviral mutations at the time of first antiretroviral therapy (Kuritzkes et al, J Infect Dis, in press). The ACTG 5095 study results showed that there was no improvement in virologic response or risk of treatment failure with the addition of abacavir to efavirenz plus zidovudine/lamivudine after a median of 144 weeks. The case-cohort study was performed because assessment of baseline samples in patients in whom therapy was failing in ACTG 5095 showed an appreciable frequency of resistance at baseline.

Patients in whom therapy had failed and in whom baseline genotypic testing had subsequently been performed were pooled with a randomly selected subpopulation in the trial. Overall, baseline genotypic testing was available for 191 treatment failures and 151 nonfailures. Baseline efavirenz resistance was present in 8% of patients with treatment failure versus 2% of nonfailures; lamivudine resistance was present in 1% versus 0%; and PI resistance was present in 3% versus 2%. Overall, the risk of treatment failure was markedly higher for patients with efavirenz resistance at baseline versus no efavirenz resistance (relative hazard, 2.27). Each of the 3 patients with baseline efavirenz resistance who did not have treatment failure had received the 4-drug regimen.

**Testing Methods**

Genotypic and phenotypic testing each have advantages and disadvantages. Advantages of genotypic testing include that it is less expensive and faster than phenotypic testing. In addition, some idea of potential resistance to a new drug in an established class can be gained from knowing the resistance mutations for other members of the class. Genotypic testing also permits determination of viral subtype and ruling out of contamination or sample mix-up by phylogenetic analysis. A disadvantage of genotypic testing is its reliance on algorithms for interpretation, given the fact that algorithms rely on expert opinion and thus emerge and are updated slowly. It is also difficult to predict the net effect of mutational interactions (eg, resistance mutations for a particular drug may increase or decrease susceptibility to another drug) solely on the basis of genotyping. Because this problem is fairly common with PI mutations, phenotypic testing may be more useful when attempting to identify resistance or sensitivity of virus to individual PIs and in highly treatment-experienced patients.

Advantages of phenotypic testing include the fact that the amount of drug needed to inhibit the virus (at least in the laboratory) is specified, a measurement that includes the net effect of multiple mutations, if present. For this reason, as noted, phenotypic testing results may be more helpful for decisions regarding PIs. Phenotypic testing also detects resistance that arises from previously unidentified resistance mutations. Disadvantages of the assays include their high cost and lengthy turnaround time, and the fact that values in the susceptible range may be reported when there are resistant minority variants present, with identification of the latter requiring genotypic testing. If sequencing is not provided, phenotypic testing also does not include viral subtyping or provide the ability to rule out sample contamination or mix-up. Further, the reliability of clinical cutoff values reported for some drugs is uncertain, because the values are close to assay precision limits. Owing to regulatory issues, phenotypic testing of patients with regard to new drugs is frequently not available until after US Food and Drug Administration (FDA) approval of the agents.

Virtual phenotypic testing is an approach to interpreting the genotype in which a patient’s genotype is matched in a database correlating genotype with phenotype. Advantages include the fact that, as noted for the genotypic test, virtual phenotypic testing is less expensive and time-consuming to run than performing actual phenotypic testing, and it is convenient that the virtual phenotypic testing provides upper and lower cut-off values for most drugs. Disadvantages include the fact that the current version of the virtual phenotypic test has not been validated in clinical
trials and that it provides only an estimate of the likely phenotype. Further, the predictions can be only as good as the matches in the database, thus, for example, predictions made on the basis of mutation patterns that are not represented or are underrepresented in the database may have questionable accuracy.

Regarding which of these assays to use and when, Dr. Kurtzkes’ opinion is that genotypic testing may be most useful for initial evaluation and after failure of a first- or second-line regimen, at which points resistance patterns are more likely to have a straightforward interpretation. Phenotypic testing, usually in combination with genotypic testing, may be more useful in patients with a more complex history of treatment failure that is likely associated with more complex resistance patterns. The approach to testing is limited by access, which may be affected by what tests the payer is willing to support in particular settings.

**Resistance to Newer Drugs**

**Tipranavir**

Of some 21 mutations at 16 protease codons identified as contributing to tipranavir resistance, many (eg, at codons 13, 35, 43, 58, 74, and 83) have not been associated with resistance to other PIs. Major mutations associated with resistance to other PIs do not appear to contribute to the tipranavir mutation score (eg, D30N, G48V, N88D, and perhaps L90M). Initial analyses showed that response to tipranavir-containing regimens was inversely correlated with the number of mutations present from the set including L33F; V82L or T; I84V; or L90M. Subsequent analyses led to development of a more comprehensive tipranavir resistance score based on mutations at 16 positions in protease (L10V; I13V; K20M, R, or V; L33F; E55G; 36I; K43T; M46L; 147V; I54A, M, or V; Q58E; H69K; T74P; V82L or T; N83D; and I84V). An increasing number of these mutations was associated with decreased in vitro susceptibility of HIV-1 isolates and decreased virologic response to tipranavir in the phase II and III clinical trials of this drug (Baxter et al, *J Virol*, 2006). Analysis of predictors of response to tipranavir/ritonavir in randomly selected samples from the Randomized Evaluation of Strategic Intervention in Multidrug Resistant Patients with Tipranavir (RESIST) 1 and 2 trials showed estimated effects on HIV RNA level at 24 weeks as follows: –0.24 log_{10} copies/mL per mutation in the tipranavir mutation score (each P < .01). The small effect of the active drugs in OBT suggests that resistance may have been misclassified using the genotypic or phenotypic mutation score.

The conclusions regarding tipranavir resistance are that decreased susceptibility is indicated by a 3-fold to less than 10-fold increase in the 50% inhibitory concentration (IC_{50}) value, and that resistance is indicated by a 10-fold or greater increase. For genotypic testing findings, a change of 0 to less than 3-fold in susceptibility at baseline is associated with a key mutation score (at codons 33, 82, 84, and 90) of 0 to 2 and a tipranavir score of 0 to 4; a change of 3-fold to less than 10-fold with scores of 3 and 5 to 7, respectively; and a change of 10-fold or more with scores of 4 and 8 or higher, respectively. The prominent emergent mutations with tipranavir are L33F, I, or V; V82T or L; and I84V.

**Darunavir**

In the Performance of TMC114/ritonavir When Evaluated in Treatment Experienced Patients with PI Resistance (POWER) 1, 2, and 3 studies, 11 mutations were associated with diminished response to darunavir (V11I; V32I; L33F; 147V; I50V; I54L or M; G73S; L76V; I84V; and L89V). Analysis of virologic response at 24 weeks showed reductions of 2.08 log_{10} copies/mL when baseline change in darunavir susceptibility was 10-fold or less, 1.08 log_{10} copies/mL with greater than 10- to 40-fold or less change, and 0.76 log_{10} copies/mL with a greater than 40-fold change; proportions of patients with reduction in viral load to less than 50 copies/mL were 50%, 25%, and 13%, respectively (De Meyer et al, *Antivir Ther*, 2006). Regression analysis indicated estimated fold-changes in darunavir susceptibility of less than 2 with mutations V11I, I54L, G73S, and L89V; 2- to 3-fold with V32I, L33F, and 147V; 3- to 4-fold with I54M, L76V, and I84V, and greater than 4-fold with I50V. Proportions of patients with viral load reductions to less than 50 copies/mL were 64% with no mutations, 50% with 1 mutation, 42% with 2 mutations, 22% with 3 mutations, and 10% with 4 mutations. Darunavir and amprenavir n-fold changes are highly correlated in patient samples, reflecting the sharing of the I50V mutation and other key amprenavir mutations. Darunavir and tipranavir n-fold changes exhibit no clear correlation (Elston et al, 14th CROI, 2007).

The conclusions regarding darunavir resistance in the POWER studies are that baseline darunavir susceptibility is the strongest predictor of virologic response and that clinical cut-off values for intermediate susceptibility and resistance are a 10-fold increase and a 40-fold increase in IC_{50} value, respectively. Darunavir resistance mutations generally occur along with a large number of other PI resistance mutations, and there is diminished response to darunavir when 3 or more of these mutations are present. Resistance data remain to be developed in the treatment-naive and early treatment-failure settings.

**Etravirine**

Week 24 data from the TMC-225-C223 trial showed a 1-log_{10} copies/mL greater reduction in viral load in the etravirine arm versus the control arm. An analysis of the effect of presence of the NNRTI mutations K103N and Y181C in patients receiving etravirine showed no effect of the K103N mutation; presence of the mutation was associated with a 1.70-fold change in susceptibility at baseline and a reduction in viral load of 1.43 log_{10} copies/mL at 24 weeks compared with a 1.95-fold change and a reduction of 1.40
log<sub>10</sub> copies/mL in the absence of the mutation (Vingerhoets et al, 15th IHWDRW, 2006). However, presence of the Y181C mutation was associated with a 4.5-fold change in baseline susceptibility and a reduction in viral load of 0.86 log<sub>10</sub> copies/mL compared with a 1.10-fold change and reduction in viral load of 1.70 log<sub>10</sub> copies/mL when the mutation was absent. Analysis of data from the phase III trials of etravirine identified 13 etravirine-resistance-associated mutations at 9 codons in reverse transcriptase: V90I; A98G; L100I; K101E or P; V106I; V179D or F; Y181C, I, or V; G190A or S (Vingerhoets et al, Antivir Ther, 2007). The IC<sub>50</sub> value for etravirine increased and virologic response decreased with the presence of increasing numbers of etravirine-associated mutations. When 3 or more of these mutations were present, the response to etravirine was no different from the response to placebo.

**Integrate Inhibitors**

In vivo data from phase III studies of the integrate inhibitor raltegravir indicate that there are 2 mutually exclusive pathways to resistance: (1) N155H as the major mutation, with minor mutations of E92Q, V151I, T97A, G163K, and L64M; and (2) Q148K, R, or H as the major mutation, with minor mutations of G140S or A and E138K (Cooper et al, 14th CROI, 2007; Steigbigel et al, 14th CROI, 2007). Resistance to the investigational drug elvitegravir was analyzed in a phase Ib trial. The most common integrate mutations identified were E92Q; E138K; Q148R, K, or H; N155H (each observed in 39%); S147G (32%); and T66I, A, or K (18%) (McColl et al, Antivir Ther, 2007). Virus from subjects experiencing virologic failure in this study showed a mean increase in IC<sub>50</sub> value of greater than 151-fold for elvitegravir and greater than 28-fold for raltegravir compared with control, providing evidence for cross-resistance between these 2 integrate inhibitors. Further confirmation of cross-resistance came from a pilot study in which 2 patients with elvitegravir-resistant virus were treated with raltegravir; virologic failure occurred promptly in both patients (DeJesus et al, IAS, 2007).

**CCR5 Antagonists**

A unique feature of the pattern of resistance being observed with the chemokine receptor R5 (CCR5) antagonist fusion inhibitors (eg, maraviroc and the investigational agent vicriviroc) is the flattening of the percent inhibition versus drug concentration curve, compared with the typical scenario in which the curve is displaced to the right. That is, instead of reduced susceptibility being indicated by the need for a higher concentration of drug to produce a given percent inhibition of virus, a plateau degree of inhibition is reached despite increasing CCR5 antagonist concentration. The mechanisms of resistance include mutations in HIV gp120 that allow recognition of and binding to the drug-bound form of CCR5, resulting in noncompetitive inhibition of the antagonist (Mosley et al, 13th CROI, 2006; Westby et al, J Virol, 2007; Pugach et al, Virology, 2007). One implication of these findings is that susceptibility and resistance will need to be defined in terms of changes in maximal achievable suppression rather than changes in IC<sub>50</sub> value.

Overall, CCR5 antagonist resistance appears to emerge slowly and involves mutations in the V3 and other regions of the viral envelope. Limited data on cross-resistance among these agents are available. Failure is more frequently attributable to emergence and outgrowth of CXC chemokine receptor 4 (CXCR4)-using viruses that preexisted as minority populations before the initiation of CCR5 antagonist therapy.


**Suggested Reading**


Mosley M, Smith-Burchnell C, Mori J, et al. Resistance to the CCR5 antagonist maraviroc is characterized by dose-response curves that display a reduction in maximal inhibition. [Abstract 598.] 13th Conference on Retroviruses and Opportunistic Infections. February 5-8, 2006; Denver, CO.


Educational Programs of the International AIDS Society–USA

Established in 1992, the International AIDS Society–USA is a not-for-profit, HIV clinical specialist-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. These activities have been approved for AMA PRA Category 1 Credit.™

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.

CURRENT PRESENTATIONS
Severe Mycobacterial Infection in a Patient with Advanced AIDS
William J. Burman, MD

HIV-related Renal Disease
Lynda Anne Szczech, MD, MSCE, FASN

HIV-associated Metabolic Complications
Roger J. Bedimo, MD, MS

HIV Correctional Health Care and Discharge Planning: Issues for the Community Provider
Douglas G. Fish, MD, and Sarah Walker, MS

COMING SOON
Initiation of Antiretroviral Therapy Including the Complicated Patient
J. Kevin Carmichael, MD and Sara Vazquez, MD

Strategic Use of Antiretroviral Drugs in Salvage Therapy
Harry W. Lampiris, MD and Elvin H. Gerg, MD

Depression and the HIV-seropositive Patient
Glenn J. Treisman, MD, PhD

New Drugs in Cases of Failure of Antiretroviral Therapy
Jeffrey L. Lennox, MD

Non AIDS-defining Malignancies
Roger J. Bedimo, MD, MS

Save the Date: 2008 Annual Continuing Medical Education Courses
Visit the IAS–USA Website at www.iasusa.org for current course information and online registration

2008 CME Course Schedule
Improving the Management of HIV Disease,® now entering its 16th year, continues to focus on cutting-edge, scientifically rigorous agendas presented by leading experts in the field.

Atlanta, GA
February 26, 2008
Westin Peachtree Plaza
Chairs: Michael S. Saag, MD, and Jeffrey L. Lennox, MD

New York, NY
March 14, 2008
New York Marriott Marquis
Chairs: Gerald H. Friedland, MD, and Paul A. Volberding, MD

Los Angeles, CA
March 31, 2008
Sheraton Los Angeles Downtown
Chairs: Ronald T. Mitsuyasu, MD, and Constance A. Benson, MD

San Francisco, CA
May 6, 2008
Grand Hyatt on Union Square
Chairs: Robert T. Schooley, MD, and Stephen E. Follansbee, MD

Washington, DC
May 13, 2008
Renaissance Washington, DC
Chairs: Henry Masur, MD, and Michael S. Saag, MD

Chicago, IL
May 19, 2008
Marriott Downtown Chicago
Chairs: John P. Phair, MD, and Harold A. Kessler, 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: info2007“at”iasusa.org • Web Site: www.iasusa.org
**2008 CME Course Schedule**

These activities have been approved for AMA PRA Category 1 Credit™

<table>
<thead>
<tr>
<th>Location</th>
<th>Date</th>
<th>Venue</th>
<th>Chairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atlanta, Georgia</td>
<td>Tuesday, February 26, 2008</td>
<td>Westin Peachtree Plaza</td>
<td>Michael S. Saag, MD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Jeffrey L. Lennox, MD</td>
</tr>
<tr>
<td>Los Angeles, California</td>
<td>Monday, March 31, 2008</td>
<td>Sheraton Los Angeles Downtown</td>
<td>Ronald T. Mitsuyasu, MD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Constance A. Benson, MD</td>
</tr>
<tr>
<td>New York, New York</td>
<td>Friday, March 14, 2008</td>
<td>New York Marriott Marquis</td>
<td>Gerald H. Friedland, MD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Paul A. Volberding, MD</td>
</tr>
<tr>
<td>San Francisco, California</td>
<td>Tuesday, May 6, 2008</td>
<td>Grand Hyatt San Francisco</td>
<td>Robert T. Schooley, MD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stephen E. Follansbee, MD</td>
</tr>
<tr>
<td>Chicago, Illinois</td>
<td>Monday, May 19, 2008</td>
<td>Marriott Chicago Downtown</td>
<td>John P. Phair, MD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Harold A. Kessler, MD</td>
</tr>
</tbody>
</table>

**NEW: Intensive Workshops on HIV Management**

NEW! The International AIDS Society—USA has designed interactive and innovative small-group CME workshops for experienced HIV clinical decision makers, led by HIV experts. These workshops are formatted to enhance professional development and improve clinical practice in an exclusive setting, and are restricted to a target audience of roughly 30 attendees.

Several of the workshops are designed to complement the annual full-day courses offered by The International AIDS Society—USA, and additional workshops will be held in various cities around the country.

Topics vary and may include:
- Antiretroviral strategies
- Investigational new antiretroviral drugs
- Managing the complications of therapy
- Managing toxicities and complications of therapy
- Management of antiretroviral failure including use of resistance testing

**Webcasts and Podcasts**

Webcasts and podcasts will be available 2 weeks after the scheduled courses. Be sure to check our website: [www.iasusa.org](http://www.iasusa.org)

**Grant Support**

These courses are supported by educational grants from several commercial companies that are committed to supporting independent CME in the field of HIV/AIDS, and that have competing products. IAS—USA programs are completely independent of the funding companies.

Be sure to visit our website for additional workshop date and location announcements: [www.iasusa.org](http://www.iasusa.org)
Registration for Spring 2008 Now Open

Early registration is strongly recommended, as attendance is limited and these programs fill to capacity quickly.

3 EASY ways to register...

- ONLINE: You can register online with secure credit card payment.
  www.iasusa.org
- FAX: Fax your completed registration form and payment.
  Fax: (415) 544-9402
- MAIL: Mail your completed registration form and payment.
  Attention: Course Registration
  International AIDS Society—USA
  425 California St, Ste 1450
  San Francisco, CA 94111-2120 USA

Comments from Last Year's Participants

“Always a superior conference. I always learn something more about mycobacteria!”

“Excellent conference!"  "Excellent conference – more superior to other conferences I’ve attended.”

“Always a superior conference. I always learn something more about mycobacteria!”

Topics are tailored to the needs of each regional audience and may include:

- Strategies for antiretroviral management
- New antiretroviral drugs and combinations
- Complications and toxicities of HIV and its therapies
- New insights into HIV disease pathogenesis
- Coinfections, such as hepatitis B and C viruses and sexually transmitted infections
- Topics in HIV clinical treatment specific to the needs of the regional HIV specialists

MAIL: Mail your completed registration form and payment.
Fax: (415) 544-9402
www.iasusa.org
Perspective

Cardiovascular Risk and Risk Management in HIV-infected Patients

Patients with HIV infection are at risk of cardiovascular disease from the same factors posing risk in the general population—eg, smoking, dyslipidemia, hypertension, obesity, and diabetes. HIV infection itself and antiretroviral therapy pose additional risk, but available data indicate that the relative rate of myocardial infarction is low and declining in the HIV-infected population. Cardiovascular risk should be addressed before initiation of antiretroviral therapy and frequently during follow-up, and decisions to alter therapy on the basis of adverse changes in metabolic risk factors should be made on an individual basis. Virologic control is the primary goal for HIV-infected persons with cardiovascular risk, and is the primary consideration in determining when to start antiretroviral therapy and when to change regimens. This article summarizes a presentation on cardiovascular risk and risk management in HIV-infected persons made by Oluwatoyin Adeyemi, MD, at an International AIDS Society–USA Continuing Medical Education course in Chicago in May 2007. The original presentation is available as a Webcast at www.iasusa.org.

Cardiovascular Risk in HIV-infected Persons

Traditional risk factors for cardiovascular disease—eg, older age, male sex, previous or family history of cardiovascular disease, hypertension, diabetes, smoking, and lipid abnormalities—increase risk of cardiovascular events in both HIV-infected and uninfected individuals. HIV disease itself may confer additional cardiovascular risk, and antiretroviral therapy may contribute to increased risk, although the absolute increase associated with antiretroviral therapy appears to be low. The best prospective data show that the relative rate of myocardial infarction (MI) in the HIV-infected population is low and decreasing over time, and from a public health standpoint, MI and other cardiovascular events are a relatively small issue compared with overall HIV-related morbidity and mortality.

Cardiovascular risk must be considered in the overall care of adults with HIV infection. However, such risk should not influence the decision of when to initiate antiretroviral therapy, and the decision of which antiretroviral regimen to use should be made based on risk and benefit analysis that includes the clear survival benefit associated with maximal viral suppression.

It should be noted that recent data support better cardiovascular outcomes among HIV-infected persons in whom antiretroviral therapy is continued without interruption, than among those with CD4+ cell count–guided interruptions in treatment. An analysis from the Strategies for Management of Antiretroviral Therapy (SMART) trial showed statistically significant increases in relative hazards for the discontinuation strategy versus continuous treatment for: (1) the composite endpoint of clinical MI, silent MI, coronary artery disease requiring invasive procedure or surgery, or cardiovascular death (hazard ratio [HR], 1.57; \( P = .05 \)); (2) this composite endpoint plus the composite endpoint of peripheral vascular disease, congestive heart failure, or coronary artery disease requiring medication (HR, 1.49; \( P = .05 \)); and (3) both of the foregoing endpoints combined, plus unobserved death from unknown cause (HR, 1.58; \( P = .009 \); Phillips et al, 14th CROI, 2007). The total cholesterol to high-density lipoprotein (HDL) cholesterol ratio was markedly higher in patients in the discontinuation group, a risk factor that may have accounted for the marginally greater risk of cardiovascular disease in that group.

Assessment of cardiovascular risk in HIV-infected individuals without prior cardiovascular disease can be performed as it is in uninfected individuals, using modified Framingham risk scoring to determine 10-year risk in individuals with 2 or more cardiovascular risk factors. The risk score is derived from age, sex, total cholesterol, HDL cholesterol, systolic blood pressure or treatment for hypertension, and presence or absence of cigarette smoking. Diabetes is considered to pose risk for coronary events equivalent to risk posed by history of coronary disease. In addition to traditional risk factors for diabetes, HIV-associated risk factors possibly contributing to insulin resistance and diabetes may include peripheral lipoatrophy, reduced adiponectin, increased liver and muscle fat, inflammatory cytokines, low testosterone levels, oxidant stress, hepatitis C virus infection, and protease inhibitor use. One analysis comparing diabetes risk in patients on antiretroviral therapy with that among matched HIV-uninfected controls found impaired glucose tolerance in 35% versus 5% of patients and a greater than 3-fold increased risk of progression to diabetes over 3 years in those receiving antiretroviral therapy (Grinspoon and Carr, N Engl J Med, 2005).

It is currently recommended that patients undergo metabolic assessment before beginning antiretroviral therapy, when switching regimens, at 3 and 6 months after starting or switching, and annually during stable therapy. In addition to blood glucose, measurements should include total cholesterol, low-density lipoprotein (LDL) cholesterol, HDL cholesterol, and triglycerides. Oral glucose tolerance testing may be considered in patients at high risk of developing diabetes—eg, those with family history of diabetes, obesity, or severe lipoatrophy and lipoaccumulation.

Although Framingham risk scoring is widely used in routine practice and

Dr Adeyemi is Assistant Professor of Medicine at Rush Medical College in Chicago, IL.
appears to be accurate in HIV-infected patients, it should be noted that there is at least preliminary evidence that an HIV-specific cardiovascular risk scoring system may prove to be more accurate in predicting outcomes. In the Copenhagen HIV Program Data Collection on Adverse Events of HIV Drugs (DAD) study, a DAD risk equation including traditional risk factors and duration of protease inhibitor exposure was compared with Framingham risk scoring. In the DAD cohort, there were 157 coronary events (more than 33,954 person-years of observation); the DAD risk equation predicted a total of 153 events, and the Framingham risk equation predicted 187 events (also a good correlation). The DAD risk equation is currently being assessed in a validation study in another DAD cohort.

Management of Cardiovascular Risk

Current guidelines support treating cardiovascular risk in HIV-infected patients in the same manner as recommended for the general population. Management may include diet and exercise intervention, smoking cessation, establishment of lipid goals and treatment of dyslipidemia, and institution of drug therapy (eg, statins, antihypertensives) in high-risk patients (eg, those with established coronary disease, diabetes, or moderate or high risk on risk scoring).

Switching of antiretroviral therapy may be considered if other methods of treating risk are not effective. Some of the decision points that arise in managing the at-risk HIV-infected patient can be appreciated through the following case history.

Case History

The patient is a 43-year-old African American man new to the practice. He smokes 1 to 2 packs of cigarettes per day, has a history of mild asthma, and his father died of an unspecified “heart problem” some time in his 50s. The patient was diagnosed with HIV infection 5 years ago. He recalls a CD4+ count of about 520 cells/µL and an HIV RNA level of approximately 20,000 copies/mL from 6 months ago. His nadir CD4+ count was approximately 300 cells/µL 2 years ago. He had begun antiretroviral therapy 2 years before, apparently with zidovudine/lamivudine/efavirenz, but took the medication only intermittently for a few months because of adverse effects (nausea and sleep problems). He is approximately 10 lbs heavier than his ideal weight, but otherwise appears well. His blood pressure is 145/85 mmHg.

General cardiovascular risk management considerations are shown in Figure 1. Initial steps in management of the patient’s disease include: obtaining fasting lipid levels and setting lipid goals if necessary; discussing smoking cessation programs; discussing high blood pressure if verified or if there is an established history of hypertension; obtaining a comprehensive family history of cardiovascular disease (death from cardiovascular disease before 50 years of age in the father may count as a risk factor for the patient); and obtaining a risk score.

The patient is seen 3 weeks later. Laboratory work shows a CD4+ count of 375 cells/µL, HIV RNA level of 47,000 copies/mL, and normal complete blood cell count and chemistry. His blood pressure is 132/80 mmHg. His fasting lipid levels as of this visit are shown in Table 1; total and LDL cholesterol and triglyceride levels are elevated, and his HDL cholesterol is low. The patient is again counseled on smoking cessation and is offered additional resources to this end. He wishes to avoid using any medications at this time. It is agreed that the patient will focus on diet, exercise, and smoking cessation, and that he will return for repeat laboratory work in 3 months.

The patient does not return for follow-up for 5 months. He has gained 5 lbs and is still smoking “due to stress of a new job.” His blood pressure is 132/80 mmHg. His fasting lipid levels have increased, as shown in Table 1. The patient’s Framingham risk score indicates 19% risk of a coronary event over the next 10 years, placing him in the high-risk category. His CD4+ count is 500 cells/µL and HIV RNA level is 78,000 copies/mL. It is decided to restart antiretroviral therapy with lopinavir/ritonavir plus tenofovir/emtricitabine. As an alternative, a ritonavir/atazanavir-

![Figure 1. Guidelines for managing dyslipidemia and cardiovascular risk in HIV-infected patients receiving antiretroviral therapy. CHD indicates coronary heart disease; LDL, low-density lipoprotein cholesterol; Non-HDL, non-high-density lipoprotein cholesterol; and TGs, triglycerides. Adapted from Dubé et al, Clin Infect Dis, 2003.](image-url)
Based regimen would provide a better lipid effect and allow once-a-day dosing. The patient is advised that lipid-lowering therapy should be instituted next if the profile is not improved at the next visit. The patient’s antiretroviral therapy is well tolerated, and after 12 weeks on treatment, his CD4+ count has increased to 390 cells/µL and his HIV RNA level is below 50 copies/mL. His blood pressure remains unchanged. He is still smoking. Total cholesterol and triglyceride levels have increased again, with HDL cholesterol increasing somewhat (see date 10/1 in Table 1). His 10-year risk of coronary disease is now 20%. The patient is started on 20 mg of pravastatin, which he tolerates well.

After 4 weeks on pravastatin, good reductions in total and LDL cholesterol and triglyceride levels are observed, and although levels are still above normal, there is improvement in HDL cholesterol (see date 11/1 in Table 1). His 10-year risk of coronary disease is now 11%. The patient is started on 20 mg of pravastatin, which he tolerates well.

If the patient were to stop smoking at this point, his 10-year risk would drop to 2%, placing him in the low-risk category. Had he stopped smoking after his first risk assessment, his 10-year risk would have decreased from 19% to 5% (borderline low/moderate risk) on the basis of smoking cessation alone.

The large effect of smoking cessation on coronary risk is of particular importance for HIV-infected patients since there appears to be a high prevalence of smoking in HIV-infected persons—as high as 70% in some clinics. At Dr Adeyemi’s center, approximately 60% to 65% of HIV-infected patients are current smokers, and the prevalence is 70% among a subpopulation aged 50 years or older with numerous other cardiovascular risk factors.

### Table 1. Patient Risk Factor Summary

<table>
<thead>
<tr>
<th>Date</th>
<th>Fasting Lipids (mg/dL)*</th>
<th>Smoker?</th>
<th>Blood Pressure (mmHg)</th>
<th>Lipid-lowering Treatment</th>
<th>10-year Risk of Coronary Event by Framingham Risk Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/1</td>
<td>TC:220 TG:240 HDL:32 LDL:140</td>
<td>Yes</td>
<td>132/80</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>7/1</td>
<td>TC:240 TG:260 HDL:32 LDL:156</td>
<td>Yes</td>
<td>132/80</td>
<td>– –</td>
<td>19%</td>
</tr>
<tr>
<td>10/1</td>
<td>TC:256 TG:310 HDL:36 LDL:158</td>
<td>Yes</td>
<td>132/80</td>
<td>– –</td>
<td>20%</td>
</tr>
<tr>
<td>12/1</td>
<td>TC:190 TG:180 HDL:44 LDL:110</td>
<td>Yes</td>
<td>132/80</td>
<td>Pravastatin, ezetimibe, omega-3 fatty acid supplement</td>
<td>8%</td>
</tr>
</tbody>
</table>

*On current National Cholesterol Education Program guidelines, total cholesterol (TC) value below 200 mg/dL is normal, low-density lipoprotein (LDL) cholesterol level below 70 mg/dL is optimal, triglyceride level below 150 mg/dL is normal, and (for men) high-density lipoprotein (HDL) cholesterol level greater than or equal to 60 mg/dL is protective (and improves risk score).

The large effect of smoking cessation on coronary risk is of particular importance for HIV-infected patients since there appears to be a high prevalence of smoking in HIV-infected persons—as high as 70% in some clinics. At Dr Adeyemi’s center, approximately 60% to 65% of HIV-infected patients are current smokers, and the prevalence is 70% among a subpopulation aged 50 years or older with numerous other cardiovascular risk factors.

**Figure 2.** Mortality over 14.5 years in a general population after a 10-week smoking intervention program among “sustained quitters,” “intermittent quitters,” and “continuing smokers.” CHD indicates coronary heart disease; CVD, cardiovascular disease. Adapted from Anthonisen et al, Ann Intern Med, 2005.
risk factors. The effect on survival of continuous or intermittent quitting with a 10-week smoking cessation program in the general population is shown in Figure 2; there is no reason to suspect that smoking cessation would not similarly benefit HIV-infected persons.

Summary

As in the general population, individual cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, and smoking have an additive or synergistic impact on overall risk and should be addressed at initiation of antiretroviral therapy and frequently during follow-up. Lifestyle modification should be the first management approach, including smoking cessation, diet modification, and increased exercise. In managing hyperlipidemia, the decision to use lipid-lowering therapy or to switch antiretroviral therapy regimens should be individualized. The impact of smoking cessation is greater than the impact of any other intervention in reducing overall risk, and although cardiovascular risk should be considered when starting or changing antiretroviral therapy, virologic control should be the overriding consideration.


Dr Adeyemi was on the Speakers’ Bureaus of Abbott and Tibotec.

Suggested Reading


Perspective

Diagnosis and Management of Hepatitis B Virus and HIV Coinfection

HIV and hepatitis B virus (HBV) coinfection increases HIV and HBV replication, hepatitis flares, and risk of progression to chronic HBV infection, cirrhosis, and hepatocellular carcinoma. HIV and HBV coinfection decreases frequency of hepatitis Be antibody (anti-HBe) and hepatitis B surface antibody (anti-HBs) seroconversion, increases risk of antiretroviral therapy-related hepatotoxicity, and reduces efficacy of HBV therapy. All newly diagnosed HIV patients should be screened for hepatitis A, B, and C viruses and vaccinated if not immune to hepatitis A or B viruses. HBV serology often is atypical in coinfection. Diagnosis of HBV coinfection in HIV infection is made on the basis of hepatitis B surface antigen (HBsAg)-negative, hepatitis B core antibody (anti-Hbc total)-positive, anti-HBs-positive status. Alanine aminotransferase levels in coinfected patients often are not reliable markers of liver inflammation. HBV infection should always be treated if coinfected patients are receiving antiretroviral therapy, since immune reconstitution under antiretroviral therapy poses risk for immune-associated liver damage in these patients. This article summarizes a presentation on HIV and HBV coinfection made by Marion G. Peters, MD, at an International AIDS Society–USA Continuing Medical Education course in San Francisco in May 2007. The original presentation is available as a Webcast at www.iasusa.org.

Hepatitis B virus (HBV) infection is a life-long dynamic disease that can be controlled but not cured. The risks of end-stage liver disease and liver cancer increase with ongoing inflammation and viremia. Fibrosis can be reversed, and drug treatment can reduce progression. The relationship between immune response and liver damage in HBV infection is of particular importance in HIV-coinfected patients. If there is no immune response, liver damage does not occur; however, if there is immune response—eg, with immune reconstitution during antiretroviral therapy—liver damage will occur.

Characteristics of Coinfection

According to some estimates, there are approximately 400 million people worldwide with HBV infection, with approximately 4 million of those coinfected with HIV. Rates of coinfection range from 5% to higher than 30% depending on the cohort and locale examined. For example, the prevalence of coinfection is 5% to 10% in injection drug use cohorts, is 8.7% in the EuroSida cohort, and has been reported at 9%, 16.9%, 25.9%, and 73% in small cohorts in Tanzania, Malawi, Nigeria, and Uganda, respectively.

In HIV-infected patients, HBV infection increases HIV replication, increases antiretroviral therapy–related hepatotoxicity, and decreases CD4+ cell counts in patients with cirrhosis and hypersplenism. There is also some evidence that HBV infection itself reduces CD4+ cell counts. In HBV-infected patients, HIV increases HBV replication, hepatitis flares, progression to chronic HBV infection, progression to cirrhosis, and risk of hepatocellular carcinoma, and it reduces hepatitis B envelope antibody (anti-HBe) and hepatitis B surface antibody (anti-HBs) seroconversion. Coinfection is also associated with reduced efficacy of anti-HBV therapy, including greater risk of lamivudine resistance and decreased response to interferon alfa.

An example of the poor outcomes associated with coinfection is provided by findings in a Multicenter Cohort Study reported by Thio and colleagues. The study population included 4967 men who have sex with men (MSM) who were hepatitis B surface antigen (HBsAg)-negative, of whom 47% had HIV infection, and 326 MSM who were HBsAg-positive, of whom 65% had HIV infection. Patients with HIV and HBV coinfection had a 19-fold higher risk of liver death than those with HBV monoinfection, with risk of liver-related mortality increasing with alcohol consumption, low nadir CD4+ cell count, and antiretroviral therapy. Rates of liver-related mortality by 1000 person-years were 14.1 with HIV and HBV coinfection, 1.7 with HIV monoinfection, 0.8 with HBV monoinfection, and 0 with neither HBV nor HIV infection (Thio et al, Lancet, 2002). More recent data from the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study showed that after AIDS (31%), liver-related mortality accounted for the most deaths (15%) in HIV-infected persons with access to antiretroviral therapy, exceeding heart disease (9%) and cancer (9%) in this regard. A multivariate model for factors associated with liver death showed that hepatitis C virus (HCV) infection was the strongest predictor (relative risk [RR], 6.7), followed by HBV infection (RR, 3.7), injection drug use (RR, 2.0), older age (RR, 1.3), and low CD4+ cell count (RR, 1.23). The rate of hepatocellular carcinoma was 82 per 10,000 in this cohort, markedly higher than that in the general population.

Initial Evaluation

At initial evaluation, patients should be screened for HBsAg, hepatitis B core antibody (anti-Hbc), and anti-HBs. Diagnosis of HBV coinfection in HIV infection is made on the basis of HBsAg-positive, anti-HBc total-positive,
anti-HBs-positive status. If patients are HBsAg-positive, hepatitis B envelope antigen (HBeAg), anti-HBe, and HBV DNA should be measured. If patients are HBsAg-negative, they should receive HBV vaccination. In addition to history and physical examination, the HIV-infected patient with newly diagnosed HBV coinfection should have a complete liver panel, complete blood cell (CBC) count, and international normalized ratio (INR), as well as measurement of alpha-fetoprotein (AFP). In addition, baseline liver ultrasound should be performed. Patients should be screened for hepatitis A virus (HAV) Ab total and vaccinated if they are anti-HAV antibody-negative. They should also be screened for hepatitis D virus if they are from endemic areas or injection drug users. Household and sexual contacts should be screened for HBV and vaccinated if they are uninfected.

The need to confirm HBV serologic status with additional testing arises because HIV infection is associated with atypical serologic results. A study in the Swiss HIV Cohort showed that infection was manifest as anti-HBc alone in 57 HIV-infected patients, with this remaining the sole marker of infection for 31 months in 98% of patients. Polymerase chain reaction (PCR) results showed that 60% were positive for HBsAg and hepatitis B core antigen (HBeAg), and 36% had necroinflammatory disease. Thus, if patients are anti-HBc-positive and negative for both HBsAg and anti-HBs, HBV DNA should be measured. If this test result is positive, patients should be treated for HBV; if negative, they should be vaccinated.

HIV-infected patients have a diminished response to the HBV vaccine and lose protective antibodies more rapidly. The response rate is greater than 87% in those with CD4+ counts above 500 cells/µL and 33% in those with counts of 200 to 500 cells/µL. A strategy of revaccinating nonresponders with a doubled dose has met with poor success. The AIDS Clinical Trials Group (ACTG) is assessing whether response can be improved by coadministration of granulocyte and macrophage colony-stimulating factor.

**Management**

The goal of treatment of HBV disease is to make active disease become inactive. Control of HBV disease is indicated by reduced inflammatory response (normalization of alanine aminotransferase [ALT] level), reduced viral replication (reduced HBV DNA level), and improved immune control (seroconversion to anti-HBe- and anti-HBs-positive status). As an example of the risk posed by uncontrolled disease, elevated HBV DNA levels among HBV-infected patients with ALT levels in the normal range dramatically increased risk for hepatocellular carcinoma in patients over age 30 years (Figure 1; Chen et al, *JAMA*, 2006). The association of HBV DNA level with risk of cirrhosis was very similar in this study. Figure 2 shows the therapeutic endpoints achievable over time in HBV-infected patients. ALT is not a very useful measure of inflammation in infected patients, with many such patients with normal ALT levels having necroinflammatory disease on biopsy.

![Figure 1](image1.png) **Figure 1.** Multivariate-adjusted relative risk of hepatocellular carcinoma by entry serum hepatitis B virus (HBV) DNA level among patients with alanine aminotransferase levels less than 1-time the upper limit of normal. Data are adjusted for sex, age, smoking, and alcohol consumption. Adapted from Chen et al, *JAMA*, 2006.

![Figure 2](image2.png) **Figure 2.** Therapeutic endpoints over time in treatment of hepatitis B virus infection. “+” indicates seropositivity; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen.
Table 1. Antiviral Drugs for Hepatitis B Virus Treatment

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Wild-type Hepatitis B Virus</th>
<th>YMDD Mutation</th>
<th>Used in HIV Treatment?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>Susceptible</td>
<td>Resistant</td>
<td>Yes</td>
</tr>
<tr>
<td>Adefovir</td>
<td>Susceptible</td>
<td>Susceptible</td>
<td>No</td>
</tr>
<tr>
<td>Entecavir*</td>
<td>Susceptible (0.5-mg dose)</td>
<td>Susceptible</td>
<td>No</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Susceptible</td>
<td>Resistant</td>
<td>Yes</td>
</tr>
<tr>
<td>Tenofovir**</td>
<td>Susceptible</td>
<td>Susceptible</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* There is a black box warning to not use entecavir in HIV and HBV-coinfected patients not receiving antiretroviral therapy. In patients with YMDD-resistant virus who are on high-dose entecavir, resistance to entecavir occurs more frequently.

** Tenofovir is not approved by the US Food and Drug Administration for the treatment of hepatitis B virus infection.

Antiviral drugs used in treating HBV infection are listed in Table 1, along with their activity against wild-type HBV, activity against HBV with the lamivudine-resistance YMDD mutation; and whether they are active against HIV. In patients with the YMDD mutation alone, adefovir, double-dose entecavir, and tenofovir generally remain active. US guidelines for treatment of coinfection are currently being revised. In drug-naive coinfected patients who are candidates for both HBV and HIV treatment, the current Department of Health and Human Services (DHHS) guidelines indicate a preference for dual anti-HBV agents, specifically tenofovir plus emtricitabine. However, other nucleoside and nucleotide reverse transcriptase inhibitor (nRTI) combinations are acceptable, including tenofovir with emtricitabine, lamivudine, or entecavir. In patients requiring treatment for HBV alone, peginterferon alfa can be used in the setting of high CD4+ cell count, high ALT level, and low HBV DNA level, all uncommon in HIV patients. Other options include adefovir or telbivudine. However, there is the theoretical possibility that HIV resistance may emerge with these drugs, as occurred with entecavir.

With regard to entecavir, use of the agent in coinfected patients has been studied only in patients on antiretroviral therapy. There was a surge in use of entecavir over the past 18 months as practitioners sought to reduce the risk of immune reconstitution by treating HBV before initiating antiretroviral therapy. There are now at least 5 reported cases of resistance associated with the M184V mutation in coinfected patients receiving entecavir alone, and treatment is associated with a reduction in plasma HIV RNA level of 0.5 log10 copies/mL; prior lamivudine treatment occurred in only 2 of these cases. This finding has resulted in a US Food and Drug Administration (FDA) black box warning indicating that entecavir monotherapy should not be used in coinfected patients not receiving antiretroviral therapy. This issue may not be specific to entecavir and it may alter HBV therapy in patients without current indications for HIV therapy.

Among newer drugs, telbivudine has no anti-HIV activity, but it is not effective in patients with the YMDD mutation. Studies of the drug in coinfection are under way. A study in monoinfected patients showed that reduction of HBV DNA to undetectable levels at 24 weeks with telbivudine treatment was associated with a high likelihood of remaining HBV DNA-negative at 1 year and having normalized ALT levels (see Table 2). Conversely, 93% of patients with HBV DNA level above 3 log10 copies/mL at week 24 failed to seroconvert by year 1 (Lai et al, Hepatology, 2005).

Clevudine, which is currently licensed in Korea but not in the United States, was shown to induce good reduction in HBV DNA levels in HBV monoinfected patients, with 59% of patients having undetectable levels at the end of 24 weeks of treatment (Table 3; Yoo et al, Hepatology, 2005). The investigational drug pradefovir has more liver targeting and thus less renal toxicity than the related drug adefovir, allowing it to be used at a 30-mg dose. In a recent study in chronic HBV monoinfection, reductions in HBV DNA level at 48 weeks were 4.09, 4.84, 4.89, and 5.54 log10 copies/mL at pradefovir doses of 5, 10, 20, and 30 mg, compared with 4.19 log10 copies/mL with adefovir 10 mg (Lee et al, EASL, 2006).

HBV infection should be treated

Table 2. One-year Outcomes in Patients Receiving Telbivudine for Hepatitis B Virus (HBV) Infection According to HBV DNA Level at Week 24

<table>
<thead>
<tr>
<th>Week 24 HBV DNA Level (copies/mL)</th>
<th>Undetectable</th>
<th>300 to &lt;3 log10</th>
<th>3 to 4 log10</th>
<th>&gt;4 log10</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA-negative (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg+</td>
<td>91</td>
<td>69</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>HBeAg-</td>
<td>94</td>
<td>67</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Normal ALT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg+</td>
<td>88</td>
<td>89</td>
<td>79</td>
<td>53</td>
</tr>
<tr>
<td>HBeAg-</td>
<td>81</td>
<td>68</td>
<td>60</td>
<td>41</td>
</tr>
<tr>
<td>Virologic breakthrough</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg+</td>
<td>1</td>
<td>4</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>HBeAg-</td>
<td>0</td>
<td>7</td>
<td>17</td>
<td>44</td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
<td>41</td>
<td>26</td>
<td>13</td>
<td>4</td>
</tr>
</tbody>
</table>

HBeAg indicates hepatitis B e antigen; “+”, seropositive; “−”, seronegative; ALT, alanine aminotransferase. Adapted from Lai et al, Hepatology, 2005.
if coinfected patients are receiving antiretroviral therapy, since immune reconstitution under antiretroviral therapy poses a substantial risk for immune-associated liver damage in these patients. ALT flares can occur in coinfected patients for a variety of reasons other than immune reconstitution. This can occur with ALT flares in association with spontaneous HBeAg seroconversion, but such seroconversion is less frequent in HIV-infected patients. Flares can occur when patients stop antiretroviral therapy (eg, through nonadherence or patient choice) or with the emergence of HBV resistance. Flares may also be due to drug hepatotoxicity or acute HCV or HAV infection.

After initiating treatment, ALT, aspartate aminotransferase, and HBV DNA levels should be monitored every 3 months. If there is no HBV DNA-level decrease by 12 to 24 weeks of therapy, the patient should be assessed for HBV resistance and adherence, and treatment should be modified by changing drugs or adding a drug. In monoinfected patients, it is recommended that imaging for hepatocellular carcinoma and measurement of AFP be performed every 6 months starting at the age of 40 years. Given the increased risk of hepatocellular carcinoma in coinfection, it may be prudent to monitor coinfected patients according to this schedule regardless of age, but there are currently no data to support this.

Presented by Dr Peters in May 2007.

Table 3. Outcome with 24 weeks of Clevudine Treatment and 24 Weeks of Follow-up in Hepatitis B e Antigen-seropositive Patients

<table>
<thead>
<tr>
<th></th>
<th>Clevudine 30 mg (n = 182)</th>
<th>Placebo (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in HBV DNA, log10 copies/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of treatment</td>
<td>–5.10*</td>
<td>–0.27</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>–2.02*</td>
<td>–0.68</td>
</tr>
<tr>
<td>HBV DNA undetectable at end of treatment, %</td>
<td>59</td>
<td>0</td>
</tr>
<tr>
<td>Normalized ALT, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of treatment</td>
<td>68*</td>
<td>18</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>61*</td>
<td>28</td>
</tr>
<tr>
<td>HBeAg seroconversion at end of follow-up, %</td>
<td>10</td>
<td>12</td>
</tr>
</tbody>
</table>

*P < .0001 versus placebo. HBV indicates hepatitis B virus; ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen. Adapted from Yoo et al, Hepatology, 2005.
Cases on the Web – www.iasusa.org/cow

Cases on the Web is an ongoing series of case-based, advanced online Continuing Medical Education (CME) activities sponsored by the International AIDS Society–USA that offers physicians access to convenient, top-quality education about HIV and AIDS care.

IMPROVED FORMAT

Our latest CME activity features an enhanced and dynamic case-based format. Participants start making clinical and case-management decisions from the outset of the activity, and each clinical decision point in the unfolding case is supported by a succinct discussion of related medical findings, scientific research, and related practice–management recommendations.

NEW

HIV-related Renal Disease
Lynda Anne Szczech, MD, MSCE, FASN

Kidney disease can be a direct result of HIV infection and the medications used to treat HIV infection, or it may be a consequence of comorbidities such as diabetes mellitus and hypertension. In this new activity, participants will identify which HIV-infected persons are at highest risk for developing kidney disease, and learn to select appropriate screening methods and therapies for persons with HIV and kidney disease.

HIV-associated Metabolic Complications
Roger J. Bedimo, MD, MS

Owing to their potential link to cardiovascular disease, dyslipemias are arguably the most important non-AIDS-related causes of morbidity and mortality among HIV-infected patients. This activity will review management strategies for HIV-infected patients with dyslipemias and insulin resistance.

UPDATED

Current Issues in HIV Disease and Substance Abuse
Chinazo Cunningham, MD
Hillary Kunins, MD, MPH, MS

Recently updated, this much-in-demand presentation is once again available for CME credit. In this activity, participants learn about treatment strategies and options for opioid-dependent and crack and cocaine-using HIV-infected patients and learn to identify drug interactions between antiretroviral medications and abused substances.

ALSO AVAILABLE

HIV Correctional Health Care and Discharge Planning: Issues for the Community Provider
Douglas G. Fish, MD
Sarah Walker, MS

This compelling presentation discusses the epidemiology of HIV among incarcerated populations. Participants will learn how discharge planning services differ between jail and prison custodial settings, and learn strategies for facilitating continuity of health care for HIV-infected former inmates.

Practical Management Issues in HIV and Hepatitis B Virus Coinfection
Camilla S. Graham, MD, MPH

This activity discusses interpreting hepatitis B virus (HBV) serologies in HIV coinfection and monitoring HBV infection after treatment is initiated. Participants also learn about possible etiologies of elevated liver enzyme tests in persons with HIV and HBV coinfection.

COMING SOON IN 2008

Look for new Cases on the Web presentations about the following topics in coming months.

• Antiretroviral Management
• Prevention Measures for HIV-seropositive Patients
• HIV and Tuberculosis Coinfection
• HIV and Endocrine Complications for HIV-infected Patients

CREDITS

These activities have been approved for AMA PRA Category 1 Credit.™

For information about any of these Cases on the Web, please contact the International AIDS Society–USA.
Phone: (415) 544-9400 • Fax: (415) 544-9401 • E-mail: info2007“at”iasusa.org
(info2008“at”iasusa.org on January 1, 2008 and thereafter) • Website: www.iasusa.org
Topics in HIV Medicine®

Subscription Request

Address Change

Topics in HIV Medicine® is published 4 to 6 times a 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 ___________ MI ___________ Last Name ___________

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

Institution or Organization ___________

Specialty / Primary Field of Interest ___________

Address (please check one) ( _____ Home Address _____ Work Address ) ___________

City ___________ State / Province ___________

Postal Code ___________

Country ___________

Telephone ( _____ Home Phone _____ Work Phone ) ___________

Facsimile ___________

E-mail Address ( _____ Home E-mail _____ Work E-mail ) ___________

For how many HIV-infected patients are you providing care? ______________

What percentage of your total number of 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
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 13,000 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 topics2007@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 work should be acknowledged by editorial staff, and unsolicited submissions are also welcome for consideration.

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

**Special Issues.** *Topics in HIV Medicine* publishes 1 or 2 issues each year with a special focus, such as reports from recent scientific meetings and summaries of special International AIDS Society–USA continuing medical education courses.

**Reprints.** Reprints of papers by expert panels convened by the International AIDS Society–USA are periodically included in *Topics in HIV Medicine*.

**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 author should complete an 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.

**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.

A Publication of the International AIDS Society–USA

Visit our Website at www.iasusa.org for...

• Updated HIV Drug Resistance Figures
• New Cases on the Web
• 2008 CME Course Agendas and Online Registration
• New: Advanced Workshops and Lectures on Relevant HIV Management: Dates, Locations, and Agendas