Perspectives

Evaluating and Managing Cardiovascular Disease Risk Factors in HIV-Infected Patients  
James H. Stein, MD  
Predicting Coronary Heart Disease Risk in the General Population • Predicting Coronary Heart Disease Risk in the HIV-Infected Population • Coronary Heart Disease Risk Reduction: Managing Dyslipidemia

Occupational Postexposure Prophylaxis for HIV:  
The PEPline Perspective  
Ronald H. Goldschmidt, MD  
The PEPline Service • Transmission Risks • Testing and Recommendations for Postexposure Prophylaxis • Selection of Postexposure Prophylaxis Regimen

Special Contribution

Update of the Drug Resistance Mutations in HIV-1:  
December 2010  
International AIDS Society–USA Drug Resistance Mutations Group

Cases From the Field

Recalcitrant Giant Molluscum Contagiosum in a Patient With Advanced HIV Disease — Eradication of Disease With Paclitaxel  
Silver Cree Sisneros, DO  
Background • Case Presentation • Therapeutic Challenge
Perspectives

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Announcements

Continuing Medical Education Credit
Correction
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Guidelines for Authors and Contributors
The following article in this issue is associated with CME credit:
Stein JH. Evaluating and managing cardiovascular disease risk factors in HIV-infected patients.

Instructions
This Continuing Medical Education (CME) activity provides a review of data regarding the management of cardiovascular disease risk factors in patients with HIV infection. To complete the activity, the learner is instructed to:
- Read the article
- Review a selection of the references
- Reflect on how the information might be applied to the clinical practice
- Take the posttest
- Complete the CME claim form and send it to the IAS–USA office.

Objectives
Upon completion of this activity, learners will be able to describe results of recent research and the potential clinical implications for their HIV-infected patients on the evaluation and management of cardiovascular disease risk factors.

Accreditation Statement
The International AIDS Society–USA is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The International AIDS Society–USA designates this activity for a maximum of 1.5 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Intended Audience
This activity is intended for physicians involved in the care of patients with HIV infection. It is also relevant to nurse practitioners, physician assistants, nurses, and other health professionals who provide care for people with HIV disease.

Author Financial Disclosures
Dr Stein has received subcontracted research support from the University of North Carolina that originated from GlaxoSmithKline and has been a member of data and safety monitoring boards for Abbott Laboratories, Eli Lilly and Co, and Takeda Pharmaceutical Co, Ltd.

Posttest Questions
Circle the single best answer to each of the questions below.
1. In the INTERHEART study, modifiable risk factors accounted for what percent of the population-attributable risk for myocardial infarction?
   A. 21%
   B. 42%
   C. 63%
   D. 84%
2. In the D:A:D study, use of which of the following protease inhibitors was associated with a statistically significant increased yearly risk of myocardial infarction?
   A. Lopinavir/ritonavir
   B. Saquinavir
   C. Nelfinavir
   D. Atazanavir
3. In the D:A:D study, use of which of the following nucleoside analogue reverse transcriptase inhibitors was associated with a statistically significant increased yearly risk of myocardial infarction?
   A. Lamivudine
   B. Stavudine
   C. Zalcitabine
   D. Abacavir
4. What are the target low-density lipoprotein cholesterol (LDL-C) and non–high-density lipoprotein cholesterol (HDL-C) levels for patients with coronary artery disease?
   A. LDL-C < 100 mg/dL, non–HDL-C < 100 mg/dL
   B. LDL-C < 100 mg/dL, non–HDL-C < 130 mg/dL
   C. LDL-C < 130 mg/dL, non–HDL-C < 100 mg/dL
   D. LDL-C < 130 mg/dL, non–HDL-C < 160 mg/dL
5. Regarding treatment of dyslipidemias, which of the following statements is correct?
   A. Statin drugs are the preferred initial treatment for all patients
   B. Pravastatin has no drug interactions with HIV treatment medications
   C. Statin drugs, niacin, or fenofibrate are preferred treatment strategies for patients with triglycerides levels above 500 mg/dL
   D. Statin drugs have the best evidence base for prevention of cardiovascular disease

This CME activity is offered from January 15, 2011, to January 15, 2012. Participants who complete the activity posttest and submit the registration form are eligible to receive credit. Physicians (MDs, DOs, and international equivalents) may receive CME credit for completing this activity. Nonphysician health care practitioners will receive a certificate of attendance.
Please complete and return this form to receive CME credit

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<td>Telephone ( ___Home ___Work)</td>
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<td>E-mail address to receive CME certificate ( ___Home ___Work)</td>
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<td>The amount of time (in hours) I spent on reading the article, reviewing the references, reflecting on how the information might be applied to the practice, and taking the posttest was:</td>
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<td>☐ &lt; 1 ☐ 1.5 ☐ 2 ☐ 3 ☐ other ____</td>
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</tbody>
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Fax or mail this form to:  
International AIDS Society–USA  
425 California Street, Suite 1450  
San Francisco, CA 94104-2120  
Fax: (415) 544-9401

**Correction**

There was an error in the printed version of *Topics in HIV Medicine*, volume 18, issue 3, in the article “Dyslipidemia and its Treatment in HIV Infection.” On page 116, column 2, paragraph 1, “fosamprenavir/r” in line 9 was inadvertently switched with “atazanavir/r” in line 17 below. The text should have read:

Rosuvastatin maximum concentration was increased 4.7-fold by lopinavir/r (Kiser et al., *JAIDS*, 2008) and 6-fold by atazanavir/r (Busti et al., *J Cardiovasc Pharmacol*, 2008). Thus, high-dose rosuvastatin should be avoided by patients receiving these PIs. No change in rosuvastatin concentration was observed with fosamprenavir/r (Busti et al., *J Cardiovasc Pharmacol*, 2008).

The correction has been made in the online version of the issue at [http://www.iusasa.org/pub/topics/2010/issue3/112.pdf](http://www.iusasa.org/pub/topics/2010/issue3/112.pdf). In addition, the same error has been corrected in a keyslide from the original course presentation (presentation 2, slide 24) available at [http://www.iusasa.org/keyslides/2010/slosangeles/index.html](http://www.iusasa.org/keyslides/2010/slosangeles/index.html).
Special Contribution

Update of the Drug Resistance Mutations in HIV-1: December 2010

Victoria A. Johnson, MD, Françoise Brun-Vézinet, MD, PhD, Bonaventura Clotet, MD, PhD, Huldrych F. Günthard, MD, Daniel R. Kuritzkes, MD, Deenan Pillay, MD, PhD, Jonathan M. Schapiro, MD, and Douglas D. Richman, MD

This December 2010 version of the International AIDS Society–USA (IAS–USA) drug resistance mutations list updates the figures last published in December 2009 (Johnson VA et al, Top HIV Med, 2009;17:138-145). This update includes 9 new mutations—E158G and E158K for etravirine (Haddad M et al, CROI, 2010; Abstract 574, and Vingerhoets J et al, Antivir Ther, 2010;15 [Suppl 2]:A125); E92Q for raltegravir (Geretti AM et al, Antivir Ther, 2010;15 [Suppl 2]:A62; Cooper et al, N Engl J Med, 2008;359:355-366; and Malet I et al, Antimicrob Agents Chemother, 2008;52:1351-1358); and M36L, M36V, H69R, L89I, L89M, and L89V for tipranavir/ritonavir. In addition, the tipranavir/ritonavir N83D mutation designation was changed to boldface to indicate its recognition as a major mutation rather than a minor mutation. The mutations I13V, K20M/R, E35G, and L90M were removed from the tipranavir/ritonavir bar, reflecting new understanding. For etravirine, L100I*, K101P*, and Y181C*/I*/V* are denoted with asterisks (instead of bolded) to reflect that these individual mutations each have the greatest impact (ie, highest weighting scores) on reduced phenotypic susceptibility and impaired clinical response when compared with other etravirine mutations (Haddad M et al, CROI, 2010; Abstract 574). In addition, user notes d, n, r, w, and z were revised.

Methods

Mutations Panel

The authors comprise the IAS–USA Drug Resistance Mutations Group, an independent, volunteer panel of experts charged with the goal of delivering accurate, unbiased, and evidence-based information on these mutations to HIV clinical practitioners. The group reviews new data on HIV drug resistance to maintain a current list of mutations associated with clinical resistance to HIV. This list includes mutations that may contribute to a reduced virologic response to a drug.

In addition, the group reviews only that data which have been published or have been presented at a scientific conference. Drugs that have been approved by the US Food and Drug Administration (US FDA) as well as any drugs available in expanded access programs are included (listed in alphabetical order by drug class). User notes provide additional information as necessary. Although the Drug Resistance Mutations Group works to maintain a complete and current list of these mutations, it cannot be assumed that the list presented here is exhaustive.

Identification of Mutations

The mutations listed have been identified by 1 or more of the following criteria: (1) in vitro passage experiments or validation of contribution to resistance by using site-directed mutagenesis; (2) susceptibility testing of laboratory or clinical isolates; (3) nucleotide sequencing of viruses from patients in whom the drug is failing; (4) correlation studies between genotype at baseline and virologic response in patients exposed to a drug.

The development of more recently approved drugs that cannot be tested as monotherapy precludes assessment of the impact of resistance on antiretroviral activity that is not seriously confounded by activity of other drug components in the background regimen. Readers are encouraged to consult the literature and experts in the field for clarification or more information about specific mutations and their clinical impact. Polymorphisms associated with impaired treatment responses that occur in wild-type viruses should not be used in epidemiologic analyses to identify transmitted HIV-1 drug resistance.

Clinical Context

The figures are designed for practitioners to use in identifying key mutations associated with viral resistance to antiretroviral drugs and in making therapeutic decisions. In the context of making clinical decisions regarding antiretroviral therapy, evaluating the results of HIV-1 genotypic testing includes: (1) assessing whether the pattern or absence of a pattern in the mutations is consistent with the patient’s
antiretroviral therapy history; (2) recognizing that in the absence of drug (selection pressure), resistant strains may be present at levels below the limit of detection of the test (analyzing stored samples, collected under selection pressure, could be useful in this setting); and (3) recognizing that virologic failure of the first regimen typically involves HIV-1 isolates with resistance to only 1 or 2 of the drugs in the regimen (in this setting, resistance develops most commonly to lamivudine or the nonnucleoside analogue reverse transcriptase inhibitors [NNRTIs]).

The absence of detectable viral resistance after treatment failure may result from any combination of the following factors: the presence of drug-resistant minority viral populations, nonadherence to medications, laboratory error, lack of current knowledge of the association of certain mutations with drug resistance, the occurrence of relevant mutations outside the regions targeted by routine resistance assays, drug-drug interactions leading to subtherapeutic drug levels, and possibly compartmental issues, indicating that drugs may not reach optimal levels in specific cellular or tissue reservoirs.


**Comments**

Please send your evidence-based comments, including relevant reference citations, to the IAS–USA at resistance2011@iasusa.org or by fax at 415-544-9401. Please include your name and institution.

**Reprint Requests**

The Drug Resistance Mutations Group welcomes interest in the mutations figures as an educational resource for practitioners and encourages dissemination of the material to as broad an audience as possible. However, permission is required to reprint the figures and no alterations in the content can be made.

Requests to reprint the material should include the name of the publisher or sponsor, the name or a description of the publication in which you wish to reprint the material, the funding organization(s), if applicable, and the intended audience of the publication. Requests to make any minimal adaptations of the material should include the former, plus a detailed explanation of how the adapted version will be changed from the original version and, if possible, a copy of the proposed adaptation. To ensure the integrity of the mutations figures, IAS–USA policy is to grant permission for only minor, preapproved adaptations of the figures (eg, an adjustment in size). Minimal adaptations only will be considered; no alterations of the content of the figures or user notes will be permitted.

Please note that permission will be granted only for requests to reprint or adapt the most current version of the mutations figures as they are posted on the Web site (www.iasusa.org). Because scientific understanding of HIV drug resistance evolves rapidly and the goal of the Drug Resistance Mutations Group is to maintain the most up-to-date compilation of mutations for HIV clinicians and researchers, publication of out-of-date figures is counterproductive. If you have any questions about reprints or adaptations, please contact us.

**Financial Disclosures:** The authors disclose the following affiliations with commercial organizations that may have interests related to the content of this article (previous 12 months): Dr Brun-Vezinet has received grants and research support from GlaxoSmithKline and Tibotec Therapeutics; has served as a consultant to Merck & Co, Inc, Pfizer Inc, Siemens Healthcare Diagnostics Inc, and Tibotec Therapeutics; and has served as a paid lecturer for Bristol-Myers Squibb, GlaxoSmithKline, and Tibotec Therapeutics. Dr Clotet has served as a consultant on advisory boards, participated in speakers’ bureaus, or conducted clinical trials for Abbott Laboratories, Boehringer Ingelheim Pharmaceuticals, Inc, Gilead Sciences, Inc, GlaxoSmithKline, Janssen Pharmaceuticals, Merck & Co, Inc, Tibotec Therapeutics, and ViViD Healthcare. Dr Günthard has served as a consultant and a medical advisor for Abbott Laboratories, Boehringer Ingelheim Pharmaceuticals, Inc, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Hoffman-La Roche Ltd, Merck Serono S.A., Pfizer Inc, and Tibotec Therapeutics; and has received unrestricted research and educational grants from Abbott Laboratories, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, and Pfizer Inc. Dr Johnson has received research support from Abbott Laboratories, Roche Molecular Diagnostics, and Siemens Healthcare Diagnostics Inc. Dr Kuznetzov has served as a consultant to and has received honoraria from Abbott Laboratories, Avea Ltd, Gilead Sciences, Inc, GlaxoSmithKline, Human Genome Sciences, Inc, Merck & Co, Inc, Oncolys BioPharma Inc, Pfizer Inc, Roche Pharmaceuticals, ViroStatics, and VIRaSYS Corp; and has received research grant support from Gilead Sciences, Inc, and Merck & Co, Inc. Dr Pillay has served as a consultant to Boehringer Ingelheim Pharmaceuticals, Inc, Bristol-Myers Squibb, Gilead Sciences, Inc, and Roche Pharmaceuticals. Dr Richman has served as a consultant to Biota, Bristol-Myers Squibb, Chimerix Inc, Gen-Probe Inc, Gilead Sciences, Inc, Idenix Pharmaceuticals, Inc, Johnson & Johnson, Merck & Co, Inc, and Monogram Biosciences, Inc; is a stock options holder for Chimerix Inc and Idenix Pharmaceuticals, Inc; and has received research grants from Merck & Co, Inc. Dr Schapiro has served as a consultant, advisor, or speaker for Abbott Laboratories, GlaxoSmithKline, Merck & Co, Inc, Pfizer Inc, Roche Pharmaceuticals, Tibotec-Janssen Cilag Therapeutics, Quest Diagnostics Inc, ViViD Healthcare, and Virology Education; and has received research support from Boehringer Ingelheim Pharmaceuticals, Inc, GlaxoSmithKline, Pfizer Inc, Quest Diagnostics Inc, Tibotec Therapeutics, and ViViD Healthcare. The International AIDS Society–USA has received grants in the past year for selected continuing medical education activities that are pooled (ie, no single company supports any particular effort) from Abbott Laboratories; Boehringer Ingelheim Pharmaceuticals, Inc, Bristol-Myers Squibb, Gilead Sciences, Inc, Merck & Co, Inc, Tibotec; Therapeutics; and ViViD Healthcare. Funding/Support: This work was funded by the IAS–USA. No private sector or government funding was used to support the effort. Panel members are not compensated. The authors are grateful to Ann McGuire for editorial support in convening the panel and assistance in preparing the manuscript.
MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH RESISTANCE TO REVERSE TRANSCRIPTASE INHIBITORS

**Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)**

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<td>Multi-nRTI Resistance: 151 Complex</td>
<td>(affects all nRTIs currently approved by the US FDA except tenofovir)</td>
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**Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)**

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### MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS

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### MUTATIONS IN THE ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS

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### MUTATIONS IN THE INTEGRASE GENE ASSOCIATED WITH RESISTANCE TO INTEGRASE INHIBITORS

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</tbody>
</table>

**Amino acid abbreviations:** A, alanine; C, cysteine; D, aspartate; E, glutamate; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine.

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**Notes:**
- **Asterisk** indicates amino acids that are associated with resistance to multiple classes of inhibitors.
- **Minor** (lightface type; protease only) indicates amino acids that are associated with resistance specifically to the protease inhibitors.
- **Protease only** indicates amino acids that are associated with resistance that do not confer resistance to other classes of inhibitors.
a. Some nucleoside (or nucleotide) analogue reverse transcriptase inhibitor (nRTI) mutations, like T215Y and H208Y, may lead to viral hypersusceptibility to the nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs), including etravirine, in nRTI-treated individuals. The presence of these mutations may improve subsequent virologic response to NNRTI-containing regimens (nevirapine or efavirenz) in NNRTI-naive individuals, although no clinical data exist for improved response to etravirine in NNRTI-experienced individuals.

b. The 69 insertion complex consists of a substitution at codon 69 (typically T69S) and an insertion of 2 or more amino acids (S-S, S-A, S-G, or others). The 69 insertion complex is associated with resistance to all nRTIs currently approved by the US FDA when present with 1 or more thymidine analogue–associated mutations (TAMs) at codons 41, 210, or 215. Some other amino acid changes from the wild-type T at codon 69 without the insertion may be associated with broad nRTI resistance.

c. Tenofovir retains activity against the Q151M complex of mutations.

d. Mutations known to be selected by thymidine analogues (M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E, termed TAMs) also confer reduced susceptibility to all approved nRTIs. The degree to which cross-resistance is observed depends on the specific mutations and number of mutations involved. Mutations at the C-terminal reverse transcriptase domains (amino acids 293-560) outside of regions depicted on the figure bars may prove to be important for HIV-1 drug resistance. However, to date clinical relevance of these in vitro findings has not been established because the connection domain mutations appear mostly in conjunction with TAMs and M184V and do not seem to have major independent effects.

e. Although reverse transcriptase changes associated with the E44D and V118I mutations may have an accessory role in increased resistance to nRTIs in the presence of TAMs, their clinical relevance is very limited.

f. The M184V mutation alone does not appear to be associated with a reduced virologic response to abacavir in vivo. When associated with TAMs, M184V increases abacavir resistance.

g. As with tenofovir, the K65R mutation may be selected by didanosine, abacavir, or stavudine (particularly in patients with nonsubtype-B clades) and is associated with decreased viral susceptibility to these drugs. Data are lacking on the potential negative impact of K65R on clinical response to didanosine.

h. The presence of 3 of the following mutations—M41L, D67N, L210W, T215Y/F, K219Q/E—is associated with resistance to didanosine. The presence of K70R or M184V alone does not decrease virologic response to didanosine.

i. K65R is selected frequently (4%-11%) in patients with nonsubtype-B clades for whom stavudine-containing regimens are failing in the absence of tenofovir. Accumulation of viruses containing major mutations associated with resistance to all nRTIs currently used only at low dose as a pharmacologic booster of other PIs.

j. The presence of M184V appears to delay or prevent emergence of TAMs. This effect may be overcome by an accumulation of TAMs or other mutations.

k. The T215A/C/D/E/G/H/I/L/N/S/V substitutions are revertant mutations at codon 215 that confer increased risk of virologic failure of zidovudine or stavudine in antiretroviral-naive patients. The T215Y mutant may emerge quickly from 1 of these mutations in the presence of zidovudine or stavudine.

l. The presence of K65R is associated with a reduced virologic response to tenofovir. A reduced response also occurs in the presence of 3 or more TAMs inclusive of either M41L or L210W. The presence of TAMs or combined treatment with zidovudine prevents the emergence of K65R in the presence of tenofovir.

m. The sequential use of nevirapine and efavirenz is not recommended because of cross-resistance between these drugs.

n. Resistance to etravirine has been extensively studied only in the context of coadministration with darunavir/ritonavir. In this context, mutations associated with virologic outcome have been assessed and their relative weights (or magnitudes of impact) assigned. In addition, phenotypic cutoff values have been calculated, and assessment of genotype-phenotype correlations from a large clinical database have determined relative importance of the various mutations. These 2 approaches are in agreement for many, but not all, mutations and weights.

o. Often, numerous mutations are necessary to substantially impact virologic response to a ritonavir-boosted protease inhibitor (PI). In some specific circumstances, atazanavir might be used unboosted. In such cases, the mutations that are selected are the same as with ritonavir-boosted atazanavir, but the relative frequency of mutations may differ.

p. Resistance mutations in the protease gene are classified as “major” or “minor.” Major mutations in the protease gene are defined as those selected first in the presence of the drug or those substantially reducing drug susceptibility. These mutations tend to be the primary contact residues for drug binding.

q. Ritonavir is not listed separately, as it is currently used only at low dose as a pharmacologic booster of other PIs.

r. Many mutations are associated with atazanavir resistance. Their impacts differ, with I50L, I84V, and N88S having the greatest effect. Higher atazanavir levels obtained with ritonavir boosting increase the number of mutations required for loss of activity. The presence of M461I plus L76V might increase susceptibility to atazanavir when no other related mutations are present.

s. HIV-1 RNA response to ritonavir-boosted darunavir correlates with baseline susceptibility and the presence of several specific PI mutations. Reductions in response are associated with increasing numbers of the mutations indicated in the figure bar. The negative impact of the protease mutations I47V, I54M, T74F, and I84V and the positive impact of the protease mutation V82A on virologic response to darunavir/ritonavir were shown in 2 data sets independently. Some of these mutations appear to have a greater effect on susceptibility than others (eg, I50V vs V111). A median darunavir phenotypic fold-change greater than 10 (low clinical cutoff) occurs with 3 or more of the 2007 IAS–USA mutations listed for darunavir and is associated with a diminished virologic response.

t. The mutations depicted on the figure bar cannot be considered comprehensive because little relevant research has been reported in recent years to update the resistance and cross-resistance patterns for this drug.

u. In PI-experienced patients, the accumulation of 6 or more of the mutations indicated on the figure bar is associated with a reduced virologic response to lopinavir/ritonavir. The product information states that accumulation of 7 or 8 mutations confers resistance to the drug. However, there is emerging evidence that specific mutations, most notably I47A (and possibly I47V) and V32I, are associated with high-level resistance. The ad-
dition of L76V to 3 PI resistance-associated mutations substantially increases resistance to lopinavir/ritonavir. 

v. In some nonsubtype-B HIV-1, D30N is selected less frequently than are other PI mutations.

w. Clinical correlates of resistance to tipranavir are limited by the paucity of clinical trials and observational studies of the drug. The available genotypic scores have not been validated on large, diverse patient populations. The presence of mutations L24I, 150LV, F55Y/L/W, I54L, and L76V have been associated with improved virologic response to tipranavir in some studies.

x. Resistance to enfuvirtide is associated primarily with mutations in the first heptad repeat (HR1) region of the gp41 envelope gene. However, mutations or polymorphisms in other regions of the envelope (eg, the HR2 region or those yet to be identified) as well as coreceptor usage and density may affect susceptibility to enfuvirtide.

y. The activity of CC chemokine receptor 5 (CCR5) antagonists is limited to patients with virus that uses only CCR5 for entry (R5 virus). Viruses that use both CCR5 and CXCR4 as coreceptors have been shown to be resistant to CCR5 antagonist treatment. Virologic failure of these drugs frequently is associated with emergence of dual coreceptor-utilizing variants in infected individuals receiving highly active antiretroviral therapy (HAART) treatment. Such viruses may be resistant to CCR5 antagonists and may have mutations in CXCR4 that contribute to resistance.

z. Raltegravir failure is associated with integrase mutations in at least 3 distinct genetic pathways defined by 2 or more mutations including (1) a signature (major) mutation at Q148H/K/R, N155H, or Y143R/H/C; and (2) one or more additional minor mutations. Minor mutations described in the Q148H/K/R pathway include L74M plus E92Q, E92Q plus T97A, Y145H, G163K/R, V151I, or D232N. Another major mutation, E92Q, has also been described.

References to the User Notes


21. Winters MA, Shafer RW, Jellinger RA, Mamorta G, Gingeras T, Merigan TC. Human immunodeficiency virus type 1 reverse transcriptase genotype and drug susceptibility changes in infected individuals receiving di-


**Perspective**

**Evaluating and Managing Cardiovascular Disease Risk Factors in HIV-Infected Patients**

The primary risk factors for cardiovascular disease (CVD) in patients with HIV infection are the same as those for the general population. Some antiretroviral drugs are associated with a small increase in short-term risk of CVD that may become greater over longer periods of exposure. However, the absolute risk associated with use of these drugs is of greatest importance for patients already at moderate or high risk of CVD. The guiding principle in managing CVD risk for HIV-infected patients is to maintain control of the HIV infection while addressing the metabolic abnormalities that increase CVD risk. Lipid-lowering therapy with statins is very effective in reducing CVD risk, with levels of low-density lipoprotein cholesterol and non–high-density lipoprotein cholesterol constituting the primary treatment targets for most patients with dyslipidemia. This article summarizes a lecture by James H. Stein, MD, at the International AIDS Society–USA continuing medical education program held in Washington, DC, in June 2010.

Many HIV-infected patients now live long enough to acquire the diseases common in the HIV-seronegative population in the United States, such as cardiovascular disease (CVD). Special consideration needs to be given to predicting and managing CVD risk in the aging HIV-infected population.

**Predicting Coronary Heart Disease Risk in the General Population**

Along with aging, male sex, and a family history of premature heart disease, modifiable causes of coronary heart disease (CHD) in the general population include smoking, high blood pressure, high cholesterol levels, and diabetes mellitus. Data from 21 years to 50 years of follow-up from 3 large epidemiologic studies—the Chicago Heart Association Study, Framingham Heart Study, and MRFIT (Multiple Risk Factor Intervention Trial)—have shown that 85% to 100% of young and middle-aged men and women who develop CHD have at least 1 established CHD risk factor, and 96% to 100% of persons in whom CHD develops have at least 1 risk factor above optimal levels (ie, total cholesterol level of 200 mg/dL or greater or use of cholesterol medication; systolic blood pressure [BP] greater than 120 mm Hg, diastolic BP greater than 80 mm Hg, or use of BP medication; current cigarette use; or diabetes mellitus) (Greenland et al, *JAMA*, 2003).

In the large, ongoing international INTERHEART study, comparisons between 52,000 myocardial infarction (MI) cases and 52,000 control subjects showed that 90% of the population’s attributable risk was accounted for by 9 risk factors: high lipid levels, smoking, diabetes mellitus, and hypertension, as well as inadequate consumption of fruits and vegetables, lack of adequate exercise, excessive alcohol consumption, abdominal obesity, and high levels of psychosocial stress. A noteworthy finding was that modifiable lifestyle risk factors accounted for 63% of attributable risk (Yusuf et al, *Lancet*, 2004). Thus, in 2010, when such risk factors are highly prevalent in the general population, the problem in predicting CHD is one of specificity—separating out the people with risk factors who will experience a CVD event from those with risk factors who will not.

**Predicting Coronary Heart Disease Risk in the HIV-Infected Population**

Similar considerations apply with regard to CHD risk in the HIV-infected population. The D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study showed that a statistically significant increased risk of MI was associated with such traditional risk factors as increasing age, male sex, family history of heart disease, current and former smoking, and a prior CVD event, with current smoking (relative risk [RR], 2.83) and prior CVD event (RR, 4.30) having the highest RRs. In addition, 5-year exposure to protease inhibitor (PI) therapy was a statistically significant risk factor (RR, 2.01 per 5 years) (D:A:D Study Group, *N Engl J Med*, 2007). However, the primary analysis of the D:A:D study omitted diabetes mellitus, hypertension, and total and high-density lipoprotein cholesterol (HDL-C) levels from the risk models. When these factors were included, all had a substantial effect in predicting MI; the RR associated with PI treatment remained statistically significant but was reduced to 1.61 per 5 years of exposure, lower than that associated with prior cardiovascular event (RR, 4.64), male sex (RR, 2.13), diabetes mellitus (RR, 1.86), and current (RR, 2.92) and former (RR, 1.63) smoking.

Despite the fact that some antiretroviral drugs may pose longer-term risks of CVD via metabolic effects, it is clear that antiretroviral therapy has had a profound effect in reducing all-cause mortality in HIV-infected patients with no discernible increase in short-term risk of CVD events or death. For example, a large retrospective study showed

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See page 154 regarding CME credit for this article.
that between 1996 (the advent of the potent antiretroviral therapy era) and 2001, all-cause mortality declined dramatically, but there was no discernible increase in rates of death from CVD or cerebrovascular disease, hospital admission for CVD or cerebrovascular disease, or hospital admission for CVD compared with prior years (Bozzette et al, *N Engl J Med*, 2003).

Indeed, a recent study suggests that antiretroviral therapy may reduce CVD risk over the short term by improving endothelial function. In that study, 82 treatment-naïve, HIV-infected patients were randomly assigned to receive a nRTI-sparing regimen (efavirenz plus ritonavir-boosted [r] lopinavir), a PI-sparing regimen (efavirenz plus nRTIs), or a nonnucleoside analogue reverse transcriptase inhibitor (NNRTI)-sparing regimen (lopinavir/r plus nRTIs) for 24 weeks. Brachial artery flow–mediated dilation, a measure of endothelial function, increased by 1.48% (*P < .001*) in all subjects considered together, and similar improvements were observed in each group despite substantial differences in lipid changes among the groups (Torriani et al, *J Am Coll Cardiol*, 2008).

The findings indicating that control of HIV viremia can improve endothelial function are consistent with CVD risk data from the SMART (Strategies for Management of Antiretroviral Therapy) trial, which compared a drug-conservation strategy based on CD4+ cell count (off treatment when CD4+ cell count > 350/µL and resume treatment when count falls < 250/µL) with a continuous-viral-suppression strategy. Overall, patients in the viral-suppression group had a statistically significantly higher risk of death (RR, 2.6) than did patients in the viral-suppression group.

With regard to CVD events, the hazard ratios (HRs) for MI, percutaneous coronary intervention, or CVD death (HR, 1.57; *P = .05*) plus (inclusive of preceding endpoint) peripheral vascular disease, congestive heart failure, or coronary artery disease requiring medication (HR, 1.49; *P = .03*) plus (inclusive of preceding 2 endpoints) unobserved death of unknown cause (HR, 1.58; *P = .009*) were substantially higher in the drug-conservation group than in the viral-suppression group. CVD events were not associated with being off antiretroviral therapy or with viral load. The ratio of total cholesterol level to HDL-C level was higher in the drug-conservation group because of a decrease in the level of HDL-C (Phillips et al, *Antivir Ther*, 2008; SMART Study Group et al, *N Engl J Med*, 2006).

Nevertheless, some antiretroviral drugs have been associated with increased risk of MI. A recent analysis from the D:A:D study assessed risk of MI associated with use of individual antiretroviral drugs (Worm et al, *J Infect Dis*, 2010). Overall, MI occurred in 580 of 33,308 patients. Among PIs, indinavir and lopinavir/r (both of which are associated with increased metabolic abnormalities) were associated with a statistically significant increase in RR of MI per year of exposure (Figure 1). No increase in RR was observed with the NNRTIs nevirapine or efavirenz.

Among nRTIs, didanosine and abacavir were associated with a statistically significant increase in RR of MI for recent or current use, and abacavir was associated with a statistically significant increase in the RR per year of use. An analysis of patients receiving continuous antiretroviral therapy in the SMART study also showed that abacavir (but not didanosine) was associated with a higher risk of CVD than that of other nRTIs, with adjusted HRs

Figure 1. Top, Relative rate of myocardial infarction (MI) per year associated with protease inhibitor (PI) and nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) use in the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study. Bottom, Relative rate of MI according to recent or current use and relative rate per year of use associated with nucleoside analogue reverse transcriptase inhibitor (nRTI) use in the D:A:D study. PYFU indicates patient-years of follow-up; r, ritonavir boosted. Adapted from Worm et al, *J Infect Dis*, 2010, and Lundgren et al, CROI, 2009.
for abacavir use of 4.3 for MI, 1.8 for major CVD, and 1.9 for CVD using an expanded definition (SMART/INSIGHT and D:A:D Study Groups, AIDS, 2008). Abacavir also was associated with increased levels of high-sensitivity C-reactive protein and interleukin-6.

In summary, integrating the effects of traditional CVD risk factors and antiretroviral therapy–associated risk factors in HIV-infected patients, the following points should be considered:

- The associations between use of certain antiretroviral therapies with increased CVD are derived from observational data, which can be subject to biases and unmeasured confounding factors.
- The RR for CVD associated with use of certain antiretroviral therapies is small over the short term but may be relevant clinically over longer periods of exposure.
- Some degree of increased CVD risk can be attributed to cumulative metabolic effects (such as dyslipidemia).
- Absolute risk associated with antiretroviral therapy is most clinically relevant in patients with moderate or high CHD risk.

The guiding principle in considering CHD risk in HIV-infected patients is to first maintain control of the HIV infection. Metabolic and other risk factors can and should be managed without compromising treatment for HIV infection.

### Coronary Heart Disease Risk Reduction: Managing Dyslipidemia

In CHD risk assessment and management, a patient’s absolute CHD risk determines the intensity of risk-reducing interventions. CHD risk is assessed in 3 steps: evaluating for the presence of CHD or risk equivalents (ie, for stroke or transient ischemic attack, peripheral artery disease, and/or diabetes mellitus); counting risk factors; and using the Framingham risk assessment if 2 or more risk factors are present. The absolute risk determined by the risk assessment process is used to set goals for lipid-lowering and other preventive interventions.

The current National Cholesterol Education Panel goals for lipid-lowering therapy are summarized in Table 1 (Grundy et al, Circulation, 2004). The primary target of lipid-lowering therapy is the low-density lipoprotein cholesterol (LDL-C) level; although the target level is based on risk assessment, a LDL-C level below 100 mg/dL is optimal for everyone. The categorical CHD risk factors that modify LDL-C goals include age (men ≥ 45 years; women ≥ 55 years), family history of premature CHD (ie, CHD in a male or female first-degree relative < 55 or 65 years of age, respectively), cigarette smoking, hypertension (BP ≥ 140/90 mm Hg or taking antihypertensive medication), and low HDL-C level (< 40 mg/dL).

Triglycerides (TG) are a primary target of lipid-lowering therapy only when levels are greater than 500 mg/dL because such levels pose an increased risk of pancreatitis. Hypertriglyceridermia is associated with other coronary risk factors (eg, low HDL-C level, hypertension, and insulin resistance) and is mechanistically linked with increased levels of atherogenic remnant lipoproteins and the presence of small, dense low-density lipoprotein (LDL) particles. Meta-analyses have shown that hypertriglyceridermia is an independent risk factor for CVD, but it is not as strong a predictor of CVD as other categorical risk factors.

The non–HDL-C level is a secondary lipid-lowering target when the TG level is greater than 200 mg/dL. Non–HDL-C level is equal to the level of total cholesterol minus the level of HDL-C, and it serves as a measure of all cholesterol present in atherogenic lipoproteins including LDL, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein, and lipoprotein(a). The non–HDL-C level is strongly correlated with the concentration of LDL and apolipoprotein B-100 particles (although not equivalent as a risk predictor) and is a better predictor of CVD events than is LDL-C level. Calculation of the non–HDL-C level does not contain assumptions about the relationship between TG and VLDL cholesterol (eg, as in the Friedewald equation). The target level for non–HDL-C in lipid-lowering therapy is equal to the LDL-C target plus 30 mg/dL.

CHD risk assessment for HIV-infected patients is similar to that for the general population. Patients should have lipid levels measured before starting antiretroviral therapy, and mea-

<table>
<thead>
<tr>
<th>Coronary Heart Disease Risk Category</th>
<th>Features</th>
<th>LDL-C Level Goal</th>
<th>Consider Drug Treatment if LDL-C Level Is:</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (<em>“Very high”</em>)</td>
<td>Coronary heart disease or risk equivalent&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;100 mg/dL (optional &lt;70 mg/dL)</td>
<td>≥ 100 mg/dL</td>
</tr>
<tr>
<td>Moderately high</td>
<td>≥ 2 risk factors (10-year risk, 10%–20%)</td>
<td>&lt;130 mg/dL</td>
<td>≥ 130 mg/dL</td>
</tr>
<tr>
<td>Moderate</td>
<td>≥ 2 risk factors (10-year risk &lt;10%)</td>
<td>&lt;130 mg/dL</td>
<td>≥ 160 mg/dL</td>
</tr>
<tr>
<td>Low</td>
<td>0–1 risk factor</td>
<td>&lt;160 mg/dL</td>
<td>≥ 190 mg/dL</td>
</tr>
</tbody>
</table>

<sup>a</sup>Coronary risk equivalent is 10-year risk > 20% or presence of diabetes mellitus, history of stroke or transient ischemia, or presence of peripheral arterial disease.

<sup>b</sup>Consider drug options if the level is below the listed goal but above the goal for the next higher risk level.

measurements should be repeated every 3 months to 6 months thereafter. After risk assessment, interventions should be undertaken for modifiable nonlipid risk factors, including smoking and adverse dietary habits. If lipid goals are not met with such interventions, lipid-lowering drugs or modification of antiretroviral therapy should be considered. Initial lipid-lowering therapy consists of a statin if LDL-C or non–HDL-C level is elevated and TG level is less than 500 mg/dL, and a fibrate if the TG level is 500 mg/dL or greater. The general sequencing of lipid-lowering therapy for patients not achieving lipid goals with single-drug treatment is shown in Table 2.

Statin treatment is remarkably effective and safe in reducing CVD risk. A meta-analysis by the Cholesterol Treatment Trialists, which included 90,056 patients from 14 randomized statin trials between 1994 and 2004, showed that over a mean follow-up period of 5 years, each 39 mg/dL reduction in LDL-C level with statin treatment was associated with statistically significant reductions of 12% in all-cause mortality, 19% in coronary mortality, 23% in MI or CHD death, 24% in percutaneous coronary interventions or coronary artery bypass grafting, and 17% in stroke (the preventive benefit was for ischemic stroke only) (Baigent et al, Lancet, 2005). Approximate dose-equivalence values for available statins are listed in Table 3. Adverse effects associated with these drugs are generally dose dependent.

With regard to the effects of statins in patients with HIV infection, 8 weeks of pravastatin therapy in individuals receiving antiretroviral therapy was associated with improvement in endothelial function (Hürlimann et al, Heart, 2006; Stein et al, Am Heart J, 2004). Data are lacking, however, on the prevention of CVD events with statin therapy for HIV-infected patients. Thus far, the best-studied statins for HIV-infected patients are atorvastatin and pravastatin. For patients receiving antiretroviral or other medications that inhibit cytochrome P450 3A4, lovastatin and simvastatin should be avoided, and atorvastatin should be used with caution. Pravastatin is not a very potent statin for lowering LDL-C level, and pravastatin serum levels are increased by concomitant use of darunavir. Rosuvastatin levels are increased by concomitant use of lopinavir/ritonavir; but its potency is reduced; it should be used with caution for Asian patients and patients with advanced kidney disease.

For patients not achieving desired reductions in LDL-C and non–HDL-C levels with starting doses of a statin, the first steps are to increase the statin dose and revisit lifestyle interventions. With regard to subsequent options, bile-acid sequestrants have not been evaluated in HIV-infected patients. Extended-release niacin has been used mainly to raise HDL-C and lower TG levels in HIV-infected patients. Ezetimibe has weak effects in lowering LDL-C and minimal effects in improving HDL-C and TG levels.

With regard to treating hypertriglyceridemia, LDL-C and non–HDL-C levels should be targeted to reduce the CVD risk for patients with TG levels less than 500 mg/dL. For higher TG levels, as noted above, TG level should be targeted to prevent pancreatitis and to assist in lowering the non–HDL-C level. Dietary changes have dramatic effects on TG levels; effective changes including restriction of saturated fats and trans fats, increased consumption of omega-3 and monounsaturated fats, reduced consumption of simple carbohydrates and calories, and restriction of alcohol consumption.

Treatment of hypertriglyceridemia or combined dyslipidemia usually requires combination therapy. Statins have the best evidence for prevention of CVD and a good safety record. Niacin has good evidence for CVD prevention and is safe to use with statins; it is, however, associated with adverse effects that require management. Fish oils have less evidence for CVD prevention; they are safe to use with statins but have a high pill burden. Among fibrates, gemfibrozil has good evidence for CVD prevention. Although fenofibrate has an uncertain effect on CVD risk, it is safer than gemfibrozil to use in combination with statins. Fibrates are the initial treatment option for very high TG levels (> 1000 mg/dL). It is important to treat insulin resistance in patients with ele-

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Equivalence (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>5 10 20 40 80</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>20 40 80</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>10 20 40 80</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>20 20 40 80</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>5 10 20 40</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>5 10 20 40</td>
</tr>
</tbody>
</table>

Adapted from Stein and McBride, University of Wisconsin Health et al, 2008.

Table 2. General Sequencing of Lipid-Lowering Therapy Based on Triglycerides Level

<table>
<thead>
<tr>
<th>Medication Sequence</th>
<th>Triglycerides Level</th>
<th>Initial Treatment</th>
<th>Second-Line Therapy</th>
<th>Third-Line Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 200 mg/dL</td>
<td>Statin</td>
<td>Add niacin or bile-acid sequestrant</td>
<td>Add niacin, bile-acid sequestrant, or ezetimibe</td>
</tr>
<tr>
<td></td>
<td>200–499 mg/dL</td>
<td>Statin or niacin</td>
<td>Statin + niacin</td>
<td>Add ezetimibe</td>
</tr>
<tr>
<td></td>
<td>≥ 500 mg/dL</td>
<td>Niacin, fish oils, or fibrate</td>
<td>Combination of niacin, fish oils, or fibrate</td>
<td>Add third triglyceride-lowering drug, considering adding statin</td>
</tr>
</tbody>
</table>

Adapted from Stein and McBride, University of Wisconsin Health et al, 2008.
vated TG levels and combined dyslipidemia, with treatment including diet and exercise modifications and medications (eg, metformin or pioglitazone).

Lecture presented by Dr Stein in June 2010. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Stein in November 2010.

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Suggested Reading


Case Report From the Field

Recalcitrant Giant Molluscum Contagiosum in a Patient With Advanced HIV Disease — Eradication of Disease With Paclitaxel

Silver Cree Sisneros, DO

Background

Molluscum contagiosum is a poxvirus skin infection that is self-limited and harmless, usually causing numerous single, umbilicated papules in immunocompetent people. However, a patient with immunodeficiency such as that associated with HIV disease may present with giant, widespread, and chronic lesions, for which no single intervention has been shown to be convincingly effective for curative treatment. Poxviruses utilize the microtubule cytoskeleton within the cytoplasm of eukaryotic cells for movement into the human host cell during the establishment of infection and for facilitating the continued spread of virus infection. Paclitaxel, a chemotherapeutic drug used for treatment of cancer, targets the host cell’s microtubule cytoskeleton, resulting in apoptotic programmed cell death and potential disruption of the molluscum contagiosum virus (MCV) lifecycle. This, in turn, potentially leads to decreased viral replication and ultimately decreased burden of disease. We report here an unusual case of giant molluscum contagiosum lesions in a person with AIDS, refractory to conventional therapy but responsive to treatment with paclitaxel. No similar case appears to have been described previously.

Case Presentation

A 25-year-old, HIV-infected, heterosexual man from Mexico presented for an initial consult, reporting a 12-month history of extensive groin and facial lesions. The lesions had worsened despite the initiation of antiretroviral treatment 3 months earlier. At the time antiretroviral therapy was initiated, the patient’s CD4+ cell count was 23/µL and plasma HIV RNA level was 32,640 copies/mL. His antiretroviral treatment consisted of atazanavir 300 mg daily, ritonavir 100 mg daily, and fixed-dose combination emtricitabine/tenofovir 200 mg/300 mg daily. Additional medications included fixed-dose combination trimethoprim/sulfamethoxazole 800 mg/160 mg daily and clarithromycin 500 mg twice daily, for prophylaxis of Pneumocystis pneumonia and disseminated Mycobacterium avium complex disease, respectively. On initial presentation to the clinic, 3 months after starting antiretroviral treatment, his CD4+ cell count was 59/µL and plasma HIV RNA level was 337 copies/mL.

Initial examination revealed large papules, nodules, and plaques, some of which were extensive, ulcerating lesions, predominantly affecting the groin area and bilateral thighs, with perinodular scarring, evidence of bleeding, and hyperpigmentation. The lesions ranged in diameter from 4 mm to 20 mm, were quite tender to palpation, and caused tremendous pain during ambulation (Figure 1). Numerous facial lesions were also present that ranged in diameter from 3 mm to 5 mm. Biopsy specimens from 2 thigh lesions revealed positive pathology for MCV infection, with characteristic histologic features of large, eosinophilic, intracytoplasmic inclusion bodies (Figure 2).

Therapeutic Challenge

In patients with advanced HIV disease, molluscum contagiosum can present as an opportunistic infection and cause widespread, giant lesions that are particularly resistant to therapy.1,2 Antiretroviral therapy may result in reconstitution of the host’s immunity and may assist with resolution or improvement of MCV lesions, but success may be difficult to achieve. Historical treatment approaches, such as excision, topical treatment, and cryotherapy, are often minimally effective for treatment of extensive and severe disease.

Initial treatment with continued antiretroviral therapy in addition to topo-
Hypergranulosis (100 mg/m²) has been used successfully in the treatment of ovarian, breast, or other dose than that recommended for the US Food and Drug Administration (FDA) with intravenous paclitaxel because of the drug's potential ability to alter the life-cycle of the MCV via disruption of the host's cellular microtubule cytoskeleton kinetics.

The patient was administered “off-label” treatment (ie, not approved by the US Food and Drug Administration [FDA]) with intravenous paclitaxel 100 mg/m² (108 mg), which is a lower dose than that recommended for the treatment of ovarian, breast, or non–small cell lung cancer. This dose (100 mg/m²) has been used successfully for the treatment of AIDS-related Kaposi sarcoma. There are no known drug-drug interactions between the patient’s antiretroviral drugs and paclitaxel. Paclitaxel was administered intravenously on an outpatient basis every 21 days for 4 cycles of therapy, along with standard pretreatment with famotidine, dexamethasone, and diphenhydramine. Within 15 days of receiving the first injection, the patient experienced rapid and complete resolution of all skin lesions, despite persistent immune suppression (Figure 3).

The patient continued with the 4 scheduled cycles of chemotherapy without any complications and remained free of MCV disease at his last visit, 7 months after the initial consultation (Figure 4). Complete resolution of molluscum contagiosum persisted despite the patient’s nonadherence with his antiretroviral therapy and an increase in his plasma HIV RNA level to 10,600 copies/mL. The CD4+ cell count at the last follow-up visit was 145/µL.

**Discussion**

MCV was first described in the medical literature in 1817 and in 1905, molluscum contagiosum was found to be caused by a large DNA poxvirus (reviewed in reference 3). A major breakthrough came in 1996, when the genome of this tumorigenic virus was sequenced. With the eradication of smallpox, MCV is now the only member of the poxvirus family that currently causes substantial disease in humans. The study of MCV has been hampered by the inability to grow this virus in the laboratory and the lack of an animal model to study the infection. Vaccinia virus has therefore become the laboratory prototype and most-studied DNA poxvirus, and our knowledge of poxvirus biology is derived largely from studies of this virus. These studies show that poxviruses utilize the microtubule cytoskeleton within the cytoplasm of eukaryotic cells for movement into the human host cell during establishment of infection and for facilitating the continued spread of virus infection. Microtubules are protein-based structural components of the host cell cytoskeleton and are involved in maintaining cell shape, intracellular transport, and cell signaling, along with cell movement, reproduction, and division.

Infection with MCV has a worldwide incidence of as much as 8%. Up to 18% of patients with HIV infection have symptomatic molluscum contagiosum, an incidence that increases to 33% for patients with CD4+ cell counts less than 100/µL.11 In the United States from 1990 to 1999, the estimated number of physician visits for MCV infection was 280,000 per year.12 Acquisition of the virus follows contact with infected persons or contaminated objects and sources such as towels, sponges, swimming pools, public baths, tattoo instruments, gymnasium equipment, instruments used in beauty salons, and public benches.3,11,13 The estimated incubation period ranges from 14 days to 6 months.14 Three distinct disease patterns are observed in 3 different patient populations: children who are generally healthy; adults who are generally healthy; and immunocompromised children and adults.11

MCV infection is most common in children who become infected either directly through skin-to-skin contact or indirectly through skin contact with contaminated objects. In adults, MCV infection is considered primarily a sexually transmitted disease. In immunocompetent children and adults, MCV infection is a harmless, self-limited disease that produces a papular erupt-
tion of numerous benign, umbilicated tumors. The individual tumors are small, skin colored, firm, smooth, and painless, and they have a central white caseous plug. Individual lesions heal spontaneously and are seldom present longer than 2 months. In patients who are severely immunocompromised or have advanced HIV disease and low CD4+ cell counts, the tumors may become a widespread, chronic opportunistic infection characterized by giant, nodular, necrotic, symptomatic, and disfiguring lesions, with secondary infection. In these patients, the impaired cell-mediated immunity can interfere with the resolution of disease and the tumors may be very resistant to therapy. In immunocompromised patients, the differential diagnosis of MCV disease is important to consider; it can include atypical mycobacterial infection, cryptococcosis, pyogenic granuloma, basal cell carcinoma, histoplasmosis, penicilliniosis, pneumocystosis, and keratoacanthoma.

Little data exist with regard to the best treatment of MCV infection. No single intervention has been shown to be convincingly effective, and no reliable evidence-based recommendations exist. In healthy adults and children, treatment is not necessary for recovery, and awaiting spontaneous resolution is a potential management strategy. Treatment, when used, is intended to hasten this process. Three broad categories of treatment options have been used historically for MCV disease: physical destruction of the tumor, topical treatment, and systemic treatment. Cryotherapy, curettage, and evisceration are examples of destructive therapy. Treatment may be painful and result in scarring. Topical treatments include cantharidin, potassium hydroxide, podophyllotoxin, tretinoin, liquefied phenol, imiquimod, and cidofovir. Systemic treatments that have been tried include cidofovir and cimetidine.

Traditional antiviral drugs are directed against the proteins and functional pathways of the virus itself. Because poxviruses rely on cellular pathways to propagate, another possible antiviral treatment approach is to direct treatment that interferes with the viral functions that are dependent on the functional machinery of the cell. The microtubule cytoskeleton pathway plays a role in the lifecycle of poxviruses and may thus represent a new target for poxvirus therapy.

Paclitaxel targets the host cell’s microtubule cytoskeleton. The drug was discovered in 1964 and is derived from the bark of the Pacific yew tree (Taxus brevifolia). Paclitaxel is approved by the US FDA as a chemotherapeutic drug for the treatment of ovarian cancer, breast cancer, non-small cell lung cancer, prostate cancer, and AIDS-related Kaposi sarcoma. It belongs to the class of drugs called taxanes, which are antitumor drugs that have validated the concept of microtubules as effective cancer chemotherapeutic targets.

Cells treated with paclitaxel produce too many microtubules and as a result are unable to coordinate cell division; they die after continued attempts to replicate their DNA without the ability to divide. The rapid clearance of disease in this case supports the possibility that treatment with intravenous paclitaxel might disrupt the MCV lifecycle, thereby resulting in decreased viral replication and ultimately, decreased burden of disease. Further clinical studies are recommended to fully characterize the nature of this response.

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References


Figure 4. Photograph of the patient 4 months after the first administration of paclitaxel, showing sustained resolution of disease despite the patient’s nonadherence to his antiretroviral regimen.


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.

### Continuing Medical Education Courses

IAS–USA CME course announcements are paperless. Please watch for e-mail updates, and visit the IAS–USA Web site at www.iasusa.org for general course information, agendas, and online registration. Early registration is strongly recommended.

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

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### Improving the Management of HIV Disease®

The full-day advanced CME course, now in its 19th year, continues to focus on cutting-edge, scientifically rigorous issues presented by leading experts in the field, providing the latest insights and data on the full spectrum of HIV- and AIDS-related treatment issues.

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### 2011 Full-Day HIV Courses

**Spring 2011 Full-Day HIV Courses**

**Atlanta, Georgia**
- Monday, March 14, 2011
  - Renaissance Waverly Hotel

**Los Angeles, California**
- Monday, March 28, 2011
  - California Endowment Center

**Washington, DC**
- Wednesday, May 4, 2011
  - Capital Hilton

**San Francisco, California**
- Monday, May 16, 2011
  - Grand Hyatt San Francisco

**New York, New York**
- Tuesday, April 5, 2011
  - New York Marriott Marquis

**Chicago, Illinois**
- Monday, June 13, 2011
  - Marriott Chicago Downtown

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### Emerging Strategies in Viral Hepatitis Management

Part of the new IAS–USA focus on the management of viral hepatitis, this effort will include half-day, small-group, intensive CME workshops and a full-day CME course presented by leading experts in viral hepatitis.

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### 2011 Intensive Viral Hepatitis Workshops

**Spring 2011 Half-Day Intensive Viral Hepatitis Workshops**

**Atlanta, Georgia**
- Tuesday, March 15, 2011
  - Renaissance Waverly Hotel

**Los Angeles, California**
- Tuesday, March 29, 2011
  - California Endowment Center

**San Francisco, California**
- Tuesday, May 17, 2011
  - Grand Hyatt San Francisco

**Chicago, Illinois**
- Tuesday, June 14, 2011
  - Marriott Chicago Downtown

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### 2011 Full-Day Viral Hepatitis Course

**Spring 2011 Full-Day Viral Hepatitis Course**

**New York, New York**
- Friday, April 15, 2011
  - Grand Hyatt New York

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**Educational Resources:** CME resources from past live courses are available on the IAS–USA Web site at www.iasusa.org, including Webcasts (available for CME credit), Podcasts, downloadable key slides from lectures, and various handouts from presenters.

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

Phone: (415) 544-9400 • Fax: (415) 544-9402 • E-mail: Registration2011”at”iasusa.org • Web site: www.iasusa.org
Transmission of HIV through occupational exposure in healthcare personnel is rare. Risk of transmission from an HIV-infected source person is estimated at 0.3% for percutaneous exposures and 0.09% for mucous membrane or nonintact skin exposures, with risk modulated by exposure and source-patient characteristics. Counseling on risk assessment, postexposure prophylaxis (PEP), and baseline and follow-up testing after exposure is provided through PEPline, the National Clinicians’ Post-Exposure Prophylaxis Hotline. PEPline receives approximately 900 calls per month, most from treating clinicians. HIV PEP consists of a 28-day course of a basic or an expanded regimen, depending on the severity or volume of exposure and HIV infection characteristics of the source person. An update to the 2005 US Department of Health PEP drug recommendations is expected in 2011. This article summarizes a lecture given by Ronald H. Goldschmidt, MD, at the 13th Annual Ryan White HIV/AIDS Program Clinical Conference held in August 2010 in Washington, DC.

Healthcare personnel (HCP) have been reported to encounter more than 500,000 bloodborne pathogen exposures annually, about 400,000 of which occur in the hospital (Panlilo et al, Infect Control Hosp Epidemiol, 2004). Given the improvement in safety devices and protocols, however, this figure very likely overestimates the current burden of exposure among HCP. Female HCP account for the majority of exposures, consistent with the greater proportion of women in the healthcare field.

Actual HIV transmission to HCP as a result of occupational exposure is rare. Nevertheless, exposure can have an enormous emotional impact. As a survey by the National Clinicians’ Post-Exposure Prophylaxis Hotline (PEPline) revealed, sustaining an exposure was highly stressful and many HCP felt personally responsible for their exposure, most often because of technique problems or not thoroughly following established procedures (Cocohoba JM, Myers J, Goldschmidt RH, unpublished data, 2006). Colleagues, treating clinicians, and consultants, including PEPline consultants, were reported as having provided exposed HCP invaluable support for decision making regarding postexposure prophylaxis (PEP). Most HCP who initiated PEP reported experiencing adverse effects with variable severity, and adverse effects played a major role in compounding stress for many HCP. This article summarizes the PEPline approach to risk assessment and counseling for HCP with potential exposures to HIV.

The PEPline Service

Official guidelines for managing exposures and prescribing PEP for occupational exposure to HIV have been published by the US Public Health Service (USPHS) (Centers for Disease Control and Prevention [CDC], MMWR, 2005; CDC, MMWR, 2001); the 2005 report provides updated recommendations for drugs used for PEP and is expected to be further updated online in 2011.

The PEPline service is available free of charge at 888-448-4911 (www.nccc.ucsf.edu). The goals for postexposure management are to prevent transmission, avoid unnecessary PEP and PEP toxicity, and provide counseling and follow-up for exposed HCP. PEPline faculty members are HIV-expert physicians and clinical pharmacists. The PEPline is available 24 hours per day, during nonstaffed hours, an answering service pages on-call faculty clinicians, with an average response time of 3 minutes.

The PEPline receives approximately 900 calls per month, of which approximately 76% concern occupational exposures. In 72% of these calls, the caller is a HCP’s treating clinician; the caller is the exposed HCP in 14% of cases and “other” in 14%. Physicians account for 42% of calls, with registered nurses (RNs), nurse practitioners (NPs), physician assistants (PAs), certified nurse midwives (CNMs), and licensed vocational nurses (LVNs) jointly accounting for 45%. The professions of the remainder are categorized as “other” or “unknown.” Most (64%) of the exposed individuals are RNs, PAs, CNMs, or LVNs; physicians are 16% of exposed HCP, and “other” or “unknown” are 20%. The setting of exposure is a hospital in 26% of cases; an emergency department in 5%; an operating room, labor-and-delivery setting, or other surgical setting in 10%; an outpatient or other medical setting in 20%; and a dental, laboratory, ambulance, or other setting in 38%. The majority (64%) of exposures are percutaneous; other exposures include mucous membrane exposures in 20% and cutaneous exposures in 16%. The exposure substance is blood in 56% of cases, saliva in 16%, and “other” or “unknown” in 28%.

PEPline consultants provide the caller with advice on: (1) assessing the risk associated with the exposure by ascertaining the nature of the injury, the type of substance involved, and source-patient factors; (2) determining whether PEP should be considered; and (3) selecting the PEP regimen. Faculty clinicians also provide advice.
Transmission Risks

The overall risk of transmission of HIV from percutaneous exposure is estimated as 0.3% (3 per 1000 exposures) (Bell, Am J Med, 1997). Factors that increase risk of transmission include exposure through a visibly bloody device (odds ratio [OR], 6.2), through a device used in an artery or vein (OR, 4.3), via a deep injury (including intra-muscular and subcutaneous exposure) (OR, 15.0), and from a source individual with more advanced HIV disease (and plasma HIV RNA level > 1500 copies/mL) (OR, 5.6) (Cardo et al, N Engl J Med, 1997). Risk of transmission through mucous membrane exposure is estimated as 0.09% (Ippolito et al, Arch Intern Med, 1993). For HIV transmission, substances or fluids that are considered infectious include blood, tissue, semen, vaginal secretions, and pus, as well as cerebrospinal, amniotic, pericardial, peritoneal, pleural, and synovial fluids. Unless visibly bloody, substances considered noninfectious include urine, feces, nasal secretions, saliva, gastric fluid, sputum, tears, sweat, and vomitus.

Testing and Recommendations for Postexposure Prophylaxis

The PEP decision depends on knowing or assessing the source-patient HIV serostatus. For PEP decisions, rapid HIV antibody testing of the source person can sometimes be performed if the patient is available and no HIV test results are available. Results from rapid tests are considered as accurate as standard test results for making PEP decisions. HIV antibody testing of the exposed HCP should occur pretreatment and at 6 weeks, 3 months, and 6 months postexposure.

The possibility of HIV transmission from a source person during the window period between infection and...
positive HIV antibody test results is a common topic of calls to PEPline. Because most acute HIV infections can be detected by seroconversion within 3 weeks and most cases of acute infection are identifiable by the source person’s history of exposure or presence of a viral syndrome, the likelihood of the source being in an unrecognized infectious window period is extremely small. Additional reassurance can be given by the finding that no cases of occupational transmission involving exposure during the window period have been reported to date in the United States.

Table 1 provides guidance from the CDC on whether PEP is indicated and if so, whether a basic or expanded regimen is recommended after percutaneous exposure, mucous membrane exposure, or nonintact skin exposure. HIV-seropositive class 1 refers to a source individual with an asymptomatic infection or a plasma HIV RNA level less than 1500 copies/mL, and HIV-seropositive class 2 refers to a source individual who is symptomatic, has AIDS, has a high viral load, or has acute seroconversion illness. For percutaneous exposures, less severe exposures are those involving, for example, a solid needle or a superficial injury, whereas more severe exposures are those involving, for example, large hollow-bore needles, deep injury, visible blood, or a device used in an artery or vein. For mucous membrane exposures, small volume refers to a few drops, and large volume refers to a major splash. Eye exposures that contact the conjunctiva are thought to carry a risk similar to that of other mucous membrane exposures. Nonintact skin includes any compromised skin integrity, for example, dermatitis, abrasions, and open wounds.

For any percutaneous exposure from an infected source, an expanded PEP regimen is warranted. In cases in which the source is unknown or is of unknown HIV serostatus, PEP is generally not warranted, although a basic regimen should be considered for any exposure to a source with HIV risk factors or in settings in which exposure to HIV-infected persons is likely.

The PEPline receives numerous inquiries about “found needles,” which refer to needles left in garbage cans, parks, or elsewhere in healthcare facilities or public places. There have been 2 apparent cases of transmission in HCP involving found needles in the hospital setting. Thus far, there have been no documented cases of transmission involving found needles in the community. Testing of discarded needles for HIV should not be performed because such a practice results in false-positive and false-negative results.

There are some practical approaches used at the PEPline that are helpful in managing most exposures:

- When the source person’s HIV serostatus is not known, risk factors (when known) need to be considered, but the decision whether to recommend PEP needs to be made despite the incomplete source information. The decision should not be delayed pending receipt of laboratory results or additional history data, unless the results of a rapid HIV test or additional patient history are expected within a few hours.

- The determination about whether to recommend PEP is made by the treating clinician, but the decision to take PEP is made by the exposed HCP after hearing the assessment of risk of the specific exposure and the benefits and risks of PEP. For the HCP, deciding whether to take PEP is a highly personal decision in most cases.

- Initiating PEP, when indicated, should never be delayed. There has been misunderstanding of the current guidelines that (correctly) state that PEP should not be initiated past 72 hours. This does not mean, however, that there is a 72-hour window to initiate PEP, only that there is no evidence of efficacy when initiated past 72 hours.

- When PEP is indicated but the HCP is undecided about whether to take PEP (which often occurs in the emotionally charged postexposure state), the PEPline service encourages the HCP to initiate PEP immediately and reconsider the longer term decision the next day. The reasoning is that PEP can always be discontinued, but once the chance to initiate PEP as early as possible is missed, it cannot be retrieved. This message can be reassuring to exposed HCP and allows time for test results to be obtained and for HCP to reconsider whether they want to continue treatment on the basis of additional risk assessment or test results. Conversely, delaying initiation of PEP and then realizing hours later that the opportunity to take early PEP has been missed can be emotionally (and possibly clinically) devastating.

Selection of Postexposure Prophylaxis Regimen

PEP is administered for 28 days. The duration of treatment is not based on controlled studies, although some animal evidence indicates that shorter duration PEP is not as effective. Similarly, there are no comparative studies of the various drugs used for PEP, so recommendations are based on presumed efficacy and known tolerability. The recommended basic regimens for HIV PEP (CDC, MMWR, 2005) are tenofovir plus emtricitabine or zidovudine plus lamivudine. Tenofovir-containing regimens are generally better tolerated in PEP but should not be used when renal insufficiency is present. The recommended expanded regimen, if warranted, is formed by adding ritonavir-boosted (r) lopinavir to either of the 2-drug regimens. Once-daily darunavir/r is better tolerated than lopinavir/r. Alternatives for constructing the expanded regimen in cases of resistance, drug interactions, or intolerance include darunavir/r, atazanavir/r, or raltegravir. The expanded drug regimens are associated with more toxicity and less adherence than the basic
regimens. New York state guidelines (available at http://www.ceiwidget.com/online/) recommend that PEP always consist of 3 nucleoside analogue transcriptase inhibitors: either fixed-dose zidovudine/lamivudine plus tenofovir or fixed-dose tenofovir/emtricitabine plus zidovudine.

Newer drugs might have some advantages and likely will replace some of the currently recommended drug regimens. A recent survey showed that PEPline recommendations differed from USPHS guidelines recommendations in 14% of cases. Predictors for recommendations outside of the guidelines regimens included the following source-person characteristics: current use of specific antiretroviral drugs, prior antiretroviral drug exposure, antiretroviral drug resistance, and clinical status. Alternatives for the expanded regimen recommended by PEPline faculty in this 14% of cases included darunavir/r in 36% of cases, raltegravir in 31%, atazanavir/r in 18%, and maraviroc in 6% (Hensic and Dong, CROI, 2011).

Overtreatment in cases of occupational exposure to HIV is common. As long as the HCP is aware of the risks and benefits of PEP, initiating basic PEP even when there is minimal risk from the exposure or prescribing expanded regimens as a precaution when a basic regimen might suffice can be reassuring to the exposed HCP that everything possible has been done. Such overtreatment actually constitutes a conservative approach from the perspective of the treating clinician as well, ensuring the best chance that transmission does not occur. This approach seems to be working, as no new cases of transmission via occupational exposures have been reported in more than 5 years and few serious toxicities from PEP have been reported. In addition to use of PEP, other factors contribute to the reduced risk of occupational exposure and transmission of HIV, including improvement in safety devices, better safety habits among HCP, better institutional adherence to safety procedures, the presence of fewer HIV-infected patients in the hospital setting, and reduced viral load in the infected population as the result of effective treatment.

Lecture presented by Dr Goldschmidt in August 2010. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Goldschmidt in December 2010.

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Suggested Reading


Hensic L, Dong B. Non-guideline post-exposure prophylaxis regimens for occupational percutaneous exposures to HIV+ source patients. [Abstract.] Accepted for presentation at the 18th Conference on Retroviruses and Opportunistic Infections (CROI). February 27-March 2, 2011; Boston, MA.


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**PEPline**

National Clinicians’ Post-Exposure Prophylaxis Hotline

(888) 448-4911

www.nccc.ucsf.edu
Management of Depression and Alcohol Dependence in an HIV/HCV Coinfected Patient
Gareen Hamalian, MD, MPH, and Joseph Z. Lux, MD
CME Credit Available: 1.5 AMA PRA Category 1 Credits™
Level: Advanced
Treatment of psychiatric illness in HIV-infected patients, especially when this illness is accompanied by substance abuse, is a common and complex concern for HIV health care providers. On completion of this COW activity, the learner will be able to compare psychopharmacologic treatment options for depressed HIV-infected patients, discuss neuropsychiatric concerns related to the use of efavirenz, and discuss prophylaxis and treatment options for HIV/hepatitis C virus coinfected patients on interferon alfa therapy.

Care of HIV-Infected Women During Pregnancy
Deborah Cohan, MD, MPH
CME Credit Available: 2.0 AMA PRA Category 1 Credits™
Level: Advanced
Although remarkable strides in HIV medicine have dramatically lowered the risk of perinatal HIV transmission, clinicians continue to encounter numerous challenges in providing care for HIV-infected pregnant women. This COW activity addresses the risk of birth defects resulting from antiretroviral therapy and identifies treatment regimens that pose low risk to the woman and the fetus. Indications for elective cesarean delivery, as well as postpartum management of HIV disease, are discussed. This activity also presents the particularly challenging situation of HIV infection diagnosed late in pregnancy.

Viral Blips in the HIV-Infected Patient
Timothy J. Henrich, MD, and Daniel R. Kuritzkes, MD
CME Credit Available: 1.5 AMA PRA Category 1 Credits™
Level: Advanced
Episodes of intermittent low-level viremia (ie, viral blips) are often detected during routine laboratory monitoring of HIV-infected patients. Viral blips may lead clinicians to order unnecessary tests and alter medication regimens for patients whose infection is otherwise well controlled. This COW presentation discusses the sparse and sometimes conflicting research about the etiology of blips. The relationship of blips to medication adherence and antiretroviral drug resistance, as well as management strategies for patients with blips, are also described.

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Look for these new Cases on the Web activities in coming months:
- **Dermatologic Complications of HIV Infection** — Identify the unusual skin eruptions, skin diseases with exaggerated presentations (eg, seborrheic dermatitis), sudden acute exacerbations, and treatment failures that should alert the clinician to the possibility of underlying HIV infection.
- **Acute HIV Infection** — Compare the benefits and risks of initiating antiretroviral therapy for acute HIV infection.

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

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HIV/AIDS Practitioners

We thank our audience—the participants in our continuing medical education (CME) courses and our readers—for actively participating in our programs and providing feedback on how we can continually improve the quality and relevance of our activities. In 2010, approximately 2800 practitioners attended our live full-day, half-day, or multi-day CME courses, more than 12,000 received each issue of *Topics in HIV Medicine*, approximately 77,500 participated in the *Cases on the Web* CME program, and more than 2000 viewed Webcasts of sessions from the live CME courses.

Funders

For support of the 2010 educational effort, *Improving the Management of HIV Disease*: *HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management*, which encompasses live CME courses, the 2010 volume of *Topics in HIV Medicine*, and the CME *Cases on the Web* program, we gratefully acknowledge:

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Volunteers

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Donors

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IAS–USA courses this year included the series Improving the Management of HIV Disease®, completing its 18th year, the new Intensive Workshop on Evolving Strategies in Viral Hepatitis Management, and the 13th Annual Clinical Conference for the Ryan White HIV/AIDS Program. The IAS–USA held interactive sessions at the 50th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, the 18th International AIDS Conference, and the 10th International Congress on Drug Therapy in HIV Infection.
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Drug Resistance Mutations Group

The Drug Resistance Mutations Group was convened in 2000 to maintain an ongoing, up-to-date list of HIV drug resistance mutations. Each year, the group convenes during scientific conferences to review recent data and prepare updates to its list of mutations. For more information, visit www.iasusa.org/resistance_mutations.

IAS–USA Panel on Antiretroviral Treatment of Adult HIV Infection


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In Memoriam

Andy I. Choi, MD, MAS
1975-2010

The HIV/AIDS research community suffered a profound loss when Andy Choi, MD, MAS, passed away unexpectedly on August 15, 2010. Dr Choi was assistant professor of medicine, Division of Nephrology, in the Department of Medicine at the University of California San Francisco (UCSF). His clinical research interests included HIV-related kidney diseases, the racial disparities of kidney disease, and the epidemiology of chronic kidney disease. UCSF has renamed one of its mentoring programs in his honor: the Andy I. Choi Mentoring Program of the UCSF-GIVI Center for AIDS Research.

Jeffrey Nadler, MD
1950-2010

Dr Jeffrey Nadler is remembered as a dedicated HIV researcher, teacher, and clinician. During 19 years at the University of South Florida (USF), Dr Nadler was a professor of medicine and public health and also served as the director of research in the Division of Infectious Disease. At USF, he oversaw clinical trials of more than 20 antiviral drugs that are now routinely used to treat HIV. Dr Nadler traveled frequently to India and Brazil to treat HIV patients in local clinics. In recent years, Dr Nadler served as director of the therapeutics research program in the division of AIDS at the National Institute of Allergy and Infectious Diseases.
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