

# Topics in HIV Medicine®

A publication of the International AIDS Society–USA

## Perspectives

Update on Cardiovascular Complications in HIV Infection 98

*Judith S. Currier, MD*

*Epidemiology of Cardiovascular Disease in HIV-Infected Persons • Host Factors • Virus Factors  
• Antiretroviral Therapy Factors*

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Occupational and Nonoccupational Postexposure Prophylaxis 104  
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*Management of Occupational Exposure to HIV • Management of Nonoccupational Exposure to HIV*

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## About This Issue

This issue features 2 *Perspectives* articles from presentations given at recent International AIDS Society–USA continuing medical education courses, and a *Review* article. The first *Perspective* article summarizes a presentation given by Judith S. Currier, MD, in Los Angeles in February 2009 on cardiovascular complications in HIV infection. The increased risk of cardiovascular disease reflects an interaction of risks associated with host, virus, and antiretroviral therapy factors. A second *Perspective* article, based on a presentation by Raphael J. Landovitz, MD, at the same Los Angeles course in February 2009, discusses data supporting the current recommendations on managing HIV postexposure prophylaxis in health care workers as well as in nonoccupational settings. The *Review* article, by John T. Brooks, MD, Jonathan E. Kaplan, MD, and Henry Masur, MD, describes changes and additions in the 2009 guidelines on the prevention and treatment of opportunistic infections in people with HIV. The multiagency-sponsored document has expanded previous information on hepatitis B virus infection, tuberculosis, and immune reconstitution inflammatory syndrome, and it includes detailed discussions on the use of antiretroviral therapy in prevention and treatment of opportunistic infections.

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### 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

Web site: <http://www.iasusa.org>  
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## Perspective

# Update on Cardiovascular Complications in HIV Infection

*HIV-infected patients are at increased risk of cardiovascular disease (CVD), reflecting interaction of risk associated with host, virus, and antiretroviral therapy factors. Although traditional risk factors appear to increase risk to a similar degree in HIV-infected and HIV-uninfected persons, some risk factors (eg, smoking) may be more common in HIV-infected persons. HIV infection per se may further increase CVD risk via proatherosclerotic effects on smooth muscle cells and macrophages or by increasing inflammation. Some drugs in the protease inhibitor class are associated with increased risk, at least partly in association with adverse lipid effects. The magnitude and mechanisms of risk reported to be associated with recent use of abacavir remain undefined. This article summarizes a presentation on cardiovascular complications in HIV infection made by Judith S. Currier, MD, at an International AIDS Society–USA continuing medical education course in Los Angeles in February 2009. The original presentation is available as a Webcast at [www.iasusa.org](http://www.iasusa.org).*

### Epidemiology of Cardiovascular Disease in HIV-Infected Persons

In the context of declining rates of HIV-related death, proportions of HIV-infected patients dying of other causes have increased. For example, a death certificate study in New York City showed that the proportion of deaths among HIV-infected patients due to non-HIV-related causes increased from 19.8% to 26.3% between 1999 and 2006, reflecting mortality resulting from cardiovascular disease (CVD), substance abuse, and non-AIDS-defining cancers (Sackoff et al, *Ann Intern Med*, 2006). Among individuals aged 55 years or older, CVD was the leading cause of death.

Numerous studies have indicated increased risk of myocardial infarction (MI) in HIV populations, with HIV infection considered at least a partial CVD risk factor in these studies. Klein and colleagues reported hospital-admission rates for coronary heart disease (CHD) in HIV-infected versus HIV-uninfected populations of 6.5 versus 3.8 per 1000 person-years (Klein et al, *JAIDS*, 2002) and 4.5 versus 2.9 per

1000 person-years in updated analyses with further follow-up time (Klein et al, *CROI*, 2007), respectively. Currier and colleagues found a higher risk of coronary artery disease (CAD) admissions among younger HIV-infected than among HIV-uninfected patients (Currier et al, *JAIDS*, 2003); Triant and colleagues found a 75% increase in risk of MI admissions in HIV-infected patients (Triant et al, *J Clin Endocrinol Metab*, 2007); and Obel and colleagues found a 39% to 112% increased risk of CAD admissions in HIV-infected patients (Obel et al, *Clin Infect Dis*, 2007).

The study by Triant and colleagues was performed using data from a Massachusetts administrative hospital da-

tabase including 3851 HIV-infected patients and more than 1 million HIV-uninfected patients from 1996 to 2004. The mean MI rates were 11.13 versus 6.98 per 1000 person-years, respectively. MI rates were higher in HIV-infected patients in all age groups, with very high rates in older patients (Figure 1). These investigators have also reported that levels of the acute-phase reactant C-reactive protein (CRP) were predictive of risk of MI in HIV-infected patients, despite the fact that CRP levels generally are nonspecifically elevated in HIV infection (Triant et al, *JAIDS*, 2009).

These findings underscore the need to determine why the rates of CVD are higher in HIV-infected than -uninfected individuals. Understanding the relative contributions of host, virus, and antiretroviral therapy to risk of CVD in HIV infection will help inform development of strategies for prevention and treatment.

### Host Factors

Traditional CVD risk factors, as well as HIV infection and its treatment, contribute to the risk of CVD in HIV-infected individuals. The risk of MI in both HIV-infected and -uninfected populations is increased in a similar manner by the risk factors of increasing age, male sex, diabetes, smoking, and hy-

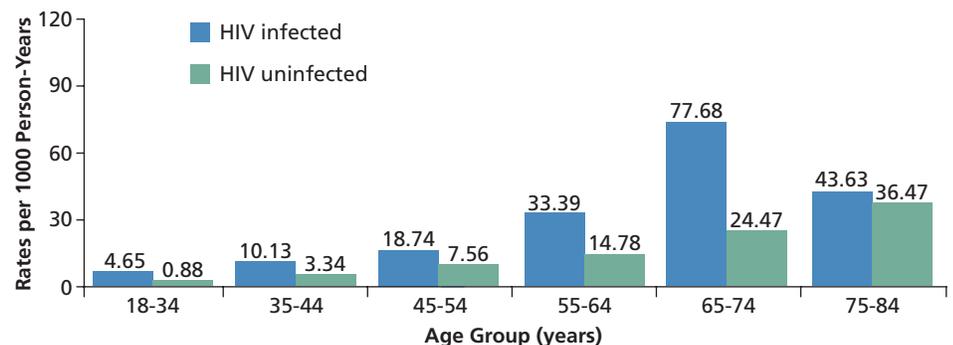


Figure 1. Myocardial infarction rates in HIV-infected (n = 3851) versus HIV-uninfected (n = 1,044,589) patients in a Massachusetts administrative hospital database, for 1996-2004. Adapted from Triant et al, *J Clin Endocrinol Metab*, 2007.

Dr Currier is professor of medicine at the University of California Los Angeles (UCLA) and codirector of the UCLA Center for Clinical AIDS Research and Education.

**Table 1.** Contribution of Traditional Risk Factors to Risk of Myocardial Infarction in HIV-Infected and HIV-Uninfected Populations

Risk Factor	Unit	HIV-Infected	HIV-Uninfected (No. of studies)	
		lloeje et al, <i>HIV Med</i> , 2005	Friis-Moller et al, <i>N Engl J Med</i> , 2003	
Age	Year increase	9%	6%	6%-9% (7)
Sex	Male vs female	--	110%	110%-160% (2)
Diabetes	Yes vs no	260%	90%	140%-252% (3)
Smoking	Yes vs no	140%	290%	70%-290% (3)
Hypertension	Yes vs no	30%	80%	80%-90% (3)

Adapted from Currier et al, *Circulation*, 2008, and Sabin and Worm, *Curr Opin HIV AIDS*, 2008.

pertension (Table 1) (Currier et al, *Circulation*, 2008; Sabin and Worm, *Curr Opin HIV AIDS*, 2008). The prevalence of some risk factors may be higher in HIV-infected populations, however. In the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study in 23,468 HIV-infected persons, at baseline 11.4% had a family history of coronary disease, 1.4% had a prior history of coronary disease, 51.5% were current smokers, 3.5% had a body mass index greater than 30 kg/m<sup>2</sup>, 8.5% had hypertension, 2.5% had diabetes, 22.2% had elevated levels of total cholesterol, and 33.8% had elevated triglyceride levels (Friis-Moller et al, *AIDS*, 2003). A recent analysis of modifiable risk factors and death in the D:A:D study showed that smoking (rate ratio, 1.20), hypertension (rate ratio, 1.53), and diabetes (rate ratio, 1.83) were independently associated with risk of death during treatment for HIV infection (Smith et al, *CROI*, 2009). Smoking is common in many HIV-infected populations, and programs aimed at cessation have thus far been largely unsuccessful (Tashima et al, *CROI*, 2009). Greater attention needs to be given to smoking and other modifiable CVD risk factors in HIV-infected patients.

Increased carotid artery intima-media thickness (IMT), a marker for subclinical atherosclerosis, is associated with increased risk of MI. An analysis from the FRAM (Fat Redistribution and Metabolism) study showed that HIV

infection was associated with statistically significant increases in internal carotid (0.15 mm;  $P < .001$ ) and common carotid (0.033 mm;  $P < .01$ ) IMT compared with IMT values for a large population of HIV-uninfected persons (Grunfeld et al, *CROI*, 2009; Grunfeld et al, *AIDS*, 2009). Because most HIV-infected patients in the FRAM study were receiving antiretroviral therapy, any potential effect of antiretroviral therapy on this finding is uncertain. Other traditional risk factors associated with increased IMT in the FRAM patients were male sex, current and past smoking, diabetes, age per 10-year increase, systolic blood pressure increase, and total cholesterol level increase, with high-density lipoprotein (HDL) cholesterol level increase associated with a statistically significant reduction in IMT.

### Virus Factors

The SMART (Strategies for Management of Antiretroviral Therapy) study examined the potential for reducing antiretroviral therapy toxicity by limiting time on treatment, with 5472 patients with CD4+ counts higher than 350 cells/ $\mu$ L randomly assigned to a treatment-interruption plan (termed drug-conservation strategy) or to continuous treatment (viral-suppression strategy). The drug-conservation strategy increased risk over the viral-suppression strategy of opportunis-

tic disease or death (rates, 3.4% vs 1.3%, respectively; hazard ratio [HR], 2.6) and of CVD, renal, or liver events (rates, 1.8% vs 1.1%, respectively; HR, 1.7) (El-Sadr et al, *N Engl J Med*, 2006). The study brought into focus the importance of serious non-AIDS-related events among patients without viral suppression on antiretroviral therapy. Subsequent analysis did not find an association between viral load and risk of CVD but confirmed increased risk of CVD among patients who discontinued antiretroviral therapy.

A number of mechanisms have been proposed to explain how HIV infection might contribute to atherosclerosis. HIV has been reported to infect smooth muscle cells in vitro and in vivo and increases secretion of a monocyte chemoattractant (CCL2, or MCP-1), which facilitates development of foam cells (Eugenin et al, *Am J Pathol*, 2008). Macrophages, which play a pivotal role in atherosclerosis, are also hosts for HIV. The HIV Nef protein impairs the adenosine triphosphate binding cassette (ABCA-1) transporter in macrophages, which is important to reverse cholesterol transport. This inhibition may lead to conversion of macrophages into foam cells and initiate plaque formation in vessel walls (Mujawar et al, *PLoS Biol*, 2006). This effect of Nef inhibition of the ABCA-1 transporter has been demonstrated in simian immunodeficiency virus (SIV)-infected macaques (Bukrinsky et al, *CROI*, 2009).

HIV may also directly impair HDL metabolism, thus enhancing transfer of HDL to atherogenic apolipoprotein B lipoproteins (Rose et al, *Atherosclerosis*, 2008). This potential mechanism is consistent with findings in the recent SMART trial analysis indicating an association of total HDL particles with risk of CVD in patients in the drug-conservation group (Duprez et al, *CROI*, 2009). In particular, risk was elevated in patients with declining HDL cholesterol levels after stopping nonnucleoside reverse transcriptase inhibitor (NNRTI) treatment. Collectively, these findings suggest that untreated HIV infection could contribute to the development of atherosclerosis,

although the magnitude of the effects remains unclear. Strategies to increase HDL cholesterol levels in HIV-infected individuals should be investigated.

Another mechanism by which HIV infection itself may contribute to CVD risk is inflammation. CRP is a marker of inflammation that independently predicts risk of CVD in adults in the general population. In HIV infection, elevated CRP levels predict HIV disease progression and mortality in untreated women after adjustment for viral load and CD4+ count. Uncontrolled HIV infection is associated with elevated markers of inflammation, including CRP. Levels of these markers decline with treatment but not to normal levels. Little is known about how different antiretroviral drugs affect CRP levels during successful antiretroviral therapy. Recent data from ACTG (AIDS Clinical Trials Group) study 5095 demonstrated that CRP levels did not improve during 96 weeks of treatment with efavirenz; in fact, among women CRP levels rose (Shikuma et al, CROI, 2009). Elevated baseline levels of the inflammatory marker interleukin-6 (IL-6) and the coagulation marker D-dimer were associated with all-cause mortality (not specifically with CVD events) in the SMART trial, and levels of these markers rose after treatment interruption (Kuller et al, CROI, 2008).

Despite the potential association of inflammation with increased CVD risk, a number of small studies have not found a strong association between higher levels of high-sensitivity CRP (hsCRP) and IMT. Hsue and colleagues found no association of hsCRP or immune activation (CD38+, CD4+, CD8+ cell responses) with IMT, but they reported an association between IMT and cytomegalovirus-specific T-cell responses, suggesting that response to latent or persistent viral infection might be driving a proatherosclerotic response (Hsue et al, *AIDS*, 2006). Other findings include improved endothelial function (measured by brachial artery reactivity) after 24 weeks of antiretroviral therapy in treatment-naive patients but no significant change in hsCRP level. In a pilot study in patients with untreated HIV infection, 8 weeks

of treatment with the tumor necrosis factor inhibitor pentoxifylline resulted in improvements in the endothelial activation marker VCAM-1 and brachial artery flow-mediated dilation (Gupta et al, CROI, 2008). The effects of such an approach to reducing inflammation in antiretroviral therapy-treated patients with viral suppression are being investigated.

### Antiretroviral Therapy Factors

Numerous studies have been performed in the effort to sort out the potential effects of antiretroviral therapy on risk of CVD. Obtaining more definitive information in this regard would likely require additional randomized trials to control for potential confounding factors.

Although there are differences between individual drugs in the protease inhibitor (PI) class with respect to lipid-altering effects, several studies have described how PI treatment is associated with adverse effects on lipids, and numerous studies have reported an adverse effect on CVD risk. Among 10 studies of the effects of PI treatment (conducted before the availability of newer PIs) considered in a recent review including randomized, controlled trials, prospective observational cohort studies, retrospective reviews, and administrative database studies, 6 found an effect of PIs, 2 found an effect of antiretroviral therapy, and 2 found no effect of PIs on risk of CVD, MI, or CAD hospital admissions (Currier et al, *Circulation*, 2008). With regard to risk associated with particular PIs, the D:A:D study investigators found that lopinavir/ritonavir and indinavir were associated with increased risk of MI; there was no association between risk and ritonavir-boosted PIs as a group; and there was insufficient information to assess risk associated with atazanavir use. Data from the French Hospital Database indicate increased risk of MI with use of lopinavir/ritonavir and ritonavir-boosted fosamprenavir (Lang et al, CROI, 2009).

The general conclusion with regard to the effect of PIs on CVD risk is that it is cumulative and at least partly medi-

ated by lipid changes. Data on the effects of newer PIs on cardiovascular events are limited, however. Future research needs to focus on the effects of individual drugs rather than on drug classes, given the heterogeneity of metabolic effects of drugs within the PI class.

More recently, attention has focused on the effects of nucleoside analogue reverse transcriptase inhibitors (nRTIs) on CVD risk. The D:A:D study included a preplanned analysis of CVD risk associated with thymidine analogue nRTIs, which have known effects on lipid levels. No association between zidovudine or stavudine use and risk of MI was found in the initial report (D:A:D Study Group et al, *Lancet*, 2008), and subsequently no association for tenofovir was observed (Lundgren et al, CROI, 2009). However, recent exposure to abacavir and didanosine were each associated with increased risk of MI.

Several analyses have been performed in an attempt to better understand the association between abacavir and to a lesser extent didanosine and CVD events. A retrospective analysis of the abacavir clinical trials database involving 1570 abacavir-treated patients and 1692 patients not receiving abacavir with 24 weeks to 48 weeks of follow-up showed no association of abacavir treatment with risk of any or acute MI (relative risk [RR], 0.863; 95% confidence interval [CI], 0.40-1.86) or risk of any ischemic CAD or disorder (RR, 0.593; 95% CI, 0.35-1.01) (Cutrell et al, IAC, 2008). Similarly, an analysis of 119 CVD events in the HOPS (HIV Outpatient Study) cohort showed no association with abacavir treatment (Lichtenstein et al, IAC, 2008). Analysis of data from the observational group in the SMART study showed higher levels of hsCRP (27% increase;  $P = .02$ ) and IL-6 (16% increase;  $P = .02$ ) in patients receiving abacavir without didanosine than in those receiving other nRTIs (Lundgren et al, IAC, 2008).

However, analysis of inflammation biomarkers in the randomized HEAT (Head-to-Head Epzicom and Truvada) trial showed reduced hsCRP and IL-6 levels after 48 weeks and 96 weeks, both in treatment-naive patients receiving abacavir/lamivudine and in

patients receiving tenofovir/emtricitabine (Smith et al, IAC, 2008). A case-control study in the French Hospital Database (MI cases,  $n = 289$ ; controls,  $n = 884$ ) indicated an increased risk of MI (odds ratio, 1.97) among patients receiving abacavir for less than 1 year or who had stopped abacavir within 6 months, but no association of abacavir with MI risk in those exposed for more than 1 year or who had stopped for more than 6 months. In the STEAL (Switching to Tenofovir/Emtricitabine or Abacavir/Lamivudine) trial, 360 virologically suppressed patients were randomly assigned to receive abacavir/lamivudine or tenofovir/emtricitabine; 7 CVD events occurred in the abacavir/lamivudine group versus 1 in the tenofovir/emtricitabine group. An analysis in the ALLRT (AIDS Clinical Trials Group Longitudinal Linked Randomized Trials) study involving 3205 patients on randomized antiretroviral therapy showed no statistically significantly increased risk of MI with recent abacavir use (RR, 1.2; 95% CI, 0.5-3.1).

Where does this leave us with regard to potential CVD risk associated with abacavir use? Observational studies with control for known confounders have suggested an association of recent abacavir use with MI risk; however, this risk has not been confirmed in randomized trials. In addition, the risk does not appear to accumulate over time and appears to fade after the drug has been stopped. This suggests a mechanism of action that is triggered soon after the drug is started and that resolves when the drug is stopped. The increased risk with abacavir treatment has been observed to be heightened in patients with conventional risk factors and possibly in virologically suppressed patients for whom abacavir is substituted (Reiss, CROI, 2009).

Thus, for the present, any potential risk associated with abacavir use needs to be interpreted in the context of the overall benefits of antiretroviral treatment and the presence of modifiable risk factors. To date, any potential interaction between risk posed by PI use and that associated with abacavir remains unclear and should be evalu-

ated. The potential mechanisms for abacavir-associated risk also remain undefined. One small study thus far has suggested an effect of the drug on platelet function.

For the present, Dr Currier's opinion is to consider an individualized approach to the management of a patient on a stable abacavir-containing regimen. In a patient with 5 cardiovascular risk factors who has alternative antiretroviral therapy options, a switch can be considered. Because successful treatment of HIV is the priority, switching is far less attractive if there are limited antiretroviral therapy options. Switching likely does not need to be considered in patients without cardiovascular risk factors. Control of traditional risk factors is essential; for example, smoking cessation should be a higher priority than changing the nRTI component of antiretroviral therapy. Although the populations are too small to reach definitive conclusions regarding MI risk, data from ongoing randomized trials comparing abacavir and tenofovir in treatment-naïve patients should provide additional information on potential abacavir-related CVD risk.

## Summary

CVD risk in HIV infection is likely a product of host, virus, and antiretroviral therapy factors (Figure 2). The benefits of antiretroviral therapy outweigh CVD

risks. Delaying antiretroviral therapy is not the answer to reducing these risks. Indeed, because HIV infection that is not suppressed may be accelerating atherosclerosis, earlier treatment may be of benefit in reducing CVD risk; the potential impact of such a strategy currently is being studied. Understanding the differences between antiretroviral drugs with regard to CVD risk is crucial when planning treatment that is to be maintained for decades, and more work needs to be done in this area. The ability to tailor antiretroviral therapy based on individual patient CVD risk profile also awaits further information. Finally, much work remains to be done in understanding the mechanisms of risk posed by antiretroviral therapy and by HIV infection itself. The prospective assessment of inflammatory markers in cohorts and controlled trials with patients at comparable stages of disease provide a beginning to this process.

*Presented by Dr Currier in February 2009. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Currier in July 2009.*

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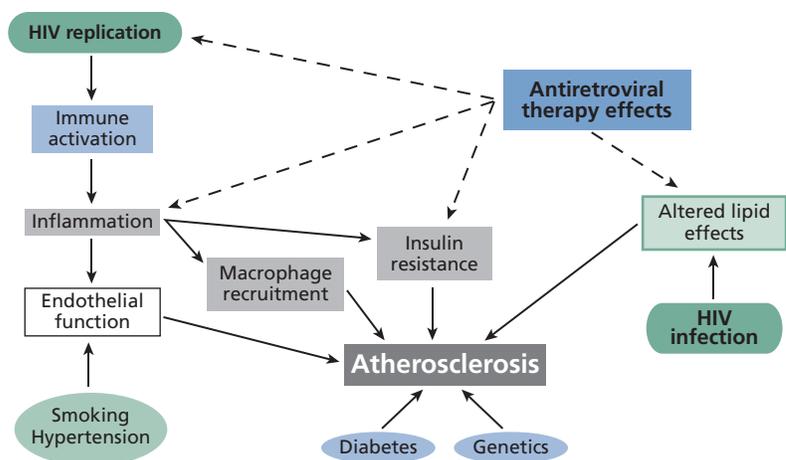


Figure 2. Interaction of host, virus, and antiretroviral therapy effects in cardiovascular disease risk.

and safety monitoring boards for Achillion Pharmaceuticals, Inc, and Koronis Pharmaceuticals.

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## Cases on the Web



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### The Use of Chemokine Receptor Antagonists in Antiretroviral Treatment Failure

by David M. Margolis, MD, FACP, and Gretchen Shaughnessy Arnoczy, MD

HIV engages in complex interactions with host cell-surface receptors to gain cellular entry and begin viral replication. The use of entry inhibitors such as chemokine receptor antagonists offers the potential for achieving virologic suppression in highly drug-experienced patients in whom this state was previously difficult to attain. This activity discusses the interpretation and the significance of certain HIV tropism assay results and the implementation of a chemokine receptor antagonist in a treatment-experienced patient with numerous treatment failures.

### End-Stage Renal Disease in the HIV-Infected Patient

by Christina M. Wyatt, MD

HIV-infected patients are at heightened risk of kidney disease related to HIV and coinfections and to the direct toxicity of antiretroviral therapy and concomitant medications. This expertly developed activity discusses current recommendations for the screening and management of chronic kidney disease (CKD) and end-stage renal disease in HIV-infected patients. Issues unique to the diagnosis and management of CKD in the HIV-infected are discussed as are criteria for identifying HIV-infected patients with end-stage renal disease who may be eligible for kidney transplantation.

### Pregnancy Planning and Preconception Health Care for HIV-Infected Individuals and Couples

by Erika Aaron, MSN, CRNP, and Shannon M. Criniti, MPH

Owing to effective antiretroviral therapy, many HIV-infected individuals and couples are choosing to have children. This activity discusses a comprehensive preconception plan of health care for HIV-infected women of child-bearing age, contraception choices, and promoting safer conception in HIV-infected women and serodiscordant couples who desire pregnancy. Learners will identify interactions between antiretroviral drugs and hormonal contraceptives and be able to explain assisted reproduction methods such as sperm washing that reduce the risk of HIV transmission to the noninfected partner.

### Initiation and Maintenance of HIV Treatment in Adolescents

by Jaime Martinez, MD

Estimates of the number of HIV and AIDS cases continue to increase among adolescents in the United States despite advances in antiretroviral therapy and the development of targeted HIV prevention and testing programs. Adult HIV treatment settings are not wholly sufficient to meet the needs of HIV-infected adolescents, whose unique developmental and psychosocial needs complicate the provision of care. This activity describes features of adolescent development that should be considered when planning care for HIV-infected adolescent patients and considerations for initiating antiretroviral therapy in such patients.

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**Perspective****Occupational and Nonoccupational Postexposure Prophylaxis for HIV in 2009**

*Data supporting the efficacy of HIV postexposure prophylaxis (PEP) come largely from a small number of older studies and case reports in health care workers, studies of transmission from infected mothers to their infants, and animal studies. These data also provide support for the current recommendations regarding duration of PEP and the window of time within which PEP should be started. Although much of the available data are from experience with older 2-drug regimens, newer potent 2- and 3-drug regimens are increasingly used in occupational exposure management, and drugs with mechanisms of action targeting early events in infection (eg, entry inhibitors, integrase inhibitors) may in the future become attractive options. Nonoccupational PEP remains controversial, although its feasibility and safety have been demonstrated in a number of programs. Existing recommendations generally call for its use within 72 hours of high-risk contact with a high-risk or HIV-infected source individual. This article summarizes a presentation on PEP for HIV infection made by Raphael J. Landovitz, MD, at the IAS—USA continuing medical education course held in Los Angeles in February 2009. The original presentation is available as a Webcast at [www.iasusa.org](http://www.iasusa.org).*

**Management of Occupational Exposure to HIV**

Data from the Centers for Disease Control and Prevention (CDC) for the period 1985 to 2001 indicate that there were 57 confirmed HIV seroconversions in health care workers (HCWs) after occupational exposure to HIV and 138 cases of possible transmission in which HIV infection or AIDS occurred in workers with no known risk factors for HIV infection other than occupational exposure in which postexposure seroconversion was not documented (Table 1). The cases of transmission occurred primarily through percutaneous exposures involving punctures or cuts from sharp objects, mostly hollow-bore needles. However, transmission also occurred via mucous membrane and nonintact skin exposures, mostly to HIV-infected blood, but occasionally via concentrated laboratory virus or visibly bloody body fluids. Most cases of transmission occurred in HCWs who

routinely have the most direct contact with HIV-infected patients or their blood—nurses, laboratory workers handling specimens, surgeons, health aides, and emergency medical technicians working in the field.

With regard to factors affecting risk of transmission, deep injury was associated with the greatest risk (adjusted odds ratio [OR], 15), with elevated risk also associated with the presence of visible blood on device (OR, 6.2), terminal illness of the source patient (OR, 5.6), and contact with a needle in the source patient's artery or vein (OR, 4.3). "Terminal illness of the source patient" in this analysis likely represents exposure to a high level of HIV viremia (the ability to measure viral load was not always available during the period covered by the analysis). Although the source person's viral load is likely a surrogate for transmission risk, the use of viral load for assessing risk in this regard has not yet been established. Low or undetectable viral load in the source person does not rule out the possibility of transmission.

The rationale for occupational and nonoccupational postexposure prophylaxis (PEP) comes from various analo-

gous fields. Studies of HIV pathogenesis have demonstrated that systemic infection does not occur immediately after exposure to virus, presenting a "window of opportunity" for potential intervention. Generally, virus can be found in antigen-presenting cells translocating across the mucosa approximately 24 hours after acquisition of virus and in regional lymph nodes within 48 hours to 72 hours. Viremia is detectable in blood as early as 5 days after acquisition. Limited studies and case reports have provided data demonstrating the feasibility, safety, and efficacy of PEP in HCWs.

Evidence of efficacy also comes from studies of HIV transmission from mother to child. Although antiretroviral therapy is now standard care during pregnancy and delivery in an infected mother and postpartum in the neonate, the finding that administration of antiretroviral treatment to an infant within 48 hours after birth has approximately 65% efficacy in preventing transmission from an untreated, infected mother stands as an example of successful true postexposure prophylaxis in humans. In addition, animal data indicate that durable infection with simian immunodeficiency virus (SIV) can be prevented with antiretroviral treatment after intravenous, intravaginal, and transrectal inoculation.

A CDC case-control study in HCWs reported in 1997 remains the core research supporting PEP (Cardo et al, *N Engl J Med*, 1997). In this study, 33 HCWs infected with HIV via occupational exposure (94% with needlestick injuries, all hollow needles) were compared with 679 HCWs who had been exposed to the virus but did not seroconvert. Postexposure prophylaxis with zidovudine monotherapy had been given to 27% of case patients and 36% of control patients, and the reduction in risk associated with zidovudine

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Dr Landovitz is assistant professor of medicine at the University of California Los Angeles, Center for Clinical AIDS Research and Education.

**Table 1.** Early Cases of Transmission of HIV to Health Care Workers, 1985 to 2001

Occupation	Documented Transmission/ Possible Transmission
Nurse	24/35
Laboratory worker	19/17
Physician, nonsurgical	6/12
Physician, surgical	–/6
Surgical technician	2/2
Dialysis technician	1/3
Other technician/ therapist	–/9
Respiratory therapist	1/2
Health aide	1/15
Morgue technician	1/2
Housekeeper	2/13
Dental worker/dentist	–/6
Emergency medical technician	–/12
Other	–/4
Route of exposure	Documented cases
Percutaneous (puncture/cut injury)	48
Mucocutaneous (mucous membrane or skin)	5
Percutaneous and mucocutaneous	2
Unknown	2
Source of exposure	Documented cases
Blood	49
Concentrated virus in laboratory	3
Visibly bloody fluid	1
Unspecified fluid	4

Dashes indicate data not reported.

Adapted from Do et al, *Infect Control Hosp Epidemiol*, 2003.

use was calculated to be 81% (OR, 0.19; 95% CI, 0.02-0.52). In current practice, monotherapy would not be considered

advisable, and the multidrug regimens now in use would be expected to provide even greater protective benefit. However, available data indicate that even multidrug therapy is not always successful in preventing infection. In a report on the first 21 known instances of failure of occupational PEP by the CDC, multidrug therapy was used in 5, including zidovudine plus didanosine in 2 HCWs, a 3-drug combination in 1, a regimen of zidovudine, didanosine, lamivudine, and indinavir in 1, and a combination of didanosine, stavudine, and nevirapine in 1, with all treatment started within 2 hours of exposure.

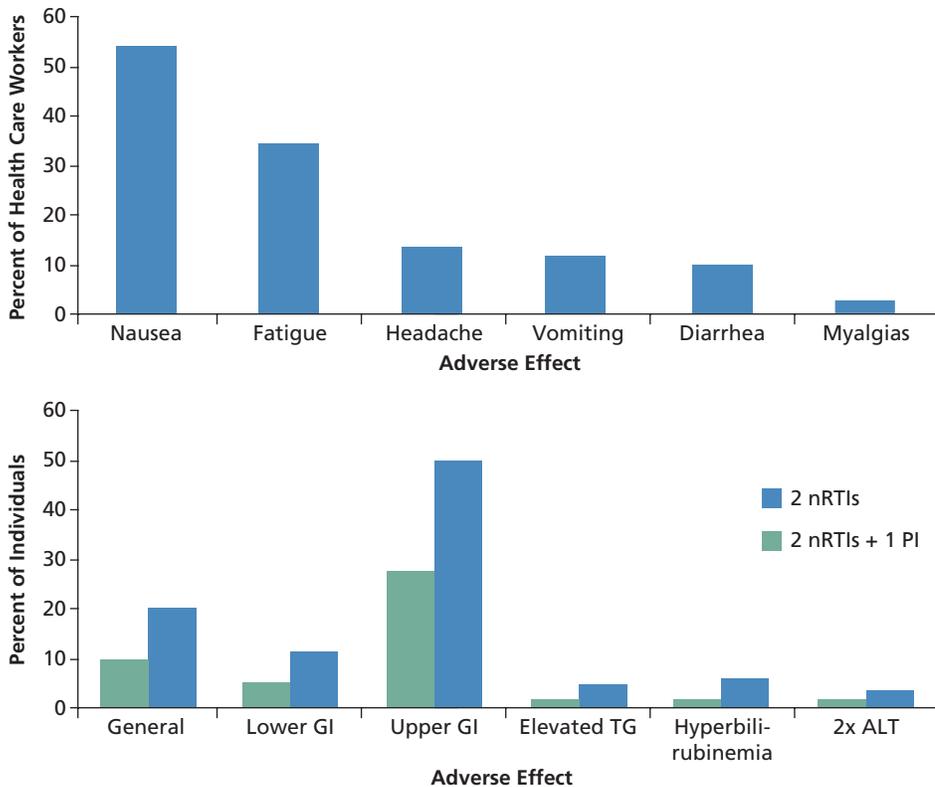
The adverse-effect profiles of PEP consisting primarily of lamivudine/zidovudine or the addition of early protease inhibitors (PIs) to lamivudine/zidovudine are shown in Figure 1 (Wang et al, *Infect Control Hosp Epidemiol*, 2000; Puro et al, *CROI*, 2002). The increase in adverse events with 3-drug treatment reflected in such data has contributed substantially to arguments that 2-drug combinations are preferred. The unproven correlate of that argument is that such toxicity compromises a PEP-taking patient's ability to complete the recommended 28-day treatment course, which is considered crucial to maximizing the potential for protective efficacy. Drugs used in more current regimens are better tolerated than were early combinations. A crucial component of maximizing the risk-to-benefit ratio of PEP is choosing to treat, and therefore to place at risk for adverse events, only the highest risk subset of exposures. Exposures with very small chances of transmitting infection likely fall on the disadvantageous side of a risk-benefit analysis; that is, the risks may outweigh the potential benefits.

The current recommendation for 28 days of prophylactic treatment is derived in large part from animal studies. A study in which 24 macaques were inoculated intravenously with SIV showed that PEP with (R)-9-(2-phosphonylmethoxypropyl)adenine (PMPA, tenofovir) initiated 24 hours after inoculation was associated with seroconversion in 50% of animals with 3 days of treatment, 25% with 10 days

of treatment, and 0% with 28 days of treatment (Tsai et al, *J Virol*, 1998). With the potentially devastating consequences of a shorter course potentially providing less effective prophylaxis, this 28-day threshold has become standard. Ongoing studies in perinatal transmission may provide information about protective benefits of shorter courses of treatment that can be applied to adults.

In a similar macaque model, tenofovir prophylaxis was started 48 hours before or 4 hours or 24 hours after inoculation and continued for 28 days, with a control group left untreated after exposure. None of the animals receiving treatment and all control animals were infected (Tsai et al, *Science*, 1995). Additional findings with regard to exposure during birth in humans indicate protective benefit to the infant if treatment is started within 48 hours postpartum; the precise "cutoff" point after which PEP will not have any activity will likely never be delineated, but expert consensus clearly centers on the notion that PEP should be administered as soon as possible postexposure.

Taken together, these findings are the basis for current recommendations regarding the window of time after exposure during which prophylaxis should be initiated. To date, no evidence in humans indicates that treatment started after 48 hours is protective. However, most guidelines, including those by the World Health Organization, CDC and Department of Health and Human Services (DHHS), and the states of California, Massachusetts, and Rhode Island, recommend a window of 72 hours within which to start treatment; New York state has chosen to endorse a 36-hour window. A recent large, community-based cohort study of the safety, feasibility, and acceptance of PEP in men who have sex with men (MSM) showed that the median time to receipt of the first dose of treatment was 33 hours (interquartile range, 18-53 hours) (Kahn, *J Infect Dis*, 2001), indicating that approximately half of those exposed would be ineligible for treatment if a 36-hour window were used.



**Figure 1.** Incidence of common adverse effects of postexposure prophylaxis (mainly lamivudine/zidovudine) in health care workers (top), and comparison between regimens of 2 nucleoside analogue reverse transcriptase inhibitors (nRTIs) (lamivudine/zidovudine) alone or in combination with early protease inhibitor (PI) regimens, mostly indinavir or nelfinavir (bottom). Top graph is adapted from Wang et al, *Infect Control Hosp Epidemiol*, 2000, and bottom adapted with permission from Puro et al, *CROI*, 2002. ALT indicates alanine aminotransferase; GI, gastrointestinal; TG, triglycerides.

## Management of Nonoccupational Exposure to HIV

There is considerable controversy over implementation of nonoccupational PEP (nPEP) strategies. To date, no placebo-controlled data are available on the efficacy of nPEP; the limited data that do exist on efficacy of PEP are from the occupational exposure literature. It is unlikely that controlled trials will be performed, both because current analogy to occupational exposures combined with the devastating nature of the outcome of seroconversion make placebo-controlled trials unethical, and active-controlled trials would have to be prohibitively large to demonstrate adequate power given that rates of seroconversion after sexual exposure in reality are quite low.

Data in the occupational exposure setting are not perfectly analogous to data

in the sexual exposure setting for a number of reasons: the immunologic milieu of a mucosal exposure, especially a genital exposure, differs substantially from that in a percutaneous exposure, and viral loads and resistance patterns of virus in genital secretions differ from those in blood. In addition, repeated exposures are more common in the nonoccupational setting, and there are concerns that nPEP would become a “morning-after pill,” although existing data do not support increased engagement in high-risk behaviors as a consequence of PEP availability. Moreover, source testing is frequently impossible, and in most cases the source individual’s HIV serostatus is not known, further complicating triage decisions as to the risk-to-benefit ratio of PEP initiation, even in the era of rapid testing availability.

The official recommendation of the CDC on nPEP, published in 2005, is “The

provision of antiretroviral drugs to prevent HIV infection after unanticipated sexual or injection drug-use exposure might be beneficial. For persons seeking care <72 hours after nonoccupational exposure to . . . a person known to be HIV infected . . . a 28-day course of highly active antiretroviral therapy is recommended. Antiretroviral medications should be initiated as soon as possible after exposure.” In practice, nPEP is becoming an increasingly common strategy, although there are important operational difficulties in locating nPEP services within 72 hours in many settings (including Los Angeles County; Landovitz et al, *Clin Infect Dis*, 2009). For all patients, local hospital emergency departments may not be comfortable with administration of antiretroviral medications, and follow-up is made more difficult, especially for uninsured patients, who lack, as yet, an HIV diagnosis and thus are not likely to be eligible for state drug-assistance programs to pay for PEP medications. The CDC launched and then closed a voluntary registry for practitioners administering nPEP, and no further data from this initiative are available. Safety and feasibility of nPEP programs, mostly in MSM, have been demonstrated in initiatives in the United States in San Francisco, Boston, and Los Angeles; in the European cities Amsterdam and Paris; as well as in Brazil.

The CDC has estimated risk of acquisition per 10,000 exposures to an infected source (Table 2). Many believe that these estimates are too low, with other data for receptive anal intercourse, for example, suggesting 3% to 5% risk per exposure (rather than the CDC estimate of 0.5%). Recent meta-analysis data suggest that sexual transmission rates, at least via heterosexual intercourse, may be up to 8-fold higher than previously reported and that the commonly cited values should be thought of as “lower bounds” for the risk of transmission (Powers et al, *Lancet Infect Dis*, 2008). Most guidelines recommend that nPEP should be instituted for patients presenting within 72 hours of an index event of anal or vaginal intercourse (some recommendations include receptive oral intercourse with ejaculation) with no condom or condom failure in which the source individual is

**Table 2.** Centers for Disease Control and Prevention Estimates of HIV Transmission Risk per 10,000 Exposures to Infected Source

Route	Estimated Number of Transmitted Infections per 10,000 Exposures (% Risk)
Blood transfusion	9000 (90%)
Needle-sharing injection-drug use	67 (0.67%)
Receptive anal intercourse	50 (0.5%)
Percutaneous needlestick	30 (0.3%)
Receptive penile-vaginal intercourse	10 (0.1%)
Insertive anal intercourse	6.5 (0.065%)
Insertive penile-vaginal intercourse	5 (0.05%)
Receptive oral intercourse	1 (0.01%)
Insertive oral intercourse	0.5 (0.005%)

Adapted from Centers for Disease Control and Prevention, *Morb Mortal Wkly Rep*, 2005.

known to be HIV-seropositive or is an individual with unknown HIV serostatus engaging in high-risk behavior. The CDC has issued a flow diagram assisting clinicians in making PEP-initiation triage decisions (Figure 2). In brief, the guidelines recommend treatment for cases involving exposure of mucous membranes or nonintact skin to genital fluids, breast milk, or visibly bloody secretions within 72 hours.

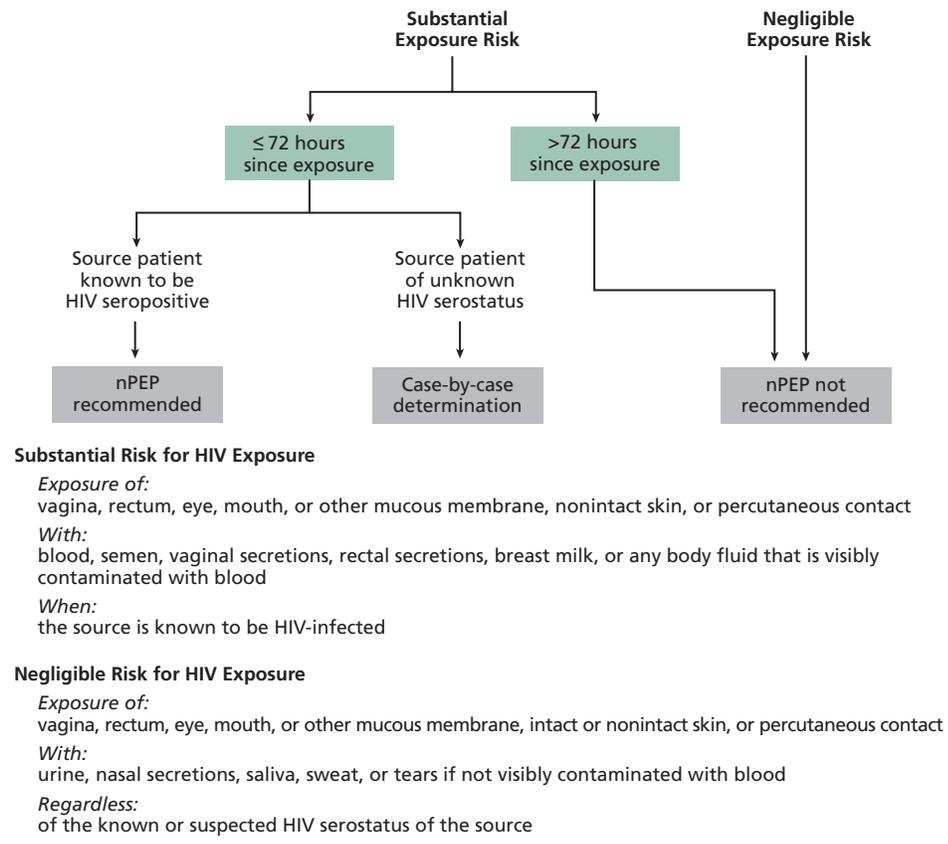
Nonoccupational PEP, like occupational PEP, can fail. A patient of the author's presented at 50 hours after receptive anal intercourse and was started on a 28-day regimen of zidovudine/lamivudine plus ritonavir-boosted lopinavir. The patient claimed 100% adherence and no new exposures but tested HIV-seropositive at 5 months postexposure, with wild-type virus and a low viral load. He was subsequently lost to follow-up. A recently published, well-characterized case report suggests that seroconversion through antiretroviral

prophylaxis does not oblige the acquisition of drug-resistant virus (as many assumed would be the case) and may portend slower clinical progression and lower virologic set points (Prada et al, *JAIDS*, 2008). This observation needs further validation in larger cohorts and clinical trials before it can be routinely accepted, and it likely is dependent on many viral and host-related factors.

Controversy continues over whether 2-drug or 3-drug regimens are preferred. Mathematical modeling suggests using a 3-drug regimen if baseline antiretroviral drug resistance in the source patient population is greater than 15% (Bassett et al, *Clin Infect Dis*, 2004). For 2-drug regimens, dual nucleoside analogue reverse transcriptase inhibitors (nRTIs) are recommended; the most experience is with zidovudine/lamivudine, but there is increasing use of and safety data with tenofovir/emtricitabine (Mayer et al, *JAIDS*, 2008). With regard to which drugs to add for 3-drug combinations,

nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs) are not recommended because of their associated risk of hepatotoxicity, particularly for nevirapine. Efavirenz should also be avoided because of the potential emergence of NNRTI resistance. Ritonavir-boosted PIs are attractive options, particularly in cases of high-risk exposure.

HIV entry inhibitors and integrase inhibitors are potentially attractive on the basis of their mechanisms of action; both target an early stage of HIV replication and therefore likely affect early infection pathogenesis. In a case report involving the entry inhibitor maraviroc, a medical student was exposed via a small-gauge needle puncture to a multi-drug-resistant virus from a source patient who was taking a regimen of tenofovir, ritonavir-boosted lopinavir, fosamprenavir, and enfuvirtide (plasma HIV RNA level, 3.8 log<sub>10</sub> copies/mL) (Mechai et al, *J Med Virol*, 2008). The student received PEP with tenofovir, lamivudine, fosam-



**Figure 2.** The Centers for Disease Control and Prevention (CDC) flow diagram for nonoccupational postexposure prophylaxis (nPEP) decision making. Adapted from CDC, *Morb Mortal Wkly Rep*, 2005.

prenavir, and maraviroc and remained HIV-seronegative at 6-month follow-up with no adverse events.

There have been 2 case reports of use of the integrase inhibitor raltegravir (Siegel et al, *AIDS*, 2008). In one, a surgical resident was exposed to multidrug-resistant virus from a source patient (plasma HIV RNA level, 215,000 copies/mL) via scalpel laceration and received emtricitabine/tenofovir, ritonavir-boosted atazanavir, and raltegravir. Development of jaundice prompted rapid discontinuation of the ritonavir-boosted atazanavir, with no additional adverse events observed. In the other case, a laboratory technician was exposed via puncture with a capillary tube containing HIV-infected blood and received emtricitabine/tenofovir, ritonavir-boosted darunavir, and raltegravir with no adverse events. Both patients were HIV-seronegative at 6-month follow-up.

A larger case series presented recently suggests a salutary safety profile of emtricitabine/tenofovir plus raltegravir in MSM after potential sexual exposure to HIV (Mayer et al, IAC, 2009). Although such limited case reports and case series neither confirm nor refute efficacy, they contribute important safety information about the use of such drugs in HIV-seronegative at-risk populations and increase confidence in their safety profiles in an era when the use of nevirapine as part of PEP regimens was also mechanistically attractive but ultimately shown to have unacceptable safety issues when used in this capacity.

## Conclusion

Generally, management of exposure to HIV should include risk assessment of the event to determine likelihood of transmission; discussion of PEP with antiretroviral drugs; emotional and psychological counseling and support; counseling on safe-sex practices during the period of monitoring; and close medical follow-up with repeat serologic testing.

In patients with nonoccupational exposure, practitioners should take advantage of “the PEP moment” to

discuss risk-reduction behavior with the exposed patient; make appropriate referrals to substance-abuse, domestic-violence, or mental health support services; and initiate other sexually transmitted disease testing or treatment and hepatitis screening as necessary. During follow-up, practitioners should maintain vigilance for signs and symptoms of acute HIV infection. It remains unclear who will pay for nPEP treatment and management, particularly for uninsured patients.

*Presented by Dr Landovitz in February 2009. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Landovitz in July 2009.*

*Financial Disclosure: Dr Landovitz has no relevant financial affiliations to disclose.*

## Suggested Reading

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## Review

# What's New in the 2009 US Guidelines for Prevention and Treatment of Opportunistic Infections Among Adults and Adolescents With HIV?

John T. Brooks, MD, Jonathan E. Kaplan, MD, and Henry Masur, MD

*Despite dramatic declines in the incidence of opportunistic infections (OIs) in the United States, they remain an important cause of morbidity and mortality for HIV-infected persons. Previously separate guidelines on the prevention of OIs and on the treatment of OIs have been combined recently into an updated single document; the present article reviews salient changes to and new information contained in this guidance. Chapters on hepatitis B virus infection and tuberculosis have been expanded substantially, and each chapter now includes information on immune reconstitution inflammatory syndrome. In addition, there is detailed discussion on the role of antiretroviral therapy in OI prevention and issues concerning the initiation of antiretroviral therapy during treatment of an acute OI. In the future, these guidelines will likely be maintained as an internet-based document to facilitate wider dissemination and more rapid updates.*

This year, guidelines for the prevention and treatment of opportunistic infections (OIs) in HIV-infected adults and adolescents were updated.<sup>1</sup> Published as part of the *Morbidity and Mortality Weekly Report's Recommendations and Reports* series, these guidelines embody the contributions of more than 140 content matter experts collaboratively edited by the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA). The 2009 report updates and combines earlier versions of separate guidelines: recommendations for the prevention of OIs last published in 2002<sup>2</sup> and recommendations for the treatment of OIs first published in 2004.<sup>3</sup> The 2009 document can be downloaded at <http://www.cdc.gov/mmwr/PDF/rr/rr5804.pdf>. Here, we highlight and discuss some of the important changes that have been made to the guidelines since their last update. A parallel set of pediatric guidelines will be published later in 2009.

These guidelines are intended for use by clinicians in the United States. In other regions of the world, especially sub-Saharan Africa and southeast Asia, the spectrum of OIs differs and the di-

agnostic testing (including radiologic imaging), antimicrobial therapy, and vaccines available are typically more limited. Different guidelines for prevention and treatment of OIs might be appropriate for these regions.

With advances in antiretroviral therapy and OI prophylaxis, the incidence of OIs in the United States and many other resource-rich nations has fallen dramatically (see Figure 1).<sup>4</sup> Although there has been an increase in morbidity and mortality from what are often termed non-AIDS-defining conditions in the United States, OIs remain a leading cause of hospitalization and death for persons with HIV infection.<sup>5-9</sup> Persistent health disparities in the United States exacerbate the disproportionate number of

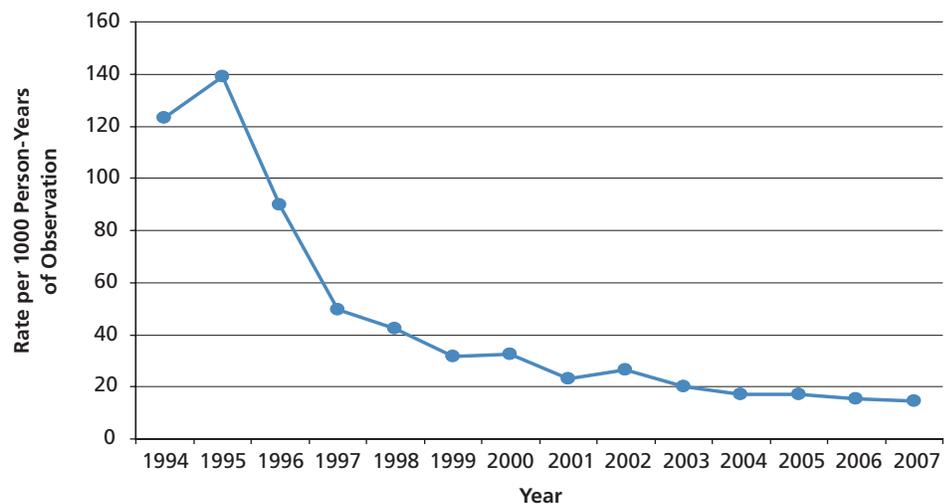


Figure 1. Annual incidence of first AIDS-defining opportunistic infection in the HIV Outpatient Study, 1994–2007. Figure adapted from Brooks et al, *Clin Infect Dis*, 2009.<sup>4</sup>

Dr Brooks is leader of the Clinical Epidemiology Team, Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP), Centers for Disease Control and Prevention (CDC). Dr Kaplan is chief of the HIV Care and Treatment Branch, Global AIDS Program, NCHHSTP, CDC. Dr Masur is chief of the Critical Care Medicine Department, Division of AIDS, National Institutes of Health.

Send correspondence to John T. Brooks, MD, Centers for Disease Control and Prevention, 1600 Clifton Road NE, Mailstop E-45, Atlanta, GA 30333. Received June 9, 2009; accepted July 27, 2009.

**Table 1.** Organization of Information by Chapter Subsections in the Guidelines

Epidemiology
Clinical Manifestations
Diagnosis
Preventing Exposure
Preventing Disease
– Initiating Primary Prophylaxis
– Discontinuing Primary Prophylaxis
Treatment of Disease
Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome
Management of Treatment Failure
Preventing Recurrence
Discontinuing Secondary Prophylaxis (Chronic Maintenance Therapy)
Special Considerations During Pregnancy

Adapted from Kaplan et al, *Morb Mortal Wkly Rep*, 2009.

patients with acute OIs presenting to urban and public health care facilities. As the number of persons living with HIV infection in the United States continues to increase and the existing clinical work force ages and retires, we must ensure that practitioners remain competent in the management of HIV-associated OIs.

### Organization of the Guidelines

The update includes sections on 29 OIs, with each section organized according to the same series of subsections (Table 1). As in previous editions of the guidelines, prevention and treatment recommendations are rated by a system that includes a letter (A through E) to indicate the strength of the recommendation and a Roman numeral (I through III) to indicate the quality of the evidence supporting the recommendation (Table 2). The guidelines now contain 11 tables, 2 figures, and an appendix with recommendations for lowering the risk of acquiring OIs associated with a variety of specific exposures (eg, sexual or pet-related exposures).

### Definition and Selection of Opportunistic Infections for Inclusion

In 1995, authors from the CDC, NIH, and IDSA defined OIs as “infections that cause disease with increased frequency and/or of increased severity among HIV-infected persons, presumably because of immunosuppression.”<sup>10</sup> That publication included more than 100 infections satisfying this definition. The OIs most predictive of severe HIV infection define AIDS, and those OIs are included among the AIDS-defining conditions in the CDC AIDS case definition.<sup>11</sup>

The OIs included in the 2009 guidelines encompass all AIDS-defining infections and other infections that (1) are more prevalent among HIV-infected persons residing in the United States, (2) cause more severe clinical illness among HIV-infected persons, (3) are uniquely related to noninfectious AIDS-defining conditions, or (4) have aspects of prevention or treatment that are

unique to HIV-infected persons. In addition to the CDC AIDS-defining OIs, these OIs include bartonellosis, syphilis, aspergillosis, human herpesvirus-6, -7, and -8 infections, human papillomavirus infection, and hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. The guidelines also include recommendations on 5 “geographic” OIs—diseases that are endemic outside the United States but might be acquired by HIV-infected persons as a result of foreign travel, or diseases that may be seen in the United States among immigrant populations (see below).

### Chemotherapy for Prevention and Treatment of Acute Opportunistic Infections

The guidelines provide small refinements to prior editions regarding the management of major OIs such as *Pneumocystis pneumonia* (PCP), toxoplasmosis, cytomegalovirus (CMV) infections, disseminated *Mycobacterium avium* complex (MAC) infection, and

**Table 2.** System Used to Rate the Strength of Recommendations and Quality of Supporting Evidence

Rating Strength of Recommendation	
A	Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. Should always be offered.
B	Moderate evidence for efficacy—or strong evidence for efficacy but only limited clinical benefit—supports recommendation for use. Should generally be offered.
C	Evidence for efficacy is insufficient to support a recommendation for or against use. Or evidence for efficacy might not outweigh adverse consequences (eg, drug toxicity, drug interactions) or cost of the treatment or alternative approaches. Optional.
D	Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered.
E	Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should never be offered.
Rating Quality of the Evidence Supporting the Recommendation	
I	Evidence from at least 1 properly designed randomized, controlled trial.
II	Evidence from at least 1 well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than 1 center), or from multiple time-series studies, or dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Adapted from Kaplan et al, *Morb Mortal Wkly Rep*, 2009.

cryptococcosis. For each OI included in this revision of the guidelines, Table 1 of the guidelines summarizes primary prevention recommendations, and Table 2 of the guidelines summarizes preferred and alternate treatment recommendations.

### The Role of Antiretroviral Therapy for Preventing Opportunistic Infections

Effective antiretroviral therapy remains the mainstay for preventing OIs. Increasing the CD4+ cell count (CD4+ count) and reducing plasma HIV RNA level, regardless of pretreatment CD4+ count, each reduce the risk of acquiring OIs. The introduction to the guidelines emphasizes the importance of identifying HIV-infected persons before their CD4+ counts fall to levels that increase their susceptibility to OIs.

### When to Start Antiretroviral Therapy in Patients With Acute Opportunistic Infections

Initiating antiretroviral therapy during an acute OI poses a variety of dilemmas. It can complicate the clinical scenario by introducing antiretroviral therapy-related drug toxicities and drug-drug interactions between antiretroviral drugs and antimicrobial therapy for the OI. Alterations in renal and hepatic function related to the acute OI can distort antiretroviral therapy pharmacokinetics (eg, metabolic clearance, volumes of distribution) and reduce antiretroviral efficacy or increase antiretroviral toxicity. Acute gastrointestinal OIs can decrease antiretroviral drug absorption, producing serum levels that only partially suppress HIV RNA level and thereby generate selection pressure favoring emergence of antiretroviral drug resistance.

Antiretroviral therapy-mediated immune reconstitution, which is the goal of antiretroviral treatment, can also substantially complicate acute OI treatment by augmenting inflammatory responses that intensify end-organ injury. This immune reconstitution inflammatory syndrome (IRIS) has now been reported in association with a wide va-

riety of OIs, although it has been best characterized for tuberculosis, disseminated MAC infection, PCP, cryptococcosis, and CMV retinitis.

In addition to managing the acute OI and the patient's HIV infection, IRIS can be a third condition the clinician must address. The term IRIS describes both the paradoxical worsening of an existing OI after initiating antiretroviral therapy as well as the unmasking of OIs that were clinically latent or subclinical and unrecognized before initiation of antiretroviral therapy. IRIS typically occurs within 4 weeks to 8 weeks of starting antiretroviral therapy. Risk of IRIS is highest among persons who experience rapid increases in CD4+ counts, especially if initiating therapy at very low CD4+ counts (ie, < 100 cells/ $\mu$ L) with high plasma HIV RNA levels. IRIS can be very difficult to distinguish from active, acute infections and can manifest at sites other than the anatomic location where the OI was first diagnosed. Treatment of IRIS ranges from "watchful waiting" to therapy with nonsteroidal or steroidal antiinflammatory drugs and can include change in or intensification of the OI antimicrobial regimen. Each section in the guidelines now includes information on whether IRIS has been described in association with the particular OI.

Initiating antiretroviral therapy during treatment for an acute OI requires careful consideration and close clinical monitoring. For some OIs for which no specific therapy has been shown to be effective, such as cryptosporidiosis, certain microsporidiosis, progressive multifocal leukoencephalopathy (PML), and some infections caused by highly drug-resistant pathogens (eg, multiresistant herpes simplex virus), immediate initiation of antiretroviral therapy is warranted, even though IRIS can occur and would worsen the patient's clinical condition (eg, PML). However, for OIs for which directed therapy is available, should antiretroviral therapy be deferred until the OI has been substantially treated? Results of a recently completed clinical trial referenced in the guidelines as an abstract have since been published<sup>12</sup> and suggest the answer is no.

This study examined survival among patients with acute OIs randomly assigned to early antiretroviral therapy (initiated within 16 days of starting acute OI treatment) versus deferred antiretroviral therapy (6-12 weeks later). The findings demonstrated that in the absence of major contraindications, antiretroviral therapy should be initiated early in patients with an acute OI. Notably, this study of predominately North American patients excluded persons with tuberculosis, which remains a low-incidence OI in the United States. However, a recently completed randomized, controlled clinical trial from South Africa has suggested that initiating antiretroviral therapy during antituberculosis treatment is also superior to deferral.<sup>13</sup> The recommendations in the guidelines regarding initiation of antiretroviral therapy in patients with an acute OI are summarized in Table 3.

### Management of Antiretroviral Therapy in Patients With Opportunistic Infections

As noted above, OIs that occur within the initial 12 weeks of antiretroviral therapy are typically attributed to latent or incubating infections unmasked when antiretroviral therapy was started (ie, IRIS). OIs presenting during this phase of antiretroviral therapy do not represent antiretroviral failure, and both the OI antimicrobial regimen and the antiretroviral therapy should be continued. OIs that occur after 12 weeks to 24 weeks of antiretroviral therapy in patients who have demonstrated an initial response to therapy (ie, increased CD4+ count, decreased plasma HIV RNA level) are not necessarily an indication to change antiretroviral therapy; such patients warrant close monitoring to determine whether maximal antiretroviral therapy benefit has been achieved.

OIs that occur in patients with virologic failure, defined as either the inability to suppress HIV RNA level after 12 weeks to 24 weeks of antiretroviral therapy or as a rebound of HIV RNA level after a period of suppression despite adequate adherence, indicate the need to reassess the antiretroviral

**Table 3. Summary Recommendations On When to Initiate Antiretroviral Therapy in Antiretroviral Therapy–Naïve Patients With an Acute Opportunistic Infection (OI)**

In the absence of compelling contraindications, early initiation of antiretroviral therapy near the time of initiating OI treatment should be considered for most patients with an acute OI, excluding tuberculosis (TB).

Other elements that should be considered when making this decision are degree of immunosuppression, availability of effective therapy for the OI, risk of drug interactions, overlapping drug toxicities, risk of developing immune reconstitution inflammatory syndrome (IRIS) and associated consequences, and willingness of the patient to adhere to the drug regimens.

In cases of cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy, Kaposi sarcoma, *Pneumocystis pneumonia*, and invasive bacterial infections, the early benefits of antiretroviral therapy outweigh the risk related to these other factors, and antiretroviral therapy should be started as soon as possible.

In the setting of TB disease, the following guidance for initiating antiretroviral therapy should be considered:

CD4+ count < 100 cells/μL	After 2 weeks (during intensive phase of therapy)
CD4+ count 100-200 cells/μL	After 2 months (at end of intensive phase of therapy)
CD4+ count sustained > 200 cells/μL	After 2 months (during maintenance phase of therapy)
CD4+ count sustained > 350 cells/μL	After completing TB therapy

Adapted from Kaplan et al, *Morb Mortal Wkly Rep*, 2009.

therapy. OIs occasionally occur in patients with robust CD4+ counts and suppressed HIV RNA levels; there is no evidence that changing or enhancing antiretroviral therapy in such cases is beneficial. Likewise, data are lacking with regard to the optimal management of patients who develop OIs in the context of discordant immunologic and virologic responses.

### Opportunistic Infections During Pregnancy

There are few studies of the effects of interventions to prevent and treat OIs in HIV-infected pregnant women and their fetuses. The guidelines review available information about the physiologic changes pregnant women experience that might affect the efficacy or toxicity of drugs used to treat each OI. They also include information on the risks to the fetus of exposure to these agents and to radiation from diagnostic procedures. The guidelines emphasize the importance of focusing on the health of the mother as well as the child.

### Prevention of Opportunistic Infections with Chemoprophylaxis

Chemoprophylaxis to prevent first episodes of OIs (primary prophylaxis) and to prevent OI recurrences and relapses (secondary prophylaxis, also called chronic maintenance therapy) remains essential for patients (1) who are not taking antiretroviral therapy or who have recently initiated antiretroviral therapy and still have a CD4+ count below the recommended thresholds for chemoprophylaxis, (2) who are unable to achieve a CD4+ count above these thresholds despite antiretroviral therapy, or (3) whose CD4+ count has fallen below these thresholds in association with virologic failure. For most pathogens, there have been no major changes in the drugs recommended for chemoprophylaxis or in the CD4+ count thresholds for initiating, discontinuing, or reinitiating chemoprophylaxis.

For patients resident in areas of the United States endemic for coccid-

iodomycosis, the guidelines now suggest that prophylaxis with fluconazole or itraconazole be considered for persons seropositive for anticoccidioidal IgG or IgM who have a CD4+ count below 250 cells/μL. Experts also suggest that annual serologic testing might be appropriate for patients previously seronegative for these immunoglobulins.

### Prevention of Opportunistic Infections with Immunizations

As in previous guidelines, administration of 23-valent polysaccharide pneumococcal vaccine (PPV) is recommended to prevent pneumococcal disease in persons with a CD4+ count of 200 cells/μL or higher, unless the patient has received this vaccine within the prior 5 years. PPV should be offered to patients with a CD4+ count below 200 cells/μL as well. Because the vaccine's efficacy in this latter patient population is not well documented, revaccination after achieving a CD4+ count of at least 200 cells/μL can be considered. The duration of the protective effect of primary pneumococcal vaccination is unknown; the guidelines note that revaccination every 5 years may be considered, although definitive data on the clinical benefit of this intervention are lacking.

Annual administration of the inactivated influenza vaccine is also recommended to reduce the risk of influenza and of postinfluenza bacterial pneumonia. Administration of the live influenza vaccine is not recommended for HIV-infected patients. Given the prominence of influenza infections domestically and globally since the guidelines were formulated and data that suggest influenza illness might be more severe in HIV-infected patients than in HIV-uninfected patients,<sup>14-16</sup> influenza vaccination with inactivated vaccine products as they become available seems especially relevant.

The guidelines suggest that administration of varicella vaccine be considered for those rare HIV-infected adults who are seronegative against varicella-zoster virus (VZV) and have a CD4+ count above 200 cells/μL. Routine serologic testing to determine the VZV

serostatus of HIV-infected adults is not recommended but might be indicated under certain circumstances (ie, HIV-infected contact of a person with active VZV infection). For patients who are VZV seronegative and have been exposed to VZV infection, especially chicken pox (which poses higher risk than localized herpes zoster), varicella-zoster immune globulin should be administered within 96 hours of exposure.

Despite substantial interest regarding the use of vaccines against herpes zoster and against human papillomavirus (HPV) in HIV-infected persons, data on the safety, immunogenicity, and efficacy of these vaccines are inadequate to support a recommendation for or against their use. Administration of HPV vaccine is considered optional for women aged 15 years to 26 years. The guidelines recommend that the herpes zoster vaccine not be administered to HIV-infected persons until additional data are available.

## Hepatitis B Virus Infection

In this revision, guidance on the prevention and treatment of HBV coinfection in HIV-infected persons has been substantially expanded. The guidelines emphasize the importance of screening all patients for HBV infection. Up to 90% of certain HIV-infected populations (eg, intravenous drug users) can have at least 1 serum marker of previous exposure to HBV, and approximately 10% of HIV-infected patients have evidence of chronic HBV coinfection. HBV disease is accelerated in HIV-infected patients compared with HIV-uninfected patients, and HBV- and HIV-coinfected patients who start antiretroviral therapy without concurrent anti-HBV treatment, for instance if their HBV-infection is undetected, can experience substantial flares in hepatic transaminase levels and hepatic necrosis.

Clinicians should consider confirmatory HBV DNA screening for persons who test positive only for anti-HBV core antibody (anti-HBc) because false-positive anti-HBc test results appear to be more common in HIV-infected persons, especially those coinfecting with HCV. Administration of HBV vaccine is rec-

ommended for all HIV-infected persons who have no serologic evidence of HBV exposure (ie, negative for HBV surface antigen, anti-HBV surface antibody, and anti-HBc). Patients testing positive solely for anti-HBc can be given the complete primary vaccine series; however, some specialists would test for HBV DNA to rule out HBV infection. Patients without detectable HBV DNA should be vaccinated. Despite evidence that serologic responses to vaccination are improved at higher CD4+ counts, vaccination should not be deferred for susceptible persons while awaiting a rise in CD4+ count. Serologic responses should be checked 1 month after completing the vaccine series for all patients; if no response is observed, revaccination should be considered. Some experts recommend vaccinating patients, both for initial vaccination and for revaccination, with double doses of vaccine.

Guidance on the treatment of HBV infection in these guidelines has been harmonized with parallel guidance in the antiretroviral treatment guidelines disseminated by the US Department of Health and Human Services<sup>17</sup> and by the International AIDS Society–USA panel.<sup>18</sup> Dually infected patients who require anti-HBV therapy should be given highly active combination antiretroviral therapy for HIV infection regardless of their CD4+ count. The guidelines review in detail the available anti-HBV agents and stress the importance of using at least dual combination therapy against HBV as part of the HIV antiretroviral regimen. For HBV-infected patients who require anti-HBV therapy but who wish to defer therapy for HIV infection, drugs active solely against HBV should be selected to prevent emergence of antiretroviral drug resistance. The advantages and disadvantages of liver biopsy for patient management are discussed, and guidance is provided for individualizing the decision to perform liver biopsy.

## Tuberculosis

Guidance on prevention and treatment of tuberculosis (TB) has been expanded substantially, in particular the recom-

mendations on the diagnosis of latent TB and issues related to coadministration of antiretroviral therapy and anti-TB therapy. The importance of testing all HIV-infected persons for latent TB disease is emphasized, even though TB remains an uncommon OI in the United States. This update provides new information comparing the traditional tuberculin skin test (TST) with recently available interferon gamma release assays (IGRA) for the diagnosis of TB. A detailed comparison of these tests is provided in Table 10 of the guidelines document. Evidence suggests that the IGRAs have more consistent and higher specificity than the TST, better correlation with surrogate measures of exposure to *Mycobacterium tuberculosis*, and less cross-reactivity because of BCG vaccination or other nontuberculous mycobacteria exposure. However, results from comparative studies of TST and IGRAs in HIV-infected patients indicate that concordance between the tests is not complete.

Discussions regarding the diagnosis of active TB with nucleic acid amplification testing of sputum smears have been updated and aligned with recent general TB management guidelines.<sup>19</sup> The guidelines now recommend 9 months of isoniazid as preferred therapy for the treatment of latent TB and specifically note that the 2-month regimen of pyrazinamide plus rifabutin should no longer be offered.

## Updated Information on Drug Interactions

The tabulated drug information in the guidelines has been extensively updated. Table 5 of the guidelines document summarizes toxicities of drugs used to treat and prevent OIs by drug class; Table 6 of the guidelines document summarizes the numerous known pharmacokinetic interactions between drugs used to treat and prevent OIs and antiretroviral drugs; and Table 7 of the document summarizes combinations of antiretroviral and other anti-infective drugs that should be avoided. Data in these tables on drug interactions affecting use of rifamycins for prevention and treatment of TB have been particularly improved.

## Geographic Opportunistic Infections

Geographic OIs (ie, OIs that occur predominantly in regions outside the United States) deserve special attention. As life expectancy for HIV-infected patients receiving antiretroviral therapy increases, more Americans with HIV are travelling overseas. In addition, a substantial number of immigrants with HIV infection come to the United States from tropical countries and may present with OIs not typically seen here. Malaria, penicilliosis, leishmaniasis, trypanosomiasis, and isosporiasis are included. Clinicians in the United States need to be familiar with the diagnosis and management of these OIs in the presence of HIV infection.

## Future Directions

Although clinical experience regarding the prevention and treatment of OIs has increased dramatically since the 1980s, important knowledge gaps remain. Effective programs must be identified and established to identify persons as early as possible after HIV infection has occurred and to link them to and retain them in care. Simpler, less invasive, and more rapid diagnostic methods are still needed for many OIs. Such diagnostics would have considerable value for resource-poor settings outside the United States, where our understanding of the spectrum of OIs and their empiric treatment remains limited. The safety and effectiveness of new vaccines, especially for infections such as HPV and herpes zoster that cause substantial morbidity among HIV-infected persons, remain largely unknown. Effective treatments for some OIs such as PML and cryptosporidiosis are still needed. Consideration is also being given to maintaining these guidelines in an online format with more frequent updates so that clinicians can have access to pivotal new information in the timeliest fashion possible.

*The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.*

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## Letter

### HIV Neurocognitive Disease Continues in the Antiretroviral Era

**To the Editor:** In his excellent summary of current topics in HIV neurocognitive disease, Dr David Clifford showed a table of our approach to categorize the effectiveness of antiretroviral drugs in the nervous system, with our permission.<sup>1</sup> Unfortunately, an older version of the table was published that includes an error: ritonavir-boosted atazanavir was incorrectly categorized in the higher (1) category rather than the intermediate (0.5) category.

Because several older and preliminary versions of the table were shown in oral presentations between 2006 and 2007, we are striving to standardize our approach to antiretroviral drug categorization on the version used in the analysis that was published in *Archives of Neurology* in 2008.<sup>2</sup> This version is shown here (Table 1).

**Table 1.** Categorization of the Effectiveness of Antiretroviral Drug Central Nervous System Penetration

	Better	Intermediate	Worse
nRTIs	Abacavir Zidovudine	Emtricitabine Lamivudine Stavudine	Didanosine Tenofovir Zalcitabine
NNRTIs	Delavirdine Nevirapine	Efavirenz	
PIs	Amprenavir/r <sup>a</sup> Indinavir/r Lopinavir/r	Amprenavir <sup>a</sup> Atazanavir Atazanavir/r Indinavir	Nelfinavir Ritonavir Saquinavir Saquinavir/r Tipranavir/r
Fusion Inhibitors			Enfuvirtide

nRTI indicates nucleoside analogue reverse transcriptase inhibitor; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor; /r, ritonavir-boosted.

<sup>a</sup>Amprenavir or fosamprenavir.

Adapted from Letendre et al, *Arch Neurol*, 2008.

Please accept our apology for the confusion this may have caused and our gratitude for your assistance in correcting it.

**Scott Letendre, MD**

sletendre@ucsd.edu

HIV Neurobehavioral Research Center, Antiviral Research Center  
University of California San Diego

1. Clifford DB. HIV-associated neurocognitive disease continues in the antiretroviral era. *Top HIV Med*. 2008;16:94-98.

2. Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS penetration-effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol*. 2008;65:65-70.

**In Reply:** I am delighted that Dr Letendre is providing us with an updated version of the central nervous system penetration effectiveness (CPE) scoring system. This important contribution to analysis of the issues of drug penetration will require periodic updates necessitated by emerging data and the inclusion of newer drugs that must be considered in our thinking about how well we target HIV therapy for the central nervous system. This updated version of the CPE table was unavailable at the time I reviewed the manuscript but will be of interest to readers now. We look forward to elucidation of the true clinical impact of these considerations as prospective data are collected testing the hypothesis that optimal therapy can be achieved by considering CPE when designing HIV therapy, particularly for the many patients who have some degree of cognitive impairment.

**David B. Clifford, MD**

cliffordd@neuro.wustl.edu

Washington University School of Medicine  
St Louis, MO

**Editor's Note:** The original table has been updated on the IAS–USA Web site version of the article (at [www.iasusa.org/pub/2008.html](http://www.iasusa.org/pub/2008.html)).

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 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 )

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 Postal Code Country

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\_\_\_\_\_  
 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)

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# 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 topics2009“at”iasusa.org.

## Categories of Articles

**Perspectives.** *Perspective* 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.

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1. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Updated October 2008. Available at <http://www.icmje.org>. Accessed July 7, 2009.

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