

# Topics in HIV Medicine®

A publication of the International AIDS Society—USA

## Reviews

- HIV Infection and Travel: Pretravel Recommendations and Health-Related Risks 2

*Carlos Franco-Paredes, MD, MPH, Alicia Hidron, MD, Ildefonso Tellez, MD, MPH, Jeffrey Lesesne, MD, and Carlos del Rio, MD*

*Travel Recommendations for HIV-Infected Travelers • Border-Crossing Considerations • Vaccine-Preventable Diseases • Routine Vaccines • Recommended Travel-Related Vaccines • Required Travel-Related Vaccines • Prevention of Malaria and Other Vector-Borne Pathogens • Prevention of Enteric and Other Infections • Health Risks and Posttravel Management*

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- A Review of HIV Antiretroviral Adherence and Intervention Studies Among HIV-Infected Youth 14

*Sari L. Reisner, MA, Matthew J. Mimiaga, ScD, MPH, Margie Skeer, MSW, MPH, Brandon Perkovich, Carey V. Johnson, ScM, and Steven A. Safren, PhD*

*Data Sources, Search Procedures, and Inclusion Criteria • Coding and Abstracting of Adherence Studies • Measurement of Adherence • Factors Related to Adherence Among HIV-Infected Youth • Adherence Interventions With HIV-Infected Youth*

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## Telling Stories

- When Silence Isn't Golden 13

*Jacqui Scipio-Bannerman, RNC*



## About This Issue

This issue contains 2 Review articles and a *Telling Stories* contribution. In the opening article, travel-related issues faced by HIV-infected patients are discussed by Carlos Franco-Paredes, MD, MPH, Alicia Hidron, MD, Ildefonso Tellez, MD, MPH, Jeffrey Lesesne, MD, and Carlos del Rio, MD. The authors present recommendations for pretravel consultation to address the increased risks faced by these patients as they travel worldwide. They also discuss the evaluation of ill returned HIV-infected travelers. A second review article, by Sari L. Reisner, MA, Matthew J. Mimiaga, ScD, MPH, Margie Skeer, MSW, MPH, Brandon Perkovich, Carey V. Johnson, ScM, and Steven A. Safren, PhD, looks at studies published between 1999 and 2008 in the United States on HIV-infected youth, focusing on adherence to antiretroviral regimens and interventions designed to enhance adherence. Jacqui Scipio-Bannerman, RNC, contributes a *Telling Stories* column, sharing a recent experience as an HIV care provider.

## Topics in HIV Medicine®

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## Telling Stories

- When Silence Isn't Golden

13

*Jacqui Scipio-Bannerman*

## Announcements

- Educational Programs of the International AIDS Society–USA

12

Correction

13

Cases on the Web

26

Subscription Request/Address Change Form

28

Guidelines for Authors and Contributors

29

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## Review

# HIV Infection and Travel: Pretravel Recommendations and Health-Related Risks

**Carlos Franco-Paredes, MD, MPH, Alicia Hidron, MD, Ildefonso Tellez, MD, MPH, Jeffrey Lesesne, MD, and Carlos del Rio, MD**

*In the current era of globalization and ease of air travel combined with the increased survival attained since the advent of potent antiretroviral therapy, HIV-infected individuals are traveling to remote and resource-limited areas of the world. Travel-related health risks in a patient with HIV depend on the patient's immune status, destination, travel itinerary, and type of travel. HIV-infected patients with a CD4+ count of 200 cells/ $\mu$ L or lower, particularly those who are treatment-naïve and newly diagnosed, are at increased risk of complications when traveling to resource-poor settings. These increased risks include those of acquiring gastrointestinal, respiratory, and endemic tropical infectious diseases. Individuals with a CD4+ count higher than 200 cells/ $\mu$ L (whether receiving antiretroviral treatment or not) are considered to have limited immune deficiency for the purpose of travel-related recommendations; in general, they may safely receive most recommended and required vaccines. Pretravel consultation before departure is crucial to address strategies to protect against vaccine-preventable diseases (routine, recommended, and required vaccinations); vector-borne diseases, particularly malaria; gastrointestinal infections; and sexually transmitted diseases. HIV-infected travelers who are ill, particularly those with fever, should undergo an immediate medical evaluation to rule out the possibility of a life-threatening infectious disease such as malaria.*

In the current era of globalization, mobility across international borders is part of the lives of thousands of people. Destinations include developed and developing regions.<sup>1</sup> This trend has also been associated with complex travel itineraries and includes individuals with chronic medical conditions.<sup>2–7</sup> The number of persons with HIV infection traveling from developed countries to tropical and subtropical areas of the world has increased substantially as a result of the clinical and survival benefits achieved with the use of effective antiretroviral therapy.<sup>4,6,8</sup> Indeed, reports indicate that 10% to 20% of HIV-infected patients with different levels of immunosuppression travel from the

United States to foreign destinations, and often to resource-constrained settings.<sup>3,4,9</sup>

For the healthy immunocompetent traveler, international travel poses certain health risks.<sup>10–14</sup> For a patient with HIV, these risks become even more important to consider.<sup>9</sup> The concern is 2-fold, that the underlying disease might worsen during travel and that HIV-infected travelers are at increased risk of complications from infectious diseases acquired at the destination.<sup>8,15</sup> Because patients with advanced immunosuppression are at higher risk of acquiring severe disease associated with some tropical infectious diseases,<sup>6,8</sup> HIV practitioners should emphasize

the need for their patients to obtain expert travel-health advice before undertaking international travel.<sup>3,8,10</sup>

Travel-related risks in the HIV-infected traveler depend largely on the immune status of the patient.<sup>8</sup> Thus, it is crucial that a recent assessment of the CD4+ cell count and percentage and of the plasma HIV RNA level be available at the pretravel consultation.<sup>8</sup> In addition, it is important for the practitioner and patient to review and discuss the decision to travel and the proposed itinerary, duration, and type of travel.<sup>16</sup>

Protective strategies in patients with HIV infection involve (1) overall travel-planning issues; (2) awareness of restrictions on HIV-infected individuals for entering specific countries; (3) prevention of vaccine-preventable diseases; (4) effective chemoprophylaxis against malaria and other vector-borne infections; and (5) prevention or self-treatment of gastrointestinal and other infections. Guidelines have been jointly issued by the US National Institutes of Health, the US Centers for Disease Control and Prevention, and the Infectious Diseases Society of America for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. These guidelines are available at <http://AIDSInfo.nih.gov>.

## Travel Recommendations for HIV-Infected Travelers

International travel poses unique medical challenges for HIV-infected per-

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sons. It is crucial that HIV practitioners understand the medical assessment and care that their patients need before traveling, especially for those traveling to resource-limited areas. One of the International AIDS Society–USA's recently published *Cases on the Web* (*COW*) presents an in-depth discussion of travel recommendations for HIV-infected travelers and offers CME credit (<http://www.iasusa.org/cow/>).

When planning travel to resource-constrained settings, HIV-infected individuals are encouraged to identify reliable medical institutions at the destination before they travel and to seek prompt medical care if becoming ill while traveling. In addition, medical insurance coverage should be verified and additional travel insurance purchased if necessary. Depending on the type of travel and itinerary, evacuation insurance should be considered.<sup>8</sup>

Pretravel consultation with HIV-infected individuals is considered a window of opportunity to update routine immunizations and provide required and recommended travel-related vaccines and chemoprophylactic regimens.<sup>15,17</sup> Most travel-health practitioners concur that HIV-infected patients with a CD4+ count of 200 cells/ $\mu$ L or lower, particularly those who are antiretroviral treatment-naïve and newly diagnosed with HIV, are at increased risk of complications when traveling to resource-limited settings, where they may face increased risk of acquiring gastrointestinal, respiratory, and particular tropical endemic infectious diseases.<sup>2,4,5</sup> Such individuals are generally advised to delay their travel to resource-limited areas pending immune reconstitution with the use of antiretroviral therapy.<sup>8</sup> This delay will minimize the risk of acquiring new infections and allow for immunologic recovery that will potentially lead to a higher immunogenic response to some travel-related vaccines.

Individuals with a CD4+ count from 200 cells/ $\mu$ L to 500 cells/ $\mu$ L, whether receiving antiretroviral therapy or not, are considered to have limited immune deficiency from the perspective of travel-related recommendations. Nevertheless, such patients are gener-

ally advised to defer travel for at least 3 months after starting antiretroviral therapy to minimize the possibility that immune-reconstitution syndromes would occur during travel.<sup>8</sup>

In addition to antiretroviral drugs, travelers should bring with them a well-planned medical travel kit containing over-the-counter medications for symptom relief.<sup>2</sup> A detailed list of recommended medications to include is available (<http://www.cdc.gov/travel/yellowBookCh2-HealthKit.aspx>).

### **Border-Crossing Considerations for HIV-Infected Travelers**

Potential travelers should review country-specific guidelines before planning international travel. A list of legal requirements for entry to individual countries is available at the US State Department Web site ([http://travel.state.gov/travel/cis\\_pa\\_tw/cis\\_pa\\_tw\\_1168.html](http://travel.state.gov/travel/cis_pa_tw/cis_pa_tw_1168.html)). A comprehensive guide related to travel restrictions for HIV-infected patients is also available at the Joint United Nations Programme on HIV/AIDS (UNAIDS) Web site ([http://www.unaids.org/en/PolicyAndPractice/KeyPopulations/PeopleHIV/mobility\\_technical\\_policies.asp](http://www.unaids.org/en/PolicyAndPractice/KeyPopulations/PeopleHIV/mobility_technical_policies.asp)).

The key issues to explore include any potential administrative or legal problems travelers might encounter at the destination country or countries and assurance of a reliable supply of antiretroviral medications. Antiretroviral drugs should be kept in carry-on bags and a backup supply stored in the checked luggage. In addition, travelers must carry with them official documentation of medications for use when crossing borders.<sup>8,16</sup>

### **Vaccine-Preventable Diseases in HIV-Infected Travelers**

Travel-related vaccines can be categorized into 3 main groups for HIV-infected and -uninfected persons traveling to developing areas of the world: (1) routine vaccines to update immunizations for children, adolescents, and adults; (2) recommended vaccines, depending on the destination and travel itinerary; and (3) required vaccines to

obtain a visa or for entry into some countries.<sup>10,11,18</sup>

Inactivated vaccines are generally acceptable for use in HIV-infected patients (eg, pneumococcal, tetanus, hepatitis A virus [HAV] and hepatitis B virus [HBV], inactivated polio, meningococcal, and inactivated trivalent influenza vaccines). Conversely, live viral and bacterial vaccines (eg, yellow fever, oral Ty21 typhoid, oral cholera, measles-mumps-rubella, or BCG vaccines) are generally avoided in patients with HIV infection, particularly those with advanced immunosuppression (CD4+ count < 200 cells/ $\mu$ L, CD4+ cell percentage < 14%, or history of AIDS-defining opportunistic infections).<sup>3-5</sup> Some vaccines may stimulate viral replication and therefore transiently increase plasma HIV RNA level, which has not been found generally to be of clinical importance.<sup>8</sup> Immune response to some vaccine antigens improves with immune reconstitution brought about by antiretroviral therapy. For some vaccines, specific antibody titers should be measured after vaccination to ensure an adequate level of protection.

### **Routine Vaccines in HIV-Infected Travelers**

Routine immunizations must be brought current in HIV-infected travelers bound for developing settings; these include HAV and HBV, tetanus toxoid, inactivated influenza, and polysaccharide pneumococcal vaccines (Table 1).<sup>8</sup> HAV infection and influenza are considered the most frequent vaccine-preventable diseases among international travelers.<sup>19</sup>

HIV-infected travelers not immune to HAV should receive hepatitis A vaccine regardless of their CD4+ cell count.<sup>8,19</sup> The 2-dose regimen of hepatitis A vaccine at regular antigen dose provides an adequate level of protection even in patients with severe cellular immunosuppression.<sup>20</sup> However, the response to hepatitis A vaccine is improved after immune reconstitution with antiretroviral therapy.<sup>21</sup> Some experts recommend checking the hepatitis A serologic response 1 month after

**Table 1.** Recommendations for the Use of Live Attenuated and Inactivated Vaccines in HIV-Infected Patients Planning Travel

Live Attenuated Vaccines	CD4+ Count
	$\geq 200 \text{ cells}/\mu\text{L}$ , with Asymptomatic infection, or On antiretroviral therapy with immune reconstitution
	< 200 cells/ $\mu\text{L}$ , with Symptomatic infection including history of AIDS-defining illness, or On antiretroviral therapy without immune reconstitution <sup>a</sup>
BCG	Contraindicated
Live attenuated influenza	Contraindicated
Measles-mumps-rubella	Recommended in those without evidence of immunity <sup>b</sup>
Ty21a oral typhoid	Contraindicated <sup>c</sup>
Varicella-zoster virus (adults)	Use as indicated in immunocompetent hosts <sup>b,d</sup>
Yellow fever	Use as indicated in immunocompetent hosts who will be exposed to substantial risk of infection; careful attention should be given to travel itinerary <sup>d</sup>
Inactivated Vaccines	CD4+ Count
	$\geq 200 \text{ cells}/\mu\text{L}$ , with Asymptomatic infection, or On antiretroviral therapy with immune reconstitution
	< 200 cells/ $\mu\text{L}$ , with Symptomatic infection including history of AIDS-defining illness, or On antiretroviral therapy without immune reconstitution <sup>a</sup>
Cholera	Live attenuated oral vaccine contraindicated; use killed recombinant vaccine if substantial risk exists <sup>e</sup>
Combined tetanus and diphtheria or combined tetanus, diphtheria, and pertussis	If indicated
<i>Haemophilus influenzae</i>	If indicated
Hepatitis A	Recommended
Hepatitis B	Recommended <sup>f</sup>
Inactivated trivalent seasonal influenza	If indicated
Inactivated polio	If indicated (live attenuated oral polio vaccine contraindicated)
Japanese encephalitis	Recommended if substantial risk exists
Meningococcal polysaccharide or conjugate	Consider if travel-required or -recommended
Pneumococcal polysaccharide	If indicated
Rabies	If indicated <sup>f</sup>
Typhoid capsular polysaccharide	If indicated <sup>h</sup>
	If indicated <sup>h</sup>

<sup>a</sup> Data unavailable for those on antiretroviral therapy with CD4+ count between 200 cells/ $\mu\text{L}$  and 500 cells/ $\mu\text{L}$ .<sup>b</sup> For patients in this category who meet age requirements and lack evidence of immunity (ie, no documentation of vaccination or evidence of prior infection).<sup>c</sup> Possible use if CD4+ count is > 200 cells/ $\mu\text{L}$ , but no evidence-based recommendation is available in this regard.<sup>d</sup> Serologic testing recommended after vaccination to ensure optimal response to immunization.<sup>e</sup> Unavailable in the United States; Centers for Disease Control and Prevention does not recommend use.<sup>18,43</sup><sup>f</sup> Measure antibody titers after immunization to ensure adequate protection in HIV-infected patients.<sup>g</sup> Best protection achieved if given 6 to 12 months after initiation of antiretroviral therapy.<sup>h</sup> Vaccine of choice among HIV-infected individuals regardless of CD4+ cell count.

administration if time permits. Nonresponders should ideally be revaccinated prior to traveling.<sup>22</sup> Additional protection may be afforded by the use of HAV immune globulin in those with a CD4+ count of 200 cells/ $\mu$ L or lower and who lack serologic evidence of immunity.<sup>23</sup>

Vaccination for HBV is recommended for patients at all stages of HIV infection or AIDS, particularly those traveling to resource-limited settings.<sup>8</sup> The serologic response should be assessed 1 month after completion of the vaccine course.<sup>22</sup> A hepatitis B vaccine schedule that is started 6 months to 12 months after the initiation of antiretroviral therapy offers the best immunogenicity. If there is no response, revaccination should be considered. Some experts might delay revaccination until after a sustained increase in CD4+ count is achieved with antiretroviral therapy.<sup>22</sup>

Immunogenicity to tetanus toxoid is influenced by HIV infection and by malaria.<sup>24</sup> Antitoxin antibody levels are often lower in HIV-infected patients than in uninfected individuals, particularly in those with a CD4+ count of 300 cells/ $\mu$ L or lower.<sup>24</sup> Despite these limitations, vaccination with tetanus toxoid is currently recommended for HIV-infected persons of all age groups regardless of the presence of advanced immunosuppression because most groups appear to achieve protective antitoxin levels.<sup>25</sup>

The serologic responses to diphtheria, tetanus, and possibly pertussis vaccines are diminished in children with HIV infection.<sup>26</sup> However, there is no evidence of a lack of vaccine effectiveness or increased risk of vaccine adverse events with the combination vaccines for diphtheria, pertussis, and tetanus (DPT) or for tetanus and diphtheria (Td) in HIV-infected individuals.<sup>26-28</sup> An acellular vaccine to prevent pertussis in adults was approved for use in 2006 in the United States (tetanus, diphtheria, and pertussis, or Tdap).<sup>27</sup> The vaccine is recommended for 1-time dose administration to all adults age 64 years or younger whose most recent Td booster was received 10 or more years ago; it is considered

safe to administer in HIV-infected individuals.<sup>25</sup> The Tdap vaccine may be substituted for the recommended Td booster that adults should receive every 10 years.

Influenza is considered a year-round infection in the tropics, and in the Southern Hemisphere, the influenza season runs from April through October.<sup>29</sup> Inactivated trivalent influenza vaccine is currently recommended for HIV-infected individuals with a CD4+ count of 100 cells/ $\mu$ L or higher as a pretravel vaccination, taking into account the influenza season at the destination. When a specific inactivated trivalent vaccine is not available or may potentially not protect travelers because of the season of travel, use of the antiviral drug oseltamivir for self-treatment is considered an alternative in travelers at high risk of acquiring influenza and developing potential complications from this infection.<sup>8,29</sup>

Most travelers are protected against measles by either natural exposure or previous immunization. However, the risk of exposure to measles may be increased in some resource-constrained settings, and the disease can become more severe in the HIV-infected patient.<sup>3,4,9</sup> Previous immunity should be determined by serologic analysis and measles vaccines recommended for nonimmune travelers to resource-constrained settings with high prevalence rates of measles, unless their CD4+ count is 200 cells/ $\mu$ L or lower.<sup>8</sup> Measles immune globulin may be administered for short-term protection of those traveling to high-risk areas and for whom a measles, mumps, and rubella (MMR) vaccine is contraindicated.<sup>20</sup> There is only 1 case report of fatal vaccine-related disease in an adult patient with advanced immunosuppression and who developed fatal pneumonia.<sup>26,30-32</sup> An important concern yet to be resolved is whether HIV-infected children who receive measles vaccine may experience any substantial delayed adverse events as a result of the possible persistence and later replication of the attenuated virus.<sup>32</sup>

In a study of HIV-seropositive children, overall vaccine-induced immunogenicity to many polysaccharide

and protein antigens was decreased.<sup>26</sup> Indeed, the vaccines currently recommended by the World Health Organization (WHO) for use in national immunization programs in children infected with HIV are generally considered safe and beneficial. Nonetheless, HIV-associated immunosuppression reduces the benefit compared with that seen in HIV-seronegative children. No serious complications have been reported in this group with the use of yellow fever vaccine. The benefits of inactivated polio vaccine and measles vaccination in HIV-infected children outweigh any potential risks.<sup>32</sup>

### **Recommended Travel-Related Vaccines in HIV-Infected Travelers**

Japanese encephalitis (JE) vaccination using the inactivated mouse-brain-derived JE vaccine in HIV-infected persons follows the same recommendations as for HIV-seronegative persons (3 doses over 28 days).<sup>33,34</sup> Varicella-zoster vaccine is an important consideration for nonimmune travelers bound to tropical and subtropical areas of the world. It has been given safely to some children with HIV infection, and current recommendations state that HIV-infected children with a CD4+ cell percentage of 15% or greater should receive varicella-zoster vaccine.<sup>35,36</sup> In this group of HIV-seropositive children, varicella-zoster vaccine produces adequate immunogenicity and minimal reactogenicity.<sup>36</sup>

With regard to the use of the live varicella-zoster vaccine to prevent herpes zoster, the Shingles Prevention Study excluded patients with impaired T-cell immunity, including HIV-infected individuals; thus, this vaccine is currently contraindicated in people with HIV infection. HIV-infected patients with moderate to advanced immunosuppression may be at higher risk of adverse effects given the higher dose of live attenuated virus contained in the herpes-zoster vaccine.<sup>36</sup> An ACTG (AIDS Clinical Trials Group) study (A5247) is currently being planned to study the efficacy of the varicella-zoster vaccine in HIV-infected patients.

HIV-infected adolescents and adults should ensure that their vaccination with inactivated polio vaccine is up-to-date before traveling to some areas of western Africa and the Indian subcontinent (India, Pakistan, and Afghanistan).<sup>8,18</sup> Rabies vaccination recommendations follow the same criteria in HIV-infected individuals as in HIV-seronegative individuals (Table 1). In addition, the serologic response to the rabies vaccination should be checked in HIV-infected individuals after preexposure rabies vaccination.<sup>8</sup> Preexposure vaccination with rabies vaccine is generally indicated for long-term travelers to rural areas highly endemic for rabies who will be too far from adequate medical care to seek postexposure prophylaxis within 24 hours of exposure. In this regard, an important benefit of preexposure prophylaxis is avoiding the need for administering rabies immune globulin. In some settings, the use of locally available immune globulin may be of concern because of the unknown safety of some of these products. Preexposure prophylaxis requires 3 doses of rabies vaccine on days 0, 7, 21, or 28.

Typhoid fever may produce life-threatening complications in HIV-infected patients.<sup>37,38</sup> Although there is no evidence of sustained bacterial replication using the oral vaccine from the Ty21a strain of *Salmonella* Typhi among HIV-infected individuals, the typhoid Vi polysaccharide vaccine is preferred over the live attenuated vaccine regardless of the CD4+ level.<sup>8,20</sup> This vaccination is particularly important for HIV-infected patients bound to typhoid fever–endemic areas, particularly Latin America, Southeast Asia, and the Indian subcontinent.<sup>38</sup>

Tick-borne encephalitis vaccine (3 doses over a 9-month period) is recommended only for travelers visiting rural, forested areas of Scandinavia, western and central Europe, and countries of the former USSR from March through November.<sup>39</sup> Transmission occurs through tick bites or ingestion of unpasteurized goat products. This vaccine is not available in the United States but can be obtained in Canada and some parts of Europe and is gen-

erally considered safe to use in immunocompromised populations.<sup>5</sup> Use of protective insect repellent and avoidance of unpasteurized goat milk are also recommended preventive measures for HIV-infected travelers.<sup>18,40</sup>

### Required Travel-Related Vaccines in HIV-Infected Travelers

Documentation of meningococcal vaccination or yellow fever vaccination is required for entry into some countries (Table 1).<sup>18</sup> Use of the quadrivalent meningococcal conjugate vaccine or polysaccharide vaccine (for serogroups A, C, Y, and W-135) is indicated based on the patient's travel itinerary and follows similar recommendations as for people without HIV infection.<sup>8,18</sup> Currently available meningococcal vaccines are considered safe and efficacious in patients with HIV infection. The only identified limitation is that patients with HIV may have a decreased response to serotype C of *Neisseria meningitidis*, but the most important serotypes to protect travelers to high-risk areas of the world against are serotypes A and W-135. High-risk situations include travel to the “meningitis belt” in sub-Saharan Africa or to attend the Hajj pilgrimage in Saudi Arabia.<sup>18</sup>

Yellow fever is a mosquito-borne illness that has been reported rarely in travelers, and the risk varies widely within recognized areas of transmission.<sup>33,41</sup> Appropriate administration of yellow fever vaccine to travelers requires an assessment of the patient's risk of acquiring infection during travel versus the risks associated with vaccine adverse events.

Yellow fever vaccine is a live attenuated vaccine made with the 17D yellow fever virus strain. Three distinct but related lineages of the yellow fever vaccine strains (17D-204, 17DD, and 17D-213) have been developed, with more than 99.9% nucleic acid sequence homology among them.<sup>33</sup> Although this vaccine has been considered among the safest, recent reports of adverse events in the form of neurotropic and viscerotropic disease have raised concern about the vaccine's safety. So far,

yellow fever vaccine–associated severe adverse events, particularly viscerotropic disease, have been associated with persons aged 60 years and older and persons with thymoma or a history of thymectomy, but no cases of viscerotropic disease have been reported in patients with HIV infection. The lack of detection of these severe adverse events in HIV-infected individuals may, however, simply be a reflection of the low number of immunized, HIV-infected travellers.<sup>33</sup>

After primary vaccination, vaccine strain viremia occurs frequently in nonimmunocompromised persons. Because of a concern of uncontrolled viremia, yellow fever vaccine is not recommended for patients with a CD4+ count of 200 cells/ $\mu$ L or lower.<sup>5</sup> Therefore, this group should be discouraged from traveling to areas where yellow fever is highly endemic. In addition, many experts recommend postvaccination testing for the presence of neutralizing antibodies in HIV-infected patients planning travel to high-risk areas.<sup>33</sup> A recent study identified 102 HIV-infected patients in Europe who had received the yellow fever vaccine. No serious adverse events were identified, but HIV-infected persons had lower neutralization titers after vaccination, more often demonstrated nonprotective titers, and experienced a more rapid decline in titers during follow-up.<sup>42</sup> At this time, if travel to a yellow fever–endemic zone by severely immunocompromised persons is unavoidable, a medical exemption letter can be written. Additionally, travelers should be instructed in detail about methods to avoid mosquito bites through personal protection measures.

Evidence suggests that cholera vaccination affords some protection and carries an apparently safe profile for use in HIV-infected individuals. A recent clinical trial in Mozambique demonstrated a 78% protection rate using a strategy of mass vaccination with 2 doses of recombinant cholera-toxin B subunit, killed whole-cell (rBS-WC) oral cholera vaccine. This rBS-WC vaccine was highly effective against clinically important cholera in an urban,

sub-Saharan African population with a high prevalence of HIV infection. Although this study suggests the vaccine offers protection to HIV-infected persons, data on the safety of the vaccine in HIV-infected persons could not be assessed directly. In other trials performed in different settings, however, this same vaccine was not associated with adverse reactions in HIV-infected persons or with progression of HIV disease, although a transient increase in HIV viral load was identified in 1 study.<sup>45</sup> In summary, the use of rBS-WC oral cholera vaccine may be considered in HIV-infected travelers to areas of ongoing cholera outbreaks such as refugee camps.<sup>18</sup>

### **Prevention of Malaria and Other Vector-Borne Pathogens**

The risk of malaria acquisition is increased in HIV-infected individuals.<sup>44,45</sup> Thus, pretravel consultation must include a thorough discussion of malaria prevention.<sup>46</sup> Adherence to recommended chemoprophylactic regimens is a concern among HIV-infected individuals. A study from Toronto about behaviors of HIV-seropositive travelers showed that less than 7% of international travelers took adequate chemoprophylaxis against malaria,<sup>3,4</sup> thus, adherence and safety concerns should be addressed specifically.

Most drugs used for malaria prevention and treatment are considered safe in HIV-infected persons receiving antiretroviral drugs.<sup>9</sup> Nevertheless, drug interactions can occur and should be considered before prescribing malaria chemoprophylactic regimens.<sup>9</sup> Although potential interactions exist theoretically between some HIV protease inhibitors, particularly ritonavir with atovaquone-proguanil, chloroquine, and mefloquine, no evidence documents any clinically relevant events and no dose adjustments are recommended. Atovaquone-proguanil may increase the level of zidovudine, warranting closer monitoring of hemogram results.<sup>8</sup> In the authors' clinical opinion, atovaquone-proguanil and doxycycline are the antimarial drugs of choice for the prevention of malaria

among HIV-infected persons receiving antiretroviral therapy.

HIV-infected travelers need to take personal protective measures to avoid bites from mosquitoes (vectors for yellow fever, malaria, dengue fever, JE, West Nile virus, and other arboviral infections) and other disease-transmitting insects (eg, sandflies, vectors for leishmaniasis or bartonellosis in South America, and ticks, vectors for rickettsiosis).<sup>40,47</sup> Prevention measures include remaining in well-screened locations, using repellent-impregnated mosquito nets, and wearing, as practical, clothing that covers most of the body surface. The most effective repellent against a wide range of arthropods is *N,N*-diethyl-m-toluamide (currently named *N,N*-diethyl-3-methyl-benzamide, or DEET), an ingredient in many commercially available insect repellents.<sup>40,47</sup> Insect repellents that contain DEET at concentrations up to 50% (range, 30%-50%) are recommended for adults and children older than 2 months. Also, permethrin is available as a spray or liquid to treat clothes and bed nets if required, and bed nets pretreated with permethrin are also available. Picardin is as effective as a long-acting DEET formulation.<sup>18,40</sup>

HIV-infected travelers to malaria-endemic settings should be educated that malaria-preventive strategies do not guarantee protection. Thus, such patients must be instructed to seek expert medical assistance early in any febrile illness.<sup>8,9</sup>

Treatment of malaria in HIV-infected patients, particularly that caused by *Plasmodium falciparum*, follows the same recommendations as for HIV-seronegative patients.<sup>22</sup> There are, however, safety concerns regarding the use of quinidine or quinine in combination with nelfinavir or ritonavir because of the potential for cumulative cardiotoxicity.<sup>8</sup> Another potential interaction occurs between lumefantrine, alone or in combination with artemether (used in some African countries) and ritonavir and potentially other HIV protease inhibitors; the risk of life-threatening cardiac arrhythmias may increase as a result of prolongation of the QT interval.<sup>8,9</sup> Minimal data are available re-

garding the safety of other artemisin-based combinations in patients with HIV infection.<sup>9</sup> The risk of life-threatening consequences associated with malaria infection in HIV-infected individuals necessitates the use of these various regimens, which must include careful monitoring for potential drug interactions.

### **Prevention of Enteric and Other Infections**

HIV-infected travelers need to take precautions to avoid acquiring enteric or other opportunistic infections.<sup>22</sup> Unpasteurized milk and dairy products may transmit brucellosis, *Salmonella* species, Q fever, and tick-borne encephalitis.<sup>15,18</sup> To reduce the risk of acquiring cryptosporidiosis, giardiasis, and leptospirosis, patients should avoid swallowing water during swimming and avoid swimming in rivers, lakes, or other potentially contaminated water.<sup>15,18</sup> Use of proper hand hygiene with water and soap or alcohol-based solutions is necessary to reduce the risk of acquiring gastrointestinal infections, particularly on cruise ships. The risk of acquiring norovirus infection can also be minimized by adequate handwashing and avoidance of possibly contaminated food.<sup>48</sup>

Some of the important causes of acute diarrheal episodes in HIV-infected persons include the organisms *Cyclospora cayetanensis*, *Cryptosporidium parvum*, and *Isospora belli*, which are food borne (through raw vegetables or contaminated water) and may lead to chronic diarrhea and extraintestinal complications.<sup>8,22</sup> Many of these diarrheal episodes require longer treatment periods in HIV-infected patients than in HIV-uninfected people. Among the bacterial pathogens, infections with *Campylobacter* species, *Shigella* species, and *Salmonella* species often produce more severe disease with associated bacteremia in HIV-infected than in uninfected patients.<sup>3,4</sup> With the advent of antiretroviral therapy, the incidence of nontyphoid salmonellosis has decreased in some settings, but a substantial rise in quinolone-resistant strains has been identified.<sup>49</sup>

Discussion of water and food safety and methods of boiling and filtering water may provide the greatest impact to prevent infection with enteric pathogens. Filtration of water using a pore size of less than 1 μm may not remove all bacteria, and viruses and *Microsporidia* species may be too small to be removed by this degree of filtration. Purification by boiling is adequate for elimination of all important enterobacteria and is the most reliable method of water treatment, although some bacterial spores such as those of *Clostridia* species may be resistant to boiling.<sup>17</sup>

Routine antimicrobial prophylaxis for traveler's diarrhea is not recommended for HIV-infected travelers.<sup>8,22</sup> Rather, these patients should be instructed on self-treatment of traveler's diarrhea using azithromycin or a quinolone<sup>17</sup> such as ciprofloxacin or levofloxacin. For individuals with severe immunosuppression, a preventive regimen of daily-dose quinolone, doxycycline, bismuth, or rifaximin may be considered. The use of oral rehydration solutions in combination with antidiarrheal agents and presumptive self-treatment with a quinolone or macrolide regimen (azithromycin) should be encouraged in the HIV-infected traveler.

Leptospirosis may occur in adventure travelers and those who engage in water-recreation activities. In this group, a weekly chemoprophylactic dose of doxycycline (200 mg) is recommended.<sup>18,50</sup>

Sexual activity increases during international travel,<sup>51,52</sup> with only a limited number of travelers reporting consistent use of condoms. The safest recommendation for the HIV-infected traveler is abstinence. However, safe-sex preventive strategies should be discussed and reinforced.

## Health Risks and Posttravel Management of HIV-Infected Individuals

The likelihood of an HIV-infected person developing a medical condition during travel relates to the individual's medical history, travel destination and planned activities, duration of travel, type of accommodations, immuniza-

tion history, adherence to indicated chemoprophylactic regimens and, especially, history of exposure to infectious agents before and during travel.<sup>8,15</sup> Eliciting a detailed history of the sites visited, the timing of travel relative to the onset of symptoms, the exact arrival and departure dates, and specific risk behaviors is essential in determining potential exposure to infectious pathogens and the likely incubation period.

The exposure history should include a history of contact with animals (including bites), new sexual partners, fresh water, insects, medical equipment (needles, blood transfusions), and ill persons.<sup>15,53-55</sup> Also, a history of ingestion of unpasteurized dairy products or uncooked meat as well as an occupational history might be important. The immunization history will often rule out entities such as HAV, HBV, yellow fever, meningococcal meningitis, and JE in those who have been immunized. However, prior typhoid immunization does not rule out infection because the vaccine is only 70% effective. A history of malaria chemoprophylaxis should include the name of the drug, the dose, the patient's adherence to the regimen, and whether the patient is still taking the drug after returning.<sup>15,16,56</sup>

Fever is frequently reported by ill returned travelers.<sup>57-62</sup> In a patient with HIV, this symptom may indicate an infectious, inflammatory, or neoplastic disorder but is most likely to have an infectious origin. The fever may be caused by a geographically restricted infection, such as malaria, dengue fever, typhoid fever, viral hepatitis, or bacterial pneumonia,<sup>62</sup> or it may be due to an infectious syndrome not geographically restricted, such as a urinary or upper respiratory tract infection.<sup>15,16</sup> Some fever episodes may represent life-threatening conditions such as *P falciparum* malaria that, if not treated appropriately and early, can be lethal in HIV-infected individuals.<sup>9,15</sup>

Several tropical pathogens can lead to opportunistic infection and disease in people with HIV (Table 2).<sup>6,7</sup> The presence of HIV infection or AIDS may alter the natural history of tropical in-

fectious diseases in different ways, and individuals coinfected with HIV and some parasitic infections may pose clinical diagnostic dilemmas because of their atypical clinical manifestations.<sup>63,64</sup> Furthermore, patients coinfected with HIV and some tropical infectious diseases require longer treatment courses at the risk of experiencing more serious adverse effects. In addition, a higher pathogen burden in patients with HIV and AIDS may lead to higher morbidity and mortality.<sup>65,66</sup>

Geographically focal infections that pose an increased risk of severe clinical manifestations in HIV-infected patients include visceral leishmaniasis,<sup>63,67</sup> *Penicillium marneffei* in Southeast Asia,<sup>68</sup> *Trypanosoma cruzi* in South America,<sup>69</sup> paracoccidioidomycosis, and coccidioidomycosis in the Americas (Table 2).<sup>6,64</sup> Coinfection with visceral leishmaniasis and HIV is an increasing problem in southern Europe, Ethiopia, Sudan, Brazil, and India, and gastrointestinal symptoms are among the most frequent complaints.<sup>67</sup> Hyperinfection with *Strongyloides* species occurs in immunocompromised patients, including those with HIV.<sup>70</sup> Although it may seem paradoxical, *Strongyloides* species hyperinfection rarely develops in patients with AIDS because the disseminated infection requires the direct development of infective larvae in the gut, and HIV-associated immunosuppression may hamper these events.<sup>6,70</sup> *Trypanosoma cruzi* and HIV coinfection may produce necrotizing meningoencephalitis (Table 2).<sup>69</sup>

The geographic overlap between HIV infection and malaria has attracted much interest in their potential synergistic interactions.<sup>65</sup> HIV-infected adults appear to be more prone to clinical malaria than are HIV-seronegative adults.<sup>44</sup> A study from Zambia identified that HIV-infected patients with malaria and a CD4+ count of 300 cells/μL or lower have a higher risk of experiencing recrudescence infection.<sup>66,71,72</sup> Thus, the response of HIV-infected persons to malaria treatment must be carefully monitored.

Respiratory infections including community-acquired bacterial pneumonia, influenza, and pulmonary tu-

Table 2. Clinical Manifestations of Geographically Restricted Infections in HIV-Infected Patients

Infectious Disease <sup>a</sup>	Features in Patients With HIV or AIDS
American trypanosomiasis, or Chagas disease ( <i>Trypanosoma cruzi</i> )	Reactivation disease in the form of meningoencephalitis, myocarditis, or rarely, cutaneous disease
Malaria ( <i>Plasmodium falciparum</i> )	Increased frequency of clinical malaria episodes; increased risk of malaria treatment failure; and increased HIV transmission by malaria episodes
<i>Isospora</i> , <i>Cyclospora</i> species infection	Chronic diarrhea; extraintestinal disease (biliary tract)
<i>Strongyloides stercoralis</i> infection <sup>b</sup>	Hyperinfection syndrome and disseminated strongyloidiasis
African trypanosomiasis ( <i>Trypanosoma brucei rhodesiense/gambiense</i> )	Unclear clinical impact of HIV infection on African trypanosomiasis but often have more severe toxicity to treatment for African trypanosomiasis
Schistosomiasis ( <i>Schistosoma mansoni</i> , <i>Schistosoma haematobium</i> ) <sup>b</sup>	Genitourinary schistosomiasis may predispose individuals to acquire HIV infection. Response to antiretroviral therapy improves when treating schistosomiasis with praziquantel
Visceral leishmaniasis <sup>b</sup>	Similar clinical presentation as in non-HIV-infected individuals. More atypical locations, particularly the upper gastrointestinal system, lung, pleural and peritoneal cavities, and skin. Splenomegaly is less frequent in HIV-infected persons
Cutaneous leishmaniasis <sup>b</sup>	Isolated reports of more severe and higher number of cutaneous lesions
<i>Penicillium marneffei</i> infection	Endemic in Southeast Asia. Disseminated disease with fever, skin lesions, reticuloendothelial system effects
Paracoccidioidomycosis	Endemic in South America. Disseminated disease with skin lesions, adenopathy, mucosal lesions, pulmonary infiltrates, and fever
Nontyphoid <i>Salmonella</i> species bacteremia	Risk of recurrent bacteremia. In some settings, the advent of antiretroviral therapy has decreased risk, but isolates from HIV-infected persons are increasingly resistant to quinolones in many settings
Tuberculosis ( <i>Mycobacterium tuberculosis</i> )	Increased risk of extrapulmonary disease. Worsening immunosuppression induced by tuberculosis. Paradoxical reactions with the use of antiretroviral therapy in patients coinfected with HIV and tuberculosis
Typhoid fever ( <i>Salmonella Typhi</i> )	Adults with HIV infection often have diarrhea instead of constipation

<sup>a</sup> No data suggest that melioidosis, which is endemic in Southeast Asia, is more frequent or severe in HIV-infected patients, nor that HIV alters the clinical course of brucellosis, *Mycobacterium leprae* infection, yellow fever, dengue fever, West Nile virus infection, or the hemorrhagic fevers (caused by infections with hantaviruses, phleboviruses, arenaviruses, or filoviruses).

<sup>b</sup> This parasitic infection has been associated with immune reconstitution manifestations in patients receiving antiretroviral therapy.<sup>74</sup>

berculosis are important risks for HIV-infected travelers.<sup>22,62</sup> The risk of acquiring tuberculosis is thought to correlate directly with destination, duration of stay in the endemic area, degree of contact with local populations, and occupation.<sup>73</sup>

Any returned, febrile international HIV-infected traveler should be evaluated immediately, preferentially by an infectious diseases clinician or tropical medicine expert.<sup>15</sup> The workup of such

patients should be considered a medical emergency and, if indicated, the diagnosis to be malaria until proven otherwise. Prompt evaluation should be made of the results of the following diagnostic tests: peripheral blood smears or rapid antigen detection for *Plasmodium* species; a complete blood cell count and differential; liver function tests; urinalysis; blood, stool, and urine cultures; chest radiography; and specific serologic assays, such as those

for the diagnosis of dengue fever, rickettsial infections, schistosomiasis, and leptospirosis. Travelers who report having engaged in high-risk sexual behavior should be tested for HIV, syphilis, HBV, and hepatitis C virus, and cultures should be taken for gonorrhea and chlamydial infection. Finally, in some cases, people with HIV should undergo tuberculin skin testing before and after travel to identify potential exposure to *Mycobacterium tuberculosis*.<sup>15</sup>

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David Alain Wohl, MD

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Tuesday, February 24, 2009  
Faculty: Steven G. Deeks, MD  
Andrew R. Zolopa, MD

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Tuesday, April 21, 2009  
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Faculty: Eric S. Daar, MD  
Joel E. Gallant, MD, MPH

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Thursday, March 12, 2009  
Faculty: Marshall J. Glesby, MD, PhD  
David Alain Wohl, MD

##### **Washington, DC**

Thursday, May 7, 2009  
Faculty: Michael S. Saag, MD

##### **Denver, CO**

Thursday, June 11, 2009  
Faculty: Steven C. Johnson, MD  
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Wednesday, April 1, 2009  
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Local host: Lisa M. Chirch, MD

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Monday, May 18, 2009  
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## Telling Stories When Silence Isn't Golden

**Jacqui Scipio-Bannerman, RNC**

Ring...

"Hello, this is Jacqui, can I help you?"

"Miss, I am HIV-positive, and I passed the virus to my 17-year-old son at birth. He got one of your patients there at the clinic pregnant and he won't tell her that he is infected with the virus." She sighed and went on. "I don't know her last name but her first name is Angelica, and she is 16. Miss, that baby is my grandchild."

I asked the caller again how I could be of assistance to her. I explained that HIPAA (Health Insurance Portability and Accountability Act) laws mandate that I must not discuss any patient information. Then I thanked her for calling and placed my head on my desk.

I know Angelica. She is the sweetest little thing. She is also very excited about her first pregnancy. To make matters worse, she recently told me that she had "broken up" with her

child's father. To translate that into the current generation Y vernacular, she was no longer in a relationship with her "baby daddy."

My mind was reeling as I thought of all the consequences, probabilities, and possible outcomes, yet I was having strong feelings of déjà vu. In March 1998, I wrote an article titled, "Accessory to Murder..." that was published in *Nursing Spectrum*. That story was similar to my current reality. I had written about an HIV-infected woman who was not willing to disclose her seropositive HIV status to her sex partner. However, the major difference between that situation and the current one is AGE. These current parents-to-be are teenagers!

Regardless of their ages, though, my hands are still tied, and a Pennsylvania law (Act 148, Confidentiality of HIV-Related Information Act) has silenced my voice. Once again, I find myself emotionally torn. As a nurse who is committed to public health, I want to do primary and secondary teaching. Yet legally, I can do neither or say anything in this situation. It is almost as if "don't ask, don't tell" applies to HIV prevention.

Luckily, Angelica was found to be HIV-seronegative at her initial prenatal visit. But, though they are no longer involved, her baby's father is still having sex. He is possibly (probably) still engaging in unprotected sex. According to the Pennsylvania law, physicians *may* disclose confidential HIV-related information. The physician must "reasonably believe disclosure is medically appropriate and that there is significant risk of future infection to the contact."

Read between the lines. Any such disclosure would sever the physician-patient relationship and possibly alienate an individual who is in dire need of healthcare himself. Face it! An HIV test is \$25. However, a good, working, trusting relationship between a healthcare worker and patient is priceless. Though I want to pull that young man aside and talk to him, I will remain quiet.

Who said "silence is golden"?

*Ms Scipio-Bannerman has no relevant financial affiliations to disclose.*

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## Correction

There was an error in the figures accompanying the article "Update of the Drug Resistance Mutations in HIV-1: December 2008" published in Volume 16, Issue 5, of *Topics in HIV Medicine*. On page 141, the wild-type designation of a drug resistance mutation for darunavir/ritonavir was listed incorrectly. The correct designation is T74P not L74P. The figures and downloadable slides posted on our Web site ([www.iasusa.org](http://www.iasusa.org)) show the correct designation, but the error remains in the printed journal copies and in the folded pocket cards inserted with the issue. Corrected pocket cards are available on request through our Web site, where updates are posted as they become available.

## Review

# A Review of HIV Antiretroviral Adherence and Intervention Studies Among HIV–Infected Youth

Sari L. Reisner, MA, Matthew J. Mimiaga, ScD, MPH, Margie Skeer, MSW, MPH, Brandon Perkovich, Carey V. Johnson, ScM, and Steven A. Safren, PhD

*Advances in antiretroviral medications have resulted in precipitous declines in HIV-associated morbidity and mortality; however, high levels of adherence are crucial to the success of HIV therapies. This article reviews published studies in the United States on HIV-infected youth (ages 13 to 24 years), focusing on adherence to antiretroviral regimens and interventions designed to enhance adherence. A systematic search yielded 21 articles published between 1999 and 2008 that reported data on medication adherence in HIV-infected youth, of which 7 described unique interventions to enhance medication adherence. Five thematic areas were identified to classify factors associated with adherence. Findings suggest psychosocial factors, in particular depression and anxiety, were consistently associated with poorer adherence across studies. Three types of adherence interventions with HIV-infected youth were found. Results suggest that examining adherence within the broader contextual issues present in the lives of youth, including HIV stigma and disclosure, caregiver stress, peer relations, mental health and substance use, and length of time on medications, may be most important to understanding how best to intervene with adherence among this population. Secondary HIV prevention interventions for youth represent a possible mode through which to deliver individually tailored adherence skill building and counseling to improve medication adherence.*

According to the Centers for Disease Control and Prevention, an estimated 5259 young people aged 13 years to 24 years received a diagnosis of HIV infection or AIDS in the United States in 2006, a 25% increase from estimated diagnosed cases among youth in this age range in 2003 ( $n = 4209$ ).<sup>1</sup> These youth represented 25% of the estimated 475,871 persons living with HIV or AIDS in 2005 in the 33 states with long-term, confidential, name-based HIV reporting in the United States ( $n = 19,134$ ).<sup>1</sup> Advances in medical treatment, specifically antiretroviral medications, have resulted in precipitous declines in HIV-associated

morbidity and mortality,<sup>2–5</sup> allowing for HIV-infected adolescents and young adults to manage their HIV infection as a chronic, rather than imminently life-threatening, disease. However, maintaining high levels of adherence (90% to 95%) to antiretroviral therapy is crucial to treatment success,<sup>6–10</sup> and promoting adherence remains an essential element of modern HIV care.<sup>11,12</sup>

In providing HIV care for youth, practitioners may follow the US Department of Health and Human Services guidelines.<sup>10</sup> Although substantial advances have been made to simplify regimens and develop combination therapies,<sup>12</sup>

the behaviors associated with adherence (eg, taking doses at the same time every day, following food restrictions, and not skipping doses as the result of irregularity in routines) remain a challenge, especially for young people living with HIV infection.<sup>13</sup>

The normal developmental trajectory of adolescence and young adulthood involves behavioral experimentation, risk taking, and confronting a host of difficult choices with regard to romantic relationships, sexual behavior, alcohol and drug use, and identity formation (eg, Arnett, 2004).<sup>14</sup> The complexity of these choices is compounded for HIV-infected youth and emerging adults,<sup>14</sup> who must negotiate these developmental stages within the framework of having a chronic and stigmatizing disease.<sup>15–17</sup> Medication adherence may be particularly challenging at a time of life when adolescents do not want to be different or perceived as different from their peers.<sup>10</sup> Moreover, developmental processes, such as concrete thinking,<sup>18</sup> may contribute to difficulties in taking medications when adolescents are asymptomatic, particularly if the medications have taxing adverse effects.

Previous reviews of antiretroviral adherence studies in the United States have focused on HIV-infected adults.<sup>19–22</sup> This article reviews published adherence studies on HIV-infected youth (ages 13 to 24 years), focusing on rates of adher-

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ence to antiretroviral regimens and interventions designed to enhance adherence. Included are possible directions for future research and suggestions for intervention development to improve antiretroviral adherence among HIV-infected youth.

## Methods

### Data Sources, Search Procedures, and Inclusion Criteria

Articles were identified through searches conducted on MEDLINE, PubMed, and PsychInfo using combinations of the keywords HIV/AIDS, youth, adolescents, young adults, adherence (or compliance), nonadherence (or noncompliance), medical treatments, highly active antiretroviral therapy (HAART), antiretroviral, resistance, and intervention (also keywords associated with specific types of interventions, such as education, telephone, and peer). In addition, bibliographies of relevant articles were reviewed for additional studies.

Included were quantitative and qualitative studies reporting original data on medication adherence among HIV-infected youth (ages 13 to 24 years) and on exercising an intervention technique to enhance antiretroviral adherence among this population. Studies that included children as well as adolescents and young adults were incorporated for review as long as the mean age of participants fell within the 13-to 24-year-old age range; data relevant to adolescents and youth from these studies were reported where available, with the exception of 2 intervention studies<sup>23,24</sup> that included data from all participants.

The systematic search yielded 21 articles dating from 1999 to 2008; of the 21 articles reporting data on medication adherence, 7 described unique interventions to enhance adherence among HIV-infected youth. Given the early stage of research in this field, all relevant studies were included in the review, regardless of methodologic rigor. Common methodologic limitations of studies (eg, lack of randomization, lack of control group, or insufficient power) are reported where relevant.

### Coding and Abstracting of Adherence Studies

A coding manual was developed to extract descriptive information on setting, study design, population and sample characteristics, definition of adherence used, adherence measurement method, key study variables, and reported findings. In accordance with the approach utilized in prior literature reviews (eg, Fogarty et al, 2002),<sup>19</sup> names and definitions of variables were extracted verbatim from study authors, generating a list of 46 variables. A combination of content analysis<sup>25</sup> and an iterative process of variable sorting and concept formation common in qualitative research<sup>26</sup> was employed to identify 9 categories in which all the variables could be classified. These categories were further refined into 5 broad thematic areas associated with adherence: (1) demographic factors (eg, age, sex); (2) psychosocial factors (eg, family/caregiver, psychologic/developmental); (3) disease factors (eg, clinical status, disease stage); (4) treatment regimen factors (eg, regimen complexity, adverse effects); and (5) practitioner factors. Intervention components and relevant outcomes are also described.

Variables were often worded in both the positive and negative directions (for example, predictors of adherence and predictors of nonadherence). Findings were classified in 1 of 3 ways: (1) variables statistically significantly associated with adherence, (2) variables statistically significantly associated with nonadherence, or (3) variables inconsistently associated or failing to demonstrate an association with adherence.

### Measurement of Adherence

Accurate measurement of HIV medication adherence presents challenges to researchers, and few studies are consistent in their classification of adherence.<sup>27</sup> Three categories were used in this review to classify how studies measured adherence: (1) subjective measures of adherence based on self-report or others' report of adherence; (2) pharmacologic measures of adherence (eg, pill count, pharmacy refill records, use

of mechanical monitors of pill or drug use); (3) physiological methods or indicators (eg, plasma HIV RNA level below detection limits, CD4+ count, plasma assay results, other laboratory reports).

## Results

Overall rates of adherence in the 30 days before study enrollment ranged from 28.3%<sup>28</sup> to 69.8%.<sup>29</sup> Table 1 provides a descriptive overview of the 14 adherence studies reviewed.

### Factors Related to Adherence Among HIV-Infected Youth

Five broad thematic areas of factors associated with medication adherence among HIV-infected youth were identified (Table 2). Each is described in detail below.

**Demographic factors.** Age, sex, and race were inconsistently associated with adherence across studies.<sup>29-33</sup> For example, 1 study found that younger age was associated with poorer adherence;<sup>29</sup> others found no association to either adherence or nonadherence.<sup>31,32</sup> With respect to education level and socioeconomic indicators, being in school was associated with better adherence,<sup>29</sup> whereas having repeated a grade in school and having unstable housing were each associated with poorer adherence to antiretroviral medications among HIV-infected youth.<sup>34</sup>

**Psychosocial factors.** Much of the research on adherence among HIV-infected youths (48%) focused on social and psychologic factors.

a. Family/caregiver. Family and caregiver factors associated with adherence were having an adult other than the biological parent as the primary caregiver (eg, relative or other adult) and higher caregiver education level.<sup>33</sup>

b. Social support. In the studies that tested it, no association was found between social support and adherence.<sup>31,35</sup> However, HIV stigma and discrimination by friends and family were strongly associated with nonadherence, and skipping doses was often attributed to fear that friends and family would discover their HIV status.<sup>36</sup> Similarly, less HIV disclosure overall was associated

**Table 1.** Published Studies Assessing Factors Associated With Adherence Among HIV-Infected Youth

Reference Study Design	Sample Measures	Major Results and Health/Immune Outcomes
Becker et al, 2002 <sup>30</sup> Retrospective analysis of pharmacy claims data on nucleoside analogue reverse transcriptase inhibitor prescription refills to estimate adherence	3788 HIV+, treatment-naive youth (ages 18–24 years)  Adherence defined as proportion of days on which drugs were taken during first 365 days of therapy	Overall adherence rate, 53%. No differences by sex detected in adherence rates ( $P = .30$ ). 26% of individuals were 80% adherent or better. Age was associated with adherence by chi-square examination ( $P = .001$ )
Belzer et al, 1999 <sup>39</sup> Explored correlates of adherence to antiretroviral therapy, including reasons for missing doses, medical and mental health histories, and substance use histories	Surveyed 31 HIV+ youth (ages 13–24 years) from adolescent HIV clinic  One-time 22-question interview administered to participants. Demographics, mental health, medical history, and substance use gleaned from medical records. Data analyzed to explore correlates of antiretroviral adherence	61% reported > 90% compliance with medications in previous 90 days. Youth who believed medications would “most definitely” improve quality of life were more likely to have $\geq 90\%$ adherence at 3 months. Most commonly reported reason for missing medications: having too many pills to take
Comulada et al, 2003 <sup>31</sup> Examined factors associated with antiretroviral drug use and adherence among young HIV+ people, particularly sexual and substance use transmission acts	Recruited 253 HIV+ youth (mean age, 22.9 years) in Los Angeles, San Francisco, and New York HIV/AIDS clinical care sites  2-hour ACASI interview with each participant; participants queried regarding lifetime and recent behavior, including antiretroviral drug use, health status, sexual behavior, substance use, mental health, quality of life, and social support	54% were currently using antiretroviral drugs; 63% of users adhered to 90% of their medications ( $n = 85$ ). Adherers were less likely than nonadherers to have been sexually abused, attempt suicide, report a lower life satisfaction, and use depression withdrawal or self-destructive escape coping mechanisms. Frequency of recent drug use was statistically significant predictor of antiretroviral adherence
Dodds et al, 2003 <sup>37</sup> Analyzed preliminary data from subset of adolescent/young women from mental health–perinatal HIV care project	Recruited 21 perinatally HIV+ women (ages 20–25 years) from obstetric/gynecologic HIV clinics enrolled in Whole Life project  Examined sociodemographic patterns, HIV risk, health status, and mental health status among participants	Central to nonadherence: patient fears about unwanted HIV disclosure, drug adverse effects and their interference with social life, and relationships with partners. Validating and praising small concrete steps proved especially important to help teen mothers  Achieving maximum patient adherence required: developmental framework, patient peer culture, meaningful patient-practitioner relationships, careful medication selection, mental health services, substance abuse treatment, and trauma-informed systems for HIV care  Suggested program services to these ends: case management, developmental and education services, one-stop/colocation of key services, home visits, transportation provisions, childcare, food, patient incentives, engaging patient in conversation, buddy systems/peer advocates, reminder phone calls and letters, and support groups
Hosek et al, 2005 <sup>38</sup> Self-report questionnaire and 1-hour interview. Data examined for correlation with adherence	Recruited 42 HIV+ youth (age 16–25 years; 25 male, 17 female patients) from CORE Center, Chicago, IL  Surveys assessed adherence, perceived reasons for nonadherence, factors to consider before starting a new regimen, cognitive ability, negative affective, and substance use. Regression analysis examined associations to adherence	44% reported being 95% adherent. Only 19% of participants always properly took all medication. 40% of male and 35% of female participants indicated depressive symptoms; 33% of all participants exceeded the cutoff for medium-high trait anxiety. Depression/anxiety and age of first marijuana use were statistically significant predictors of nonadherence ( $P < .05$ ). Most common reason for missing a dose: forgetting

ACASI indicates audio computer-assisted self-interviewing; CI, confidence interval; HIV+, HIV seropositive; OR, odds ratio; PTSD, posttraumatic stress disorder.

**Table 1.** (Continued)

Reference	Sample	Major Results and Health/Immune Outcomes
Study Design	Measures	
Martinez et al, 2000 <sup>34</sup>	Consecutive review of 25 charts of HIV+ youths (ages 13–21 years) from 1/1993 to 5/1998	13/18 (72%) of patients on antiretroviral therapy were nonadherent; 67% of females and 80% of males reported missing doses. Housing instability and length (months) of treatment with antiretroviral medications correlated with nonadherence ( $P < .04$ ). Living situation stability was the most statistically significant correlate of adherence
Retrospective analysis of patient charts	Measures were sociodemographic factors (eg, age, race/ethnicity, sex, housing stability) and health variables (eg, CD4+ count and viral load, length of time on antiretroviral drugs) associated with adherence	
Murphy et al, 2005 <sup>29</sup>	231 HIV+ adolescents (mean age, 18.4 years) infected primarily through sexual behaviors	69% of adolescents reported being adherent. Adolescents in later HIV disease stages were less likely to be adherent. Less alcohol use and being in school were associated with adherence. Median time to nonadherence was 12 months, and failure to maintain adherence was associated with younger age and depression
Longitudinal study of cohort of HIV+ adolescents to investigate long-term antiretroviral therapy adherence and its correlates	Validated self-reported adherence measures by comparison with plasma HIV RNA level; assessed behavioral factors associated with antiretroviral therapy adherence	
Murphy et al, 2003 <sup>28</sup>	114 HIV+ adolescents (ages 12–19 years) prescribed antiretroviral therapy and in REACH Project. All participants infected through risk behaviors	Only 28% of adolescents reported taking all prescribed antiretroviral medications in previous month. Plasma HIV RNA level was associated with self-report of adherence ( $P = .02$ ). Medication-related adverse effects and complications in daily routines accounted for largest proportion of variance. Adherence was tied closely with daily routine; working closely with adolescents to improve their organizational skills may improve adherence
Structured interviews conducted to determine barriers to adherence; principal component factor analysis performed on scores of 19 barrier variables	Main outcome measures were self-report of adherence and barriers to adherence and plasma HIV RNA level	
Murphy et al, 2001 <sup>32</sup>	Recruited 161 HIV+ adolescents (ages 13–18 years) from 13 US cities into REACH Project. All adolescents infected through sexual or injection drug use behaviors	41% reported consistent adherence. 83% reported taking all medications at least "some of the time," but only 50% of these subjects reported full adherence. Strong association between adherence and reduced viral load. CD4+ level $\geq 500$ cells/ $\mu$ L was associated with adherence. Number of drugs prescribed was inversely associated with adherence, with more drugs associated with lower adherence. Higher levels of depression strongly associated with decreased adherence. Adherence was not associated with age, race, or sex
Combination of face-to-face interview, ACASI, laboratory analysis, and medical chart review to find associations between self-reported medication adherence, depression, anxiety, social support, and demographics	Antiretroviral drug adherence investigated. Assessed associations between variables using various statistical methods, including chi-squares, logistic regression, analysis of variance, and Pearson correlation	
Naar-King et al, 2006 <sup>35</sup>	Recruited 24 HIV+ youth (ages 16–24 years) from single clinic site. 79% infected through risk behavior	Self-efficacy and psychologic distress were correlated with adherence. Social support was not, but social support with medications was correlated with self-efficacy. In regression analysis, self-efficacy and psychologic distress were independently related to adherence (accounting for 47% of the variance)
Tested predictors of adherence previously identified in adults among youth (self-efficacy, social support, and psychologic distress)	Self-administered questionnaires measured medication adherence, self-efficacy, social support, psychologic distress, and participant plasma HIV RNA level	
Radcliffe et al, 2006 <sup>41</sup>	Recruited 30 HIV+ youth (ages 18–24 years) from urban pediatric hospital-based HIV clinic	Participants experienced a mean of 6 potentially traumatic events, with HIV diagnosis being traumatic 93% of the time. HIV diagnosis was "biggest, worst experience" 59% of the time. 13% of sample met full criteria for PTSD. Percent of clinic visits kept was correlated with practitioner adherence ratings. No relationship found between adherence and care team connection
Trained interviewers conducted survey to assess demographic characteristics, sense of connection with care team, trauma history, and traumatic stress responses	Participants asked to identify their "biggest, worst experience" and their next "worst" incident or HIV diagnosis. The PTSD Checklist was used to measure stress responses to both above events	

(Continued on next page)

Table 1. (Continued)

Reference Study Design	Sample Measures	Major Results and Health/Immune Outcomes
Rao et al, 2007 <sup>36</sup>  HIV+ adolescents and young adults were asked to participate in focus groups, which explored attitudes and experiences around medication adherence	Recruited 25 HIV+ youth (mean age, 22 years) from young-adult clinic where they received HIV treatment. Most participants infected during sexual contact  Each focus group was recorded and professionally transcribed. Thematic categories were identified and responses coded accordingly. Frequency with which each theme occurred was tabulated	Social factors and HIV stigma represent strong barriers to adherence for youth; 50% of respondents indicated that they skipped doses because of fear that family or friends would discover status. Youthful feelings of "invulnerability" do not seem to be important barriers to HIV medication adherence. 64% of participants indicated side effects did not bother them
Schwartz et al, 2001 <sup>40</sup>  HIV+, REACH program adolescents observed for 24 months, assessed every 3 months. Health history, demographics, and laboratory results obtained via patient interviews, ACASI, and medical records	215 HIV+, antiretroviral therapy-naïve adolescents (aged 12–18 years at entry into REACH) seen at 15 REACH clinical sites  Generalized estimating equations applied to identify associations between demographics, risk behaviors, perceived health, and clinical status with initiation of antiretroviral therapy during first 24 study months	Antiretroviral therapy prescribed for 115 (53%). Statistically significant univariate associations with antiretroviral prescription: lower CD4+ cell count (OR, 1.7; 95% CI, 1.1–2.6), higher plasma HIV RNA level (OR, 2.7; 95% CI, 1.5–5.0), and calendar year of antiretroviral therapy prescription (OR, up to 2.4; 95% CI, 1.1–5.2). Multivariate results: higher plasma HIV RNA level ( $\leq$ 10,000 copies/mL), having a high school diploma/General Education Degree but no further education (OR, 2.7; 95% CI, 1.3–5.5), and patient perception of poor health status (OR, 0.99; 95% CI, 0.98–0.99) were independently associated with antiretroviral therapy
Williams et al, 2006 <sup>33</sup>  Cross-sectional evaluation using Pediatric AIDS Clinical Trials Group (PACTG) 219C study data. Medical/clinical histories and sociodemographics obtained via clinic records, reviews, interviews. Follow-up visits held every 3 months	PACTG 219C participants with self-assessed adherence (n = 772; median age, 14.4 years). All participants infected through perinatal exposure  Obtained and compared information on past antiretroviral therapy, clinical/neurologic diagnoses, CD4+ count, plasma HIV RNA level, and sociodemographics. Age-adjusted logistic regression models measured possible predictors of nonadherence. "Adherent" defined as $\geq$ 95%, measured via self-reporting on medication adherence in the 3 days before the visit	78% reported complete adherence over past 3 days. Variables associated with increased risk of nonadherence: female sex, plasma HIV RNA level, depression, and anxiety. Variables associated with decreased risk of nonadherence: having an adult primary care giver other than a biological parent, primary care giver education level, and CD4+ level

ACASI indicates audio computer-assisted self-interviewing; CI, confidence interval; HIV+, HIV seropositive; OR, odds ratio; PTSD, post-traumatic stress disorder.

with poorer adherence to antiretroviral drug therapy.<sup>37</sup>

c. Substance use. Less alcohol use in the past week<sup>29</sup> and less recent drug use in the previous 3 months<sup>31</sup> were predictive of adherence. Younger age of first marijuana use was associated with poorer adherence.<sup>38</sup>

d. Psychologic/developmental and coping skills. Lower levels of psychologic distress,<sup>35</sup> higher levels of life satisfaction,<sup>31</sup> and higher self-efficacy for adopting medication compliance behaviors<sup>35</sup> were associated with increased adherence. The belief that medication would "most definitely"

improve quality of life was also associated with better adherence.<sup>39</sup>

Depression and depressive symptoms were consistently and strongly associated with nonadherence<sup>29,32,33,38</sup> as were symptoms of anxiety.<sup>31</sup> Nonadherent youth were more likely to have experienced sexual abuse under age 12 years and to have had a prior suicide attempt.<sup>15</sup>

Youthful feelings of "invulnerability," defined as participants feeling invulnerable to the consequences of HIV, were not statistically significantly associated with adherence<sup>36</sup>; however, "concrete" thinking<sup>18</sup> was positively associated

with adherence measures.<sup>38</sup> In general, withdrawal or self-destructive escape coping mechanisms were associated with nonadherence.<sup>31</sup>

e. Sexual risk. Only 1 study examined sexual risk among adherers (n = 85) versus nonadherers (n = 51).<sup>31</sup> In this study, HIV-infected youth adhering to their medications were more likely to have used condoms with recent sexual partners, were less likely to have bartered sex during their lifetime, and were less likely to have had a sexually transmitted disease since learning they were HIV-infected.

**HIV disease factors.** Several disease

**Table 2.** Factors Associated With Adherence or Nonadherence Among HIV-Infected Youth

Patient and Family Factors	Association
<b>Demographic Factors</b>	
Individual patient attributes	Associated with adherence: Being in school <sup>29</sup> Inconsistent or no association with adherence or nonadherence: Age, <sup>29,32</sup> sex, <sup>30-33</sup> race <sup>31,32</sup>
<b>Socioeconomic status</b>	
Socioeconomic status	Associated with nonadherence: Housing instability <sup>34</sup>
<b>Psychosocial Factors</b>	
Family/caregiver	Associated with adherence: Having an adult other than the biologic parent as primary caregiver, <sup>33</sup> higher caregiver education level <sup>33</sup>
Social support	Associated with nonadherence: HIV stigma and discrimination by friends and family (eg, skipping doses out of fear that friends and family will discover HIV serostatus) <sup>36</sup> Inconsistent or no association with adherence or nonadherence: Social support <sup>31,35</sup>
Substance use and coping skills	Associated with adherence: Less alcohol use, <sup>29</sup> less recent drug use (past 3 months) <sup>31</sup> Associated with nonadherence: Depression-withdrawal coping style or self-destructive escape coping style, <sup>31</sup> younger age of first marijuana use <sup>38</sup>
Psychologic/developmental	Associated with adherence: Self-efficacy, <sup>35</sup> higher life satisfaction on the quality-of-life scale, <sup>31</sup> lower levels of psychologic distress, <sup>35</sup> concrete rather than abstract reasoning skills, <sup>38</sup> belief that medication would "most definitely" improve their quality of life <sup>39</sup> Associated with nonadherence: Depressive symptoms, <sup>29,32,33,38</sup> symptoms of anxiety, <sup>33</sup> sexual abuse under age 12 years, <sup>31</sup> prior suicide attempt(s) <sup>31</sup> Inconsistent or no association with adherence or nonadherence: Youthful feelings of "invulnerability" <sup>36</sup>
Sexual risk	Associated with adherence: Less likely to have bartered sex during their lifetime, <sup>31</sup> more likely to have used condoms with recent sex partners, <sup>31</sup> less likely to have had a sexually transmitted disease since learning their serostatus <sup>31</sup>
<b>Disease Factors</b>	
	Associated with adherence: Reduced viral load, <sup>28,32</sup> CD4+ level $\geq 500$ cells/ $\mu$ L <sup>32</sup> Associated with nonadherence: Detectable viral load, <sup>33</sup> later disease stage <sup>29</sup>
<b>Treatment Regimen Factors</b>	
	Associated with adherence: Fewer drugs prescribed, <sup>32</sup> medication-related adverse effects (both physical and psychologic) <sup>28</sup> Associated with nonadherence: Length of treatment with antiretroviral medications, <sup>34</sup> self-assessment of adherence by patient <sup>33</sup>
<b>Practitioner Factors</b>	
	Associated with adherence: Practitioner adherence ratings <sup>41</sup> Inconsistent or no association with adherence or nonadherence: Care team connection <sup>41</sup>

factors related to HIV were associated with adherence, namely undetectable plasma HIV RNA<sup>28,32</sup> and CD4+ count greater than or equal to 500 cells/ $\mu$ L.<sup>32</sup> In contrast, detectable plasma HIV RNA<sup>33,40</sup> and later disease stage<sup>29</sup> were associated with nonadherence.

**Treatment regimen factors.** Reduced regimen complexity (ie, fewer drugs prescribed)<sup>32</sup> was associated with improved adherence. Both physical and psychologic medication-related adverse effects were associated with poorer adherence.<sup>28</sup> Notably, length of antiretroviral

medication treatment (eg, longer term in years)<sup>34</sup> was associated with poorer adherence. Self-assessment of adherence by the patient was also strongly associated with decreased reports of adherence, compared with reports of adherence by a caregiver or medical practitioner.<sup>33</sup>

**Practitioner factors.** Few studies explore practitioner factors in investigating adherence among HIV-infected youth. The only study that examined this relationship<sup>41</sup> found that maintaining regular follow-up care and treatment with a medical practitioner was associated with increased adherence.

### Adherence Interventions With HIV-Infected Youth

Seven intervention studies targeting improved adherence to antiretroviral medications among HIV-infected youth were reviewed (Table 3). Of these, 3 utilized directly observed therapy (DOT), in which participants met with a medical practitioner who administered their HIV medication, and involved a retrospective analysis of chart information.<sup>23,24,42</sup> Two studies applied regimen-related interventions prospectively that ranged in duration from 12 weeks to 96 weeks,<sup>13,43</sup> and 2 studies utilized education and counseling sessions to promote adherence to antiretroviral medications with study periods between 8 weeks and 12 weeks.<sup>44,45</sup>

**Directly observed therapy interventions.** Hospital-based DOT interventions were associated with substantial changes in the plasma HIV RNA level and CD4+ count of participants. All studies that used DOT involved a retrospective analysis of information from a variety of clinical sources, including admitted children's or adolescents' medical charts, electronic medical records, and a clinic laboratory database. Parsons and colleagues,<sup>24</sup> who observed 19 admissions between 2000 and 2003, found the mean plasma HIV RNA level at admission to be  $5.7 \log_{10}$  copies/mL, at discharge to be  $4.7 \log_{10}$  copies/mL, and at 6 months after discharge to be  $5 \log_{10}$  copies/mL. A decrease in plasma HIV RNA level for patients on DOT indicates prior nonadherence when the patient was not under direct supervision. Glikman and colleagues<sup>23</sup> reported a statistically significant decrease in mean plasma HIV RNA level ( $0.8 \pm 0.55 \log_{10}$  copies/mL) for the DOT period; they also reported a rise in mean plasma

**Table 3. Published Studies of Interventions Designed to Enhance Adherence Among**

Reference Study Design	Population
Glikman et al, 2007 <sup>23</sup> Reviewed medical charts of HIV+ patients admitted to Comer Children's Hospital for directly observed therapy. Patients hospitalized for 7 days	9 perinatally infected patients (median age, 13 years), 13 total admissions; 8 patients had been treated with numerous antiretroviral therapy regimens
Lyon et al, 2003 <sup>45</sup> Intervention: 6 biweekly family and youth education sessions; 6 biweekly youth-only education sessions. Devices to increase antiretroviral adherence introduced	23 HIV+ youths (ages 15-22 years) and 23 family members or "treatment buddies"; 18/23 youths completed a group
McKinney et al, 2007 <sup>13</sup> Prospective observational study at 16 sites of 37 therapy-naive, HIV+ children and adolescents	37 therapy-naive HIV+ participants (43% age 14-21 years)
Parsons et al, 2006 <sup>24</sup> Evaluated directly observed therapy of HIV+ children and adolescents with elevated viral loads and nonadherence. Retrospective chart review performed	19 child and adolescent admissions (58% age 13-16 years) included in analysis
Puccio et al, 2006 <sup>43</sup> Pilot—small sample. Patients received free cell phones with local service and reminder phone calls for 12 weeks. Call frequency was tapered at 4-week intervals	8 HIV+ adolescents and young adults (ages 16-24 years) beginning either their initial antiretroviral regimen or a new regimen
Purdy et al, 2008 <sup>42</sup> Retrospective chart review to identify subjects and glean relevant health and adherence information	5 patients (ages 14-19 years; all vertically acquired HIV) identified as having received directly observed therapy for $\geq 4$ contiguous days after $\geq 8$ weeks of a stable antiretroviral regimen
Rogers et al, 2001 <sup>44</sup> Longitudinal study of cohort of adolescents enrolled in TREAT program to observe movement through Stages of Change Model toward acceptance of and adherence to antiretroviral therapy	288 HIV+ adolescents (ages 15-22 years) in REACH program: 147 receiving antiretroviral therapy, 29 receiving nonantiretroviral therapy, 112 no therapy (65 accepted TREAT program)

HIV+ indicates HIV seropositive.

## HIV-Infected Youth

Measures	Results and Health/Immune Outcomes
Demographics, clinical/immune class category, previous/current antiretroviral medications, drug resistance tests, plasma HIV RNA level, and CD4+ cell count and percentage before and after directly observed therapy	Three patterns of change in plasma HIV RNA level were observed over time: (1) drop at the end of the directly observed therapy period, remaining low thereafter; (2) drop at the end of the period, but not sustained; (3) no change during or after directly observed therapy. Plasma HIV RNA level at end of directly observed therapy was lower than at admission in 8 patients (mean standard deviation, decrease of $0.8 \pm 0.55 \log_{10}$ copies/mL)
Baseline participant viral load, CD4+ count, and HIV knowledge compared with same measurements from 3 months after program completion. Survey administered pre-/post-intervention	91% of youths self-reported increased adherence after completing a group. 4 participants experienced a $1 \log_{10}$ reduction in viral load to levels below detection during intervention. 2 participants continued to decline use of antiretrovirals after intervention and demonstrated no decrease in viral load. Participants tested 5 devices and rated multiple alarm watch as best aid. Family/treatment buddies rated overall program highly helpful, citing social support as most valuable. Unanticipated benefit was increase in other health behaviors
Participants observed for $\geq 96$ weeks. Signs, symptoms, plasma HIV RNA level, CD4+ count, and safety laboratory tests measured	32/37 subjects (85%) achieved suppression of plasma HIV RNA level to $< 400$ copies/mL, and 26/37 (72%) maintained sustained suppression at $< 50$ copies/mL through week 96. Median baseline CD4+ count increased by 18%. Pill amount reduction (to once-daily) used as intervention
Differences in CD4+ count and plasma HIV RNA level at admission, before discharge, and 6 months after discharge were evaluated using Wilcoxon signed-ranks test	Mean CD4+ count at discharge (492) and 6 months after discharge (429) were statistically significantly higher than at admission (262) ( $P < .01$ ). Mean plasma HIV RNA level at discharge ( $4.7 \log_{10}$ copies/mL) and 6 months after discharge ( $5 \log_{10}$ copies/mL) were statistically significantly lower than at admission ( $5.7 \log_{10}$ copies/mL) ( $P < .004$ ). Majority of admissions (74%) involved a change in antiretroviral regimen. Directly observed therapy resulted in immediate, sustained (up to 6 months) reduction in plasma HIV RNA level and increase in CD4+ count
Participants received a cell phone with 250 free minutes and \$10 for questionnaires. Calls were received for 12 weeks. Assessment at 4-week intervals to determine perceived intrusiveness and helpfulness of calls and missed medication doses. Assessment done at week 24 with the same questions	(1) 5/8 patients recruited completed the 12 weeks of cell phone reminders; (2) participants not experiencing institutionalization or major chaotic life changes did very well receiving phone calls, did well with adherence to medication doses, and experienced statistically significant decreases in plasma HIV RNA levels that tracked positively with adherence to call reminders; (3) initially, call reminders were reported to be "annoying, but helpful" but by 12-week follow-up, subjects reported calls to be "less annoying"
Retrospective chart review obtained plasma HIV RNA level before and after directly observed therapy intervention	All 5 participants were highly treatment experienced (median, 4 previous antiretroviral regimens), and all had genotypic evidence of resistance to antiretroviral drugs. All were prescribed a twice-daily regimen containing ritonavir-boosted protease inhibitors; 3 patients received more complex regimens because of their specific antiretroviral resistance. 4/5 patients had a decrease in plasma HIV RNA level while on directly observed therapy (ranging from $0.5\text{--}2.46 \log_{10}$ copies/mL; mean, $1.15 \log_{10}$ copies/mL). All patients later exhibited viral rebound
(1) Acceptability evaluated by reaction to program video ( $n = 65$ ); (2) movement across Stages of Change Model assessed by comparing first recorded stage evaluation to last ( $n = 18$ ); (3) acceptance of adherence measured from medical records. Adherence based on self-report, clinical judgment, and suppression of plasma HIV RNA level ( $n = 18$ )	(1) Acceptability of the program: 25% "expressed real approval," 49% "were positive and found it helpful," 25% "noncommittal," and 1% "negative"; (2) Subject movement across Stages of Change Model: 78% ( $n = 14$ ) moved forward, 11% ( $n = 2$ ) no movement, 11% ( $n = 2$ ) regressed; (3) Subject acceptance and adherence to antiretroviral therapy: 2/3 ( $n = 12$ ) accepted and began antiretroviral therapy, and 1/2 ( $n = 6$ ) maintained adherence "most to all of the time"

HIV RNA level when the participants or their caregivers again became responsible for maintaining treatment in the absence of DOT. Purdy and colleagues<sup>42</sup> observed 5 admissions, of which 4 had a decrease in plasma HIV RNA level while receiving DOT (range, 0.5-2.46 log<sub>10</sub> HIV RNA copies/mL; mean, 1.15 log<sub>10</sub> HIV RNA copies/mL). All DOT studies showed that plasma HIV RNA level increased as time after discharge increased, suggesting that hospital-based DOT has a limited effect on adherence among HIV-infected youth, as long-term benefits were not observed.

**Regimen-related interventions.** One of the 2 regimen-related interventions focused on medication scheduling (ie, reduction to once-daily dosing) and evaluated viral load and CD4+ count as outcomes. Sampling 37 therapy-naïve individuals, McKinney and colleagues<sup>13</sup> evaluated the efficacy of a regimen that included emtricitabine, didanosine, and efavirenz. The median CD4+ count at baseline was 310 cells/mL with an increase to 673 cells/mL by week 96 of the intervention, resulting in a gain of approximately 18% and demonstrating successful viral load decreases and suppression over time.

A second study incorporated the use of cell phone reminder calls to assist HIV-infected adolescents to adhere to their antiretroviral therapy.<sup>43</sup> Of the 8 participants recruited, 5 completed the entire 12-week study period of cell phone reminders. Although the intervention technique was reported as “annoying” by participants, the 5 participants who completed the study experienced clinically important decreases in their viral loads (for example, 1 participant had a plasma HIV RNA level of 342,536 copies/mL at baseline and 242 copies/mL at 24-week follow-up).

**Education and counseling interventions.** One of these studies evaluated the efficacy of an 8-week program that involved antiretroviral therapy education via 2 videotapes, information booklets, and a set of 5 audiotapes using the transtheoretical model to increase adherence across stages of change.<sup>44</sup> The video- and audiotapes

followed a newly HIV-infected youth coming to terms with her condition as she joins a support group in which other HIV-infected youth receiving antiretroviral therapy answer questions, discuss difficult issues, and model stage-specific processes. Of the 18 of 112 participants who completed the program, two-thirds initiated antiretroviral therapy, and half self-reported maintaining adherence “most” to “all of the time.” An important limitation of this study was difficulty retaining participants.

Lyon and colleagues had more success in retention of study participants.<sup>45</sup> Initially recruiting 30 pairs of HIV-infected youths between the ages of 15 years and 22 years and a family member or “treatment buddy,” they retained 23 pairs for the final assessment. The program consisted of 12 weeks of education sessions, 6 of which were exclusive to just the HIV-infected youth, and the other 6 of which incorporated all participants. The curriculum focused on the dynamics of HIV; the purpose of antiretroviral therapy; medication choices and managing adverse effects; nutrition, exercise, and alternative treatments; communication with doctors and health care practitioners; and the media.

On alternate weeks, the youths met to discuss issues with medication adherence in a group psychotherapy format. To further help participants adhere to medication, a new device (such as a pillbox, beeper, calendar, multiple-alarm wristwatch, or gym bag) was introduced to the youths at each youth-only session. Upon entry into the program, 43.5% of the 23 HIV-infected youth had a CD4+ count between 200 cells/ $\mu$ L and 499 cells/ $\mu$ L, and the other 56.5% had a count of less than 200 cells/ $\mu$ L. By the end of the 12-week study period, 17.4% had more than 500 CD4+ cells/ $\mu$ L, 30.4% had between 200 cells/ $\mu$ L and 499 cells/ $\mu$ L, 26% had less than 200 cells/ $\mu$ L, and 13% were deceased. In addition to the positive changes in the CD4+ counts, 91% of the study participants self-reported increased adherence to antiretroviral medication as a result of the group education sessions.

## Discussion

Consistent with the literature on HIV adherence among adults<sup>19</sup> and general adherence literature,<sup>27</sup> our review of research on HIV-infected youth suggests that individual demographic factors and readily observable patient characteristics failed to distinguish adherent from nonadherent individuals. No consistent, predictive sociodemographic relationships with adherence to antiretroviral medications emerged. In contrast, psychosocial factors such as depression and anxiety were most consistently associated with nonadherence across studies. Continuing to examine adherence within the broader contextual issues present in the lives of youth is essential to understanding how to improve medication adherence and long-term survival for young people living with HIV.

The most promising strategies for improving treatment adherence among HIV-infected youth involve patient and caregiver education, self-monitoring, peer support, and telephone follow-up. Consistent with adult adherence interventions,<sup>21,22,27,46</sup> multicomponent strategies tended to be most effective in improving poor adherence. A commonly cited reason for nonadherence to medication among youths is “simply forgetting.”<sup>29,38</sup> Interventions that include simple treatment regimens with once-daily dosing<sup>13</sup> seek to address this barrier to adherence.

However, once-daily dosing provides other challenges in a population with adherence difficulty. For example, missing a once-daily dose means 24 hours without medications, whereas missing 1 dose of twice-daily regimens means only 12 hours uncovered. Hosek and colleagues note that nonadherence relates more to difficulty incorporating the medication regimen into patient lifestyle than to regimen complexity itself.<sup>38</sup> Thus, interventions might consider skill building around taking medications during a specific time that is integrated into a routine behavior, such as after brushing one’s teeth or eating breakfast.

Findings suggest that providing DOT, while considered impractical for

all youth because of its cost, might be important for selected adolescents infected with HIV,<sup>10,52</sup> such as those with active substance use disorders. To date, no studies have examined the use of multidisciplinary treatment teams (eg, teams with case managers, physicians, nurses, psychologists) versus physicians alone in working with HIV-infected youth.<sup>47</sup> However, multidisciplinary treatment teams are more successful than physicians alone in providing and implementing successful adherence interventions among adults.<sup>27,48</sup> Future research with HIV-infected youth may benefit from investigating intervention delivery mode (eg, team treatment vs individual treatment).

An estimated 2% to 6% of US youth have a depressive disorder, and approximately 15% have elevated depressive symptoms.<sup>49,50</sup> Among HIV-infected youth, elevated levels of psychologic distress have been documented, with rates of depressive symptoms ranging from 18% to 45%.<sup>15,50</sup> Evidence from studies in adults demonstrates the effectiveness of treating depression as a means of improving adherence.<sup>51,52</sup> Findings that depressive symptoms are strongly associated with nonadherence among HIV-infected youth<sup>29,32,33,39</sup> suggest that treatments for adolescent depression may assist in improving medication adherence. A recent study demonstrated that treating HIV-infected adults with cognitive behavioral therapy for depression and adherence skill building effectively reduced depression over time and improved medication adherence.<sup>53</sup>

Limitations bear mention when interpreting review findings. Given the early stage of research in this field, all relevant studies were included in our review, regardless of methodologic rigor. The few studies conducted to date, small sample sizes, and paucity of research on specific subgroups (eg, gay and lesbian youth, racial or ethnic minority youth) limit generalizability. In addition, studies often presented adherence and nonadherence as opposing or opposite constructs. However, findings suggest that distinguishing between and understanding the differences between these concepts may yield val-

uable insight as to the roles that diverse factors play in adherence and may be especially productive in helping develop new interventions. Thus, differences between adherence and nonadherence should not be reduced but should instead be expanded and each concept thoroughly investigated.

Given the range of complex factors associated with nonadherence, different sets of targeted interventions may be warranted that focus on specific populations of youth (eg, homeless, sexual minorities, substance abusing). Randomized controlled trials are needed that incorporate solid theoretic frames, satisfactory sample sizes, psychometrically sound outcome measures, consistent operationalization of adherence, and better adherence assessment measurements.<sup>22</sup> Cost-effectiveness data to assess the practical value of different adherence interventions in the long-term would be beneficial.<sup>22,54</sup> Finally, because the psychosocial needs of HIV-infected persons are changing to more closely resemble the needs of the chronically rather than the terminally ill individual,<sup>15</sup> investigating how psychosocial issues such as distorted body image, substance use, anxiety, history of childhood sexual abuse, and influence of peer norms relate to antiretroviral adherence may be particularly crucial to promoting long-term survival and quality of life among HIV-infected youth.<sup>15-17,55</sup> Secondary HIV prevention interventions<sup>54,56</sup> may provide useful means of not only reducing HIV transmission through sexual risk taking but also improving health outcomes through the incorporation of strategies to increase antiretroviral adherence.

This review indicates that more research on adherence among HIV-infected youth, as well as more rigorously evaluated interventions, are needed. Maximizing adherence may not only be fundamental to the well being of HIV-infected youth but may also have a far-reaching and broader impact on public health.<sup>12</sup> Nonadherence may lead to drug resistance and cross-resistance that may render HIV treatments ineffective and may be implicated in the emergence of drug-resistant strains of HIV.<sup>9,57,58</sup> Consequently, gaining a

more thorough and contextualized understanding of factors associated with adherence and nonadherence, including individual demographic, social and psychologic, disease-related, treatment-regimen, and practitioner factors, represents an important step in helping people live longer and in intervening to address infectious disease rates. Further culturally tailored, intervention development research for HIV-infected youth is warranted.

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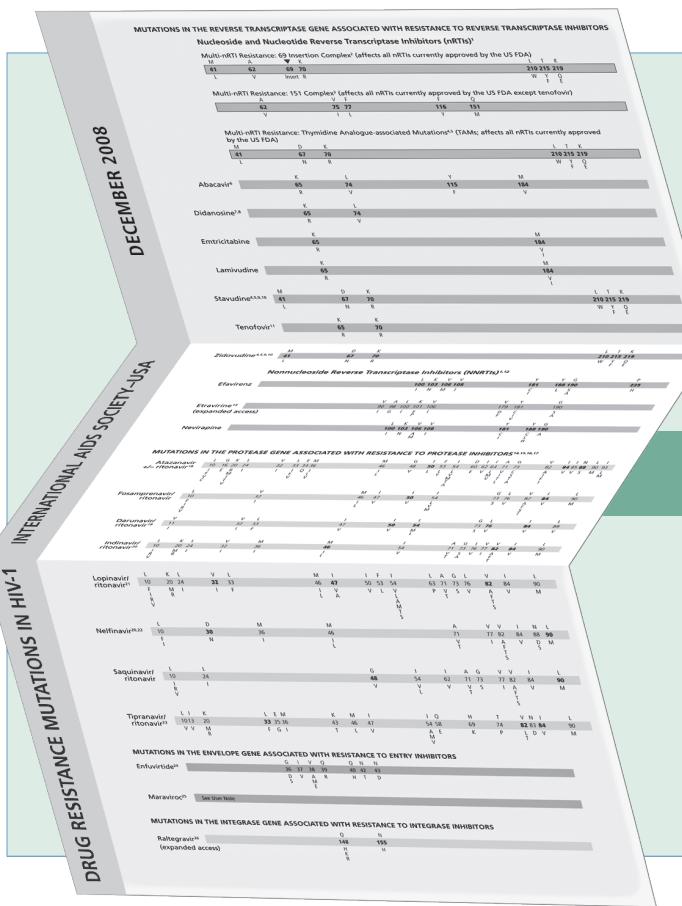
*Top HIV Med.* 2009;17(1):14-25  
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## December 2008 Updated (and Corrected\*) Drug Resistance Mutations Figures

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\*See page 13 for Correction to previous figures



## Cases on the Web



### 2008 YEAR IN REVIEW

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#### **Initial Evaluation of a Patient with a New HIV Diagnosis**

by Michael Melia, MD, and Howard Libman, MD

More than 56,000 people receive an HIV diagnosis in the United States each year, and a substantial number present to primary care physicians for initial management. A systematic approach to the initial evaluation of patients with a recent HIV diagnosis should be adopted owing to the numerous and potentially complex issues that can affect care. This case will help learners identify relevant aspects of the medical history of those with a new HIV diagnosis, select diagnostic and screening tests that should be part of an initial evaluation, plan for antimicrobial prophylaxis for opportunistic infections, and determine necessary and contraindicated immunizations in this population.

#### **Management of Cryptococcal Meningitis in the Antiretroviral Therapy Era: More than Just Antifungals**

by Anuradha Ganesan, MD, and Henry Masur, MD

In many urban areas, one-third of patients presenting with an initial HIV diagnosis have CD4+ counts below 200 cells/ $\mu$ L, and many such patients present with opportunistic infections. This case reviews the epidemiology and major clinical manifestations of cryptococcal infections in HIV-infected patients and discusses an approach to the diagnosis of such infections. Learners will identify preferred treatment strategies for cryptococcal infections using amphotericin B, flucytosine, and azole antifungal drugs, review risk factors for immune reconstitution inflammatory syndrome (IRIS), and distinguish *Cryptococcus*-related IRIS from active cryptococcal infection.

#### **Immune Reconstitution Inflammatory Syndrome in HIV-Infected Patients: Diagnostic and Management Challenges**

by Jaime C. Robertson, MD, and Carl J. Fichtenbaum, MD

Despite the increase in the number of CD4+ lymphocytes and partial recovery of immune responses from starting antiretroviral therapy, some patients experience a clinical deterioration that is believed to be related to the restored ability of the immune system to mount an inflammatory response. This activity provides a comprehensive focus on the diagnosis and management of IRIS as a complication

of antiretroviral therapy. Learners will identify the clinical criteria for the diagnosis of IRIS, examine considerations for starting antiretroviral therapy in HIV-infected patients with opportunistic infections, and identify approaches to managing patients with IRIS.

#### **Issues in the Care of HIV and Hepatitis C Virus—Coinfected Patients: Antiretroviral Pharmacokinetics, Drug Interactions, and Liver Transplantation**

by David L. Wyles, MD

An understanding of the sequelae of chronic hepatitis C virus (HCV) coinfection, such as antiretroviral drug intolerance and decompensated liver disease, is vital to the optimal management of coinfected patients. This presentation explains the impact of hepatic dysfunction on antiretroviral pharmacokinetics and the effect of antiretroviral therapy on the natural history of HCV infection. Learners will also identify unique issues in liver transplantation for end-stage liver disease resulting from HCV coinfection.

#### **HIV-Associated Cognitive Impairment**

by Miguel G. Madariaga, MD, and Susan Swindells, MBBS

HIV-associated cognitive impairment remains a difficult diagnosis that requires the exclusion of several other conditions including psychiatric illness, substance use, opportunistic infection, neoplasia, and other causes of dementia. This case will help learners distinguish between the clinical manifestations of HIV-associated cognitive impairment and those of conditions with a similar presentation. Learners will also consider the choice of appropriate diagnostic tests and clinical management strategies for an HIV-infected patient with this condition.

#### **Treatment of Hepatitis C Virus (HCV) and HIV Coinfection: Selecting Candidates for HCV Therapy and Managing Side Effects of Treatment**

by Melissa K. Osborn, MD

Treatment of HCV is crucial in HIV-coinfected patients to slow progression to cirrhosis and end-stage liver disease. This state-of-the-art activity describes the differences in response to HCV therapy in HIV-coinfected patients compared with HCV-monoinfected patients. Learners will identify candidates for HCV therapy, management of adverse effects of therapy, and treatment options for those who do not respond to peginterferon alfa and ribavirin therapy or who experience recurrence of active infection.

#### **Special Cases in Antiretroviral Therapy Initiation: Focus on Acute HIV and HIV/Hepatitis B Virus Coinfection**

by Charles Hicks, MD, and Elizabeth Reddy, MD

HIV clinicians should be aware of special situations such as acute HIV infection or HIV and hepatitis B virus (HBV) coinfection that may affect the timing of antiretroviral therapy. In this comprehensive activity, learners will compare the benefits and risks of initiating therapy for acute HIV infection and consider the role of resistance testing in such situations. The activity also discusses appropriate choices for therapy in patients with acute HIV or HIV/HBV coinfection and alerts learners to the risks of discontinuing antiretroviral therapy, particularly in HIV/HBV-coinfected patients.

## **Sexual Addiction in an HIV-Infected Patient**

by Edward R. Hammond, MD, MPH, and Glenn J. Treisman, MD, PhD

Persons who engage in a variety of specific sexual practices are at increased risk of acquiring and transmitting HIV. Some of these sexual practices have been associated with sexual addiction, also called paraphilia. Unfortunately, paraphilia in HIV-infected patients often goes undiagnosed and untreated. This fascinating activity describes features of paraphilic behavior and introduces options for its management. Learners will also identify comorbid conditions that could complicate the treatment of paraphilic behavior in HIV-infected patients.

## **Managing Oral Health Problems in People with HIV Infection**

by David A. Reznik, DDS

Late diagnosis of HIV is common, and a substantial portion of new patients with HIV infection receive an AIDS diagnosis. Such patients are more likely to present with oral diseases that are associated with HIV disease progression. This activity discusses common oral lesions that HIV practitioners can address in the absence of a dental health care professional. On completing this activity, learners will be able to explain the association between necrotizing ulcerative periodontitis and advanced HIV disease, discuss the role of biopsy for oral hairy leukoplakia, and differentiate and explain how to manage the 2 most common presentations of oral ulcers in HIV-infected patients.

## **Strategic Use of Antiretroviral Drugs in the Patient with Numerous Treatment Failures and Multidrug Resistance**

by Harry W. Lampiris, MD, and Elvin H. Geng, MD

The use of 2 newer classes of antiretroviral drugs and several newer antiretroviral drugs has led to virologic suppression in many patients in whom this state was previously unattainable. This case focuses on evaluating treatment-experienced, HIV-infected patients and developing optimal treatment regimens using recently available antiretroviral drugs. Learners will be able to identify key mutations associated with resistance to nucleoside and nonnucleoside analogue reverse transcriptase inhibitors, identify genotypic and phenotypic predictors of resistance and cross-resistance among HIV protease inhibitors, and discuss strategic approaches to using new antiretroviral drugs in preexisting drug classes as well as those in new classes.

## **Syphilis in the HIV-Infected Patient**

by Jeanne M. Marrazzo, MD, MPH

The incidence of syphilis has increased dramatically among HIV-infected persons in the United States. Diagnosing this ancient dis-

ease is complicated by the fact that many cases of syphilis manifest only as reactive serology. Even when symptoms are present, they can be diverse. Completing this activity will enable learners to describe an approach to routine screening for sexually transmitted diseases in the HIV-infected patient, interpret the significance of a reactive nontreponemal serologic test for syphilis, and determine the management of latent syphilis in the HIV-infected patient.

## **Using Biomedical Prevention as Part of HIV Prevention**

by Raphael J. Landovitz, MD

The use of postexposure prophylaxis (PEP) after sexual exposure to HIV has been recommended by the Centers for Disease Control and Prevention and is endorsed by many state, national, and international health organizations. After studying this presentation, learners will be able to describe the appropriate use of PEP after sexual exposure to HIV, identify considerations for creating strategies to avoid HIV infection in high-risk, HIV-seronegative patients, list the signs and symptoms of acute HIV seroconversion, and discuss what is known about preexposure prophylaxis (PrEP) and its use.

## **HIV-Associated Dyslipidemias: 2008 Edition**

by Roger J. Bedimo, MD

Arguably, dyslipidemias are among the most prevalent and important of the HIV-associated metabolic complications because of their relationship to cardiovascular disease. After completing this popular activity, substantially revised for 2008, learners will be able to describe risk factors for dyslipidemias in HIV-infected patients, determine management strategies for HIV-infected patients with dyslipidemias, identify potential interactions between antiretroviral drugs and statin drugs, and describe possible adverse reactions to combination lipid-lowering therapy using statin and fibrate drugs.

## **COMING IN WINTER 2009!**

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