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Announcement

Change the Name, but not the Letters—New Directions in Education and Care for the IAS–USA

To Our Audience:

To reflect an important expansion of its mission, the IAS–USA is changing its name—but not its letters.

When the International AIDS Society–USA was formed in 1992 to support improved AIDS care with rigorous, balanced, and unbiased education, the organization’s name was chosen almost as an afterthought. I was then the president of a completely separate organization, the International AIDS Society (IAS), then, as now, a European-based body. Over the years, the IAS and IAS–USA have accommodated to this awkward name game, although many of our IAS–USA panelists and speakers have gotten used to board members correcting their use of the “wrong” organizational name with a whispered or shouted “USA” to set the record straight. In contrast and adding some confusion, the IAS–USA is primarily an American, not international, body (though its global reach, especially through guidelines panels, is increasing). And it is not a true society; there are no members, just our dedicated staff, volunteer Board of Directors, and the impressive members of our Core Faculty.

Leaders of the IAS–USA regularly considered changing the organization’s name. But as so many professionals know and respect the IAS–USA through our educational programs, journal, and guidelines on antiretroviral therapy and drug resistance testing, the leadership has never felt an urgency to do so—until now.

The IAS–USA board has appreciated the dramatic pace of drug development for the treatment of other viral infections, particularly hepatitis B and C viruses, and the similarity in providing care to patients infected with those viruses as with HIV itself. We see a growing need, and important contributions we can make, in the education required to support the care of patients with these other viral infections. The IAS–USA has already initiated new educational programs to that end—including the renaming of this journal to Topics in Antiviral Medicine—and soon will announce more.

Taking the next, logical step to align the organization’s name with the broader mission, we will henceforth be known as the “International Antiviral Society–USA”—for short, IAS–USA! Our expanded mission is as follows:

The mission of the International Antiviral Society–USA is to improve the treatment, care, and quality of life for people with HIV or other viral infections through high-quality, relevant, balanced, and needs-oriented education and information for practitioners who are actively involved in medical care for people with viral infections.

This name change will be welcomed, we think, by our friends and colleagues in the IAS, as it clarifies our separate yet complementary structures and missions. But it is our change of mission, more than name, that is truly momentous. We possess much of the knowledge and a growing set of tools to improve the outcome of chronic viral infections affecting millions worldwide. With this name change, we signal our commitment to offer to a broader universe of practitioners what we have long offered our colleagues in HIV medicine: high-quality, relevant, needs-oriented, and balanced educational programs.

The International Antiviral Society–USA looks forward to this fruitful new chapter.

Paul A. Volberding, MD
Founding Chair
IAS–USA Board of Directors

Dr Volberding is professor of medicine and vice-chair of the department of medicine at the University of California San Francisco. He is also chief of the medical service at the San Francisco Veterans Affairs Medical Center.

We welcome our new viral hepatitis advisory panel, an impressive group of experts who are already deep into planning our educational programs addressing hepatitis B and C viruses. The panel consists of:

Raymond T. Chung, MD
Harvard Medical School

Charles W. Flexner, MD
The Johns Hopkins University

Marshall J. Glesby, MD, PhD
Weill Cornell Medical College

Susanna Naggie, MD
Duke University

Marion G. Peters, MD
University of California San Francisco

Michael S. Saag, MD
The University of Alabama at Birmingham

Robert T. Schooley, MD
University of California San Diego

Kenneth E. Sherman, MD, PhD
University of Cincinnati

David L. Thomas, MD, MPH
The Johns Hopkins University

David L. Wyles, MD
University of California San Diego
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Continuing Medical Education Credit
Educational Programs of the International Antiviral Society–USA
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Guidelines for Authors and Contributors

Available Online (www.iasusa.org/pub)

HIV Disease in the Caribbean
Jean William Pape, MD
The following article in this issue is associated with CME credit:

Instructions

This journal-based continuing medical education (CME) activity provides a review of retention in HIV care. To complete the activity, the learner is instructed to:

- Read the article
- Review a selection of the references
- Reflect on how the information might be applied to the clinical practice
- Take the posttest
- Complete the CME claim form and send it to the IAS–USA office.

Learning Objectives

Upon completion of this activity, learners will be able to describe results of recent research on retention in HIV care and the potential clinical implications for their HIV-infected patients.

Accreditation Statement

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

The IAS–USA designates this journal-based CME activity for a maximum of 1.5 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Intended Audience

This activity is intended for physicians involved in the care of patients infected with HIV or other viruses. It is also relevant to nurse practitioners, physician assistants, nurses, and other health professionals who provide care for people with viral diseases.

Conflicts of Interest

IAS–USA policy requires that the IAS–USA resolve any real or apparent conflict of interest that may influence the development, content, or delivery of its educational activity prior to the activity’s being delivered to learners. The IAS–USA has several mechanisms for resolving conflicts of interest in educational activities. If the conflict of interest cannot be resolved through these mechanisms, the party will be removed from the activity.

Dr Giordano has no relevant financial affiliations to disclose.

Posttest Questions

Check the box next to the single best answer to each of the questions below. To earn CME credit, you must receive a passing score of 80% or more correct.

1. Which of the following new patients to your clinic is most likely to have a problem with retention in HIV care?
   - A. A 33-year-old, asymptomatic, antiretroviral therapy–naive man with a CD4+ cell count of 380/µL
   - B. An HIV-infected person who just was admitted to the hospital with cryptococcal meningitis
   - C. A person who is transferring care to your clinic and whose partner is HIV-infected

2. The Health Resources and Services Administration HIV/AIDS Bureau (HRSA-HAB) standard for retention in HIV care requires:
   - A. At least 1 visit each quarter-year
   - B. At least 3 visits per year, with the first and last visits at least 90 days apart
   - C. At least 2 visits per year, with the first and last visits at least 90 days apart
   - D. Fewer than 25% missed visits over 1 year

3. Which strategy will likely be the most effective in helping a homeless patient stay in care?
   - A. Educating the patient about the importance of HIV care and antiretroviral therapy
   - B. Assisting the patient in meeting his housing needs
   - C. Encouraging and motivating the patient to stay in HIV care
   - D. Withholding antiretroviral therapy until the patient makes at least 3 appointments in a row

4. A patient’s problem with retention in care is most likely to be solved by:
   - A. The physician
   - B. The patient
   - C. A case manager
   - D. A collaboration between the patient and care team

5. Which of the following is an example of a structural barrier to HIV care?
   - A. Side effects from antiretroviral therapy
   - B. Clinic hours limited to 2 days per week
   - C. Heavy “crack” cocaine use
   - D. Low trust in a health care practitioner

This CME activity is offered from March 25, 2011, to March 25, 2012. Participants who receive a passing score on the posttest and submit the registration and evaluation forms are eligible to receive credit. Physicians (MDs, DOs, and international equivalents) may receive CME credit for completing this activity. Nonphysician health care practitioners will receive a certificate of attendance.
To receive CME credit, please complete the posttest, participant information, and evaluation forms and return all to the IAS–USA.

### Participant Information

Number of CME credits I am claiming (maximum 1.5): __

First Name ____________________      MI _____      Last Name ____________________

Address (Please check one: ___ Home ___ Work)

Address 2nd Line

City ____________________      State/Province ____________________

Postal Code ________      Country ____________________

Degree or License (MD, RN, PA, none, etc) ____________________

Institution or Organization ____________________

Telephone ( ___Home ___Work) (Facsimile)

E-mail address to receive CME certificate ( ___Home ___Work)

The amount of time (in hours) I spent on reading the article, reviewing the references, reflecting on how the information might be applied to the practice, and taking the posttest was:

☐ ≤ 1 ☐ 1.5 ☐ 2 ☐ 3 ☐ Other _____

### Evaluation

Please complete the following evaluation form for the *Topics in Antiviral Medicine* article for which you are currently claiming CME credit:

<table>
<thead>
<tr>
<th></th>
<th>Excellent</th>
<th>Very Good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
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<tr>
<td>Content and presentation of article</td>
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<td>Value in fulfilling learning objectives</td>
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<tr>
<td>Value to your practice/responsibility</td>
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<td>Freedom from commercial bias</td>
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Please list 3 specific measurable changes you will make in your practice based on the information presented in the article:

1. __________________________________________________________________________________________________________________
2. __________________________________________________________________________________________________________________
3. __________________________________________________________________________________________________________________

Which parts of this journal-based CME activity could have been improved?

_______________________________________________________________________________________________________________________
_______________________________________________________________________________________________________________________

Other comments (please feel free to comment on any aspect of *Topics in Antiviral Medicine*):

_______________________________________________________________________________________________________________________
_______________________________________________________________________________________________________________________

Fax or mail this page along with the completed posttest to:

IAS–USA
425 California Street, Suite 1450
San Francisco, CA 94104-2120
Fax: (415) 544-9401
Perspective

Vitamin D and HIV: Letting the Sun Shine In

Vitamin D is important for cell growth, immunity, and metabolism. Deficiency has classically been associated with rickets and decreased bone density and more recently with increased risk and severity of autoimmune diseases, cancers, myocardial infarction, diabetes, and infectious diseases. How vitamin D can affect these diverse conditions is the subject of much research. The active form of vitamin D (vitamin D₃) has been implicated recently in an intracellular process known as autophagy. In addition to its role in maintaining cellular homeostasis during conditions of stress, autophagy plays an important role in the control of many intracellular microorganisms including Mycobacterium tuberculosis. Recent work has identified that HIV-1 reduces autophagy during permissive infection and that agents that induce autophagy, including vitamin D₃, can inhibit HIV-1 replication. These findings help provide a biological explanation for the increased risk of more rapid disease progression observed in HIV-infected persons with low levels of vitamin D or with genetic variants within the vitamin D receptor that alter binding to vitamin D. Controlled trials are needed to determine the potential for therapeutic benefit of vitamin D supplementation in HIV disease. This article summarizes a presentation by Stephen A. Spector, MD, at the IAS–USA continuing medical education program held in Chicago in April 2010.

Vitamin D is important for cell growth, immunity, and metabolism, and vitamin D deficiency is common in developed as well as developing countries. Despite much research, there is still disagreement as to the optimal level of vitamin D needed for health. 25-hydroxyvitamin D is the metabolite usually measured in serum, with lower limits of “normal” considered to be between 20 nmol/L and 38 nmol/L. However, optimal bone health may require levels of at least 50 nmol/L to 80 nmol/L (20–32 ng/mL) in adults. Vitamin D deficiency is classically associated with rickets, which still occurs in developed countries and remains an important problem in resource-poor countries, and with decreased bone mineral density. It is also associated with increased risk and severity of bone diseases, autoimmune disease, cancer (of the colon, prostate, and breast), myocardial infarction, infectious diseases, and possibly diabetes. Evidence indicates that vitamin D deficiency is also associated with increased risk of HIV infection and disease progression.

Vitamin D Sources

Lanolin in the skin is converted to 7-dehydrocholesterol, which is converted to pre–vitamin D with exposure to ultraviolet (UV) rays from the sun. Pre–vitamin D enters the circulation and is metabolized to 25-hydroxyvitamin D, the major circulating form of the vitamin (which has a circulating half-life of approximately 15 days). It is subsequently converted to the active form, 1,25-dihydroxyvitamin D₃ (called vitamin D₃), in the kidneys. In addition to exposure to sunlight, vitamin D sources include natural foods such as salmon and other “oily” fish, cod liver oil, shiitake mushrooms, and egg yolk, as well as fortified foods and vitamin supplements (Table 1).

The main factors affecting an individual’s vitamin D status are the extent of sunlight exposure, degree of skin pigmentation, use of sunscreen (with sun protection factor [SPF] ≥ 8), latitude and season of the person’s locale, time spent outdoors, use of protective clothing, body mass and percentage of fat (which are inversely related to vitamin D levels), diet (specifically the intake of fish oil, oily fish, and foods with vitamin D supplementation), and vitamin D supplementation. Persons with HIV infection frequently have low vitamin D levels. Moreover, patients treated with nonnucleoside reverse transcriptase inhibitors and protease inhibitors are at increased risk of vitamin D deficiency. Thus, vitamin D deficiency is common in HIV-infected persons regardless of treatment status, viral load, or CD4+ lymphocyte count.

Vitamin D and Autophagy

In 1903, Niels Ryberg Finsen was awarded a Nobel Prize in Medicine and Physiology in part for showing that extensive exposure to sunlight was frequently effective in treating “lupus vulgaris,” (ie, cutaneous tuberculosis [TB]). This effect is now known to be associated with the role of vitamin D in autophagy, a critical process in cell death and survival. Under normal conditions involving infection with many intracellular pathogens, the organism is taken into an endosome that joins with an autophagosome in the cytoplasm of a macrophage. The autophagosome fuses with a lysosome, acidifying the autophagosome to form an autolysosome; the autolysosome exerts antimicrobial activity and kills the microorganism.

In latent Mycobacterium tuberculosis infection, however, the organism impairs the recruitment of hepatocyte growth factor–regulated tyrosine kinase substrate (Hrs), which plays a central role in late endosome sorting and autophagosomal maturation (Figure 1). This effect leads to the inhibition of autophagy and thus, the retention of live organisms in autophagosomes. Under such conditions, autophagy in cells can be induced by certain means—for example, through cell starvation,
by drugs, and from environmental stress—so that the autophagosome containing the bacteria fuses with the lysosome, forming the autolysosome and resulting in bacterial killing.

Autophagy is often referred to as programmed cell death-2 (PCD-2), in distinction to apoptosis (which is considered programmed cell death-1, or PCD-1), although some believe that once cells are programmed for death, autophagy and apoptosis are indistinguishable. Under conditions of infection or other stress, cells proceed down one of the PCD pathways. The apoptosis pathway invariably leads to cell death. However, the autophagy pathway is primarily involved in processes of adaptation and survival through the recycling of cytoplasmic proteins and organelles in an attempt to promote cell survival and function. Too much or too little autophagy in response to challenges can result in cell dysfunction and eventually cell death.

In addition to playing a role in innate immunity by clearing or destroying intracellular organisms, autophagy is important in adaptive immunity by assisting with major histocompatibility complex class I and II antigen presentation. Microorganisms under the control of autophagy include numerous bacteria, such as Mycobacterium tuberculosis, and viruses, including Dr. Spector and colleagues believe, HIV-1 (Table 2).

Vitamin D and HIV

There is growing recognition of an association between vitamin D deficiency and the pathogenesis and course of HIV disease. Vitamin D deficiency is common in HIV infection. It is present in 25% to 75% of infected persons and has been associated with more rapid disease progression. Infants born to HIV-infected women with vitamin D deficiency are at increased risk of infection and have decreased survival.

Persons in resource-limited regions often have low vitamin D levels. In addition, darkly pigmented skin reduces the amount of UV light available in the skin for production of pre–vitamin D. Numerous studies of black people in the United States and Africa have shown an increased risk of vitamin D deficiency, suggesting that insufficient levels of vitamin D may be one of several other risk factors contributing to the severity of HIV disease in persons living in many developing countries.

A number of studies have indicated associations between low vitamin D levels and HIV disease. One such study performed in white injection drug users with HIV infection in Spain showed that persons with vitamin D receptor variants associated with reduced vitamin D binding (ie, people homozygous for the BB allele) had a statistically significantly more likely to have a CD4+ cell count less than 200/µL (HR, 1.25-dihydroxyvitamin D₃ binding to the vitamin D receptor (VDR), which promotes the formation of the PI3KC3 kinase complex and leads to autophagosome elongation and subsequent fusion of the autophagosome with a lysosome. In the second pathway, after binding of 1,25-dihydroxyvitamin D₃ to the VDR, there is upregulation of the antimicrobial peptide cathelicidin, resulting in the fusion of autophagosomes with lysosomes. The induction of autophagy through both pathways ultimately leads to the elimination of microorganisms such as Mycobacterium species.

Table 1. Dietary, Supplemental, and Pharmaceutical Sources of Vitamin D₂ and Vitamin D₃

<table>
<thead>
<tr>
<th>Source</th>
<th>Approximate Vitamin D Content</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Natural Sources</strong></td>
<td></td>
</tr>
<tr>
<td>Salmon</td>
<td>600–1000 IU of vitamin D₁</td>
</tr>
<tr>
<td>Fresh, wild (3.5 oz)</td>
<td>100–250 IU of vitamin D₁ or D₂</td>
</tr>
<tr>
<td>Fresh, farmed (3.5 oz)</td>
<td>300–600 IU of vitamin D₁</td>
</tr>
<tr>
<td>Canned (3.5 oz)</td>
<td></td>
</tr>
<tr>
<td>Sardines, canned (3.5 oz)</td>
<td>300 IU of vitamin D₁</td>
</tr>
<tr>
<td>Mackerel, canned (3.5 oz)</td>
<td>250 IU of vitamin D₁</td>
</tr>
<tr>
<td>Tuna, canned (3.6 oz)</td>
<td>230 IU of vitamin D₁</td>
</tr>
<tr>
<td>Cod liver oil (1 tsp)</td>
<td>400–1000 IU of vitamin D₁</td>
</tr>
<tr>
<td>Shiitake mushrooms</td>
<td>100 IU of vitamin D₁</td>
</tr>
<tr>
<td>Fresh (3.5 oz)</td>
<td>1600 IU of vitamin D₂</td>
</tr>
<tr>
<td>Sun-dried (3.5 oz)</td>
<td></td>
</tr>
<tr>
<td>Egg yolk</td>
<td>20 IU of vitamin D₁ or D₂</td>
</tr>
<tr>
<td>Exposure to sunlight, ultraviolet B radiation (0.5 minimal erythemal dose)</td>
<td>3000 IU of vitamin D₁</td>
</tr>
<tr>
<td><strong>Fortified foods</strong></td>
<td></td>
</tr>
<tr>
<td>Fortified milk</td>
<td>100 IU/8 oz, usually vitamin D₁</td>
</tr>
<tr>
<td>Fortified orange juice</td>
<td>100 IU/8 oz vitamin D₁</td>
</tr>
<tr>
<td>Infant formulas</td>
<td>100 IU/8 oz vitamin D₁</td>
</tr>
<tr>
<td>Fortified yogurts</td>
<td>100 IU/8 oz, usually vitamin D₁</td>
</tr>
<tr>
<td>Fortified butter</td>
<td>50 IU/3.5 oz, usually vitamin D₁</td>
</tr>
<tr>
<td>Fortified margarine</td>
<td>430 IU/3.5 oz, usually vitamin D₁</td>
</tr>
<tr>
<td>Fortified cheeses</td>
<td>100 IU/3 oz, usually vitamin D₁</td>
</tr>
<tr>
<td>Fortified breakfast cereals</td>
<td>100 IU/serving, usually vitamin D₁</td>
</tr>
<tr>
<td><strong>Supplements</strong></td>
<td></td>
</tr>
<tr>
<td>Prescription</td>
<td></td>
</tr>
<tr>
<td>Vitamin D₂ (ergocalciferol)</td>
<td>50,000 IU/capsule</td>
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<tr>
<td>Drisdol (vitamin D₃) liquid supplements</td>
<td>8000 IU/mL</td>
</tr>
<tr>
<td>Over the counter</td>
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</tr>
<tr>
<td>Multivitamin</td>
<td>400 IU vitamin D (D₂ or D₃)</td>
</tr>
<tr>
<td>Vitamin D₁</td>
<td>400, 800, 1000, and 2000 IU</td>
</tr>
</tbody>
</table>

Adapted from Holick.²
The viral products released by HIV-infected CD4+ lymphocytes (eg, gp120) induce programmed cell death of uninfected lymphocytes. In fact, during acute infection, bystander lymphocytes are killed more rapidly than infected cells. Although programmed cell death through apoptosis has been the mechanism most commonly described, recent studies suggest that autophagy may play an important role in bystander CD4+ cell death.19-21

In contrast to CD4+ lymphocytes that are killed during HIV-1 infection, infected macrophages are productively infected by HIV-1 but not killed by the virus. Based on Dr Spector and colleagues’ recent laboratory findings, it appears that HIV infection of macrophages and CD4+ T lymphocytes results in a downregulation of autophagy that permits viral replication but also allows sufficient autophagy for cell survival.22

Regarding other potential effects of autophagy in HIV disease, Spector and Zhou hypothesize that toxins produced by HIV replication in microglial cells (eg, viral products, neurotoxins, and cytokines) cause increased autophagic dysfunction and eventually cell death of neurons, which plays a role in HIV neurocognitive impairment.23 This premise is supported by postmortem findings that brains of patients with HIV encephalopathy contain higher levels of indicators of autophagy than do those of HIV-seronegative persons or HIV-infected persons without HIV encephalopathy.24 These findings suggest that aberrant autophagy may be important in the pathogenesis of HIV-associated neurocognitive disorders.

It thus appears that HIV controls autophagy in infected macrophages and, to some extent, in infected lymphocytes. That is, the virus, by altering autophagy within the cells, allows the lymphocyte to survive longer than uninfected bystander cells undergoing programmed cell death from viral products. Moreover, the drug rapamycin, which induces autophagy (via inhibition of the mammalian target of rapamycin [mTOR] pathway), inhibits HIV replication in monocytes.22 Similarly, calcitriol, the active form of vitamin D3, can also inhibit viral replication.

Figure 2. Association of vitamin D status with HIV disease progression (left) and all-cause mortality (right) in HIV-infected women in Tanzania. Shaded areas represent confidence intervals. Adapted from Mehta et al.16

Potential Effects of Vitamin D on HIV-1 Infection

The viral products released by HIV-infected CD4+ lymphocytes (eg, gp120) induce programmed cell death of uninfected lymphocytes. In fact, during acute infection, bystander lymphocytes are killed more rapidly than infected cells. Although programmed cell death through apoptosis has been the mechanism most commonly described, recent studies suggest that autophagy may play an important role in bystander CD4+ cell death.19-21

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of decreased bone mineral density in HIV disease.25 A study of vitamin D as supplementary treatment for TB in HIV infection showed no benefit, although the dose used in the study (100,000 IU of cholecalciferol at baseline, 5 months, and 8 months) is considered likely to be too low to provide a therapeutic response.26

In addition to improved bone health, the potential benefits of vitamin D supplementation in HIV disease may include improved control of HIV replication, increased CD4+ cell count, slower rate of disease progression, improved control of opportunistic infections, decreased risk of HIV-related neurocognitive impairment, and improved overall survival. It remains unclear what the optimal dosage of vitamin D supplementation might be to provide some level of benefit for prevention or treatment of HIV or other infectious diseases. Current recommended dietary allowances (RDA) of vitamin D are 600 IU for persons 1 year to 70 years old and 800 IU for individuals older than 70 years. An adult therapeutic dose of cholecalciferol could be as high as 10,000 IU daily. Controlled clinical trials are needed to determine the optimal dosage of vitamin D supplementation and its potential benefits for HIV-infected persons.

Presented by Dr Spector in April 2010. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Spector in March 2011.

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

References


**Dermatologic Manifestations of HIV Infection in Africa Resource Card**

Based on the *Topics in HIV Medicine* article from February/March 2010, this folding card is available on request by visiting www.iasusa.org. Included are brief descriptions of selected dermatologic manifestations, along with their differential diagnoses and treatment options.
Established in 1992, the IAS–USA is a not-for-profit, viral diseases education organization. The mission of the IAS–USA is to improve the treatment, care, and quality of life for people with HIV or other viral infections through high-quality, relevant, balanced, and needs-oriented education and information for practitioners who are actively involved in medical care for people with viral infections. The organization's educational activities are particularly intended to bridge clinical research and patient care.

Continuing Medical Education Courses
IAS–USA CME course announcements are paperless. Please watch for e-mail updates, and visit the IAS–USA Web site at www.iasusa.org for general course information, agendas, and online registration. Early registration is strongly recommended. These live activities have been approved for AMA PRA Category 1 Credit™.

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

Spring 2011 Full-Day HIV Courses

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

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

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

Washington, DC
Wednesday, May 4, 2011
Capital Hilton

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

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

Management of Hepatitis C Virus in the New Era: Small Molecules Bring Big Changes
Part of the new IAS–USA focus on the management of viral hepatitis infection, this effort will include half-day, small-group, intensive CME workshops and a full-day CME course presented by leading experts in viral hepatitis.

Spring 2011 Half-Day Intensive Viral Hepatitis Workshops

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

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

Washington, DC
Tuesday, May 3, 2011
Capital Hilton

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

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

Spring 2011 Full-Day Viral Hepatitis Course

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

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

For information about any of these programs, please contact the IAS–USA.
Phone: (415) 544-9400 • Fax: (415) 544-9402 • E-mail: Registration2011"at"iasusa.org • Web site: www.iasusa.org
Perspective

Retention in HIV Care: What the Clinician Needs to Know

Poor retention in HIV disease care is a common, modifiable risk factor associated with poor outcomes, including higher rates of antiretroviral therapy failure, increased HIV transmission risk behaviors, and worse survival. Predictors of poor retention include younger age, female sex, racial or ethnic minority status, low socioeconomic status, no usual source of health care, less advanced HIV disease, fewer non-HIV-related comorbidities, and greater unmet psychosocial needs. Thus far, there have been few published randomized trials of interventions to improve retention. The fact that most clinics are understaffed and underresourced in a flat funding environment raises serious questions about the translation, dissemination, and sustainability of interventions found to be successful in the research setting. Efforts to improve retention in care should incorporate informational, motivational, and behavioral skills components. Practical steps can be taken by clinics to improve retention. This article summarizes a lecture by Thomas P. Giordano, MD, MPH, at the 13th Annual Clinical Conference for the Ryan White HIV/AIDS Program held in Washington, DC, in August 2010.

Retention in HIV care is a modifiable risk factor that profoundly affects outcomes of HIV disease at the individual and population levels. It is clear that any test-and-treatment strategy is not going to be effective unless strong attention is paid to linkage to and retention in care. As stated recently: “Significant barriers impede the efficient movement of a patient infected with HIV from diagnosis to care. . . . As with voluntary testing, a public health-systems research agenda will be needed to define efficient and effective means of entering and retaining patients in care.”

From the clinic perspective, retention also affects quality of care measures, including those used by the Health Resources and Services Administration (HRSA) HIV/AIDS Bureau (HAB) and HIVQUAL (a national project for HRSA grantees to build quality improvement). Retention in care will also impact the provider’s and the clinic’s productivity and efficiency. Fortunately, HIV care clinicians can effect substantial changes in retention in care.

Magnitude of the Problem

Findings in several studies illustrate the extent of the problem in retaining patients in HIV care. The HCSUS (HIV Cost and Services Utilization Study), a landmark HIV health services study performed in the late 1990s, found that one-third to two-thirds of persons infected with HIV in the United States were not in regular care, with half of these persons knowing their HIV serostatus. A Centers for Disease Control and Prevention (CDC) study showed that 17% to 40% of persons who knew their HIV serostatus were not in regular care. A study in British Columbia found that 69% of 554 nonaccidental deaths evaluated from 1997 to 2001 were HIV related; among the persons dying of HIV-related causes, the estimated median proportion of time receiving antiretroviral therapy before death was 20%, and more than 50% were not taking antiretroviral therapy at the time of death. The ARTAS (Antiretroviral Treatment Access Study) showed that 40% of patients newly diagnosed with HIV infection did not see an HIV care practitioner within 6 months of diagnosis, and approximately 50% did not see a practitioner during both the first and second 6-month intervals after diagnosis.

Impact on Outcomes

Numerous studies describe the adverse impacts of poor retention in care on patient outcomes. In particular, poor retention in care is associated with the following outcomes:

- Decreased likelihood of receiving antiretroviral therapy
- Higher rates of antiretroviral therapy failure
- Increased HIV transmission risk behavior
- Increased hospitalization rates
- Worse survival

An example of poorer outcome associated with initial poor retention is provided by a study using nationwide Veterans Affairs data for patients who initiated antiretroviral therapy in the late 1990s. Only patients who had at least 1 visit and remained alive during the first year after receiving their antiretroviral therapy prescriptions were included in the analysis. Among 2619 such patients, 64% (n = 1685) had an HIV care visit in each of 4 quarters during the first year, 18% (n = 479) in each of 3 quarters, 11% (n = 286) in each of 2 quarters, and 6% (n = 169) in only 1 quarter. Patients with greater initial retention in care had the greatest survival over 5 years of follow-up, and patients with the worst initial retention had the poorest survival (Figure 1). After adjustment for other risk factors (age, race or ethnicity, baseline CD4+ cell count, antiretroviral therapy use, hepatitis C virus [HCV] coinfection, non–HIV-related comorbidities, excessive alcohol use, hard-drug use, and social instability), the hazard ratio (HR) for death compared with patients who had
A visit in each quarter was 1.41 ($P < .01$) for those with visits in 3 quarters; 1.68 ($P < .001$) for those with visits in 2 quarters; and 1.94 ($P < .001$) for those with a visit in 1 quarter. Patients in the group with the worst retention had nearly twice the risk of death as those with the best initial retention in care.

**Predictors of Poor Linkage and Retention**

Predictors of poor linkage to and poor retention in HIV care include demographic, disease severity, psychosocial, and ancillary services use factors (Table 1). An example of difficulties in relinking with and staying in care is provided by a recent study of patients’ accessing of antiretroviral therapy after release from prison in Texas. In Texas, HIV-infected inmates are released with a 10-day supply of antiretroviral drugs. Among 1215 HIV-infected persons released from prison between 2004 and 2007, the proportion with antiretroviral therapy prescriptions filled by 10 days was approximately 5%, increasing to only approximately 18% at 30 days, and 50% at 60 days.\(^8\)

Retention in care is more likely when patients are engaged in the care process. As shown in the HRSA Special Projects of National Significance (SPNS) Outreach Initiative studies (a group of prospective, nonrandomized intervention studies), baseline engagement in care predicts, but not completely, subsequent engagement in care. In this study, the proportions of patients engaged in care at 12 months were 75.9% among 290 engaged in care at baseline, 59.6% among 260 “somewhat” engaged in care at baseline (odds ratio [OR] compared with those engaged at baseline, 0.52; $P = .002$), and 52.9% among 68 not engaged at baseline (OR, 0.41; $P = .001$).\(^6\) Although persons presently in care were more likely to remain engaged in care, it is noteworthy that one-fourth of the patients “engaged” at baseline were poorly engaged at 12 months.

**Interventions**

The study of interventions to retain patients in care is a fairly young science in the HIV disease field and has lagged behind the study of interventions to improve medication adherence. Few randomized trials have been reported thus far, although there is a considerable amount of ongoing work in this area. Published studies include ARTAS, which was a randomized study of care linkage rather than retention. This study showed that 90-day intensive case management using a strength-based approach produced a 12% to 15% improvement in successful linkage to care.\(^8\) This approach also proved transferrable from the research setting to the clinic setting, and it may soon be promoted by the CDC as an evidence-based intervention for improving linkage.

The HRSA Ancillary Services Use studies, which used retrospective observational data, found that use of ancillary services reduced patients’ unmet needs and resulted in better retention in care.\(^7\) In addition to finding that baseline engagement in care predicts subsequent engagement, the HRSA SPNS Outreach Initiative studies found that factors associated with retention at 12-month follow-up (with analysis adjusted for race and most recent CD4+ cell count) were discontinued street drug use, decreased structural barriers, decreased unmet needs, and no negative health beliefs about HIV disease and care.\(^6\)

Ongoing studies in the area include evaluation of patient navigation and peer outreach approaches (used by some sites in the SPNS initiative). A major collaborative program sponsored by HRSA-HAB is under way in 5 states (Connecticut, New Jersey, Pennsylvania, Texas, and Virginia) and in-

**Table 1. Predictors of Poor Linkage to and Retention in HIV Care**

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
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<tbody>
<tr>
<td>Younger age</td>
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<tr>
<td>Female sex</td>
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<tr>
<td>Racial or ethnic minority status</td>
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<tr>
<td>No insurance or public health insurance</td>
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<tr>
<td>Lower socioeconomic status</td>
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<tr>
<td>Rural residence</td>
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<tr>
<td>No usual source of health care</td>
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<table>
<thead>
<tr>
<th>Disease Severity</th>
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<tr>
<td>Less advanced HIV disease</td>
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<tr>
<td>Fewer non–HIV-related comorbidities</td>
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<thead>
<tr>
<th>Psychosocial Characteristics</th>
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<tbody>
<tr>
<td>Substance dependence</td>
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<tr>
<td>Low readiness to enter care</td>
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<tr>
<td>Less social support</td>
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<tr>
<th>Ancillary Services Use</th>
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<tbody>
<tr>
<td>Less use of ancillary services (eg, case management)</td>
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<tr>
<td>Greater unmet social services needs</td>
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cludes assessment of retention-in-care strategies, as do a number of current research projects funded by the National Institutes of Health. Perhaps most notable at present is a randomized, controlled intervention jointly sponsored by HRSA and CDC in 6 clinics in Baltimore, Birmingham, Boston, Houston, Miami, and New York City. This study, which is enrolling 300 patients per site, will compare retention outcomes using an intensive intervention, a limited intervention, or usual care. The intervention goes beyond a straightforward case-management approach to include skills building with motivational interviewing and a strength-based approach to add value to the services already available at the study clinics. The study is just completing enrollment, and results will be available in 2013.

Challenges in Retention

Challenges in assessing and improving retention in HIV care include measurement issues; patient-, provider-, and system-level issues; and staffing and resource issues. Currently, there is no single best way to measure and define retention. Methods include counting missed visits (eg, using an absolute count or a minimum number of missed visits), appointment adherence (proportion of scheduled visits that are kept), persistence or constancy (a minimum standard of visits per time period; eg, attending at least 1 visit every 90 days), and gaps in care (eg, no 6-, 9-, or 12-month gaps in visits).

The HRSA-HAB measure of retention requires at least 2 visits in a year, at least 90 days apart (Figure 2). In the figure, Patient A, for example, missed 1 of 5 scheduled visits and thus had appointment adherence of 80%, had 100% constancy, had no gap in care, and met the HRSA-HAB criterion. Patient D had only 1 missed visit (adherence 67%) but missed a scheduled visit in the second quarter and had no scheduled visits in the last 2 quarters; thus, this patient had low visit constancy and a gap in care and failed to meet the HRSA-HAB criterion. A method of measuring retention should be selected that best suits the objectives and needs of the researcher, clinician, or clinic.18

At the patient level, challenges include:

- Changing retention-adherence behavior, in a manner similar to changing medication-adherence behavior
- Improving trust, including improving patient communication with the clinic and removing the stigma associated with requiring care for HIV infection
- Removing structural barriers and addressing unmet needs (eg, transportation, housing, child care, and financial needs)
- Reducing substance dependence

With regard to the effect of reducing structural barriers, a study conducted in Chicago randomly assigned hospitalized homeless persons to receive either immediately secured housing at the time of discharge or usual care including housing assistance. The study found a statistically significant improvement in the composite outcome of survival and CD4+ cell count greater than 200/µL in the housing-first group.19

Challenges at the practitioner and system levels include:

- Improving practitioner communication and decision making
- Improving appointment-scheduling systems (eg, considering open-access systems)
- Improving clinic access, for example, by extending clinic hours
- Improving processes for maintaining accurate contact information
- Defragmenting health insurance and health care processes

- Reorganizing health care delivery for HIV-infected patients to meet the demands of a population requiring care over decades
- Addressing staffing and resource limitations

Financial constraints limit our ability to address some of these challenges.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Number of Missed Visits</th>
<th>Appointment Adherence</th>
<th>Visit Constancy</th>
<th>Gap in Care?</th>
<th>Meets HRSA-HAB Criterion?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1 of 5</td>
<td>80%</td>
<td>100%</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>B</td>
<td>4 of 6</td>
<td>33%</td>
<td>50%</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>C</td>
<td>0 of 3</td>
<td>100%</td>
<td>75%</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>D</td>
<td>1 of 3</td>
<td>67%</td>
<td>25%</td>
<td>Yes</td>
<td>No</td>
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Figure 2. Examples of measuring retention in care. Top, quarterly tracking of attended appointments (checked boxes) and missed appointments (X). Bottom, various measures of the tracking results for Patients A through D. HRSA indicates Health Resources and Services Administration; HAB, HIV/AIDS Bureau. Adapted from Mugavero et al.18
Data from studies of interventions that have shown benefits highlight the fact that clinics are understaffed and underresourced. For example, estimates from ARTAS were that each of the case managers involved could provide care for approximately 120 clients per year. In Houston, there are approximately 1500 new diagnoses of HIV infection annually, indicating the city’s need for 10 to 15 new case managers per year. The SPNS outreach initiative had an average of 4.9 contact hours per new client per month for 12 months. Assuming a workload of 168 hours per month, each outreach worker could serve 34.3 clients.

At Thomas Street Health Center in Houston, Dr Giordano and colleagues care for approximately 300 patients with newly diagnosed HIV infection per year, indicating a need for an additional 9 dedicated outreach workers. The SPNS study found that their intervention was effective when there were at least 9 contacts within 90 days. At Thomas Street Health Center, approximately 1000 patients (of more than 4000 total) have poor retention; assuming 15 minutes per contact, taking care of this population would require 5 additional dedicated outreach workers. The SPNS outreach intervention strategies.

What We Can Do Now

Neither patient admonishment nor information alone is successful in keeping patients in HIV care. One model for retention in care posits that information, motivation, and behavioral skills determine retention in care. The model was first developed to promote condom use and later adapted for medication adherence; now it has been adapted for retention in care. In essence, people who know they have HIV infection know they should seek health care, but for many, this behavior will not be achieved without (1) support that motivates them to seek and stay in care and (2) the behavioral skills that enable them to enter and navigate the health care system. Thus, steps toward improving retention can be made on 3 separate fronts: improving information, improving motivation, and improving behavioral skills.

Clinics can implement 10 measures immediately to some degree to improve retention in care: (1) Track no-show rates and rates of patients who leave care; the first step in improving retention is to measure it. (2) Examine processes of retention with the understanding that bringing patients back is much more difficult once they are completely out of care. (3) Work with personnel from hospital emergency departments and inpatient services, community-based organizations, public health agencies, jails and prisons, and other HIV care practitioners to identify patients poorly retained in care and to build and strengthen relinkage processes. (4) Build and strengthen outreach or peer-navigator programs. (5) Working with existing resources, highlight the importance of retention to staff and have staff members advocate with patients for retention.

Additional measures to implement include those focused on the patient: (6) Improve the patient’s experience; good “customer service” likely leads to return visits. (7) Minimize unmet psychosocial needs by strengthening receipt of substance-use, mental health, case-management, and social services. (8) Minimize the time between scheduling appointments and the date of appointments. (9) Do a pilot trial of wider appointment availability and consider open appointment access if suitable. (10) Remember that patients generally know they should be in care. Corollaries to this recognition are: (a) reminders help but are likely not enough; (b) admonishment will not work and neither will encouragement alone; and (c) problem solve collaboratively with patients just as in attempts to improve medication adherence.

Presented by Dr Giordano in August 2010. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Giordano in January 2011.

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References

11. Berg MB, Safren SA, Mimiaga MJ, Grasso C, Boswell S, Mayer RH. Nonadherence to medical appointments is associated with increased plasma HIV RNA and decreased CD4 cell counts in a community-


HIV and Hepatitis B Virus Coinfection
Elizabeth Reddy, MD, and Susanna Naggie, MD
CME Credit Available: 1.75 AMA PRA Category 1 Credits™ Level: Advanced
Hepatitis B virus (HBV) infection rates are higher among HIV-infected persons than in the general population, owing to common modes of transmission and a decreased likelihood that the HBV infection will clear. In addition, HIV/HBV-coinfected persons are more susceptible to liver disease and related mortality than monoinfected persons. This COW presentation discusses risks of acquiring HBV infection, means of prevention, and treatment options for coinfect persons.

Treatment of Opioid Dependence in Patients with HIV/AIDS
Hillary Kunins, MD, MPH, MS, and Chinazo Cunningham, MD, MS
CME Credit Available: 1.75 AMA PRA Category 1 Credits™ Level: Advanced
HIV-infected patients with opioid dependence can now receive buprenorphine treatment in HIV care, primary care, or substance abuse treatment settings. Offering colocated treatment provides the opportunity to improve HIV outcomes and to reduce substance use among patients. This COW presentation discusses the use of opioid agonist medications and explains specific pharmacotherapeutic properties of buprenorphine that can pose challenges in clinical practice.

Human Papillomavirus Infection in the HIV-Infected Woman
Erna Milunka Kojic, MD, and Susan Cu-Uvin, MD
CME Credit Available: 1.75 AMA PRA Category 1 Credits™ Level: Advanced
The widespread use of potent antiretroviral therapy has resulted in dramatic improvements in life expectancy among HIV-infected women, but the incidence of human papillomavirus (HPV)-related diseases remains high and continues to rise. This COW presentation discusses the epidemiology of HPV among HIV-infected women, explains the effect of antiretroviral therapy on HPV-related anogenital diseases, and reviews the use of the prophylactic HPV vaccine.

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

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

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

COMING SOON
Look for these new Cases on the Web activities in coming months:

- **Dermatologic Complications of HIV Infection** — Identify the unusual skin eruptions, skin diseases with exaggerated presentations (eg, seborrheic dermatitis), sudden acute exacerbations, and treatment failures that should alert the clinician to the possibility of underlying HIV infection.

- **Acute HIV Infection** — Compare the benefits and risks of initiating antiretroviral therapy for acute HIV infection.
**Perspective**

**HIV Diagnostic Testing: Evolving Technology and Testing Strategies**

Detection of acute HIV infection is important to public health because this stage is one of high infectiousness and appears to account for a disproportionate amount of HIV transmission. Newer technologies in HIV testing, including third-generation enzyme immunoassays (EIAs) that detect anti-HIV IgM and IgG antibodies, fourth-generation combination EIAs that detect both anti-HIV antibodies and HIV p24 antigen, and nucleic acid–based testing for HIV RNA, have markedly reduced the interval between infection and detection of infection. Rapid diagnostic tests including assays for IgG and IgM anti-HIV antibodies have high sensitivity and specificity. The availability and wide use of these newer technologies have motivated review of recommended HIV testing algorithms. Individuals’ knowledge of their HIV serostatus contributes to reducing transmission risk behaviors. Thus, widespread testing, facilitated by newer technology, allows more individuals to know their serostatus and is the first step in any successful effort to curb the incidence of HIV infection. This article summarizes a lecture by Demetre Daskalakis, MD, at the New York City IAS–USA continuing medical education program held in November 2009 and re-presented in December 2010.

The US Public Health Service HIV testing algorithms have not changed substantially since 1989, despite the introduction and wide use of new technology.\(^1\) It is still recommended that positive test results not be given to test recipients until screening test results are repeatedly positive on the same specimen and supplemental, more-specific tests such as the Western blot have been used to validate initial results.\(^2\) There is considerable interest in revising testing guidelines to more accurately reflect new technology and associated challenges.

**New Technology: Focus on Acute Infection**

The various measures of HIV infection have specific “detectable moments” during the natural history of infection (Figure 1).\(^3,4\) For example, the early peaking of plasma virus level is matched in time by a peak in the HIV p24 antigen level, and the declines in viral load and p24 antigen levels are coincident with increased levels of HIV anti-p24 antibody and then HIV envelope antibody.

**Old and New Enzyme Immunoassays**

In first- and second-generation (“indirect”) enzyme immunoassays (EIAs), plasma or serum is added to antigen-coated wells containing viral lysate (first-generation assays) or recombinant HIV proteins or synthetic peptides (second-generation assays). Anti-HIV IgG antibody in a sample binds to the antigens, and an enzyme linked to anti-human IgG antibody is added to the well and binds to the anti-HIV IgG. A color reagent is then added, and any color change indicates the presence of anti-HIV IgG in the sample.

In third-generation (“sandwich”) EIAs, the antigen-coated well contains recombinant proteins or synthetic peptides, and anti-HIV IgG and IgM antibodies in a sample bind to the antigen. In the enzyme-detection step, an enzyme linked to HIV antigen (rather than to anti-IgG antibody) is added to the well and binds to anti-HIV IgG and IgM. A change in color upon addition of the color reagent indicates the presence of anti-HIV IgG and IgM in the sample. Because third-generation assays detect IgM as well as IgG, they allow antibody responses to be detected earlier than with the first- and second-generation anti-IgG–based systems.

In fourth-generation (“combination”) EIAs, the wells are coated with HIV antigen and p24 antibody (Figure 2). HIV antibodies in the sample bind the antigen, and the anti-p24 antibody captures free p24. The detection system uses both enzyme-linked HIV antigen and enzyme-linked p24 antibody. A color change after addition of the color reagent indicates the presence of either anti-HIV antibody or p24 antigen, and 2 different fluorescent labels can be used for independent detection of p24 antibody or HIV antigen. By detecting p24 antigen, fourth-generation assays permit even earlier detection of HIV infection than previously available assays, because they can detect viral antigen before an antibody response can be detected.

**Rapid Diagnostics**

Available rapid diagnostic tests using samples of oral fluid, whole blood, plasma, or serum are lateral flow devices able to detect anti-HIV IgG and IgM but not HIV antigen. A sample added to a well moves along filter paper via capillary action through a zone containing colloidal gold conjugated to protein A or HIV antigen. Protein A nonspecifically binds antibody and HIV antigen binds anti-HIV antibody (Figure 3). The fluid reaches a test line coated with HIV antigen, and the colloidal gold produces a color change at the line if cross-binding with antigen occurs. The fluid then reaches an internal control line coated with anti-human IgG; binding at this line also causes a color change, indicating that the device has worked properly. Color
change at both lines indicates a positive result.

The sensitivities and specificities of available lateral flow devices range from 99.3% to 100% and 99.7% to 99.9%, respectively, with narrow 95% confidence intervals, per the product information of these rapid diagnostics. Tests recently approved by the US Food and Drug Administration (FDA) include rapid automated serologic tests with enhanced sensitivity and specificity. In addition, an improved nucleic acid–based test has been approved that can be used both to detect acute HIV infection and to confirm positive serology results, although its use in the latter capacity remains outside of current guidelines.

**Comparison of New Technologies with Western Blot Testing**

Newer diagnostic techniques permit earlier detection of HIV infection during acute infection than does Western blot testing (Figure 1). After infection, symptoms may appear within 2 weeks. HIV p24 levels (measurable with fourth-generation EIA) typically peak after the onset of symptoms, at about 2.5 weeks to 3 weeks after infection; plasma HIV RNA levels (measurable by nucleic acid amplification tests [NAATs]) begin to increase at about 1.5 weeks to 2 weeks, peaking at around 3 weeks to 6 weeks after infection. With the subsequent occurrence of antibody response, third-generation EIA can detect antibody as early as 3 weeks to 4 weeks after infection, and second-generation tests can return positive results at around 4.5 weeks to 5 weeks after infection. By comparison, Western blot testing first begins to show positive results at around 5 weeks. Direct comparison of some of the newer techniques with Western blot testing has shown that positive results are obtained days to weeks before the Western blot test yields positive or even indeterminate results.

Indeterminate Western blot test results are frequently associated with detection of anti-p24 antibody in the setting of both false-positive and negative screening EIA. Indeed, anti-p24 antibody is the most commonly detected antibody in the setting of false-positive EIA and indeterminate-result Western blots. The fact that rapid HIV testing techniques do not include a p24 assay may allow such tests to avoid a proportion of false-positive results.

The potential value of rapid testing in this respect is illustrated by findings in a study in which women in labor for whom no HIV test results were available were screened. Among 7680

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**Figure 1.** *Left,* Time of appearance and relative levels of HIV viral load, p24 antigen, and anti-HIV antibodies during the natural history of untreated HIV infection. Adapted from Daskalakis et al.3 *Right,* Time during acute infection at which positive results of diagnostic tests can be obtained. Vertical dashed line indicates the earliest time at which Western blot testing could fully confirm a positive result. EIA indicates enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay. Adapted from Fiebig et al; original illustration courtesy of Bernard M. Branson, MD.

**Figure 2.** Schematic of fourth-generation combination enzyme immunosorbent assay. Adapted from original figure courtesy of Bernard M. Branson, MD.
women screened, 54 (0.7%) new HIV infections were identified. Oral rapid testing yielded 6 false-positive results and no false-negative results. EIA testing yielded 15 false-positive results, of which 7 were positive for p24 only and 8 were negative on Western blot testing. Overall, specificities for the oral rapid test and the EIA were 99.92% and 99.80%, respectively, and positive predictive values were 90% and 76%, respectively. Such findings indicate that p24-excluding rapid tests may be less prone to false-positive results in the labor and delivery setting, potentially avoiding unnecessary exposure of mothers and infants to antiretroviral drugs.

Given the intricacies and interactions of rapid HIV testing, standard EIA testing, and Western blot testing, workgroups from the Centers for Disease Control and Prevention (CDC) currently are investigating new HIV testing algorithms for both point-of-care and laboratory settings. Possibilities being considered are the use of combinations of rapid tests and the use of NAAT-based confirmatory testing. It is also possible that the Western blot test may be phased out of use.

**HIV Antigen Detection: Technology and Strategies**

Detection of acute HIV infection is essential to public health, as the acute phase is a period of enhanced infectiousness. Data from Montreal indicate that 50% of HIV transmission is attributable to recently infected persons, and other data indicate that recent and late-stage infections are associated with enhanced transmission regardless of viral load. Standard HIV testing, with the exception of the fourth-generation EIA, misses much of the acute stage of infection. Diagnosis of acute infection is hampered by the fact that many patients may not have major symptoms during acute infection and that symptoms, even when present, frequently are missed in history and examination. It is estimated that some symptoms are present in 92% of cases of acute infection, but that the diagnosis on the basis of symptoms is missed 80% of the time.

Options for testing for acute HIV infection include enhancing the screening test with pooled results from HIV NAAT; however, this tends to be available only through specific programs. An alternative is to request an individual NAAT test to assess viral load after a negative rapid test result or while awaiting results of a standard EIA. In pooled screening, 100 patient samples are arrayed in 10 pools of 10 samples each. For any pool that includes positive test results, samples from each of the patients contributing to that pool are individually retested using a NAAT. A positive viral load test result is indicative of acute infection in an individual with a negative rapid test result and positive EIA result, and the viral load test should likely be repeated to confirm that HIV viremia has been detected in the setting of no detected seroconversion.

Investigations of pooled RNA screening have shown the ability to detect infections missed by antibody testing. In a study in North Carolina (2003), 0.02% of 109,250 individuals (0.5% antibody-positive) were found to have HIV antibody-negative and HIV RNA–positive test results with pooled screening. In Florida (2007), 0.02% of 45,288 individuals (1.2% antibody-positive) yielded antibody-negative and HIV RNA–positive results. In Los Angeles (2007), 0.05% and 0.09% of 50,289 individuals had antibody-negative and HIV RNA–positive results in studies using 3 different screening tests (1.2% were antibody-positive on both tests).

Other investigations have used pooled RNA screening in high-risk settings. A study in San Francisco City Clinic in 2004 found a 0.3% frequency of antibody-negative and HIV RNA–positive individuals among 3789 tested (3.2% antibody-positive), and another in 2007 found a 1.1% rate among 1092 tested (7.5% antibody-positive). A study in Los Angeles (2004) found that 0.05% of 2523 individuals (0.9% antibody-positive) had antibody-negative and HIV RNA–positive pooled-screening results. In Atlanta (2004), a frequency of 0.2% in 2202 individuals was found (2.9% antibody-positive). In Seattle, 0.2% of 3525 individuals (2.3% antibody-positive) had antibody-negative and HIV RNA–positive results. The use of fourth-generation EIA has also increased the ability to detect acute HIV infection. For example, an Australian study found that a third-generation versus a fourth-generation EIA identified 66% versus 92% of 53 cases of acute infection in 2005, 67% versus 97.7% of 43 cases in 2006, and 56.5% versus 90% of 30 cases in 2007, respectively (Bernard M. Branson, MD; written communication, September 2009). For all 3 years combined, the third-generation assay identified 63.2% of acute infections, and the fourth-generation assay identified 93.2%.

**HIV Testing Expansion**

According to 1 model, the estimated 25% of individuals unaware of their HIV infection are responsible for 54% of new infections. Many HIV health care practitioners believe that individuals’ knowledge of their HIV serostatus is an effective preventive intervention, and this belief is supported by available data. A meta-analysis of 11 studies showed a 68% reduction in unprotected anal or vaginal sex in HIV-infected
patients aware of their serostatus versus those who were unaware. Quantitative analysis of a cohort of 28 persons showed statistically significant behavior changes at 2 months after receipt of a diagnosis of acute or recent HIV infection, including reductions in total number of partners and the proportion of unprotected sexual acts occurring with uninfected partners (serosorting). The subjects reported that these changes occurred because they were motivated to prevent transmission, although it was also found that there was no increase in condom use.

The test-and-treat model of HIV intervention indicates that there would be a dramatic reduction in HIV incidence with widespread testing and immediate institution of antiretroviral therapy for individuals with positive test results (thereby lowering the “community” viral load). Testing is the first step in any effort to substantially curb the HIV epidemic. In recognition of this fact, the 2006 revised CDC guidelines for testing recommended HIV screening for patients in all health care settings once the patients are notified that testing will be performed unless they decline (opt-out screening). It is also recommended that patients at high risk of infection be screened at least annually. Separate written consent for testing is not required because general consent for medical care is considered sufficient to encompass consent to HIV testing. Not all locales comply with these recommendations, however.

Testing Initiatives in New York City

A number of efforts to increase HIV testing are under way in New York City (NYC). For example, the NYC Health and Hospital Corporation (HHC), the largest public health delivery system in the United States, has committed to increasing routine HIV testing in its facilities. In fiscal year 2005, 62,023 tests were performed, representing 6.3% of the 984,265 eligible HHC clients. In fiscal year 2008, a total of 160,900 tests were performed, representing 15.4% of the eligible population (n = 1,040,432) (Judith A. Aberg, MD; written communication, October 2009).

The aim of the Bronx-Wide HIV Testing Initiative (the Bronx Knows: What’s Your Status? at www.nyc.gov/bronxhivtesting) is to increase testing with the goals of having all Bronx residents aged 18 years to 64 years aware of their HIV serostatus and ensuring that all infected persons have access to good-quality care and prevention services. Testing is being performed at community health clinics, hospitals, community-based organizations, NYC Department of Health clinics, and jails in partnership with the Department of Health and Mental Hygiene (DOHMH). Testing increased by 28% in the first year of the program.

Project BRIEF is an emergency department–based initiative started at the HHC Jacobi Hospital Center that combines informatics, including multimedia counseling, and a client-centered “white glove” connection to care. Upon receipt of a positive result indicating HIV infection, patients receive an escort to the HIV clinic for an automatic connection to care. On a recent assessment of performance of this program, 33,487 patients had been screened, and 0.45% of patients were found to be HIV-seropositive; 85% of HIV-infected persons were connected to care and 89% of eligible patients were receiving antiretroviral therapy (Jason Leider, MD, Yvette Calderone, MD; written communication, September 2009).

The NYC DOHMH recently initiated the use of pooled NAATs at their sexually transmitted disease (STD) clinics, and an analysis indicated detection of acute infection in 0.17% of patients tested. Many of these infections were in men who have sex with men (MSM), raising the possibility of more-targeted use of pooled NAAT in the MSM population.

A recent analysis was made of outcomes from the Bellevue/New York University Men’s Sexual Health Project (www.hivinfosource.org/testingproject), which operates from satellite diagnostic areas of Bellevue Hospital Center and is based at commercial sex venues, events, and parties (eg, bathhouses, sex clubs). The analysis showed that of more than 3000 testing visits conducted, 3.2% of individuals had newly diagnosed HIV infection and 0.5% had acute infection detected using pooled viral load testing (a rate approximately 3 times higher than that reported in DOHMH STD clinics). The program has achieved a 96% connection-to-care rate. High rates of syphilis, chlamydial infection, and gonorrhea were also detected, indicating the need to integrate HIV testing with testing for other STDs.

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**Perspective**

**Prevention of Perinatal HIV Transmission: The Perinatal HIV Hotline Perspective**

Among the most frequently asked questions by callers to the National Perinatal HIV Hotline are those on the use of hormonal contraception in women receiving antiretroviral therapy. Estradiol levels are reduced by ritonavir-boosted protease inhibitors (PIs), nelfinavir, and nevirapine and increased by non–ritonavir-boosted PIs (except nelfinavir), efavirenz, and etravirine. Oral contraceptives do not affect antiretroviral drug levels, and several options are available for hormonal contraception that can compensate for or avoid the effects of antiretroviral drugs on estrogen levels. Other common questions on the hotline involve interpretation and management issues that arise from indeterminate Western blot test results early and late in pregnancy and from positive rapid test results during labor. Many questions focus on appropriate selection of antiretroviral drugs in pregnancy and the need to change regimens to reduce risk of birth defects in the child. This article summarizes a presentation by Jess Fogler Waldura, MD, at the 13th Annual Clinical Conference for the Ryan White HIV/AIDS Program held in August 2010 in Washington, DC.

**Hormonal Contraceptives in HIV-Infected Women**

Many questions to the National Perinatal HIV Hotline (Table 1) involve the use of hormonal contraceptive drugs by HIV-infected women receiving antiretroviral therapy. Major concerns with the concomitant use of combined oral contraceptive (COC) drugs and antiretroviral drugs are the potential effects of protease inhibitors (PIs) and non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) on estrogen levels. Decreased levels of estradiol are observed with ritonavir-boosted (r) PIs, nelfinavir, and nevirapine; increased estradiol levels are observed with non–ritonavir-boosted PIs (except nelfinavir), efavirenz, and etravirine. Conversely, the hormones in COCs do not substantially affect antiretroviral drug levels.

Although the effects of antiretroviral therapy on estrogen levels have led many clinicians to avoid use of COCs for their patients, a number of options are identified in current guidelines. These include use of atazanavir/r with contraceptive drugs containing high-dose estrogen (≥35 µg ethinyl estradiol), non–ritonavir-boosted atazanavir with low-dose estrogen contraceptive drugs (≤30 µg ethinyl estradiol), and any COC with etravirine. Efavirenz increases estrogen levels by about 37%, but the clinical importance of such an increase is unknown; some clinicians use efavirenz with low-dose estrogen COCs. Drugs from other classes, including maraviroc, enfuvirtide, and raltegravir, have no effects on estrogen levels. No studies have assessed the effects of antiretroviral therapy on hormone levels with use of contraceptive patches or vaginal rings.

The effects of antiretroviral therapy on progesterone levels with hormonal contraception are variable and may be less clinically important. Depot medroxyprogesterone, which requires an injection every 3 months, is a popular option, and most studies show that antiretroviral drugs have little or no effect on progesterone levels when the progesterone is administered as an injectable. New forms of implantable progestin that consist of a single rod that releases progestin for 5 years are also increasing in popularity; however, these have not been studied in HIV-infected women receiving antiretroviral therapy. Progesterone-containing intrauterine devices (IUDs) are safe and effective for women with HIV infection. They are very comfortable for most women, easy to insert, and effective for 5 years. Because the hormonal effect of IUDs is localized, drug interactions with antiretroviral drugs are not a concern.

**HIV Testing in Pregnancy**

Many questions to the Perinatal HIV Hotline concern indeterminate Western blot test results after a positive result on a screening HIV test during pregnancy. A positive Western blot test result requires that there be a full complement of positive bands representing antibody reactivity to specific HIV components. For patients in the process of seroconverting, Western blot results become positive over a period of days to weeks (Figure 1). In the United States, a positive Western blot interpretation requires detection...
of at least 1 HIV envelope protein (eg, gp160, gp120, or gp41) plus the GAG protein p24 and usually the POL protein p32.

An indeterminate Western blot test result is one in which positive bands are detected but are not sufficient to meet the criteria for a positive result. The indeterminate result indicates either that the patient is in the process of seroconverting or that the prior screening HIV test result was a false positive.

Pregnancy is associated with increased false-positive results on HIV antibody tests, as it is a highly immune-stimulated state that includes alloantibody production, and some of these antibodies cross-react with the HIV tests. The incidence of false-positive results increases with higher parity (number of deliveries).

For a patient who receives an indeterminate Western blot result relatively early in pregnancy, the test should be repeated approximately 4 weeks later. This timing allows for Western blot reactivity to become apparent in the majority of patients who actually have HIV infection. An option is to perform an HIV viral load test immediately, as acute seroconversion is generally accompanied by very high viral titers. However, the HIV viral load test can show false-positive results in the form of a low viral load (usually < 1000 copies/mL but can reach 10,000 copies/mL). Further, the viral load test is not approved by the US Food and Drug Administration (FDA) for diagnosis of HIV infection.

For patients later in pregnancy, there may not be time to wait 4 weeks to repeat the Western blot test before taking steps to prevent perinatal HIV transmission. In these cases, a risk assessment should be performed to help decide how likely a positive screening test result is to be a true-positive result and whether antiretroviral therapy should be started while awaiting results of the confirmatory Western blot test. The goal of treatment at this point is to have undetectable viral load in the patient by late third trimester or, at the latest, by the time of delivery.

Other hotline questions on HIV testing in pregnancy include whether a positive rapid test result during labor should prompt antiretroviral therapy initiation in women with a negative first-trimester result and no third-trimester test. Rapid testing during labor is recommended for women without documented HIV serostatus, for women with a negative first-trimester result but ongoing risk, and for women who missed their third-trimester test. Third-trimester tests are recommended in certain states (Figure 2) and in facilities with an incidence of HIV infection in pregnancy of at least 0.1%. The positive predictive value (ie, the ratio of true-positive results to all positive results) of rapid testing in labor is higher in settings where the background incidence of HIV infection in pregnancy is higher. For example, considering a typical HIV rapid test sensitivity of 99.6% and a specificity of 99.9%, if the HIV infection prevalence in the population of women of childbearing age is 0.5%, the positive predictive value of the rapid test is 83%. In settings where the HIV infection prevalence is 0.1%, the positive predictive value is 50%, meaning that about half of the positive results are false positives.

Despite the potential for false-positive results with rapid testing during labor, all positive results should be treated as true positives until HIV infection can be ruled out. That is, a Western blot confirmatory test should be sent, but treatment should begin while awaiting the results, which usually take at least a few days. For women in labor, prophylaxis should be started immediately with intravenous zidovudine for the mother, which can be discontinued when the infant is delivered. The infant should be started on zidovudine and continue receiving it for 6 weeks, unless HIV testing confirms that the woman is HIV uninfected.

In high-risk situations, many practitioners would add a single dose of nevirapine for both mother and infant. There is no published evidence to date that the addition of nevirapine to zidovudine reduces risk of transmission versus 6 weeks of zidovudine alone. However, an international study is in progress comparing 6 weeks of zidovudine to 6 weeks of zidovudine combined with other drugs, including nevirapine. Early analysis of this study suggests that combination antiretroviral drugs may be more effective than zidovudine alone for infants whose mothers have received no antepartum antiretroviral therapy.

Although the risk of nevirapine toxicity with single-dose administration is minimal, the main risk of adding nevirapine is the emergence of NNRTI resistance. Nevirapine has a long half-life, and levels of the drug can be detected for up to 3 weeks in adults and possibly even longer in infants with poor renal function. If antiretroviral therapy is discontinued after single-dose nevirapine, the continued exposure to the nevirap-
Antepartum Antiretroviral Treatment

Antiretroviral drugs currently recommended for use in pregnancy are lamivudine, zidovudine, and lopinavir/ritonavir, with nevirapine also recommended for women with CD4+ cell counts less than 250/µL (Table 2). These drugs have been used for many years in pregnancy and are generally well tolerated.

Among alternative options or options for use under special circumstances, tenofovir poses potential risks of bone and renal toxicities. Decreased fetal bone porosity and decreased fetal growth have been observed in monkeys given tenofovir, and long-term use has been associated with bone demineralization in children (as well as in adults). There has been a fully reported study of the safety of tenofovir in pregnancy, and a number of other studies have been reported in scientific conference abstracts. One study indicated that use of tenofovir during pregnancy was associated with smaller birth size in infants (not intrauterine growth restriction), who then caught up to normal size within 1 year to 2 years (Richard Linde, MD; oral communication, February 2010). Thus far, there has been no evidence of statistically significant fetal bone or renal defects, but the numbers of cases studied remains small. Although there is a growing sense of comfort with use of tenofovir in pregnancy, it is prudent to reserve its use for select women, such as those who have been taking and tolerating it for a long time, or those who may be unwilling to take a twice-daily antiretroviral regimen.

The main concerns with atazanavir use are the risk of hyperbilirubinemia (which theoretically can lead to infant kernicterus) and inadequate drug levels in the second and third trimesters. In the small number of cases studied thus far, use of atazanavir has been associated with a predictable rise in bilirubin level in mothers and a proportional rise in bilirubin level in infants, but no pathologic or dangerous elevations have been observed to date. No cases of exchange transfusions or kernicterus in infants have been reported. Levels of atazanavir in mothers receiving atazanavir/ritonavir may be low (sometimes undetectable) during the second and third trimesters, and there is interest in assessing the effects of increasing the atazanavir/ritonavir dose during this period. Pregnant women with prior antiretroviral therapy experience who are taking atazanavir/ritonavir along with either tenofovir or a histamine 2 (H2) receptor antagonist should increase the oral atazanavir/ritonavir dose to 400 mg/100 mg daily.

The main concern with efavirenz is the potential for serious central nervous system defects. Efavirenz is rated as FDA category D in pregnancy. Monkeys exposed to efavirenz have exhibited anencephaly, anophthalmia, and cleft palate, and there have been 7 reports of central nervous system defects in infants with first-trimester exposure. However, the overall incidence of birth defects reported in the antiretroviral pregnancy registry (involving 600–700 cases of efavirenz exposure), is 2.8%, equivalent to the rate in the general population. The birth defects appear to be largely a risk during first-trimester exposure, before the neural tube has closed. Currently, there is increasing use of efavirenz in the second and third trimesters of pregnancy, and there are no reports of adverse outcomes in exposed infants.

Intrapartum Care

No major changes have been made recently in recommendations for intrapartum care. It is still recommended that the mother receive intravenous zidovudine and that instrumentation and artificial rupture of membranes be avoided. Caesarean section should be scheduled at 38 weeks gestation if the maternal plasma HIV RNA level is greater than 1000 copies/mL.
Pneumocystis jiroveci Pneumonia Prophylaxis for HIV-Exposed Infants

A major change was made in 2008 to the US Public Health Service infant HIV testing recommendations with introduction of the “presumptive” ruling out of HIV infection. Thus, prophylaxis for Pneumocystis jiroveci pneumonia in the infant can be avoided if HIV infection is presumptively ruled out on the basis of negative HIV test results at 14 days and 1 month. In practice, this means that most HIV-exposed infants can avoid months of trimethoprim-sulfamethoxazole prophylactic treatment.

Summary

The National Perinatal HIV Hotline is a source to clinicians for free, around-the-clock advice about the management of HIV-infected pregnant women and their exposed infants. Experience with callers to the hotline shows that common questions include the use of hormonal contraception in conjunction with antiretroviral therapy, the interpretation of indeterminate HIV tests in pregnant women, and the optimal choice of antiretroviral drugs in pregnancy. Staff answering the calls provide expert guidance on these and related issues, helping practitioners incorporate the latest information into their clinical decision making.

Lecture presented by Dr Waldura in August 2010. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Waldura in February 2011.

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Perspective
HIV Disease in the Caribbean

The 2007 estimated prevalence of adult HIV infection in the Caribbean region was 1.1%. Prevalence rates in the large Caribbean countries ranged from 1.1% in the Dominican Republic to 3% in the Bahamas, with the highest rates in men who have sex with men, female sex workers, tuberculosis (TB) patients, crack-cocaine users, children living on the streets, and prisoners. HIV disease is the leading cause of death among Caribbean people aged 25 years to 44 years. There are an estimated 20,000 new infections per year, representing 2 new infections for every patient starting antiretroviral therapy. The CIPRA HT001 trial, which assessed 2006 World Health Organization guidelines for antiretroviral therapy initiation, showed substantial reduction of mortality and new-onset tuberculosis with treatment starting at CD4+ cell counts between 200/µL and 350/µL versus initiating at counts below 200/µL. However, in practice, CD4+ cell count at the start of treatment remains well below 200/µL in the majority of locales. Successes in the battle against HIV disease in the Caribbean include reduction in prevalence and mother-to-child transmission rates in some locales, increased use of antiretroviral therapy, increased use of condoms by female sex workers, and vastly improved safety of donated blood units. Much work remains to be done. This article summarizes a presentation by Jean William Pape, MD, at the International AIDS Society–USA continuing medical education program held in New York City, just weeks before the devastating earthquake in Haiti on January 12, 2010. The original presentation is available as a Webcast at www.iasusa.org.

Note:
The following article summarizes an overview of the HIV epidemic in the Caribbean that was presented by Dr Pape mere weeks before Haiti was struck by the devastating earthquake of January 12, 2010. With editorial assistance from Dr Pape’s colleague, Dr Daniel W. Fitzgerald, the presentation summary was updated, while Dr Pape focused on the immediate and continuing effects of the earthquake’s destruction. In January 2010, the IAS–USA selected Haiti’s largest provider of HIV and AIDS care, education, and research, GHESKIO (the Haitian Group for the Study of Kaposi’s Sarcoma and Opportunistic Infections, of which Dr Pape is Director), as its 2010 Charitable Partner. Throughout 2010, individual donors from IAS–USA live CME courses generously provided more than $21,000, which went directly to GHESKIO for its rebuilding efforts. GHESKIO also used these funds to continue providing humanitarian assistance to those affected by the disaster and life-saving medications to people with HIV and AIDS. For updates on the progress of GHESKIO, or to contribute additional funds, visit www.gheskio.org.

Introduction
The Caribbean region consists of 29 nations or territories with Spanish, Dutch, French, and British influences. The total population includes approximately 39 million individuals of African, European, and Asian descent, and indigenous groups. There is extensive cultural and religious diversity among groups and substantial mobility within the population. Approximately 20 million visitors travel to the Caribbean each year from the United States. Data from 2007 indicate that the Caribbean was the largest contributor of new diagnoses of HIV infection in the US foreign-born population in New York City, accounting for 38% of cases, with the total increasing to 55% if new diagnoses in individuals born in Puerto Rico are included (New York City Department of Health and Mental Hygiene, 2009).

Characteristics of the Epidemic
In 2007, the estimated prevalence of adult HIV infection in the Caribbean was 1.1%, compared with 0.6% in North America and 0.5% in Latin America (Joint United Nations Programme on HIV/AIDS [UNAIDS], 2009). The epidemic is both generalized and sustained (rates, 1%–3%) in the general population, reflecting largely heterosexual transmission, and it is concentrated at much higher prevalences in men who have sex with men (MSM), female sex workers, prisoners, tuberculosis (TB) patients, crack-cocaine users, and children living on the streets. HIV disease is the leading cause of death among people aged 25 years to 44 years. An estimated 20,000 new infections occur annually, a rate of approximately 55 new infections per day.

No infections with HIV-2 have been documented in the Caribbean, and the predominant HIV-1 subtype is B. Subtypes C, D, F, G, H, and J and recombinants have been reported in Cuba; subtype A in Martinique; A and F in French Guiana; D and B/F in Puerto Rico, and B (Trinidad variant) and D in Trinidad and Tobago (Cuevas et al, AIDS, 2002; Kazanjii et al, AIDS Res Hum Retroviruses, 2001; Cleghorn et al, Proc Natl Acad Sci USA, 2000; Flores et al, Emerg Infect Dis, 1999; Oueta et al, J Acquir Immune Defic Syndr Hum Retroviral, 1998).

Of the estimated 261,000 persons living with HIV infection in the Caribbean as of 2007, approximately 70% live on the island of Hispaniola, which comprises Haiti (~120,000 cases, 46%)

Dr Pape is professor of medicine at the Weill Medical College of Cornell University in New York, New York, and director of Les Centres GHESKIO in Port-au-Prince, Haiti. Dr Fitzgerald, assistant article editor, is associate professor of medicine at the Weill Medical College of Cornell University.
and the Dominican Republic (~62,000 cases, 24%). Among the remaining larger countries, these 2 are followed by Jamaica (~27,000 cases), Trinidad and Tobago (14,000), Guyana (15,000), Surinam (6800), the Bahamas (6200), Belize (3600), and Barbados (2200) (data compiled from the UNAIDS, GHESKIO, and the World Health Organization [WHO]). Apart from Cuba, with its estimated HIV seroprevalence rate of less than 0.05%, seroprevalence rates in the larger countries range from 1.1% in the Dominican Republic to 3% in the Bahamas.

In some regions, the epidemic has been stabilized, with current prevalence rates in the Dominican Republic, Jamaica, Haiti, Guyana, and the Bahamas representing marked reductions from peak prevalence rates in prior years (Figure 1). Seroprevalence rates reported from several of the countries are much higher in MSM and female sex workers than the national rates, as are seroprevalence rates reported in prison populations (Figure 2). It is noteworthy that very high seroprevalence rates in MSM are found in locales that criminalize same-sex sexual practices (eg, Trinidad and Tobago, Jamaica).

Currently, heterosexual transmission is implicated in approximately 60% to 80% of cases of infection, with homosexual or bisexual transmission accounting for 10% to 15%, mother-to-child transmission (MTCT) for 6% to 10%, and unknown risk factors (which could largely reflect risk in MSM) for 17% to 20%. Injection drug use (IDU) is an uncommon mode of transmission except in Puerto Rico (where it contributed substantially to the early epidemic) and Bermuda; elsewhere, it primarily reflects a risk factor in US criminal deportees.

Although HIV transmission through infected blood and blood products was a primary driver of the early epidemic in many locales, it is now rare. The epidemic has grown among women, with the percentage of cases in women increasing from 24% in 1990 to 43% in 2007 (UNAIDS, 2010). Various studies in Caribbean populations have shown that cofactors for transmission in HIV-serodiscordant couples include absence of condom use, clinical disease in index cases in both men and women, and sexually transmitted infections in the HIV-seronegative partner (including genital ulcers, seropositive syphilis, and genital discharge) (Deschamps et al, Ann Intern Med, 1996). In Jamaica, a comprehensive program has led to a marked reduction in sexually transmitted infections (Figueroa,
West Indian Med J, 2001), and another program in the Dominican Republic has been successful in preventing infections in female sex workers.

Behavioral and cultural factors contributing to the epidemic include sexual relations that notably feature the “macho” concept, which encourages men to have numerous sex partners and initiate sexual activity early in life. As part of this concept, men who have sex with both women and men do not consider or report themselves as MSM. IDU continues to fuel the epidemic in Puerto Rico, and drug use among men continues to account for most of the transmission in the heterosexual population (Centers for Disease Control and Prevention [CDC], MMWR, 2009). Studies in the Caribbean have shown that consistent condom use is protective, although there is difficulty in interpreting self-reported condom use. Poverty is certainly a factor limiting consistent condom use. Policies supporting consistent condom use in female sex workers are needed in many locales.

Natural History of HIV Infection and Effects of Treatment

Studies in Caribbean populations have shown rapid progression of HIV disease after initial infection (Inciardi et al, AIDS Care, 2005). In Haiti, patients progressed to symptomatic HIV disease an average of 3 years after primary infection and to AIDS after 5.2 years, and died after 7.4 years (Deschamps et al, AIDS, 2000). A study in Trinidad showed progression to AIDS by 4.8 years after infection and death by 5.6 years (Blattner et al, J Infect Dis, 2004). Interaction of HIV-1 with human T-cell lymphotropic virus type 1 (HTLV-1), which has a prevalence of 2% to 5% in persons of African ancestry in the region, may be a factor in this rapid progression rate. Studies in Trinidad indicate that HTLV-1 coinfection is associated with rapid progression to AIDS, with other studies indicating that HIV-1 coinfection does not increase the viral load of HTLV-1 (Cé saire et al, AIDS Res Hum Retroviruses, 2001). CD4+ cell counts can be artificially increased in coinfection, posing difficulties in management.

TB also appears to accelerate HIV disease. In an early study, HIV-infected patients were randomly selected to receive preventive treatment with isoniazid plus vitamin B₆ or vitamin B₆ alone. Isoniazid treatment reduced risk of active TB and risk of progression to AIDS (Figure 3; Pape et al, Lancet, 1993). Another study found that whereas HIV-seropositive patients were at increased risk of TB recurrence compared with HIV-seronegative patients, use of isoniazid markedly reduced this risk in HIV-infected patients (Fitzgerald et al, Lancet, 2000).

A study reported in 1999 showed that without antiretroviral therapy, approximately 80% of HIV-infected children in Haiti were dead within 2 years of acquiring HIV infection (Jean et al, Pediatr Infect Dis, 1999). A 2007 study showed that with antiretroviral therapy, 80% remained alive at 2 years after infection (George et al, J Infect Dis, 2007). In adults in the Caribbean, 1-year survival after initiation of antiretroviral therapy is approximately 90% (Severe et al, N Engl J Med, 2005). Five-year survival has been estimated at 75%, with rates of 64% in patients aged 13 years to 24 years, 78% in those aged 25 years to 50 years, and 64% in those older than 50 years (Leger et al, N Engl J Med, 2009). At GHESKIO, 5 consecutive yearly cohorts of all patients receiving antiretroviral therapy were assessed from 2003 to 2007, with 1-year survival ranging from 90% to 95%. Factors associated with early mortality included CD4+ cell count below 50/µL, low body mass index, hemoglobin value below 8.5 g/dL, and coinfection with active TB.

A recent study in 201 patients coinfected with AIDS and TB found that patients starting TB treatment within 3 months after initiating antiretroviral therapy had a markedly lower 2-year survival rate than did patients receiving antiretroviral therapy and TB treatment at other times relative to each other (Koenig et al, Clin Infect Dis, 2009). Two-year mortality was 27% in patients starting TB treatment within 3 months after initiating antiretroviral therapy, 10% in those starting TB treatment before antiretroviral therapy, and 2% in those starting TB treatment more than 3 months after initiating antiretroviral therapy. The high mortality rate in patients starting TB treatment within 3 months is likely attributable to the masking effect of HIV disease. Patients probably had TB at the time of antiretroviral therapy initiation, but TB was diagnosed only after reconstitution of the immune system or with more careful clinical surveillance (Koenig et al, Clin Infect Dis, 2009). In part, this finding may reflect the increased frequency of multidrug-resistant TB (MDR-TB) in HIV-infected patients.

![Figure 3](image-url) Effectiveness of preventive treatment with isoniazid (I) on risk of active tuberculosis (left) and progression to AIDS (right) in patients receiving supplementation with vitamin B₆. Adapted from Pape et al, Lancet, 1993.

![Figure 3](image-url)
One study showed that MDR-TB was found in 11 (10%) of 115 HIV-infected patients compared with 5 (3%) of 166 HIV-seronegative patients (relative risk, 3.2; P = .03) (Joseph et al, AIDS, 2006). MDR-TB was implicated in 10 (20%) of 49 cases of recurrent TB.

A more recent trial (CIPRA HT 001 trial) in Haiti compared standard timing of antiretroviral therapy initiation, following 2006 WHO guidelines, with earlier initiation of antiretroviral therapy (Severe et al, N Engl J Med, 2010). Patients were randomly selected to receive early initiation at CD4+ cell counts between 200/µL and 350/µL (n = 408) or standard WHO-recommended initiation at CD4+ cell counts of 200/µL or less (n = 408). Patient groups were comparable with regard to age, sex, body mass index, and CD4+ cell count at entry (median, 282/µL; median time of follow-up was 21 months. The trial was stopped early because of excess mortality in the standard treatment group. Standard treatment was associated with a statistically significant increased risk of death (23 events vs 6 events; hazard ratio, 4.0; P = .0011) and a statistically significant increased risk of incident TB (36 events vs 18 events; hazard ratio, 2.0; P = .0125). As with other findings indicating benefits of earlier initiation of antiretroviral therapy, it is difficult to say what impact these results will have on clinical practice when average CD4+ cell counts at the start of antiretroviral therapy remain well below 200/µL, according to the most recent data from most locales in the Caribbean (Figure 4).

Public health initiatives need to be much more aggressive in early identification of HIV infection and earlier initiation of treatment.

Surveys in 2005 and 2006 showed that there was a high general awareness of HIV disease across all countries, with 98% of respondents indicating that they had heard of HIV (World Bank, 2009). There was poorer understanding of the details of HIV disease. In Guyana, for example, 27% of respondents believed that HIV is transmitted by sharing utensils. In Trinidad, 69% knew the difference between HIV and AIDS. In the Organization of Eastern Caribbean States, only 27% of in-school youths and 44% of taxi drivers were able to reject major misconceptions about HIV transmission. In Haiti, less than 50% were aware that MTCT of HIV can be decreased with antiretroviral therapy.

**Successes and Challenges**

There have been successes in the battle against HIV disease in the Caribbean. UNAIDS data from 2005 to 2007 indicate that 96% of female sex workers in the Dominican Republic and 90% in Haiti reported using a condom during their last sexual contact with a client; rates were 89% in Guyana, 84% in Jamaica, 80% in Barbados, 68% in Surinam, and 56% in Cuba. With regard to screening of donated blood, data from 2006 and 2007 indicate that 100% of blood units were screened in a quality-assured manner in the vast majority of locales in the Caribbean, with the exception of Grenada and Antigua (UNAIDS, 2009). Other signs of progress include the following:

- In Jamaica, the prevalence of HIV infection has stabilized at 1.6%, and MTCT has decreased from 25% in 2000 to less than 5% in 2009 (Jamaica National HIV/STI Programme, UNGASS Country Progress Report, 2010).
- In the Bahamas, prevalence was estimated to remain at 3% in 2008, and MTCT decreased from 30% in 1997 to less than 1% since 2005 (The Commonwealth of The Bahamas National HIV/AIDS Centre, UNGASS Country Progress Report, 2010).
- In the Dominican Republic, prevalence decreased from 2.7% in 2001 to 1.1% in 2006.
- In Haiti, prevalence decreased from 6.2% in 1993 to 2.2% in 2006, and the number of patients receiving antiretroviral therapy increased from less than 300 in 2002 to greater than 26,000 in 2009.

Many challenges remain:

- There are many new HIV infections; the approximately 20,000 new infections in 2007 represent 2 new infections for every patient initiating antiretroviral therapy that year.
- Patients must be sought aggressively to initiate early antiretroviral therapy.
- Adherence to treatments (particularly among adolescents) must be monitored closely.
- HIV disease and TB programs must be integrated from the central level to the point of care, and MDR-TB must be monitored.

The HIV epidemic is far from over, and there is continuing need for more ev-

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**Figure 4.** CD4+ cell counts at initiation of antiretroviral therapy at various Caribbean locales. Based on data from the TCHARI (Trans-Caribbean HIV/AIDS Research Initiative) Network, 2010. IMIS indicates Institute of Infectious Diseases and Reproductive Health; INLR, National Institute Research Laboratory; MRF, Medical Research Foundation; PIH, Partners in Health.
idence-based interventions and sustained long-term commitment to address the numerous barriers to controlling the epidemic. Prevalence rates of HIV infection continue to be high in TB patients, patients with other sexually transmitted infections, the homeless population, sex workers, incarcerated persons, and substance users. Also, stigma and discrimination with regard to HIV infection must be overcome.

Haiti was devastated by the January 2010 earthquake, which is estimated to have killed more than 316,000 people and destroyed the infrastructure of the capital, Port-au-Prince. How the rate of HIV in Haiti may change as a result of the disruptions to the society and its health care delivery systems is difficult to predict (Koenig et al., HIV Ther., 2010). The challenge remains for the Haitian government to work with HIV care providers to continue HIV disease and AIDS treatment, care, and screening as the capital is rebuilt.

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Suggested Reading


