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Topics in Antiviral Medicine™

A publication of the IAS–USA

Perspectives

Cases From the Field

Topics in Antiviral Medicine™

Between Clinical Research and Patient Care — 20 years — Bridging The Gap

2012 marks the 20th year of the IAS–USA and *Topics in Antiviral Medicine*.

IAS–USA International Antiviral Society–USA

Topics in Antiviral Medicine™

Topics in Antiviral Medicine (formerly *Topics in HIV Medicine*) is published by the IAS–USA. This journal is intended to be a resource for physicians and other health care practitioners who are actively involved in the care of patients with HIV, hepatitis C virus, or other viral infections.

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Announcements

2012 marks the 20th year of the IAS–USA

Educational Programs of the IAS–USA

Established in 1992, the IAS–USA is a not-for-profit, professional education organization. The mission of the IAS–USA is to improve the treatment, care, and quality of life for people with HIV, hepatitis C virus (HCV), 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 educational activities are particularly intended to bridge clinical research and patient care*.

Fall 2012 Live Continuing Medical Education Courses

IAS–USA CME course announcements are paperless. Please watch for e-mail updates, and visit 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™*.

Management of Hepatitis C Virus in the New Era: Small Molecules Bring Big Changes

Part of the IAS–USA focus on the management of HCV infection, these half-day, small-group, intensive CME workshops and full-day CME courses are presented by leading experts in the field. Attendance is limited to 35 practitioners, so ***early registration is encouraged.***

Half-Day, Small Group, Intensive Hepatitis C Virus Workshops

Miami, Florida
Thursday, September 20, 2012
Miami Marriott Dadeland
Workshop Leaders: Michael S. Saag, MD, Alexander Kuo, MD, Kristen Marks, MD

Cleveland, Ohio
Friday, October 12, 2012
Hyatt Regency Cleveland
Workshop Leaders: Charles W. Flexner, MD, Melissa K. Osborn, MD, Kenneth E. Sherman, MD

Raleigh-Durham, North Carolina
Thursday, October 25, 2012
McKimmon Conference Center
Workshop Leaders: Susanna Naggie, MD, Kenneth E. Sherman, MD

Boston, Massachusetts
Tuesday, October 30, 2012
Omni Parker House
Workshop leaders: Raymond T. Chung, MD, Charles W. Flexner, MD, Robert T. Schooley, MD

Full-Day Hepatitis C Virus Courses

Atlanta, Georgia
Tuesday, October 23, 2012
Georgia Tech Global Learning Center
Cochairs: Susanna Naggie, MD, Michael S. Saag, MD

South San Francisco, California
Monday, November 5, 2012
South San Francisco Conference Center
Cochairs: Marion G. Peters, MD, David L. Wyles, MD

Improving the Management of HIV Disease®

The full-day advanced CME course, now in its 20th 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.

New York, New York
Wednesday, October 3, 2012
New York Marriott Marquis
Cochairs: Roy M. Gulick, MD, MPH, and Scott M. Hammer, MD

Educational 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 presentation handouts.

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Topics in Antiviral Medicine™

Continuing Medical Education

The following article in this issue is associated with continuing medical education (CME) credit: Wyatt CM. The kidney in HIV infection: beyond HIV-associated nephropathy. *Top Antiviral Med*. 2012;20(3):106-110

Instructions

This journal-based continuing medical education (CME) activity provides a review of kidney disease and HIV infection. To complete the activity, the learner is instructed to:

- Read the article (see pages 106-110)
- Review a selection of the references
- Reflect on how the information might be applied to clinical practice
- Complete the posttest and CME claim form on page 100 and send both to the IAS–USA office.

Learning Objectives

On completion of this activity, the learner will be able to: describe the causes of acute kidney injury and chronic kidney disease in HIV-infected persons; describe guidelines for chronic kidney disease screening in the HIV-infected population; and list the options for treating end-stage renal disease in HIV-infected patients.

Accreditation Statement

The International Antiviral Society-USA (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, hepatitis C virus, 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.

Conflict of Interest and Financial Disclosures

IAS–USA policy requires that the IAS–USA resolve any real or apparent conflict of interest of persons in control of the development, content, or delivery of its educational activity prior to the activity's being delivered to learners.

Dr Wyatt has received grants and research support from the Gilead Foundation.

Dr Richman has been a consultant to Biota, Bristol-Myers Squibb, Chimerix, Gen-Probe Inc, Gilead Sciences, Inc, Merck & Co, Inc, Monogram Biosciences, Inc, and Tobira Therapeutics. He has been the recipient of research grants or contracts from Merck & Co, Inc. He has held stock options for Chimerix.

Drs Hirsch and Benson have no relevant financial affiliations to report. Dr Benson's spouse, Dr Robert T. Schooley, has served as a consultant to 3-V Biologicals, Gilead Sciences, Inc, Inhibitex, Inc, Johnson & Johnson Services, Inc, Laboratory Corporation of America, Merck & Co, Inc, Santaris Pharma, and Tobira Therapeutics. He has stock options for Achillion Pharmaceuticals, Inc, and GlobeImmune, Inc.

CME Posttest

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

1. Which statement most accurately describes the health outcomes associated with acute kidney injury (AKI) in HIV-infected patients?

- ❑ **A.** A symptomatic increase in serum creatinine level is associated with increased risk of heart failure, cardiovascular events, end-stage renal disease, and death.
- ❑ **B.** A symptomatic increase in serum creatinine level is associated with increased risk of heart failure, cardiovascular events, and end-stage renal disease, but not death.
- ❑ **C.** Even an asymptomatic increase in serum creatinine level is associated with increased risk of heart failure, cardiovascular events, end-stage renal disease, and death.
- ❑ **D.** Even an asymptomatic increase in serum creatinine level is associated with increased risk of heart failure, cardiovascular events, and end-stage renal disease, but not death.

2. Which statement best describes the causes of AKI in HIV-infected patients?

- ❑ **A.** The most common underlying cause is systemic infection, including AIDS-defining and non-AIDS infections.
- ❑ **B.** The most common underlying cause is antiretroviral drug toxicity, in particular related to the use of tenofovir and protease inhibitors.
- ❑ **C.** The most common underlying cause is adverse effects of medications other than antiretroviral therapy, including antibiotics and radiocontrast agents.
- ❑ **D.** The most common underlying cause is liver failure, primarily in patients with hepatitis C virus (HCV) coinfection.

3. Which statement is true regarding the causes of chronic kidney disease (CKD) in HIV-infected patients?

- ❑ **A.** The spectrum of CKD causes is changing and shows more HIV-associated nephropathy (HIVAN) and less comorbid kidney disease, such as that caused by hypertension and diabetes.
- ❑ **B.** The spectrum of CKD causes is changing and shows less HIVAN and more comorbid kidney disease, such as that caused by hypertension and diabetes.
- ❑ **C.** The spectrum of CKD causes shows little change in recent years, with nearly half of cases caused by HIVAN.
- ❑ **D.** The spectrum of CKD causes shows little change in recent years, with most cases caused by HIVAN.

4. The guidelines for screening HIV-infected patients for CKD are being revised. Which statement most accurately describes current guidelines?

- ❑ **A.** HIV-infected patients should be screened for creatinine-based estimated glomerular filtration rate (eGFR) and urine protein once they develop advanced HIV disease.
- ❑ **B.** HIV-infected patients should be screened for creatinine-based eGFR and urine protein, if they have risk factors for CKD, including advanced HIV disease, HCV coinfection, diabetes, or hypertension.
- ❑ **C.** HIV-infected patients should be screened at the time of HIV diagnosis for creatinine-based eGFR and urine protein, with no further screening recommended unless antiretroviral therapy is initiated.
- ❑ **D.** HIV-infected patients should be screened at the time of HIV diagnosis for creatinine-based eGFR and urine protein, with annual screening for high-risk patients including those with HCV coinfection, advanced HIV disease, diabetes, or hypertension.

5. Which statement is true regarding options for HIV-infected patients with end-stage renal disease?

- ❑ **A.** They do not make good candidates for peritoneal dialysis because survival rates are lower than with hemodialysis.
- ❑ **B.** They do not make good candidates for kidney transplantation because survival rates are low.
- ❑ **C.** Selected patients—with undetectable viral load, CD4+ cell count greater than 200 /μL, and stable antiretroviral therapy—have post-transplant survival equivalent to the general transplant population.
- ❑ **D.** Selected patients—with undetectable viral load, CD4+ cell count greater than 200/μL, and stable antiretroviral therapy—have post-transplant survival intermediate between that in the overall transplant population and that among transplant recipients older than 65 years.

This continuing medical education activity is offered from September 1, 2012 to September 1, 2013. Physicians (MDs, DOs, and international equivalents) who receive a passing score on the posttest and submit the registration and evaluation forms are eligible to receive CME credit. Nonphysician health care practitioners will receive a certificate of participation.

Mail or fax this page along with the completed posttest to:
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Number of CME credit hours I am claiming (maximum 1.5): _____

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The approximate amount of time (in hours) I spent on reading the article, reviewing the references, and reflecting on how the information might be applied to the practice was:
❒ >.5 ❒ 1.0 ❒ 1.5 ❒ 2.0 ❒ other _____

Evaluation

Please complete the following evaluation form for this journal-based CME activity:

	Excellent	Very Good	Good	Fair	Poor
Please rate the activity in terms of meeting the stated learning objectives (see page 99 for objectives)	❍	❍	❍	❍	❍
Please rate the extent to which the information presented was supported by the evidence	❍	❍	❍	❍	❍
Please rate the overall quality of the activity	❍	❍	❍	❍	❍
Please rate the activity's freedom from commercial bias	❍	❍	❍	❍	❍
Please rate the overall value of this activity to your practice	❍	❍	❍	❍	❍

Do you expect to make changes in your clinical practice based on the information presented in this activity? ❒ Yes ❒ No

If so, please list up to 3 measurable changes you expect to make:

1. _____

2. _____

3. _____

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

_____

_____

What percentage of your patients has HIV infection?
❒ 0% ❒ 1%–10% ❒ 11%–25% ❒ 26%–50% ❒ 51%–75% ❒ 76%–90% ❒ 91%–100%

Please rate your expertise in treating HIV infection: ❒ 1 (novice) ❒ 2 ❒ 3 ❒ 4 ❒ 5 (expert)

What percentage of your patients are members of an underrepresented minority group?
❒ 0% ❒ 1%–10% ❒ 11%–25% ❒ 26%–50% ❒ 51%–75% ❒ 76%–90% ❒ 91%–100%

Are you a member of an underrepresented minority group? ❒ Yes ❒ No

Perspective

Aging, Inflammation, and HIV Infection

Prolonged survival in HIV infection is accompanied by an increased frequency of non-HIV-related comorbidities. A number of age-related comorbidities occur earlier in HIV-infected patients than in individuals without HIV infection. This "accelerated aging" appears to be largely related to chronic inflammation, chronic immune activation, and immunosenescence in HIV infection. Levels of markers of inflammation and coagulopathy are elevated in HIV-infected patients, and elevations in markers such as high-sensitivity C-reactive protein, D-dimer, and interleukin 6 (IL-6) have been associated with increased risk for cardiovascular disease, opportunistic conditions, or all-cause mortality. In both HIV infection and aging, immunosenescence is marked by an increased proportion of CD28-, CD57+ memory CD8+ T cells with reduced capacity to produce interleukin 2 (IL-2), increased production of IL-6, resistance to apoptosis, and shortened telomeres. A number of AIDS Clinical Trials Group studies are under way to examine treatment aimed at reducing chronic inflammation and immune activation in HIV infection. This article summarizes a presentation by Judith A. Aberg, MD, at the IAS–USA live continuing medical education course held in New York City in October 2011.

Patients with HIV infection have had a dramatic increase in life expectancy with the use of potent antiretroviral therapy. However, life expectancy for many patients—particularly those with low CD4+ cell counts and those on salvage regimens—is still shorter than that for the general population. Among the data showing increased life expectancy in HIV infection are the findings in the ATHENA (AIDS Therapy Evaluation in the Netherlands) cohort (N = 4174) indicating that HIV-infected persons who are asymptomatic on antiretroviral therapy have an estimated life expectancy nearly identical to that of the general population. This model suggested that HIV-infected patients aged 25 years and asymptomatic at 24 weeks after starting antiretroviral therapy had an estimated 52.7 life-years remaining, compared with 53.1 life-years for 25-year-old persons in the general population.[1] The modeled life expectancies of HIV-infected patients presenting for care at older ages and HIV-infected women were somewhat lower than those in the general population.

Increased survival in HIV-infected persons has been accompanied by an increase in comorbidities compared with the general population, although the precise prevalence and distribution of such comorbidities have yet to be defined. HIV treatment guidelines issued in 2010 generally recommended that patients with HIV infection start antiretroviral therapy at CD4+ cell counts of 500/µL, and that those with certain comorbid conditions begin therapy regardless of CD4+ count.[2,*] Although there is no threshold above which initiation of therapy is contraindicated, it is not yet known if initiating antiretroviral therapy earlier reduces (or increases, eg, via chronic toxicity from treatment) the frequency of comorbidities. Patients starting antiretroviral therapy at higher CD4+ cell counts do have persistent recovery of CD4+ counts, suggesting better preservation of immune function.

A study in the HOPS (HIV Outpatient Study) cohort of 1378 patients observed from 1996 to 2007 showed that median CD4+ cell count peaks were progressively higher ($P < .001$) in patients with higher CD4+ cell counts at treatment initiation (Figure 1).[4] Multivariate analysis showed that compared with patients with initial CD4+ cell counts of 350/µL or above, mortality was 4.6 times more likely in patients with initial CD4+ cell counts below 50/µL and 2.6 times more likely in those with initial counts of 50/µL to 199/µL. A lower CD4+ cell count at initiation of treatment was also associated with increased risk of mortality from non–AIDS-related causes, suggesting that

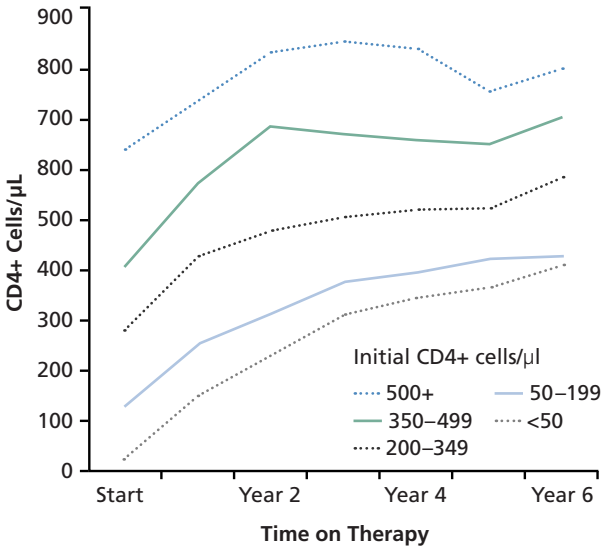

Figure 1. Median CD4+ cell count during first 6 years of antiretroviral therapy according to initial CD4+ cell count category. Adapted from Palella et al.[4]

Dr Aberg is Professor of Medicine, Director of the Division of Infectious Diseases and Immunology, and Principal Investigator of the AIDS Clinical Trials Unit at New York University School of Medicine. She is also the Director of Virology at Bellevue Hospital Center in New York, NY.

*Since Dr Aberg's presentation, the IAS-USA guidelines have been revised and recommend antiretroviral therapy for all patients with HIV infection regardless of CD4+ cell count, with the strength of the recommendation increasing as CD4+ cell count decreases. See Thompson et al.[3]

earlier initiation of therapy and preservation of CD4+ cell count might influence the frequency and nature of comorbidities in HIV infection.

A number of age-related morbidities occur at earlier ages in individuals with HIV infection than in the general population. As discussed further below, this phenomenon of "accelerated aging" may reflect chronic inflammation in HIV infection. Given the observation of earlier onset of age-related morbidities in HIV infection, it is questionable whether primary care practice guidelines for the general population are applicable to the HIV-infected population. For example, there is some evidence that HIV-infected patients develop colorectal cancer precursor lesions and more advanced disease at an earlier age than do persons in the general population,[5] raising the question of whether screening for colorectal cancer should begin earlier (eg, at age 40 years rather than 50 years) in HIV-infected patients. It remains to be determined whether primary care guidelines specific to the HIV-infected population might reduce the frequency of comorbidities in this population.

Aging and HIV Infection

Considerable attention has been given to the idea that patients with HIV infection age more rapidly than HIV-uninfected individuals, as suggested by the occurrence of age-related comorbidities at earlier ages in those with HIV infection. This phenomenon appears to reflect, in large part, the increased risk for a number of disease states stemming from chronic inflammation and immunosenescence, both of which occur in HIV infection.

Studies in women with systemic lupus erythematosus have shown that they have a dramatically increased risk of myocardial infarction (MI) compared with age-matched controls in the general population. Yet few would say that patients with lupus are at increased risk for MI because they are aging faster. Instead, it can be said that patients with lupus have a chronic inflammatory disease that puts them at risk for comorbidities. Patients with HIV infection have begun to think of themselves as aging faster—it may be better if practitioners, when confronted with this message, explain that HIV infection is a chronic inflammatory condition that may be associated with comorbidities. Patients should be informed that there appears to be a higher prevalence of comorbidities at all ages among persons with HIV infection. Treatment of lupus reduces inflammation, as demonstrated by observation of validated biomarkers of inflammation, and reduces risk for cardiovascular disease. It is hoped that treatment of HIV infection will have similar results.

To emphasize the distinction between chronic inflammation and aging, age-related hearing loss (a hallmark of aging) can be considered.[6] Hearing impairment was recently assessed in MACS (Multicenter AIDS Cohort Study) and WIH (Women's Interagency HIV Study), involving 334 men with a median age of 54 years, 46% of whom had HIV infection, and 178 women with a median age of 45 years, 77% of whom had HIV infection. Testing for hearing impairment via distortion-product otoacoustic emissions showed that risk factors for impairment were a 10-year increase in age, male sex, and nonblack race. HIV infection was not a risk factor for hearing loss, and neither were antiretroviral therapy, nadir CD4+ cell count, nor HIV RNA level. In fact, greater hearing loss was detected in persons without HIV infection.

Comorbidities in HIV Infection: Inflammation and "Inflamm-Aging"

Chronic adverse effects of antiretroviral therapy, HIV infection itself, traditional risk factors, or a combination of all of these contribute to increased risk of coronary heart disease in HIV-infected patients, as well as increased frequency of a number of metabolic abnormalities and other comorbidities. Osteoporosis and hypogonadism occur at an earlier age in HIV-infected persons. There is no reason to expect that antiretroviral therapy provides protection from development of malignancies at the ages at which they are seen in the general population, including esophageal, lung, rectal (human papilloma virus–related), renal, and liver cancers. In fact, lung cancer is more prevalent in HIV-infected persons than in the general population after adjustment for smoking, with any potential interaction between HIV and this malignancy remaining undefined.[7] As noted previously, colorectal cancer precursor lesions and more advanced disease are more prevalent at a younger age in HIV-infected individuals.

It is clear that the vast majority of deaths in HIV-infected patients in developed countries are currently not caused by AIDS-defining illnesses. In a study reported in 2008 that examined mortality in patients from 3 randomized HIV clinical trials, AIDS-defining illnesses accounted for only 10% of mortality. Non–AIDS-defining malignancies accounted for 21% of mortality and unknown causes accounted for 18%; other specific causes, including cardiovascular disease, liver disease (excluding malignancy), non–AIDS-defining infection, suicide, trauma-related or accidental causes, and drug overdose or acute intoxication, each accounted for 9% or less of mortality.[8]

There are also data to indicate that, compared with the general population, HIV-infected patients have greater rates of mortality per given level of comorbidity as classified by the Charlson Comorbidity Index (CCI). The CCI is a scale that was initially developed for use in longitudinal studies to classify comorbid conditions that alter the risk for 1-year mortality after hospitalization, with a greater number of points indicating greater severity of the condition. For example, an MI is assigned a value of 1 point, whereas diabetes with end-organ damage is 2 points. Lymphoma is 2 points whereas a metastatic solid tumor is 6 points. In a recently reported study, Lohse and colleagues adapted the CCI to determine if survival from time of HIV diagnosis in HIV-infected persons differed from that in age- and sex-matched HIV-uninfected persons with identical CCI scores.[9] Survival was statistically significantly reduced among HIV-infected persons with CCI scores of

0, 1, or 2 at diagnosis, suggesting that the impact of preexisting conditions may be worsened in HIV infection (Figure 2).

Role of Inflammation and Immunosenescence

Inflammation can be described as part of the body's complex biological response to harmful stimuli such as pathogens and cell damage. Franceschi and colleagues coined the term "inflamm-aging" to describe the interplay between inflammation and aging, mediated by proinflammatory cytokines and other proinflammatory and procoagulant factors, in such conditions as atherosclerosis, Alzheimer's disease, type 2 diabetes, osteoporosis, arthritis, cerebrovascular disease, chronic pulmonary disease, and thromboembolic disorders.[10,11]

HIV infection does indeed share numerous clinical similarities with aging, including an increased incidence of cardiovascular disease, malignancy, infection, chronic viral reactivation, sarcopenia and osteopenia, neurocognitive decline, and frailty. HIV infection results in T-cell activation and immunosenescence, which is characteristic of aging. In both HIV infection and aging, immunosenescence is marked by an increased proportion of CD28-, CD57+ memory CD8+ T cells with reduced capacity to produce interleukin 2 (IL-2), increased production of interleukin 6 (IL-6), resistance to apoptosis, and shortened telomeres. Up to half of peripheral CD8+ T cells are activated in HIV-infected patients; less than 10% are activated in healthy persons without HIV infection. One study of HIV-infected persons with a median age of 56 years and good immune reconstitution and viral suppression showed that they had T-cell characteristics similar to those of a group of HIV-uninfected subjects with a median age of 88 years.[12]

A very similar phenomenon of "inflamm-aging" has been observed in persons with cytomegalovirus (CMV) infection. CMV-seropositive persons older than 65 years have a much greater expansion of CD28- cells than age-matched CMV-seronegative control subjects, with many of these cells representing the oligoclonal expansion of CMV-specific T cells. Although the clinical significance of these findings remains unclear, it has been observed that older CMV-seropositive persons are less likely to respond to vaccines than age-matched CMV-seronegative persons,[13] and that CMV-associated immune system changes are predictive of early mortality among older persons.[14]

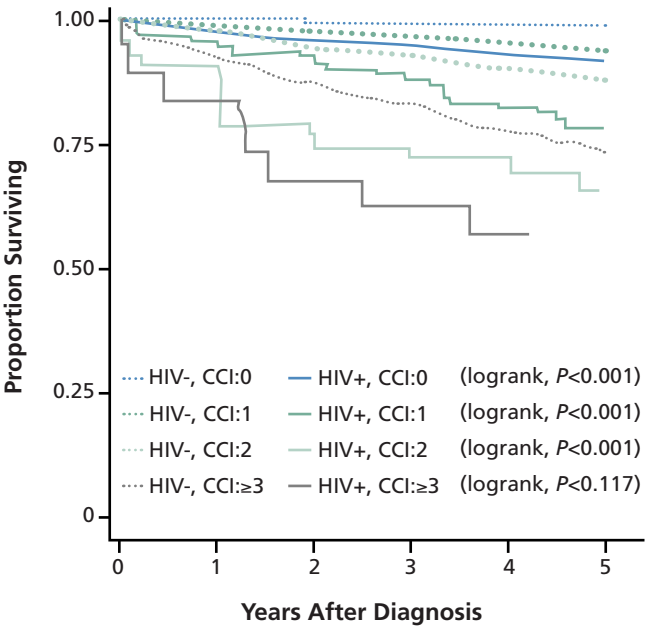

Figure 2. Survival after HIV diagnosis in HIV-infected patients (HIV+) and matched HIV-uninfected controls (HIV-) according to Charlson Comorbidity Index (CCI) score at time of diagnosis. Adapted from Lohse et al.[9]

Several studies have shown increased levels of biomarkers of inflammation in HIV-infected patients and an association of these elevated levels with increased risk for poorer outcomes and all-cause mortality. A case-control study in the SMART (Strategies for Management of Antiretroviral Therapy) trial population measured levels of the biomarkers high-sensitivity C-reactive protein (hs-CRP), IL-6, and D-dimer in patients with an opportunistic infection (OI) event. Levels of these markers were statistically significantly increased at the last measurement before OI onset, compared with levels at matched time points in control patients without an opportunistic infection.[15] Median CD4+ cell count was statistically significantly lower and plasma HIV RNA level was statistically significantly higher among patients with an OI event. The association of OI occurrence with elevated hs-CRP and IL-6 remained statistically significant on multivariate analysis, indicating an effect independent of low CD4+ cell count and elevated viral load.

Another study compared levels of inflammatory markers in patients in the SMART trial with levels in a long-term cohort of non–HIV-infected subjects without coronary heart disease who were being observed for atherosclerosis (MESA, Multi-Ethnic Study for Atherosclerosis). The study showed that after adjustment for age, sex, race, and factors such as dyslipidemia and smoking (which were more prevalent among HIV-infected patients), HIV-infected patients exhibited an approximately 50% higher hs-CRP level, 150% higher IL-6 level, 90% higher D-dimer level, and 25% higher cystatin-C level.[16]

Another nested case-control study in the SMART population examined the association of inflammatory markers with all-cause mortality, with adjustment for numerous potential cofactors including age, race, antiretroviral therapy, HIV RNA level, CD4+ cell count, body mass index, total and high-density lipoprotein (HDL) cholesterol, smoking, diabetes, hepatitis B virus (HBV) and hepatitis C virus (HCV) coinfection, and use of lipid-lowering and antihypertension medication. On this analysis, the adjusted odds ratios (ORs) for mortality when comparing the highest quartile of values for each biomarker with the lowest quartile were 3.1 for hs-CRP ($P = .02$), 3.1 for amyloid A ($P = .05$), 12.4 for IL-6 ($P < .0001$), and 41.2 for D-dimer ($P < .0001$).[17] The SMART trial included

a group receiving continuous antiretroviral therapy and a treatment interruption group. Among patients in the treatment interruption group who had plasma HIV RNA levels of 400 copies/mL or below at the time of antiretroviral therapy interruption, D-dimer levels increased by 27% ($P < .001$). Among patients not receiving antiretroviral therapy at study entry, initiation of therapy was associated with a 22% decrease in D-dimer level ($P < .001$).

A case-control study in the FIRST (Flexible Initial Retroviral Suppressive Therapies) trial population of antiretroviral therapy–naive patients examined the association between pretreatment biomarker levels and risk for AIDS or death. Pretreatment patients who developed AIDS or who died had statistically significantly elevated median levels of D-dimer (OR, 2.4; $P < .01$), CRP (OR, 2.1; $P < .01$), IL-6 (OR, 1.8; $P = .01$), IL-10 (OR, 1.5; $P = .02$), and hyaluronate (OR, 1.7; $P < .01$), with an increase in IL-8 approaching statistical significance (OR, 1.5; $P = .08$). Pretreatment interferon gamma (γ) and tumor necrosis factor alpha (TNF-α) levels were not statistically significantly increased in case patients.[18]

A summary of the relationships between inflammatory and coagulopathy markers and adverse outcomes in randomized controlled trials in HIV-infected subjects indicates that in addition to being associated with mortality, elevated D-dimer is associated with increased risk of cardiovascular disease; hs-CRP and IL-6 are associated with cardiovascular disease and opportunistic disease, and soluble CD14 (sCD14) is associated with microbial translocation.[19] Antiretroviral therapy has been found to reduce D-dimer levels and may reduce IL-6 levels, but has not been found to reduce hs-CRP levels, and its effect on sCD14 is unknown. It has been observed that although antiretroviral therapy reduces levels of some biomarkers, these levels still remain elevated compared with levels in HIV-uninfected persons.

Studies of Modulation of Immune Activation and Inflammation in HIV Infection

Although we are beginning to identify inflammation markers that appear to be associated with risk of poor outcome in HIV infection and are observing changes in some of these markers with antiretroviral therapy, it is still unclear how patients should be treated on the basis of this information or whether these markers should be used to assess potential risk reduction. Studies examining these issues are under way.

ACTG (AIDS Clinical Trial Group) A5275 is evaluating modulation of immune activation with statin therapy (atorvastatin) in HIV-infected patients without hyperlipidemia.[20] In addition to lowering low-density lipoprotein (LDL) cholesterol, the blocking of HMG-CoA reductase by statins reduces activation of guanosine triphosphate (GTP)-binding proteins (Ras and Rho) that act as molecular "switches" and regulate transcription of inflammatory response genes. Statins have been shown to reduce CD8+ T cell activation and reduce expression of IL-6, hs-CRP, D-dimer, sCD14, and TNF-α, with reductions in these biomarkers observed in numerous other settings including sepsis, pneumonia, influenza, chronic obstructive pulmonary disease, hepatocellular carcinoma, and cardiovascular disease.

In the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) study,[21,22] treatment with rosuvastatin statistically significantly reduced mortality and risk of venous thrombotic disease in apparently healthy subjects with elevated hs-CRP (> 2 mg/dL) and "normal" LDL cholesterol (< 130 mg/dL). It should be noted that the protective effects of statin therapy in this trial were only weakly correlated with the reductions in hs-CRP and LDL cholesterol, leaving it unclear precisely how statins are producing such benefits in this setting.

In addition to ACTG A5275, a number of other trials are examining immune activation, immunosenescence, and inflammation in HIV infection. Effects of rifamixin and sevelamer (which binds lipopolysaccharide) on microbial translocation are being examined, as are anticytokine or immunomodulatory effects of chloroquine, vitamin D, statin therapy, and HDL cholesterol–raising therapy with niacin or fibrates. Other potential strategies that warrant investigation include attempts to reduce inflammatory effects on end organs with such agents as aspirin, methotrexate, colchicine, fish oil, or a polypill regimen including a statin and low-dose warfarin or some combination of antiinflammatories.

Summary

In summary, although cohort studies demonstrate that patients who are virologically suppressed on antiretroviral therapy are still at greater risk of developing comorbidities at all ages, the precise mechanism has not been identified. Immune activation in HIV-infected patients suppressed on antiretroviral therapy has been attributed to endotoxemia resulting from a compromise in immunity caused by destruction of T cells in gut-associated lymphoid tissue and by residual HIV viremia. Lichtfuss and colleagues have also shown that natural killer cells remain activated in virologically suppressed patients on antiretroviral therapy and that defective natural killer cell antibody-dependent cell-mediated cytotoxity signaling is not restored by therapy, therefore contributing to such risk.[23] However, studies that clearly demonstrate a cause and effect that the latent virus is responsible for this increased risk of comorbidities are not available nor are there data to confirm that targeting inflammation and reducing markers of immune activation will, in fact, reduce this risk.

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Perspective

The Kidney in HIV Infection: Beyond HIV-Associated Nephropathy

Acute kidney injury (AKI) and chronic kidney disease (CKD) are more common in HIV-infected persons than in the general population. AKI is associated with poor health outcomes, including increased risk of heart failure, cardiovascular events, end-stage renal disease (ESRD), and mortality. The most common causes of AKI in HIV-infected persons are systemic infections and adverse drug effects. The prevalence of CKD is rising in the HIV-infected population and CKD is increasingly likely to be caused by comorbid conditions, such as diabetes and hypertension, that frequently cause CKD in the general population. Guidelines for CKD screening in HIV-infected patients are being revised. It is currently recommended that all patients be screened for creatinine-based estimates of glomerular filtration rate and for urine protein at the time of HIV diagnosis. Annual screening is recommended for high-risk patients. Hemodialysis, peritoneal dialysis, and kidney transplantation are all options for treating ESRD in HIV-infected patients. Hemodialysis and peritoneal dialysis offer similar survival in HIV-infected patients with ESRD. In selected patients with well-controlled HIV infection, kidney transplantation is associated with survival intermediate between that in the overall transplant population and that among transplant recipients older than 65 years. This article summarizes a presentation by Christina M. Wyatt, MD, at the IAS–USA continuing medical education program held in Chicago in May 2012, describing AKI and CKD using case illustrations.

HIV-associated nephropathy (HIVAN) is not the only cause of kidney disease in patients with HIV infection. Acute kidney injury (AKI) is more common in HIV-infected persons than in the general population and is associated with poor health outcomes. The prevalence of chronic kidney disease (CKD) is also increasing in the HIV-infected population, with a growing burden of CKD related to comorbid diabetes and hypertension. Dr Wyatt presented a series of cases to illustrate the issues of kidney disease in HIV infection.

Acute Kidney Injury

Case Illustration 1

A 56-year-old African-American woman presents with a 2-week history of nausea and vomiting. She has a history of AIDS, with a last measured CD4+ cell count of approximately 300/µL and well compensated cirrhosis due to hepatitis C virus (HCV) infection. Her antiretroviral medication consists of tenofovir/emtricitabine and ritonavir-boosted lopinavir. She has been taking ibuprofen for the past week for general malaise. She had missed her most recent follow-up visit with her physician. Her laboratory evaluation shows a serum creatinine level of 21 mg/dL, up from the prior measurement of 1.4 mg/dL. Apart from acidosis, routine electrolytes including sodium, chloride, potassium, and glucose are unremarkable. Urinalysis shows elevated protein, ketones, and glucose. An x-ray taken to rule out gastrointestinal obstruction is normal.

Characteristics of AKI. As noted, AKI is more common in HIV-infected individuals than in the noninfected general population. Several studies have indicated that risk factors for acute injury include underlying CKD, advanced HIV disease (whether measured by CD4+ cell count or HIV viral load), and HCV coinfection.[1-3] AKI is predictive of poor health outcomes in HIV-infected patients as well as in the general population, with even an asymptomatic increase in serum creatinine being associated with increased risk of heart failure, cardiovascular events, end-stage renal disease (ESRD), and death (Figure 1).[2,4]

In a cohort of approximately 750 patients followed prospectively at a single institution,[1] more than 10% developed at least 1 episode of AKI. Most of these cases required hospitalization or occurred as part of a concurrent illness

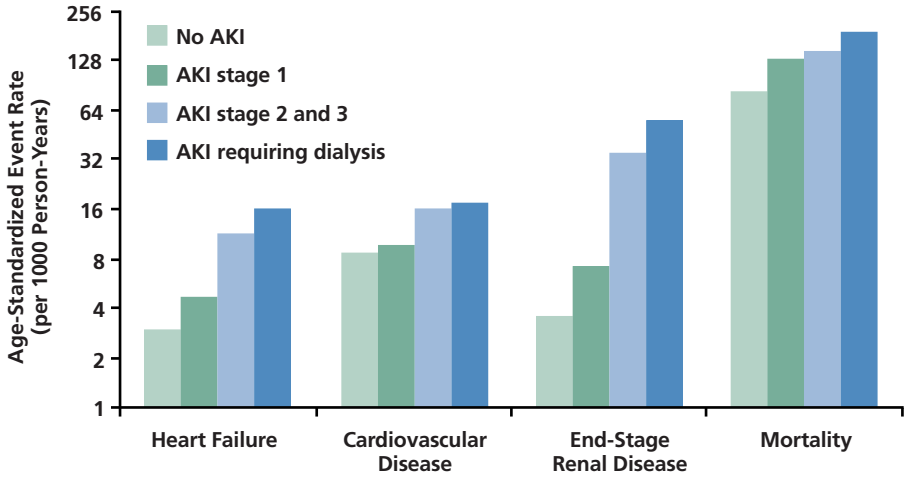

Figure **1**. Outcomes in HIV-infected patients with no acute kidney injury (AKI) or AKI of increasing severity. Adapted from Choi et al.[4]

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and hospitalization. In 52% of cases, the injuries were attributed to systemic infections, with 76% of these being AIDS-defining infections. These cases usually presented as a prerenal disorder or acute tubular necrosis (ATN).

Drug treatment was identified as the cause of acute injury in 32% of cases, with implicated drugs including antibiotics (eg, beta-lactams and aminoglycosides), indinavir or tenofovir, radiocontrast agents, nonsteroidal antiinflammatory drugs (NSAIDs), and lithium. The clinical presentation was variable, including ATN, interstitial nephritis, crystalluria/obstruction, or prerenal presentations associated with gastrointestinal effects of illness. Liver failure accounted for 10% of cases, with 90% of these being attributed to HCV disease.

Case Illustration 1, continued

Subsequent laboratory evaluation showed that the patient had a phosphorus level of 5.2 mg/dL and urine sodium level of 60 mEq/L. Among the potential causes of AKI that should be considered in this patient are prerenal effects, hepatorenal syndrome in association with cirrhosis, and tenofovir toxicity. Postrenal causes are unlikely, since there is no evidence of obstruction. Diabetic ketoacidosis generally needs to be considered in the differential diagnosis of AKI with glycosuria, but is unlikely in this patient because she has no history of diabetes and has a normal blood glucose level. In fact, the only reason a patient with normal serum glucose should have glucose in the urine is tubular dysfunction. Whether or not a patient is diabetic, the presence of "euglycemic" glycosuria is a sign of proximal tubular injury—and this is a typical presentation of tenofovir toxicity.

Tenofovir toxicity. The typical presentation of tenofovir toxicity is proximal tubulopathy. Approximately 2% of patients taking tenofovir develop substantial toxicity, with subclinical abnormalities being more frequent. Numerous studies have shown small reductions in estimated creatinine clearance or glomerular filtration rate (eGFR) in tenofovir recipients, with one meta-analysis indicating a mean difference of 3.9 mL/min in estimated creatinine clearance rate between patients receiving tenofovir and patients not receiving tenofovir (Figure 2).[5] The clinical relevance of these findings

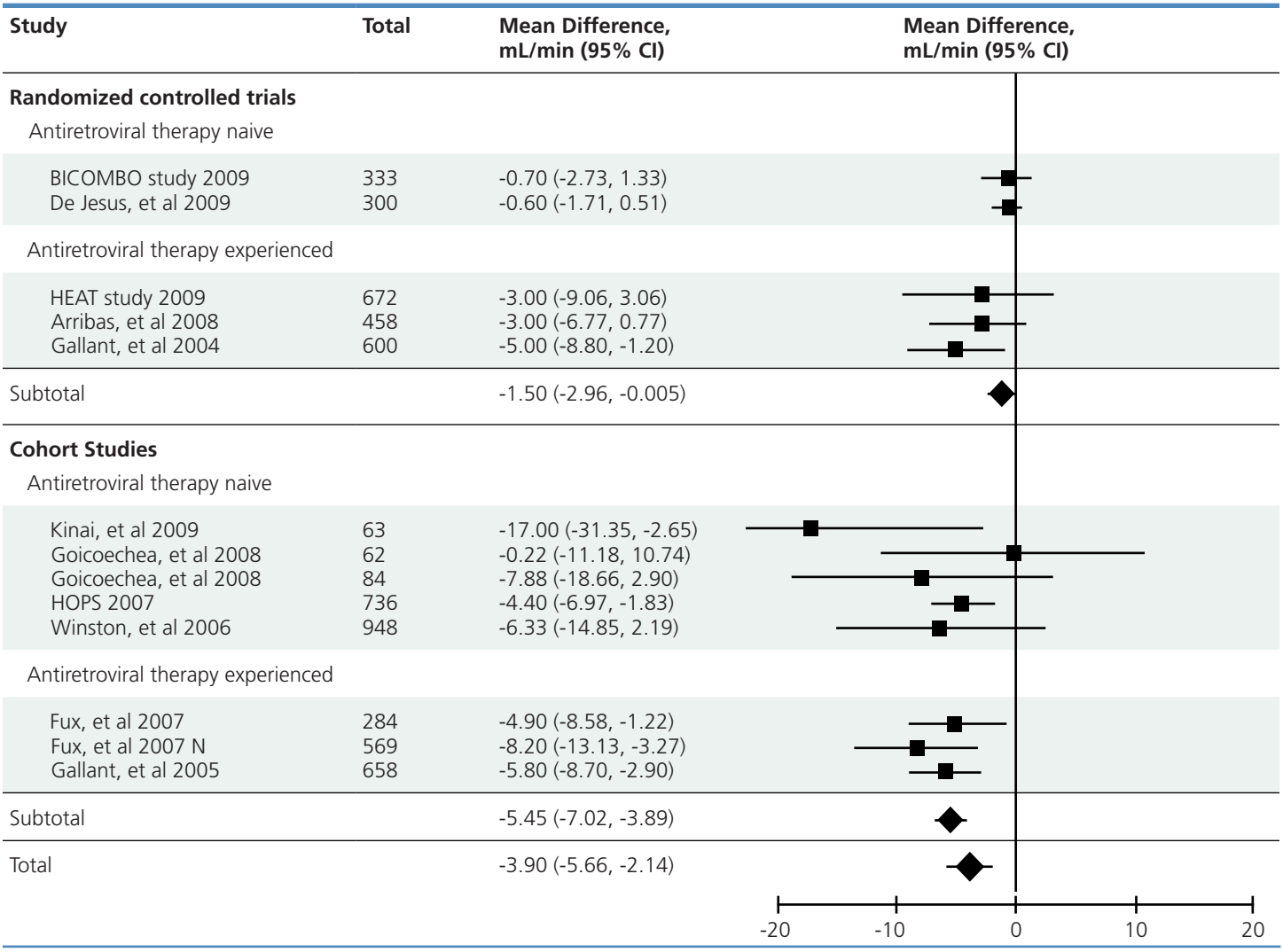

Figure 2. Mean difference and 95% confidence interval (CI) in estimated creatinine clearance rate between patients receiving tenofovir and patients not receiving tenofovir in selected randomized controlled trials and cohort studies. Adapted from Cooper et al.[5]

is unclear, and to date there have been no tenofovir-specific studies examining the implications of subclinical abnormalities for longer-term outcomes. A 2010 report from the EuroSIDA cohort indicated that cumulative exposure (up to more than 3 years) to tenofovir, indinavir, and ritonavir-boosted lopinavir was associated with a small but statistically significant increase ($P < .0001$ for each drug) in risk of CKD, defined as an eGFR of less than 60 mL/min.[6] A higher risk of CKD was associated with cumulative exposure to atazanavir ($P < .0001$), although the magnitude of increased risk (from 1 case per 100 patient-years at the start of treatment to 4 cases per 100 patient-years at more than 3 years of follow-up) observed in the EuroSIDA cohort has not been seen in other studies.

In a recent retrospective study conducted by the Veterans Affairs Medical Center in San Francisco, cumulative exposure to tenofovir was found to be statistically significantly associated with increased risk of CKD (defined as eGFR less than 60 mL/min or more rapid decline in eGFR) in every patient subgroup examined, except for patients with diabetes and patients with preexisting CKD (Figure 3).[7] The hazard ratios for the subgroups did not exceed 1.51 and generally were in the range of 1.2 to 1.4, representing a relatively small increase in risk over a low baseline risk. The findings of this study have sometimes been misinterpreted by patients as showing absolute risk of kidney dysfunction (ie, the hazard ratios of 1.2 to 1.4 have been misinterpreted as indicating an absolute risk of 20% to 40%).

The risk factors for tenofovir toxicity are not well defined, but likely include unrecognized low GFR or reduced GFR associated with concomitant conditions. In addition, ritonavir-boosted protease inhibitors (PIs) have been associated with an increased risk of tenofovir toxicity. Some initial data suggested that tenofovir renal toxicity may be associated with single nucleotide polymorphisms in renal transporters, although such findings have not been confirmed in larger studies. Given the association of tenofovir

Characteristic	Number of Events	Number of Participants	Hazard Ratio (95% CI)	Interaction *P* Value
Age < 46 years	1761	4525	1.29 (1.20-1.39)	.58
Age ≥ 46 years	1636	4100	1.33 (1.22-1.46)	
Black	1776	3897	1.30 (1.20-1.40)	.70
Nonblack	1624	4738	1.33 (1.22.1.44)	
No chronic kidney disease	3189	8261	1.33 (1.24-1.43)	.15
Chronic kidney disease	211	374	1.09 (0.84-1.42)	
No smoking	2872	7094	1.29 (1.20-1.39)	.071
Smoking	528	1541	1.51 (1.30-1.75)	
No cardiovascular disease	3154	8038	1.30 (1.21-1.40)	.19
Cardiovascular disease	246	597	1.49 (1.23-1.80)	
No Dyslipidemia	2972	7402	1.30 (1.20-1.40)	.43
Dyslipidemia	428	1233	1.38 (1.21-1.58)	
No diabetes	3142	8130	1.33 (1.24-1.43)	.14
Diabetes	258	505	1.09 (0.84-1.41)	
No Hypertension	1868	5501	1.36 (1.24-1.49)	.23
Hypertension	1532	3134	1.27 (1.18-1.36)	
No drug abuse	2142	5609	1.29 (1.19-1.39)	.22
Drug abuse	1258	3026	1.40 (1.26-1.55)	
HIV-RNA <100,000 copies/mL	2300	5947	1.39 (1.28-1.50)	.011
HIV-RNA >100,000 copies/mL	1100	2688	1.17 (1.05-1.30)	
CD4+ cell count 0-199/μL	1512	3544	1.33 (1.18-1.49)	.13
CD4+ cell count 200-350/μL	753	1859	1.49 (1.29-1.71)	
CD4+ cell count > 350/μL	1135	3232	1.19 (1.05-1.35)	
Body mass index < 25 kg/m^2	1826	4518	1.35 (1.23-1.48)	.27
Body mass index 25-30 kg/m^2	1101	2754	1.29 (1.14-1.47)	
Body mass index >30 kg/m^2	417	1026	1.27 (1.03-1.57)	

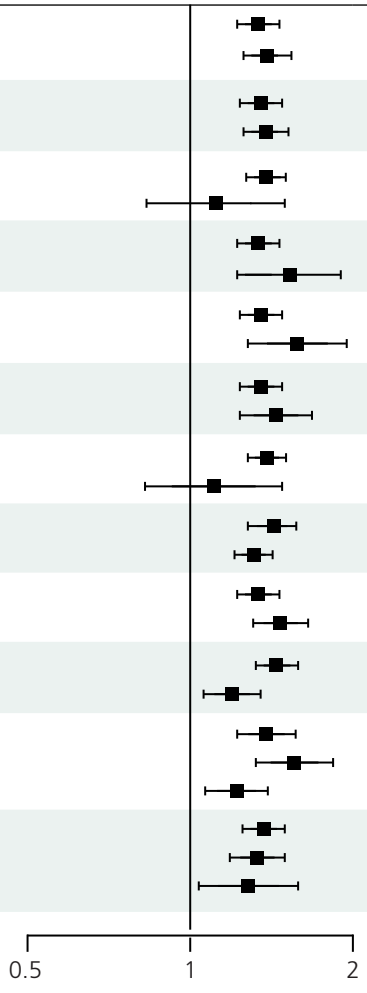

Figure **3**. Hazard ratios and 95% confidence intervals (CI) for chronic kidney disease (defined as glomerular filtration rate [GFR] of less than 60 mL/min or more rapid decline in GFR) according to subgroups of patients receiving tenofovir. *P* value is for interaction within subgroups. Adapted from Scherzer et al.[7]

renal toxicity with concomitant use of ritonavir-boosted PIs, initial studies focused on alterations in the proximal tubular transporter gene multidrug resistance-associated protein 2 (MRP2), which is known to be inhibited by ritonavir. However, tenofovir is trafficked from proximal tubular cells by a different transporter, multidrug resistance-associated protein 4 (MRP4), and it remains unclear how genetic alterations in MRP2 would affect tenofovir transport. It has also been thought that the decline in GFR observed with tenofovir may be the result of inhibition of tubular secretion of creatinine, similar to what has been observed with trimethoprim-sulfamethoxazole and what has been suggested to occur with the investigational antiretroviral-boosting agent cobicistat. However, available data indicate that such inhibition does not occur with tenofovir.

With regard to other issues involving tenofovir renal toxicity, tenofovir is used to treat hepatitis B virus (HBV) infection and to date there is no signal of renal toxicity from trials in HIV-uninfected HBV-infected patients. However, it bears noting that initial trials of tenofovir in HIV-infected patients also provided little indication of potential renal toxicity. Tenofovir is also used in HIV preexposure prophylaxis (PrEP), and to date there is no evidence of significant renal toxicity in HIV-uninfected individuals receiving tenofovir-containing PrEP. There was a nonsignificant trend toward increased creatinine levels in subjects from the iPrEx (Chemoprophylaxis for HIV Prevention in Men) study of tenofovir/emtricitabine in PrEP (2% versus 1% in placebo-treated patients, $P = 0.08$), but no difference in serum creatinine or phosphorus abnormalities in the Partners PrEP study.

There is interest in performing a pooled analysis of potential tenofovir renal toxicity in numerous PrEP study populations. Use of an investigational fixed-dose pill containing tenofovir/emtricitabine, the HIV integrase strand transfer inhibitor elvitegravir, and the elvitegravir-boosting agent cobicistat results in a decrease in eGFR compared with fixed-dose tenofovir/emtricitabine/efavirenz. Cobicistat is associated with a rapid and reversible decrease in estimated GFR, but no change in measured GFR, because it interferes with creatinine secretion. Although there is no evidence that cobicistat is nephrotoxic, use of tenofovir and cobicistat together may complicate the diagnosis of tenofovir renal toxicity. Whether the tenofovir prodrug in development poses a decreased risk of renal toxicity compared with tenofovir disoproxil fumarate also remains to be seen.

Chronic Kidney Disease

Case Illustration 2

A 43-year-old African-American woman presents with stage 5 CKD. She has HIV and HCV coinfection, with a nadir CD4+ cell count of more than 200/μL. She has had hypertension for 20 years and type 2 diabetes for 8 years and has a body mass index of 31 kg/m^2. She currently is receiving, at her own choice, suboptimal antiretroviral therapy with zidovudine and lamivudine, yet her viral load has remained below detection limits and her CD4+ cell count is currently 598/μL. She receives amlodipine and lisinopril for hypertension and insulin for diabetes, but blood pressure and blood glucose are poorly controlled. Her blood pressure is 156/98 mm Hg, serum creatinine level is 6.2 mg/dL, and serum phosphorus value is 6.4 mg/dL. Urinalysis shows 3+ proteinuria and 1+ glycosuria, and the urine:creatinine ratio is 3.2, indicating approximately 3 grams of proteinuria/24 hours.

Potential CKD diagnoses in this patient include diabetic nephropathy, hypertensive nephrosclerosis, and HCV-related glomerulonephritis, and further workup is necessary to arrive at a definitive diagnosis. It is unlikely that the patient has HIVAN. African-American patients have excess risk of HIVAN, which has been linked to single nucleotide polymorphisms on chromosome 22, although debate continues on which gene or genes are affected. However, HIVAN is classically associated with advanced HIV disease, and the patient has undetectable viral load and an elevated CD4+ cell count.

Changing spectrum of CKD. Data published in 2004 indicated that nearly half of cases of CKD in HIV-infected patients were caused by HIVAN. Smaller, roughly equal proportions of CKD were caused by immune complex disease, membranous/membranoproliferative glomerulonephritis in association with viral hepatitis, and diabetes or hypertension. An even smaller proportion was caused by acute interstitial nephritis.[8] However, studies since then suggest that the spectrum of CKD in HIV-infected patients is changing with less HIVAN and more comorbid kidney disease, such as that caused by hypertension and diabetes.[9]

Dr Wyatt believes that if all HIV-infected patients with CKD underwent renal biopsy, results would show that diabetes and hypertension are the leading causes of the disease, as they are in the general population. Indeed, kidney biopsy is underused for diagnosis, and would likely clarify the diagnosis in the patient in this case illustration. There is a longstanding perception that HIV-infected patients are at increased risk for complications of kidney biopsy; however, a large retrospective case series from The Johns Hopkins University School of Medicine did not demonstrate any increased risk of complications in HIV-infected individuals, apart from a small increase in risk in those coinfected with HCV.[10]

Guidelines for CKD screening in HIV-infected patients are in the process of being revised. It is currently recommended that all patients be screened for creatinine-based eGFR and urine protein at the time of HIV diagnosis. Annual screening is recommended in high-risk patients, including African-American patients and those with HCV coinfection, advanced HIV disease, diabetes, or hypertension.

Case Illustration 2, continued

The patient agreed to a kidney biopsy, because she was considering changing her antiretroviral regimen and it was agreed that she would do so if HIVAN

was demonstrated on biopsy. The biopsy showed advanced diabetic nephropathy and hypertensive vascular changes. There is no reason to believe that management of the CKD in this patient should differ from management of CKD from these causes in the general population. Thus, management should include tight blood pressure and glycemic control, weight loss, and cardiovascular risk modification, as well as a nephrology referral. Improved blood pressure and glycemic control are effective in delaying progression of CKD in the general population. Cardiovascular risk modification, including weight loss and smoking cessation when necessary, are important not only because they might improve the natural history of the kidney disease, but because patients with CKD are at increased cardiovascular risk. Drug regimens and dosing should also be reviewed. Apart from any need for diagnostic testing, referral to a nephrologist is appropriate for ESRD planning. In ESRD planning, hemodialysis, peritoneal dialysis, and kidney transplantation should be discussed with the patient.

HIV and ESRD. Data on prevalence of ESRD in HIV-infected patients are limited to ESRD caused by HIVAN. These data show an increasing prevalence of ESRD in the HIV-infected population, despite stabilization of the incidence of HIVAN-related ESRD that has occurred with wide use of antiretroviral therapy. It is likely that the prevalence of ESRD from any cause has also increased among HIV-infected patients. The prevalence of HIV infection in dialysis units is variable, with higher prevalence in urban centers such as New York City and Baltimore.

Hemodialysis, peritoneal dialysis, and kidney transplantation are all options for managing ESRD in HIV-infected patients. Survival rates are very similar with hemodialysis and peritoneal dialysis in HIV-infected patients with ESRD. Thus, it is reasonable to offer both options to patients and let them decide based on quality-of-life issues. Many patients have a strong preference for one modality or the other. For patients in whom hemodialysis is planned, early referral for fistula creation is essential to avoid use of a tunneled catheter. Development of a functioning fistula requires at least 8 weeks and may take up to 6 months in some patients. For patients on dialysis, antiretroviral drug regimens and doses should be carefully reviewed and adjusted if necessary.

A National Institutes of Health–sponsored study assessed outcomes of kidney transplantation in 150 HIV-infected patients with undetectable viral load, CD4+ cell count greater than 200/µL, and stable antiretroviral therapy.[11] Patient and graft survival rates were acceptable, being somewhat poorer than rates in the overall transplant population and somewhat better than those among HIV-uninfected transplant recipients older than 65 years. No increase in frequency of opportunistic infections was observed, and the 5 AIDS-defining illnesses that occurred can also be observed in HIV-uninfected kidney transplant recipients. However, substantial drug interactions occurred, particularly with PIs and nonnucleoside analogue reverse transcriptase inhibitors. It is crucial that any potential changes in antiretroviral regimens in the posttransplantation period be discussed with patients' transplant team. There can be large swings in trough levels of tacrolimus or cyclosporine, the calcineurin inhibitors used for immunosuppression, with changes in antiretroviral regimen, and some patients have lost their grafts due to changes in antiretroviral regimens in the posttransplantation period.

It should be noted that the patient under discussion likely would not be considered a candidate for transplantation unless her antiretroviral regimen were optimized and it was found that she could tolerate a stable optimal regimen.

Summary

AKI is common in HIV-infected patients and is associated with poor outcomes. Antiretroviral nephrotoxicity may be difficult to distinguish from AKI or CKD from other causes. Comorbid CKD is increasingly prevalent in HIV-infected patients. HIV-infected patients are candidates for hemodialysis or peritoneal dialysis, and select patients may be candidates for kidney transplantation.

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Perspective

Travel Medicine and Vaccines for HIV-Infected Travelers

For the purposes of vaccination, persons with asymptomatic HIV infection and CD4+ cell counts of 200/µL to 500/µL are considered to have limited immune deficits and are generally candidates for immunization. HIV-infected persons with CD4+ cell counts less than 200/µL or history of an AIDS-defining illness should not receive live-attenuated viral or bacterial vaccines because of the risk of serious systemic disease and suboptimal response to vaccination. Available data indicate that immunization during antiretroviral therapy restores vaccine immunogenicity, improves the rate and persistence of immune responses, and reduces risk of vaccine-related adverse events, although vaccine responses often are suboptimal. Major issues for travelers to the developing world are vaccine-preventable illnesses (hepatitis A virus, yellow fever, and typhoid fever), traveler's diarrhea, and malaria. This article summarizes a presentation by D. Scott Smith, MD, at the IAS–USA continuing medical education program held in San Francisco in April 2012.

An estimated 8% of travelers to the developing world require medical treatment during or after travel.[1] Major disease risks include vaccine-preventable diseases (hepatitis A virus, yellow fever, and typhoid fever) as well as diarrheal illness and malaria. The Centers for Disease Control and Prevention (CDC) Yellow Book 2012 provides a review of considerations for vaccination of immunocompromised travelers.[2] Following is a summary of these considerations in HIV-infected individuals.

Travelers With Limited Immunodeficiency

For the purposes of vaccination, persons with asymptomatic HIV infection and CD4+ cell counts of 200/µL to 500/µL are considered to have limited immune deficits. Most vaccines can elicit seroprotective levels of antibody in most HIV-infected patients in this category, although seroconversion rates and geometric mean titers of antibody in response to vaccines may be lower in HIV-infected individuals than in healthy people. Current CD4+ cell counts (increased by antiretroviral therapy), rather than their historical nadir counts, should be used to categorize immunologic status. In patients with CD4+ cell counts of 200/µL to 500/µL, the exact time at which reconstituted lymphocytes are fully functional is not well defined. To achieve a maximal vaccine response with minimal risk, many clinicians thus advise delaying immunization until 3 months after immune reconstitution, if urgency is not indicated.[2] Transient increases in HIV RNA levels, which return quickly to baseline, have been observed after administration of several different vaccines in HIV-infected people. Although the clinical significance of such increases is not known, these increases do not preclude the use of any vaccine.

Travelers With Severe Immunodeficiency

HIV-infected persons with CD4+ cell counts less than 200/µL or history of an AIDS-defining illness should not receive live-attenuated viral or bacterial vaccines because of the risk that the vaccine could cause serious systemic disease.[2] In addition, response to inactivated vaccines is suboptimal in these individuals. Thus, HIV-infected persons who have been immunized while CD4+ cell counts were less than 200/µL should be revaccinated at least 3 months after immune reconstitution with undetectable HIV RNA on antiretroviral therapy. Newly diagnosed, treatment-naive patients with CD4+ cell counts less than 200/µL should delay travel until CD4+ counts have been reconstituted with antiretroviral therapy. This delay will minimize risk of infection and avoid immune reconstitution illness during travel. Household contacts of severely immunocompromised patients may be given live-virus vaccines, such as yellow fever, measles-mumps-rubella, or varicella vaccines, but should not be given the live-attenuated influenza vaccine.[2]

There are few controlled studies on the effectiveness of vaccination in patients taking effective antiretroviral therapy. The available data indicate that antiretroviral treatment restores immune responsiveness to vaccines, improves the rate and persistence of immune responses, and reduces risk of vaccine-related adverse events. Despite effective antiretroviral therapy, vaccine responses in HIV-infected people often are suboptimal compared with response in HIV-seronegative individuals, although responses improve with higher and more frequent vaccine doses.

Vaccination for Hepatitis A Virus, Yellow Fever, and Typhoid Fever

Hepatitis A Virus

The CDC Advisory Committee on Immunization Practices has not made this an official recommendation, but it is generally agreed that HIV-infected persons should receive hepatitis A vaccination if their titers are negative, regardless of whether they are traveling. No revaccination is necessary.[3]

Yellow Fever

The mosquito that carries the organism that causes yellow fever, *Aedes aegypti*, is an aggressive daytime biter (unlike the malaria-transmitting *Anopheles*

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mosquito, which feeds at night) that can also transmit dengue and chikungunya viruses. The CDC's Yellow Book[2,4] gets its name in recognition of the health impact of yellow fever and its vaccine. The World Health Organization estimates that there are some 200,000 cases of yellow fever annually worldwide and 30,000 related deaths. Yellow fever is endemic in areas of South America (13% of reported cases) and Africa (87% of reported cases). Areas of South America and Africa where yellow fever vaccine is recommended are shown in Figure 1.

The yellow fever vaccine is a live-attenuated virus vaccine and thus is associated with risk of infectious complications in immunocompromised individuals. Major complications of yellow fever vaccination are vaccine-associated viscerotropic disease and vaccine-associated neurologic disease. These complications are reported to occur at rates of 0.4 and 0.8 cases per 100,000 doses distributed, although it is likely that cases are underreported.

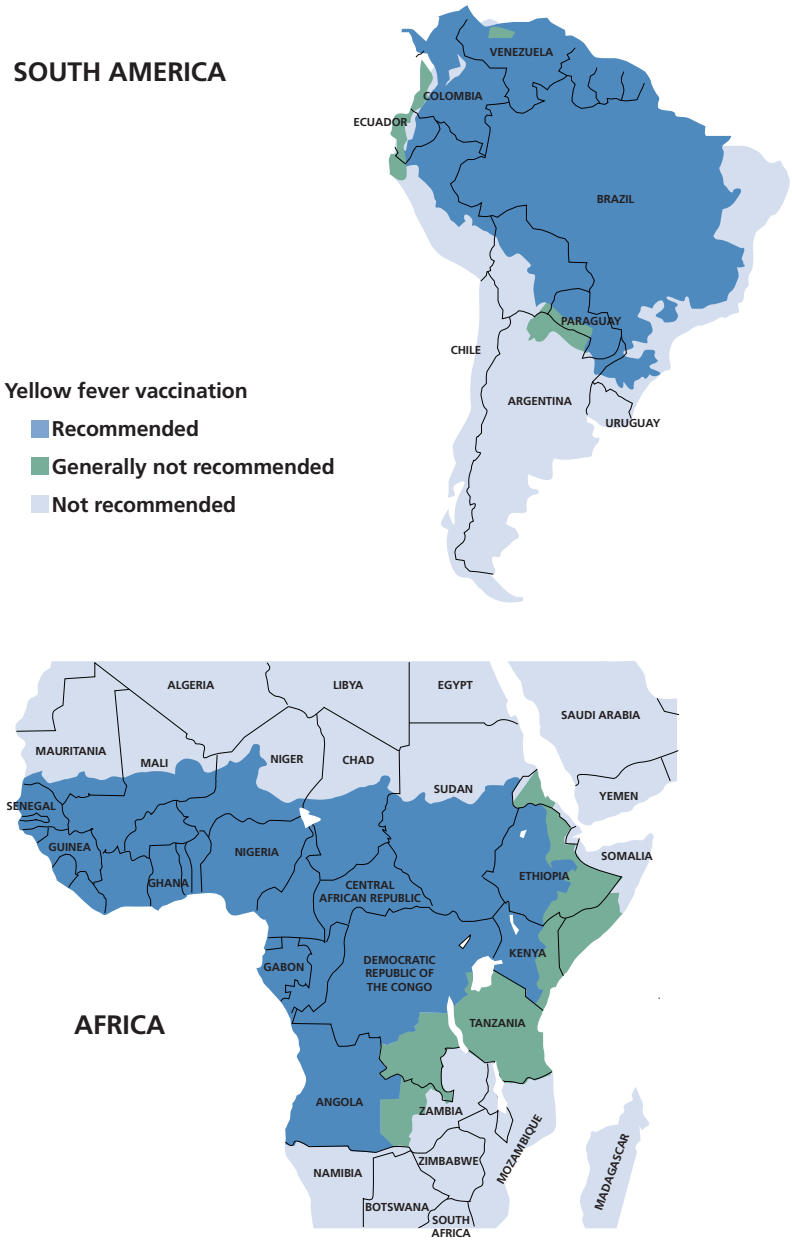

Figure **1**. Areas in South America (top) and Africa (bottom) where yellow fever vaccination is recommended (blue), generally not recommended (green), and not recommended (light blue). Adapted from the Centers for Disease Control and Prevention Yellow Book.[4]

Travelers with severe immune compromise, including those with symptomatic HIV infection and AIDS, should be strongly discouraged from travel to destinations that present a true risk for yellow fever. If travel to an area where yellow fever vaccine is recommended is unavoidable, these travelers should be carefully instructed in methods to avoid mosquito bites and be provided with a vaccination medical waiver.

Persons with limited immune deficits or asymptomatic HIV infection traveling to areas where yellow fever is endemic may be offered the vaccine and monitored closely for possible adverse effects. Since vaccine response may be suboptimal, persons receiving the vaccine are candidates for serologic testing 1 month after vaccination. Data from clinical and epidemiologic studies are insufficient at this time to evaluate the actual risk of severe adverse effects associated with yellow fever vaccine among recipients with limited immune deficits.

A recently reported study in 364 patients with HIV infection showed antibody response to the yellow fever vaccine in 93% of patients after a mean duration of 8.4 years after vaccination.[5] The key determinant of antibody response was HIV RNA level at the time of vaccination; lower neutralizing antibody titers were associated with shorter duration of undetectable HIV RNA and higher HIV RNA level at immunization, with no correlation observed between CD4+ cell count and antibody response. The authors concluded that the key determinant of antibody response was the HIV replication status at immunization. No association was found between antibody response and CD4+ cell count. The CDC recommendation about yellow fever vaccination for only those with CD4+ cell counts greater than 200µ/L remains for now.

Vaccination "by pen" may be in order for some HIV-infected travelers. If international travel requirements—and not true exposure risk—are the only reasons to vaccinate a traveler with asymptomatic HIV infection or a limited immune deficit, the physician should provide a waiver letter.

The exemption letter, signed by the physician, simply states "Yellow fever vaccine for 'NAME' is medically contraindicated because of the following condition: [age, pregnancy, immunocompromised status]." However, international health regulations do not allow an exemption from yellow fever vaccination for travel to a country that has a vaccination requirement for entry, even for medical reasons. Thus, travelers should be warned that vaccination waiver documents may not be accepted by some countries. If the waiver is rejected, the option of deportation might be preferable to receipt of vaccine at the destination. For countries that require vaccination for entry, travelers must have proof that the vaccine was administered at least 10 days prior to entry.

Typhoid Fever

Typhoid fever is most commonly caused by the gram-negative bacterium *Salmonella typhi*. It has an incubation period of 1 to 3 weeks, and its clinical presentation is characterized by high fever (with gradual increase), headache, fatigue, anorexia, dizziness, abdominal pain, nausea, and constipation or diarrhea. Diarrhea may become hemorrhagic or dysenteric. Transmission occurs through person-to-person contact or through contaminated food, drink, or water. Humans are the sole reservoir hosts. Typhoid can be contracted even when care is taken with food and water. Areas of high, intermediate, and low typhoid prevalence are shown in Figure 2.

Two typhoid vaccines are available, both with approximately 50% to 80% efficacy. The oral live-attenuated vaccine requires 4 doses over 7 days and is protective for more than 5 years. The parenteral Vi capsular polysaccharide vaccine, which consists of a bacterial capsule of *S typhi,* is given as a single intramuscular dose and is protective for approximately 2 years. HIV-infected people with CD4+ cell counts below 200/µL can receive the parenteral vaccine—but not the oral vaccine (which is live). Although the parenteral vaccine is less immunogenic the more immunosuppressed the patient is, this vaccination can be offered (and is recommended) when a live vaccine is not appropriate and the travel destination would lead to significant typhoid exposure. Vaccination is recommended for anyone traveling for 3 weeks or more in endemic areas and anyone traveling for any duration in the Indian subcontinent or off usual tourist routes in endemic areas. Vaccination ideally should be given or started at least 2 weeks prior to exposure.

Diarrhea

Diarrheal illness accounts for 20% to 40% of reported disease in travelers.[1] Traveler's diarrhea may be caused by a large number of different foodborne and waterborne pathogens (a few common examples include *Salmonella*, *Campylobacter*, *Giardia*, and *Cryptosporidium* species), and can be severe or become chronic in immunocompromised people. Enteroaggregative *Escherichia coli* is an emerging enteric pathogen that can also cause persistent diarrhea in HIV-infected people. A meta-analysis of randomized trials examining the effect of modifying behaviors to avoid contracting diarrheal illness indicates no preventive impact.

Bacteria account for most cases of traveler's diarrhea. The most common antibiotic treatment is ciprofloxacin (500 mg twice daily for 1-3 days). Ciprofloxacin (or another fluoroquinolone) or azithromycin (1 g once daily for 3 days) is used for illness contracted in Southeast Asia. Because *Campylobacter* infection is common in Thailand and fluoroquinolone resistance has been reported in 70% to 90% of cases, azithromycin is the treatment of choice there. There are high resistance rates to trimethoprim-sulfamethoxazole worldwide, and it is rarely used for treatment of diarrheal illness outside of that contracted in Mexico or Central America. Rifaximin is an effective drug, but it is relatively expensive and requires twice-daily dosing.

There are few concerns over interaction of antibiotic treatment with antiretroviral drugs. Fluoroquinolones have no clinically significant interactions with HIV protease inhibitors (PIs), with nucleoside analogue reverse transcriptase inhibitors (nRTIs), or with nonnucleoside analogue RTIs (NNRTIs). Interactions between macrolide antibiotics and antiretroviral drugs include increased clarithromycin levels with ritonavir, atazanavir, and lopinavir; decreased zidovudine levels with

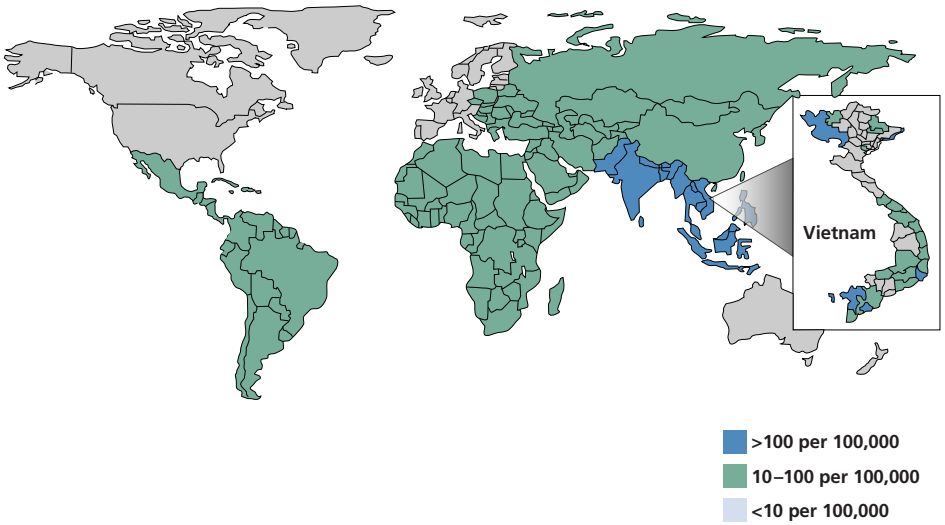

Figure **2**. Incidence of typhoid fever per 100,000 persons. Country-specific mean annual incidence rates, some of which are estimates, are for 2000. Province-specific incidence rates for Vietnam are for children to 5 to 14 years of age, between 1999 and 2003 (inset). Adapted from DeRoeck et al.[6]

clarithromycin; and potential interactions between clarithromycin and efavirenz or nevirapine. Azithromycin appears to pose little risk of drug interactions with antiretroviral drugs. There are no data available on potential interactions between rifaximin and antiretroviral drugs; rifaximin acts in the gut lumen, with little systemic exposure.

Antibiotic prophylaxis for traveler's diarrhea is not recommended, because it poses risk of adverse effects, may contribute to drug resistance, and may contribute to poor judgment in terms of exposure (eg, among adventurous eaters). Such risks should be weighed against the potential outcome of prompt, early self-treatment. Data on prophylactic use of probiotics are inconclusive. Bismuth subsalicylate is effective as prophylaxis. This agent has antisecretory, antiinflammatory, and antibacterial effects, and has been found to be 40% to 65% protective and to reduce the number of stools and duration of illness by 50%. Bismuth subsalicylate decreases antibiotic absorption, and must be taken 6 hours before or after an antibiotic dose. It may also cause blackening of the tongue and stools and has been associated with risk of tinnitus. Because bismuth subsalicylate contains aspirin, it must be avoided by persons who have aspirin allergy; it also should be avoided by those taking warfarin. As prophylaxis, bismuth subsalicylate should be taken at a dose of 2 tablets 4 times a day (eg, before each meal and at bedtime).

In addition to antibiotic treatment, traveler's diarrhea can be safely treated with antimotility agents (eg, synthetic opiates such as loperamide or diphenoxylate), and oral rehydration therapy.

Malaria

A study published in 2006 indicated that for travelers returning with fever, malaria was the cause in 62% of cases from sub-Saharan Africa; 13% to 14% of cases from Central America, South America, Southeast Asia, and South Central Asia; and less than 1% of cases from the Caribbean.[1] As with immunocompetent travelers, immunocompromised travelers to malaria-endemic areas should receive counseling about ways to avoid mosquito bites (eg, bed netting, insect repellants, permethrin-impregnated clothing). They should also be prescribed appropriate drugs for malaria prophylaxis. However, it must be stressed that HIV infection may be associated with more serious malarial disease and that malaria increases HIV RNA level and may thus exacerbate HIV disease progression. Further, drugs used in malaria prophylaxis may interact with antiretroviral drugs and there is a general lack of data on safety and efficacy of antimalarial regimens in patients taking antiretroviral therapy.

In areas where malaria is chloroquine-sensitive, weekly chloroquine is the first choice for prophylaxis. In areas with chloroquine resistance, weekly mefloquine, daily doxycycline, daily atovaquone-proguanil, or daily primaquine are options. Advantages of mefloquine include the weekly schedule and moderate cost; disadvantages include the potential for neuropsychiatric adverse effects and the need to take it 1 to 2 weeks before and 4 weeks after exposure. Advantages of doxycycline include low cost and preventive effects against diarrhea, leptospirosis, and *Rickettsia* species infections. Doxycycline's disadvantages include the need to take it daily, associated photosensitivity, the potential for gastrointestinal upset and vaginal candidiasis, and the need to take it 1 day before and 4 weeks after exposure. Advantages of atovaquone-proguanil include its safety and the need to take it only 1 day before and 7 days after exposure; disadvantages include higher cost, the potential for headache, gastrointestinal upset, insomnia, and the need to take it daily and with food. Advantages of primaquine include low cost and the need to take the drug only 1 day before and 3 days after exposure; disadvantages include the need to measure glucose-6-phosphate dehydrogenase levels prior to taking the drug, reduced efficacy compared with other options, and the need to take the drug daily.

Potential interactions between antiretroviral drugs and antimalarial drugs are shown in Table 1. Because no clinically significant interactions are expected between tetracyclines and PIs or

Table **1**. Potential Interactions Between Antiretroviral and Antimalarial Drugs*

	HIV Protease Inhibitors	Nucleoside Analogue Reverse Transcriptase Inhibitors	Nonnucleoside Analogue Reverse Transcriptase Inhibitors
Mefloquine	Potential interaction with all protease inhibitors	No data available	Decreased mefloquine levels with efavirenz and nevirapine
Atovaquone-Proguanil	Atovaquone: potential interactions with indinavir, ritonavir, lopinavir, atazanavir, darunavir, tipranavir Proguanil: potential interactions with ritonavir, lopinavir	Atovaquone: no clinically significant interactions expected Proguanil: no data available	Atovaquone: potential interaction with efavirenz Proguanil: potential interaction with efavirenz
Doxycycline	No clinically significant interactions expected	No data available	No clinically significant interactions expected
Chloroquine	Potential interaction with ritonavir	No data available	No clinically significant interactions expected
Primaquine	No clear data	No data available	No data available

*Known potential interactions within an HIV drug class are noted in the table. Currently there are no known drug combinations with absolute contraindications to coadministration. Adapted from the Centers for Disease Control and Prevention (CDC) Yellow Book.[2]

NNRTIs, doxycycline might be a reasonable choice for malaria prophylaxis in a patient on antiretroviral therapy. Atovaquone-proguanil is a reasonable option for patients whose antiretroviral regimen includes nelfinavir or nevirapine. Although atovaquone is not expected to have substantial interaction with commonly used nRTIs, no data are available on potential interactions between proguanil and nRTIs. Few data are available on potential interactions between antimalarial drugs and HIV entry inhibitors or HIV integrase strand transfer inhibitors.

In summary, HIV-infected patients are traveling more because of the great health gains observed from antiretroviral regimens over the last decade. It is crucial in this population to ensure safe travel using the array of interventions available including vaccines and antiinfective medicines to prevent commonly observed and serious infections. We have reviewed safe choices for optimizing this prevention, paying attention to the specific HIV regimen and CD4+ cell counts with respect to choosing vaccines as well as minimizing risks for malaria and diarrheal disease.

Presented by Dr Smith in April 2012. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Smith in July 2012.

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Case Report From the Field

FDG-PET/CT Imaging in the Diagnosis of HIV-Associated Multicentric Castleman Disease: Something Is Still Missing

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Now that [^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET) has become an established imaging tool in oncology, it is attracting interest in the field of infectious diseases.[1] Several studies have used FDG-PET to examine the pathophysiology of HIV infection as well as other conditions such as lipodystrophic syndrome and HIV-related neurocognitive disorders.[2] In clinical practice, FDG-PET has been proposed to assess fever of unknown origin[3] or with lymphoproliferative disorders such as Castleman disease in individuals with HIV infection.[4]

Castleman disease has heterogeneous manifestations ranging from asymptomatic disease to recurrent episodes of widespread lymphadenomegaly with systemic symptoms.[5] Its incidence is not known, but the estimated number of cases in the United States ranges from 30,000 to 100,000.[6] Castleman disease traditionally has been classified as unicentric and multicentric disease,[7] but more recently histopathogenic taxonomy has been preferred.[8] The 4 types of Castleman disease according to this classification are in the box.

Case Presentation

Recently 2 patients attending the outpatient clinic at Niguarda Cà Granda Hospital in Milan, Italy, developed multicentric Castleman disease. Each underwent the same laboratory and imaging assessments, which elicited some different results. Although combined FDG-PET/computed tomography (CT) scans in HIV-seropositive patients with multicentric Castleman disease can demonstrate widespread nodal and spleen abnormalities that improve with remission,[9] FDG-PET/CT tested negative in the first patient and positive in the second. The clinical features and laboratory values in these patients are described in Table 1. The 2 cases were compared in an effort to explain these different results.

Patient 1

This patient was a 40-year-old man who tested HIV-seropositive in 2005. At the beginning of 2010, he started complaining of fever, and had diffuse lymphadenopathy and florid Kaposi sarcoma (KS) skin lesions. Systemic symptoms had spontaneously resolved but recurred during the year with progressive worsening. A first lymph node biopsy was performed in June 2010, but it did not result in a diagnosis. In August 2010, a total body CT scan documented superficial and deep enlarged lymph nodes in the patient's neck, axilla, mediastinum, and abdomen. Subsequently, a FDG-PET/CT was performed, but it did not show any lesions with increased metabolic activity (Figure 1). A second lymph node biopsy was performed, which showed a mantle zone hyperplasia with skin-onion features but CD31- and human herpesvirus 8 (HHV8)–negative immunohistochemistry. At the beginning of 2011, a pathologist with experience in Castleman disease reviewed the slides from the second biopsy, which had been performed at the time the FDG-PET/CT was performed, and made a diagnosis of hyaline-vascular (HV)-type Castleman disease with a weakly HHV8-positive immunohistochemistry. The patient underwent systemic chemotherapy with 4 cycles of etoposide plus rituximab, followed by 4 cycles of rituximab alone. At a 12-month follow-up, he had full remission of his disease.

Patient 2

Patient 2 was a 21-year-old man who first tested HIV-seropositive in 2009.

Box. Classification of Castleman Disease by Histopathogenic Taxonomy

- **Hyaline-vascular (HV) type**, which usually has a unicentric presentation, involving a single node or a localized group of nodes, lacks systemic signs or symptoms, and generally has a benign course
- **Plasma-cell (PC) type,** which is more commonly multicentric, presents systemic symptoms and abnormal laboratory findings, and behaves more aggressively
- **Plasmablastic (PB) type,** which occurs in immunosuppressed patients, is related to human herpesvirus 8 (HHV8) infection, and presents as mainly multicentric, with systemic symptoms and a poor outcome
- **Not otherwise specified type,** with a multicentric presentation but with few systemic symptoms

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At the end of 2010, he started complaining of fever, and had diffuse lymphadenopathy, splenomegaly, and a high serum C-reactive protein level. Systemic symptoms had resolved spontaneously but recurred during the year with progressive worsening. In June 2011, a total body CT scan documented enlarged lymph nodes in the patient's neck, axilla, abdomen, and groin, and an enlarged spleen 18 cm in diameter.

Subsequently, a FDG-PET/CT scan confirmed increased metabolic activity (Figure 1). A lymph node biopsy, performed in July 2011, documented chronic lymphadenitis with intrafollicular dendritic cell expansion. The immunohistochemistry was negative for HHV8, CD3, CD5, CD20, CD21, CD30, CD79α, BCL2, BCL6, and MIB1. At that time he had a sudden clinical worsening that led to a life-threatening multiorgan impairment. A second lymph node biopsy, performed in August 2011, showed a retained architecture, with HHV8-positive follicles of variable size, involuted germinal centers, mantle zone hyperplasia with skin-onion features, plasma cells (CD138+, MUM1p+), proliferating (Ki-67–positive), and activated plasma blasts (CD30+).

Table 1. Clinical Features and Laboratory Values

	Patient 1	Patient 2
Year of HIV diagnosis	2005	2009
HIV risk group	MSM	MSM
CD4+ cells/μL (%) at HIV diagnosis	487 (17%)	285 (16%)
HIV RNA copies/mL at HIV diagnosis	61,074	1,180,316
Nadir CD4+ cells/μL (%)	219 (15%)	196 (22%)
Zenith HIV RNA copies/mL	534,955	1,180,316
Antiretroviral regimen	Emtricitabine/tenofovir+ atazanavir/ritonavir	Emtricitabine/tenofovir+ atazanavir/ritonavir
Months of antiretroviral treatment at diagnosis of multicentric Castleman disease	58	19
Status at the time of multicentric Castleman disease diagnosis		
CD4+ cells/μL (%)	895 (28%)	171 (21%)
HIV RNA copies/mL	<40	110
HHV8 DNA copies/mL	38	958,962
HHV8 Ab (lytic antigen)	256	4,096
HHV8 Ab (latency antigen)	256	512
KS lesions site (number)	Skin (10)	None
Maximum diameter of enlarged lymph nodes (mm)		
	• Submandibular (15) • Neck (20) • Subclavian (20) • Axilla (20) • Mediastinum (15) • Abdomen (coeliac, para-aortic, iliac) (20) • Groin (15)	• Neck (25) • Supra- and subclavian (28) • Axilla (40) • Abdomen (coeliac, para-aortic, iliac) (34) • Groin (20)
Spleen diameter (cm)	15	18
Histopathogenic type	Hyaline-vascular	Plasmablastic

HHV8 DNA was assessed with real-time polymerase chain reaction in plasma; antibodies to IgG anti-HHV8 lytic/latency antigens detected by immunofluorescence assay.

MSM indicates men who have sex with men; Ab, antibody; HHV8, human herpesvirus 8; IgG, immunoglobulin G; KS, Kaposi sarcoma.

A diagnosis of plasmablastic (PB)-type Castleman disease was made, and the patient started systemic chemotherapy with rituximab. After the first dose, he developed a splenic infarct and underwent a splenectomy. Six cycles of rituximab were administered and he showed rapid clinical improvement. At a 3-month follow-up visit, the patient still had abdominal lymphadenopathy and a low HHV8 viral load. At 9 months, the patient was in good clinical condition, HHV8 viral load was undetectable, and a new FDG-PET/CT scan did not show any signs of disease activity.

Discussion

These 2 patients had quite different HIV virologic and immunologic status. Patient 1 had a high CD4+ count with undetectable viral load. Patient 2 had a very low CD4+ cell count and had detectable HIV RNA, suggesting HIV as an ancillary cause of diffuse nodal enlargement that might jeopardize the assessment of the real extent of Castleman disease. Further, there were other major differences between these 2 cases of multicentric Castleman disease. In clinical course, patient 1 had less aggressive disease. In terms of correlation with HHV8, patient 1 had a low viral load and antibody titers. As far as presence of KS, patient 1 had 10 skin lesions compared with none in patient 2. Histopathogenic type was HV in patient 1 and PB in patient 2. Such observations emphasize that HV- and PB-type Castleman disease have very different features. This could be a reason for the different FDG-PET/CT results. HV-type is generally unicentric,[10] although multicentric disease has been reported.[11] HV-type is not thought to be related to HHV8;[12] its pathogenesis is still unknown, even if vascular endothelial growth factor may have an important role.[13]

FDG-PET/CT has been described as a reliable tool in detecting Castleman disease,[14-16] but data on its usefulness for HV-type differ. Reddy and Graham showed that FDG-PET effectively revealed a thoracic HV-type mass,[17] and Murphy and colleagues found that

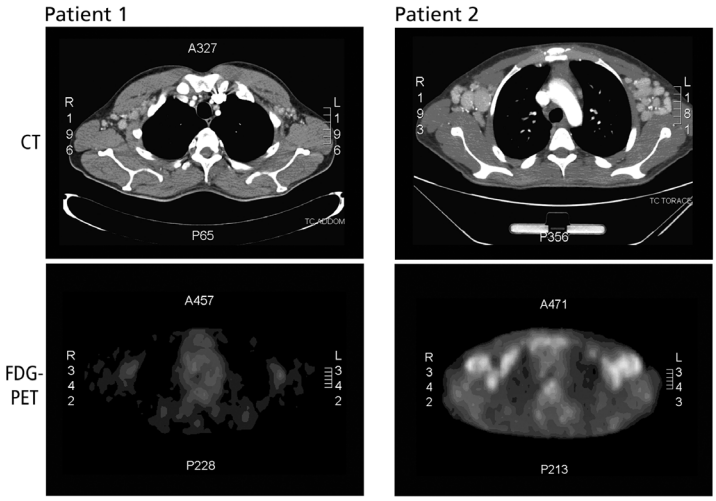

Figure **1**. Computed tomography (CT) scans (upper panels) and [^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET) scans (lower panels) on patients 1 and 2. CT scans show enlarged axillary lymph nodes in both patients. FDG-PET scan on patient 1 (lower left panel) does not show increased metabolic activity. FDG-PET scan on patient 2 has substantial pathologic accumulation of FDG.

FDG-PET detected a pelvic HV-type mass, but only with a modest accumulation of FDG.[18] Barker and colleagues evaluated the role of FDG-PET/CT in the management of PB-type and found that although FDG-PET/CT might be more sensitive than CT alone in detecting multicentric Castleman disease, it is less reliable in monitoring disease activity after treatment.[19]

The utility of FDG-PET/CT in the management of HIV-associated Castleman disease has lights and shadows. Although HV-type Castleman disease is uncommon in HIV-infected patients, this possible diagnosis, when indicated by FDG-PET/CT result, should be taken into account. Additionally, FDG-PET/CT has limited value in ruling out other causes of fever and lymphadenopathy in HIV, such as lymphoma or an opportunistic infection. In particular, there are no data on whether FDG-PET/CT can detect different metabolic activities of the recently described KS-associated herpesvirus (KSHV) inflammatory cytokine syndrome (KICS), whose clinical, biochemical, and virologic features are similar to Castleman disease but whose histopathologic findings are not.[20,21]

Despite the relatively low incidence of Castleman disease, its aggressive and life-threatening course warrants an optimization of diagnostic tools. So far, FDG-PET/CT use for diagnosing Castleman disease has been reported in only a small number of patients.[4] Data defining sensitivity and specificity of FDG-PET/CT for Castleman disease diagnosis are lacking. FDG-PET/CT might have an important role, but it should not replace biopsy for diagnosis of Castleman disease. Instead, FDG-PET/CT may help in choosing which gland to biopsy in cases in which a previous biopsy failed to confirm a diagnosis of Castleman disease.[22]

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Cases on the Web

www.iasusa.org/cow

Cases on the Web (COW) is a series of case-driven continuing medical education activities sponsored by the IAS–USA. The *COW* program was created to offer convenient online access to top-quality education in the management of HIV, hepatitis C virus, and other viral infections.

NEW Sequencing Antiretroviral Drugs in the Patient with Numerous Treatment Failures and Multidrug-Resistant Virus

Snigdha Vallabhaneni, MD, MPH, and Harry W. Lampiris, MD
CME Credit Available: 1.5 *AMA PRA Category 1 Credits*™
Level: Advanced

Antiretroviral therapy options for treatment-naive and treatment-experienced patients have dramatically expanded in the past few years. Patient-specific factors inform the decision about which new antiretroviral agents to select. Dr Vallabhaneni and Dr Lampiris describe strategic approaches to using antiretroviral drugs in new and preexisting drug classes to design antiretroviral regimens for patients with numerous treatment failures and multidrug-resistant HIV.

NEW Management of Chronic Hepatitis C Virus Infection in Advanced Liver Disease

Kenneth E. Sherman, MD, PhD, and Syed Hussain, MD
CME Credit Available: 1.25 *AMA PRA Category 1 Credits*™
Level: Advanced

Hepatitis C virus (HCV) is a leading cause of chronic liver disease worldwide. Because the disease is largely asymptomatic until advanced liver disease develops, patients are often diagnosed after years of infection. Newer treatments offer a greater chance of cure, but may be challenging and are often contraindicated in patients with advanced disease. This activity presents important information on identifying and appropriately treating patients with advanced liver disease due to chronic HCV. Dr Sherman and Dr Hussain discuss disease management, including referral for liver transplantation.

NEW Novel HIV-1 Resistance and Tropism Testing

Jonathan Li, MD
CME Credit Available: 1.25 *AMA PRA Category 1 Credits*™
Level: Advanced

When available, HIV drug-resistance testing should be used to guide the selection of an optimal antiretroviral regimen. Technologic advances in HIV sequencing and sequence detection have revolutionized the study of antiretroviral drug resistance and HIV diversity, and are increasingly moving from the laboratory to clinical practice. Dr Li addresses provides clinicians with background information to choose HIV drug-resistance testing and to guide the selection of an optimal antiretroviral regimen.

Prevention of Mother-to-Child Transmission in Highly Treatment-Experienced HIV-Infected Women

Theresa Barton, MD, and Laura N. Armas-Kolostroubis, MD
CME Credit Available: 1.25 *AMA PRA Category 1 Credits*™
Level: Advanced

The use of antiretroviral therapy and prophylaxis has dramatically reduced HIV transmission to infants. However, ongoing use of antiretroviral agents can lead to emergence of viral resistance, especially as women experience antiretroviral treatment failures. Dr Barton and Dr Armas-Kolostroubis address maintaining low perinatal transmission rates in the presence of resistant HIV, which requires knowledge of recommendations for treatment and prophylaxis in pregnant women and neonates.

Sexually Transmitted Infections in the HIV-Infected Patient

Linda M. Gorgos, MD, MSc
CME Credit Available: 1.75 *AMA PRA Category 1 Credits*™
Level: Advanced

Sexually transmitted infections (STIs) among HIV-infected persons are an important source of morbidity that impacts personal and public health. Effective detection includes routine assessment of sexual-risk behavior and regular screening for STIs regardless of symptoms. Dr Gorgos addresses a comprehensive approach to treating infected individuals and their partner(s) and discusses emerging challenges.

Drug Interactions with Medications for Treating Hepatitis C Virus Infection

John J. Faragon, PharmD, BCPS
CME Credit Available: 1.5 *AMA PRA Category 1 Credits*™
Level: Advanced

The availability of direct-acting antiviral drugs boceprevir and telaprevir has led to increased success in treating HCV infection. Dr Faragon discusses the effects of HCV protease inhibitors (PIs) and other drugs on the cytochrome P450 enzyme system, outlines strategies for preventing and managing interactions between HCV PIs and select coadministered drugs used in primary care settings, and provides sources of information about drug interactions between HCV drugs, HIV antiretroviral drugs, and selected other drugs.

These Internet enduring material activities have been approved for *AMA PRA Category 1 Credit*™.

COMING SOON

Look for these new *Cases on the Web* activities in the remaining months of 2012.

September: The Use of Hepatitis C Virus Protease Inhibitors in HIV/HCV Coinfected Patients

Jennifer Lin, MD, and David L. Wyles, MD

Hepatitis C virus (HCV) infection is now thought to be the leading chronic viral disease-related cause of death in the United States, having recently surpassed HIV infection. HIV infection in persons with HCV infection is associated with an increased risk of cirrhosis and decompensated liver failure. Use of HCV protease inhibitors (HCV PIs) has markedly increased the success of HCV treatment, but complicating issues remain, including adverse effects and drug-drug interactions between HCV PIs and antiretroviral drugs.

October: Anorectal Screening in HIV Infection

Timothy J. Wilkin, MD, MPH

November: Primary Care Issues in HIV Management

Howard Libman, MD

December: Managing and Counseling for Adolescents with HIV Infection

Donna C. Futterman, MD

For information about *Cases on the Web*, please contact the IAS–USA.
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