Volume **19** Issue **5** December **2011**/January **2012**

Topics in Antiviral Medicine™

A publication of the IAS–USA

Perspectives

Special Contribution

Topics in Antiviral Medicine™

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Current and previous issues of *Topics in Antiviral Medicine (*as well as *Topics in HIV Medicine)* are available online at www.iasusa.org.

ISSN 2161-5861 (Print)
ISSN 2161-5853 (Online)

Printed in USA on acid-free paper

IAS–USA
International Antiviral Society–USA

Grant Support

The 14th Annual Clinical Conference for the Ryan White HIV/AIDS Program was sponsored by the IAS-USA under the US Department of Health Resources and Services Administration (HRSA) contract number HHSH250200900010C.

Support for the 2011 *Improving the Management of HIV Disease* continuing medical education program, including preparation of this issue, is from the following:

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Topics in
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Continuing Medical Education

The following article in this issue is associated with CME credit: Post WS. Predicting and preventing cardiovascular disease in HIV-infected patients. *Top Antivir Med*. 2011;19(5):169-173

Instructions

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

- Read the article (see pages 169-173)
- Review a selection of the references
- Reflect on how the information might be applied to clinical practice
- Complete the posttest
- Complete the CME claim form and send it to the IAS–USA office.

Learning Objectives

On completion of this activity, learners will be able to describe evidence from observational studies regarding HIV infection and cardiovascular disease (CVD), and describe risk assessment and risk management for CVD.

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Intended Audience

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

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Dr Post and Dr Ketlogetswe have no relevant financial affiliations to disclose.

Dr Richman has been a consultant to Biota, Bristol-Myers Squibb, CHIMERx, Gen-Probe Inc, Gilead Sciences, Inc, Idenix Pharmaceuticals, Inc, Johnson & Johnson, Merck & Co, Inc, and Monogram Biosciences, Inc. He has been the recipient of research grants or contracts from Merck & Co, Inc. Dr Richman has been a stock options holder of CHIMERx and Idenix Pharmaceuticals, Inc.

Dr Benson has no relevant financial financial affiliations to disclose.

Preparation of this activity was made possible by grant support as described on the inner front cover of this issue.

This CME activity is offered from **January 30, 2012**, to **January 30, 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 attendance.

Posttest Questions

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 more correct.

1. What is the major determinant of risk for cardiovascular disease in HIV-infected patients?

- ❑ **A.** Chronic inflammation and accelerated aging associated with HIV infection
- ❑ **B.** Adverse effects of antiretroviral therapy on metabolism
- ❑ **C.** Traditional cardiovascular disease risk factors such as diabetes, smoking, hypocholesterolemia, and hypertension

2. Which statement about the Framingham Risk Score (FRS) is **correct?**

- ❑ **A.** The FRS can be used to predict 10-year risk of cerebrovascular accident
- ❑ **B.** The FRS can underestimate lifetime risk of coronary heart disease in women
- ❑ **C.** The FRS is not valid for use in the HIV-infected population

3. According to current American Heart Association/American College of Cardiology recommendations, which group has the **strongest recommendation** (Class I) for aspirin use (daily or every other day) for the primary prevention of cardiovascular disease (CVD)?

- ❑ **A.** Men with 10-year risk of coronary heart disease of 10% or higher
- ❑ **B.** Women aged 65 years and older who are at risk for CVD
- ❑ **C.** Women younger than 65 years who are at risk for CVD

4. In the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes) study, simvastatin was compared with simvastatin plus extended-release niacin. Which statement about the AIM-HIGH study findings is **correct?**

- ❑ **A.** Increases in triglyceride level occurred in the simvastatin/niacin group
- ❑ **B.** No statistically significant difference in primary endpoint was observed between the 2 treatment groups
- ❑ **C.** A greater occurrence of stroke was observed in the simvastatin-only group than in the simvastatin/niacin group

5. Evidence from the SMART (Strategies for Management of Antiretroviral Therapy) study of antiretroviral treatment interruption suggests that HIV infection itself increases the risk of coronary heart disease. Which statement about the SMART study findings is **correct?**

- ❑ **A.** Treatment interruption was not associated with an increase in risk for mortality or cardiovascular disease
- ❑ **B.** Treatment interruption was associated with an increase in risk for mortality, but was not associated with increase in risk for cardiovascular disease
- ❑ **C.** Increases in IL-6 (interleukin 6) and D-dimer in the treatment interruption group were statistically significantly correlated with plasma HIV RNA levels

To receive CME credit, please complete the posttest, participant information, and evaluation forms and return all to the IAS–USA.

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Please complete the following evaluation form for this activity:

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Please list 3 specific measurable changes you will make in your practice based on the information presented in the article:

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2. _____
3. _____

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Perspective

Predicting and Preventing Cardiovascular Disease in HIV-Infected Patients

Cardiovascular disease (CVD) is the leading cause of non–HIV-related death in HIV-infected persons. The risk of CVD in HIV-infected persons appears to reflect the contribution of a number of factors, including non–HIV-related (traditional) cardiovascular risk factors, chronic inflammation associated with HIV infection, and metabolic adverse effects of antiretroviral therapy. Traditional CVD risk factors, however, are the major determinants of risk in HIV-infected patients and this population carries a high burden of such factors. HIV infection may also be an independent risk factor for CVD, but there is not yet sufficient evidence to consider HIV infection itself a coronary heart disease risk equivalent (eg, in the same manner as diabetes) or to change calculation of risk in the HIV-infected population. In the absence of specific randomized trials in the HIV-infected population, HIV-infected persons should be treated for cardiovascular risk factors according to current national guidelines for reducing risk, including those for aspirin use and for treatment of dyslipidemia, hypertension, and metabolic syndrome. This article summarizes a presentation by Wendy S. Post, MD, at the 14th Annual Clinical Conference for the Ryan White HIV/AIDS Program held in Tampa, Florida, in June 2011. Dr Kerunne Ketlogetswe provided additional editing. The Clinical Conference is sponsored by the IAS–USA under the Health Resources and Services Administration (HRSA) contract number HHSH250200900010C.

Cardiovascular disease (CVD) is the leading cause of non-HIV-related death in people with HIV infection. Risk in HIV-infected persons appears to reflect contributions of non-HIV-related cardiovascular risk factors, the chronic inflammatory response in HIV infection, as well as metabolic adverse effects of antiretroviral therapy (namely, insulin resistance, dyslipidemia, abnormal fat distribution, and hypertension).

Evidence of Cardiovascular Risk From Observational Studies

Observational studies suggest an increased risk for coronary heart disease (CHD) associated with HIV infection and antiretroviral therapy. However, not all studies have yielded consistent results, with some studies finding an increased risk of CVD and others none, likely owing to limitations of study design among the different studies that prevent straightforward interpretation of the findings.

Compelling evidence that HIV infection itself increases the risk of CHD comes from recent data from the Strategies for Management of Antiretroviral Therapy (SMART) study. This study showed that interruption of antiretroviral treatment was associated with a statistically significant 80% increase in risk for mortality (hazard ratio [HR], 1.8; $P = .007$) compared with continuous treatment among more than 5000 patients with CD4+ cell counts above 350/μL.[1] Treatment interruption was also associated with a 70% increase in risk for major cardiovascular, renal, or hepatic disease (HR, 1.7; $P = .009$). For fatal or nonfatal CVD alone, the risk was increased by 60% (HR, 1.6; $P = .05$), suggesting that inadequately treated viral infection itself increased the risk of CVD. Inflammatory markers were strongly associated with mortality. At 1 month, increases in IL-6 and D-dimer occurred in 30% and 16% of patients, respectively, in the treatment interruption group versus 0% and 5%, respectively, in the continuous treatment group ($P < .0001$ for differences). Increases in IL-6 and D-dimer in the treatment interruption group were statistically significantly correlated with plasma HIV RNA levels ($P < .0001$).

In a case-control study in the SMART trial population, higher IL-6 and D-dimer levels were associated with dramatically increased risk of all-cause mortality, with the adjusted odds ratios (ORs) for the top quartile versus bottom quartile being 8.3 ($P < .0001$) for IL-6 and 12.4 ($P < .0001$) for D-dimer.[2] Elevated high-sensitivity C-reactive protein (hs-CRP) was also associated with increased risk of mortality (OR, 2.0; $P = .05$).

Risk Assessment

Data from the HIV Outpatient Study (HOPS) cohort show that traditional CVD risk factors predict risk for CVD in HIV-infected patients. Adjusted ORs for a CVD event were 3.3 for age greater than 40 years, 3.2 for diabetes, 1.9 for hyperlipidemia, and 1.7 for hypertension.[3]

The Framingham Risk Score (FRS), which incorporates traditional risk factors of age, total cholesterol, high-density lipoprotein (HDL) cholesterol (a negative risk factor), smoking status, and systolic blood pressure, is widely used to predict 10-year risk of myocardial infarction (MI) or CHD death. The FRS is valid and applicable in the HIV-infected population. There is increased interest in extending risk assessment beyond the 10-year interval. Particularly among younger individuals and women, in whom a cerebrovascular accident (CVA) is much more common as the initial presentation of CVD, the 10-year FRS can underestimate life-

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See page 167 for information on CME credit for this article.

time risk of CHD and preclude warranted intensive prevention strategies.[4] As such, the American Heart Association (AHA) CVD Prevention Guidelines for women have been amended to define high risk as a 10%, 10-year risk for all CVD, not just CHD alone.

Coronary Calcification

Calcium is an integral component of arterial plaque, and increased coronary calcification is a risk factor for coronary events. Atherosclerosis begins early and most plaque ruptures occur at sites where there was previously less than 40% stenosis. Stress tests detect only bloodflow-limiting stenoses, whereas coronary calcium scans can detect more diffuse atherosclerosis that is not yet limiting flow. Coronary calcium scans may thus permit targeting of patients for aggressive primary prevention.

The MESA (Multi-Ethnic Study of Atherosclerosis) trial showed that coronary artery calcium score predicted CHD in each of 4 racial/ethnic groups and in men and women after accounting for traditional risk factors.[5] The current AHA recommendations indicate that measurement of coronary artery calcium (CAC) is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (10-year risk of 10%-20%; class IIa recommendation) and may be reasonable in persons at low to intermediate risk (10-year risk of 6%-10%; class IIb recommendation). Patients at low risk (10-year risk < 6%) should generally not undergo coronary calcium scanning. The cardiovascular substudy in the Multicenter AIDS Cohort Study (MACS) did not show increased CAC in HIV-infected individuals receiving antiretroviral therapy.[6] Nonetheless, it may be considered in patients at intermediate risk to help guide the decision on how aggressively to treat such patients.

C-Reactive Protein (CRP)

In the general population, the inflammatory marker CRP has been strongly associated with risk for cardiovascular events in many, but not all, studies. CRP is also associated with other cardiovascular risk factors, particularly metabolic syndrome. High CRP levels are predictive of total mortality in HIV-infected patients.[1] The JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study examined whether treatment with rosuvastatin versus placebo could prevent cardiovascular events in more than 17,000 patients in the general population. Men aged 50 years or older and women aged 60 years or older with no prior CVD or diabetes, normal low-density lipoprotein (LDL) cholesterol level (< 130 mg/dL), and elevated high-sensitivity CRP (≥ 2 mg/L) were included.[7] Rosuvastatin treatment was associated with a statistically significant 44% reduction in risk for the combined endpoint of MI, stroke, unstable angina, revascularization, or cardiovascular death (HR, 0.56; $P < .00001$). The number of patients needed to treat to prevent 1 event was 25. An unanswered question is whether statin therapy provides substantial preventive benefit even in patients without elevated CRP and LDL cholesterol level below 130 mg/dL.

Elements of Risk Management

The following are the ABCs of CVD risk management in both HIV-infected persons and uninfected persons:

- **A**: **A**spirin when indicated
- **B**: **B**lood pressure control
- **C**: **C**holesterol management; Cigarette smoking cessation
- **D**: **D**iabetes and prediabetes management
- **E**: **E**xercise

Aspirin

Data on the preventive effects of aspirin are conflicting. The Physician's Health Study, reported in 1989, showed that aspirin 325 mg every other day dramatically reduced the risk for a first MI compared with placebo among more than 20,000 men observed for 5 years; no reduction in risk for stroke was observed.[8] However, the Women's Health Study, reported in 2005, found no benefit in preventing first major CVD event with aspirin 100 mg every other day versus placebo among nearly 40,000 women observed for 10 years. A benefit was observed in women aged older than 65 years,[9] however, and a subgroup analysis indicated a reduction in risk for stroke with aspirin treatment.

A meta-analysis of more than 50,000 women and 44,000 men receiving aspirin at dosages of 100 mg every other day to 500 mg per day for 3.7 years to 10 years in primary prevention trials showed the following: (1) women, but not men, had a statistically significantly reduced risk for stroke; (2) men, but not women, had a statistically significantly reduced risk for MI; (3) both men and women had a statistically significantly reduced risk for a major cardiovascular event; and (4) neither men nor women had reduced risk for cardiovascular event plus all-cause mortality.[10]

In light of these data, what are the recommendations for aspirin use for primary prevention of CVD? The current AHA recommendations are that at-risk women aged 65 years or older receive 81 mg a day or 100 mg every other day, with the recommendation graded class IIa (benefit exceeds risk and cost). At-risk women younger than 65 years should receive aspirin for stroke prevention, with the recommendation graded class IIb (less robust evidence for benefit, but shown to be helpful in select patients). It is not recommended that optimal-risk women younger than 65 years receive aspirin therapy (class III; ie, not recommended for use, has no or limited evidence of benefit and may cause harm). For primary prevention of CVD in men, there is a class I recommendation (ie, benefits greatly outweigh the risks) for use of aspirin 75 mg to 162 mg daily in those at intermediate risk (10-year risk of CHD ≥ 10%).

Hypertension

Prehypertension, defined as systolic BP (SBP) 120 mmHg to 139 mmHg or diastolic BP (DBP) 80 mmHg to 89 mmHg, warrants intervention through lifestyle management. For patients with

stage 1 hypertension (SBP, 140-159 mmHg or DBP, 90-99 mmHg), initial therapy is thiazide-type diuretics for most. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta blockers, calcium channel blockers, or combinations of these may be considered, and are used more frequently now that they are available in generic formlations. Most patients with stage 2 hypertension (SBP ≥ 160 mmHg or DBP ≥ 100 mmHg) require 2-drug combinations. For both stage 1 and stage 2 hypertension, there are compelling indications for particular drug treatments.[11]

LDL Cholesterol Reduction

Along with intensive lifestyle modification including diet and exercise, statin therapy has been the mainstay of reducing heart disease risk, and numerous studies over the years have shown a 30% to 40% reduction in risk for MI with statin therapy in primary prevention trials, and 20% to 30% in secondary prevention trials. The current National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) guidelines (Table 1) recommend an LDL cholesterol level goal of below 100 mg/dL (optional goal, < 70 mg/dL) in high-risk patients with CHD or CHD risk equivalents (10-year CHD risk > 20%). Moderately high-risk patients (2 or more risk factors; 10-year risk, 10%-20%) should aim for levels below 130 mg/dL (optional goal, < 100 mg/dL). Moderate-risk patients (2 or more risk factors; 10-year risk, < 10%) are recommended a goal level below 130 mg/dL, and low-risk patients (0-1 risk factor) should maintain an LDL cholesterol level below 160 mg/dL.[12] CHD risk equivalents include diabetes, peripheral vascular disease, carotid endarterectomy, and aortic aneurysm. There is evidence indicating that achieving the lower, optional LDL cholesterol level goal is associated with increased preventive benefit. Statin therapy should be monitored closely in patients receiving certain classes of antiretroviral drugs, which can potentiate the risk of myopathy.[21]

Triglyceride Reduction

Hypertriglyceridemia is common in individuals receiving antiretroviral therapy. Optimal fasting TG levels, defined as below 100 mg/dL, are a parameter of metabolic health in the recent AHA scientific statement on triglycerides and CVD.[13] The statement also indicates that nonfasting TG levels can be used to screen individuals with high fasting levels, with normal nonfasting levels defined as below 200 mg/dL.

Desirable and high TG levels have been set at progressively lower levels in recommendations over the past 25 years. Currently, levels below 150 mg/dL are considered desirable, 150 mg/dL to 199 mg/dL borderline, 200 mg/dL to 499 mg/dL high, and 500 mg/dL or above very high. In current lipid-lowering guidelines, lowering LDL cholesterol level is the primary goal, and lowering non-HDL cholesterol level is a secondary target once LDL cholesterol goals are met. The goal for non-HDL cholesterol in persons with high serum triglycerides can be set at 30 mg/dL higher than the goal for LDL cholesterol. This can be achieved either by intensifying statin therapy or adding nicotinic acid, a fibrate, or omega-3 fatty acids. If TG levels are greater than 500 mg/dL, lipid-lowering therapy is necessary to reduce the risk of pancreatitis. For lower TG levels, lifestyle modification is recommended, in part because studies of TG-lowering agents—niacin and fibrates—have yielded disappointing results.

A recent example of such studies is the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes) study.[14] The AIM-HIGH study compared treatment with simvastatin versus simvastatin plus extended-release niacin in more than 3000 men and women with vascular disease, low HDL cholesterol level (< 40 mg/dL in men, < 50 mg/dL in women), high TG levels (150-400 mg/dL), and LDL cholesterol level 180 mg/dL or below. The primary endpoint was the composite endpoint of CHD death, MI, CVA, or high-risk acute coronary syndrome hospitalization.

The mean age at study entry was 64 years. A majority of patients had CHD (92%), metabolic syndrome (81%), and hypertension (71%), and many had diabetes (34%). Nearly all (94%) were on statin therapy at study entry. At baseline, mean LDL cholesterol level was 71 mg/dL, mean HDL cholesterol level was 34.9 mg/dL, and median TG level was 161 mg/dL.[15]

The study was stopped early after an interim analysis at 32 months showed no difference in the primary endpoint (HR, 1.05; for simvastatin plus niacin versus simvastatin; *P* value not significant) despite reductions in TG and increases in HDL cholesterol in the niacin

Table 1. National Cholesterol Education Program Adult Treatment Panel Guidelines on Low-Density Lipoprotein Cholesterol Goals

Patient Category	Low-Density Lipoprotein Cholesterol Goal
High Risk Coronary heart disease (CHD) or CHD risk equivalents (10-year CHD risk > 20%)	**< 100 mg/dL** (optional goal < 70 mg/dL)
Moderately High Risk 2 or more risk factors for CHD (10-year CHD risk, 10%-20%)	**< 130 mg/dL** (optional goal < 100 mg/dL)
Moderate Risk 2 or more risk factors for CHD (10-year CHD risk < 10%)	**< 130 mg/dL**
Low Risk 0 or 1 risk factor for CHD	**< 160 mg/dL**

Adapted from Grundy et al.[12]

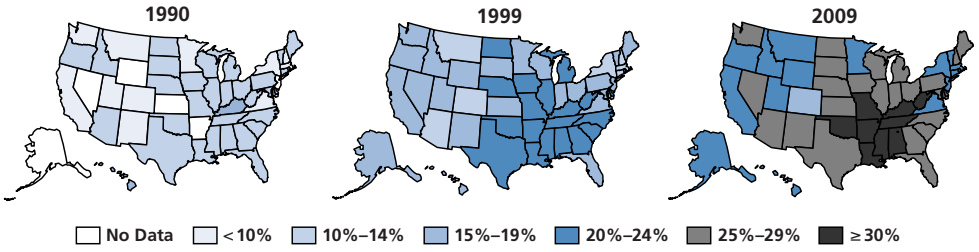

Figure **1**. Obesity rates among adults in the United States during 1990, 1999, and 2009. Obesity is defined as a body mass index greater than or equal to 30 kg/m^2, or about 30 pounds overweight for a 5-foot, 4-inch person. Adapted from Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System.[18]

group. A greater occurrence of stroke was observed in the simvastatin/niacin group versus the simvastatin-only group (1.6% vs 0.7%, respectively), although this may be a chance finding. Although the addition of niacin in this study provided no preventive benefit, these results should not be extrapolated to other populations given the well-controlled LDL cholesterol level at baseline in the study patients. It is likely that results of this study will not lead to recommendations to stop niacin in patients already receiving and tolerating the drug. However, physicians may be less likely to start niacin treatment in patients with well-controlled LDL cholesterol levels.

Smoking Cessation

There is a high prevalence of smoking in HIV-infected patients. Efforts to encourage smoking cessation, including behavioral support and pharmacotherapy with nicotine replacement, bupropion, or varenicline in appropriate patients, should be used.[16]

Metabolic Syndrome

Americans spend more money on fast food than on higher education.[17] As shown in Figure 1, the prevalence of obesity, defined as body mass index (BMI) greater than or equal to 30 kg/m^2, has increased dramatically in the United States over the past 2 decades.[18] This epidemic of obesity is accompanied by epidemics of metabolic syndrome and diabetes, both of which are associated with dramatically increased risk of CVD. For example, the risk of MI in patients with diabetes is equivalent to the risk of recurrent MI in nondiabetic patients with prior MI; the risk is increased 2-fold compared with either of these groups in patients with both diabetes and prior MI.

Metabolic syndrome is defined as the presence of any 3 of the following 5 criteria: (1) fasting glucose level 100 mg/dL or higher, (2) TG level 150 mg/dL or higher, (3) blood pressure (BP) 130/85 mmHg or higher, (4) HDL cholesterol level less than 50 mg/dL in men or less than 40 mg/dL in women, and (5) central obesity, defined as abdominal waist circumference greater than 35 inches in women and greater than 40 inches in men.

In addition to controlling other specific risk factors, management of metabolic syndrome emphasizes weight reduction through lifestyle modification. It is highly beneficial for patients with metabolic syndrome, and especially those with diabetes, to meet with a nutritionist or nurse practitioner who can spend time reinforcing lifestyle modification strategies. Goals for weight reduction are BMI of 18.5 kg/m^2 to 24.9 kg/m^2 or waist circumference of less than 35 inches for women and less than 40 inches for men, with a 10% weight reduction during the first year of treatment.[19]

Diet and Exercise

The basic approach to weight reduction is to initiate caloric restriction and increase caloric expenditure. The AHA dietary committee recommendations for CVD risk reduction are shown in Table 2.[20] For most people, changes involve eating more fruits and vegetables (a good method is to ensure that at least half the dinner plate contains vegetables), more whole-grain, high-fiber foods, and more fish, while reducing saturated fat intake and consumption of food or drinks with added sugar. Food should be prepared with little or no salt, particularly for patients with hypertension.

Exercise goals are a minimum of 30 to 60 minutes of exercise 5 times per week, with an optimal level of 30 to 60 minutes 7 times per week.[19] Aerobic activity (walking, jogging, cycling) should be encouraged and supplemented with an increase in daily activities (eg, walking breaks at work, gardening, household work). Medically supervised programs (eg, cardiac rehabilitation) should be encouraged for high-risk patients such as those with recent acute coronary syndrome or revascularization and those with heart failure. Patients should also be encouraged to perform resistance training (eg, with weight machines or free weights) twice a week.

Table **2**. American Heart Association Nutrition Committee Dietary Recommendations for Cardiovascular Disease Risk Reduction

- Balance calorie intake and physical activity to achieve or maintain a healthy body weight
- Consume a diet rich in fruits and vegetables
- Consume whole-grain, high-fiber foods
- Consume fish, especially oily fish, at least twice a week
- Limit intake of saturated fat to less than 7% of energy, trans fat to less than 1% of energy, and cholesterol to less than 300 mg/day by:
  - Choosing lean meat and vegetable alternatives
  - Choosing fat-free (skim), 1% fat, and low-fat dairy products
  - Minimizing intake of partially hydrogenated fats
- Minimize intake of beverages and foods with added sugar
- Choose and prepare foods with little or no salt
- If alcohol is consumed, do so in moderation

Adapted from American Heart Association Nutrition Committee.[20]

Summary and Recommendations

HIV-infected persons carry a high burden of traditional CVD risk factors, and these factors are the major determinants of risk in the HIV-infected population. HIV infection may be an independent risk factor for CVD—although there is not yet sufficient evidence to consider it a CHD risk equivalent. Inflammatory and coagulation markers are associated with increased mortality, and possibly CVD, in HIV infection. There is a potential role for antiretroviral therapy to decrease CVD risk, as the beneficial effects of antiretroviral therapy on immune dysfunction and inflammation appear to outweigh the proatherogenic effects of antiretroviral agents.

In the absence of specific randomized trials in the HIV-infected population, HIV-infected persons should be treated for CVD risk factors according to current national guidelines for the general population. Further studies are needed to assess the efficacy of specific interventions to prevent CHD in HIV-infected patients. For now, there are not enough data to support the use of inflammatory and coagulation markers or subclinical imaging for routine risk prediction in clinical care for HIV-infected patients. There are no data yet to support routine use of aspirin or statin treatment in all HIV-infected patients beyond use as specified in national guidelines.

Lecture presented by Dr Post in June 2011. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Post and Dr Ketlogetswe in December 2011.

Financial Disclosure: Drs Post and Ketlogetswe have no relevant financial affiliations to disclose.

References

1. Strategies for Management of Antiretroviral Therapy Study Group (SMART), El-Sadr WM, Lundgren JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med.* 2006;355:2283-2296.
2. Kuller LH, Tracy R, Belloso W, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med.* 2008;5:e203.
3. Lichtenstein K, Armon C, Buchacz K, et al. Analysis of cardiovascular risk factors in the HIV outpatient study cohort. [Abstract 735.] 13th Conference on Retroviruses and Opportunistic Infections (CROI). February 5-8, 2006; Denver, CO.
4. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. *Circulation.* 2011;123:1243-1262.
5. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med.* 2008;358:1336-1345.
6. Kingsley LA, Cuervo-Rojas J, Muñoz A, et al. Subclinical coronary atherosclerosis, HIV infection and antiretroviral therapy: Multicenter AIDS Cohort Study. AIDS. 2008;22:1589-1599.
7. Ridker PM and JUPITER Study Group. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: rationale and design of the JUPITER trial. *Circulation.* 2003;108:2292-2297.
8. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. *N Engl J Med.* 1989;321:129-135.
9. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med.* 2005;352:1293-1304.
10. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *JAMA.* 2006;295:306-313.
11. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA.* 2003;289:2560-2572.
12. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation.* 2004;110:227-239.
13. Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation.* 2011;123:2292-2333.
14. Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med.* 2011;365:2255-2267.
15. AIM-HIGH Investigators. The role of niacin in raising high-density lipoprotein cholesterol to reduce cardiovascular events in patients with atherosclerotic cardiovascular disease and optimally treated low-density lipoprotein cholesterol: baseline characteristics of study participants. *Am Heart J.* 2011;161:538-543.
16. Schroeder SA, Meriwether M. Smoking cessation: treatment strategies for the HIV practitioner. IAS–USA *Cases on the Web.* http://www.iasusa.org/cow/cow-instructions.php?cowid=185. Published July 19, 2011. Accessed January 24, 2012.
17. Schlosser E. *Fast Food Nation: The Dark Side of the All-American Meal*. New York, NY: Harper Collins; 2002.
18. Centers for Disease Control and Prevention (CDC). Behavioral Risk Factor Surveillance System Survey Data. BRFSS interactive maps. http://www.cdc.gov/brfss/index.htm. Accessed November 3, 2011.
19. Smith SC, Jr., Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update endorsed by the National Heart, Lung, and Blood Institute. *J Am Coll Cardiol.* 2006;47:2130-2139.
20. American Heart Association Nutrition Committee, Lichtenstein AH, Appel LJ, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation.* 2006;114:82-96.
21. Lo J. Dyslipidemia and lipid management in HIV-infected patients. *Curr Opin Endocrinol Diabetes Obes.* 2011;18:144-147.

Top Antivir Med. 2011;19(5):169-173

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Perspective

Evaluating Cognitive Impairment in the Clinical Setting: Practical Screening and Assessment Tools

HIV-associated neurocognitive disorders (HAND) remain a substantial problem in the era of combination antiretroviral therapy. Neither the Mini Mental State Exam nor the HIV Dementia Scale is sufficiently sensitive for HAND. The Montreal Cognitive Assessment shows promise, but current data suggest that adding an additional test will be needed to improve sensitivity for the clinical setting. Patient reporting of symptoms is insensitive as most cases of HAND are asymptomatic. Examination of cerebrospinal fluid (CSF) is sometimes warranted in select patients to evaluate for CSF HIV RNA detectability. CSF escape of virus, when CSF HIV RNA is detectable but plasma HIV RNA is not, appears to be a relatively uncommon event in the clinical setting where the level of detectability for typical clinical assays is around 50 copies/mL. In cases of CSF escape, cognitive improvement has been linked to changes in antiretroviral regimens that are aimed at either overcoming antiretroviral resistance or improving central nervous system (CNS) penetration-effectiveness. Currently, for most patients with HAND in the absence of unusual features, there are insufficient data for a recommendation to routinely intensify therapy with a neurointensive antiretroviral regimen; however, there is considerable uncertainty given emerging data and variability in approach among experts in the field. This article summarizes a case-based presentation by Victor G. Valcour, MD, at the 14th Annual Clinical Conference for the Ryan White HIV/AIDS Program held in Tampa, Florida, in June 2011. The Clinical Conference is sponsored by the IAS–USA under the Health Resources and Services Administration (HRSA) contract number HHSH250200900010C.

A number of questions are frequently raised by HIV clinicians regarding the evaluation and follow-up of cognitive impairment. These questions include: How is screening best conducted? When is a lumbar puncture indicated? How should one balance the concerns for escape of virus in cerebrospinal fluid (CSF) with the understanding that more than 50% of patients will have cognitive impairment and that CSF escape appears to be a relatively uncommon event? How can one distinguish HIV-associated neurocognitive disorders (HAND) from neurodegenerative disorders, such as Alzheimer's disease, in older HIV patients? What follows are some basics, illustrated by a case study, on how to approach HIV-infected patients with cognitive complaints in the clinical setting.

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Typical Presentations of HAND

In the era before potent antiretroviral therapy, it was already apparent that HIV entered and replicated in the brain within days following infection. Widespread involvement of virus was evident at autopsy, with greater viral density in the deeper brain structures as opposed to cortical regions. This anatomy informs the clinical phenotype of HIV cognitive impairment in contrast to neurodegenerative diseases such as Alzheimer's disease, where brain involvement early in disease typically results in more focal cortical deficits, such as that for encoding memory. The greater involvement of subcortical structures in HAND may be associated with clinical features such as slowing of processing speed; motor and psychomotor involvement; and executive, planning, or multitasking dysfunction. Behaviorally, there may be a greater impact on motivational drive, often recognized clinically as apathy.

HAND can be viewed as a neurobehavioral syndrome, affecting the 3 broad areas of cognitive, behavioral, and motor function. In the realm of cognition, problems can be seen with memory, concentration, mental processing speed, comprehension, or higher cognitive abilities. Behaviorally, one can observe apathy, depression, agitation, or in rare cases, mania. Motor dysfunction includes unsteady gait, poor coordination, abnormal tone, and tremor. A feature of HAND that is not typically seen with other dementia syndromes is the fluctuation in symptoms and testing performance that has been documented in several large series. Diagnostic transitions have been observed with serial testing, in which the performance of individuals (worse or better) varies longitudinally.[1,2] In contrast to dementia syndromes such as Alzheimer's disease, relentless progression is less common in HIV-infected subjects who are adequately treated with combination antiretroviral therapy. Such cases require more comprehensive evaluations that may need to consider contributing etiologies.

Confirming Cognitive Problems in the Clinical Setting: Limitations of Typical Bedside Screening Instruments

Dr Valcour described a hypothetical 58-year-old HIV-infected woman who was cared for by the same clinician for 10 years. She acquired HIV infection from injection drug use, and initially presented with *Pneumocystis jiroveci* pneumonia and a CD4+ cell count of 5/μL. Since diagnosis, she has been continuously treated with zidovudine, lamivudine, and efavirenz and now has a CD4+ cell count of 580/μL with a plasma HIV RNA level that has been undetectable for 10 years. She denies illicit drug use since the time of her HIV diagnosis.

The patient now complains of subtle "memory problems" affecting her work. Although she feels her memory is OK,

she is slow to recall items and has made errors while multitasking. She remarks on new interpersonal conflicts that have been brought to her attention by her supervisor. Overall, the symptoms have not bothered her, as she has learned to compensate for the inefficiency, but now she fears she may lose her job. The symptoms have been present for approximately 5 years, and do not seem to be worsening.

Should this patient be screened for cognitive impairment and if so, which instrument should be used: the Mini Mental State Exam (MMSE), the HIV Dementia Scale (HDS), the clock-drawing test, or is the report of symptoms sufficient to make a diagnosis without confirmation through cognitive testing?

First, consider the issue of screening HIV-infected patients for cognitive impairment in the clinical setting. A more comprehensive review of this topic is available elsewhere.[3] Briefly, the MMSE is in the diagnostic toolbox of most clinicians. Its familiarity, rapidity of administration, and ease of interpretation are all compelling factors. Unfortunately, it has poor sensitivity and specificity for HAND. The instrument is better utilized for cortical dementia syndromes, such as Alzheimer's disease, because it is heavily weighted on factors impacted in such syndromes. The first 10 items of the MMSE, for example, address orientation, a factor that is typically preserved in most HAND cases with the exception of advanced cases.

Areas that would be more important to test include domains of attention and working memory, but these are poorly represented in the MMSE. Published studies have shown that the MMSE is poor at detection of HAND.[4,5] In Dr Valcour's preliminary data from the UCSF HIV Over 60 Cohort (HIV-infected patients older than 60 years), the mean MMSE score was 29 in those without cognitive impairment compared with a mean of 28 in those with impairment.

The HDS was designed to identify HIV-associated dementia (HAD), a condition that is now the least common HAND diagnosis. Most HAND cases are now classified as asymptomatic neurocognitive impairment (ANI) or mild neurocognitive disorder (MND). The HDS contains items testing registration, memory recall, psychomotor speed, and attention, and works well for detecting HAD, but it is insensitive to more mild disease, which now encompasses about 95% of HAND. Removing the antisaccadic eye movement test to create the modified and international versions of the HDS further decreased sensitivity.[6] Numerous studies have shown that HDS is poor at differentiating HAND, with 1 study showing that among individuals wishing to return to work, its sensitivity was 39% compared with neuropsychologic testing.[7-9]

The clock-drawing test is part of the Montreal Cognitive Assessment (MoCA) (http://www.mocatest.org/), an instrument that shows some promise in identifying HAND (Figure 1). There are no published reports on using the clock-drawing task alone, but it is likely to be too limited for broad utility as a screening instrument for HAND. In contrast, the MoCA is more

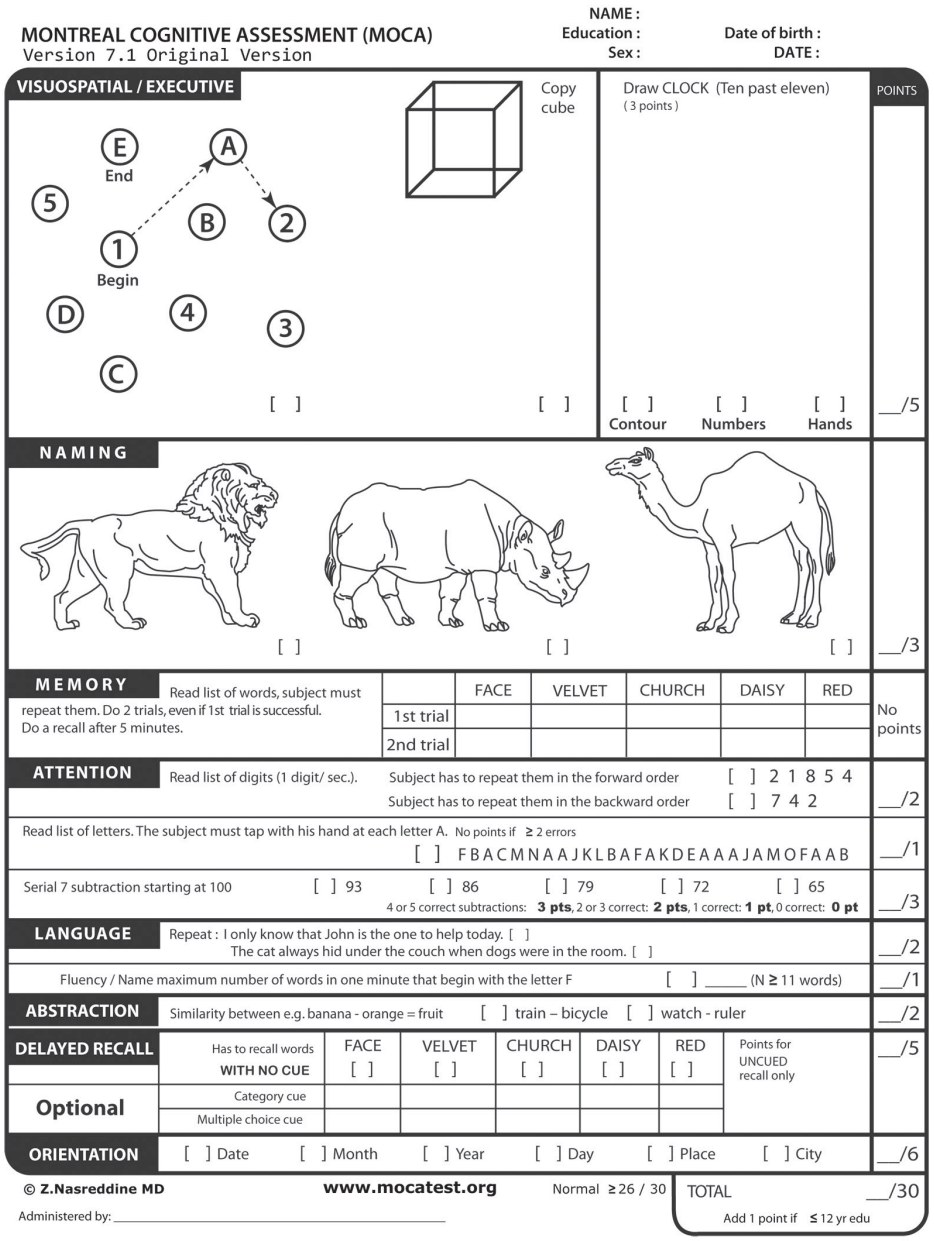

Figure **1**. The Montreal Cognitive Assessment (MoCA). Test reproduced with permission from copyright owner Ziad Nasreddine, MD.

comprehensive and designed to capture impairment caused by cortical and subcortical processes. It includes several tests likely to be sensitive for HAND, including those for attention, concentration, working memory, executive functioning, and reasoning. The instrument includes a trail-making test (follow the dots alternating from letter to number), which tests executive functioning, and the clock-drawing test, which tests executive functioning and visual and spatial skills. The memory testing includes several trials that permit the tester to give cues, including category and multiple-choice cues. It is characteristic of HAND patients and patients with other subcortical dementias to have impaired spontaneous recall, but for their recall to be improved with cues. This is less typical of more cortical dementia syndromes such as Alzheimer's disease.

In a study recently reported by Clifford and colleagues, the MoCA had a sensitivity of 59% and specificity of 81% for identifying cognitive impairment using a score cutpoint of 26.[10] Sensitivity improved to 83% with a cutpoint of 28, but such a change will decrease specificity. Accuracy may be higher in symptomatic patients or with the addition of another test. Thus, although the accuracy of the MoCA in its current form is not optimal for detecting HAND, the test may yet prove useful in the clinic as a component of a short battery.

HAND cannot be detected on the basis of symptoms alone. In the CHARTER (CNS [central nervous system] HIV Antiretroviral Therapy Effects Research) study, a study of community-dwelling adult HIV-infected subjects, more than two-thirds of subjects found to have cognitive impairment were asymptomatic, and thus deemed to have ANI.[11] The term "asymptomatic" may be misleading, because it is often based on self-report and likely to be less reliable among subjects with cognitive impairment. A study by Heaton and colleagues demonstrated that neuropsychologic impairment was associated with functional impairment irrespective of whether patients reported symptoms.[12] Similarly, preliminary data in the UCSF HIV Over 60 Cohort suggest that both ANI and MND subjects perform worse than controls on objective tests of function (data not published).

In summary, among the bedside cognitive tests, the MMSE should not be used for HAND and the HDS should not be used alone, unless one seeks to identify only the most severe form of HAND (ie, dementia). The MoCA shows promise and has empiric benefit compared with the MMSE and HDS. For clinical use, the MoCA is readily available at no cost and instructions are provided (http://www.mocatest.org/).[13] The test has been translated into many languages, although caution should be executed regarding cultural validity in these settings. It takes approximately 8 minutes to administer. Relying on symptoms or patient reports of functional change to identify HAND will result in missing most cases.

Workup for HAND

In the case scenario, the subject was referred for formal neuropsychologic testing, which revealed deficits in working memory and attention. Her memory testing demonstrated inefficiency due to poor learning and attention. Her depression screen was elevated. She returns for a workup in your office.

A typical workup for HAND should include some basic aspects to search for factors that may be modifiable or inform alternative etiologies. This should include:

- Careful neurologic examination and careful assessment for signs of opportunistic infection. This would be intensified in settings of low CD4+ cell count or in patients not on antiretroviral therapy.
- Review of histories for antiretroviral therapy, CD4+ cell counts, and plasma viral load levels with emphasis on adherence.
- Review of medications, prescribed and otherwise, to consider adverse effects that can impact cognition.
- Evaluation for depression.
- Assessment of key comorbidities, including liver, renal, cardiac, and cerebrovascular conditions.
- Evaluation for other factors that can impact cognition, including syphilis, vitamin B_{12} levels (with consideration for homocysteine and methylmalonic acid levels, particularly when white matter lesions are noted), thyroid function, sleep apnea, and hepatitis, among other potential targeted investigations.
- Brain imaging.

In our case scenario, results of the patient's neurologic examination demonstrated some inattention, neuropathy, and mild increased tone in extremities. A brain magnetic resonance imaging (MRI) was read as normal. A comprehensive blood workup that included thyroid function, vitamin B_{12} level, serum rapid plasma reagin (RPR), and renal and liver function tests yielded normal results.

The factors influencing the approach to this patient's case thus far include the following: she had a low CD4+ cell count nadir, increasing the risk for HAND. She had a history of injection drug use, which, depending on use pattern and coexisting factors, such as loss of consciousness or head injuries, could increase risk for cognitive impairment. She has had an undetectable plasma viral load for a decade and her CD4+ cell count is now in the normal range. A high CD4+ cell count and consistently controlled virus are linked to a lower risk for HAND. The normal CD4+ count suggests that opportunistic infection is unlikely.

The duration of symptoms is 5 years and appears relatively stable. The duration suggests a more indolent course common with HAND and the relative stability over 5 years is less typical of neurodegenerative disorders such as Alzheimer's disease. However, there should be some question about whether her condition has become worse recently, as the patient has identified new associated problems. Symptom reporting and testing indicate motor, behavioral, and cognitive problems that are more typical of HAND. Her

laboratory workup and MRI do not suggest an alternative etiology.

In this case, the subject was diagnosed with MND in HIV and treatment for depression was initiated. The next consideration is whether patients like this one, with cognitive impairment, should be referred to a specialist for further workup and possible lumbar puncture for CSF evaluation. There is great variability in how such cases are managed. There are a number of factors in this patient that suggest she can likely be managed without immediate evaluation of CSF. The course of her cognitive syndrome is 5 years. More rapid progression should be evaluated aggressively, but in cases with longstanding impairment that are relatively stable, there are insufficient data to suggest that CSF evaluation will meaningfully impact treatment approaches. This patient is already on effective antiretroviral treatment with a normal CD4+ cell count, suggesting that CSF evaluation for opportunistic infection is not likely to be helpful. She is also RPR-negative. Most patients seen in Dr Valcour's referral clinic have profiles similar to this patient's, in which CSF evaluation will probably not yield information that will change management. But there are no clear guidelines around referral for CSF evaluation, and the decision should be based on the combination of findings and clinical judgment based on the presence of worrisome features.

The algorithm for referral and lumbar puncture would be more aggressive in cases of subacute or acute cognitive impairment, among individuals not on antiretroviral therapy and not responding to initiation of treatment, and in cases with features not typical of HAND. However, focused studies are lacking and this approach is based on clinical judgment based on the presence of worrisome features. Initiation of antiretroviral therapy is indicated in subjects not on treatment who are diagnosed with HAND. Among individuals who do not improve after 3 to 6 months of antiretroviral therapy, evaluation of CSF may be useful to ensure adequate treatment of this compartment by ensuring that CSF HIV RNA level is undetectable. This approach is not applicable, however, for patients with a more chronic form of cognitive impairment, currently a common finding in the clinical setting. In such cases, there are insufficient published data to recommend a uniform approach, with the only clinical study not providing adequate support for a global recommendation.[14]

There are a number of potential benefits to CSF evaluation in patients with cognitive impairment. It can be used (1) in cases with high suspicion for unusual causes of cognitive impairment, including infection, that require further investigation; (2) to determine if CSF immune activation is present (typically used in research settings); and (3) to evaluate for HIV CSF escape, a relatively uncommon phenomenon in the clinical setting where the sensitivity of typical assays is to around 50 copies/mL. If a patient is sent for lumbar puncture, one should consider CSF for evaluation for virus (quantitative HIV RNA in CSF), white blood cell (WBC) count, and other markers of inflammation such as oligoclonal bands, an IgG index, and protein level. More focused evaluation for infections would be done on a case-by-case basis.

It may be helpful to review the literature on CSF escape, which has been documented in several case reports. In addition, there is a small literature on subjects with HIV RNA levels below 50 copies/mL in both CSF and plasma, but with low-level detection that is higher in CSF than in plasma. This latter finding is beyond the scope of clinical care at the current time and a subject of ongoing research. One case series presented 3 patients with meningoencephalitis due to CSF escape, each of whom improved with altering antiretroviral therapy components.[15]

A European report confirmed 11 cases from 2 university infectious diseases clinics caring for about 6000 HIV-infected patients annually (Table 1). Although this study was not designed to determine frequency of CSF escape, the identification of 11 cases in such a large setting is somewhat reassuring that clinically relevant CSF escape is likely to be uncommon.[16] Most of these patients had neurologic signs or symptoms such as cerebellar disorders or headache rather than just the cognitive symptoms of the type observed in the case described here. The patients in this case series improved when antiretroviral therapy was changed based on genotypic testing or to improve drug CNS penetration-effectiveness.

In summary, there are a number of situations in which lumbar puncture and evaluation of CSF may be advisable. Some examples are acute or subacute presentations, rapid progression of impairment, new neurologic findings, and inability to exclude other infectious etiologies (eg, syphilis) based on serum tests, history, and imaging. In some settings, a CSF evaluation may also be considered for patients with impairment in whom a change in antiretroviral therapy is being considered or in whom a change in therapy has been made in order to monitor response in the CSF; however, a universal recommendation for these reasons cannot be supported with the existing literature.

Changing Antiretroviral Therapy to Improve CNS-Penetration Effectiveness

In our case example, the patient was receiving zidovudine, lamivudine, and efavirenz. Using published data, this patient would be considered to have a moderate to high CNS-penetration effectiveness (CPE) score. According to a CNS penetration rating for antiretroviral drugs developed by Letendre and colleagues, zidovudine and efavirenz have higher levels of penetration-effectiveness and lamivudine has moderate penetration effectiveness.[17,18] Although switching from lamivudine to emtricitabine (a relatively minimal change in terms of therapy, but adding to the pill burden and possibly impacting adherence) can improve the CPE, there are no data to suggest this will improve outcomes, with one study suggesting such an empiric intensification choice will not be beneficial.[14] No data are available to guide an empiric change of therapy in a case such as the one described here. The

Table 1. European Case Series of Patients with HIV Cerebrospinal Fluid (CSF) Escape

Case number	Age (years)	CD4+ Count (cells/μL)	Time with HIV RNA Level < 50 copies/mL (months)	Neurologic Symptoms	CSF HIV RNA Level (copies/mL)	Plasma HIV RNA Level (copies/mL)
1	50	592	36	Persistent headache	12,885	147
2	49	190	11	Memory disorder, cerebellar ataxia	845	< 50
3	43	400	18	Cerebellar dysarthria, cerebellar ataxia	1190	< 50
4	50	432	68	Tactile allodynia	870	78
5	36	107	75	Glasgow Coma Score of 3	5035	< 50
6	47	631	64	Persistent headache	580	< 50
7	44	544	14	Memory disorder, cerebellar ataxia, pyramidal syndrome	558	< 50
8	53	360	12	Lower limb dysesthesia and hypoesthesia	1023	< 50
9	68	147	12	Memory disorder, left lower limb dysesthesia	586	< 50
10	68	534	18	Temporospatial disorientation, cerebellar ataxia	880	< 50
11	55	593	10	Memory disorder, cerebellar dysarthria	6999	483

Adapted from Canestri et al.[16]

decision to change therapy can create unease clinically when a patient is on an antiretroviral regimen with overall poor CPE, paired with the knowledge that higher CPE has been linked to lower CSF virus levels. In such cases, Dr Valcour sometimes considers assuring that CSF virus is below detectable limits. Changing antiretroviral therapy does carry risks, which may outweigh uncertain benefits in patients not clearly in need of a change. These risks could include new adverse effects that can impact cognition negatively, exposure to more antiretroviral medications that could impact resistance profiles for future options, and change in pill burden. Consequently, the approach to patients with HAND must be individualized and more clinical data from randomized studies are urgently needed.

Summary

Cognitive impairment remains a substantial problem in the era of antiretroviral therapy, occurring in about one-half of community-dwelling HIV-infected adults. Most patients with HAND identified in research settings are categorized as having ANI, likely due, at least in part, to difficulty in obtaining accurate reports of functional limitations from impaired patients. Current screening tools have large limitations. Neither the MMSE nor HDS is useful for distinguishing HAND, however, the MoCA test may have promise. Used alone, the performance characteristics may not be sufficient for broad use, but studies are underway aimed at determining if adding additional tests may improve performance.

There are many things that can be done in the primary care setting to initiate a workup for cognitive impairment, although referral to specialized centers will be required in some cases. The literature is not informative regarding empiric changes in antiretroviral therapy to better target the CNS in subjects with HAND. In special cases, including those involving CSF HIV escape, change in medications has been found to be of benefit. A high index of suspicion in unusual presentations is warranted, but recommendations for CSF evaluation in all cases of HAND may be premature.

Lecture presented by Dr Valcour in June 2011. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Valcour in January 2012.

Financial Disclosure: Dr Valcour has no relevant affiliations to disclose.

References

1. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology.* 2007;69:1789-1799.
2. McArthur JC, Haughey N, Gartner S, et al. Human immunodeficiency virus-associated dementia: an evolving disease. *J Neurovirol.* 2003;9:205-221.
3. Valcour V, Paul R, Chiao S, Wendelken LA, Miller B. Screening for cognitive impairment in human immunodeficiency virus. *Clin Infect Dis.* 2011;53:836-842.
4. Ganasen KA, Fincham D, Smit J, Seedat S, Stein D. Utility of the HIV Dementia Scale (HDS) in identifying HIV dementia in a South African sample. *J Neurol Sci.* 2008;269:62-64.
5. Skinner S, Adewale AJ, DeBlock L, Gill MJ,

Power C. Neurocognitive screening tools in HIV/AIDS: comparative performance among patients exposed to antiretroviral therapy. *HIV Med*. 2009;10:246-252.

6. Davis HF, Skolasky RL, Jr., Selnes OA, Burgess DM, McArthur JC. Assessing HIV-associated dementia: modified HIV dementia scale versus the Grooved Pegboard. *AIDS Read*. 2002;12:29-31, 38.
7. Smith CA, van Gorp WG, Ryan ER, Ferrando SJ, Rabkin J. Screening subtle HIV-related cognitive dysfunction: the clinical utility of the HIV dementia scale. *JAIDS*. 2003;33:116-118.
8. Morgan EE, Woods SP, Scott JC, et al. Predictive validity of demographically adjusted normative standards for the HIV Dementia Scale. *J Clin Exp Neuropsychol*. 2008;30:83-90.
9. Waldrop-Valverde D, Nehra R, Sharma S, et al. Education effects on the International HIV Dementia Scale. *J Neurovirol*. 2010;16:264-267.
10. Overton ET, Ances B, Grubb J, et al. Novel screening tools for HIV-associated neurocognitive disorders. [Abstract 401.] 18th Conference on Retroviruses and Infections (CROI). February 27-March 2, 2011; Boston, MA.
11. Heaton RK, Clifford DB, Franklin DR, Jr., et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology*. 2010;75:2087-2096.
12. Heaton RK, Marcotte TD, Mindt MR, et al. The impact of HIV-associated neuropsychological impairment on everyday functioning. *J Int Neuropsychol Soc*. 2004;10:317-331.
13. Nasreddine Z. The Montreal Cognitive Assessment. http://www.mocatest.org. Accessed October 19, 2011.
14. Marra CM, Zhao Y, Clifford DB, et al. Impact of combination antiretroviral therapy on cerebrospinal fluid HIV RNA and neurocognitive performance. *AIDS*. 2009;23:1359-1366.
15. Wendel KA, McArthur JC. Acute meningoencephalitis in chronic human immunodeficiency virus (HIV) infection: putative central nervous system escape of HIV replication. *Clin Infect Dis*. 2003;37:1107-1111.
16. Canestri A, Lescure FX, Jaureguiberry S, et al. Discordance between cerebral spinal fluid and plasma HIV replication in patients with neurological symptoms who are receiving suppressive antiretroviral therapy. *Clin Infect Dis*. 2010;50:773-778.
17. Letendre S, FitzSimons C, Ellis R, et al. Correlates of CSF viral loads in 1221 volunteers of the CHARTER cohort. [Abstract 172]. 17th Conference on Retroviruses and Infections (CROI). February 16-19, 2010; San Francisco, CA.
18. Letendre S. Central nervous system complications in HIV disease: HIV-associated neurocognitive disorder. *Top Antivir Med*. 2011;19:137-142.

Top Antivir Med. 2011;19(5):175-180

Perspective

HIV Preexposure Prophylaxis: New Data and Potential Use

HIV preexposure prophylaxis (PrEP) has demonstrated efficacy in 4 studies: 1) the CAPRISA 004 trial of pericoital administration of 1% tenofovir gel showed moderate (39%) efficacy in reducing risk of HIV acquisition in young women; 2) the iPrEx trial of daily oral emtricitabine/tenofovir had moderate (44%) efficacy in reducing risk of HIV acquisition among high-risk men who have sex with men (MSM); 3) the Partners PrEP Study in African HIV-serodiscordant couples, in which the HIV-seronegative partner received daily oral tenofovir or emtricitabine/tenofovir, showed high efficacy (62% and 73%, respectively); and 4) the TDF2 trial in young heterosexual men and women in Botswana demonstrated 62% efficacy of daily oral emtricitabine/tenofovir. Greater adherence to PrEP is associated with greater efficacy. Resistance to tenofovir and emtricitabine have been rare and were primarily observed during PrEP initiation in those with acute HIV infection. PrEP has been found to be safe and well tolerated. The FEM-PrEP trial of oral emtricitabine/tenofovir and the VOICE trials of daily 1% tenofovir gel and oral tenofovir (both studies conducted in African women) did not show protective benefit, for reasons that currently remain unknown. The Bangkok Tenofovir Study of oral tenofovir in injection drug users, and the emtricitabine/tenofovir study arm of the VOICE trial, are ongoing. Establishing PrEP programs will be a great challenge and a great opportunity. This article summarizes a presentation by Connie L. Celum, MD, MPH, at the IAS–USA live continuing education course held in Chicago in June 2011, and includes updates on PrEP trial results reported since July 2011.

Background on PrEP

Efficacy of topical and oral tenofovir-based preexposure prophylaxis (PrEP) has recently been shown in 4 studies: 1) CAPRISA (Center for the AIDS Programme of Research in South Africa) 004; 2) iPrEx (Chemoprophylaxis for HIV Prevention in Men); 3) Partners PrEP; and 4) TDF2. In contrast, 2 studies among young African women found no efficacy in oral emtricitabine/tenofovir (FEM-PrEP) or in daily tenofovir gel and oral tenofovir (VOICE [Vaginal and Oral Interventions to Control the Epidemic]). The differences in efficacy outcomes in different populations are being explored.

Other types of preventive treatment exist in the form of postexposure prophylaxis (PEP) and the reduced infectiousness resulting from effective postinfection antiretroviral therapy. There are problems with PEP, however, including accurate assessment of the risk associated with the exposure and the need for the exposed individual to present and start treatment within 48 hours of the exposure. It is thus unlikely that PEP will have a large impact from a global perspective. Problems with postinfection antiretroviral therapy, from a global perspective, include the need to scale up programs for identifying and treating HIV-infected individuals, the need for additional resources to do so, the usual problems with long-term adherence (which may present greater challenges for prevention interventions), long-term toxicities, and antiretroviral resistance, although resistance in breakthrough infections has been rare. There may thus be a considerable role for PrEP in the effort to reduce HIV acquisition and transmission.

Much of the data on PrEP has involved use of tenofovir-based approaches, including tenofovir alone as a gel or tablet, or in combination with emtricitabine as a tablet. Both tenofovir and emtricitabine/tenofovir have a number of desirable characteristics for use as PrEP drugs, including broad antiretroviral activity (including all HIV-1 subtypes, HIV-2, and R5-tropic or X4 HIV), ability to block initial infection, and rapid onset of activity (for emtricitabine; tenofovir takes longer to be metabolized). Both agents have favorable safety and tolerability profiles, and use is made easier by once-daily dosing, absence of food restrictions, and few drug interactions.

Concern remains over the potential use of these agents in PrEP, however. If efficacy is low and substantial resistance occurs in breakthrough infections in the form of nucleoside analogue reverse transcriptase inhibitor (nRTI) K65R and M184V resistance mutations and cross-resistance with other nRTIs, there is concern that this could jeopardize future treatment with non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) in those with breakthrough infections who develop resistance on PrEP.

The possibility of PrEP studies was first raised in 2001, with a trial in Cambodian sex workers planned in 2003. However, there was little scale-up of antiretroviral agents for those with HIV infection in Cambodia at this time and considerable protest took place over testing an unproven strategy. A phase II trial of tenofovir in sex workers in West Africa was also disrupted because of community concerns. After the reporting of the safety of daily oral tenofovir as PrEP among female sex workers in West Africa at the 16th International AIDS Conference in Toronto in 2006,[1] a number of phase IIb and phase III trials were initiated from 2007 to 2009. In 2010, the positive findings for tenofovir gel in CAPRISA 004 and oral emtricitabine/tenofovir in iPrEx were reported. In 2011, the positive findings from Partners PrEP and TDF2, and the lack of efficacy observed in FEM-PrEP and VOICE, were reported.

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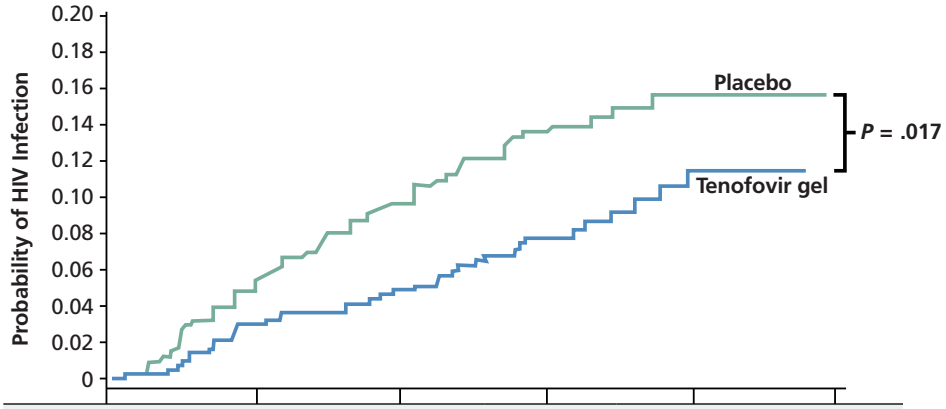
Landmark PrEP Trials: CAPRISA 004, iPrEx, Partners PrEP, and TDF2

The announcement of the CAPRISA 004 trial results was a landmark event, as it provided proof-of-concept that antiretrovirals could be effectively delivered topically. In the phase IIb CAPRISA 004 trial, 889 young unmarried women in Durban, South Africa (aged ≥ 18 years; mean age, 23 years; rural settings, 69%; urban settings, 31%), received pericoital 1% tenofovir gel applied vaginally within 12 hours before and 12 hours after sex (maximum of 2 applications over 24 hours) or placebo. Tenofovir treatment was associated with a 39% reduction in risk of acquiring HIV infection compared with placebo over 30 months of follow-up (Figure 1).[2] The study also showed a 51% reduction in risk for acquiring herpes simplex virus 2 (HSV-2) infection and no development of K65R-mediated resistance to tenofovir.

Treatment was associated with an increase in mild, self-limiting diarrhea. A sobering finding was that the incidence of HIV infection in the placebo group was 9.1%, and the incidence in the treatment group, despite the protection afforded by tenofovir treatment, was 5.6%. In the CAPRISA 004 trial, adherence was crucial for protective efficacy. Adherence of greater than 80% (38% of the treatment group) was associated with 54% protective efficacy, whereas adherence rates of 50% to 80% (20% of the treatment group) were associated with 38% protective efficacy. Adherence less than 50% (42% of treatment group) was associated with protective efficacy of 28%.

Tenofovir gel provides a very high level of active drug in cervicovaginal secretions and tissue, some 100- to 1000-fold higher than levels achieved with oral dosing of the drug.[3] Cervicovaginal tenofovir levels have been found to correlate with HIV and HSV-2 seroconversion.[4] A study comparing daily oral, vaginal, and dual dosing found that oral dosing did not increase drug concentrations in vaginal tissue beyond that achieved with vaginal application.[3] However, it also remains unknown how much active drug is needed mucosally versus systemically for a protective effect.



Months of follow-up	6	12	18	24	30
Cumulative HIV infections	37	65	88	97	98
Cumulative women-years	432	833	1143	1305	1341
HIV incidence rate (tenofovir)	6.0	5.2	5.3	5.6	5.6
HIV incidence rate (placebo)	11.2	10.5	10.2	10.2	9.1
Effectiveness (*P*-value)	47% (.064)	50% (.007)	47% (.004)	40% (.013)	39% (.017)

Figure **1**. Probability of HIV infection in young women receiving tenofovir gel or placebo in the CAPRISA (Center for the AIDS Programme of Research in South Africa) 004 trial. Adapted from Abdool Karim et al.[2]

Results of the iPrEx trial, announced in 2010, were a landmark event for oral PrEP (Figure 2). In the iPrEx trial, 2499 young, high-risk men who have sex with men (MSM) (50% aged < 25 years) from 11 sites in Brazil, Ecuador, Peru, South Africa, Thailand, and the United States (two-thirds from Ecuador and Peru) were randomly assigned to daily oral emtricitabine/tenofovir or placebo. Participants had a median of 18 sex partners in the 12 weeks before enrollment.[5] An updated efficacy estimate indicates that emtricitabine/tenofovir treatment was associated with a 42% reduction in HIV acquisition over 3 years (83 infections in placebo group, 48 in treatment group). No reduction in HSV-2 acquisition was observed, with blood drug levels being well below the 50% effective concentration (EC_{50}) for HSV-2. Effectiveness was dependent on adherence: protective efficacy was 68% in those with high adherence (90% adherence or above, which was estimated for 49% of study visits); 34% with intermediate adherence (50%-90% adherence, 33% of visits); and 16% with low adherence (less than 50% adherence, 18% of visits).

Emtricitabine/tenofovir had a very good safety profile, with the treatment group having an increase in nausea during the first month of treatment and a small decrease in bone mineral density. Among participants who were assessed for intracellular drug levels, levels were measurable in only 2 (9%) of 34 MSM with breakthrough infection in the treatment group. No antiretroviral resistance was found in the participants who acquired infection after study enrollment. Ten participants were retrospectively identified as having been in the process of HIV seroconversion at study entry: among 8 in the placebo arm, 1 had transmitted multiresistant HIV; among 2 in the treatment arm, both had virus with M184 resistance mutations. These findings underscore the need to avoid

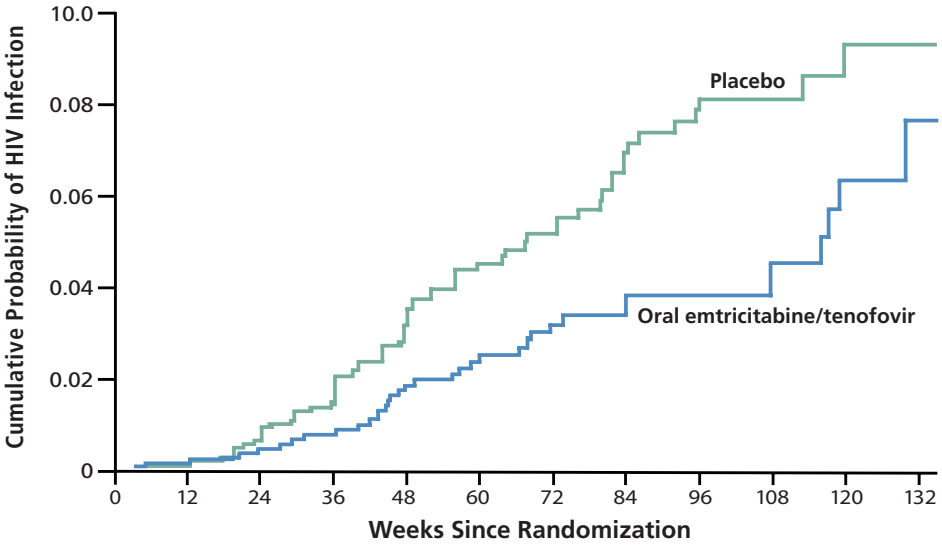


Figure **2**. Probability of HIV infection in men who have sex with men (MSM) receiving emtricitabine/tenofovir or placebo in the iPrEx (Chemoprophylaxis for HIV Prevention in Men) trial. Adapted from Grant et al.[5]

PrEP initiation in persons with acute HIV infection, because it appears likely to select for resistant mutants.

The news from the FEM-PrEP trial was not so positive.[6] This phase III study compared emtricitabine/tenofovir with placebo in a target population of 3900 female sex workers in Africa. It was announced in April 2011, after enrollment of 1951 participants, that the study was being ended prematurely because of lack of efficacy—56 new infections had occurred, evenly divided between the treatment and placebo arms. It is unclear whether lack of PrEP efficacy in this trial involved poor adherence, poor drug penetration into vaginal tissue, or lower efficacy in women for other reasons. All the women in the study were on hormonal contraceptives, and a higher rate of pregnancy was found among those using oral contraceptives; further analyses of this finding are awaited. A final study analysis in early 2012 should shed light on these issues.

The PrEP trials described above were challenging to launch and implement, but they have provided important proof-of-concept for topical and oral antiretroviral-based prevention. CAPRISA 004 and iPrEx showed that adherence is crucial to protective efficacy of PrEP. Efficacy is associated with drug levels, and the only accurate way to assess adherence is through measurement of drug levels. Adherence assessment based on patient report or pill count is unreliable. For example, data from iPrEx showed that among men with adherence greater than 90% based on pill count, only 62% had drug detected in blood samples.[7]

In July 2011, 2 studies reported high efficacy of daily oral tenofovir and emtricitabine/tenofovir—the Partners PrEP Study and TDF2. The Partners PrEP Study is an ongoing, 3-arm, placebo-controlled trial of daily oral tenofovir and tenofovir/emtricitabine in 4758 HIV-serodiscordant couples from Kenya and Uganda, among whom the HIV-infected partner is not eligible for antiretroviral therapy according to national guidelines. HIV-uninfected partners were randomly assigned to receive PrEP or placebo.[8]

On July 10, 2011, the study's Data and Safety Monitoring Board recommended the discontinuation of the placebo arm of the Partners PrEP study, because predetermined stopping guidelines for efficacy had been met. Overall, 62% efficacy of tenofovir (95% confidence interval [CI], 34%-78%) and 73% efficacy of tenofovir/emtricitabine (95% CI, 49%-85%) compared with placebo, were observed. The difference between tenofovir and tenofovir/emtricitabine was not statistically significant (P = .18). Both tenofovir and tenofovir/emtricitabine statistically significantly reduced HIV risk for both men and women in Partners PrEP. The TDF2 study enrolled 1200 heterosexual men and women aged 18 to 40 years in Botswana into a placebo-controlled trial of daily oral tenofovir/emtricitabine. The study reported 62.6% efficacy (95% CI, 21.5%-83.4%) for HIV protection due to PrEP.[9]

The VOICE 003 trial, sponsored by the Microbicide Trials Network (MTN) and National Institutes of Health (NIH) is examining daily oral tenofovir, daily oral emtricitabine/tenofovir, and daily vaginal tenofovir gel in 5000 women in South Africa, Uganda, and Zimbabwe. The Data Safety Monitoring Committee for the VOICE trial recommended discontinuation of the oral tenofovir arm in September 2011 and the tenofovir gel arm in November 2011 because of inability to demonstrate efficacy. Analyses of the VOICE trial will be crucial to understanding the lack of efficacy of daily tenofovir gel compared with the moderate efficacy of pericoital tenofovir gel in CAPRISA 004 and the lack of efficacy of oral tenofovir in women at risk.

Ongoing PrEP studies include the Bangkok Tenofovir study, also sponsored by the Centers for Disease Control and Prevention (CDC). This study is evaluating tenofovir in 2400 male injection drug users receiving directly observed therapy; the trial is fully enrolled, with results expected in 2012. The VOICE trial is anticipated to report results of the ongoing emtricitabine/tenofovir arm in 2013.

Are We Ready to Give PrEP to Men in the United States?

The CDC issued interim guidance for PrEP in MSM in January 2011. More extensive guidelines are expected from the CDC and the World Health Organization in 2012. Current key implementation issues for emtricitabine/tenofovir PrEP include determining who should receive the drug and how it should be made available. If high-risk MSM are targeted, what constitutes "high risk" needs to be de-

termined. Should PrEP be delivered at sexually transmitted infection (STI) clinics, HIV clinics, public health facilities, primary care clinics, or pharmacies? It is clear that to ensure that PrEP has a public health impact—rather than becoming a "boutique" intervention for those who can afford it—widespread access to medication and coverage of persons at highest risk of HIV acquisition is required.

Preliminary guidance from the CDC addresses risk assessment and safety monitoring for PrEP. Risk assessment is crucial before initiating PrEP, and clinicians should remind themselves of the maxim: "If I don't ask, they (often) won't tell." For PrEP eligibility, it must be determined that the individual is HIV-uninfected (ie, is antibody-negative) immediately before starting PrEP. Individuals with symptoms consistent with acute infection should delay treatment for a month until HIV-seronegative status is confirmed, or should be tested for acute HIV infection. Substantial, ongoing, high risk for HIV infection must be confirmed. Adequate renal function must also be confirmed, with the CDC recommending creatinine clearance (using the Cockcroft-Gault formula) of at least 60 mL/min. It is also recommended that patients be screened for hepatitis B virus (HBV) infection. Those who are uninfected should receive HBV vaccine; those who are infected should be treated. Patients should also be screened and treated for other STIs.

PrEP is given as fixed-dose combination tenofovir 300 mg and emtricitabine 200 mg in 1 tablet, taken once daily. Patients should receive no more than a 90-day supply at a time, with the prescription renewable only if HIV testing confirms that the patient remains uninfected and that poor adherence has not been documented. It is not clear yet how adherence should be assessed and documented in the setting of PrEP implementation, but demonstration projects are underway regarding this question. Counseling should focus on risk reduction and PrEP adherence, including the need to achieve and sustain drug levels for protective effect and discussion of adverse effects. Many patients experience mild nausea during the first few weeks of treatment, which typically resolves. There are no data yet on intermittent emtricitabine/tenofovir treatment (studies are being initiated in 2012), so patients should be discouraged from event-driven use and sharing fixed-dose emtricitabine/tenofovir with others.

Follow-up includes HIV testing every 2 to 3 months, with documentation of negative results. Adherence should be evaluated and supported, with re-emphasis that adherence is crucial to protection. Patients should receive continued risk reduction counseling and should be assessed for STI symptoms, with asymptomatic patients being screened every 6 months. Serum creatinine should be measured at 3 months after starting PrEP and annually thereafter.

For patients who become HIV-seropositive while receiving PrEP, PrEP should be stopped, resistance testing performed, and linkage to HIV care established. HIV-seronegative patients who discontinue PrEP should receive risk reduction support services. Those who discontinue PrEP who have chronic HBV infection should undergo liver function tests, as there have been case reports of hepatitis flares after discontinuing fixed-dose emtricitabine/tenofovir.

PrEP is not an inexpensive intervention. The CDC is currently working with insurance companies and payers to facilitate coverage for treatment, with an encouraging response thus far. Final decisions are awaited. Health departments are also awaiting the expanded CDC guidelines on PrEP. Based on models using data from South African women and HIV-serodiscordant couples, PrEP could be very cost-effective if efficacy is high (as has been demonstrated in some populations), if drug and delivery costs are lower than those for antiretroviral therapy (which depends on availability of generic tenofovir or emtricitabine/tenofovir and delivery models), and if it is targeted to those with highest risk (eg, young women in South Africa, MSM in the Americas, HIV-serodiscordant couples in East Africa).

In addition, it needs to be considered whether MSM will be interested in PrEP—particularly after years of telling men not to contract HIV infection because the medications are toxic. Messaging about the safety and tolerability of fixed-dose emtricitabine/tenofovir will be important to efforts to ensure that PrEP is adopted and used correctly. Helping MSM decide whether they are likely to benefit from PrEP is essential for optimal use of this intervention.

There are many unanswered questions regarding PrEP. When current trials are finished, we will have more information on PrEP in women, injection drug users, pregnant and breastfeeding women, adolescents, patients with chronic HBV infection, and on longer-term use and use of tenofovir gel in anal sex. Issues remain with regard to long-term adherence, efficacy with intermittent use, risk of antiretroviral resistance with longer times between HIV tests, potential spread of resistant virus, and potential effects on behavior. With regard to behavior, for example, will behavior become more high-risk with individuals using a partially protective treatment? And how much will an increase in risk behavior reduce the efficacy of PrEP? These key questions are being addressed in demonstration projects.

A major issue is how to roll out PrEP programs when there is a global postinfection treatment gap. Currently, we need to expand antiretroviral therapy access to the approximately 60% of HIV-infected individuals who are eligible for treatment but are not receiving it. The challenge of offering PrEP in this context should be reframed away from "prevention versus treatment" to "treatment and prevention, in parallel." To achieve this, we need to reduce antiretroviral therapy delivery costs, address the treatment gap, improve retention in care, and optimize clinical and public health benefits of antiretroviral therapy. We also need to initiate pilot programs of cost-effective PrEP delivery models and shift prevention resources to fund strategies that actually work.

Antiretroviral Therapy to Reduce Infectiousness and Transmission: Observational Data and the HPTN 052 Study

In a study by Dr Celum and colleagues of HSV disease suppression in 3400 HIV-serodiscordant couples in Africa, only 1 of 103 HIV infections in the initially HIV-seronegative partner occurred when the HIV-infected partner was receiving antiretroviral therapy.[10] In that 1 case of post–antiretroviral therapy HIV transmission, the initially HIV-infected partner had just begun antiretroviral therapy and likely had only partial viral suppression at the time of infection of the seronegative partner. Approximately 10% of HIV-infected partners initiated antiretroviral therapy during follow-up, and the protective effect was a 92% reduction in HIV transmission risk. Plasma HIV RNA level greater than 50,000 copies/mL was highly predictive of risk of transmission. When participants who had not received antiretroviral therapy were stratified by CD4+ cell count, HIV RNA level above 50,000 copies/mL was associated with a greater than 4-fold increased risk of transmission in both the 200/μL to 349/μL CD4+ cell count stratum and the 350/μL and above stratum.

Results of the HIV Prevention Trials Network (HPTN) 052 trial have provided a strong statement in favor of early treatment to further the public health goal of reducing spread of HIV infection. This trial, conducted in 9 countries (Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, United States, and Zimbabwe), assessed the impact of earlier antiretroviral therapy on HIV transmission and disease progression in 1763 HIV-serodiscordant couples. The HIV-infected partners had CD4+ cell counts of 350/μL to 550/μL and were randomly assigned to start highly active antiretroviral therapy immediately (n = 886) or when CD4+ cell count dropped to 250/μL (n = 887). All participants received HIV prevention services.

Participants were to be observed for 5 years, with the coprimary endpoints being HIV infection in the HIV-seronegative partner and HIV disease progression in the HIV-infected partner. After 2 years of follow-up, 1 case of transmission occurred in couples in the immediate-treatment group, versus 27 cases in the delayed treatment group, representing a 96% reduction in transmission risk with earlier treatment. In addition, 3 cases of extrapulmonary tuberculosis were found in the HIV-infected partners in the immediate-treatment group versus 17 in those receiving delayed treatment.[11]

Summary

The initial proof-of-concept for topical and oral tenofovir-based PrEP has been provided by the CAPRISA 004, iPrEx, Partners PrEP, and TDF2 studies. Analyses of the VOICE and FEM-PrEP studies will be crucial to understanding differences in efficacy among different populations. Ongoing PrEP trials and additional analyses of recently completed trials will provide information on safety and efficacy, adherence, and antiretroviral resistance in other populations, such as heterosexuals, injection drug users, adolescents, and pregnant or breastfeeding women. Drug costs, targeting strategies, and delivery strategies are crucial to cost-effectiveness and successful implementation of PrEP programs. Roll-out of these programs will be complicated and demonstration projects are needed to help inform the ultimate design of the programs. However, the challenge is an exciting one in the field of prevention, an area in which practitioners often contend with a sense of futility or frustration, given the many types of preventive programs that have had relatively little success in the past. We now have evidence-based tools with which to work. The strong demonstration that treatment is prevention, provided by observational data and the HPTN 052 trial, gives us another tool.

Lecture presented by Dr Celum in June 2011. First draft prepared from transcripts by Matthew Stenger. Reviewed, edited, and updated by Dr Celum in January 2012.

Financial Disclosure: Dr Celum has received grants and research support from GlaxoSmithKline and served as a scientific advisor for Merck & Co, Inc, and an unpaid scientific advisor for Gilead Sciences, Inc.

References

1. Sax PE. Report from the XVI International AIDS Conference. Preexposure prophylaxis studies move forward. *AIDS Clin Care*. 2006;18:101-102.
2. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science*. 2010;329:1168-1174.
3. Hendrix C, Minnis A, Guddera V, et al. MTN-001: A phase 2 cross-over study of daily oral and vaginal TFV in healthy, sexually active women results in significantly different product acceptability and vaginal tissue drug concentrations. [Abstract 35LB.] 18th Conference on Retroviruses and Opportunistic Infections (CROI). February 27-March 3, 2011; Boston, MA.
4. Karim SS, Kashuba AD, Werner L, Karim QA. Drug concentrations after topical and oral antiretroviral pre-exposure prophylaxis: implications for HIV prevention in women. *Lancet*. 2011;378:279-281.
5. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010;363:2587-2599.
6. Family Health International. VOICE HIV prevention trial continues, but researchers suspend oral tenofovir arm because of futility. http://www.fhi360.org/en/AboutFHI/Media/Releases/res_VOICE.htm. Accessed January 19, 2012.
7. Amico R, Liu A, McMahan V, et al. Adherence indicators and PrEP drug levels in the iPrEx study. [Abstract 95LB.] 18th Conference on Retroviruses and Opportunistic Infections (CROI). February 27-March 3, 2011; Boston, MA.
8. Baeten J. Antiretroviral pre-exposure prophylaxis for HIV-1 prevention among heterosexual African men and women: the Partners PrEP Study. [Abstract MOAX0106.] 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention. July 17-20, 2011; Rome, Italy.
9. Thigpen MC, Kebaabetswe PM, Smith DK, et al. Daily oral antiretroviral use for the prevention of HIV infection in heterosexually active young adults in Botswana: results from the TDF2 study. [Abstract WELBC01.] 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention. July 17-20, 2011; Rome, Italy.
10. Donnell D, Baeten JM, Kiarie J, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet*. 2010;375:2092-2098.
11. Cohen MS, Shaw GM, McMichael AJ, Haynes BF. Acute HIV-1 infection. *N Engl J Med*. 2011;364:1943-1954.

Top Antivir Med. 2011;19(5):181-185

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NEW HIV and Pain

Jessica S. Merlin, MD, MBA, and Rodney Tucker, MD, MMM
CME Credit Available: 2.5 *AMA PRA Category 1 Credits*™
Level: Advanced

Patients with HIV infection now have near-normal life expectancies, but 40% to 55% still report pain. Various comorbid conditions, including cardiovascular disease, frailty, and non–AIDS-defining malignancies, are prevalent in the HIV-infected population, which also has high rates of substance abuse. For this reason, HIV medical practitioners have become HIV primary care doctors who must address all of these issues. Dr Jessica Merlin and Dr Rodney Tucker present an approach to the treatment of pain, an underdiagnosed and undertreated condition in HIV-infected patients.

Quality Measures in HIV Care

Kathleen Clanon, MD, and Steven Bromer, MD
CME Credit Available: 1.75 *AMA PRA Category 1 Credits*™
Level: Advanced

Choosing a set of quality of care measures and a strategy for using them is an investment in time and resources—the resulting information can be either a powerful tool for improving care or a useless paper exercise. Dr Kathleen Clanon and Dr Steven Bromer provide guidelines and advice on selecting performance measures, determining data collection methods, and using and leveraging the eventual results to improve care.

Initiation of Antiretroviral Therapy in Treatment-Naive HIV-Infected Patients

Greer A. Burkholder, MD
CME Credit Available: 1.75 *AMA PRA Category 1 Credits*™
Level: Advanced

What impact does the timing of antiretroviral therapy (ART) initiation have on the prognosis of HIV-infected patients? Dr Greer Burkholder discusses the influence of CD4+ cell count, plasma HIV RNA level, AIDS-related and non–AIDS-related comorbidities, pregnancy, and patient willingness to take lifelong medications. Because of the evolving nature of guidelines and evidence regarding timing of ART, HIV practitioners need to update their knowledge on this topic regularly.

New Treatments for Hepatitis C Virus Infection

Melissa K. Osborn, MD
CME Credit Available: 1.5 *AMA PRA Category 1 Credits*™
Level: Advanced

Dr Melissa Osborn explains how the 2 new HCV protease inhibitors, telaprevir and boceprevir—direct-acting antiviral agents that inhibit viral replication—will affect therapy for treatment-naive and treatment-experienced patients with HCV infection. Her presentation describes the effects of telaprevir and boceprevir on sustained virologic response (SVR) rates, and includes response-guided treatment algorithms.

Smoking Cessation: Treatment Strategies for the HIV Practitioner

Steven A. Schroeder, MD and Margaret Meriwether, PhD
CME Credit Available: 1.0 *AMA PRA Category 1 Credits*™

What are the obstacles to smoking cessation, and how can they be overcome? Dr Steven Schroeder and Dr Margaret Meriwether discuss the medical practitioner's role in assisting HIV-infected patients with smoking-cessation–related issues such as weight gain and fatalism. They introduce treatment modalities that increase the likelihood of a successful quit attempt.

Approaching the HIV-Infected Patient With Addiction

R. Douglas Bruce, MD, MA, MSc
CME Credit Available: 1.75 *AMA PRA Category 1 Credits*™
Level: Advanced

Substance-use disorders are prevalent in HIV clinical settings. Impaired judgment due to ongoing substance use can mean increased sexual risk taking, which further contributes to HIV infection rates and incidence of other sexually transmitted diseases. Dr R. Douglas Bruce describes how screening, evaluation, and a compassionate approach to patient care can be combined to provide effective treatment.

Diagnosis and Treatment Options for Acute HIV Infection

Elizabeth Reddy, MD, and Charles B. Hicks, MD
CME Credit Available: 1.75 *AMA PRA Category 1 Credits*™
Level: Advanced

"Acute" HIV infection generally refers to the phase of rapidly evolving HIV antibody test results when viral replication is at its peak. "Primary" HIV infection often refers to the entire period from transmission through the first year of infection. Despite its perceived importance, diagnosing primary or acute HIV infection remains challenging for many reasons. Health care practitioners who are likely to come in contact with newly infected persons should be versed in recommendations and options for diagnosis and treatment. Dr Elizabeth Reddy and Dr Charles B. Hicks discuss important concepts in the diagnosis of and treatment options for acute HIV infection.

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Special Contribution

Update of the Past Year: A Review from IDSA 2011

David L. McCollum, MD

The Infectious Diseases Society of America Annual Meeting serves as a time of expert review of the year's most important innovations. Important new information on HIV infection incidence was discussed. The remarkable efficacy of "treatment as prevention" in the HIV Prevention Trials Network (HPTN) 052 study and the proper place of oral preexposure prophylaxis were among the important prevention topics. Key engagement-in-care research indicates that only 19% of HIV-infected persons in the United States have a plasma HIV RNA level below the limits of assay detection. Among antiretroviral topics, the role of the newly approved non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine was discussed. Primary care topics for the HIV-infected population included treatment of triglyceride level elevations and bone health. The newly published data on the proper timing of antiretroviral therapy initiation after starting tuberculosis treatment were highlighted. Finally, exciting advances in the treatment of hepatitis C virus (HCV) infection necessitate that practitioners understand the complexities of treating HIV/HCV coinfections.

The Infectious Diseases Society of America (IDSA) Annual Meeting is a forum for the presentation of new data (in abstract and poster sessions) and serves as a review of important recent advances in the field over the past year. This year's IDSA meeting, held from October 20 to 23, 2011, in Boston, presented participants with an opportunity to reflect on how recent innovations will impact their practice. This article highlights some of this year's key messages from the meeting. This content will update HIV clinicians on advances presented at IDSA 2011, focusing on the US epidemic.

Update on Incidence: For Young African American MSM, the Bad News is Getting Worse

Currier's update on HIV during the "What's Hot in ID and HIV" Symposium began with a discussion of new US HIV infection incidence data released by the Centers for Disease Control and Prevention (CDC) in August pertaining to the years 2006 to 2009.[1] The new figures are considered more accurate than those previously released, owing to new methodologies used in their calculation. The CDC report warns that as methodologies improve, total incidence is likely to undergo further revision, and that the more important data are those indicating the trends and risk groups affected.

Overall the incidence of HIV infection has not changed in recent years, with around 50,000 new infections in the United States annually. An estimated 95% of new infections occur in women, members of ethnic and racial minority groups, and injection drug users. Black/African Americans are contracting HIV at a rate 10 times that of whites. For Latinos, the rate is 3 times to 4 times the rate in whites.

Transmission in men who have sex with men (MSM) accounts for 61% of new infections. An alarming finding was the HIV infection incidence among young (aged 13-29 years) black MSM, which had increased 48% (or 12.2% annually). With the release of these data, contemporary at-risk groups to whom prevention can be targeted have been more clearly delineated.

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Update on Prevention

Treatment Takes Center Stage

Because of the remarkable efficacy shown in the HIV Prevention Trials Network (HPTN) 052 study, treatment as prevention was among Currier's most important prevention topics.[2] HPTN 052 was an international study of 1763 HIV-serodiscordant couples in which the HIV-seropositive partner did not meet current criteria for antiretroviral therapy. The HIV-seropositive partners were randomly assigned to immediate antiretroviral therapy versus standard treatment (standard treatment being antiretroviral therapy initiation based on clinical events or a CD4+ cell count < 250/μL). The primary outcomes were transmission to the seronegative partner and clinical disease progression in the seropositive partner. Viral sequencing was performed so that transmission events could be linked to the seropositive partner. Only 1 of the total 28 linked transmission events occurred in the early antiretroviral therapy group (a 96% reduction in transmission). Clinical events were also statistically significantly fewer in the early therapy group, largely because of a reduction in extrapulmonary tuberculosis.

Initial CDC Guidance Regarding Oral PrEP

Smith of the CDC discussed oral preexposure prophylaxis (PrEP) at the "State-of-the-Art in HIV" symposium. Oral PrEP refers to the active use of oral medications to protect against HIV infection. The results of the iPrEx (Chemoprophylaxis for HIV Prevention in Men) study on oral PrEP have been known for almost a year.[3] This international trial randomly assigned 2499 high-risk HIV-seronegative MSM to either daily tenofovir/emtricitabine or placebo, with all participants receiving

equivalent preventive services and education. A substantial reduction (44%) in new HIV infections occurred in the intervention group during a median follow-up of 1.2 years (100 new infections: 64 in the placebo group and 36 in the intervention group). This decrease was even more pronounced when adherence (measured by detection of serum antiretroviral drug levels) was factored in.

Although any positive trial in the field of HIV prevention is a reason for celebration, many questions regarding feasibility, safety, cost, and effectiveness of oral PrEP have been raised. Smith noted that comprehensive PrEP guidelines are forthcoming, and presented the initial guidance.[4] The target population for oral PrEP is HIV-seronegative MSM who are not monogamous with their HIV-seronegative partner and report inconsistent condom use; who have any sexually transmitted infection (STI); or who have ongoing sexual contact with HIV-seropositive partners. The CDC estimates that 275,000 persons meet these criteria. Primary care practitioners and health departments are thought to be the most likely providers of PrEP. Smith highlighted a practical challenge, which is that many primary care practitioners do not have a thorough understanding of their patients' sexual practices.

Mayer and colleagues' poster presentation focused on primary care practitioners and HIV specialist physicians' knowledge and practice regarding PrEP (Abstract 493).[5] The authors' survey of Massachusetts practitioners indicated that although self-reported knowledge of PrEP seemed to be very good (92%), very few had actually prescribed PrEP (5%). Regarding the preferred type of PrEP delivery, more respondents preferred a topical microbicide (69%) over oral PrEP. The majority thought formal guidelines would be the most helpful method of increasing physician uptake of PrEP. Detailed recommendations on technical aspects of providing oral PrEP to MSM are available in the CDC interim guidance.[4] Additionally, a recent comprehensive review of HIV prevention is available.[6]

Engagement in Care: Problems Along the Path to Viral Suppression

The "test and treat" strategy for HIV infection entails universal testing with immediate treatment for those who test seropositive. The efficacy of treatment as prevention demonstrated in HPTN 052 has reinvigorated the discussion over using a "test and treat" strategy to reduce the incidence of HIV infection in the United States. However, engagement-in-care research raises a note of caution regarding potential pitfalls in the effectiveness of this strategy.

The estimates published by Gardner and colleagues[7] are helpful in understanding this issue: Figure 1 shows the estimate of 1.1 million persons being infected with HIV in the United States and then sequentially shows the use of available data to estimate where patients are lost to care at each point along the path to viral suppression. It is estimated that 21% of HIV-infected persons are currently undiagnosed. Of those who are diagnosed, losses occur at initial linkage to care and later in care such that only 50% remain in care. Antiretroviral therapy eligibility, actual initiation, and effective antiretroviral therapy are all unique steps through which a proportion of patients do not progress, leading to the estimate of only 19% (209,773 of 1.1 million) of HIV-infected persons in the United States currently having viral load below the limits of assay detection.

Gardner and colleagues describe how maximizing only a single step in the care pathway does little to influence the final proportion of those with maximal viral suppression. For example, increasing diagnosis (as would result from an effective universal testing policy) to 90% of persons with HIV infection would only increase the percentage of persons with maximal virologic suppression by 3%. Andrews and colleagues showed a related phenomenon in a South African township in their oral abstract presentation (Abstract 148).[8] Thus, although the efficacy of treatment as prevention demonstrated in HPTN 052 is a cause of great hope, the effectiveness of a "test and treat" strategy for lowering the incidence of HIV infection requires a strengthening of *each* point along the pathway to sustained viral suppression.

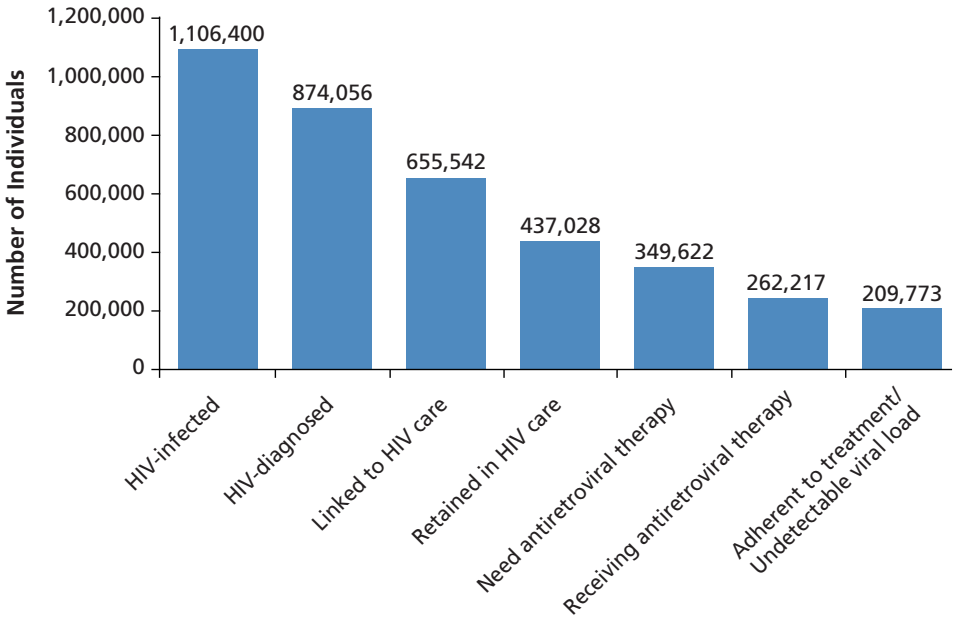

Figure **1**. Estimated loss of HIV-infected patients engaged in care, shown along each step in the care pathway. Gardner and colleagues calculate that only 19% of HIV-seropositive persons in the United States have a maximally suppressed viral load. Adapted from Gardner et al,[7] by permission of Oxford University Press.

Goetz and Rimland's poster of Department of Veterans Affairs (VA) data shows a positive example of the care pathway (Abstract 478).[9] In this group of 189 patients diagnosed after the VA increased HIV testing in 2005, a remarkable 71% had attained an undetectable viral load within 12 months. The authors conclude that an integrated health system such as the VA, in which each step in the care pathway can be efficiently linked, improves overall engagement in care.

Update on Antiretrovirals

Searching for Rilpivirine's Place

An update on antiretroviral therapy was provided by Sax during the "State-of-the-Art in HIV" symposium. The US Food and Drug Administration (FDA) approval of rilpivirine in May 2011 marked the entry of a new nonnucleoside reverse transcriptase inhibitor (NNRTI). The once-daily, fixed-dose combination of rilpivirine/tenofovir/emtricitabine was approved in August 2011. The phase III studies of rilpivirine, ECHO (Efficacy Comparison in Treatment-Naive HIV-Infected Subjects of TMC278 and Efavirenz) and THRIVE (TMC278 Against HIV in a Once Daily Regimen Versus Efavirenz), were published simultaneously in July.[10,11] The trials were randomized, double-blinded studies in antiretroviral therapy–naive patients that established noninferiority of the drug compared with an efavirenz-based regimen. The trials were identical in design except for the components of the background regimens (tenofovir/emtricitabine in ECHO and variable in THRIVE). An undetectable viral load at 48 weeks was found in 83% of ECHO and 86% of THRIVE participants in the rilpivirine arms (83% and 82%, respectively, in the efavirenz groups).

Although these trials demonstrate efficacy, questions remain regarding for whom rilpivirine is best suited.[12] Compared with efavirenz, rilpivirine had fewer central nervous system (CNS) adverse effects, rash, lipid abnormalities, and discontinuation rates. Additionally, rilpivirine is currently classified as pregnancy class B, whereas efavirenz is class D. In patients with a high plasma HIV RNA level (> 100,000 copies/mL), however, virologic failure occurred more commonly with rilpivirine than efavirenz (17% versus 7%, respectively). Resistance to rilpivirine (including the E138K mutation, also associated with etravirine resistance) largely excluded future use of the NNRTI class, whereas for those on efavirenz who developed NNRTI resistance (predominantly the K103N mutation), etravirine (and likely rilpivirine) often remained an option.

The data on tolerability and antiretroviral activity and resistance have led to rilpivirine being designated as an alternative NNRTI for treatment-naive patients in the recent Department of Health and Human Services (DHHS) treatment guidelines update.[13] The guidelines specifically recommend caution in the use of the drug in patients with baseline plasma HIV RNA levels greater than 100,000 copies/mL. Of note, rilpivirine must be taken with a full meal and concomitant proton pump inhibitors are contraindicated. Finally, "switch" studies are under way evaluating a rilpivirine-containing regimen for patients currently virologically suppressed on regimens that contain ritonavir-boosted (/r) protease inhibitors or efavirenz. In summary, rilpivirine is an efficacious NNRTI for treatment-naive patients, but has some limitations. Its long-term place amongst possible anchor drugs in initial regimens (ie, efavirenz, atazanavir/r, darunavir/r, or raltegravir) remains to be determined.

Comparing nRTI Backbones

Sax also discussed the final results of the AIDS Clinical Trials Group (ACTG) 5202 study.[14] This was a US-based, prospective, randomized equivalence trial of 4 initial once-daily antiretroviral therapy regimens: dual nucleoside analogue reverse transcriptase inhibitor (nRTI) backbones abacavir/lamivudine or tenofovir/emtricitabine (blinded) with either efavirenz or atazanavir/r (open label). The trial enrolled 1858 persons and stratified patients based on high (≥ 100,000 copies/mL) or low (< 100,000 copies/mL) plasma HIV RNA level. Regarding efavirenz versus atazanavir/r, results published in February 2011 (a median 138 weeks of follow-up) show similar virologic efficacy.[15] Regarding the comparison of nRTI backbones, an interim review in 2008 (a median 60 weeks of follow-up) led the data and safety monitoring board to recommend stopping the abacavir/lamivudine arm in the high viral load group because of statistically significant higher occurrences of virologic failures (14% versus 7%) than in the tenofovir/emtricitabine arm.[16]

In October 2011, results from the study arm with lower initial HIV RNA level (< 100,000 copies/mL) were published and the time to virologic failure for abacavir/lamivudine versus tenofovir/emtricitabine was found to be similar in this subgroup of patients.[16] These findings are in line with the DHHS guidelines, which recommend tenofovir/emtricitabine as the preferred dual-nRTI backbone and abacavir/lamivudine as the alternative choice to be used with caution in patients with greater than 100,000 HIV RNA copies/mL of plasma at baseline.[13]

The search for an nRTI-sparing regimen continues to be evasive. The ACTG 5262 single-arm open-label study of 118 antiretroviral therapy–naive patients receiving twice-daily raltegravir plus once-daily darunavir/r reported that rates of virologic failure at 48 weeks were 26% overall, including 43% in those with more than 100,000 HIV RNA copies/mL).[17] The reason for these high rates of virologic failure is not clear, and the study lacked a comparator arm. This regimen (raltegravir and darunavir/r) is being compared in a larger European study with a regimen of tenofovir/emtricitabine and darunavir/r.

Update on HIV Primary Care

The Value of Triglyceride Treatment Scrutinized

The proper management of elevated triglyceride levels in HIV-infected patients was discussed by Sax in the

"Challenging HIV Cases" session, which focused on 2 recent publications.[18,19] In 2010, the value of treating high triglyceride levels with a fibrate in a high-cardiovascular-risk, non-HIV-infected population already on an HMG-CoA reductase inhibitor (a statin) was questioned with the release of results from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study.[18] This study randomly assigned 5518 patients with type 2 diabetes to either fenofibrate or placebo. At a mean follow-up of 4.7 years, there was no benefit in terms of cardiovascular outcomes in the fibrate group.

Elevated triglyceride levels are common in the HIV-infected population because of traditional risk factors and certain antiretroviral drugs. The D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study group sought to evaluate, via an observational cohort, whether triglyceride levels were an independent risk factor for myocardial infarction (MI) in HIV infection.[19] Data from 33,308 persons (including 580 MIs) were available for evaluation.

After controlling for risk factors (other lipid, cardiovascular, HIV, and antiretroviral factors) the risk of a MI was only minimally increased with a doubling of triglyceride levels (relative risk, 1.11; 95% confidence interval, 1.01-1.23). The investigators concluded that current evidence indicates cardiovascular risk reduction strategies in HIV-infected patients should focus on risk factors other than elevated triglyceride levels.

Bone Health, Vitamin D, and the Search for Consensus

Bone health topics continued to be discussed at the IDSA meeting, including an expert panel discussion, "Challenging HIV Cases," that reviewed current clinical strategies. Although current guidelines for the general population recommend bone mineral density (BMD) screening for men older than 70 years and women older than 65 years, it may be reasonable to consider HIV infection as an additional risk factor and thus justify screening those older than 50 years.[20]

HIV infection itself and antiretroviral drugs may negatively affect bone health, but traditional risk factors must not be forgotten. This was demonstrated in a large VA cohort study of 119,318 persons that compared fracture risk in HIV-infected and -uninfected patients.[21] HIV infection itself was associated with an increased relative risk of fractures in the unadjusted comparison. However, the additional risk was negated after adjusting for traditional factors including certain demographics or comorbid diseases, smoking, alcohol abuse, and body mass index.

Regarding the effects of individual antiretroviral drugs on bone health, data were available from a substudy of ACTG 5202.[22] In the prospective substudy, 259 persons were randomly assigned to 1 of 4 initial once-daily regimens: abacavir/lamivudine or tenofovir/emtricitabine (blinded) with either efavirenz or atazanavir/r (open label). Sequential bone density results were recorded with the primary outcome being hip and spine bone changes at week 96.

Although there was no difference in bone fractures between the groups, there was a general decrease in BMD in all groups. Similar to other studies, the decrease was similar in magnitude to that seen in the immediate postmenopausal years.[23] Decreases in BMD were greater with tenofovir- than abacavir-containing regimens, and greater with atazanavir/r- than efavirenz containing regimens. The decrease occurred in the first 48 weeks of therapy, after which BMD plateaued.

An important cause of poor bone health is low vitamin D level, which is common in HIV-infected persons.[24] Supplementation is recommended for those with a serum 25-hydroxyvitamin D level below 30 ng/mL. There is concern that vitamin D deficiency may have detrimental effects beyond those on bone health. An intriguing observational study found that severe vitamin D deficiency was independently associated with death and AIDS events.[25] Ongoing investigations of bone health and vitamin D continue, including in ACTG 5280. This is a 48-week study in which efavirenz, with or without vitamin D and calcium supplementation, is compared with bone health as the primary outcome.

Update on HIV/TB Coinfection: Initiating Antiretroviral Therapy at the Right Time

Tuberculosis (TB) was excluded from the 2009 ACTG A5164 trial that showed a mortality benefit when antiretroviral therapy was initiated within 14 days of diagnosis of an opportunistic infection.[26] Now, 3 trials investigating the optimal timing of antiretroviral therapy initiation in patients on TB therapy have been simultaneously published in the *New England Journal of Medicine*.[27-29] The publication of these trials coincided with the first day of the IDSA 2011 meeting and was included in Currier's presentation as one of the year's most important findings. The 3 international trials randomly assigned patients on TB treatment to either early antiretroviral therapy initiation (mean 10-21 days after starting TB therapy) or late antiretroviral therapy initiation (mean 56-97 days after starting TB therapy).

The results of the trials showed a mortality benefit with early antiretroviral therapy initiation in those patients with severe immunosuppression (CD4+ cell count < 50/µL), but not in those with higher CD4+ cell counts. Additionally, there were more cases of immune reconstitution inflammatory syndrome (IRIS) in the early initiation group at all CD4+ cell counts. Hence, the conclusion is that for those with advanced AIDS (CD4+ cell count < 50 µL), it is beneficial to initiate antiretroviral therapy within 2 weeks of starting TB therapy. For those with higher baseline CD4+ cell counts (> 50/µL), it seems beneficial to wait until the beginning of the continuation phase (8 weeks from starting TB therapy) to initiate antiretroviral therapy. Dr Currier emphasized that most of the patients in these studies had pulmonary TB. Other forms of TB may behave differently.

Timing of antiretroviral therapy initiation in 253 Vietnamese patients

with TB meningitis has recently been reported.[30] The patients were largely young male injection drug users with advanced immunosuppression (mean CD4+ cell count, 41/μL). The study randomly assigned patients to early (7 days) versus late (2 months) antiretroviral therapy initiation. Death rates were high in both groups (greater than 50%) and no mortality benefit was shown in the early initiation group. Additionally, a higher rate of severe adverse events occurred in the early initiation group. Hence, the recommendation from this study is to initiate antiretroviral therapy in patients with TB meningitis after completion of 2 months of TB therapy.

Update on HIV/HCV Coinfection: Good News Thus Far

The approval in May 2011 of direct-acting antiviral drugs for chronic hepatitis C virus (HCV) infection was among the top innovations in medicine this year.[31,32] The trials on which the drug approvals were based excluded subjects coinfected with HIV, but promising data for these patients are beginning to accumulate. Interim data from prospective trials of coinfected patients receiving telaprevir or boceprevir were presented at this year's Conference on Retroviruses and Opportunistic Infections (CROI) and IDSA meeting, respectively.

These preliminary results showed a 68% early virologic response to a telaprevir-containing regimen at 12 weeks, compared with 14% on pegylated interferon alfa–ribavirin alone.[33] The interim results of the boceprevir trial showed a 58% early virologic response at 12 weeks compared with a 25% response in those on pegylated interferon alfa–ribavirin alone (Abstract LB-37).[34] The response rates are similar to those seen in HCV monoinfected patients.

The IDSA meeting featured an "HIV Challenges and Complications" session with expert discussion on many aspects of care for the HIV/HCV coinfected population. The topic of coinfection has also recently been reviewed.[35] Important considerations for using the new HCV drugs in HIV-infected patients also on HIV therapy, including potential drug interactions and overlapping toxic effects, were highlighted.

Telaprevir is a cytochrome P450 3A4 and P-glycoprotein substrate and inhibitor. In the previously mentioned ongoing study of telaprevir in coinfected patients, the participants were receiving tenofovir/emtricitabine/efavirenz or tenofovir/emtricitabine/atazanavir/r. The investigators increased the dose of telaprevir in the efavirenz group, and used standard telaprevir doses for those on the atazanavir/r regimen. The coadministration of the HCV and antiretroviral regimens was well tolerated. Another consideration for the clinician is that tenofovir concentrations can increase in patients using telaprevir and hence renal function should be monitored vigilantly.

In the ongoing boceprevir trial, coinfected patients on efavirenz were excluded because of concerns about reduced drug levels of efavirenz. Participants were receiving a variety of ritonavir-boosted protease inhibitor regimens and neither the HCV nor HIV drug doses required adjustment. Numerous new medications for HCV infection are in various stages of development. Staying abreast of issues related to the treatment of HIV/HCV coinfected patients will be of vital importance for providers in this rapidly evolving field.

Summary

In summary, the IDSA 2011 meeting provided a rich opportunity for clinicians to hear a review of the major findings of the previous year. Much investigation is ongoing, making the 2012 conference likely to be a similarly stimulating occasion. Next year, the conference will undergo much innovation and will have the new title, "ID Week." This conference will be held from October 17 to 21, 2012, in San Diego, CA, and will be a joint meeting of IDSA, the Society for Healthcare Epidemiology of America (SHEA), the HIV Medicine Association (HIVMA), and the Pediatric Infectious Diseases Society (PIDS).

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

The author thanks Dr James Willig for insightful comments on the manuscript.

References

* *Indicates an IDSA 2011 conference abstract.*

1. Prejean J, Song R, Hernandez A, et al. Estimated HIV incidence in the United States, 2006-2009. *PLoS One*. 2011;6:e17502.
2. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011;365:493-505.
3. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010;363:2587-2599.
4. MMWR. Interim guidance: preexposure prophylaxis for the prevention of HIV infection in men who have sex with men. *MMWR Morb Mortal Wkly Rep*. 2011;60:65-68.

*5. Mayer K, White J, Krakower D, Mimiaga M. Evolution of Massachusetts physician attitudes, knowledge and experience regarding the use of antiretrovirals for HIV prevention. [Abstract 493.] 49th Annual Meeting of the Infectious Diseases Society of America (IDSA). October 20-23, 2011; Boston, MA.

6. Padian NS, McCoy SI, Karim SS, et al. HIV prevention transformed: the new prevention research agenda. *Lancet*. 2011;378:269-278.
7. Gardner EM, McLees MP, Steiner JF, del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. *Clin Infect Dis*. 2011;52:793-800.

*8. Andrews J, Wood R, Bekker LG, Walensky R. Modeling antiretroviral therapy as prevention for HIV: the impact of population mobility and linkage to care. [Abstract 148.] 49th Annual Meeting of the Infectious Diseases Society of America (IDSA). October 20-23, 2011; Boston, MA.

*9. Bidwell Goetz M, Rimland D. Linkage to care of newly diagnosed HIV-infected patients in two VA facilities. [Abstract 478.] 49th Annual Meeting of the Infectious Diseases Society of America (IDSA). October 20-23, 2011; Boston, MA.

10. Molina JM, Cahn P, Grinsztejn B, et al. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. *Lancet*. 2011;378:238-246.
11. Cohen CJ, Andrade-Villanueva J, Clotet B, et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. *Lancet*. 2011;378:229-237.
12. Schrijvers R, Desimmie BA, Debyser Z. Rilpivirine: a step forward in tailored HIV treatment. *Lancet*. 2011;378:201-203.
13. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for

the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. October 14, 2011; 1-167. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed November 30, 2011.

14. Sax PE, Tierney C, Collier AC, et al. Abacavir/lamivudine versus tenofovir DF/emtricitabine as part of combination regimens for initial treatment of HIV: final results. *J Infect Dis*. 2011;204:1191-1201.

15. Daar ES, Tierney C, Fischl MA, et al. Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. *Ann Intern Med*. 2011;154:445-456.

16. Sax PE, Tierney C, Collier AC, et al. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. *N Engl J Med*. 2009;361:2230-2240.

17. Taiwo B, Zheng L, Gallien S, et al. Efficacy of a nucleoside-sparing regimen of darunavir/ritonavir plus raltegravir in treatment-naive HIV-1-infected patients (ACTG A5262). *AIDS*. 2011;25:2113-2122.

18. Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1563-1574.

19. Worm SW, Kamara DA, Reiss P, et al. Elevated triglycerides and risk of myocardial infarction in HIV-positive persons. *AIDS*. 2011;25:1497-1504.

20. McComsey GA, Tebas P, Shane E, et al. Bone disease in HIV infection: a practical review and recommendations for HIV care providers. *Clin Infect Dis*. 2010;51:937-946.

21. Womack JA, Goulet JL, Gibert C, et al. Increased risk of fragility fractures among HIV infected compared to uninfected male veterans. *PLoS One*. 2011;6:e17217.

22. McComsey GA, Kitch D, Daar ES, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: AIDS Clinical Trials Group A5224s, a substudy of ACTG A5202. *J Infect Dis*. 2011;203:1791-1801.

23. Brown TT, McComsey GA, King MS, Qaqish RB, Bernstein BM, Da Silva BA. Loss of bone mineral density after antiretroviral therapy initiation, independent of antiretroviral regimen. *JAIDS*. 2009;51:554-561.

24. Rodriguez M, Daniels B, Gunawardene S, Robbins GK. High frequency of vitamin D deficiency in ambulatory HIV-Positive patients. *AIDS Res Hum Retroviruses*. 2009;25:9-14.

25. Viard JP, Souberbielle JC, Kirk O, et al. Vitamin D and clinical disease progression in HIV infection: results from the EuroSIDA study. *AIDS*. 2011;25:1305-1315.

26. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One*. 2009;4:e5575.

27. Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med*. 2011;365:1492-1501.

28. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med*. 2011;365:1471-1481.

29. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med*. 2011;365:1482-1491.

30. Torok ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)-associated tuberculous meningitis. *Clin Infect Dis*. 2011;52:1374-1383.

31. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med*. 2011;364:2405-2416.

32. Poordad F, McCone J, Jr., Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med*. 2011;364:1195-1206.

33. Sulkowski M, Dieterich D, Sherman K, et al. Interim analysis of a phase 2a double-blind study of TVR in combination with pegIFN-α2a and RBV in HIV/HCV co-infected patients. [Abstract 146LB.] In: Proceedings from the 18th Conference on Retroviruses and Opportunistic Infections (CROI). 2011; Boston, MA.

***34.** Sulkowski M, Pol S, Cooper C, et al. Boceprevir plus peginterferon/ribavirin for the treatment of HCV/HIV co-infected patients: interim on-treatment results. [Abstract LB-37.] 49th Annual Meeting of the Infectious Diseases Society of America (IDSA). October 20-23, 2011; Boston, MA.

35. Soriano V, Sherman KE, Rockstroh J, et al. Challenges and opportunities for hepatitis C drug development in HIV-hepatitis C virus-co-infected patients. *AIDS*. 2011;25:2197-2208.

Top Antivir Med. 2011;19(5): 187-192

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Reviews. *Topics in Antiviral Medicine* welcomes original review articles on current issues related to infection with HIV or other viruses. *Topics in Antiviral Medicine* does not publish original research. Manuscripts should be 3000 to 6000 words (excluding references, tables, and figures) and should include numbered references and a brief introductory abstract of approximately 100 to 200 words. Original, adapted, or reprinted figures and tables may be included and should be cited in the text and accompanied by a brief title. Adapted and reprinted work requires proof of permission obtained from the original publishers and authors. Authors interested in submitting unsolicited manuscripts are encouraged to submit an outline or abstract of the proposed manuscript first; please contact the editor for further information.

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1. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Updated October 2008. Available at http://www.icmje.org. Accessed January 26, 2010.

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