TRAVEL MEDICINE ADVISOR

Your Monthly Supplement of Travel Medicine Literature

AHC Media LLC

INSIDE

Volume 17, No. 9
September 2007

Financial Disclosure:

Travel Medicine Advisor's physician editor, Frank Bia, MD, MPH, is a consultant for Pfizer and Sanofi Pasteur, and receives funds from Johnson & Johnson.

Progress Report: Researchers Make Strides in Global Battle Against HIV

Scientific advances may aid in stemming spread of disease

By Rebecca Bowers

This article originally appeared in the May 2007 issue of Contraceptive Technology Update. *Consulting Editor Robert A. Hatcher, MD, MPH, Author Rebecca Bowers, Associate Publisher Coles McKagen, and Senior Managing Editor Joy Dickinson report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.*

GOOD NEWS ON THE RESEARCH FRONT: RESULTS FROM A MAJOR STUDY indicate that treating genital herpes may help keep the AIDS virus under control in women with both infections and may reduce the spread of HIV as well.[1] In the laboratory, scientists have successfully mapped an area on the surface of HIV that may be vulnerable to an assault by antibodies, which could lead to development of an effective vaccine.[2]

Progress needs to continue at a rapid pace. In 2005, an estimated 4.1 million people worldwide were newly infected with HIV, mostly through heterosexual intercourse.[3] At the end of 2003, an estimated 1,039,000 to 1,185,000 people in the United States were living with HIV/AIDS, with 24%-27% undiagnosed and unaware of their HIV infection.[4]

Why are scientists focusing on the virus that causes genital herpes (herpes simplex virus-2, HSV-2) in relation to HIV? HSV-2 infection almost doubles the risk of HIV acquisition; results from a meta-analysis indicate.[5] Data from Rakai, Uganda, in HIV-discordant couples suggest that, on a per-contact basis, HSV-2 increases the risk of HIV acquisition fivefold.[6]

The problem is compounded when looking at the prevalence of the disease:

• Approximately one out of five sexually active adults in the United States is HSV-2-seropositive.

• In studies in Latin America and Peru, 60% of HIV-uninfected men who have sex with men are HSV-2-seropositive.

• The rate rises even higher among HIV-infected women in parts of sub-Saharan Africa, South Africa, and Zimbabwe, where the HSV-2 prevalence is 70%.[7]

To conduct the trial among women coinfected with HIV and HSV-2, scientists from the Centre Muraz in Burkina Faso, the University of Montpellier

(France), and the London (UK) School of Hygiene & Tropical Medicine enrolled 140 Burkina Faso women who were infected with the herpes and AIDS viruses. The women received valacyclovir or placebo pills for three months. Study findings indicate that having the herpes virus increased the replication of HIV and also revealed that the quantity of HIV in the blood and in the vagina was reduced by continuous anti-herpes treatment over three months.[1]

What is the next step?

These findings open new avenues for the prevention of HIV transmission and for the management of patients coinfected by the two viruses, says Philippe Mayaud, a scientist at the London School of Hygiene & Tropical Medicine and co-author of the current paper.

What are the next steps in HSV-HIV research? On the HIV transmission front, scientists will need to demonstrate that the effect seen on infectiousness or transmissibility of the virus actually translates into decreased transmission, says Mayaud. Several trials are ongoing, and results should be available within the next 18 months, he reports. Modeling studies will need to explore the population level impact of these therapies to assess their public health benefit, he notes.

When it comes to HIV disease progression, research should focus on the potential usefulness of using anti-HSV treatment during HIV disease, says Mayaud. For those infected with HSV-2, long-lasting therapies should be developed that do not depend on long-term intake of tablets, Mayaud believes. Safe and effective vaccines that would at least control the replication of HSV— if not prevent it altogether — would go a long way to prevent the transmission of HSV and HIV, he states.

"Such vaccines are currently not available," Mayaud says. "This should be an important priority area of research."

Progress on the HIV vaccine front has been challenged by the nature of the virus. Scientists led by a team at the National Institute of Allergy and Infectious Diseases (NIAID) now say they have been able to identify a key portion of an HIV surface protein as it looks when bound to an infection-fighting antibody.[2] The protein component is stable and appears vulnerable to attack from a specific antibody, known as b12, that can broadly neutralize HIV, researchers report.[2]

The HIV virus mutates rapidly and continuously, which stymies attempts by the immune system to identify and destroy it. To further compound the problem, the virus is covered by molecules, which prevent antibodies from slipping in and blocking the proteins the virus uses to latch onto a cell and infect it.

NIAID researchers have been able to decipher how the b12 antibody is able to bind to an unchanging surface on the tip of the HIV virus. They used an X-ray snapshot of the antibody as it locked into the target site on the virus, then used chemical blocks to provide a 3-D map of the target site.[2] The resulting "map" may give researchers valuable clues in designing an effective vaccine. By understanding the structure of the virus, researchers may be able to improve on nature by designing an antibody that binds better than b12 and is easier for humans to produce.

Tongqing Zhou, PhD, a staff scientist in the NIAID's

Travel Medicine Advisor (ISSN # 1930-0867) is published monthly by AHC Media LLC, 3525 Piedmont Road, N.E., Six Piedmont Center, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Application to mail at periodicals postage rates is pending at Atlanta, GA 30304. POSTMASTER: Send address changes to Travel Medicine Advisor, PO Box 740059, Atlanta, GA 30374-9815.

Subscription Information: Customer Service: (800) 688-2421 or fax (800) 284-3291. Hours of operation: 8:30am-6pm Monday-Thursday; 8:30am-4:30pm Friday ET. Email: customerservice@ahcmedia.com Website: www.ahcmedia.com. Subscription rates: USA, one year (12 issues) $449. Add $9.95 for shipping & handling. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for group subscriptions. For pricing information, call Tria Kreutzer at (404) 262-5482.

Vaccine Research Center's Structural Biology Section and lead author of the current research, says, "The detailed atomic level information from the HIV gp120:b12 structure tells us how a 'good' antibody works by attacking this weak link in the HIV armor, and it will guide us in the rational design of a future vaccine."

The next step in science is to use the information in designing and creating vaccines that will stimulate the immune system to generate large amounts of antibodies that would replicate or surpass b12's virus-killing power, says Zhou. However, the creation of such vaccines and the animal/human test processes may take a long time, and there will be many technical bumps ahead, he notes. ■

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Death in Venice — And Other Parts of the World

By Carol A. Kemper, MD, FACP

Dr. Kemper reports no financial relationship relevant to this field of study. This article originally appeared in the August 2007 issue of Infectious Disease Alert. *It was edited by Stan Deresinski, MD, FACP, and peer reviewed by Connie Price, MD. Dr. Deresinski is Clinical Professor of Medicine, Stanford University; Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center, and Dr. Price is Assistant Professor, University of Colorado School of Medicine. Dr. Deresinski serves on the speaker's bureau for Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck. Dr. Price reports no financial relationship relevant to this field of study.*

Source: MacPherson DW et al. Death and International Travel - The Canadian Experience: 1996-2004. J Trav Med *2007, 14 (2), 77-84.*

DATA SUGGEST THAT DEATH DURING INTERNATIONAL travel is increasing, in part because of wilderness and adventure travel, but also because more and more people are traveling. Deaths abroad have considerable impact on friends and family, as well as the pocketbook. As part of the Secure Integrated Global Network established in 1993, the Consular Services Bureau, part of the Foreign Affairs Office in Canada, tracks Canadian deaths abroad, including the cause of death, sex and age. Specific data on the purpose of travel, or whether work or pleasure related was not always available.

From 1996-2004, 2,410 Canadians died while traveling abroad. Interestingly, deaths in the United States (297), Germany (240) and China (115) topped the list, far exceeding deaths in Africa (95), generally considered a riskier destination. Two-thirds of the deaths occurred in men, and the average age was just over 60 years (range, 0 to 101). Natural causes of death occurred in 73%, followed by accidental death in 19%, murder in 4% and suicide in 4%. People who died of natural causes averaged age 66 compared with those who died by accident (45 years), murder (43 years), or suicide (41 years). Annual increases in accidental deaths were observed, most likely because of wilderness and adventure travel.

In examining the top 15 destinations for 2004, deaths per 1000 visits were greatest for China (241), Mexico (82), Italy (43), Japan (31), and Spain (30). Obviously the causes and risks for each of these countries vary considerably, but it is of interest that travel to China was associated with such significant risk.

It would be useful if pre-travel medicine could address these issues but the authors found that most pre-travel advice, vaccines, anti-malarials and diarrhea management would not have prevented most of these fatalities. Violent deaths from vehicular accidents remain a significant problem; traffic fatalities and injuries affect 1.2 million and 50 million persons annually around the world, and are expected to increase 65% during the next 2 decades. Murder was generally associated with robbery, assault, or sexual violence, and aside from usual advice to use common sense, there is little that travel practitioners can offer. Little is known about whether suicides, an unexpected cause of

death in 4% of international Canadian travelers, were pre-planned, occurred in persons with mental illness, or as the result of some travel-related event.

Two items that travel practitioners should include in their list for discussion are verification of insurance coverage during illness abroad (for example, some travel insurance provides only limited coverage or coverage solely for "emergencies" with a cap); as well as providing advanced directive, power of attorney and directions on handling remains. For example, shipping a whole body is hugely expensive whereas cremation is inexpensive. ■

The Efficient Diagnosis of Tuberculosis

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

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Dr. Deresinski reports no financial relationship to this field of study. This article originally appeared in the July issue of Infectious Disease Alert. It was peer reviewed by Dr. Connie Price, who is Assistant Professor, University of Colorado School of Medicine. Dr. Price reports no financial relationship relevant to this field of study.

Source: Brown M, et al. Prospective study of sputum induction, gastric washing, and bronchoalveolar lavage for the diagnosis of pulmonary tuberculosis in patients who are unable to expectorate. *Clin Infect Dis.* 2007;44:1415-1420.

Synopsis: *In patients with suspected pulmonary tuberculosis who are unable to expectorate sputum, culture of 3 induced sputum samples, all collected on the same day, is an effective and efficient means of diagnosis.*

Brown and colleagues evaluated the most efficient means of microbiological diagnosis of tuberculosis in patients. Adults in whom the presence of pulmonary tuberculosis was suspected based on the presence of compatible abnormalities on chest X-ray who were unable to produce an expectorated sputum sample were evaluated in order to determine the relative value of specimens obtained by sputum induction, gastric washing, and bronchoalveolar lavage (BAL). Also studied was the relative value of sputum induction on 3 consecutive days as opposed to obtaining all 3 samples on the same day, approximately 4 hours apart.

Three induced sputum specimens were obtained on a single day, followed by additional morning samples on 2 subsequent days. Analysis of the 79 patients from whom all 5 samples were obtained found that at least one of the 3 specimens collected on a single day were positive in 27 (34%) of patients compared to a positive result in 29 (37%; $P = 0.63$) in at least one of the 3 daily induced sputum specimens. There was no correlation between the volume of sputum obtained for testing and the results.

Twenty-one patients whose smears were negative underwent bronchoscopy, and BAL cultures proved to be positive in 5 (24%) —but all 5 had positive day-one induced sputum cultures. In addition, 2 individuals with positive day-one induced sputum samples had negative BAL cultures.

At least 3 induced sputum specimens and 3 gastric washing specimens were available for 107 of the 140 patients enrolled; Mycobacterium tuberculosis was recovered in culture from one or more cultures obtained from 46 (43%) of the 107. At least one of the first 3 induced sputum samples obtained were culture positive in 42 (39%) patients compared to gastric washings from 32 (30%; $P = 0.03$) patients.

■ COMMENTARY

This is a valuable study from which a number of conclusions regarding the diagnosis of pulmonary tuberculosis in patients unable to provide an expectorated sputum sample can be drawn:

- Culture of 3 induced sputum samples was more sensitive than culture of 3 gastric washings;
- Culture of BAL specimens did not contribute to the diagnosis obtained from the induced sputum samples;
- Collecting induced sputum samples on consecutive days was not superior to obtaining all 3 specimens on a single day.

These results have practical implications for the diagnostic management of patients with suspected pulmonary tuberculosis. The referral center in the UK where this study was performed has, in fact, altered their procedures as a consequence of these results. In patients unable to expectorate sputum, they no longer perform gastric washings and instead obtained 3 induced sputum specimens—all on the same day. Bronchoscopy is performed only in limited circumtances. Thus, in most cases, their entire evaluation is performed in one day. ■

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Oral Anticoagulant + Antiplatelet Therapy = Danger

In this issue: *Adding an anticoagulant to aspirin is of no value in patients with peripheral artery disease, older adults with coronary disease benefit from aggressive statin therapy, simvastatin may reduce the risk of dementia and Parkinson's disease by as much as 50%, MiraLAX is safe for long-term use in patients with chronic constipation, the FDA greenlights Avandia, brings back Zelnorm for limited use, and recommends approving Evista for breast cancer prevention.*

Patients with peripheral artery disease are at high risk for cardiovascular complications. Antiplatelet drugs are routinely prescribed for these patients, but is adding an oral anticoagulant of value? No, according to a new study. In fact, the combination may be dangerous. More than 2,100 patients with PAD were randomly assigned to antiplatelet therapy with an oral anticoagulant or to antiplatelet therapy alone. The first coprimary outcome was myocardial infarction, stroke, or death from cardiovascular causes. The second coprimary outcome was myocardial infarction, stroke, severe ischemia of the peripheral or coronary arteries leading to urgent intervention or death from cardiovascular causes. After an average followup of 35 months, the first coprimary outcome occurred in 132 of 1080 patients receiving combination therapy (12.2%) and 144 of 1081 patients receiving antiplatelet therapy alone (13.3%) (RR 0.92; 95% CI, 0.73 to 1.16; $P = 0.48$). The second coprimary outcome occurred in 172 patients receiving combination therapy (15.9%) compared to 188 patients receiving antiplatelet therapy alone (17.4%) (RR 0.91; 95% CI, 0.74 to 1.12; $P = 0.37$). Life-threatening bleeding occurred in 43 patients receiving combination therapy (4.0%) as compared to 13 patients receiving antiplatelet therapy alone (1.2%) (RR 3.41; is 95% CI, 1.84 to 6.35; $P < 0.001$). The authors conclude that adding an oral anticoagulant to antiplatelet therapy in patients with PAD was not more effective than antiplatelet therapy alone in preventing major cardiovascular complications, but was associated with an increase in life-threatening bleeding (*N Engl J Med* 2007; 357: 217-227). ■

High-Dose Statin Therapy, Value for Older Adults

Aggressive lipid lowering with high-dose statin therapy may be of value in older adults with stable coronary disease. The multicenter study from the United States included 3,809 patients 65 years or older with coronary artery disease and cholesterol levels less than 130 mg/dl who were randomized to receive atorvastatin 10 mg or 80 mg. Patients on low-dose atorvastatin achieved average cholesterol levels of 100 mg/dl versus 70 mg/dl for high dose therapy. The primary endpoint was occurrence of first major cardiovascular event such as death from CHD, nonfatal non-procedure-related myocardial infarction, resuscitated cardiac arrest, or fatal or nonfatal stroke. Patients treated with high-dose atorvastatin were found have a 2.3% absolute risk reduction and a 19% relative risk reduction for the primary endpoint (hazard ratio 0.81 [95% CI, 0.67 to 0.98]; $P = 0.032$). Mortality rates were

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5431. E-mail: jennifer.corbett@ahcmedia.com.

lower for CHD, nonfatal non--procedure-related myocardial infarction, and stroke in the high-dose group. High-dose therapy was not associated with elevated creatine kinase levels. The authors conclude that treating older patients with coronary heart disease more aggressively to reduce low-density lipoprotein cholesterol levels provides additional clinical benefit (*Ann Int Med* 2007;147: 1-9). ■

Simvastatin, Best for Parkinson's Disease

Simvastatin, not atorvastatin or lovastatin, is associated with a dramatically reduced risk of dementia and Parkinson's disease (PD) according to a study from Boston University and VA database of 4.5 million individuals (95% men). In the observational study, over 700,000 subjects took simvastatin, nearly 54,000 took atorvastatin, and over 54,000 patients were prescribed lovastatin. Three models were used to evaluate the data, adjusting for covariates associated with dementia or Parkinson's disease. The first model was adjusted for age; the second model adjusted for 3 known risk factors for dementia: hypertension, cardiovascular disease, or diabetes; and the third model adjusted using the Charlson index, an index that provides broad assessment of chronic disease. Using the third model, the hazard ratio for dementia was 0.46 for simvastatin (CI 0.44-0.48, $P < 0.0001$) and 0.91 for atorvastatin (CI 0.80-1.02, $P = 0.11$). Lovastatin was not associated with a reduction in the incidence of dementia. The hazard ratio for newly acquired Parkinson's disease was 0.51 for simvastatin (CI 0.49-0.55, $P < 0.001$). There was no reduction in PD with atorvastatin or lovastatin. The degree of risk reduction utilizing the other models was similar with simvastatin. The authors conclude that simvastatin is associated with a strong reduction in the incidence of dementia and PD, while atorvastatin is associated with a modest reduction in incidence of dementia and Parkinson's disease that shows a trend toward significance (*BMC Med* published online July 19, 2007). The surprising finding suggests a difference between simvastatin and atorvastatin out of proportion to their cholesterol lowering effects, which the authors suggest may be due to the ability of simvastatin to cross the blood brain barrier more readily than other statins. ■

Polyethylene Glycol for Chronic Constipation

Long-term use of polyethylene glycol is safe and effective for chronic constipation according to the results of a new study from Alabama. More than 300 patients were randomized to receive polyethylene glycol 3350 (MiraLAX) in a single 17 g dose per day or placebo for 6 months. The primary endpoint of improvement of constipation on an objective scale was reached in 52% of the PEG patients and 11% placebo patients ($P < 0.001$). Similar efficacy was seen in a subgroup of 75 elderly patients. There were no significant adverse events other than diarrhea, flatulence and some nausea associated with PEG. The authors conclude that PEG laxative is safe and effective for use in patients with chronic constipation for up to 6 months (*Am J Gastroenterol* 2007;102:1436-1441). The study is particularly important because MiraLAX is now available over-the-counter and long-term use by patients with chronic constipation is likely. ■

FDA Actions

The FDA's Oncologic Drugs Advisory Committee, on a narrow vote, recommended approval of raloxifene (Evista) for the indication of breast cancer prevention in high risk women. The approval was based on data from the Study of Tamoxifen and Raloxifene (STAR) trial, which showed a reduction of 4 cases of breast cancer per 1,000 women (50% relative risk reduction), although it was not as effective as tamoxifen in preventing noninvasive breast cancers. Similar findings were seen in the Raloxifene for Use for The Heart (RUTH) trial although this trial revealed a higher risk of fatal stroke and blood clots with raloxifene. The FDA generally follows its advisory committee recommendations. Raloxifene is already approved for the prevention of osteoporosis.

The FDA has approved restricted use of tegaserod (Zelnorm) for the treatment of irritable bowel syndrome with constipation and chronic idiopathic constipation in women under the age of 55 who meet certain criteria. The drug was taken off the market earlier this year when it was linked with a higher risk of cardiovascular events including heart attack, stroke, and unstable angina. Patients must have no history of heart disease and must be in critical need of the drug. Prescribing will be under an investigational new drug protocol program that has been set up by the FDA.

Rosiglitazone (Avandia-GlaxoSmithKline) is associated with an increase risk of heart failure and myocardial infarction. Despite this, the FDA's Endocrinologic and Metabolic Drugs Advisory committee along with the Drug Safety and Risk Management Advisory Committee has advised that the drug stay on the market, albeit with increased warnings. Type 2 diabetes patients who are on insulin for those with heart disease are not the candidates for the drug. The FDA will render a final decision on the drug this fall. ■