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IN THIS ISSUE

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Editor Melinda Young, Associate Managing Editor Jennifer Corbett and Editorial Group Head Lee Landenberger report no relationships with companies related to this field of study. Physician Reviewer Morris Harper, MD, reports consulting work with Agouron Pharmaceuticals, Gilead Sciences, Abbott Pharmaceuticals, GlaxoSmithKline, and Bristol-Myers Squibb. Nurse Planner Kay Ball is a consultant and stockholder with Steris Corp. and is on the speaker's bureau for the Association of periOperative Registered Nurses.

DECEMBER 2006
VOL. 21, NO. 12 • (pages 133–144)

Program simulates on-the-job education and clinical support for HIV doctors

Clinics in African hotspots will use system

A new electronic, interactive education system provides training and clinical management to clinicians in sub-Saharan Africa and other areas where antiretroviral drugs are now available, but the medical infrastructure has made less progress.

Training systems are needed in sub-Saharan Africa because the PEPFAR, the Global Fund and the Gates Foundation have been good about funding drugs, but have not prioritized funding HIV clinical training in that region, says **John Bartlett**, MD, chief of the Division of Infectious Diseases at The Johns Hopkins University School of Medicine in Baltimore, MD. Bartlett is also an editorial advisory board member of *AIDS Alert*.

The computer-based system, named after its development company TheraSim, of Durham, NC, is also available to HIV providers around the world through a three-hour continuing medical education course on Medscape, says **Jonathan Estes**, vice president for global health at TheraSim.

The HIV/AIDS content was developed by **Douglas Blevins**, MD, medical director of TheraSim, Bartlett and others.

"Dr. Bartlett wrote the series of cases that TheraSim generates," Estes says. "He's the spearhead behind this content and his book on HIV/AIDS is embedded into this system."

Four-year-old TheraSim has developed electronic training for other disease disorders as well, Estes notes.

"I think what [TheraSim's system] represents is a combination of the problem we have with manpower in training and the lack of funding for training and the opportunity to use new technology," Bartlett says. "It's a really good program for what it attempts to do, and it comes as close to teaching and evaluating clinical competence as anything I've seen."

It's important for HIV clinicians around the world to have access to electronic training because it's very difficult for people in such a fast-moving field to have mentors when they need them, Blevins says.

The ideal situation is to have an HIV provider with experience working in a sub-Saharan country where he or she can assist new HIV clinicians who are not as familiar with disease and treatment, Blevins says.

"But that's pretty much impossible," Blevins says.

"We all need someone to run cases by to help us improve our care, rather than to just read medical literature," Blevins adds. "Getting advice from a peer always is important, and we feel the TheraSim system is one of the approaches that people can use to obtain this advice."

The interactive system provides initial HIV/AIDS training through 20 competencies in which 60 cases are available for review and study, Estes says.

"If someone is very knowledgeable they could go through the 20 cases within 10 hours," Estes says. "If they're really new and have little experience, it could take as long as 20 hours."

When a clinician sits down to take the course, he or she is shown a case study that includes still pictures of a patient, X-rays, lab work, medical histories, interview answers, and any other pertinent information for that particular competency. The cases are based on real people, and the clinician is asked to make a diagnosis or order tests or prescribe according to the evidence presented, Estes explains.

"Each page of our simulator looks like a virtual medical record with the patient's picture, an introduction, history, physical, images, and pictures of everything from a rash to biopsy, X-rays, and information on co-infections with hepatitis B and C," Blevins says. "The next page has to do with past visits the patient has made and medications the patient is on, along with vital signs, demographics."

The third page allows the clinician to order tests, and the results appear instantaneously, Blevins continues.

The program will note that the physician has made a good choice, or it will say, "We've seen no evidence this patient has this condition," Blevins says.

A page with therapies prescribed and other orders, including special diets, hospital admission, and a variety of other things also appears, Blevins says.

When a clinician fails to make the correct decisions with a particular case, he or she is directed to similar cases for that same competency before the program advances to the next competency.

"There's a scoring mechanism that's customizable," Estes says. "Categories are given weight, such as dosing, which is given heavier weight than observation or having the patient see a counselor."

Participants have to achieve an 80 or better score to pass, and with each failed competency they are directed to additional links where answers can be found, he says.

AIDS Alert® (ISSN 0887-0292), including **AIDS Guide for Health Care Workers**®, **AIDS Alert International**®, and **Common Sense About AIDS**®, is published monthly by AHC Media LLC, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodicals postage paid at Atlanta, GA 30304. POSTMASTER: Send address changes to **AIDS Alert**®, P.O. Box 740059, Atlanta, GA 30374.

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This activity has been approved for 18 nursing contact hours using a 50-minute contact hour.

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The system has a nice feedback mechanism, Bartlett says.

"By the time the physician finishes the module, you feel the candidate really knows how to deal with clinical issues," Bartlett says. "Now it's still not quite the same as working in a clinic, but it comes awfully close to it, and it's a lot better than book reading because it's so interactive."

Even with lectures, there is the reality that people will stop paying attention unless there's an interactive element, such as a keypad punch in which people select answers to questions presented during a lecture, Bartlett says.

Each version of TheraSim that's sent to a particular country for use is customized to that country's particular epidemic needs, Estes says.

"Each country has different drugs available and different co-morbidities and opportunistic infections that people die from," Estes explains. "For example, TB would be prominent in South Africa, and in Ethiopia, it's malaria and hepatitis."

For the CME version, there are handpicked cases on very specific issues, such as HIV related to a co-morbidity, Estes says.

"There are three competencies, totaling nine cases," he explains. "Physicians are given three credits if they complete it, and we have nine to 12 programs running now."

There have been over 4,500 registered users of the CME program from 115 countries, initiating over 7,000 sessions and completing 4,300, Blevins says.

"The average duration for a case is 21 minutes," Blevins says. "But it will take some physicians five minutes to actively finish a case."

Outcomes showed an average of 32 points improvement on the Internet-based global TheraSim system, using guidelines from the U.S. Department of Health and Human Services, Blevins notes.

"We also studied how satisfied people were using the Web-based cases, and there was a 97 percent satisfaction with the activity, and 98 percent considered the simulation to be valuable," Blevins says.

"One major lesson we learned from listening to participants' questions upon doing the cases in the pilot projects was that we need to engage local experts from specified countries to reflect regional availabilities and realities," Blevins says. "Sometimes you have available a different set of drugs in places that are close together, but aren't alike."

A month after Blevins, David Hadden, and Bartlett presented an abstract about TheraSim's computerized HIV teaching at the 44th Annual Meeting of the Infectious Diseases Society of America, held October 12–15, 2006, in Toronto, Canada, the company had sold systems to sites in Ethiopia, Uganda, and South Africa, Estes says.

Typically, the company works with non-government organizations who want to improve the quality of training for physicians in the field, he notes.

Contracts include a customization of the system for a particular site and may include a clinical performance management (CPM) element in which local physicians can key-in data about their actual patients to receive medical oversight by the program, Estes says.

"It's a decision support piece that has tables, information, best practices, and a reporting feature that summarizes information," Estes explains. "CPM is being implemented first in sub-Saharan Africa and then it's being brought back here." ■

ADHERENCE STRATEGIES

23-plus years survival with fair and better adherence

Poor adherence has less than half survival time

Investigators intending to develop an economic model for HIV adherence made some surprising discoveries, including the conclusion that the initial antiretroviral therapy is the strongest one, but it doesn't matter which ART regimen is taken first.

"From a modeling perspective it really doesn't matter which one they take first," says **Teresa L. Kauf**, PhD, MS, an associate professor at the University of Florida at Gainesville.

"From a clinical practice perspective, if the first regimen is the best one, then you should think about what options are available for the

patient and make the best choice based on tolerability, side effects, and things like that," Kauf says.

The study found that among HIV patients who were first treated with a non-nucleoside reverse transcriptase inhibitor (NNRTI), there was a mean survival of 25.38 years for those who achieved greater than 95 percent adherence, and there was a mean survival of 25.01 years for those who achieved 77–94 percent adherence, and there was a mean survival of 23.36 years for those who achieved 49–76 percent adherence. Patients who were adherent less than 49 percent of the time had a mean survival of 12.41 years.[1]

The findings were very similar for patients who started on a boosted protease inhibitor regimen, with mean survivals of 25.36, 25.10, 22.85, and 12.38 years, ranging from excellent adherence to poor adherence.[1]

"If you can get the patient to adhere, it really doesn't matter if you start with NNRTI or boosted PI," Kauf says. "Just put patients on a regimen that works for them."

It wasn't a surprise to find that patients with poor adherence would have less survival time than those with excellent adherence, but Kauf says she had expected to see a bigger survival difference.

"The data underlying this are based on clinical trials," Kauf says. "Patients come in and start on one regimen in the model, and those rates are based on clinical trials."

A portion of patients will have suppressed HIV even if they are not the greatest adherers, and then it will take a while for the suppression to fail. But once it does fail, the model assumes that the patient is switched to a new regimen where suppression can be re-established, Kauf explains.

"Essentially, we assumed that regardless of whether you started with NNRTI or boosted PI, if you failed that first regimen, you'd be put on the other one, and so patients would still come into contact with a boosted PI regimen," Kauf says.

The model's findings about adherence suggest only subtle differences in survival between excellent, good, and fair adherence.

"From this analysis it seems that even for patients who are not very good adherers, who have fair adherence of 49 to 76 percent, which most physicians would say is bad, it is worth taking the drugs," Kauf says.

The study also addresses quality of life by measuring quality-adjusted life years, finding that with either regimen introduced first, patients who have 95 percent or greater adherence have a mean of 15.13 quality-adjusted life years. Those with poor adherence of less than 49 percent have a quality-adjusted, life-year mean of 7.65 for NNRTI regimens and 7.63 for boosted PI regimens.[1]

"There are several studies trying to assess HIV patients' quality of life, and we used a utility measure of quality of life," Kauf says. "People will survey patients and classify responses according to CD4 cell levels and those with lower CD4 levels generally have lower quality of life."

Investigators used this weight, multiplied it by the survival years and came up with the quality-adjusted life years, she explains.

"Every time patients in the model spent three months in a particular CD4 category, we weighed that by this utility weight," Kauf says. "Then we add up all the months they spent in different health states, and that gives us the quality-adjusted life years."

The patients in the excellent adherence category still would be expected to have a 25-year survival, but the value of their life in terms of disease burden would make it equivalent to only 15 years of a disease-free life, she notes.

"So if your survival was going to be 25 years in various states of HIV infection, that would be equivalent to 15 years if you were completely healthy," she says. "Some people would trade that extra 10 years if they could be healthy."

For the quality-adjusted life years, the mean years for 77–94 percent adherence were 14.89 years for NNRTI regimens and 14.97 for boosted PI regimens; for those whose adherence was fair at 49–76 percent, the mean quality-adjusted life years was 13.97 for NNRTI regimens and 13.59 for boosted PI regimens.[1]

The model was not able to examine the impact of adherence and the initial use of nucleoside reverse transcriptase inhibitors (NRTIs), although that's an area investigators are working on, Kauf says.

"So that could be a factor, and it might be one reason why these numbers seem like less of a range than you might expect," Kauf adds.

"NNRTIs are easy to model because once a patient develops resistance, they're not put on NNRTIs again," she says. "With a boosted PI regimen, there still is some efficacy if you could get

the patient put on a new NNRTI."

Since the study is based on a model and there are these drawbacks, it would be hard to predict what an individual patient would see in terms of treatment failure, Kauf notes.

"We're in the process of trying to validate the model, using data from a database project called CHORUS," Kauf adds. "This database followed HIV patients for several years and we'll use that data to validate some of the numbers from our model, including efficacy, side effects, and others." ■

Reference:

1. Kauf T, et al. Simulation modeling of adherence and resistance on long-term outcomes in HIV. Presented at the 44th Annual Meeting of the Infectious Diseases Society of America, held Oct. 12–15, 2006, in Toronto, Ontario, Canada. Abstract:978.

HIV/AIDS stigma — basic problems remain

Researchers look at long-term of HIV prejudice

Twenty years ago, a researcher overheard one doctor say to another: "I'm not sure AIDS is so much a problem as it may be a solution to a problem."

This stunning example of prejudice against homosexuals, injection drug users, and other victims of the epidemic prompted the researcher to spend the next two decades studying HIV stigma.

"After pursuing that whole area, the truth is, in the medical profession, there are very strong biases," says **Frederick A. Ernst**, PhD, professor of psychology in the department of psychology and anthropology at the University of Texas – Pan American in Edinburg, TX. Ernst had overheard the physician's remarks, which had shocked him initially.

"I'm not shocked by those kinds of statements anymore," Ernst says. "Early on, research has shown that the attitude of primary care doctors became more negative toward homosexuals after the advent of AIDS."

American doctors more than European doctors would admit on surveys in the early 1990s that they would avoid homosexual male patients, Ernst says.

"They were afraid that their accepting AIDS patients would scare away other patients from their practices," he adds. "And when they asked patients in their practices about this, their fears were well-founded."

Ernst and colleagues developed a questionnaire in the late 1980s to discover how widely stigma and prejudice were among both health care providers and others. Called the Meharry Questionnaire, it asks for a response from 0 for strongly disagree to 5 for strongly agree to some very pointed statements, including the following:

- AIDS is the result of God's punishment ("Divine Retribution").
- AIDS will help society by decreasing the number of homosexuals (gay people).
- People with AIDS have gotten what they deserve.
- It is easier to catch the AIDS virus than the experts are leading us to believe.

The scaled response was used to encourage more candor. For instance, a person who agreed with the statement that "AIDS will help society by decreasing the number of homosexuals" might be more willing to circle a two or three than to answer affirmatively in a "yes" and "no" format.

"For me, if you look at a statement like that, why would anyone not strongly disagree with that statement?" Ernst says. "So circling 1 is just as disturbing as circling 5."

Researchers first distributed the questionnaire to groups of doctors, including the medical staff of a historically African American college, where the physicians and medical staff could be characterized as fairly liberal, Ernst says.

"The group looked very good in their responses to the survey, and we wanted to compare their responses to a group of primarily white, Southern physicians and the medical staff of a Baptist hospital," Ernst explains. "So we went to the institution, and those groups said they were not going to give the questionnaire to their people because it was too controversial."

So researchers decided to administer the survey to a group representative of the general population, but with limited funding had to find a cost-effective way of doing this, Ernst says.

Ernst convinced the Tennessee mental health agency to permit investigators to survey all people within inpatient residential facilities.

"We thought that would give us a good demographic spread of working people and of those on the front-lines of the mental health

profession," Ernst says.

Findings from that 1989 survey showed that people's attitudes toward HIV/AIDS and the epidemic's victims were different according to the educational level of the person surveyed, he says.

There also appeared to be differences according to religious preference, but these also could be explained by educational level, Ernst notes.

"We found that if you were a member of the Assembly of God, you were far more conservative," Ernst says. "The most liberal were Catholics."

But when the religious groups were examined according to educational level, it showed that the least educated people surveyed had selected Assembly of God as their religious preference, and the most educated had selected Catholicism, he says.

"So we felt that the more education you have the less likely you are to endorse these sorts of condemnatory and prejudicial statements related to homosexuality and drug abuse," Ernst says.

Researchers repeated the survey in 1994 and then again in 2005 at the same locations, and they found some positive changes in the results in the latest survey, with responses showing less bias and stigma than in the previous years, he says.

"But the bad news is that for some reason we got a very different demographic mix in the 2005 sample," Ernst says. "Part of that was that after 1994, the mental health and mental retardation groups split in the state and became two different agencies, but the more important factor was that in the mid-1990s, there was a significant downsizing of the entire mental health residential facility staff."

When the facilities were downsized, the people with the least education lost their jobs and this led to the sample having a significantly better educated group in 2005, he explains.

"It could be the attitudes really have changed in a positive direction, but we can't say for sure because of an educational difference in this 2005 sample," Ernst says. "From a scientific standpoint, you can't make that conclusion because of the profound influence of the better-educated group."

For instance, the percent of people who strongly disagreed with the statement about how the AIDS epidemic is a fulfillment of biblical prophecy was 38 percent in 1989 and 58 percent in 2005, Ernst says.

Likewise, the statement about AIDS being the result of God's punishment elicited a strong disagreement from 52 percent in 1989 and 74 percent in 2005.

The statement that suggests AIDS will help society by reducing the number of homosexuals received strong disagreement by 44 percent surveyed in 1989 and by 73 percent in 2005, Ernst says.

What the study's findings suggest is that education is an answer to reducing HIV/AIDS stigma and prejudice, Ernst says.

"Being a scientist first, we're just saying we need to go back and get more data," Ernst says. "These are very interesting findings, but we have to clarify the confounding issue of having a better-educated group in 2005."

Investigators will try to break down this factor in future analyses to see what extent there might have been a shift in responses of people working in this environment to a more compassionate orientation, he says.

"We want to go back now and sample lower socio-economic groups in higher numbers to see if we can't get a more comparable sample to the 1994 group," Ernst says.

Future surveys may show that the general public has less prejudice against HIV patients today than 20 years ago, and anecdotal evidence suggests that medical professionals perpetuate less HIV stigma than they did in the past, Ernst says.

"I want to believe that we have more compassionate caregiving now," Ernst says. "I used to preach to physicians in medical school that to whatever extent they have a problem dealing with homosexuals in their practice, they are impaired physicians."

And Ernst says he does believe medical professionals now have a more compassionate attitude toward HIV/AIDS patients.

"I believe our physicians today are more compassionate by virtue of having a whole lot more training as of 2006 of all of the aspects of the AIDS epidemic, compared with 1986 when so little was known that even the physicians were uneducated," he says. "And there is significantly less prejudice about homosexuality in the medical community—at least as it interfaces with the AIDS epidemic." ■

FDA Notifications

FDA approves generic abacavir sulfate tablets

The FDA, on November 6, 2006, granted tentative approval for a generic formulation of abacavir sulfate tablets, 300 mg, manufactured by Cipla Limited of Mumbai, India. The application was reviewed under the expedited review provisions of the President's Emergency Plan for AIDS Relief (PEPFAR).

The FDA's tentative approval means that although existing patents and/or exclusivity prevent marketing of this product in the United States, the product meets all of the safety, efficacy, and manufacturing quality standards required for marketing in the U.S., and can thus be considered for purchase under PEPFAR.

As with all generic applications, the FDA conducts an on-site inspection of each manufacturing facility and of the facilities performing the bioequivalence studies prior to granting approval or tentative approval to these applications to evaluate the ability of the manufacturer to produce a quality product and to assess the quality of the bioequivalence data supporting the application.

This tentatively approved product, a generic version of Ziagen tablets manufactured by GlaxoSmithKline, is a nucleoside reverse transcriptase inhibitor (NRTI) for use in combination with other antiretroviral agents in the treatment of HIV infection.

Pediatric HIV infection ART guidelines revised

Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection have been revised. The revision represents a major rewriting of the main document to improve its organization and readability. Because the main document has been almost completely rewritten, there is no highlighting of changes to either its text or tables.

The document's appendix, "Characteristics of Available Antiretroviral Drugs, and Supplement I: Pediatric Antiretroviral Drug Information," has also been updated. Changes to those sections appear highlighted in yellow.

Changes in recommendations include:

- Revised guidelines on when to initiate therapy in antiretroviral-naïve children, with recommendations for four age categories (< 12 months, 1 to < 4 years, 4 to 12 years, and > 13 years).
- Revised discussion and tables of rationale for antiretroviral drug choice for antiretroviral-naïve children, with revised preferred and alternative treatment regimen recommendations.
- Revised recommendations for adolescents, including issues related to drug dosing, use of contraception, pregnancy, and transition into adult care.
- Updated Characteristics of Available Antiretroviral Drugs drug-dosing appendix and updated Supplement I: Pediatric Antiretroviral Drug Information, including information on newly approved antiretroviral agents, such as darunavir, and new pediatric studies.

Also new to the guidelines are:

- Recommendations for antiretroviral resistance testing for all antiretroviral-naïve children prior to initiation of antiretroviral therapy.
- New section and table on monitoring of children on antiretroviral therapy and management of antiretroviral toxicity/intolerance.
- New section on management of the treatment-experienced child.
- New section and tables on assessment and management of antiretroviral treatment failure and choice of new antiretroviral regimen in children with treatment failure.
- New section on therapeutic drug monitoring.
- New section on discontinuation or interruption of antiretroviral therapy.
- Inclusion of darunavir information.

The updated guidelines are available on the Pediatric Guidelines page of the Clinical Guidelines section of AIDSinfo.

FDA provides new guidance on fixed-dose combinations

The FDA announced, on October 18, 2006, the availability of a guidance for industry entitled "Fixed Dose Combinations (FDC), Co-

Packaged Drug Products and Single Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV."

The guidance encourages sponsors to develop various drug product versions of previously approved antiretroviral drugs and encourages sponsors to submit drug applications for these products to FDA for review. The availability of a wide range of safe and effective antiretroviral drug products is hoped to facilitate a wider distribution of anti-HIV drugs to better meet the demands of the global HIV/AIDS pandemic.

The draft version of this guidance entitled "Fixed Dose Combination and Co-Packaged Drug Products for Treatment of HIV," was first posted on May 2004.

The guidance has been updated to address public comments to the draft version. Significant changes to the draft are:

1. The inclusion of single entity versions, in addition to combination products, in the expedited FDA review pathway for these products;
2. The addition of tables that supply references supporting the clinical efficacy and safety of antiretroviral combinations;
3. The inclusion of more details and clarification on the amount and type of data that should be submitted in a drug application to support a potential approval or tentative approval.

The full guidance is available on the FDA Web site http://www.fda.gov/cder/guidance/6360fnl.pdf (343 KB).

FDA approves 300 mg atazanavir capsule

On October 16, 2006, the Food and Drug Administration approved a new 300 mg capsule form of Reyataz (atazanavir).

Reyataz is now available as 100 mg, 150 mg, 200 mg, and the new 300 mg capsules.

The new 300 mg capsules give treatment-experienced patients the option to take either one 300 mg capsule, or two 150 mg capsules of Reyataz, once daily, plus ritonavir 100 mg once daily, with food.

The recommended dose for treatment-naïve patients remains unchanged and is Reyataz 400 mg (two 200 mg capsules) once daily with food. Reyataz is a product of Bristol-Myers Squibb. ■

Penicillium marneffei Infection in HIV-Infected Travelers

ABSTRACT AND COMMENTARY

By Patricia Cristofaro, MD, and Maria D. Mileno, MD

Patricia Cristofaro is Assistant Professor, Department of Infectious Diseases, Brown University, and Maria D. Mileno is Director, Travel Medicine, The Miriam Hospital; Associate Professor of Medicine and Infectious Diseases; Director, International Travelers' Clinic, Brown University School of Medicine

Dr. Cristofaro reports no financial relationship relevant to this field of study, and Dr. Mileno is a consultant for GlaxoSmithKline.

This article originally appeared in the October 2006 issue of Travel Medicine Advisor. *It was originally edited by Frank Bia, MD, MPH, and peer reviewed by Mary-Louise Scully, MD. Dr. Bia is Professor of Medicine and Laboratory Medicine; Co-Director, Tropical Medicine and International Travelers' Clinic, Yale University School of Medicine, and Dr. Scully works for the Sansum-Santa Barbara Medical Foundation Clinic, Santa Barbara, CA. Dr. Bia is a consultant for Pfizer and Sanofi Pasteur, and Dr. Scully reports no financial relationships relevant to this field of study.*

Synopsis: *Disseminated* Penicillium marneffei *infection is the third most common AIDS-defining illness in parts of Southeast Asia. A review of the literature now shows that penicilliosis may represent an emergent opportunistic infection in HIV-positive travelers to endemic regions as well.*

Source: Antinori S, et al. Disseminated *Penicillium marneffei* Infection in an HIV-Positive Italian Patient and a Review of Cases Reported Outside Endemic Regions. *J Travel Med*. 2006;13:181-188.

Antinori and colleagues describe the second case of HIV-associated penicilliosis in Italy caused by P. marneffei (the first was reported by Viviani in 1993),[1] and then summarize the epidemiological, microbiological, and clinical characteristics of all cases from non-endemic regions reported in the literature, a total of 35 cases, abstracted from a Medline search covering 1988 to December 2004.[2]

Case: During an interview with a physician regarding his wife's medical care, a 36-year-old HIV-positive Italian man who had resided in northern Thailand was noted to have several maculopapular lesions on his face reminiscent of mulluscum contagiosum. He reported these lesions

had appeared about 8 weeks previously, concurrent with mild fever (37.5° C) and a 6 kg weight loss. Physical exam was unremarkable except for the presence of similar lesions on the trunk and limbs. Diagnostic testing included hematochemical blood studies, chest radiograph, skin biopsy, blood cultures, and bone marrow aspirate. He was started on empiric therapy with itraconazole (600 mg/day orally) because of high clinical suspicion for penicilliosis, given the combination of his HIV status, his residence in the province of Chiang Ray ,Thailand,3 and the character of his rash.

Laboratory examination revealed mild anemia (hemoglobin 11.1 g/dL), CD4 count of 6 cells/µl, and an HIV-RNA viral load of 213,047 copies/mL. Both skin biopsies (H&E, PAS, silver stains) and bone marrow aspirate revealed intra- and extracellular organisms consistent with *P. marneffei* — round to oval thin-walled yeast-like organisms, some with a central septum. Within 5 days blood, bone marrow, and skin cultures also grew *P. marneffei*. He was then switched to liposomal amphotericin B (3 mg/kg/d), which he received for 2 weeks, at which time his blood cultures were negative. He was then started on itraconazole (400 mg/day orally) and antiretrovirals (stavudine, lamivudine, efavirenz). At that time, his skin lesions had nearly resolved. He returned to Thailand, where his antifungal maintenance therapy was discontinued when his CD4 count reached 292.

An extensive literature review provided great detail on the epidemiological, microbiological, and clinical characteristics of all cases of penicilliosis in HIV-infected persons from non-endemic regions reported in the literature. A total of 35 cases, abstracted from a Medline search from 1988 to December 2004. Penicilliosis presented late in the course of HIV infection: the median CD4 count was 20 (range, 1-110); 3 patients had a second, concurrent AIDS-defining illness; 12 patients (34%) carried a diagnosis of AIDS. None of the patients were on successful HAART at the time of diagnosis. Twenty-two of the patients were travelers to endemic areas — 8 exclusively to Thailand, 9 to Thailand plus other Asian countries, 5 to other Asian countries including Hong Kong, China, and India.

Clinical characteristics included fever (88.9%), weight loss (66.7%), and skin lesions (52.8%), a triad frequently recognized in disseminated *P. marneffei* infection.[4] Hepatomegaly was present in 36.1%, splenomegaly in 33.3%, and lymphadenopathy in 33.3%. When a CXR was taken, it was abnormal in 51.8%. Diagnosis was made by histology plus culture in 63.9%, culture alone 30.5%, and histology alone 5.5%.

COMMENTARY

HIV-infected travelers, particularly those not taking successful HAART therapy, are at increased risk of acquiring a number of opportunistic infections when traveling. *P. marneffei* has now emerged as a cause for concern for travel to southeast Asia. Cases have been reported from HIV- infected residents of Thailand, especially Northern Thailand, Myanmar (Burma), Vietnam, Cambodia, Malaysia, Indonesia, northeastern India, Hong Kong, Taiwan, and southern China.[3,4] Despite careful case-control studies, the exact source of the infection has not yet been identified, but is suspected to be the inhalation and/or ingestion of infected soil.[5] In the article under discussion, Antinori et al describe 35 imported cases occurring over a 16-year period, 22 of which occurred in travelers. This is one of the most comprehensive descriptions of this illness in HIV-infected persons; however, the duration of travel for these patients, and the number of similar travelers exposed but not infected, is unknown. Therefore, it is difficult to predict the risk for any individual prior to departure. However, another recent case report by Carey and colleagues describes an individual with disseminated P. marneffei, CD4 count 3 cells/mL, who had traveled throughout southeast Asia and India for a duration of only 6 weeks — 4 months prior to admission for this illness;[6] therefore, prolonged residence does not seem to be required.

Of more practical concern would be the inclusion of penicilliosis in the differential diagnosis of illness in the returning immunocompromised traveler who has visited an endemic area. The most common presentation is the triad of fever, skin lesions and weight loss, often with bone marrow, lymph node, or hepatic involvement. The skin lesions are distributed over the face, ears, limbs, and occasionally genitalia, and may have central umbilication due to necrosis, resembling the lesions of molluscum contagiosum. Hepatic involvement presents with fever, abdominal pain, hepatomegaly, and elevated serum alkaline phosphatase. The diagnosis can be made rapidly by Wright staining of bone marrow aspirate, skin scrapings, or lymph node biopsy, confirmed by culture of blood and appropriate biopsy material, which should become positive after about 5 days incubation.

Consensus guidelines for the treatment of adults and adolescents are now available from a combined committee of the CDC, NIH, and the HIV Medicine Association of the Infectious Disease Society of America.[7] The recommended therapy is amphotericin B at a dose of 0.6 mg/kg/day administered IV for 2 weeks, followed by oral itraconazole solution at a dose of 400 mg/day for a duration of 10 weeks. In order to prevent relapse, chronic maintenance therapy of itraconazole 200 mg/day should be administered. Itraconazole should be avoided during the first trimester of pregnancy. There are currently no pediatric guidelines, but both amphotericin B and itraconazole have been successfully used in children for disseminated histoplasmosis.[8] HAART should be initiated concurrently, if possible. Some practitioners discontinue secondary prophylaxis after a CD4 count > 200 has been achieved for 6 months. A single report supports this approach, which is largely based on experience with other fungal opportunistic infections.[9] ■

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Hepatocyte Apoptosis in Hepatitis C/HIV Co-Infection

ABSTRACT & COMMENTARY

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This article originally appeared in the October 2006 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.*

Synopsis: *Hepatocytes exposed in vitro to Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) envelope proteins and undergo apoptosis as a result of cell surface binding of the proteins. The studies indicate that HCV/HIV envelope proteins induce hepatocyte apoptosis by activating a novel downstream STAT1 signaling pathway.*

Source: Balasubramanian A, et al. Signal Transducer and Activator of Transcription Factor 1 Mediates Apoptosis Induced by Hepatitis C Virus and HIV Envelope Proteins in Hepatocytes. *J Infect Dis*. 2006;194:670-681.

This interesting paper from Groopman's laboratory at Beth Israel in Boston, reports the results of some elegant experiments designed to elucidate potential mechanisms, accounting for the innocent bystander hepatocyte apoptosis previously observed as a result of binding of HCV and HIV proteins.[1-3] Activation of STAT1 by HCV-E2 and HIV-gp120 proteins was demonstrated in HepG2 cells by DNA binding using a label-specific probe in gel shift assays. HepG2 cells were also transiently transfected with various luciferase-containing constructs. Chemiluminescence detection showed a 2.6-fold increase in luciferase activity in the HCV-E2/HIV-gp120-costimulated cells in cells transfect-

ed with the pGAS-TA-Luc vector, compared with unstimulated transfected cells. No change, however, was detected in the transfected cells stimulated with HCV-E2 or HIV-gp120 alone.

Another set of experiments demonstrated tyrosine and serine phosphorylation of STAT1 induced by HCV-E2/HIV-gp120. Phosphorylation of STAT1 had previously been shown to result in dimerization of this protein and translocation to the nucleus, resulting in transcription of target genes. Additional experiments using both Western blotting and immunoprecipitation assays demonstrated that tyrosine phosphorylation of STAT1 was mediated by Lyn kinase. Another set of experiments demonstrated that p38 mitogen-activated protein (MAP) kinase was also involved in STAT1 tyrosine phosphorylation. A series of elegant experiments using both an inhibitor of PKCdelta and PKCdelta single-stranded inhibitory (si) RNA can mediate STAT1 serine phosphorylation after HCV-E2/HIV-gp120 costimulation. Mechanistic experiments demonstrated that STAT1 contributes to FasL-mediated apoptosis in the presence of HCV/HIV envelope protein costimulation, as well as STAT1 enhancement of mitochondrial apoptotic pathways associated with cytochrome c leakage. Finally, STAT1 mediation of caspase 3 activation in HCV-E2/HIV-gp120-induced apoptosis was demonstrated.

COMMENTARY

While modern antiretroviral therapy has been responsible for a dramatic decrease in the mortality rate of HIV over the last 10 years, increasing evidence points to the relatively greater burden of chronic liver disease due to HCV as a cause of morbidity and mortality in HIV patients. It is also generally universally accepted that the severity and rate of progression of HCV-associated chronic liver disease are greatly increased in HIV infected patients.

One of the things that I have always loved about the subspecialty of infectious diseases is the close relationship between the laboratory and the bedside. The last 140 years have shown steady progress in the understanding of the complex interface between the pathogen and the host. This particular paper caught my attention because, in a series of elegant experiments that tease out the effects of how HCV and HIV envelope proteins contribute to apoptotic hepatocyte death, it demonstrates mechanisms responsible for a clinically important phenomenon. While my personal opinion remains that real progress in treatment of HCV will be made with the development of small molecule inhibitors of viral-specific processes (such HCV protease or helicase), the demonstration of the importance of these STAT1-mediated signaling events suggest another route for development of therapeutic strategies for HCV/HIV coinfection.

It may be of interest to know a little about the senior author of this paper, Dr. Jerome Groopman, who is a Professor of Medicine at Harvard and a hematologist/oncologist by training. Many years ago when I was doing basic research in HIV, I would see Jerry at various meetings and we would occasionally talk about science or life. I was always impressed with his wisdom and kindness, which clearly went to the core of his being. Many years later, I read a review in the New York Times of his first book written for lay people, "The Measure of Our Days," published in 1997, which details the spiritual lives of several patients as they reach the end of their physical lives. His 2000 book, "Second Opinions: Stories of Intuition and Choice in the Changing World of Medicine" is excellent as well. These 2 books were later used as the takeoff for the television series, "Gideon's Crossing." Jerry is a wonderful example of that kind of person who is an excellent scientist, doctor, husband, and father, and someone who combines all of that with a deep spiritual awareness. ■

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COMING IN FUTURE MONTHS

- Rhode Island's experience offers lesson in handling HIV-infected refugees
- Here's the latest research on resistance patterns
- With a whole new Congress, will Ryan White funding finally improve?

CE/CME objectives

The CE/CME objectives for *AIDS Alert* are to help physicians and nurses be able to:
• Identify the particular clinical, legal, or scientific issues related to AIDS patient care;
• Describe how those issues affect nurses, physicians, hospitals, and clinics;
• Cite practical solutions to the problems associated with those issues.

Physicians and nurses participate in this medical education program by reading the issue, using the provided references for further research, and studying the questions at the end of the issue.

Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any question answered incorrectly, please consult the source material.

After competing this activity at the end of each semester, you must complete the evaluation form provided and return it in the reply envelope provided to receive a letter of credit. When your evaluation is received, a letter of credit will be mailed to you.

CE/CME *questions*

21. According to a recent modeling study about adherence and survival years of HIV infected patients, patients with the very best adherence of greater than 95 percent when initiated on non-nucleoside reverse transcriptase inhibitors (NNRTI) or boosted protease inhibitor regimens could expect a mean survival rate of 25 years. For patients with the worst adherence of less than 49 percent adherence, what is their expected mean survival rate?
A. 7 years
B. 12 years
C. 14 years
D. 17 years

22. A new HIV training and education program called TheraSim that also can serve as clinical management, particularly for clinicians in the developing world has which of the following advantages for physicians using the system?
A. It is interactive and responds to a clinician's wrong answer with links to additional educational material.
B. It provides "over-the-shoulder" peer advice and counsel to clinicians who often work in remote areas where peer experts are not readily available for consultations.
C. It can be adapted to a particular region's antiretroviral availability and incidences of opportunistic infections and co-morbidities.
D. All of the above

23.Which of the following statements is not true (false) about disseminated *P. marneffei* infection in the HIV positive patient?
A. Disseminated *P. marneffei* presents late in the course of HIV infection, usually when the CD4 count is < 100.
B. *P. marneffei* fungus is endemic to Thailand, Indonesia, Southern China, Hong Kong, Malaysia, Vietnam, India.
C. Disseminated *P. marneffei* infection is a difficult diagnosis to confirm because the organism is fastidiously hard to grow from blood cultures or bone marrow aspirates.
D. Facial lesions can resemble those of molluscom contagiosum because central necrosis results in umbilication.
E. The skin lesions are often found on the face, trunk, and limbs.

Answers: 21. (b); 22. (d); 23. (c)

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