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Game on: Athletes, researchers reach youth with active education

Kids retain knowledge after games like 'HIV Attack'

Thirty years into the HIV/AIDS epidemic the grandchildren of the first generation impacted by AIDS have little interest in the disease. They increasingly need inventive and compelling HIV prevention strategies and messages. AIDS education has to compete with video games, texting, and social websites. So how do you get their attention?

A dynamic group of volunteers, investigators, and educators in the nation's capital might have found an ideal solution.

A model based on programs that have worked well in sub-Saharan Africa and Latin America has moved to Washington, DC, and is successfully pairing children with top college athletes who serve as role models, educators, and coaches. Athletes visit public middle schools, sometimes as part of physical education classes and sometimes as after-school programs. They teach children, ages 10 to 15, how HIV transmission and infection works.

They combine each education session with a physical game and activity, including HIV Attack, which demonstrates how the virus attacks the immune system. They also facilitate emotional discussions about the epidemic and how it might be impacting children in the groups. (*See related story, p. 99.*)

Based on an analysis of the pilot year of the project, investigators found that children who participated in the intervention had significant increases in knowledge about HIV and AIDS, and they had improved behavioral intent to reduce HIV risk, as well as increased self-efficacy, says **Karen A. McDonnell**, PhD, an associate professor and director of the doctoral program in health behavior in the department of prevention and community health at George Washington School of Public Health in Washington, DC.

"So the students were saying they had an intention to engage in healthier behavior and HIV risk reduction," McDonnell says.

McDonnell and co-investigators have plans to study the students' risk

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behaviors to see if they actually have changed risk behaviors or continued with risk-reduction strategies as a result of the intervention.

The collaboration between Division 1 university athletes, a community-based organization, and George Washington University researchers has resulted in a program that so far has involved about 200 volunteer athletes, 500 youths, and 1,000 people in community outreach.

The grassroot project is based on the grassroot soccer's HIV education model that was piloted in Zambia and South Africa and also proved successful in Zimbabwe.[1,2]

Tyler Spencer, founder of the grassroot project and a former rower at Georgetown University, spent two summers in South Africa, volunteering in HIV prevention work in the DeBeers/Grassroot Soccer diamond mining communities. Spencer was struck when he returned to DC by how the epidemic is nearly as bad here as what he saw in some South African communities.

"I was shocked when I read the HIV statistics for DC because I'd been living there and I didn't realize the disease was as big a problem as it is," Spencer says. "In schools in DC, the fear and stigma of HIV was even greater than it is in South Africa."

Athletes as educators

The Washington, DC, area needed leaders to discuss the disease and educate youth about how HIV impacts people in the community, and Spencer thought athletes were the ideal educators for this message.

Division 1 college athletes are the nation's best college competitors. One athlete who now is an advisory board member, Somdev Devvarman, twice won the NCAA national singles championship in tennis and now is number 150 in the world ranking in tennis.

The project recently received a Division 1 NCAA Student-Athlete Advisory Committee award of excellence

College athletes are goal-driven and disciplined, and they like extra challenges, Spencer says.

But they're also very busy, and when the program began in 2009, Spencer aimed to recruit maybe a dozen athletes to give up two weekends per semester and three hours per week for visiting schools. Instead he had 40 athletes sign up for the original group, and now there are nearly 200 athletes involved in the project.

One impact Spencer and researchers have observed is similar to what was noted in earlier studies in sub-Saharan Africa with the grassroot soccer project, and that is the spreading of HIV-prevention information beyond the children enrolled in the project.

For one thing, parents became very enthusiastic supporters of the program.

"Some parents would show up to pick up their kids from the after-school program, and then the next time they would show up 30 minutes early and participate in the game," Spencer says. "Our whole goal was not just to give kids information; the focus was on giving them information and empowering them to share the information throughout the community."

For example, at the end of each eight- to 10-week program, the children would have a graduation program witnessed by friends and relatives. They'd be offered an opportunity to provide HIV education at the graduation program, and they'd sometimes volunteer to talk about family members who had AIDS and how that impacted them. Or they might play a game of HIV Attack in front of an audience, he says.

"They'd get up and have their parents play the part of germs and diseases while they led the game and showed them what they learned," Spencer says.

The games facilitate learning and make the subject matter interesting and dynamic to the youths.

"We think it's more effective to make learning participatory," Spencer says. "The curriculum overall is a series of games that builds on each other."

The reason athletes are involved as coaches/mentors/educators is because the pre-teens and teens are more likely to listen to role models who are seen as successful and who are closer to their age, he notes.

"Sometimes kids aren't always comfortable talking about these issues with someone who is a generation older," Spencer says.

What's intriguing about the grassroot project model is the way it engages youth in behavior change, McDonnell notes.

"Whenever you do behavior change work and have curriculum based on health, students don't tend to be as engaged, she says. "But this program is amazing."

McDonnell visited one of the graduation ceremonies and watched the children have fun playing AIDS Attack.

"This is how you reach kids," she says. "You let them have fun, and then they integrate the message into their own thinking."

Also, the children communicated their experiences and messages with the adults in their lives, and they could show their friends in their own words how the virus and immune system work.

"They get it — you can see it in their eyes," McDonnell says. "They feel like they're mastering this material."

So far, the program has met several goals, including training youths to be social entrepreneurs of change in their own communities, she says.

"We found with this program that it really increased their knowledge, and we don't know yet about their behavior, but we know it's going in the right direction," McDonnell says.

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Ball game shows kids how HIV attacks

Immune system tries to fight with no hands

The Grassroot Project program was adapted from curriculum implemented across sub-Saharan Africa and Latin America, where it was more commonly known as Grassroot Soccer.

In its first manifestation in the United States, the Washington, DC-based program uses ball games to teach children how the HIV/AIDS epidemic spreads.

The intervention is based around sports, and it's taught by college athlete volunteers, says **Tyler Spencer**, founder and director of Grassroot Project.

"These are interactive, participatory games," Spencer says. "The students learn different key messages about HIV, and one of the games is HIV Attack."

Here's how HIV Attack works:

• One student stands still in the middle of a circle of children. This person represents a healthy human body.

• Another student stands with the student in the middle, and this student's role is to pretend to be the human body's immune system and protect the other student against viral attack.

• The students are told to think of viruses and diseases they sometimes get, including the flu and measles. Then they're told that the students with a soccer ball will represent one of these viruses. So students standing around the circle throw a soccer ball at the static student in the middle, and the defender student blocks the throws, just as the human body's immune system might defend against influenza or measles viruses.

"This gives the students the message that the immune system can do a good job of protecting the body," Spencer says.

• Coaches then say the next virus will be HIV. In this example, the student who is the body's defender has his or her hands held behind the back by another student. The student might be able to block one or two balls, but typically cannot block all of them, and so the human body is hit a few times with the virus.

"At each level of the game, we discuss what this means," Spencer says. "At this level, we talk about how the immune system cannot block all of the balls representing HIV."

• Then, coaches show students how antiretroviral therapy (ART) works by having additional students hold the virus students' hands behind their backs, so they have to make attacks on the human body without their hands.

"The human body gets hit less because the ART prevents the virus from doing its job," Spencer says.

The game quickly moves from a simple demonstration and fun game to a complex game with complex messages, he says.

"You challenge kids to understand that this is what happens when you get HIV," he says. "We show them that this is why people with HIV have to take their drugs every day."

At the end of the participatory game session, coaches help students personalize the message by leading discussions about people they might know who have HIV and sharing their stories about these relationships.

The program has another game that demonstrates how people cannot tell who has the virus and who doesn't.

This game has students lined up in two lines facing each other. Each child is shoulder to shoulder and has their hands behind their backs. The coach puts a ball in the hands of one member of each team and asks the students to pass the ball from one to another without saying who has it. Meanwhile, they need to guess who has the ball on the other team. The ball represents HIV infection, so whoever holds the ball is HIV positive.

Students will guess incorrectly who has the ball, and the coach then explains that they also would not be able to guess who has HIV infection just by looking at them. The game leads to a discussion about HIV testing and myths involving the disease and transmission.

As the program's curriculum continues, students eventually talk about social issues affecting HIV transmission and the stigma of having HIV, Spencer says. ■

Research suggests new path to HIV prevention

Drug concentrations high in rectal tissue

Investigators are studying the way antiretroviral (ART) drugs penetrate the body, particularly focusing on the genital tracts to examine the potential for these drugs to impact the areas where HIV transmission most often occurs.

In a pilot study, researchers made a startling discovery that rectal tissue exposure after multiple dosing with the CCR5 antagonist maraviroc was 10-fold higher than what had been measured for vaginal tissue and much higher than blood plasma exposure.[1]

"We were surprised at the high exposures in rectal tissue," says **Kevin Brown**, PharmD, an academic HIV pharmacology fellow at the University of North Carolina School of Pharmacy in Chapel Hill.

After a week of dosing, the concentrations were 26 times higher than concentrations in blood plasma, he adds.

"We went through calculations to make sure these numbers were correct," Brown says. "We were pretty conservative with the data we got."

Their findings also showed that semen concentrations were lower than concentrations found in blood plasma, but cervical/vaginal concentrations were several times higher than concentrations found in blood plasma, Brown adds.

"We chose to study maraviroc because it's an entry inhibitor and prevents the virus from get-

ting into the cell," says **Angela Kashuba**, PharmD, an associate professor at the University of North Carolina School of Pharmacy.

"If we can block the receptor, we block most of the viruses transmitted," she adds.

Researchers are unsure of why the drug's concentration levels are so high in rectal tissue.

"It could be part of the vasculature as rectal tissues are very vascularized," Brown says. "For multiple doses we can explain the concentrations with the idea that they're building up and not necessarily clearing as quickly."

With maraviroc, about 25% of the dose that is swallowed passes through the gastrointestinal tract unmetabolized, he adds.

So when the drug is seen on the inside of the rectum, it's an extra source of the drug as opposed to the drug being completely absorbed in the small intestine and distributed throughout the body, he explains.

These study findings could point to a promising way to provide primary protection of HIV infection, Brown says.

"The problem is we don't know what concentrations are required to prevent HIV infection, and so we can't say right now whether it will work," Kashuba says. "Anything active therapeutically should be active for preventing HIV infection, but we don't know for sure."

With the study's data, researchers could explore the relationship between concentration and effect, she adds.

"So we can do that either in tissues in the culture system or in an animal model, and we could understand whether these concentrations we are seeing in people could be protected in a lab setting or in an animal model," Kashuba says. "And if that looks promising then it could move forward to a clinical trial; but we need those data to link exposure to efficacy."

This research is focusing on oral drugs as an HIV prevention strategy, she notes.

"Just recently, the power of the pharmacokinetic-pharmacodynamics relationship in prevention strategies has been apparent, but it's hard to move drugs from animal exposure to humans," Kasuba says. "No one has been measuring drug exposures, and very little drug exposure material has come out of the prevention field, so we're leading that effort."

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Drug concentrations as measure of ART adherence

'Adherence is far less than what people reported'

Adherence is one of the largest variables in the concentrations achieved of antiretrovirals (ARTs). So when HIV researchers are conducting clinical trials designed to determine efficacy of new ARTs, they cannot be certain how big a role adherence played in their results.

"If at the end of the study you don't get the results you were looking for, and it appears the drug did not work, then was it because the drug was not taken properly?" says **Craig Hendrix**, MD, director of the drug development unit and professor of medicine at Johns Hopkins University School of Medicine in Baltimore.

This has been a vexing question, particularly for microbicides trials, he notes.

"You gave the drug to animals and know they received the right concentration, and the animal model suggests the drug works," Hendrix says.

But it's trickier to interpret results when the drug is given to people, who might report having used it properly 95% of the time they are having sex, he adds.

"In some studies the objective measures show the adherence is far less than what people reported, and we don't know why that is," Hendrix says. "Recall is imperfect, and people want to see themselves as a certain kind of person."

Hendrix wanted to see if researchers could use drug concentrations as a measure of adherence in the context of clinical trials.

"The gold standard so far is the so-called MEMS Cap, which is a computer chip that goes into the top of the medicine bottle, and every time you unscrew it the cap registers the date and time the bottle is opened," he says. "That is great because that gives you information right at the time of the event."

Its drawback is that there is no way to be certain whether or not the person who opened the cap actually took the pill or took the correct dose.

Other adherence monitoring strategies include having a pharmacist check patients' bottles and

count pills, having patients keep a diary, or having study subjects recall how many pills they took in the past week.

"Pill count is more objective, but it's subject to errors, as well," Hendrix says. "We want people to be good subjects, and it's hard to know what happens with all the medications."

The advantage to using drug concentration levels as a measure of adherence in either clinical studies or clinical practice is that this is the most direct way of measuring how much of the drug got into the body, he adds.

There are issues with inter-variability and intra-variability, he notes.

"I could give people pills for a month, draw their blood right before the next dose, and their blood could change 30% to 40%," he explains. "And if I took 10 people and drew their blood, I'd get 10 different concentrations, and they could vary several-fold because of variability between individuals."

There is a third source of variability, and this involves the assays, Hendrix says.

Hendrix and co-investigators are studying how drug concentration as an adherence measurement might work, and they have good, reproducible assays.

"I can take care of intra-variability if I observe a subject take a dose and see what the typical samples look like over time," Hendrix says. "We give them an observed dose, measure a few points in time, and doing that enough we can reasonably predict what the concentrations will be after a single dose."

If investigators know what a subject's concentration levels look like at two, four, and six hours after a dose, then they can predict what the concentration looks like in the steady state.

The next step is to do a paired analysis in which the subject's concentrations are compared between an observed dose and an unobserved dose.

The obstacle is this method costs money and resources and would be difficult to replicate in clinical care, Hendrix says.

"I'm hoping to show in a research setting that it's worth it," Hendrix says. "It's of tremendous value to rule out adherence as a reason for a drug's failure because you'd hate to throw out a drug that works perfectly fine if people take it."

The value of this approach might be less clear in clinical settings.

"We're a long way from having insurers pay for this as an adherence test," he says. ■

Special Focus: Occupational HIV in the emergency room

By **Lisa Freeman Grossheim**, MD, FACEP, and **Katrin Takenaka**, MD, FACEP, assistant professors of emergency medicine, Department of Emergency Medicine, University of Texas Medical School at Houston.

Preventing HIV transmission from patients to health care providers has been the subject of extensive research throughout the course of the HIV epidemic. Although it is an uncommon event,[1,2] the consequences of occupational HIV transmission can be devastating. The overall risk of seroconversion after a percutaneous needlestick from a known HIV-positive source is widely reported to be 0.3% per exposure, as demonstrated by prospective data from almost 4000 health care workers.[3] Mucous membrane exposure to HIV-positive blood has a lower transmission rate of 0.09%. Seroconversion in at least five health care workers has been reported after this form of exposure.[4,5]

The Centers for Disease Control and Prevention (CDC) defines occupational HIV exposure as a "percutaneous injury (e.g., needlestick, cut from a sharp object) or contact of mucous membranes on nonintact skin (e.g., skin that is chapped, abraded, or affected by dermatitis) with blood, tissue, or other body fluids that are potentially infectious."[6] Potentially infectious fluids include cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids. Fluids not considered to be infectious unless visibly bloody include feces, nasal secretions, saliva, sputum, sweat, tears, urine, and vomitus.[7]

The incidence of occupationally transmitted hepatitis B infection has dramatically decreased since the widespread vaccination of health care providers and the general population.[8] The CDC estimates that approximately 400 new occupational HBV infections occurred in 1995 among U.S. health care workers, down from 17,000 in 1983.[8] The exact incidence of occupational hepatitis C infection transmission is unknown. There were an estimated 19,000 new HCV infections in 2006 in the United States, with 1.5% of the cases having a reported occupational exposure to blood.[9] Although the risk of transmission of HIV and hepatitis to health care providers as a result of an occupational exposure is relatively low, the

potential consequences of disease transmission are significant.

Percutaneous injury, often inflicted with a hollow-bore needle, is the most common mechanism of occupational HIV transmission.[2,10] The handling of sharp instruments ("sharps") represents the greatest risk of HIV transmission to health care workers. Needlesticks are the most commonly reported occupational exposure route, accounting for approximately 80% of exposures.[10] Recapping needles is the single most common activity that results in needlestick injuries.[3] Needles should never be recapped, manipulated, bent, or broken. Other high-risk activities include improper disposal of used needles and transferring blood/body fluids between different containers.[11] Risk of transmission of HIV to health care workers is increased when the device causing the injury was visibly contaminated with blood, when the device had been used for insertion into a deep vein or artery, when the device caused a deep injury, or when the source patient died within two months of the exposure.[7,12-14] Latex gloves can be another source of exposure. Glove perforations are more likely when gloves are worn for longer periods, are used during critical care procedures, or are worn during more than one procedure.[15]

The CDC recommends that the best way to prevent transmission of bloodborne illness is to avoid exposure.[7] Standard precautions should be used with all procedures that carry a potential risk of exposure. However, "universal precautions" are not used routinely by many health care providers. As many as 40% of needlestick injuries are preventable.[3] Unfortunately, more than 50% of health care workers engage in inadequate infection control practices. Physician universal precaution compliance rates were highest for wearing gloves and disposing of sharps, but lowest for wearing protective clothing and not recapping needles.[16]

The emergency department management of precutaneous or mucus membrane exposure includes determining the type of exposure, evaluating the source of exposure, the health and immunization history of the exposed health care worker at the time of exposure, and providing appropriate follow-up of the health care worker after exposure. After sustaining an exposure, the health care worker should report the contact as outlined by institutional protocols.

Evaluation of a Potential Exposure

There is no simple way to determine the likelihood that an unknown or untested source is infected with HIV or hepatitis. A step-wise approach considering each variable is a reasonable approach to management of occupational exposures.[17]

Evaluate the Exposure Incident. The first step is to consider the specific incident that led to concern over potential exposure. Did percutaneous, mucous membrane, or nonintact skin contact potentially infectious material? Percutaneous injuries should be assessed as either less severe (solid needle and superficial) or more severe (large-bore needle, deep puncture, visible blood on device, or needle in patient's artery or vein). Mucocutaneous exposures are deemed either small (few drops) or large (major blood splash) volumes.[7,18]

There is a risk of disease transmission if the health care worker is exposed to blood, body fluids containing visible blood, cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids.[19] If the exposure occurred to intact skin only, it is unlikely that a significant exposure occurred.

Determine the Status of the Source. The next step is to determine the HIV and hepatitis status of the source patient, if possible. The person whose blood or body fluid is the source of an occupational exposure should be evaluated for HIV, HBV, and HCV infection. Information available in the medical record at the time of exposure (e.g., laboratory test results or previous medical history) or questioning of the source might confirm HIV or hepatitis infection. If the source person is known to have HIV infection, obtain as much information as possible regarding the person's stage of infection (e.g., asymptomatic, symptomatic, or AIDS), CD4+ T-cell count, viral load, and current and previous antiretroviral therapy, as this is needed to assist in choosing an appropriate post-exposure prophylaxis (PEP) regimen. An exposure to a high-risk source patient may warrant an expanded PEP regimen. High-risk sources are patients with symptomatic HIV infection, AIDS, acute seroconversion, or high viral load. Low-risk sources are patients with asymptomatic HIV infection or viral load of less than 1,500 copies/mL.[19,20]

Testing to determine the HBV, HCV, and HIV infection status of an exposure source should be performed as soon as possible. If the HBV, HCV, and/or HIV infection status of the source is unknown, the source person should be informed of the incident, and his or her consent should be obtained for HIV and hepatitis testing. If the patient refuses or cannot give consent for testing, that patient should be considered to be infected.[3] Some states allow test-

ing the source patient without informed consent. Confidentiality should be protected while still ensuring that the appropriate information is provided to all exposed persons.[6,20] Any individual diagnosed with HBV, HCV, or HIV should be referred for appropriate counseling and treatment.

The use of rapid HIV ELISA testing can result in decreased use of PEP and spare the health care provider both undue anxiety and the potential adverse effects of antiretroviral PEP.[7] An FDA-approved rapid HIV-antibody test kit, if available, should be used to test the source. Confirmation of a reactive result with additional testing is not necessary to make initial decisions regarding post-exposure management, but should be done to complete the testing process and before informing the source person of a positive result on preliminary testing. A negative result on rapid testing is adequate for a decision to withhold or discontinue therapy if initiated.[6] If the source person is HIV seronegative and has no clinical evidence of AIDS or symptoms of HIV infection, no further testing of the person for HIV infection is indicated. The likelihood of the source person being in the "window period" of HIV infection in the absence of symptoms of acute retroviral syndrome is extremely small.[6] No case of transmission involving an exposure source during the window period has been reported in the United States.[2]

Unknown sources pose a more complicated problem. An example of an unknown source is a needle in a sharps container or a suture needle left on a tray. Testing of needles or other sharp instruments implicated in an exposure, regardless of whether the source is known or unknown, is not recommended. The reliability and interpretation of findings in such circumstances are unknown.[6] If the exposure source is unknown or cannot be tested, information about where and under what circumstances the exposure occurred should be considered for the likelihood for transmission of HBV, HCV, or HIV. Expert consultation should be considered in this situation.

HIV Postexposure Prophylaxis

Because the majority of occupational HIV exposures do not result in transmission of HIV, the benefits of prescribing PEP should outweigh the risks of potential toxicity. The use of PEP is not justified for exposures that do not pose a credible risk for transmission of HIV. PEP should be provided following exposure of nonintact skin (through percutaneous sharps injury or skin abrasion) or mucous membranes (through splashes to the eyes, nose, or oral cavity) to a potentially infected body fluid from a source that is HIV-positive or has unknown HIV status.[17] Because of the complexity of selection of HIV PEP regimens, consultation with an infectious disease specialist is strongly recommended in complicated cases.[7]

Although preventing exposures to blood and body fluids is the primary way to prevent occupationally acquired HIV infection, when an exposure occurs, appropriate post-exposure management is necessary.[7] PEP is thought to prevent the establishment of HIV infection by blocking the replication of the viral inoculum.[12] Initial guidelines for PEP were developed from an early study that demonstrated that health care personnel who were treated with zidovudine after needlestick exposures were less likely to seroconvert to HIV.[21] Subsequently, the effectiveness of combination therapy for PEP was suggested from studies that showed multidrug therapy was superior to monotherapy in the treatment of HIV infection and in the prevention of perinatal transmission.[7] Prospective, randomized studies to evaluate the efficacy of PEP in preventing HIV are unlikely to ever be conducted because the body of data that are generally supportive of its use create difficulty in withholding PEP for ethical reasons.[17] Failure of PEP may result from repeated exposures to HIV, delayed initiation or short duration of PEP, drug-resistant viral strains, a large inoculum, or host factors.[7,12]

The preferred PEP regimen depends on the type of exposure as well as the HIV status of the source patient.[6,7] There are no prospective data on the relative efficacy of two- and three-drug HIV PEP regimens. In most cases, when the source is unlikely to have HIV infection that is resistant to antiretroviral therapy, two-drug therapies are likely to be sufficient to prevent HIV transmission. The advantages of using two drugs as opposed to three include ease of administration, lower costs, and fewer side effects. In most cases, the addition of the third drug is considered to supply only a small increase in efficacy but adds significantly to the risk of side effects and reduced compliance.[17]

Current public health guidelines recommend a four-week regimen of two drugs for most HIV exposures that have occurred by percutaneous or mucous membrane routes.[7]

Psychological Issues

The emotional impact of a known or suspected HIV exposure is usually significant, especially in the

first hours to days after the episode.[24,25] Objective information about exposure risk and the pros and cons of post-exposure prophylaxis must be explained to an individual who is often emotionally upset.[26,27] Health care workers who are too confused or upset to make a decision about PEP can sometimes be helped by suggesting that treatment be started immediately, with the option to stop it later. Health care workers who sustain exposure to HIV should be counseled to avoid potential transmission to others during the follow-up period, especially during the first 6-12 weeks after exposure, when seroconversion is most likely to occur.[7] Sexual abstinence or condom use should be encouraged in high-risk exposures, as well as avoiding breast feeding.

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Treatment update: HIV and HCV co-infection

By **Dean L. Winslow**, MD, FACP, FIDSA, Chief, Division of AIDS Medicine, Santa Clara Valley, Medical Center; Clinical Professor, Stanford University School of Medicine. Dr. Winslow serves as a consultant for Siemens Diagnostics and is on the speaker's bureau for GSK and Cubist.

Synopsis: Sixty-four patients with HIV/HCV coinfection being treated with pegylated interferon alpha (IFN) plus ribavirin (RBV) were evaluated for mitochondrial toxicity (MT). Patients receiving concomitant HAART showed greater increases in lactate levels than those not receiving HAART, and lactate levels were correlated with RBV dose. While pancreatitis and hepatic steatosis were more common in patients concomitantly receiving HAART plus IFN/RBV, those patients demonstrating evidence of MT achieved higher rates of sustained virologic response (SVR) than did patients without evidence of MT.

Source: Reiber T, et al. Mitochondrial toxicity is associated with virological response in patients with HIV and hepatitis C virus coinfection treated with ribavirin and highly active antiretroviral therapy. *Clin Infect Dis*. 2010;202:156-160.

Data for 64 HIV/HCV co-infected patients treated in a prospective study of pegylated IFN alpha + RBV were analyzed. IFN was administered at 180 mcg SQ/week and RBV was dosed at 800 mg daily for patients with HCV genotype 2 or 3 and 1,000-1,200 mg/day for the first 12 weeks in patients with genotype 1 or 4, then reduced to 800 mg/day until completion of therapy. In addition to standard laboratory studies, venous lactate and various pancreatic enzymes were measured during the course of the trial. MT toxicity also was assessed by liver biopsy, which was performed at baseline and six months following cessation of therapy by presence or absence of hepatic steatosis.

Adverse events were significantly more common in the 48 patients who received concomitant HAART vs. the 16 patients who did not receive HAART: hyperlactemia 25% vs. 12%, pancreatic enzyme elevation 38% vs. 12%, hepatic steatosis after therapy 52% vs. 17%, LDH elevation 27% vs. 12%, and hemolytic anemia 13% vs. 0%. These toxicities were most strikingly seen in the 34 HAART-treated patients who received high-dose RBV.

SVR was achieved in 56% of patients who received HAART and in 31% of those who did not receive HAART. SVR was achieved in 73% of patients with MT vs. 44% of patients without an MT event.

Commentary

A large proportion of the patients receiving care at the HIV clinic I direct in San Jose, CA, are coinfected with HCV. While all of our clinicians attentively diagnose and treat (when appropriate) these patients with IFN+RBV, frankly only a small proportion of these patients actually complete the course of therapy, and an even smaller proportion achieve SVR. (Data from the APRICOT study show only a 29% SVR rate in HIV/HCV patients with HCV genotype 1 infection; consistent with our clinical experience.) I also have been impressed that IFN+RBV therapy is a tough regimen for many of our patients to take. In addition to the commonly recognized adverse effects of RBV-related anemia, IFN-related neutropenia, and depression, I have been impressed by how many of our patients just look and feel sick during their time on IFN+RBV, often appearing to age years in just a few months.

Data from this study suggest that the cumulative toxicities of IFN+RBV and HAART are largely related to mitochondrial toxicity (most likely due to the additive effects of nucleoside/nucleotide analogue antiretroviral RT inhibitors plus the nucleoside analogue RBV). Perhaps the "silver lining" from this study is that it appears that the presence of mitochondrial toxicity in these co-infected patients actually correlates with SVR. Sharing this information with patients might help give them hope to "hang in there," at least through 12 weeks of therapy, at which point the presence or absence of HCV RNA by a sensitive qualitative assay can help guide whether or not continued IFN+RBV therapy has a good chance of producing SVR. Of course, we desperately need more effective and less toxic small-molecule inhibitors of HCV. However, in the next few years, it appears that even these candidate agents (for example, the HCV protease inhibitor, teleprevir) need to be given in combination with IFN+RBV. ■

FDA Notifications

Generic Zidovudine injection approved

The FDA has granted approval to a generic formulation of zidovudine injection USP, 10 mg/mL, packaged in 200 mg/20 mL single-use vials, manufactured by Pharmaforce Inc., of Columbus, OH. The FDA has determined that the generic formulation is bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Retrovir® IV Infusion, 10 mg/mL, of VIIV Healthcare Co.

Approval of this generic formulation means that it may be marketed in the United States. A list of approved generic formulations of antiretroviral drugs used in the treatment of HIV infection is available at http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm118944.htm.

Fixed dose combination is approved by FDA

On July 8, 2010, the FDA granted tentative approval for fixed-dose combination lamivudine, nevirapine, and zidovudine tablets for Oral Solution, 30 mg/50 mg/60 mg, indicated in combination with other antiretrovirals for the treatment of HIV-1 infection in pediatric patients, manufactured by Matrix Laboratories Limited of Hyberdad, India. This is the first tentative approval for this fixed-dose combination product for pediatric use.

Each constituent ingredient of this generic tablet is currently approved to treat HIV-1 in combination with other antiretroviral agents. The safety and effectiveness of the combination of lamivudine/nevirapine/zidovudine in lowering viral load and increasing CD4+ cells has been demonstrated in previous studies of the individual ingredients used together.

The FDA's tentative approval means that although a product meets all of the safety, efficacy, and manufacturing quality standards required for marketing in the U.S., existing patents and/or proprietary issues currently prevent marketing of the product in the United States.

CNE/CME QUESTIONS

9. An HIV/AIDS prevention intervention created for middle school children was found to have what type of impact on the target audience?
A. Children who participated in the intervention had significant increases in knowledge about HIV and AIDS
B. Children participating in the intervention had improved behavioral intent to reduce HIV risk
C. Children participating in the intervention had increased self efficacy
D. All of the above

10. In an HIV prevention game called HIV Attack, coach/instructors use a soccer ball to demonstrate which of the following?
A. How HIV kills its host
B. How people cannot predict which person they know is infected with the virus
C. How HIV can cripple a person's immune system and more effectively attack the body
D. All of the above

11. In a pilot study, researchers found that which part of the genital tract had the highest concentrations of CCR5 antagonist maraviroc after multiple dosing?
A. Vaginal/cervical tissue
B. Rectal tissue
C. Semen
D. Female genital tract

Answers: 9. D; 10. C; 11. B.

COMING IN FUTURE MONTHS

- Physicians can successfully use prevention for positives
- Prevention measure for discordant couples shows success
- Novel biomarkers associated with clinical outcome and aging
- Osteoporosis and HIV are more frequent comorbidities now
- HIV-infected women feel stigmatized if they desire children

Tentative approval, however, does qualify the product for consideration for purchase under the President's Emergency Plan for AIDS Relief, or PEPFAR, program.

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

These products were reviewed for PEPFAR under the FDA guidance titled Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously approved Antiretrovirals for the Treatment of HIV developed to clarify what regulatory requirements apply to such applications, what issues might be of concern, and how these issues should be addressed. The guidance is intended to encourage sponsors to submit applications for combination and co-packaged products, and to facilitate submission of such applications to FDA. The pediatric indication, fulfilling unmet medical need, qualified this tentative approval priority review. ■

CNE/CME OBJECTIVES

The CNE/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.