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HIV clinicians and patients should prepare now for fall pandemic flu

Recent novel H1N1 flu outbreak offers lessons

By early May it appeared that the novel H1N1 influenza outbreak was beginning to ebb and worst-case scenarios would be averted. But the outbreak highlighted at least one big uncertainty in our response to what nearly was labeled a worldwide flu pandemic: How would HIV/AIDS patients respond to an infection of a new influenza virus?

"H1N1 is a neoantigen, and HIV patients can have difficulty mounting responses to neoantigens," says **Cliff Lane**, MD, clinical director, National Institute of Allergies and Infectious Diseases (NIAID) of the National Institutes of Health (NIH).

"We know how well an HIV-infected person handles seasonal flu, but this is the first time we've had anything like this, and it's the first time we're seeing this since the HIV epidemic began," Lane says.

The other big unknown is what will happen with this virus in the fall and winter when flu season returns.

"Flu is remarkably unpredictable, and it mutates rapidly," says **John T. Brooks**, MD, a medical epidemiologist who leads the HIV clinical epidemiology team at the Centers for Disease Control and Prevention (CDC) in Atlanta, GA.

Influenza epidemic history has taught infectious disease experts that the influenza virus generally takes one of two routes: "There's genetic drift, and it changes a little and a little more," Brooks says. "Or there is a major shift, and a whole new influenza appears, and the population doesn't have immunity because we haven't seen this one before."

Before the 2009 H1N1 flu, there were three significant flu pandemics within the past century. **(See flu pandemic timeline, p. 63.)**

It's the potential of a repeat of the 1918 flu which quickly struck and killed tens of millions worldwide that most worries public health officials. The 2009 flu virus is not like that one, however.

"To the extent they've looked at it in the lab, this strain of H1N1 doesn't have the same virulent markers as the strain of 1918," Brooks

says.

However, it has the potential to infect a large percentage of people because of its novelty. Seasonal flu typically has a clinical attack rate of 5% to 15%. Influenza pandemics, by contrast, have a clinical attack rate of 25% to 50%.

"It's one we haven't been exposed to before," Brooks says. "What it means is a larger fraction of the population is at risk for infection."

For HIV clinicians and their patients, this suggests a policy of caution when the influenza season returns. **(See story about specific recommendations for HIV patients, p. 64.)**

"Flu is a pretty unpredictable virus, and we'll have to watch and see what happens," Lane says. "All we can do is to prepare for the worst."

What this means for HIV clinicians and patients is they should not take any chances this upcoming flu season and take the precautions that are always recommended, but not always followed.

"We'd make the same recommendations for people to prepare themselves as they would for any flu season," Brooks says.

For example, HIV patients should be vaccinated against influenza infection. While it's not clear when a vaccine will be available for the new strain, they should take both that vaccine and the regular flu vaccine as soon as they are distributed, he says.

HIV patients should receive the inactive vaccine, not the live, attenuated vaccine, Brooks adds.

"We don't recommend the live vaccines for HIV patients," he says.

"I also would encourage all of the doctors, nurses, and health care providers who have contact with HIV patients to be vaccinated, as well," Brooks says.

"HIV patients should be taking the usual precautions to prevent getting an infection, and these include washing hands and covering your cough if you get ill," he says. "People with HIV need to be particularly vigilant for signs and symptoms of infection."

Health care officials believe that HIV patients are not any more predisposed to becoming infected with seasonal flu than are other people, Brooks notes.

"But once they're infected, a person with HIV/AIDS who has influenza might experience a somewhat more prolonged or severe force of disease," he says. "They could have a longer hospitalization, and that's what we want to avoid."

So HIV patients and their clinicians should be vigilant to the signs and symptoms of infection, including cough, sore throat, diffused muscle aches, headache, fever, and in some cases in Mexico this spring, there were gastrointestinal symptoms, including diarrhea, Brooks says.

Also, it would be a good policy for HIV clini-

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cians to advise patients to stay away from the clinic or doctor's office if they suspect they have the flu, he notes.

"Sometimes you can be assessed for the flu over the phone," Brooks says. "To the extent that doctors can use email and telephone calls to contact patients, that would reduce the risk that if the person has influenza that he brings other patients into contact with it."

If patients do come into the clinic due to flu symptoms, then they should be asked to wear a mask, he adds.

Also, flu treatment should be started within 48 hours of symptoms appearing. The available evidence suggests that HIV patients can take the flu drugs while being treated with antiretrovirals, and there are no drug-drug interactions.

Public health officials have determined that two flu drugs effectively fight the new H1N1 strain, and these are oseltamivir (Tamiflu®) and zanamivir (Relenza®). **(See emergency flu drug recommendations in FDA Notifications, p. 69.)**

"We recommend prophylaxis use [of oseltamivir and zanamivir] only for persons with close contact with a confirmed probable case," Brooks says. "You might want to consider prophylaxis if you're at home, and you have HIV, and your kid goes to school and has influenza symptoms after a class of kids went to Mexico, and one was a confirmed case."

But HIV clinicians should encourage patients to not overreact and ask for Tamiflu if they were on the subway and someone coughed on them, Brooks says.

"We do not recommend prophylaxis when there are only suspected cases," he adds.

Another consideration is how to handle time off from work or school and quarantine in the event of a pandemic flu.

"People with HIV infection might want to think about what they would do if they had to take one to two weeks off of work," Brooks says.

"They would need to be adherent to their antiretroviral therapy (ART) and take care of themselves to stay healthy," he adds. "They should always be adherent to following their medication regimen, and particularly now it's important because they need to concentrate on keeping their immune system as healthy as possible."

HIV patients also should consider volunteering to enroll in clinical trials involving influenza vaccines and treatment, Brooks and Lane say.

"I'm quite sure they'll be testing the [new H1N1 flu] vaccine in HIV patients," Lane says.

"Typically speaking you do initial studies in healthy volunteers, and then you do additional studies in people you think have altered immune responses," he adds.

"We always welcome HIV-infected persons to volunteer to participate in clinical trials," Brooks says.

They could find out more about which trials are available by visiting the Web site: www.clinicaltrial.gov and searching for "influenza," he suggests.

Researchers don't have a lot of good data on HIV-infected persons with influenza, Brooks notes. **(See story about vaccine trial and HIV patients, below.)**

Flu pandemic timeline

New influenza strains are rare, and pandemics are even rarer. If the 2009 Mexican flu virus disappears entirely, this year's neoantigen flu likely will be considered a pandemic scare. But if it returns and causes illness and deaths later this year and next winter, it will join the three other influenza pandemics of the past century.

They are as follows:

- 1918 Spanish flu: An estimated 20 to 40% of the worldwide population became ill, and 20 to 40 million people died across the globe. There were more than 500,000 deaths in the United States. The flu had the worst impact on people between the ages of 20 and 50, often killing them within hours of their first symptoms.
- 1957 Asian flu: First identified in Asia, this pandemic virus was quickly identified and vaccine was available by August, 1957. There were small outbreaks in the U.S. during the summer, and the disease spread quickly that fall. School children had the highest infection rate, and about 69,800 people, mainly the elderly, in the U.S. died from it.
- 1968 Hong Kong flu: The pandemic began in Hong Kong early in 1968 and spread to the United States by September. The virus impacted the elderly the most, and deaths peaked in December, 1968, and January, 1969. It was the 20th century's mildest pandemic with around 33,800 deaths.

There were three flu scares that were highly localized and did not result in a spike in morbidity and mortality. These were the 1976 swine flu scare at Fort Dix, the 1977 Russian flu that caused illness primarily in children, and the 1997 avian flu scare that caused a handful of deaths before China slaughtered 1.5 million chickens and ended the spread of the virus.

"We need more information," he adds. "And during this outbreak, they're looking to see if people who are immunocompromised are at greater risk with the experience." ■

Recent flu vaccine and HIV trial holds promising news

HIV patients could quickly, safely enroll

A new study suggests that a clinical trial to test a new flu vaccine, such as a vaccine against the novel 2009 H1N1 influenza virus, could enroll HIV patients both quickly and safely.

"The study very rapidly recruited almost 300 HIV patients, and we had 80% of them in the first few weeks," says **Curtis Cooper**, MD, FRCPC, an associate professor of medicine at the University of Ottawa, and a physician in the division of infectious diseases at the Ottawa Hospital in Ottawa, Canada.

The Ottawa Hospital clinical trial site will be one of the Canadian sites that will evaluate the H1N1 influenza vaccine when it first becomes available for study, Cooper notes.

"Canadian researchers have established an influenza network funded by the Public Health Agency of Canada and the Canadian Institutes of Health Research," Cooper says. "Part of our mandate is to rapidly evaluate vaccine candidates in the event of a pandemic. I'm an investigator with that project."

The flu vaccine study was conducted last summer and evaluated the vaccine that was distributed for the 2008-2009 flu season.

"The reason we did the study is because people living with HIV are more susceptible to symptoms of influenza," Cooper says. "The recommendations are made on pretty tenuous data of studies conducted in the pre-HAART [highly active antiretroviral therapy] era."

So Cooper and co-investigators conducted a randomized clinical trial that looked at different vaccination strategies in HIV patients. They examined increasing the dose of vaccine for HIV patients and also at providing a booster dose of influenza vaccine.

The study's findings are still being analyzed, but one of the more positive outcomes was that a flu vaccine trial can enroll HIV patients very rapidly, which would be necessary under pandemic conditions.

Within a month, almost all HIV-infected participants were enrolled, Cooper says.

"We were able to recruit and vaccinate all our patients in a very rapid period of time while still doing it safely and capturing clinical and laboratory information necessary to evaluate a vaccine," he says.

Investigators are still collecting case report forms, but initial findings suggest there were no severe adverse events related to the dosing strategies they used, including when they increased the vaccine dose, Cooper says.

"In general the vaccines were well tolerated," he says. "It was a slow flu season last year, so we didn't have a lot of flu-like illness presenting to our research units."

With further analysis, researchers hope to answer the question of whether alternative types of vaccination strategy would produce higher levels of antibodies than the usual vaccination strategy, he adds.

Also, investigators studied HIV patients' receptivity to being vaccinated against the flu virus.

"For this study we had a questionnaire that we gave to each participant and the control population, asking about factors that would make them more or less likely to receive the flu vaccine and make them more or less likely to participate in a clinical trial," Cooper says. "This is all very important information to guide mass immunization against swine flu." ■

CDC issues guidance for HIV patients regarding H1N1 flu virus

The Centers for Disease Control and Prevention (CDC) of Atlanta, GA, has published interim guidance for clinicians regarding management of patients with HIV who have been exposed to, or who have contracted the swine influenza (H1N1 virus).

The guidance, issued at the end of April, 2009, is titled, "Interim Guidance — HIV-Infected Adults and Adolescents: Considerations for Clinicians Regarding Swine-Origin Influenza A (H1N1) Virus." It's available online at http://www.cdc/gov/swineful/guidance_HIV.htm.

"The recommendations we give are for today, and what we know is things can change," says **John T. Brooks**, MD, a medical epidemiologist who leads the HIV clinical epidemiology team at the Centers for Disease Control and Prevention (CDC) in Atlanta, GA.

"The CDC and other agencies are looking closely at trends in the epidemiology of the virus to see whether there's evidence of it becoming more virulent," Brooks adds.

The CDC cautions HIV patients and their providers that any influenza carries potential risks for HIV-infected persons, particularly for people with low CD4 cell counts, who are at higher risk for viral and bacterial lower respiratory tract infections and recurrent pneumonias.

Adults and adolescents infected with HIV experience more severe complications from seasonal influenza, so they're also at higher risk for swine influenza complications, the CDC states.

Here is a brief summary of the recommendations:

• **Clinical Presentation:** HIV-infected patients with Influenza A (H1N1) virus would present with typical acute respiratory illness, including cough, sore throat, rhinorrhea, fever, headache, and muscle aches.

Patients with low CD4 cell counts might have a rapidly-progressing illness that is complicated by a secondary bacterial infection, such as pneumonia. If their flu is suspected to be the H1N1 strain, then a specimen should be obtained and tested. If the specimen tests positive for unsubtypeable influenza A virus, then it should be sent to the state public health laboratory for additional testing.

HIV patients who are experiencing signs and symptoms of the flu or who have been exposed to someone with a confirmed, probable or suspected case of influenza infection, whether it is seasonal flu or H1N1 flu, should consult their doctor for evaluation about whether they should receive anti-influenza treatment or prophylaxis.

• **Treatment and chemoprophylaxis:** The currently circulating swine-origin influenza A (H1N1) virus is sensitive to the neuraminidase inhibitor antiviral medications zanamivir and oseltamivir, but it's resistant to adamantane antiviral medications, amantadine and rimantadine.

HIV patients who meet current case-definitions for confirmed, probable, or suspected swine-origin influenza A (H1N1) infection should receive empiric antiviral treatment. Those HIV patients who have been in close contact with probable or confirmed cases of this particular flu strain should receive antiviral chemoprophylaxis.

Antiviral treatment with zanamivir or oseltamivir should be initiated as soon as possible after the onset of influenza symptoms. The benefits are greatest if it is started within 48 hours of onset. The treatment is given for five days, and if a prophylaxis is administered, the treatment is for 10 days after last exposure.

Clinicians should monitor the treated patient closely and consider whether to extend therapy based on the course of illness.

There have been no adverse effects reported among HIV patients from the anti-influenza treatment, and there are no absolute contraindications for co-administration of the flu drugs with antiretroviral medications.

• **Other ways to reduce risk for HIV-infected adults and adolescents:** The vaccine is not currently available, but these steps can reduce risk of exposure:

- Hand-wash frequently;
- Cover coughs;
- Keep ill persons home except to seek medical care;
- Minimize contact with others in household who might have the flu;
- Voluntarily home quarantine members of households with confirmed or probable swine flu cases;
- Reduce unnecessary social contacts and avoid crowded settings;
- Maintain one's health and adhere to prescribed antiretroviral treatment. ■

Q&A on H1N1 for people with HIV/AIDS

Drug-drug reactions not clear, should be reported

The Centers for Disease Control and Prevention has posted the following answers to common questions about novel H1N1 influenza A and adults with HIV/AIDS:

Are people with HIV/AIDS at greater risk than other people of infection with novel H1N1 flu?

At the present time, we have no information about the risk of the novel H1N1 flu in people with HIV/AIDS. In the past, people with HIV/AIDS have not appeared to be at any greater risk than the general population for infection with routine seasonal influenza. However,

HIV-infected adults and adolescents, and especially persons with low CD4 cell counts or AIDS, can experience more severe complications of seasonal influenza. It is therefore possible that HIV-infected adults and adolescents are also at higher risk for complications from infection with the H1N1 flu virus.

What can people with HIV/AIDS do to protect themselves from novel H1N1 flu?

HIV-infected patients should take precautions to protect themselves from novel H1N1 flu.

1. Wash your hands often (or using an alcohol-based hand sanitizer if soap and water aren't available)
2. Avoid touching your eyes, nose or mouth with your hands – germs spread this way
3. Try to avoid close contact with sick people

HIV-infected persons should maintain a healthy lifestyle; eat right, get enough sleep, and reduce stress as much as possible. Staying healthy reduces your risk of getting infected by influenza and other infections. Staying health also helps your immune system fight off a flu infection should it occur.

If you are currently taking antiretrovirals or antimicrobial prophylaxis against opportunistic infections you should adhere to your prescribed treatment and follow the advice of your health care provider in order to maximize the health of your immune system.

What are the signs and symptoms of HN1 influenza?

Signs and symptoms of infection with the novel H1N1 influenza are generally the same as for seasonal influenza: fever, cough, sore throat, runny or stuffy nose, headache, body aches (muscle aches or joint pain), chills and fatigue. Some people have reported diarrhea and vomiting associated with novel H1N1 flu.

What should people with HIV/AIDS do if they think they may have novel H1N1 flu?

HIV-infected people should do the same things as they would do for routine seasonal flu – contact your health care provider and follow his or her instructions. He or she will determine if laboratory testing or treatment is needed.

If you are sick, stay home. If you have novel H1N1 flu, you should stay at home for 7 days after your symptoms begin or until you have been symptom-free for 24 hours, whichever is longer. Staying at home will help prevent others from catching your illness.

If you need to go to a doctor's office, to an emergency room, or to any other healthcare facility to be evaluated, cover your mouth and nose with a facemask (or ask for one at the healthcare facility) and tell them that you are there because you think you might have novel H1N1 flu.

Is there a vaccine against this the H1N1 flu virus?

No. There is currently no vaccine for the novel H1N1 flu. The vaccine given for seasonal flu does not protect against the novel H1N1 flu. If a vaccine against novel H1N1 flu becomes available, CDC will make recommendations for people with HIV/AIDS. Researchers are presently working to develop a vaccination against novel H1N1 flu.

Is there treatment against novel H1N1 flu for people with HIV/AIDS?

Yes. The novel H1N1 flu virus is sensitive to two antiviral drugs: zanamivir and oseltamivir. HIV-infected adults and adolescents who meet current case-definitions for confirmed, probable or suspected infection with novel H1N1 flu should receive antiviral treatment. Treatment is most effective if started within 48 hours of symptom onset. Please check the CDC website frequently for updates in recommendations for antiviral treatment.

When should people with HIV/AIDS be prescribed antiviral medications for the prevention (also called "chemoprophylaxis") of novel H1N1 flu?

HIV-infected adults and adolescents who are close contacts of persons with novel H1N1 flu should receive antiviral chemoprophylaxis. Please check the CDC website frequently for updates in recommendations for antiviral chemoprophylaxis.

Are the medicines used to treat and prevent infection with the novel H1N1 flu virus safe for people with HIV/AIDS?

There is not a lot of information on the interaction between anti-flu medications and HIV antiretrovirals. No adverse effects have been reported among HIV-infected adults and adolescents who received oseltamivir or zanamivir. There are no known major drug interactions between oseltamivir or zanamivir with currently available antiretroviral medications used to treat HIV infection. If you are prescribed oseltamivir or zanamivir and think you might be having a reaction to the drug, contact your health care provider. Healthcare providers should observe patients for possible adverse drug reactions to anti-influenza agents, especially patients with neurologic problems or decreased kidney function.

How else should people with HIV/AIDS prepare?

Stay informed. Health officials will provide additional information as it becomes available on

the CDC website. Consult your doctor and make sure all your vaccinations are up-to-date, including vaccination against seasonal influenza and vaccination against bacterial pneumonia caused by the Streptococcus pneumoniae. Bacterial pneumonia from Streptococcus pneumoniae can be a problem for people with HIV/AIDS and can also cause complications for people who have the flu. The vaccine against Streptococcus pneumoniae is different than the vaccine from the influenza vaccine.

Follow local public health advice regarding school closures, avoiding crowds and other social distancing measures based on illness in specific communities.

If you haven't developed a family emergency plan yet, consider developing one now as a precaution. In particular, make sure to keep your antiretroviral prescriptions and other prescriptions filled and up-to-date and to take all of your antiretrovirals as prescribed.

What is CDC doing about H1N1 flu for people with HIV/AIDS?

CDC, in coordination with state and local health departments and with WHO is working aggressively to understand the epidemiology of this novel H1N1 flu and determine if it affects HIV-infected people and people with other immunocompromising conditions differently. As additional information about the situation become available, the CDC's recommendations may change. Please check the CDC H1N1 Flu website frequently at: http://www.cdc.gov/h1n1flu/index.htm. ■

HIV prevention trials require sophisticated community preparation

Controversial PrEP trials serve as cautionary tale

HIV biomedical prevention researchers are leading the way in developing successful models or engaging community involvement and education about research.

For example, the AIDS Vaccine Advocacy Coalition (AVAC) and UNAIDS have published a set of guidelines about building rapport and trust with communities. The 10 principles of Good Participatory Practice (GPP) guidelines for biomedical HIV prevention trials could serve as a model for all clinical trial research.[1]

The guidelines were developed when pre-exposure prophylaxis (PrEP) trials were launched, says **Lori Miller**, MHS, a senior program manager of AVAC.

"There were many controversies around community engagement with researchers, including controversies around the PrEP trials in Cambodia, Cameroon, and Thailand," Miller says.

Researchers working in biomedical HIV prevention trials also have learned ways to communicate effectively to potential research participants what their trials are about and how they work.

This also has been a trial and error experience.

For example, investigators conducting HIV prevention trials in Africa, Latin America, and other international sites learned through anecdotal reports that community members misunderstood the intention of blood draws.

"People had some interesting ideas about why we would want to collect blood and what would be done with it," says **Kathleen MacQueen**, PhD, MPH, a senior social scientist and coordinator of interdisciplinary research ethics at Family Health International in Research Triangle Park, NC.

"We heard about rumors of witchcraft and vampirism or using samples to do genetic engineering that would make people in the United States rich, but leave people in the developing world poor," MacQueen adds.

HIV researchers and experts held a special session to discuss these reports. About 80 people from Asia, Latin America, Africa, and the United States met to discuss this situation.

The meeting was fruitful. Researchers and sponsors learned that if researchers do not fully explain what they're doing and why they're doing it in a way that participants can fully understand then people will jump to their own conclusions based on their own life and culture experiences, MacQueen explains.

"If they don't understand what a laboratory is and how you would use blood to understand the disease, and if they only understand the use of blood in the context of witchcraft, then that's the model they'll use," she adds.

Armed with this new understanding of how cultural and experiential differences can lead to huge misunderstandings, researchers began to educate communities and potential participants in new ways.

For instance, HIV biomedical researchers rou-

tinely ask community advisory boards (CABs) to help them identify research terminology that could be misconstrued or research practices that might negatively impact a particular cultural belief or practice.

HIV researchers also understand as well as any investigators how important it is to build trust in a community from which people will be recruited for clinical trials.

"Laying the groundwork in the community can be very important to that process," MacQueen says.

For example, HIV prevention researchers learned from community advisors in Africa that potential participants did not understand the term "vial" when they were told that two vials of blood would be taken, she says.

The word "vial" was translated to the word "bottle," and to participants this meant a Coca Cola bottle. So they thought researchers wanted to take enough blood to fill two Coke bottles.

Investigators found a simple solution: they brought in a liter jug and explained that the blood in the human body could fill four or five of these jugs, MacQueen says.

"Then they showed them a vial and said, 'We use this to collect a small amount of your blood,'" she adds. "Then they also explain that their bodies are constantly making more blood."

Occasionally in HIV research, small misunderstandings can escalate and become major problems for the trial site.

The controversy that erupted over the PrEP trials in Cambodia, where the government cancelled the PrEP trial in 2004 is a good example of this.

Researchers began meeting with community members in Cambodia in preparation of enrolling sex workers in the HIV tenofovir trial for PrEP in 2003. At this time, organizations that assisted sex workers were treated like pariahs by many established HIV organizations. This was because the President's Emergency Plan for AIDS Relief (PEPFAR) prohibited funding to any group that did not have a policy explicitly prohibiting prostitution and sex trafficking.[2]

Some non-governmental organizations (NGOs) thought the PrEP trials were connected to the U.S. Agency for International Development (USAID). And they feared USAID would restrict their funding if they assisted researchers with tenofovir PrEP trials. This fear also made them suspicious of researchers' motives.[2]

The situation was made worse by communication problems. For instance, the people attending community meetings to discuss the trials did not have basic research literacy, and the information presented was not presented as simply as needed.

Community members were particularly concerned about how future access to care and antiretroviral therapy (ART) would be assured to seroconverters.

As community discussions progressed, the community members representing sex workers decided to ask that participants be given long-term insurance protection to offset the risk of a side effect from tenofovir that would impact their ability to work. They also decided that the clinical trials should pay them more than the study compensation incentive of $3 per month for their participation.

As a result of their concerns and the publicity they sought to express their disagreement with parts of the trial, the Cambodian government cancelled the trial, and in August, 2004, all work stopped.

The experience proved costly and led to setbacks to PrEP research, but HIV investigators learned that community engagement and trust-building were extremely important to the success of their work.

"Our informed consent process can take a half day or more since some HIV trials are so complex with screening, informed consent, and behavioral interviews," MacQueen says.

"If you don't really talk to people and listen to them and understand what they think, then all of your best intentions can go haywire," she says.

And the best way to ensure this level of understanding is to build research literacy in communities that are targeted for HIV research. This is one of the 10 key principles in the GPP guidelines.

"It should be one of the most important principles because you can't expect to work with communities and have conversations with them if you haven't educated them enough so that they can understand how research is done," Miller says.

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FDA Notifications

EUA issued for treating novel 2009 H1N1 flu

On April 26, 2009, the Acting Secretary of Health and Human Services (HHS) declared a public health emergency related to the current outbreak of "swine flu" (now designated "novel 2009 H1N1").

In response to this public health emergency, the CDC requested Emergency Use Authorization (EUA) for the use of oseltamivir (Tamiflu®) and zanamivir (Relenza®) for treatment and prophylaxis of influenza for broader populations than are currently included in the product labeling, including pediatric populations, and others who fall outside of the indicated uses.

Influenza viruses cause serious, sometimes fatal, disease in immunocompromised patients, including HIV infected infants, toddlers, and young children.

Currently, zanamivir is approved to treat acute uncomplicated illnesses due to influenza in adults and children 7 years and older who have been symptomatic for less than two days, and for the prevention of influenza in adults and children 5 years and older. Oseltamivir is approved for the treatment and prevention of influenza in patients 1 year and older.

The EUAs allow for oseltamivir also to be used to treat and prevent influenza in children under 1 year, and to provide alternative dosing recommendations for children older than 1 year. In addition, under the EUAs, both medications may be distributed to large segments of the population without complying with the label requirements otherwise applicable to dispensed drugs, and accompanied by written information pertaining to the emergency use. They may also be distributed by a broader range of health care workers, including some public health officials and volunteers, in accordance with applicable state and local laws and/or public health emergency responses.

These temporary extensions of the indication, which will terminate when the emergency no longer exists, are summarized below:

1. Use of oseltamivir for treatment and prophylaxis of influenza in infants less than 1 year of age. Oseltamivir is currently approved for use in patients 1 year of age and older. New dosing recommendations in infants less than 1 year were based on expedited review of safety and pharmacokinetic data submitted by Roche and the Collaborative Antiviral Study Group of NIAID/NIH. In addition, age-based dose recommendations in older children were included in these new recommendations. These EUA recommendations are intended for use with Tamiflu for Oral Suspension and are shown here:

Expanded EUA Tamiflu Dose Recommendations for Treatment of Influenza in Pediatric Patients Body Weight (kg) Body Weight (lbs) Dose by Age Recommended Treatment Dose for 5 Days:

- Greater than 40 kg, greater than 88 lbs, and 10 years of age or older: 75 mg twice daily;
- Greater than 23 kg to 40 kg, greater than 51 lbs to 88 lbs, 6-9 years: 60 mg twice daily;
- Greater than 15 kg to 23 kg, greater than 33 lbs to 51 lbs, 3-5 years: 45 mg twice daily;
- 15 kg or less, 33 pounds or less, 1-2 years: 30 mg twice daily;
- Dosing for infants younger than 1 year is not based on weight: 6-11 months: 25 mg twice daily; 3-5 months: 20 mg twice daily; Less than 3 months: 12 mg twice daily.

The Tamiflu Oral Suspension bottle comes with a dispenser marked for 30, 45, or 60 mg. For children who weigh more than 40 kg (or 88 lbs) or adults who can't swallow capsules, you will need to measure out a dose of 30 mg plus another dose of 45 mg. For infants less than 1 year old, a different measuring device must be used that will dispense 2 mL (about 25 mg), 1.6 mL (about 20 mg) or 1 mL (12 mg).

Doses for prevention of the novel 2009 H1N1 are the same for each weight group, but doses are administered only once per day rather than twice. Prevention dosages should be taken for 10 days following close contact with an infected person or during a community outbreak.

2. Use of oseltamivir and zanamivir in patients

not included in the current labeling. These drugs are currently indicated for use in patients with acute, uncomplicated influenza who have had symptoms for less than 48 hours. The EUA allows for use of Tamiflu and Relenza in patients who have more severe influenza disease or who have been ill for longer than 48 hours based on limited published data and the understanding that the novel 2009 H1N1 may have different presentations. Depending on available products and susceptibility data, clinicians may wish to make individual risk-benefit assessments regarding the appropriate use of the products.

More detailed information about Influenza Antiviral Drugs is available on the FDA web site at http://www.fda.gov/cder/drug/antivirals/influenza/default.htm. The TAMIFLU® FACT SHEET FOR HEALTH CARE PROVIDERS contains information specific to the expanded pediatric dosing recommendations for Tamiflu. ■

Tenofovir in India receives tentative approval

On April 29, 2009, the Food and Drug Administration granted tentative approval for tenofovir disoproxil fumarate tablets, 300 mg, manufactured by Cipla, Limited, of Mumbai, India, indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. The application was reviewed under expedited review provisions for the President's Emergency Plan for AIDS Relief (PEPFAR).

"Tentative approval" means that FDA has concluded that a drug product has met all required quality, safety and efficacy standards, but is not eligible for marketing in the U.S. because of existing patent protections. Tentative approval does, however, make the product eligible for consideration for purchase outside the United States under the PEPFAR program.

This product is a generic version of Viread Tablets, 300 mg, a Nucleoside Reverse Transcriptase Inhibitor (NRTI), made by Gilead Sciences Inc. Patent information is available in the FDA Orange Book.

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

Kaletra product label changed

The FDA approved, on April 20, 2009, changes to the product label for lopinavir/ritonavir (Kaletra®) Tablets and Oral Solution, to include results from Study 730 comparing treatment with lopinavir/ritonavir 800/200 mg once-daily plus tenofovir DF and emtricitabine versus lopinavir/ritonavir 400/100 mg twice-daily plus tenofovir DF and emtricitabine in antiretroviral treatment-naïve patients.

Results from this study were included in section 6, "Adverse Reactions," and section 14, "Clinical Studies," as follows.

The statement about diarrhea comparing once daily and twice daily dosing of lopinavir/ritonavir capsules was removed from the label because capsule formulation is no longer marketed. Information regarding incidence of diarrhea in Study 730 is included in section 6, "Adverse Reactions." Study 730 provides the more relevant longer term data for once daily and twice daily dosing with lopinavir/ritonavir tablets.

It reads as follows:

"6.1 Adults - Clinical Trials Experience

The most common adverse reaction was diarrhea, which was generally of mild to moderate severity. In study 730, the incidence of diarrhea of any severity during 48 weeks of therapy was 60% in patients receiving KALETRA tablets once daily compared to 57% in patients receiving KALETRA tablets twice daily. More patients receiving KALETRA tablets once-daily (14, 4.2%) had ongoing diarrhea at the time of discontinuation as compared to patients receiving KALETRA tablets twice-daily (6, 1.8%). In study 730, discontinuations due to any adverse reaction were 4.8% in patients receiving KALETRA tablets once-daily as compared to 3% in patients receiving KALETRA tablets twice-daily."

Also, the FDA approved, on April 6, 2009, changes to the product label for lopinavir/ritonavir (Kaletra) Tablets and Oral Solution, reflecting new warnings and precautions regarding QT/QTC interval and PR interval prolongation information.

QT/QTC interval and PR interval prolonga-

tion refer to changes in electrical activity and rhythm of the heart.

The following information was added to the product label:

"5 WARNINGS AND PRECAUTIONS

"5.5 PR Interval Prolongation:

Lopinavir/ritonavir prolongs the PR interval in some patients. Cases of second or third degree atrioventricular block have been reported. KALETRA should be used with caution in patients with underlying structural heart disease, preexisting conduction system abnormalities, ischemic heart disease or cardiomyopathies, as these patients may be at increased risk for developing cardiac conduction abnormalities.

"The impact on the PR interval of co-administration of KALETRA with other drugs that prolong the PR interval (including calcium channel blockers, beta-adrenergic blockers, digoxin and atazanavir) has not been evaluated. As a result, co-administration of KALETRA with these drugs should be undertaken with caution, particularly with those drugs metabolized by CYP3A. Clinical monitoring is recommended.

"5.6 QT Interval Prolongation

"Postmarketing cases of QT interval prolongation and torsade de pointes have been reported although causality of KALETRA could not be established. Avoid use in patients with congenital long QT syndrome, those with hypokalemia, and with other drugs that prolong the QT interval."

In addition to these label changes, a new Medication Guide is now available for Kaletra.

Medication Guides are paper handouts that are dispensed with some prescription medicines. These handouts are required by FDA for certain drugs, but are created by the drug manufacturer. They are different from the routine information handouts provided by some pharmacies. The guides address issues that are specific to particular drugs and drug classes, and they contain FDA-approved information that can help patients avoid serious adverse events. ■

CNE/CME *questions*

16. Which of the following is a concern among public health officials regarding the "swine flu" H1N1 outbreak from this spring in Mexico and the United States and its potential impact on HIV patients?
    A. HIV patients are more susceptible to infection of flu viruses
    B. H1N1 is a neoantigen, and HIV patients can have difficulty mounting responses to neoantigens
    C. HIV patients might have difficulty with taking anti-flu drugs
    D. All of the above

17. Which of the following is a CDC-recommended action for HIV patients to take to prevent flu infection?
    A. Hand-wash frequently;
    B. Maintain one's health and adhere to prescribed antiretroviral treatment.
    C. Reduce unnecessary social contacts and avoid crowded settings;
    D. All of the above

18. HIV biomedical prevention researchers have found that one of the most important ways to build trust in a community in which clinical trials will be conducted is to do which of the following?
    A. Ask community advisory boards (CABs) to help them identify research terminology that could be misconstrued or research practices that might negatively impact a particular cultural belief or practice
    B. Market the research and its purpose on billboards, sides of street vendor kiosks, and on church bulletin boards
    C. Seek governmental support and marketing through public health mailings
    D. All of the above

Answers: 16. B; 17. D; 18. A.

COMING IN FUTURE MONTHS

- Generalist approach also needed for HIV care and treatment
- HPV infection might increase risk of HIV infection
- Survey on HIV/AIDS in US has interesting findings
- HIV programs, ADAP, Ryan White funding revealed

CDC launches new AIDS awareness campaign

A new AIDS awareness campaign is being launched by FDA's sister agency, the U.S. Centers for Disease Control and Prevention's (CDC).

HIV is still a significant public health problem in the United Sates. Although HIV infection is preventable, every 9½ minutes, someone in the U.S. is infected with the virus.

The new Act Against AIDS campaign is designed to contribute to the goal of reducing HIV incidence in the United States.

You can get the facts about the epidemic, learn how to prevent transmission of the virus, delay the onset of AIDS with proper treatment for HIV infection, and find out ways to stem the tide of HIV infection in the United States by spreading the word about AIDS at a new CDC Act Against AIDS website http://www.cdc.gov/nineandahalfminutes/. ■

CNE/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.