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HIV patients who take herbals may be putting their drug therapy at risk

FDA advisory on St. John's Wort may start trend

The Food and Drug Administration's recent advisory on how St. John's Wort reduces the effectiveness of certain HIV drugs is a reminder that herbal remedies are not always harmless ways to promote HIV patients' health or placebos that can be ignored. It also means clinicians will have to be proactive in finding out what over-the-counter supplements their patients are taking and will need to determine if there's a possibility those herbal remedies could have adverse interactions with antiretroviral medications, herbal experts say.

"Anyone taking herbals needs to know there is a risk, because herbals are bioactive compounds, just like any other agent you ingest," says **Michael Cirigliano**, MD, an assistant professor of medicine at the University of Pennsylvania Medical Center in Eddystone. Plus, herbal use has increased dramatically in recent years, Cirigliano notes.

Since the beginning of the HIV epidemic, dating back to the years when there were no or few treatments available, HIV patients have experimented with and sometimes relied on alternative medicine, including herbal remedies. In his book *And the Band Played On*, writer Randy Shilts described how vitamin and herbal companies exploited dying gay men in the early 1980s by promising that the products they sold would help the men maximize their immune systems. "The sewers of Manhattan and San Francisco flowed with the most vitamin-rich urine in the nation," Shilts wrote.[1]

Since those more desperate years, HIV patients have had access to better-proven treatments, but

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COMING IN FUTURE ISSUES

■ **Protease inhibitors and long-term problems:** An international committee of researchers and pharmaceutical companies is studying whether protease inhibitors cause heart disease or blood sugar problems over the long term

■ **Gene research may open doors to future advances in HIV treatment:** Philadelphia researchers have had some success in testing a genetic process that could render HIV harmless

■ **New testosterone gel product is on the market:** UNIMED Pharmaceuticals Inc. of Buffalo Grove, IL, recently received U.S. Food and Drug Administration approval for a gel that delivers testosterone effectively in high doses

■ **Viral load self-test kits on the horizon:** Michigan researchers are designing a new test kit that will let HIV patients check while at home whether their viral load is remaining stable or increasing

■ **If patients take the drugs consistently, HIV will stay away:** A study conducted of incarcerated HIV patients found that 100% adherence, as determined by directly observed therapy, resulted in undetectable viral load after 48 weeks

herbal remedies still hold some attraction for people who have a chronic and often fatal illness.

Until the recent FDA advisory, some HIV patients used St. John's Wort because of reports that it not only alleviated depression but also had an antiretroviral effect on HIV, says **Mary L. Hardy**, MD, medical director of the Cedars-Sinai Integrative Medicine Medical Group in Los Angeles. Hardy specializes in herbal-drug interactions.

The St. John's Wort study published in a February 2000 issue of *The Lancet* showed that the herb is an inducer of the cytochrome P450, which is the same pathway in which antiretroviral drugs such as indinavir are metabolized, Hardy says. **(See related story, p. 53.)**

St. John's Wort significantly decreased blood concentrations of the protease inhibitor, putting patients at risk of developing drug-resistant HIV strains, she adds.

HIV patients frequently take St. John's Wort in doses two to three times the regular dose because the herb has been shown in in vitro testing to be active against HIV, Hardy says. This makes the study immensely important.

"Often, HIV patients were taking St. John's Wort as self-medicating for its antiretroviral effect, and before this study, that was a good choice to make," she adds.

The FDA issued an advisory in February that warns clinicians and HIV patients of the possible dangerous interaction between St. John's Wort and the HIV protease inhibitor indinavir. The FDA also warned that St. John's Wort might cause problems with other HIV drugs, both protease inhibitors and nonnucleoside reverse transcriptase inhibitors.

"So it's imperative that physicians know what their patients are taking, because St. John's Wort has been found to have lots of drug interactions," Cirigliano says.

Hardy recommends that no HIV patients take St. John's Wort, because they are better served by conventional antiretroviral therapy and other antidepressants.

The FDA currently is collecting case studies of herbal interactions with medications and other adverse events reported by consumers or health care professionals. As part of the Special Nutritionals Adverse Event Monitoring System, established in 1993, health care professionals may report any cases they have of patients who have had an adverse reaction to a particular herbal remedy, whether or not it was in connection with another

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Herbal remedy checklist

Herbal products may have side effects or adverse interactions with over-the-counter or prescription drugs. This checklist will help health care providers and patients can determine the best strategy for HIV treatment.

Herb that the Food and Drug Administration specifically recommends not be used by HIV patients who are taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors:

St. John's Wort

Herbs with known adverse effects or drug interactions:

Asian ginseng: may interact with digoxin, increasing levels of digoxin in blood

Black cohosh: may cause hypotension, weight gain, nausea, and may interact poorly with antihypertensives and interfere with hormonal medications

Blue cohosh: may increase blood pressure and provoke angina

Cayenne: may cause stomach upset, diarrhea; should be monitored when a person is on antiplatelet drugs

Chamomile tea: people with ragweed allergies may be allergic to this

Chaparral: believed to be carcinogenic

Chaste tree berry: also called chasteberry and monk's pepper, the herb may cause gastrointestinal and lower abdominal complaints, headache, allergic reactions, and increased menstrual flow

Comfrey: potentially causes liver damage

Echinacea (Purple cone flower): cross-sensitivity in patients allergic to sunflower seeds and daisy pollen; not recommended to people using immunosuppressants

Evening primrose oil: not recommended for use when a person is taking drugs that lower seizure threshold; should be monitored when a person is on antiplatelet drugs

Feverfew: when leaves are chewed, they may cause aphthous ulcers; should be monitored when a person is on antiplatelet drugs

Garlic: may cause gastrointestinal (GI) irritation and may not be recommended when a person is taking antihypertensives; should be monitored when a person is on antiplatelet drugs

Ginger: high doses cause GI discomfort; should be monitored when a person is on antiplatelet drugs

Ginkgo biloba: may cause GI discomfort and headache; should be monitored when a person is taking antiplatelet drugs

Ginseng: may cause breast tenderness, nervousness, excitation; should be monitored when a person is taking anticoagulant drugs

Grapeseed extract: should be monitored in patients on antiplatelet drugs

Guarana: possibly carcinogenic with long-term use; also may cause same symptoms as caused by caffeine, which it contains: restlessness, nervousness, excitement, insomnia, diuresis, GI disturbances, cardiac arrhythmias, fibrocystic breast disease, and tachycardia; may render benzodiazepines less effective, may lower lithium levels, and may increase blood pressure if used with decongestants

Kava kava: may cause GI discomfort, allergic reactions; may not be recommended when person is taking sedatives, antianxiety drugs, and antidepressants

Milk thistle: may cause allergic reaction

Peppermint: may cause skin rash, heart burn, muscle tremor

Saw palmetto: may cause headache, mild abdominal pain, nausea, dizziness

Soy: may interfere with absorption of supplemental thyroid hormones

Valerian: may cause drowsiness, headache, excitability, dizziness, cardiac disturbances; could have additive effect with other central nervous system depressants and should be monitored when a person is taking blood pressure medications

Additional herbs used as remedies:

Absinthe
Agrimony
Aloe vera
Angelica
Anise
Balm
Balm of Gilead
Basil
Bearberry
Betony
Bistort
Black elderberry
Black haw
Black poplar
Burdock
Centaury
Cloves
Dandelion
Elderberry (black)
Eucalyptus
Fennel
Gentian
Hawthorne
Hibiscus
Hops
Ivy
Juniper
Lady's mantle
Lavender
Lovage
Mallow
Marigold
Mexican tea
Milk thistle
Nettle
Orrisroot
Parsley
Peppermint
Poppy
Prickly lettuce
Rosemary
Sage
Senna
Thyme
Uva Ursa
Willow
Yarrow

(Chart continued on next page)

These herbs are believed to be toxic and potentially fatal, and therefore should be avoided:

American bittersweet, American holly, American yew, Baneberry, Belladonna, Black locust, Bloodroot, Blue flag, Bracken fern, Buckeye, Buttercup, Canada moonseed, Cedar (Northern white), Celandine, Chokecherry, Common nightshade, Corn cockle, Dogbane, Fern (Bracken), Flag (Blue), Foxglove, Heart-leaved four o'clock, Hellebore, Horsechestnut, Horse nettle, Jessamine (Yellow), Jimsonweed, Lambkill, Leatherwood, Lily of the Valley, Locust (Black), Lupine (Wild), Mayapple, Mistletoe, Moonseed (Canada), Mountain Laurel, Pasqueflower, Pink-root, Poison Hemlock, Pokeweed, Rhododendron, Skunk cabbage, Staggerbush, Strawberry bush, Tansy, Virgin's bower, Virginia creeper, Wahoo, Wormseed

Sources: Pharmacy Today, August 1999; Klepser T, Nisly N. Chaste tree berry for premenstrual syndrome. *Alternative Medicine Alert* 1999; 2:64-66; Doug Murray, PharmD, Director of Pharmacy and Clinical Services, Kershaw County Medical Center, Camden, SC; Medicinal Herbs Online (www.egregore.com/herb/herbindx.htm).

medication. To do so, they contact the FDA through its Web site at www.fda.gov/medwatch/how.htm or call (800) FDA-1088, or fax the information to (800) FDA-0178.

Lacking hard data about herb-drug interactions with antiretrovirals, clinicians should use common sense, pharmacy experts say.

When to avoid echinacea

For example, people with autoimmune disorders should avoid herbs such as echinacea, which is used to stimulate the immune system, say **Teresa Klepser**, PharmD, assistant professor and pharmacist at the University of Iowa College of Pharmacy in Iowa City, and **Marjorie Robinson**, PharmD, assistant professor for pharmacy at Nova Southeastern University in Ft. Lauderdale, FL.

Echinacea is not recommended because it could increase an HIV patient's viral load at the same time that it is stimulating immune system cells, Robinson explains.

"Anybody who has an autoimmune or immune disorder should not use echinacea, including echinacea teas," Klepser says. "Usually tea preparations are weaker, and whether they have that much effect is questionable, but to be on the safe side, you don't want their disease to be affected."

Because HIV patients sometimes have dual diagnoses, including diabetes, hypertension, and heart disease, there are other herbs they should avoid that might interact with medications used to treat these other conditions, Klepser notes.

For instance, when a patient is taking an anticoagulant, antiplatelet, or antihypertensive drug, patients should avoid the herbs ginkgo biloba, garlic, feverfew, and ginseng, she says.

Patients on diabetes medications should avoid herbs that lower blood sugar, such as ginseng, Klepser adds.

If an HIV patient is taking antidepressants or drugs for insomnia, then the patient should avoid herbs that may potentiate that effect, including kava kava and valerian.

The herbal remedy market was given a boost in 1994 when Congress passed the Dietary Supplement Health and Education Act of 1994 (DSHEA), which established a new category called dietary supplements. These are products that contain a vitamin, a mineral, an herb or botanical, an amino acid, or a dietary substance used to increase the total dietary intake. Extracts, concentrates, or combinations of these also are included under the definition of dietary supplement.

Essentially, DSHEA means the FDA cannot regulate herbal remedies to the extent that it regulates prescription and over-the-counter drugs, or even food items. For example, herbal supplements are permitted to make some claims about the product without offering proof in the form of clinical trials.

This underscores why clinicians should monitor patients' use of herbal remedies, experts say.

"If you have a certain drug therapy and then you add another drug, there are certain parameters you want to monitor to ensure outcome and potential for drug interactions," says **Donna Lee**, RPh, president of Natural Alternatives Inc. and the director of nutritional new product concepts for Banner Pharmacaps, both of Greensboro, NC.

"View herbs as drugs and follow the same guidelines as if you were adding or taking away a medication," Lee adds. "I see no difference in herbs or drugs except regulatory issues and misinformation that's sometimes made available."

Reference

1. Shilts R. *And the Band Played On*. New York: St. Martin's Press; 1987, p. 182. ■

Clinicians need to review what herbals patients take

Nonjudgmental, receptive approach is best

The discovery of a dangerous herb-drug interaction between St. John's Wort and indinavir highlights the need for more clinical data on herbal remedies, experts say.

"There are a lot of theoretical discussions about herb-drug interactions, but they have not been validated clinically," says **Mary L. Hardy**, MD, medical director of the Cedars-Sinai Integrative Medicine Medical Group in Los Angeles.

Clinicians should be aware that HIV patients might be taking other herbs that have the potential to affect their antiretroviral therapy adversely. Patients who have little hope for a cure via mainstream medicine are willing to turn to alternative treatments, says **Anna Garrett**, PharmD, a clinical pharmacist with High Point (NC) Regional Health System. "The thinking is that if there's anything out there that could help maintain health, herbal or otherwise, they're willing to try it," says Garrett, who has worked with HIV populations in the past.

People with HIV want to have some control over their disease, so they'll look into alternative medicine treatments, notes **Michael Cirigliano**, MD, an assistant professor of medicine at the University of Pennsylvania Medical Center in Eddystone.

"They feel empowered to research and treat themselves with agents they think might be of benefit, and that includes a lot of alternative, complementary medical treatments," Cirigliano says.

Clinicians at Nova Southeastern University in Ft. Lauderdale, FL, have documented a case of an HIV patient being treated with efavirenz who also was using St. John's Wort, which may have interacted poorly and contributed to the patient's feelings of anxiety, depression, and suicidal ideation.

"She said she felt like running down the street and screaming," recalls **Jason Villano**, PharmD, an infectious disease resident at Nova Southeastern University.

"We asked her if she had been doing anything different, had anything changed, and her answer was 'No,'" Villano says. "Then we asked her if she was taking anything over the counter, and she said, 'Yeah, St. John's Wort.'"

Clinicians asked her to stop taking the herbal, and by the next day the patient reported that she felt better, Villano says.

While this single case does not offer valid proof of an interaction between efavirenz, a nonnucleoside reverse transcriptase inhibitor, and St. John's Wort, it at least highlights how important it is for clinicians to monitor the herbal remedies their patients are taking, Villano says.

Villano suggests clinicians have patients undergo a sort of wash-out period by stopping the use of all herbs before starting antiretroviral therapy, and continuing it for a number of weeks until the clinician and patient are aware of all of the adverse effects from the antiretroviral drugs.

Then, if the patient still wants to take some herbal remedies, it's a good idea to have the patient take one at a time, while being monitored for signs of anything going wrong, such as viral load increases or symptoms of anxiety, Villano says.

Questions should be specific, direct

Clinicians need to ask patients specific and direct questions about herbal remedies, because patients rarely volunteer this kind of information, says **Marjorie Robinson**, PharmD, assistant professor for pharmacy at Nova Southeastern University.

"They don't think of herbal medications as drugs," Robinson says.

Robinson suggests clinicians use an herbal remedy checklist and ask patients these types of questions:

- Have you changed your diet in any way?
- Have you changed your antiretroviral dosage?
- Are you taking any over-the-counter drugs?
- Are you taking any vitamins, minerals, or herbal supplements, and if so, which ones are you taking?
- Are you drinking any herbal teas, and which ones are they?

Although it may seem redundant to ask patients about over-the-counter drugs and herbal remedies, it's important to ask both questions, says Klepser.

"Usually, I ask what are their prescription meds, what are their over-the-counter meds, and then I ask the third question of what are their dietary supplements, herbs, and vitamins," Klepser explains. "A lot of times patients will say they are not taking any meds, but then when you

Check out these herbal supplement resources

Although there still is too little clinical research into herbal remedies' attributes and drawbacks, a number of organizations and publishers recently have produced resource guides and books on these products.

Here is a brief listing of some of the resources available:

• ***Alternative Medicine Alert***, American Health Consultants, Atlanta. This monthly newsletter features articles about herbal remedies and other alternative medicine therapies. For more information, call (800) 688-2421. E-mail: customerservice@ahcpub.com. Web site: www.ahcpub.com. Address: P.O. Box 740059, Atlanta, GA 30374.

• **Herbal chart for health care professionals**, published in *Pharmacy Today*, August 1999, by the American Pharmaceutical Association. The chart, which costs $2 plus $4 for shipping and handling per order, can be obtained by calling (202) 429-7557. Address: American Pharmaceutical Association, 2215 Constitution Ave., N.W., Washington, DC 20037. E-mail: pt@mail.aphanet.org.

• ***Herbal Medicine: Expanded Commission E Monographs***, developed by the American Botanical Council, and edited by Mark Blumenthal, Alicia Goldberg, and Josef Brinckmann. This book costs $55 for non-members of the American Pharmaceutical Association and $42 for members. For more information, call APhA at (800) 878-0729. Fax: (802) 864-7626. Address: APhA Publications Sales, P.O. Box 571, Williston, VT 05495-0571.

• ***Integrative Medicine Access: Professional Reference to Conditions, Herbs & Supplements***, published by Integrative Medicine Communications. This is a subscription service with monographs provided in a loose-leaf binder. It costs $299 for non-members of APhA and $199 for members. For more information, call (800) 878-0729.

• ***Natural Medicines Comprehensive Database***, written by Jeff M. Jellin, PharmD, and published by Therapeutic Research Faculty, Stockton, CA. The second edition was published in 1999. The 1,164-page book costs $59.

• ***Natural Therapeutics Pocket Guide***, written by James B. LaValle, Daniel L. Krinsky, Ernest B. Hawkins, and Ross Pelton. The guide costs $40 for non-members of APhA and $32 for members. The guide will be available July 2000. For more information, call (800) 878-0729.

• ***1999 Physicians' Desk Reference for Nonprescription Drugs and Dietary Supplements***, published by Medical Economics Co., Five Paragon Drive, Montvale, NJ 07645. The 400-page book costs $48.95. For more information, call (800) 737-9206.

• ***Physicians' Desk Reference for Herbal Medicines***, published by Medical Economics Co., Five Paragon Drive, Montvale, NJ 07645. The first edition was published in December 1998. The book costs $59.95. For more information, call (800) 737-9206.

• ***Professional's Handbook of Complementary and Alternative Medicines***, written by Charles W. Fetrow, PhD, and Juan R. Avila, PhD, and published February 1999 by Springhouse (PA) Publishers. The 768-page book costs $39.95. ■

ask the third question, they say, 'Oh yes, I take about 20 of those.'"

After questioning patients, it's a good idea to pull out the herbal checklist and have them review that. The checklist should include both common names and official names for the herbs, Robinson says. Also, if a clinician's patient population includes people who do not speak English, the checklist should be translated into the appropriate language. **(See sample herbal checklist, p. 51.)**

"The whole point to the checklist is [that] it alerts patients to be better historians of what they're taking, and it makes them realize that herbal products are alternative drugs," Robinson says.

It might seem that the simplest action to take is to advise HIV patients to stay away from all herbal remedies while they are being treated with antiretrovirals. But this isn't a good policy because patients will find this to be too restrictive and judgmental, and possibly will just go on using the herbal remedies anyway, Klepser says.

"Health care practitioners have the perception that herbs are not as well proven as prescription medications, but if you come across like that, then patients won't confide in you," she adds.

Hardy recommends that clinicians treat HIV patients like partners, using a nonjudgmental questioning style and remaining open and receptive to what the patients tell them.

"Then if the clinician would like to recommend that a patient not take a particular product or not take a particular combination, the clinician should do so in a real respectful manner," Hardy says. "They should say something like, 'I know you are really trying to help yourself and with everything you've read about St. John's Wort, of course you think it would be great, but we have new data that shows this.'"

Villano suggests that the best approach is to let patients know that you are seeking information that will help improve their HIV treatment. When patients explain which herbs they have been taking, then the clinician can research how that herb works in the body and therefore determine whether it is advisable to take that herb along with the antiretroviral drugs. **(For more herb resources, see box, p. 54.)**

For example, Villano treated a woman who was on an antiretroviral regimen and who wanted to take an herb called cat's claw. Villano found that the herb would not be metabolized in the same way as the HIV drugs and would have a benign effect on her treatment, so he gave her the green light. "Even if what they want to take is a placebo, I don't like to say 'no' to something that might give them a boost in their quality of life," he says.

Villano monitored the woman after she began taking the herb, and she reported no signs or symptoms of changes.

So far, there is little research information available about herbal medications interacting with antiretroviral drugs, or with any drugs for that matter. The American Pharmaceutical Association of Washington, DC, last year published in its *Pharmacy Today* newsletter a chart listing 17 herbs and their potential adverse effects and/or drug interactions. But there are few studies available on the literally hundreds of herbs that have been used throughout the ages to treat various ailments, including more than 50 that are potentially fatal.

Within the next decade, many more studies of herbs will be conducted, and clinicians will have a great deal more hard data to review before making recommendations to patients.

"Now there is a renaissance of study and science looking at herbal medicine, which has not been done historically," Cirigliano says, referring to a recent influx of federal grant money to fund such research. ■

Special Coverage of the 7th Conference on Retroviruses and Opportunistic Infections

More potent, easier-to-use drugs are on the horizon

Studies tout durability of some PI combinations

Clinicians soon will hear a great deal more about new antiretroviral drugs, including new classes of drugs such as nucleotide reverse transcriptase inhibitors (RTI) and pyrophosphate reverse transcriptase inhibitors (PPRTI). Pharmaceutical companies also are focusing on making current treatments more potent, easier to administer, and durable for the long haul.

For example, at the 7th Conference on Retroviruses and Opportunistic Infections, held Jan. 30 - Feb. 2, 2000, in San Francisco, researchers presented an abstract on Triavir, a combination tablet formulation with three nucleoside reverse transcriptase inhibitors (NRTIs): abacavir, zidovudine (AZT), and lamivudine (3TC). The study found that the three separate drugs work as well when taken in one pill every 12 hours as when they're taken simultaneously as separate pills.[1]

In other research presented at the conference, investigators demonstrated the high potency and durability of the twice-daily combination of the nonnucleoside reverse transcriptase inhibitor (NNRTI) nevirapine when combined with AZT and 3TC.[2]

"The therapy is quite active in patients with greater than 100,000 viral copies, and even in a few folks with greater than 500,000 copies," says **Richard Pollard**, MD, an investigator for the study and professor of internal medicine, microbiology, immunology, and pathology at the University of Texas Medical Branch in Galveston. Boehringer Ingelheim Pharmaceuticals Inc. of Ridgefield, CT, which is part of Boehringer Ingelheim GmbH International of Ingelheim, Germany, sponsored the research and is the company that developed nevirapine.

The research showed that 45% of patients taking the triple-drug combination of nevirapine, zidovudine, and lamivudine achieved suppression of HIV below the limit of detection at one year. These were 171 antiretroviral-naive patients who were randomized to receive the nevirapine combination or a placebo plus zidovudine and

lamivudine. By contrast, 3% of the placebo plus AZT/3TC group achieved suppression to undetectable levels at 12 months.[2]

Nevirapine was developed as a twice-a-day drug, but many clinical studies have used it as a once-a-day drug, Pollard adds. "So the message is that it's a fairly easy drug to give, and it's very potent."

More than 1,000 HIV drug trials under way

While the retrovirus conference showcased a plethora of promising studies, clinicians will see many more in the next five years. There are more than 1,000 clinical trials under way involving drugs to treat HIV/AIDS patients. **(See related story on current clinical research, p. 57.)**

Adefovir dipivoxil, which is part of the new RTI class of antiretrovirals has been studied in 20 clinical trials and is being studied for the treatment of patients who are infected with both HIV and hepatitis B.

Tenofovir disoproxil fumarate, an acyclic nucleotide analogue that's similar to adefovir, is in phase III trials that will administer one dose daily vs. a placebo to patients who have plasma HIV-1 RNA levels between 400 and 10,000 copies/mL.

An in vitro study of a PPRTI drug was presented at the retroviruses conference by U.S. Department of Veterans Affairs researchers.

Laboratory tests show that two foscarnet (PFA) prodrugs, MB-PFA and EB-PFA, are highly active against a panel of drug-resistant HIV strains, including those resistant to NRTIs like zidovudine and lamivudine.

"The prodrugs act on the HIV reverse transcriptase at a different place than the NRTIs and the NNRTIs," says **Karl Hostetler**, MD, professor of medicine at the University of California - San Diego and a researcher at the U.S. Veterans Affairs Medical Center of San Diego in La Jolla.

If the drug succeeds in clinical trials, it could be an ideal salvage therapy because of its potency against drug-resistant virus, Hostetler says.

Hostetler and co-investigator **John W. Mellors**, MD, director of AIDS research at the VA's Pittsburgh Health Care System, have been working on this new class of drugs for more than 10 years.

The researchers took an old drug called phosphonoformate, which had weak activity against HIV, and found a way to increase its potency. "We had the idea that we could disguise phosphonoformate as a naturally occurring lipid, fat material, so the fat would help promote its entry into the cell," Hostetler says.

"We designed it so that every cell would have the ability to take this little molecule apart and release it within the cell interior," he adds. "And we believe that is how it works and why it shows 50 times greater activity in HIV-infected cells than the free phosphonoformate compound."

The drug will be easy to make, could be taken in pill or liquid form, and could be relatively cheap to manufacture because it has no expensive materials, Hostetler says.

VA funding dries up

Their research already has prompted clinicians to call them and ask if they are taking volunteers for clinical trials. But the researchers' main problem now is obtaining funding for clinical trials because the VA has not expressed any interest in funding further research, Hostetler says.

"If we had a backer right now and enough money, it'd be 18 months to two years before we'd start clinical trials," he says.

The protease inhibitor (PI) ABT-378 is one of the new drugs in the most advanced stages of development. Several studies about ABT-378, developed by Abbott Laboratories in Abbott Park, IL, were presented at the retroviruses conference.

Studies focused both on treatment of naive patients and on patients who already had failed PI therapy. "What we found was that patients who came into the study with significant test-tube resistance to ABT-378 — even up to 20-fold — responded equally well to ABT therapy as did the patients who came into the study with nonresistant virus in the test tube," says **Dale Kempf**, PhD, senior project leader of antiviral research at Abbott Laboratories' Pharmaceutical Products Division.

Kempf explains that ABT-378 works well clinically — even in patients who have PI resistance — because it has a high pharmacokinetic barrier that keeps the virus from replicating.

"There will come a point at which the virus becomes so resistant in the test tube that it's able to overcome the high dam put forth by ABT-378, so what we're doing now is studying other patients

who have an even more highly resistant virus to PIs," Kempf says.

The treatment-naive study looked at a regimen of ABT-378 with a low dose of ritonavir combined with stavudine (d4T) and 3TC. At 72 weeks, the combination proved potent, with a viral load below 400 copies / mL in 98% of patients on treatment and below 50 copies / mL in 96% of patients.[3]

"We saw a very impressive suppression of HIV RNA," says **Roy Gulick**, MD, MPH, assistant professor of medicine at Weill Medical College of Cornell University in New York. Gulick was a lead investigator on the study.

Patients on triple-drug therapy often will have trouble taking the drugs over time because they may be experiencing unpleasant side effects or they may find their regimen to be too complicated, Gulick notes. "So they miss doses and this leads to viral breakthrough."

But with the ABT-378 study, only one person out of the 100 enrolled dropped out because of side effects, he says.

Also, the combination proved to be more convenient to patients because the capsules only needed to be taken twice a day, once with breakfast and once with dinner, Gulick adds.

"On the pro side, the combination therapy with ABT-378 and ritonavir certainly looks to be a very active drug against the virus, providing impressive virologic activity and durability of effect," Gulick says.

Still, clinicians may side with the school of thought that it is better to start with a regimen that spares PIs, and the long-term side effects of PIs are only now just being described, he adds.

"The field is growing, and what we're really talking about now is treating people with antiretrovirals for years and years," Gulick says. "We want strong drugs that are well-tolerated over the long-term and easy to fit into people's lives."

Now that PIs have been available for almost five years, there are more studies with long-term data showing the durability of that class of antiretrovirals.

For instance, the PIs ritonavir and saquinavir showed sustained viral suppression after 144 weeks, which was the longest study on PI therapy.[4] About 85% of the 141 participants had undetectable HIV RNA levels during their three years of therapy, and 53 patients remained on the dual-PI therapy after three years.

"The study looks at people who were studied previously, had interrupted their treatment, and then went on to various doses of saquinavir and ritonavir," explains **William Cameron**, MD, lead investigator and professor of medicine at the University of Ottawa and Ottawa Hospital in Ottawa, Canada. The study was sponsored by Abbott Laboratories, manufacturer of ritonavir (Norvir).

"What the analysis means to me is that the majority of patients responded to ritonavir and saquinavir alone without any of the nucleoside drugs," Cameron adds.

References

1. Yuen G, et al. The bioequivalence of a fixed dose triple-NRTI combination tablet containing abacavir, lamivudine, and zidovudine. Abstract 98. Presented at the 7th Conference on Retroviruses and Opportunistic Infections. San Francisco; Jan. 30-Feb. 2, 2000.

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3. Gulick R, King M, Brun S, et al. ABT-378 / ritonavir (ABT-378 / r) in antiretroviral-naïve HIV+ patients: 72 weeks. Presented at the 7th Conference on Retroviruses and Opportunistic Infections. San Francisco; Jan. 30-Feb. 2, 2000.

4. Cameron DW, Xu Y, Rode R, et al. Three-year follow-up and conditional outcomes survival analysis of ritonavir plus saquinavir therapy in HIV infection. Presented at the 7th Conference on Retroviruses and Opportunistic Infections. San Francisco; Jan. 30-Feb. 2, 2000. ■

A guide to experimental HIV drugs in clinical trials

A quick look at the experimental HIV drugs involved in clinical trials will reassure any clinician that there will be new and more potent agents fighting the virus for decades to come. *AIDS Alert* offers this guide to some of the new antiretroviral drugs that are involved in Phase I, II, or III clinical trials, including many that are still recruiting patients.

• **Capravirine:** A nonnucleoside reverse transcriptase inhibitor (NNRTI) first called AG1549 by

Agouron Pharmaceuticals of La Jolla, CA, this drug is being studied in several trials, including a Phase II, single-blind, randomized, placebo-controlled study in combination with nelfinavir. That study involves patients who have begun to fail an antiretroviral combination of NNRTIs and nucleoside reverse transcriptase inhibitors (NRTIs).

Another study will judge the effectiveness of the drug in a combination that includes nelfinavir plus a combination table containing zidovudine and lamivudine.

• **Dextrin 2-sulfate:** Sponsored by Steinhart Medical Associates of Miami, this Phase I study will look at the effectiveness of dextrin 2-sulfate in advanced AIDS patients who have failed conventional antiretroviral treatment. Patients will have a catheter placed in their abdominal area through which the drug will be administered three times a week for eight weeks.

• **BMS-232632:** Bristol-Myers Squibb of Plainsboro, NJ, is sponsoring this study on the safety and effectiveness of a new protease inhibitor. Patients are assigned randomly to a group that receives BMS-232632 plus saquinavir and two other antiretrovirals, a second group that receives a higher dose of the experimental PI plus saquinavir and two other antiretrovirals, and a third group that receives ritonavir plus saquinavir plus two other antiretrovirals. Participants are those who have been on an anti-HIV combination that includes a PI or NNRTI and they have begun to experience an increase in viral load.

• **Interleukin-2:** Sponsored by Chiron Corp. of Emeryville, CA, the study is looking at the effectiveness of giving HIV patients L2-7001, a type of interleukin-2, plus antiretroviral therapy. Interleukin-2 is produced by the body's white blood cells and helps the body fight infection. The Phase I trial will assess safety, as well as whether the drug will boost HIV patients' immune systems.

• **HE2000:** This experimental drug is an anti-HIV hormone that should make it more difficult for HIV to live in cells. The Phase I and Phase II open label, dose-response study, sponsored by Hollis-Eden Pharmaceuticals of San Diego, will assess the safety and effectiveness of the drug when administered to HIV-infected patients on salvage therapy.

• **Tenofovir disoproxil fumerate:** Sponsored by Gilead Sciences Inc. of Foster City, CA, the Phase III, open-label trial will study the safety and effectiveness of the drug when given in combination of other antiretrovirals. Participants have a viral load of 10,000 copies / mL or greater and have had an opportunistic infection within 90 days of the study entry. A second Phase III trial will evaluate people who have between 400 and 10,000 copies / mL when they are given one active dose of tenofovir DF daily vs. a placebo, when added to stable antiretroviral therapy. That study is a double-blind, randomized study.

• **WF10:** Sponsored by OXO Chemie of South San Francisco, CA, the study will evaluate the safety and effectiveness of this new drug among patients who have a CD4 cell count of less than 50 cells / mm^3 and who have received antiretroviral drugs in the past. The drug will be administered intravenously. A macrophage regulator, WF10 modifies the function of the monocyte / macrophage system by stimulating phagocytosis in macrophages and oxidative burst in monocytes. It is thought to enhance the immune function in late-stage HIV infection.

• **L-756423:** Sponsored by Merck & Co. of Whitehouse Station, NJ, the Phase II trial is examining the effectiveness of a new protease inhibitor when combined with indinavir and two other anti-HIV drugs in patients who have failed an indinavir-containing regimen. It's an open-label pilot study.

• **MKC-442:** Triangle Pharmaceuticals of Durham, NC, is sponsoring the Phase II and III study of the virologic efficacy, short-term safety, and tolerability of this new antiretroviral when it is offered in triple-drug combination to patients who previously were treated with NRTIs and PIs but are naive to NNRTIs.

• **Zintevir:** Sponsored by Aronex Pharmaceuticals of The Woodlands, TX, this study focuses on a drug from a new class of drugs — integrase inhibitors — that block the protein integrase, which HIV uses to infect a cell. Integrase inhibitors potentially could stop HIV replication. The Phase I and II trials gives zintevir to patients who have CD4 cell counts of greater than 200 cells / mm^3 and have a viral load of greater than 4,000 copies / mL. They receive doses of the drug for 14 days.

• **PMPA Prodrug:** Gilead Sciences Inc. of Foster City, CA, has sponsored a Phase II study of the new anti-HIV drug to evaluate the drug's effectiveness and side effects when it's added to an antiretroviral combination. Patients have viral

loads of 400-50,000 copies / mL and have been taking a triple-drug regimen for at least eight weeks prior to the study.

• **Fozivudine Tidoxil:** This new antiretroviral drug has been studied for adverse events, tolerability, and anti-viral activity over a four-week period. Boehringer Mannheim Corp. of Gaithersburg, MD, sponsored the study. ■

Free HIV test entitles you to one movie pass

Los Angeles clinic's model to be tested elsewhere

As any restaurant owner will tell you, the best way to increase business is through word of mouth. Friends tell friends to check out a place, and this helps the business grow in popularity. Using the same philosophy, a Los Angeles clinic attracts new patients who are at risk for HIV infection and have never been tested.

Called the "Bring in a Friend" program, the model works so well that it has attracted interest from drug companies that may set up similar programs in other cities, says **Wilbert C. Jordan**, MD, director of the OASIS Clinic and AIDS program at King Drew Medical Center in Los Angeles.

Jordan came up with the idea after talking with a patient who was a drug user, who pointed out that none of the people waiting in line to be tested for HIV were the people he shoots up with.

"I said, 'Can you bring them in?'" Jordan recalls. "He said, 'Yeah, for $10,' and I said, 'OK, I can't give you $10, but I'll give you a pass to the movies,' and so he brought them in."

Following up on that small success, Jordan and colleagues at the OASIS Clinic began to ask other HIV patients to bring in their friends to be tested in exchange for movie passes.

"We had one patient bring in 22 people, and 15 were positive, so we got high numbers of positives," Jordan says.

The program's method of attracting people who are at risk for HIV appears to be highly successful. Of people who came to be tested through the friend referral program, 48% were positive, Jordan says. This compares with a positive rate of 1.5% in the Los Angeles County's program in which individuals can come in for anonymous, confidential testing.

Jordan presented data from a study of the program at the 37th Annual Meeting of the Infectious Diseases Society of America, held in Philadelphia in November 1999.

Jordan asked 31 HIV-positive patients at the OASIS Clinic to bring people who might be at risk for HIV in to the clinic for free testing and counseling. Patients brought in 79 people, and 77 stayed for the testing. Thirty-seven of those who were tested were HIV-positive.

For 66 of the 77 people, this was their first HIV test. The 11 people who had been previously

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tested were still HIV-negative. Of the 37 HIV-positive patients, 35 have begun antiretroviral therapy. Three of the 37 patients were female; 24 were men; and 10 were transgender, meaning they were men who were living as women. Most of the patients were African-American or Hispanic, and most of the men reported having sex with men.

The OASIS Clinic serves a population that is mainly African-American and Hispanic, and the friend referral approach works well with people in these communities, Jordan says.

"There's a lot of anxiety in the gay community and gay black community about names reporting," he explains. So at-risk minorities are more likely to trust a friend when told to come in for a confidential HIV test.

"I'm just amazed at how much better and more cooperative people are when they come in with someone to be tested," Jordan says.

Also, the HIV patients who make the referrals often are hanging out in the places where at-risk people might be, including bath houses, parks, shooting galleries, and sex clubs. They also know who has just been released from jail and may have become infected while behind bars, Jordan says.

The program's referral method also gets around the problem of finding men who have sex with men but don't identify themselves as being gay or bisexual. Typical methods for finding at-risk gay men would target gay hang-outs. But some of the men who engage in gay behavior either would ignore messages aimed at these groups or may not visit these places. Still, they may have gay friends who know that they are at risk and need to be tested for HIV, and they might follow their friends' lead on being tested.

Another benefit of the program is that Jordan has observed that the people who become HIV patients after being referred by a friend for testing are more compliant patients. "They see that their friends who bring them in are relatively healthy and are doing well from treatment," he says.

About 95% of the referrals sought treatment within a week or two of finding out they're positive, and 80% of them stayed with the OASIS Clinic, Jordan says.

"I was not expecting that to be a benefit, but it's a big benefit," he adds. "If you've been kind of wishy-washy about treatment and then you bring in a friend, then you both will do better and be more compliant."

The program's only expense is the movie tickets. The person who brings in a friend is given a movie pass, and the friend is given a movie pass. Drug companies have paid for the passes.

"I tell drug reps that rather than bringing us food, bring us movie passes, and they do that," Jordan says. ■

CE objectives

After reading this issue of *AIDS Alert*, CE participants should be able to:

- identify the particular clinical, legal, or scientific issues related to AIDS patient care;
- describe how those issues affect nurses, physicians, hospitals, clinics, or the health care industry in general;
- cite practical solutions to the problems associated with those issues, based on overall expert guidelines from the Centers for Disease Control and Prevention or other authorities and / or based on independent recommendations from specific clinicians at individual institutions. ■

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HIV/AIDS response differs among Latin American countries

Some nations offer antiretrovirals; others cannot afford drug treatments

While the HIV epidemic has not caused as much devastation south of the U.S. border as it has in other regions of the world, it still taxes financial and health care resources among many Latin American nations, some of which have spent hundreds of millions of dollars treating those infected.

Plus, UNAIDS of Geneva, Switzerland, reports that the epidemic is picking up speed, particularly in certain southern nations, Central America, and the Caribbean. **(See story on HIV in the Caribbean, p. 3.)**

An estimated 1.3 million people in Latin America have HIV, and there have been more than 520,000 deaths in the region from AIDS, according to statistics from UNAIDS.

The adult HIV prevalence rate in Latin America is 0.57%, which is nearly identical to the prevalence rate in North America. Also in both regions, about 20% of HIV-positive adults are women and the chief mode of transmission is men who have sex with men, followed by injection drug use and heterosexual sex.

But the epidemic's trends differ greatly among Latin American nations. For example, in Bolivia, the disease hasn't reached epidemic proportions, with little more than 300 AIDS cases. In this nation, HIV spreads chiefly through heterosexual contact, and Bolivian officials say the rate of infection is equal between men and women, says **Adriana F. Gómez Sagüéz**, advisor to UNAIDS for the Andean Region. She works in Lima, Peru.

Surveillance numbers cannot accurately reflect the epidemic's spread in Ecuador, but UNAIDS officials say the disease also is chiefly a heterosexual problem in that nation, Gómez Sagüéz says.

"Economics and the political situation of this country make it very difficult to keep the surveillance work up to date," she adds.

Peru, which has more than 10,000 AIDS cases, has three times as many infected men as women, and the chief mode of transmission there is through homosexual contact.

Brazil, the largest Latin American country, has more than 530,000 HIV cases, which are believed to be chiefly due to heterosexual transmission. A recent Brazil health ministry study showed that more than three-quarters of the population had not used a condom during the previous 12 months, and nearly half of men and 32% of women had sex before reaching age 15.

In some southern nations, injection drug use plays a big role in HIV's spread. For instance, in Argentina, which has more than 16,000 AIDS cases, the number of people infected with HIV via drug use is nearly 40%. In Uruguay, drug use accounts for about 27% of AIDS cases, while heterosexual transmission accounts for about 40% of cases, says **Mercedes Weissenbacher**, MD, who works with HIV patients in Buenos Aires, Argentina, and who is the former inter-country program advisor for the Southern cone in South America.

Heterosexual and homosexual transmission are nearly identical in Argentina, with each accounting for 25% of cases, she adds.

"But in Chile, there mostly are homosexual cases, with more than 70% of HIV transmitted homosexually," Weissenbacher says.

Paraguay also has many cases due to men who have sex with men, with about 50%.

Prevention and treatment programs vary widely in the region. Some countries, such as Brazil, Argentina, and Chile, provide antiretroviral medications to HIV patients. Other, poorer nations, including Ecuador, have no funds for any antiretroviral drugs or for medications to treat opportunistic infections.

"In Bolivia, they provide some medications for people who are infected and who are covered by a

Estimated Adult and Child Deaths due to HIV/AIDS from the Beginning of the Epidemic through December 1999

North America: 450,000
Caribbean: 160,000
Latin America: 520,000

Western Europe: 210,000
North Africa / Middle East: 70,000
Sub-Saharan Africa: 13.7 million

Eastern Europe / Central Asia: 17,000
East Asia / Pacific: 40,000
South / Southeast Asia: 1.1 million
Australia / New Zealand: 8,000

Total: 16.3 million

Adults and Children Estimated to Have HIV/AIDS as of December 1999

North America: 920,000
Caribbean: 360,000
Latin America: 1.3 million

Western Europe: 520,000
North Africa / Middle East: 220,000
Sub-Saharan Africa: 23.3 million

Eastern Europe / Central Asia: 360,000
East Asia / Pacific: 530,000
South / Southeast Asia: 6 million
Australia / New Zealand: 12,000

Total: 33.6 million

Source: UNAIDS and World Health Organization, Geneva.

social security plan," Gómez Sagüéz says. "In Peru, they only have medication for pregnant women to cut down the mother-to-child transmission."

On the other hand, Argentina and Uruguay each provide antiretrovirals to all people who test positive for HIV. They each receive at least three antiretroviral drugs, Weissenbacher says.

This has led to a decline of more than 40% in the number of new AIDS cases reported each year in Argentina.

Brazil spent $300 million in 1999 providing antiretroviral drugs to about 75,000 people with HIV. The Brazilian government estimates that this program has saved more than $100 million in hospital admission and treatment costs.

Paraguay had been paying for three antiretroviral drugs for each person with HIV, but due to economic constraints, the government had to cut back in 1999 to providing two drugs per person.

More problems arise in the area of prevention, testing, and counseling. Social barriers might be as big an issue as funding in some nations.

While Argentina does very well with drug assistance, the nation fares poorly in the area of prevention, Weissenbacher says.

"For example, if you ask me, prevention among injecting drug users is very low, and for men who have sex with men it is very low," she adds.

Prevention efforts are beginning to pick up, however. "I think now things are changing," Weissenbacher says. "Not very much, but some actors, movie stars, and football players are doing short TV ads about HIV prevention."

This is a notable change, considering that five years ago it was nearly impossible for anyone to mention condoms in Argentina, she adds.

The Catholic Church has played a large role in discouraging any prevention education for school children that includes discussion of condoms, Weissenbacher says.

"There are many private Catholic schools, and we were working with them on programs that talk about sexual education, drug use, and prevention of HIV, without discussing condoms," Weissenbacher explains.

Also, UNAIDS has sponsored a pilot project on HIV prevention through risk reduction among injection drug users in four countries. But while the program appears to be working, it can only reach a handful of the targeted drug users, and a broader-based government effort is needed, Weissenbacher says.

In Chile, HIV experts work with schools and through peer counseling with men who have sex with men on HIV prevention. Uruguay has many good TV prevention campaigns, and the nation provides prevention education in schools. Last year, the nation began preparing programs for men who have sex with men and for injection drug users.

In Paraguay, there are programs that work with female sex workers on how to use the female condom, and condoms were distributed for free in one project. "There has been a high acceptance of the condom by female prostitutes and their clients," Weissenbacher says.

Farther north, Bolivia is providing prevention education to sex workers, and in Peru, HIV experts are working with young people through peer education, Gómez Sagüéz says.

An international Catholic Church organization, called International CARITAS, has an agreement at the global level with UNAIDS to work in the prevention of HIV / AIDS. The program reinforces sexual responsibility and abstinence, and obviously, no condoms promotion program is planned, Gómez Sagüéz says. "You can't expect the Catholic Church to hand out condoms."

Instead, the group discusses responsibility and how HIV is transmitted, and promotes abstinence until marriage.

Prevention programs are limited chiefly because of economic difficulties, Gómez Sagüéz says. "The poor countries are not getting everything the rich countries are, which is not only information, but resources, medications, treatments, and access." ■

Growing rate of HIV/AIDS gets little notice on islands

As tourism thrives in the Caribbean, so does HIV

The HIV / AIDS epidemic continues to exact a heavy price among the Caribbean islands that are chiefly known for cruise ship ports and vacation beach getaways made popular by affluent Americans.

Ironically, it's precisely because of these islands' popularity among tourists, particularly those engaging in sexual tourism, that the epidemic has penetrated the islands to the extent that it has, an HIV expert in the region says.

In Haiti, where HIV still is spreading out of control, the epidemic was brought to the island by homosexual tourists some two decades ago, says **Peggy McEvoy**, DrPH, a team leader for UNAIDS Caribbean in Port of Spain, Trinidad and Tobago.

The theory that tourism is largely responsible for the high prevalence rate would seem to be supported by Cuba's HIV statistics. That one Caribbean nation, which has not been a favored or easily accessible tourist spot since Fidel Castro's revolution, has an HIV prevalence rate of 0.02%. This is the only Caribbean country where virtually every case of HIV is counted. This compares to the Caribbean's overall HIV / AIDS prevalence rate of 1.96% of all adults, which is second only to sub-Saharan Africa.

Other factors contributing to the Caribbean's high HIV infection rate are:

- societal pressures for homosexuals to have heterosexual relationships;
- authorities continuing to deny that sexual activity is going on in prisons;
- commercial sex work among school girls and housewives;
- poor partner communication on sexual needs and concerns;
- women's emotional and socioeconomic dependence on men;
- substance abuse of alcohol and drugs.

While official estimates suggest 360,000 people in the Caribbean territories have HIV / AIDS, experts say that number is too conservative.

"When we look at a mathematical modeling based on other countries, it has to be well over half a million people with HIV," McEvoy says.

Haiti has the worst problem in the region, and it's estimated that there will be between 240,000 and 330,000 Haitians with HIV by the end of 2000, McEvoy says.

Here are other estimates:

- In Haiti, 12% of the urban population and 5% of the rural population have HIV / AIDS.
- An estimated 150,000 people in the Dominican Republic have HIV / AIDS.
- A sentinel surveillance in the Dominican Republic found an HIV / AIDS incidence rate among pregnant women in one town to be 8% positive.
- In Guyana, 13% of people seeking treatment for sexually transmitted diseases were found to be HIV-infected, and HIV prevalence was 3.2% among blood donors in that country.
- Urban sex workers in Guyana, surveyed in 1997, showed a 46% infection rate.
- Nearly 40% of hospital admissions in Kingston General Hospital of St. Vincent and the Grenadines were due to HIV / AIDS-related conditions.
- In Trinidad and Tobago, there has been a drain on manpower caused by the epidemic, and this is expected to reach 20% within five years.

The Caribbean, while identified as one group, consists of 24 countries with four different national languages: Spanish, French, Dutch, and English. What most of the islands have in common is a general lack of health care resources and prevalent poverty, McEvoy says.

Except for Cuba, the Caribbean has the same problem as Southern Africa — no health care infrastructure. There is too little money for medications to treat opportunistic infections or for antiretroviral drugs to treat HIV.

Also, the Caribbean governments have not put resources into stopping mother-to-child HIV transmission, which now accounts for 6% of reported AIDS cases in the Caribbean. Pilot programs, funded through UNAIDS and UNICEF, have helped with treatments to prevent vertical transmission, but these efforts are not enough to stop the transmission, McEvoy says.

"Ultimately the governments have to take over, and there's a lot involved, because it's not just giving one shot or some pills," she adds. "They have to give counseling and teach mothers not to breast-feed."

Moreover, the disease's stigma is a major problem.

"People living with AIDS are so stigmatized that in some countries they're not allowed in the health system," McEvoy says.

Like Africa, the Caribbean has a problem with orphans due to the epidemic. An estimated 83,000 children under the age of 15 are without families, and there are expected to be as many as 25,000 orphans in Haiti by the end of 2000.

Caribbean children also are at risk for becoming infected with HIV at very young ages. A recent Caribbean adolescent survey, conducted in English-speaking countries, found that of 8,096 school children surveyed, 42% had engaged in sex before the age of 10. Another 20% had sex before age 12. Broken down by gender, it was more than two boys for every girl who first had intercourse at a very young age.

Both girls and boys are at risk for having sex in exchange for money to pay for schoolbooks and living necessities, McEvoy says.

Some statistics show that seven out of eight youths ages 10 to 19 who are infected with HIV are female.

"It's driven by economics," McEvoy says. "Young school girls need books and have sex with men, and there is a lot of rape, which is politely called date rape in the States."

Another problem is that social taboos — and, in some of the nations, religious mandates — prevent sexual education in schools or the distribution of condoms, she adds.

Nonetheless, there are a few good prevention programs under way, McEvoy says, including the following:

• Jamaica has formed national AIDS councils at every parish level. These councils meet regularly and work with church groups, rotary groups, in schools, and with street theater groups on how to prevent HIV infection.

• In Haiti, there is work being done with adolescent clinics that teach young people about reproductive health.

• Both the Bahamas and Jamaica offer counseling services, and counseling is offered in the Dominican Republic through health clinics.

• The Dominican Republic has a public health care program that tests female sex workers each month, providing them with medications for sexually transmitted diseases.

"But everywhere across the board there is a need for training and counseling and confidential testing, especially in smaller countries," McEvoy says. ■