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New classes of HIV inhibitors raise promise for future treatments

HIV experts discuss the most intriguing research

HIV researchers acknowledge it's difficult to stay ahead of a virus that can remain deadly after major mutations, but they're hopeful a variety of new antiretroviral strategies will improve the long-term outlook for HIV patients.

"On the close horizon are new classes of inhibitors of HIV," says **Warner C. Greene**, MD, PhD, director of the Gladstone Institute of Virology and Immunology and professor of medicine and microbiology and immunology at the University of California, San Francisco.

Some potential new treatments target the very early stages of HIV's interaction with CD4 cells. Other possibilities include the study of strengthening the body's own antiviral fighter APOBEC 3G, which is deactivated by an HIV protein. Also, investigators have begun to look into theories regarding the immune system's complicity in producing AIDS and how this knowledge might lead to new avenues of treatment.

"The drugs on the market are effective, but the virus becomes resistant over time, so it's important to have multiple drugs," says **Peter Prevelige**, PhD, professor of microbiology at the University of Alabama, Birmingham.

"The more targets one has, the better one can deal with inevitable resistance, so a lot of interest in the pharmaceutical and research community is to identify new targets, and the most recent are the fusion inhibitors," he says.

Greene and other researchers explain what some

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of these new treatment possibilities are and how they might work:

- **CCR5 inhibitors.**

One such new class being investigated is the CCR5 antagonist, which appears to have a very good response in some clinical trials, Greene says.

Discovered in 1996, the CCR5 and CXCR4 chemokine coreceptors for HIV were thought to hold promise as a target for treatment when it was found that 1% of Caucasians lack cell surface expression of CCR5, which in turn made them highly resistant to HIV infection.[1]

However, investigators have feared that a CCR5 receptor inhibitor, which is designed to produce the same effect that was found in nature in that small population, may cause the virus to shift to using the CXCR4 receptor, Greene notes.

"And when viruses shift to that, they become more pathogenic — there are a lot more CXCR4 target cells," he adds.

Fortunately, early clinical trials suggest this shift is not occurring, so a CCR5 inhibitor may prove successful on its own, Greene says.

"CCR5 inhibitors are deep into clinical trials and showing great effectiveness," he adds, predicting that a CCR5 inhibitor drug might make it to market within the next two years.

- **Attachment inhibitors.**

Another new area of study involves attachment inhibitors, which are much further behind in the pipeline than CCR5 inhibitors, Greene explains.

For example, an attachment inhibitor might block the insertion of CD4 residues into the gp120 pocket, disrupting the high-affinity interaction of the two proteins and, therefore, inhibiting HIV.[1]

"The attachment inhibitors haven't generated as much interest," Greene notes. "They're lagging a little behind the CCR5 antagonists, but it'd be nice to be able to use both of those drugs."

- **Fusion inhibitors.**

"These are the first of a class of drugs looking at the entry of the virus," says **William Powderly**, MD, professor of medicine and the head of the department of medicine at the University College Dublin (Ireland).

"There are a lot of drugs being developed in this class, and they offer potential for not only usefulness in patients who are resistant to existing drugs, but obviously in the future, the option to be a first-line therapy," he says. "The current infusion inhibitor is not one that would be offered to people as a first-line therapy."

Fusion inhibitors attend to the third part of the process in which HIV binds to CD4 cells, Greene says. Through a change, the virus fuses to target cells, and the fusion facilitates the virus's ability to microinject its contents into the cytoplasm of the host cell, he explains.

"That fusion process is mediated by a protein called gp41," Greene adds.

T20 peptide inhibitor of gp41 Env-mediated fusion has been approved by the Food and Drug Administration (FDA) for treatment of HIV. Since the drug only can be administered through subcutaneous injection, it's not widely used, he says.

Effective, just not convenient

"It's not very convenient, but it's effective," Greene says. "What I'd like to see are small molecules that could be engineered into drugs and taken by mouth and would do the same thing, but so far none have been identified."

This is an area that needs increased research emphasis, he notes.

"With the attachment inhibitors, the chemokine receptor antagonist and the fusion inhibitors, in essence, you have a new triple drug cocktail," Greene says. "All of these are blocking the earliest sequential steps in the viral life cycle as it tries to get into the cell in the first place — it's pretty exciting that this could be done."

- **Assembly inhibitors.**

"Generally, people are interested in coming up with compounds that inhibit virus assembly," says **Andrew H. Kaplan**, MD, an associate professor of medicine at the University of North Carolina, Chapel Hill.

"That's an area that hasn't been aggressively pursued," he notes. "We're talking about things that would disrupt the process of virus assembly, and those aren't near clinical use, but people are thinking about those questions." **(See story on assembly inhibitors, p. 124.)**

- **Integrase inhibitors.**

Although the development of integrase inhibitors has proven more difficult than expected, there has been progress, Greene says.

After the virus fuses and undergoes reverse transcription, which is where a lot of the inhibitors of the drugs pass on the reverse transcriptase, the virus makes its double-stranded DNA version of the single-stranded RNA, he explains.

This is integrated into the nucleus and then it integrates into the host chromosome, establishing what is called the HIV pro-virus, Greene adds.

"Then there's a viral enzyme called integrase which mediates that reaction," he says.

Investigators have spent a long time looking for integrase inhibitors, which is the third enzyme target of HIV: reverse transcriptase, protease, and integrase, Greene says.

Finally, some pharmaceutical companies have developed compounds that show promise, although there may be some toxicity issues. "So the integrase inhibitors are much further behind, but there is progress being made there." he adds.

- **APOBEC 3G.**

"Most HIV biologists would regard APOBEC-3G as the single most exciting drug target since the discovery of chemokine receptors," Greene says.

"So this is really hot in HIV molecular biology now," he adds. "We're searching for small molecules even as we speak."

Still, it will be a long time before this early investigation leads to an HIV medication, Greene notes. APOBEC 3G is a very potent anti-HIV factor that already exists within the human body, he says. The reason APOBEC 3G has not prevented the AIDS epidemic is because HIV uses its protein called viral infectivity factor (VIF) to target APOBEC 3G and get rid of it, Greene explains.

"VIF binds to APOBEC 3G and targets its antiviral enzyme for destruction," he adds. "That raises the question of whether we could come up with small molecules that interfere with VIF binding to APOBEC 3G." Investigators now are exploring this possibility, Greene says.

- **Immune system.**

The HIV field is experiencing an emerging new thought about how HIV kills t-cells, he says.

"It turns out that most of the CD4 t-cells that are dying in HIV infection are not the cells that actually are infected with HIV, but are bystander cells," Greene explains. "So this has led to the notion that, in fact, a lot of the cell death, and therefore, the disease, is caused by immune response against HIV."

This new concept in HIV biology could lead to novel new treatments, if it proves to be true as investigators further study the idea.

"It sounds strange, but maybe what you really want to do is to somehow convince the immune system to ignore HIV, to allow it to kill a few CD4 t-cells because the body can quickly replace those," Greene notes. "But perhaps the vigorous immune response against HIV — this activation — is really what's driving the pathogenesis.

" A lot of research work will need to be done to secure the hypothesis, he notes.

"The mechanism by which t-cells are chronically destroyed over time in HIV infection still is unclear," Powderly continues. "It may be part of an accelerated destruction of t-cells that ordinarily goes on, and that's mediated by the immune reaction or by the virus's reaction to being infected."

However, this debate is a straw man in terms of the epidemic because what drives the process is HIV replication, he adds.

"If you control HIV replication, you get t-cell recovery and recovery of the immune system, and it's the virus that's responsible for the process," Powderly says. "It's the mechanism by which that happens that still is controversial and unclear."

Reference

1. Greene WC. The brightening future of HIV therapeutics. *Nature Immunology* 2004; 5(9):867-871. ■

Assembly inhibitors offer hope for future treatment

Researchers explain their work in this area

Some very early research into a nontraditional target holds promise for a new line of defense against HIV in decades to come. New compounds that are tentatively being called maturation or assembly inhibitors provide a very early target in HIV's activity within the body, researchers say.

Protease inhibitors block the cleavage and have been extremely successful therapeutically, says **Peter Prevelige**, PhD, professor of microbiology at the University of Alabama, Birmingham.

"But data suggest that you need both cleavage and rearrangement, and so another target is blocking the rearrangement," he says.

"In order to do that, you need to know what the action is between subunits in the rearranged, mature form, and that's been difficult to do because viruses are not amenable to traditional, structural biology techniques, such as crystography and electron microscopy and imaging construction." Prevelige and co-investigators have developed a technique called mass spectrometry to identify those interfaces, Prevelige says.

"And we identified an interface formed from immature virus to mature virus, and that's a

potential drug target," he adds. "The category of compounds would be something like maturation inhibitors or assembly inhibitors."

To beat the virus, researchers need to continually identify new targets, Prevelige notes.

"The idea behind the new potential new class of assembly inhibitors is this: Proteins in the virus are translated into a long string of proteins linked together and HIV's enzyme called the protease cuts this precursor protein into an individual mature protein, which is then liberated," says **Andrew H. Kaplan**, MD, an associate professor of medicine at the University of North Carolina, Chapel Hill.

The process of the protease becoming active and cleaving happens as the virus assembles, he adds. "Most of the proteins that make up the core of the particle are translated, made, and part of the precursor," Kaplan explains.

The cells are infected and taken over as a virus factory, and then a piece of the virus assembles at the membrane and buds out from the surface of the cell, which is the process of viral assembly, he says.

"If the protease does not do this job, then the virus particles are produced from infected cells, but these are not infectious, and that's the basis of protease inhibitors," Kaplan adds. "The protease itself is embedded within this precursor, so one of the earliest steps is that the protease embedded within the precursor needs to become activated, and once it becomes activated, it can make these cleavages or cuts as the precursor liberates the mature protein."

Two of the precursors need to come together for the protease region to find itself and become active, he points out. "Now, almost all of the work on protease has been on the mature protease after it has become liberated from the precursor," Kaplan says. "We study activity within the precursor because this activity is a cascade."

Since the process is a cascade, anything that can be done to interrupt an early step in the cascade will have its effect magnified throughout the whole process of the protease doing its cleaving, he explains.

"If you interrupt it early, then you can prevent that exponential increase in protease activity that is required," Kaplan says.

The work Kaplan and a few others are doing has focused on finding ways to disrupt those early interactions, particularly looking at ways to interrupt the interaction of the two precursors, which would in turn disrupt protease interaction and kill the virus.

"We have designed a high throughput assay to look at large collections of different chemicals called compounds," Kaplan says. "These large collections are called libraries of compounds, and you can take a large library of maybe 100,000 and look at every single compound to see if it has an activity you're interested in."

Researchers already have generated large libraries of compounds, but the next big challenge is to find a way to screen these compounds quickly, he says. "So there's a lot of interest right now in developing an assay or test that can very rapidly screen 100,000 compounds to find ones that have some promise," Kaplan explains.

"What we've done is we have applied for patent protection for the development of an assay that determines whether or not two precursors can come together effectively or not and activate the protease," he adds. With this system, investigators can screen thousands of compounds a day and quickly learn whether the protease activates, he points out.

So far, Kaplan's and co-investigator's research indicates that it requires high levels of HIV-1 protease inhibitors to inhibit the earliest steps of precursor processing.[1]

Reference

1. Kaplan AH, Pettit SC, Everitt L, et al. Inhibition of the HIV-1 protease within the GagPol precursor: implications for precursor processing, protease activation, and treatment. Presented at the IDSA conference. Boston; September/October 2004. Poster: 740. ■

Study finds depression higher among inpatients

Motor functioning problems also may play role

When New Orleans investigators analyzed data about HIV patients who were hospitalized and those who weren't, what they found was surprising: Only a few significant differences existed between these groups, and one of the most prominent was that depression was more common among the hospitalized group.

The other differences were those in the group that used hospital resources were less likely to be able to name one of the medications, more likely to test positive for opiates, and more likely to say they had difficulty walking or moving than previously.[1]

"We have a very nicely furnished inpatient AIDS ward that we're proud of, but we're not proud of how full it is all the time," says **Ruth E. Berggren**, MD, an assistant professor of medicine for infectious diseases at Tulane University Medical Center in New Orleans.

Berggren, who co-authored the study, says that while New York and California have had large decreases in the numbers of HIV-related hospital admissions, the New Orleans HIV clinic's hospitalization rate has remained high.

Things are getting better

"I think we can infer that things are not getting better in New Orleans, the way things seem to be getting better in New York and California," she says.

"Here in New Orleans we have a state-of-the-art AIDS clinic, which takes care of about 3,000 people and is funded by Ryan White," Berggren explains. "It's well-staffed by expert physicians. It has all the social services that you could want, and we have a multidisciplinary clinic, and so our patients have access to care and an entire supplemental package of services with free medications if they need them."

And yet hospitalization rates remain dismaying, she says. "We're part of a trend that's being seen in the Southeast. So what's the problem?"

The case control study analyzed the similarities and differences between patients admitted to the AIDS ward and patients who had low CD4 cell counts, but were seen only in outpatient settings during the previous 12 months, she says.

The study group and control group were given a urine toxicology screening for street drugs, a Beck Depression Inventory, a Substance Abuse Subtle Screening Inventory (SASSI), and an Alcohol Use Disorders Identification Test (AUDIT). The CD4 cell counts, viral load, and hepatitis status were reviewed for each group, and each participant was asked questions about medication, mobility, incarceration, employment, and other items, Berggren notes.

Whether the subjects were inpatients or outpatients, there was a 25% prevalence of urinary cocaine, she says. "We found that 18% tested positive for marijuana; 32% were positive on the AUDIT for problem alcohol ingestion, and 72% have a history of incarceration."

The patients in both groups also had very low incomes with a median income of $6,700, and 43% had less than a high school education, adds Berggren. "The thing is that all of these are risk factors for hospital admission," she explains. "So we're looking within a very high-risk population to see who are the folks at the very highest risk of getting themselves in a hospital."

The idea is that if researchers can prospectively identify these very high-risk individuals then the HIV clinic can target people who fit that profile for special interventions, Berggren says.

With all of the similarities between the hospitalized group and the control group, the few differences were striking, she adds.

For one thing, more than 20% of the group with hospital admissions tested positive on the Beck Depression Inventory, while fewer than 5% of the outpatients tested positive, Berggren says. "These are associations, and we cannot infer causality, because by virtue of getting hospitalized, someone's depression score may go up, and we recognize that."

"There also was a highly striking difference in response to the question about motor impairment," she notes. HIV patients were asked, "In the last year, have you lost the ability to walk or move around like you did before?" Among the hospitalized group, 35% said, "Yes," while only 8% of the outpatient group said, "Yes," Berggren says.

When asked whether they could name any of their medications, more than 40% of the hospital admission group said, "No," while more than 80% of the outpatient group said they could name at least some of their medicines, she says.

And while both groups had high levels of cocaine and marijuana in the toxicology screening, about 32% of the patients who had been hospitalized also tested positive for opiates, compared with 5% of the outpatient controls. Also, about 10% of the hospital admission group tested positive for benzodiazepines, compared with 1% to 2% of the controls, Berggren adds. "In a high substance-using population, there are certain substances that are more likely to lead you to a bad end."

The benzodiazepines, which include Valium and Xanax, might be prescribed by mental health care providers, which might fit in with the finding that investigators found more depression among the hospital admission group, she notes.

Finally, the inpatients were significantly less likely to take antiretroviral medication and opportunistic infection prophylaxis, she adds.

Another difference was that outpatients were much more likely than inpatients to be the primary caretaker of children, Berggren says.

"We thought it'd be the other way around,"

she explains. "We thought these would be the women who were not taking care of themselves and doing badly."

About 60% of the outpatients were primary caretakers of children, Berggren points out.

Rather, it appears that the women who are doing well enough to take care of their children also are taking better care of themselves, she says.

"The viral load was higher in the hospital admission group than in the outpatients, but the outpatients had a pretty high viral load, as well," Berggren says. "There was high unemployment in both groups with 80% unemployment in the hospital admission group and 60% in the controls."

The inpatients were less likely to adhere to their antiretroviral therapy regimen and opportunistic infection prophylaxis.

Investigators also screened subjects with the Rapid Evaluation of Adult Literacy in Medicine (REALM) test, and found low literacy in both groups, Berggren says.

"The average subject had a literacy level that would place them around seventh grade, and that's a level where medical literature suggests they might struggle with most currently available patient education materials," she says.

As a result of the research, Berggren has created a screening tool that targets these very high-risk HIV patients in hopes of reducing hospitalization rates and health care costs.

HIV clinicians may be able to identify people at the greatest risk of hospitalization by asking patients to name their medications and providing remedial education to those who are unable to name even one drug, and they could ask that the patient recruit a family member or friend to be an adherence monitor, she suggests.

Assessing substance use and depression is another strategy for identifying this population.

"There's a fair amount of undiagnosed and untreated depression, and if that's addressed, you could potentially make an impact in their hospitalization rates," Berggren adds.

"Opiate addiction should be addressed more proactively, and methadone clinics need to be easier to use and more accessible," she notes.

Reference

1. Tompkins JC, Berggren RE. A root-cause analysis of HIV/AIDS-related hospital admissions: A case-control pilot study. Presented at the IDSA conference. Boston; September/October 2004. Poster: 843. ■

Attention HIV doctors: You're doing a good job

Study finds racial differences in responses

HIV patients surveyed about their medical care reported overall satisfaction, although many continued to experience side effects, a new study reports.

"They still said they were satisfied with their treatment and care and the physicians' decisions," says **Jeffrey Smith**, director of clinical research at the American Foundation for AIDS Research (amFar) in New York City.

Even the 3% of the 490 patients surveyed who reported that their overall health had gotten worse since initiating antiretroviral medication appeared to be satisfied with their medical care, he notes.

Among that group, 77% reported excellent or good medical care, Smith adds. "They were able to separate what they experienced from antiretroviral drugs and overall health from how they perceived the physicians treating them."

The ratings from HIV patients were very positive for physicians.

Liking their doctors

"We wanted to see if they thought their physicians were experienced enough to provide good medical care, and 89% reported they felt their overall medical care was excellent or very good," Smith says. "And another 88% reported their physicians were very knowledgeable about HIV."

About 14% of the people who completed the survey were antiretroviral naïve, so investigators studied the difference between that group and those who were on antiretroviral regimens to see if there was any difference in how they reported their satisfaction with medical care, and there was no difference, he explains.

The main reason reported by patients who were not on an antiretroviral regimen — their decision was based on a recommendation by their physician, Smith notes. "The take-home message for physicians is they know what they're doing, prescribing to people who need the drugs and not to the people who don't."

There were significant differences between ethnic groups with regard to improvements in overall health. The survey had been administered in both English and Spanish.

For example, 77% of Hispanics and 67% of African Americans, compared with 57% of whites reported an improvement in their overall health after initiating antiretroviral therapies, Smith adds.

"That was interesting because there's this whole idea that African Americans are not willing to take antiretroviral drugs, but our surveys showed that once blacks took the drugs they were significantly happier than whites," he says.

Also, significantly more blacks and Hispanics than whites reported not being sexually active, and significantly more respondents, age 50 and older, abstained from sex when compared with other age groups, Smith says. "And significantly more women than men reported they were not sexually active."

Who's using condoms?

"The other thing that struck me as interesting was that 67% of Hispanics and 53% of blacks reported always using a condom, compared with 39% of whites," he points out. "Those were both statistically significant compared to whites."

Investigators also found that patients were more receptive to taking some of the newest drugs, including those that required injections, than their physicians might believe, Smith says.

"Physicians say patients don't want to take that two-injections-a-day drug until the last moment, but patients say they don't mind if it's their best hope until the next treatment comes in," he says.

"Over the years, patients have gotten more involved in their medical care decisions," Smith adds. "They may not be community activists, but for these types of chronic diseases that impact life so much, the patient has to be involved." ■

HCV rates outpacing HIV in NYC, study finds

New IDUs had greatest HCV burden

New research in New York City shows that injection drug users (IDUs) are acquiring hepatitis C (HCV) at a faster rate than HIV.

Investigators looked for a correlation between HCV and HIV among IDUs in the Bronx, Harlem, and other areas, and were surprised to find that where there were high HCV rates, there were not necessarily high HIV rates.

"The most important thing was that the duration of injection was most predictive of hepatitis C prevalence," says **Crystal Fuller**, PhD, infectious disease epidemiologist at the center for urban epidemiologic studies at the New York Academy of Medicine and an assistant professor at Columbia University's Mailman School of Public Health in New York City.

"People who had recently started injecting had the most HCV burden," she says. "We saw a very high HCV prevalence at about 61%, and we also saw a low HIV prevalence among our population, which was 5.4%.

"Those two pieces of information coupled together, we think, suggest IDUs are not acquiring HIV as rapidly as hepatitis C," Fuller adds.

"And lastly, this lack of association we saw between neighborhood-level HIV and HCV rates and IDUs provides us with more evidence of sexual transmission of HIV among IDUs than drug-related transmission," she notes.

HCV developing first

Researchers didn't see much evidence of coinfection, but where it existed, it was clear that the HCV infection occurred first and that the HIV infection probably came from sexual transmission, she says.

The study's findings suggest that the epidemic has changed, Fuller explains. "The rates of HIV have been going down among drug users for some time now." The study concludes that the dynamics of HIV and HCV transmission may vary by neighborhood.[1]

She notes a number of possibilities for these findings. "First of all, the rates of HIV have gone down, so you don't have the same HIV burden in the community as we used to have in the late 1980's and early 1990's," Fuller says. "Even if you share a needle a few times, you're not as likely to share the needle with someone who has contaminated the syringe with HIV."

The other issue is that HIV is not as efficient a virus as is HCV, which is why investigators saw high rates of HCV infection among new IDUs, she says.

Syringe exchange programs may play an important role in the lower HIV transmission rates among IDUs, Fuller explains.

Although the study did not specifically examine needle exchange use, the initial analysis found that the overall rate of syringe exchange

use is about 35%, she says.

"People have time to access syringe exchange in time to prevent HIV infection," Fuller notes. "With hepatitis C, if you don't have access to clean needles from the start, you're in trouble."

With credit going to IDU and HIV prevention strategies, there's been measurable success in lowering HIV rates, but those same strategies have not had an impact on HCV transmission, she says.

Getting help early

"It comes down to the fact that people need to access services early," Fuller says. "It takes new injectors a while to access prevention services, and because they're not immediately identified as an injector, they're hidden and much harder to locate by outreach workers."

Future prevention strategies should focus on the very beginning of the cycle in which a noninjection drug user becomes an injection drug user, she suggests.

"We've talked about this issue of reaching people earlier and preventing them from injecting in the first place," Fuller says. "Then the second thing we can do is to try to reach those who've recently started injecting."

Fuller is involved in research that will use social network-based strategies, such as a peer network model, to reach people and convince them to share information with their friends and people with whom they hang out, she says.

"In addition to that, we have to find viable information about accessing sterile syringes," Fuller says. "It's possible they may choose to go to pharmacies to acquire needles because in 2001, New York passed a public health law to allow syringes to be sold without a prescription to anyone over age 18."

Interestingly, researchers found that younger IDUs were using pharmacies more than older people, she points out. "In a pharmacy, there's no way anyone can identify you as an injector because you could be a diabetic," Fuller adds. "It's cheaper than buying needles on the street, and pharmacies can sell a person up to 10 syringes at a time."

Reference

1. Nash D, Fuller C, Blaney S, et al. The relationship between neighborhood HIV prevalence and other neighborhood level indicators to prevalence in a sample of recently initiated injecting drug users in New York City. *eJIAS* 2004. Abstract: WePeC6046. ■

Access to affordable drugs hinges on competition

Study notes lowest prices in India, South Africa

Developing nations with greater market competition for antiretrovirals and more generic drugs tend to have cheaper antiretrovirals available through the private sector, according to a new study.

"We found, as expected, that in countries where a monopoly for a certain drug, exists they have higher drug prices on those drugs," says **Jan Ostermann**, PhD, research associate at the center for health policy, law, and management at Duke University in Durham, NC.

"Patent holders charge significantly higher prices than generic producers, and the magnitude of those factors is quite substantial," Ostermann says. "In a monopolistic market, the prices are nearly 50% higher than in a competitive market, and the patent holder charges, on average, 75% more for a drug than a nonpatent holder."

The study concluded that competition has the greatest impact on antiretroviral drug prices, although patent laws, advocacy strength, international scrutiny, and political pressure also play a role.[1]

Investigators looked at nine antiretroviral medications that are sold in private-sector markets, including retail sales to pharmacies, but did not include prices of drugs in government-sponsored programs, notes **Kermit Jones**, an MD/JD student at Duke University.

Declining prices

The drugs included in the study were selected based on their acceptability and use, he adds.

"What we wanted to do is look at several factors, including the measures of patent strength of a particular country, and we wanted to use a variable that looked at actual economic strength of that country," Jones explains. "We used per-capita gross domestic product (GDP) for that; and as a control, we had the prices of several medications used to treat opportunistic infections."

The expectation was that if prices were higher in a country for one kind of drug, then antiretroviral medication prices also would be higher, Ostermann says.

"We looked at a time trend overall and found

prices on average declined 8% per year over the study period of 1995 to 2002," he adds.

The study does not break down the estimates by individual drugs, so they are an average across countries, Ostermann notes.

During the study, there was an increase in GDP that was associated with a decrease in the price of antiretrovirals, Jones says.

"The estimate on GDP reflects changes in wealth, and it's correlated with time, basically," Ostermann says. "During that seven-year period, we noticed an increase in the GDP, a general strengthening of the patent index, and a trend to lower antiretroviral medication prices."

Since these three trends happened together, investigators are not able to say how they relate to one another, he says.

"If the patent index increases in a country, we might expect manufacturers to be able to command a higher price for the drugs. But over time and with increases in the GDP, we might expect a lower price," Ostermann adds.

In reality, India showed the greatest increase in per-capita GDP during that period and also had the greatest strengthening in patent law, and yet had among the lowest prices in antiretroviral drugs, he says.

In 1995, the antiretroviral prices in India were comparable to other developing countries, Jones says. However, by the end of the study period, India's prices were much lower and its HIV prevalence was higher, Ostermann points out.

Increasing suppliers

"One way to decrease prices and make antiretrovirals more available is to increase suppliers in a particular country," he says. "Eliminating monopolies on particular drugs will have the greatest effect on price levels."

The research may contribute to the international debate over antiretroviral medications and cheap, generic alternatives.

"We realize that part of the debate is that pharmaceutical companies have a legitimate point about property rights and protecting their investment interests and encouraging the continuation of drugs," Jones says.

"But it seems from any economic standpoint, the most amount of money is spent in upfront research costs, and once these medications are discovered, generic competitors have proved they can come in here and produce them for pennies on the dollar," he notes.

One possible solution would be to find a way to decrease the upfront research costs through a regulated research bank or tax incentives to offset research costs, Jones adds.

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Internet use for dating tied to sexual risk taking

Nearly 1 in 5 surveyed have looked for dates on-line

The phenomenon of people searching Internet sites for sex partners apparently is common among the general population and not just among men who have sex with men (MSM), according to a new study.

A random digit-dialing survey of more than 900 people in Seattle between the ages of 18 and 39 found that 18% of those surveyed had searched for sex partners on the Internet, and 3% had met with sex partners whom they contacted on-line.[1]

"We asked people if they had ever searched for partners on the Internet, and if they did search for them, did they meet them and have sex with those partners," says **Betsy Foxman**, PhD, professor of epidemiology and director of the Center for Molecular and Clinical Epidemiology of Infectious Diseases at the University of Michigan School of Public Health in Ann Arbor.

The study was designed to assess the prevalence of Internet-based sex partner recruitment in the general population of a city that has been among the places where Internet sex recruiting has been associated with outbreaks of syphilis among MSM.[1]

"We found that people who looked for partners on the Internet and met them and had sex with them increasingly had more sex partners over their lifetime or the last 12 months," Foxman explains.

The sexual orientation difference

"We also found that those who reported having opposite-sex partners were less likely to find sex partners on the Internet," she says. "It was

more likely in the homosexual community."

There was a very low reported HIV rate among the people surveyed, Foxman notes.

The people who reported Internet use for recruiting sex partners and who also had same gender sex partners had an indirect association to increased risk for HIV and sexually transmitted disease (STD) infection, she adds.

"There really weren't differences in terms of the number of hours they spent searching, although men reported slightly more hours than women," Foxman says.

"Also, men reported slightly more friends and partners than women, but that doesn't take into account sexual orientation," she explains.

Older people more open about Internet use

Another trend the survey observed was that older people surveyed were more likely to report that they had searched the Internet for sex partners, Foxman adds.

Future analyses of the data will look more thoroughly at the STD history and correlate that with other high-risk sexual behaviors, such as use of sexual enhancement aides, she says.

"What was striking to me was how common it was," Foxman points out. "We haven't analyzed yet, but we do know where people found their partners in terms of what web sites they went to, and that's something we'll be looking at."

Investigators also will analyze what survey respondents said about their intentions when they were looking for sex partners, she says.

"I think intention might be very important in terms of STD risk," Foxman says. "It's not intrinsically true that finding a partner on the Internet is a risk factor."

However, if someone searches sites, such as one called "bugchasers," which is directed at people who may wish to become HIV-infected, then that would be a risk factor, she notes.

"That's different from searching match.com where someone is trying to find a marriage partner," Foxman continues. "And that's something that's going to have to be explored and sorted out."

Reference

1. Aral SO, Patel D, Holmes KK, et al. Powerful predictors of sexual risk taking: Sex partner recruitment on the Internet and sexual orientation. Presented at the IDSA Conference. Boston; September/October 2004. Poster: 796. ■

CE/CME *questions*

17. Which of the following represents a potential new class of drugs targeting HIV?
    A. assembly inhibitors
    B. CCR5 inhibitors
    C. integrase inhibitors
    D. all of the above

18. A study of HIV patients in New Orleans found many similarities between those who had recent hospitalizations and those who had not. Among the differences between the two groups was the fact that those in the group that had hospital admits were more likely to be depressed, to have mobility problems, and to be using which of the following drugs?
    A. marijuana
    B. opiates
    C. cocaine
    D. ecstasy

19. Research looking at the rates of hepatitis C and HIV infection among injection drug users in New York City, found prevalences of which percentages?
    A. HCV prevalence at 61%; HIV prevalence at 5.4%
    B. HCV prevalence at 32.3%; HIV prevalence at 18.9%
    C. HCV prevalence at 29%; HIV prevalence at 22.8%
    D. HCV prevalence at 27.8%; HIV prevalence at 29.1%

20. A study examining prices of antiretroviral drugs in developing nations found that which two factors are the most important in lowering prices?
    A. less patent protection and greater gross domestic product
    B. greater competition and generic drugs
    C. greater competition and lower gross domestic product
    D. less patent protection and generic drugs

CE/CME *directions*

To complete the post-test for *AIDS Alert*, study the questions and determine the appropriate answers. After you have completed the exam, check the answers **on p. 132**. If any of your answers are incorrect, re-read the article to verify the correct answer. At the end of each six-month semester, you will receive an evaluation form to complete and return to receive your credits.

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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. ■

CE/CME *answers*

17. D	18. B	19. A	20. B

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Breast-feeding guidelines: An implementation puzzle

Experts say there is no easy solution

In the United States, it's a case for the courts when an HIV-infected mother wishes to breast-feed. In most of the nations where HIV proliferates, women are faced with a Sophie's choice: Should they breast-feed and risk transmitting HIV to their infant, or should they use substitute nutrition, which may place their infant at greater risk of dying within the first year?

The World Health Organization (WHO) of Geneva has weighed in with recommendations that skirt a fine line. WHO basically recommends substitute nutrition for infants born to HIV-infected mothers wherever that is acceptable, affordable, sustainable, and safe. However, the organization also recommends exclusive breast-feeding where it isn't, followed by early breast-feeding cessation and replacement feeding.

More than 30 studies about breast-feeding and HIV transmission were submitted to the XV International AIDS Conference, held July 11-16, 2004, in Bangkok, Thailand, and a number of research projects are ongoing. Yet no one who works in the field of mother to child transmission (MTCT) will say the solution is an easy one.

"It's a difficult decision," says **Ellen G. Piwoz**, MHS, SCD, nutrition advisor for support for analysis and research in Africa project and director of the center for nutrition at the Academy for Educational Development in Washington, DC.

"The vast majority of women who are HIV-positive actually do not know they're HIV-infected," she adds. "And not all women have the same risk of transmitting HIV to their infant."

While the WHO guidelines sound logical and easy to implement, the reality is there are many problems women have to face as they make these decisions, says **Margaret Bentley**, PhD, professor of nutrition and associate dean for global health at the School of Public Health at the University of North Carolina at Chapel Hill.

"First of all, making the decision about whether you're going to provide replacement food or not is a tough one because women are very knowledgeable about the risks of HIV transmission," she says. "But they also understand the risks of not breast-feeding in terms of malnutrition, disease, growth problems."

After childbirth, the risk of an HIV-infected mother transmitting the virus to her infant for up to two years of breast-feeding is 10% to 20%, Piwoz notes.

"But if a mother is asymptomatic and has a good immune system and a CD4 cell count of greater than 500, then her risk of transmitting during breast-feeding appears to be somewhere between 1% and 6% over two years," she continues. "If the mother is immune deficient, the risk is five to eight times greater."

While researchers know a great deal about the risk of HIV transmission, far less is known about the risk of illness and death if an infant, who lives in a resource-poor nation, is not breast-fed, Piwoz points out.

"The data most often used to estimate these risks come from studies that were not done in the context of HIV and not done in high-risk populations of Africa where women have the least resources in terms of education and alternative feeding and safe water," she says.

One study in Kenya found mortality rates were similar between infants who were breast-fed and those who weren't.

Many who were breast-fed acquired HIV, and those who weren't died from diarrheal and other diseases, Piwoz adds.

A recent study in Kigali, Rwanda, followed 770 children from 1999 to 2003 and found that formula feeding was not associated with a higher rate of mortality than breast-feeding in HIV-negative infants born to HIV-positive mothers who

had been counseled on feeding practice.[1]

However, studies that use selective populations to compare breast-feeding and formula feeding may not tell us about the true risks because participants have access to clean water and other protective measures that typically are not available in the general population, Piwoz explains.

"We don't have population-based data that would let us know in real-life settings what the true risks are for infants born to HIV-positive women who do not breast-feed," she says. "So we can counsel women that, 'This is your risk of passing the virus from breast-feeding,' but we can't say with the same degree of certainty, 'If you don't breast-feed, these are the risks.'"

New data from the Bangkok conference and other research have confirmed WHO's recommendations that women in poor nations exclusively breast-feed to reduce the risk of diarrhea, but then stop early to reduce the risk of HIV, Piwoz adds.

"WHO says they should stop as soon as they can, but the truth is we don't know whether or not at the end of the day this is going to result in the best outcome for their kids," she notes. "Some programs say to stop breast-feeding at three months, and some at six months; but the reality is that most mothers don't exclusively breast-feed that long."

Even the guidance to stop breast-feeding at six months is problematic because there still are real challenges in terms of providing a high-quality diet to older infants, Bentley says.

"The idea is to transition to other milks and complementary foods after the first six months of life; and in many resource poor areas, that is really a challenge and women don't necessarily understand what the ingredients would be for a diet that would provide appropriate nutrients for their infants without breast milk," she explains.

The Academy for Educational Development (AED) LINKAGES in Washington, DC, provides technical assistance to mostly African nations to improve and strengthen infant and child feeding within the context of HIV.

"The purpose of those programs in the practical sense is to help departments of health and ministries of health to strengthen maternal-child health services and to encourage mothers to get tested for HIV," says **Carolyn Kruger**, MSN, PhD, senior technical manager for country and regional programs. **(See story on programs and strategies to reduce MTCT postpartum, p. 3.)**

"We look at the delicate balance of the life-saving benefits of breast-feeding vs. HIV transmission," she says. "The access to food for infants and mothers is usually very poor in these countries." One problem is that MTCT programs often work with women who are of unknown HIV status, in which case the advice is to exclusively breast-feed unless replacement nutrition is acceptable, affordable, sustainable, and safe, Kruger says.

"We find in many places where replacement feeding has been promoted, women are not able to get a good supply for six months, and the children become sick from other diseases and become nutritionally compromised," she says.

Dangers of mixed feeding studied

The way women are counseled is very important, because some women mistakenly believe that if they both breast-feed and provide formula to their infants that their infants will have a reduced risk of HIV infection, Kruger notes.

"The infant's gut is specifically made to assimilate breast milk in the early months, but it changes if there is replacement feeding, and that change makes it more permeable to HIV," she adds. "One of the worst processes is combining breast-feeding with replacement feeding, which we call mixed feeding."

Piwoz was the lead author of a study that showed how mixed feeding doubled the risk of postnatal HIV transmission among Zimbabwe women. Also, the study found two-thirds of postnatal HIV transmission could have been prevented by stopping breast-feeding at six months.[2]

However, women may breast-feed and supplement also because they can breast-feed in the day and formula feed at night to avoid the stigma nonbreast-feeding African women feel if they are seen bottle feeding their infants, Kruger says.

"One of the problems with replacement feeding is they have to boil the water and prepare the bottles hygienically, and typically, having bottles and boiling water over that many times is not possible," she explains.

While boiling breast milk will kill the virus, it's also not feasible for women to pump and boil breast milk eight to 12 times a day, Kruger adds.

Whatever choice a woman makes regarding breast-feeding, it's important she receives community support for her choice and that she maintains her own health, Piwoz, Kruger, and Bentley say.

"The nutrition community and those who

work in HIV disease have been kind of operating in parallel and not working together as they need to on this issue," Bentley says.

"That's a real problem because in nutrition, we understand very well the problems of complementary feeding and breast-feeding and infant nutrition and growth," she adds. "And sometimes infectious disease doctors who are trying to keep HIV prevalence low don't understand all of the issues related to what happens to an infant who doesn't get breast milk anymore after six months."

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2. Piwoz E, Iliff P, Tavengwa N, et al. Early introduction of non-human milk and solid foods increases the risk of postnatal HIV-1 transmission in Zimbabwe. *eJIAS* 2004. Abstract: MoPpB2008. ■

Programs aim to reduce MTCT in poor nations

Here's a look at what can and is being done

There are no easy answers to preventing HIV transmission between HIV-infected mothers and their nursing infants, but a number of programs have developed strategies for reducing the risk among women in poor nations.

"Our strategies are to support existing systems and provide better services for pregnant and lactating mothers," says **Carolyn Kruger**, MSN, PhD, senior technical manager for country and regional programs at the Academy for Educational Development (AED) LINKAGES of Washington, DC.

"If there's a maternal child clinic, we help district health teams provide better support services for antenatal mothers, care for prevention of malaria, education in preventing HIV, nutrition counseling, and helping them see the benefits of coming to clinics for labor and delivery so they can be managed safely," she says.

The truth is that most mother to child transmission (MTCT) programs involve interventions aimed at preventing transmission with antiretroviral treatment late in pregnancy, during labor and delivery, and immediately postnatal, says **Ellen G. Piwoz**, ScD, MHS, nutrition advisor for the support for analysis and research in Africa project and director of the center for nutrition at AED.

"Even those simple interventions aren't that widely implemented in many countries," she says. "The coverage of those programs is still pretty limited."

However, some innovative strategies have been employed, including the following, Piwoz and Kruger say:

- **Teach women healthy breast-feeding habits.**

Since the World Health Organization (WHO) of Geneva and MTCT experts recommend that women who are unable to provide safe and affordable breast milk replacement to their infants should breast-feed exclusively for up to six months whenever their status is HIV-positive or unknown, some MTCT programs have begun to teach women how to make breast-feeding safer.

For example, women are taught how to properly position and attach their baby to their breast to avoid breast engorgement and resulting inflammation and cracked and bleeding nipples, Piwoz says.

"The way to prevent HIV transmission is to have good attachment and positioning, frequent suckling, and treatment of breast conditions," Kruger says.

Women are told to seek medical help if they have any problems with breast-feeding, Piwoz says.

She is involved in a study program in Zimbabwe in which some women knew their HIV status and others did not, by choice.

"We tested women when they entered the study and gave them the opportunity to learn their status," Piwoz says. "We counseled women on safer breast-feeding practices, including both women who knew their HIV status and those who didn't because they lived in an area where one-third of women were infected."

But even women who were not infected or were of unknown status need HIV prevention counseling and risk-reduction strategies because if they become infected while breast-feeding, they could place their infants at risk of infection.

"Acute HIV infection results in a jump in viral load in the blood, and that higher viral load is associated with higher risk of HIV infection," Piwoz says.

"What we found was safer breast-feeding resulted in a reduction of HIV transmission

among the population who didn't know their HIV status," she notes. "Although in an ideal world, everyone will learn their status and want to know because of services available to protect their own health and the health of their children, we're far from the ideal world."

- **Provide education and support for alternatives.**

If a woman follows the WHO guidelines and exclusively breast-feeds for six months, she still will need support to make the transition to replacement feeding.

Such support includes information on weaning and providing safe and nutritional alternative food, Kruger says.

"She can feed the infant heat-treated breast milk by bringing expressed milk to a boil, and it does kill the virus," she says.

A study presented at the 15th International AIDS Conference in Bangkok, Thailand, in July 2004, found that flash-heated expressed breast milk was a safe and practical infant feeding option.[1]

"African women are pretty good at expressing milk, but it's not well known right now as an option," Kruger says. "And it does take resources — fuel — and fuel is hard to find in Africa."

A woman also could provide the infant with an HIV-negative wet nurse, Kruger adds.

"Breast-feeding with an HIV-negative wet nurse has drawbacks, and not all communities accept this," Kruger says. "The wet nurse has to be tested frequently and educated on HIV prevention."

A study in Kenya looked at the use of surrogate grandmothers as wet nurses and found that these older, HIV-negative women were able to re-establish a nutritious and adequate milk supply and that the practice was acceptable to mothers.[2]

- **Support lactating mothers' health.**

Breast conditions contribute to increasing the risk of transfer of HIV to infants, so breast health is very important, Kruger says.

"If a mother is HIV-positive, and she wants to exclusively breast-feed her baby, she needs support in the community to do that," Kruger says.

Women who have difficulty breast-feeding may think there's something wrong with their breast milk, when the amount of milk a woman produces is based on how often she breast-feeds, and women need emotional support to become successful at breast-feeding, Piwoz explains.

"We pay too little attention to the health of the mother," she points out.

"Keeping the mother healthy is the best road to child survival, in general, and keeping the mother healthy reduces the risk of the mother transmitting HIV to the child," Piwoz says,

- **Work to reduce stigma of HIV-positive mothers.**

Piwoz works in Southern Africa where if a woman is seen bottle feeding, it's assumed the woman is HIV-infected.

"She may be assumed to be promiscuous, and it might be assumed that the baby does not belong to her husband," she says. "Women who stop breast-feeding early may hear gossip about being pregnant or HIV-positive."

Typically, in Southern African homes, the babies sleep with their mothers, and if they cry, the mother offers the infant a breast to nurse, says Piwoz.

"If the baby is in a home where no breast is offered, then there's pressure on the mother to quiet the baby; and if she has not disclosed her HIV status to anybody, then she's facing that pressure, which is not always easy to do," she explains.

Most programs do little to help women cope with the stigma and peer pressure, when this also is an important aspect of preventing HIV infection, Piwoz notes.

"The services for postnatal care of HIV-positive mothers are limited," she says. "Those programs are not well equipped to deal with infant feeding and nutrition issues, so we haven't given women adequate support."

These MTCT programs are all relatively new, so this isn't meant as huge criticism, Piwoz adds.

"The community is extremely important in dealing with these issues, so our challenge in all of the programs is how to develop community strategies, and we're doing that with the communities themselves," Kruger says.

"We're talking with the leaders, mothers and helping them understand the issues and how we can bring about behavior change so the epidemic can be decreased," she adds.

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