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AIDS ALERT

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IN THIS ISSUE

With infection rates rising, will the new administration stay focused on AIDS?

Activists worry that HIV prevention will be ignored

The recent bad news out of San Francisco and New York City that new HIV cases are rising among certain populations is an uncomfortable reminder to clinicians that the battle against HIV rages on.

The good news is that the fiscal year 2001 federal budget increases were fairly hefty, topping 10% in some cases, and there was an injection of $350 million targeted specifically to prevention and treatment in racial and ethnic minority communities.

Also positive was the nearly $240 million increase in the FY2001 budget for assistance to other nations struggling with the AIDS epidemic. This increase more than doubled the FY2000 figure. **(For a summary of FY2001 spending, see chart on p. 32.)**

Unfortunately, the epidemic appears geared for a rebound in industrial nations that have made great progress in improving life spans and quality of life among HIV-infected people. The worse-case scenario is this: As patients continue on antiretroviral therapy for years, their viral loads often begin to climb, and the virus eventually finds ways to thwart the medications. Combined with increasing HIV infection rates among those most at risk of infection, there may be a simultaneous national increase in new HIV infections, AIDS cases, and AIDS deaths in the next decade.

The stage has been set in San Francisco and New York City. New York's HIV infection rate among young African-American men who have sex with men (MSM) has climbed to 33%, according to city

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COMING IN FUTURE ISSUES

■ **Antiretroviral conference update:** Here's the latest in research, trials

■ **Search for an HIV vaccine:** An expert discusses where we are and where we will be in the next decade or two

■ **Back to the future:** Researchers study the use of interleukin-2 in HIV patients

■ **Holistic approach to HIV treatment:** North Carolina physician takes medical, psychological, and spiritual approach to treating patients

■ **Overuse of ER:** Study examines how some HIV patients repeatedly use emergency rooms to manage their illnesses

health department data. In San Francisco, the rate of new infections per year among MSM has doubled since 1997, from 1.04% to the current rate of 2.2%. **(See story on San Francisco's HIV data and report, p. 31.)**

San Francisco's latest data on new HIV cases should be a sobering wake-up call to clinicians and public health officials across the country, says **Mike Shriver**, AIDS and HIV policy advisor to San Francisco Mayor Willie I. Brown, Jr.

"If other jurisdictions and other cities were smart, and they are, they'd look at what's happening here and say, 'You know, we're not going to wait until it gets as bad as it is there before we act, because every time they start a trend, we follow it,'" Shriver says.

Some AIDS activists say they are most concerned about whether the new presidential administration will continue to make AIDS treatment, research, and prevention a national priority.

"People start to say, 'Why should we have to continue spending money on prevention?' And we say it's because prevention is an ongoing activity," says **Tanya Ehrmann**, director of public policy for AIDS Action in Washington, DC.

"Prevention isn't telling somebody one time to not have sex or to not use drugs and then just walking away and expecting we won't have increases in new infections," Ehrmann says.

New prevention messages are needed

"It's a different world now because of the success of protease inhibitors, and we need to develop new prevention messages that incorporate and recognize this," Ehrmann adds.

People who are diagnosed with AIDS today may live longer than they would have a decade ago, but it doesn't mean people are no longer dying from the disease, Ehrmann says.

One of President Bush's first announcements was that he would discontinue foreign aid to international organizations that perform or promote abortions. The restriction could affect some health agencies that provide HIV prevention and treatment services in sub-Saharan Africa and other developing regions. This action, coupled with hints that President Bush may reverse President Clinton's executive order permitting parallel importing of AIDS drugs into sub-Saharan Africa, raised hackles among AIDS activists.

The San Francisco AIDS Foundation was so concerned about how President Bush's administration would treat HIV / AIDS issues that less

than a week after the inauguration, the organization sent the president a list of HIV priority guidelines and recommendations.

"It is something we felt compelled to do now, because during the course of the presidential election, health care — and, specifically, HIV / AIDS — were barely mentioned at all," says **Ernest Hopkins**, director of federal affairs for the foundation.

The foundation's concerns were heightened when they learned that their package could not be delivered to the National Office of AIDS Policy because the office had moved and there was no forwarding address, Hopkins says.

"The last administration called AIDS a national security issue, and the president embraced it," Hopkins says. "AIDS is destabilizing nations all across the world, and we feel like the president and the people around him need to be made aware of HIV."

The foundation's letter to President Bush, which is available on the foundation's Web site (www.sfaf.org / policy / recommendations / index.html), calls to his attention that this year the HIV pandemic marked its 20th anniversary of the first diagnosed case in the United States.

"Presidential leadership in addressing this public health crisis both nationally and internationally remains critical," states the letter, which is signed by both Hopkins and **Fred Dillon**, the foundation's policy director.

Group wants more HIV prevention funding

The foundation's letter included requests for the following items:

- increased federal funding for HIV prevention activities;
- an endorsement of scientific evidence showing that syringe exchange programs reduce HIV infections without encouraging drug use;
- the development of new strategies to reduce HIV infections among gay men. **(See story on the foundation's requests, p. 34.)**

AIDS Action also wrote President Bush, urging him to let stand the previous administration's executive order that allowed parallel importing of AIDS drugs in Africa.

"Sub-Saharan Africa is in the midst of the worst plague the modern world has ever seen," writes **Claudia French**, executive director of AIDS Action. "Twenty-five million men, women, and children are living with HIV / AIDS in Africa. The cost of their treatment can be two to three times higher than the average GDP of some African countries, and easily outpaces the health budgets for many African nations."

AIDS advocacy groups are poised to react if the administration moves to reduce HIV / AIDS funding for prevention, treatment, or services.

"We have great concerns about potential funding levels for AIDS programs in this environment of budget cuts and increased defense spending," Hopkins says. "Our fear is that those will be the only priorities that we actually see in the revised budget that we expect in early spring. And if that's the case, then we'll have to do even more work with Congress to get the numbers where they need to be."

Shriver, who is open about the fact that he is HIV-positive, says he remains optimistic that President Bush will continue the previous administration's advocacy of funding for HIV / AIDS programs.

"I have to believe, because it's my life on the line, that this president will continue to make sure we stay in the leadership [position] we are in and not damage HIV programming in this country," Shriver says. "His father signed the Ryan White Care Act into law, and don't forget the American with Disabilities Act." ■

San Francisco notes HIV rise in MSM population

About two MSM a day will be newly infected in SF

It wasn't entirely a surprise given the steep rise in male rectal gonorrhea in recent years, but the numbers still are frightening: San Francisco's population of men who have sex with men (MSM) is becoming infected with HIV at a much higher rate now than four years ago, according to public health data.

In 1997, data showed that 1.04% of MSM became newly infected with HIV within one year; the most recent data put that figure at 2.2%. **(See chart on San Francisco HIV incidence rates, p. 33.)**

San Francisco's total population of gay men is estimated to be 46,800. Of these, 12,786 or 27.3%

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FY 2001 Appropriations Levels for Federal AIDS Programs

(As of January 2, 2001; increases or decreases from previous year are shown in parentheses)

PROGRAM	FY 2000 FINAL	FY 2001 President's Budget Request 2/7/00	FY 2001 HIV/AIDS Need	House Action L, HHS 5/24/00 VA, HUD 6/20/00	Senate Action L, HHS 5/11/00 VA, HUD 9/13/00	FY 2001 FINAL* L, HHS P.L. 106-554 VA, HUD P.L. 106-377
CDC: Prevention	$694.7m (+$36.9m)	$734.7m (+$40.0m)	$984.7m (+$290.0m)	$724.4m (+$29.7m)	$762.4m (+$67.7m)	$760.9m (+$66.2m)
HRSA: Ryan White CARE Act Total	$1,594.8m (+$183.7m)	$1,719.8m (+$125.0m)	$1,931.4m (+$336.6m)	$1,725.0m (+$130.2m)	$1,650.1m (+$55.3m)	$1,776.0m (+$181.2m)
Title I	$546.6m (+$41.5m)	$586.6m (+$40.0m)	$635.6m (+$89.0m)	$586.6m (+$40.0m)	$556.5m (+$9.9m)	$596.5m (+$49.9m)
Title II: Care Services	$296.1m (+$19.2m)	$310.1m (+$14.0m)	$341.1m (+$45.0m)	$310.1m (+$14.0m)	$296.1m (+$0m)	$315.0m (+$18.9m)
Title II: ADAP	$528.0m (+$67.0m)	$554.0m (+$26.0m)	$658.0m (+$130.0m)	$554.0m (+$26.0m)	$538.0m (+$10.0m)	$589.0m (+$61.0m)
Title III	$138.4m (+$44.1m)	$171.4m (+$33.0m)	$184.4m (+$46.0m)	$173.9m (+$35.5m)	$166.4m (+$28.0m)	$168.9m (+$30.5m)
Title IV	$51.0m (+$5.0m)	$60.0m (+$9.0m)	$70.0m (+$19.0m)	$60.0m (+$9.0m)	$58.4m (+$7.4m)	$65.0m (+$14.0m)
Part F: AETCs	$26.7m (+$6.7m)	$29.2m (+$2.5m)	$30.3m (+$3.6m)	$31.6m (+$4.9m)	$26.7m (+$0m)	$31.6m (+$4.9m)
Part F: Dental Reimbursement	$8.0m (+$0.2m)	$8.5m (+$0.5m)	$12.0m (+$4.0m)	$9.0m (+$1.0m)	$8.0m (+$0m)	$10.0m (+$2.0m)
NIH: AIDS Research	$2,006.0m (+$207.6m)	$2,111.0m (+$105.0m)	$2,329.0m (+$323.0m)	$1.02b NIH increase overall; OAR increase uncertain	$2.7b NIH increase overall; OAR increase uncertain	$2,267.0m (+$261.0m)
SAMHSA (Substance Abuse Prevention & Treatment Blockgrant)	$1,600.0m (+$15.0m)	$1,631.0m (+$31.0m)	$2,000.0m (+$400.0m)	$1,631.0m (+$31.0m)	$1,631.0m (+$31.0m)	$1,651.2m (+$51.2m)
HUD: HOPWA	$232.0m (+$7.0m)	$260.0m (+$28.0m)	$292.0m (+$60.0m)	$250.0m (+$18.0m)	$232.0m (+$0m)	$258.0m (+$26.0m)

*The final totals do not include the FY01 increases for the minority AIDS initiative or the global LIFE initiative, see next page for those totals.

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are HIV-positive. By contrast, the national prevalence of HIV infection is estimated at 0.3%.

The city's 2001 HIV Consensus Panel issued a draft paper on the topic Jan. 30, but has refrained from commenting on what the cause of the sharp increase might be. What the panel will say is that this high rate of new infection will continue unless some major changes are made. For instance, the panel predicts that this year there will be 748 new cases of HIV among San Francisco MSM. Injection drug users will add 144 new HIV cases to the total.

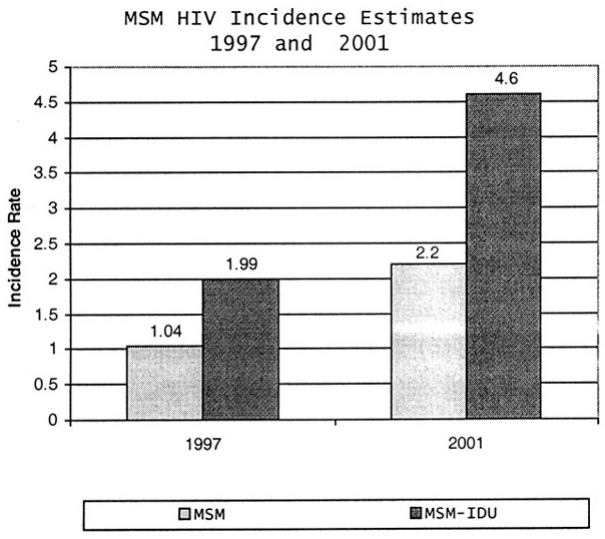
"We know what will happen in 2001 if we don't do anything different," says **Mike Shriver**, advisor on AIDS and HIV policy to Mayor Willie L. Brown, Jr. "We've been visited by the ghost of Christmas yet to come, and it's deeply troubling."

Targeted prevention efforts lacking

Shriver points out that the increase in new HIV infection rates does not mean prevention efforts have failed; it only means that not enough national effort has been put into prevention efforts targeting MSM populations, especially directed toward changing behavior among men who already are HIV-positive.

"We have put almost nothing into HIV prevention for gay men in this country," Shriver says.

HIV Prevalence in San Francisco



Source: Draft document by the San Francisco Department of Public Health AIDS Office; Jan. 30, 2001

"We don't have incidence rates higher than this because communities have done the best they could with the limited resources they have available, and it's almost pennies compared to what it should be."

The panel's data are a conservative estimate that mirrors what many people working on the front lines of the epidemic have seen among their MSM populations, says **Brian Byrnes**, MPhil, director of prevention services for the San Francisco AIDS Foundation.

"We still have a long way to go to fully understand the 'why' behind this trend," Byrnes says.

The foundation, which researches the epidemic and provides education to at-risk populations, has collected some data suggesting possible causes for the resurgence in new infections.

Despite the general public opinion that gay men don't care about HIV anymore, this is not the case, Byrnes says. "They care deeply about HIV, but sexual decision-making is becoming increasingly complex as the epidemic changes."

At-risk men have incomplete info about HIV

But they sometimes will attempt to protect themselves through methods they've invented based on incomplete information, he explains.

For example, a man may decide it's safe to not use a condom with a man who appears to be in good health. The man may assume that even if his partner is positive, the partner is on antiretroviral therapy, which should make him less infectious.

"Men develop their own science and their own facts based on little bits of information they pick up, and it's usually a science that justifies their desires," Byrnes says. "They create that science in the absence of information, and we need to make information much more available to the men."

In educating men who have sex with men, it's important to address the myths and spell out details, Byrnes says. For instance, educational materials should discuss pre-seminal fluid and its potential to be infectious. Just as heterosexual men might use the withdrawal method to prevent impregnating their partners, so do homosexual men use the withdrawal method to prevent infecting their partners.

The San Francisco AIDS Foundation began its own campaign on Feb. 1 to attack the myths often

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AIDS Foundation makes suggestions to Bush

Guidelines call for more funding, new strategies

The San Francisco AIDS Foundation wasted no time in letting President Bush know what needs to be done about the HIV / AIDS epidemic by sending the president its own wish list.

The foundation asked the president to:

• Increase federal funding for HIV prevention activities and ensure that federally funded HIV prevention efforts remain responsive to community-based planning and focused on populations at greatest risk for HIV.

• Unequivocally endorse the scientific evidence showing that syringe exchange programs reduce HIV infections without encouraging drug use and advocate for federal funding for local syringe exchange programs.

• Develop new strategies and / or refine existing strategies to reduce HIV infections among gay men.

• Recognize the essential link between housing and health care for people living with HIV and ensure that this understanding serves as the foundation for administration policy in this area.

• Expand federal funding for programs that provide affordable housing to people living with HIV and other disabling conditions. In particular, increase the availability of affordable housing for individuals with multiple diagnoses, including substance abuse, mental illness, and HIV disease.

• Increase funding for National Institutes of Health research on critical public health concerns, including research specifically related to HIV / AIDS prevention and treatment.

• Support the Office of AIDS Research, which coordinates the variety of HIV research that occurs within the Institutes of Health.

• Encourage rigorous research and timely development of the next generation of safe and effective pharmaceuticals and diagnostic tools to treat HIV infection. Prioritize the development of drugs that are affordable, easily delivered, and tolerable for people living with HIV and AIDS.

• Recognize the national security, economic, and humanitarian implications of the global HIV pandemic and assert our nation's responsibility to be a leader in the global fight against HIV / AIDS.

• Increase access to HIV / AIDS-related treatments throughout the world through trade agreements, development grants, indigenous country generic drug development, and multinational negotiations with industry.

• Increase federal appropriations for HIV-related public health medical and support service programs, including the highest possible funding levels for the Ryan White Comprehensive AIDS Resources Emergency Act.

• Ensure the medical providers who treat people living with HIV are educated about the Public Health Service Guidelines for HIV Treatment.

• Expand coverage for medical treatment of low-income and uninsured individuals living with HIV disease by extending Medicaid eligibility to those in the earlier stages of HIV infection.

• Establish an affordable and accessible drug benefit for all Medicare beneficiaries. The benefit should provide coverage for all necessary pharmaceuticals, including "off-label" medications.

• Bolster funding to the Racial and Ethnic Approaches to Community Health (REACH 2010) initiative.

• Continue to provide the highest possible levels of funding for the Congressional Black Caucus Minority HIV / AIDS Initiative.

• Increase funding for programs that provide critical HIV prevention and care services in the developing world.

• Promote the human rights of people living with HIV and work to minimize HIV-related discrimination and stigmatization throughout the world.

• Increase access to HIV / AIDS-related treatments throughout the world through trade agreements, developing grants, indigenous country generic drug development, and multinational negotiations with industry.

[Editor's note: To read the entire San Francisco AIDS Foundation letter, visit the foundation's Web site at: www.sfaf.org/policy/recommendations/index.html.] ■

100% Condom Use Among MSM

Year	Number of men interviewed	Number reporting 100% condom use with anal sex	Percent
1994	3556	2474	69.6
1995	3526	2393	67.9
1996	3276	2131	65.0
1997	2544	1546	60.8
1998	2813	1634	58.1
1999	2179	1180	54.2

Source: Data reported in the 2001 HIV Consensus Panel draft paper.

held about HIV infection. The campaign includes billboards and posters displayed in areas frequented by gay men. One advertisement will show a picture of two attractive men in an embrace. The picture shows thought bubbles above their heads. One man is thinking, "He'd tell me if he was negative," and the other man is thinking, "He'd tell me if he was positive." Then beneath the picture there is a question: "How do you know what you know?"

Using the medicine-cabinet test

Another assumption men who have sex with men often make is that someone's HIV status can be guessed by paying attention to certain clues, Byrnes says.

A man might say, "I looked in his medicine cabinet and didn't see any medicine, so he must be negative," Byrnes says. Or an HIV-positive man might say, "Well, I left *POZ* magazine on my coffee table, so he should know I'm HIV-positive."

While communication skills and assertiveness techniques would appear to be important issues, these skills are not always easy to provide to this population, Byrnes says. "Skills building only works for people who are willing to participate in skills-building exercises."

One of the big hurdles in prevention work is reaching the core at-risk group of MSM who are not interested in learning about HIV or preventing HIV because they are unaware of how their own sexual decisions are placing them at risk, Byrnes says.

"So the onus falls back on us to develop fresh and new interventions and go back to our populations and ask what they want from us so we get a better understanding of what they need in order to build better programs," he says. "That's what this data in San Francisco means to me: We need to learn how to reach those men who are most likely to be one of the 748 new HIV infections this year."

Here are some statistics and details about San Francisco's HIV epidemic, reported in the city's draft paper:

• MSM and who use injection drugs have an incidence rate of seroconversion that is about twice as high as the seroconversion rate for MSM in general, at 4.6% a year.

Transgendered HIV rate appears high

• Statistics on the transgendered population, representing men who became women, were included for the first time. The new HIV seroconversion rate was an alarming 7.8%, and the total incidence rate was estimated to be 35%. Shriver cautions that these statistics are from one study and therefore may not be confirmed in later data collection.

• The number of MSM reporting that they always used condoms during anal intercourse during the last six months has been steadily declining since 1994. **(See condom use chart, above.)**

• The number of cases of male rectal gonorrhea have more than doubled since 1994, steadily rising each year, beginning with 72 in 1994 and peaking at nearly 200 in 2000.

• Another trend that points to the lack of safe sex practices among MSM who already have AIDS shows that the STD incidence rate has nearly doubled from 0.69% in 1995 to 1.37% in 1998, the last reported year. ■

One-third of HIV patients were not aware of their risk

Should physicians screen all patients for HIV?

HIV testing remains controversial, despite clear evidence that routine testing and early diagnosis can help HIV-infected patients receive the medical care they need earlier in their disease progression, which could have a positive impact on their long-term prognoses.

New research shows that more than one-third of HIV-infected patients at two urban hospitals were not aware of their HIV risk before they were tested for the virus, especially if their source of infection was through heterosexual sex rather than homosexual sex or injection drug use.

"Acknowledging that awareness of your risk is the first step to getting tested," says **Jeffrey H. Samet**, MD, MA, MPH, associate professor of medicine and public health at Boston University School of Medicine and Public Health.

"We've done a reasonable job in the last 20 years of making it clear that people who inject drugs and have unprotected sex with men are at higher risk of infection," Samet says. "But what's happening is that more than those risk groups are at risk. Anyone having sex without condoms with a partner who is not known to be HIV-negative is also at risk."

Samet argues that because the down side of HIV testing is so negligible and the up side of knowing one's HIV status is so significant, the medical community should have a very low threshold for HIV testing.

Already, nearly one-third of adults in the United States have been tested for HIV. Some of those adults have voluntarily sought their HIV status, but for many others the testing is done routinely as part of blood donor screening, life insurance screening, and military service.[1]

"Those generally are people who are not in risk groups," Samet adds.

In the Boston study, investigators found that 80% of HIV-infected patients initially presented to medical care with CD4 cell counts of less than 500/µml, and 37% had counts of 200/µml or less.[2]

The study population included 203 outpatients at the Boston Medical Center (previously called the Boston City Hospital) and Rhode Island Hospital in Providence between February 1994 and April 1996.

Although this time period encompassed the pre-protease inhibitor era, the findings would likely be the same today, Samet notes.

"This was all post-Magic Johnson's HIV disclosure," Samet says.

When pro basketball star Magic Johnson announced that he was infected with the virus, public health officials hoped that the public would finally realize that many more people were at risk than they had believed, he adds.

The study shows that people continue to remain ignorant about their risk-taking behaviors. And although the investigators have not formally studied more recent data, it would appear that the problem still exists, Samet says.

"We've made a little progress, but without a doubt there are many, many people coming in with opportunistic infections and still coming in quite late," he says.

The study found that HIV-infected patients who first presented with lower CD4 cell counts were more likely to have these characteristics:

- no or only one close friend;
- had not been in jail in the past 10 years;
- had been voluntarily tested;
- had lower hope and a poor quality of life;
- had more symptoms of HIV infection;
- were older.[2]

Another interesting finding was that among the patients who knew they were at risk for HIV, they still would wait months to years before being tested. The median time lapse between when a person first felt at risk and when he or she was tested was one year. The mean time lapse was 2.5 years.

Based on an analysis of the subjects' CD4 cell counts, investigators theorized that many HIV-infected patients have had the disease for 6.0 to 11.6 years before being tested. This is their approximation of a mid-range period of delay.

This brings the issue back to medical treatment and policy, Samet suggests.

"It was the heterosexual group that was least aware of HIV risk at time of testing, and that finding to me is totally compatible with what we're seeing clinically," Samet says.

The solution is for clinicians to lower their threshold for recommending HIV testing, he adds.

Rather than providing testing as a diagnostic tool in the cases of patients who have symptoms that could signify HIV disease, primary care physicians could use HIV testing as a screening tool. As such, it would be similar to Papanicolaou

smears for cervical cancer or mammography of older women for breast cancer.

A Pap smear is given routinely in the case of a disease that has a prevalence rate of 0.1%. By contrast, the national prevalence rate of HIV infection is 0.3%.[1]

Samet admits that routine universal testing, while ideal from an epidemiological perspective, will not be feasible. However, physicians could lower their threshold for when to suggest testing.

Here are some possible scenarios in which routine HIV testing could be applied:

- A hospital has one or more patients with newly diagnosed AIDS per 1,000 patient population. Hospitals with an incidence rate this high could routinely test all inpatients for the disease.
- Patients presenting with varicella zoster virus, community-acquired pneumonia, tuberculosis, or hepatitis C, or who have a history of any sexually transmitted disease or recurrent vaginal candidiasis should be tested.
- Patients who have experienced sudden weight loss, unexplained lymphadenopathy, or dermatological diseases should be tested.
- Physicians should offer testing to patients who have reported on their physical report a history of alcohol dependence, cocaine abuse, homelessness, or psychiatric hospitalization.
- Clinicians could routinely approach the subject by asking new patients to consider having an HIV test if they have had any unprotected sexual contact with a person who is either HIV-positive or who has an unknown HIV status.

Clinics and clinicians who promote testing under these circumstances will undoubtedly find additional cases of HIV that otherwise would have fallen through the cracks. At least that was the experience Samet had when his hospital made a major push for HIV testing of all untested patients. Unfortunately, the time and energy needed to maintain such an effort proved too difficult to maintain, Samet says.

"It's hard to implement because people are in and out of the hospital or clinic," he explains. "But it was clearly a useful policy in our setting."

References

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Investigators learn how HIV targets the gut

Findings may explain inflammatory effects

The image of HIV spreading throughout the body rarely conjures up thoughts of a person's gut. Yet the gut is one of HIV's primary target sites, perhaps especially when a person is infected with HIV through rectal intercourse, oral sex, or ingestion of infected breast milk.

"People need to know that this underscores the need for preventive efforts and prophylactic measures," says **Peter Anton**, MD, principal investigator and associate professor of medicine in the division of digestive diseases at the UCLA AIDS Institute, a part of the University of California at Los Angeles.

UCLA researchers have found that HIV may replicate more easily within the gut than through the circulatory system. This would suggest that HIV transmission through oral sex and anal sex is even riskier than previously thought.

The study compared the expression of chemokine receptor CCR5, which is the co-receptor most associated with HIV-1 in early infection, on mucosal mononuclear cells (MMCs) to that of peripheral blood mononuclear cells (PBMCs), and found an enhanced expression on MMCs. The proportions of mucosal CD4 cells expressing CCR5 and the amount of CCR5 expressed per cell were increased, Anton says.

Investigators further showed that these enhanced levels were functionally correlated with a greater level of productive infection of MMCs than of PBMCs, suggesting that HIV can do more damage more quickly in the gastrointestinal tract.

"The gut is the largest immune organ of the body, with more lymph cells than all the other organs combined," Anton says. "It has to have a lot of protective immunity lining it to determine what's nutritious and safe to absorb and what's pathogenic."

For this reason, a large proportion of the gut's T-cells are activated, and HIV targets activated T-cells more than resting naive T-cells, Anton adds.

The investigators also are studying how HIV disease causes diarrhea, malabsorption, and wasting, much like what occurs in an inflammatory disease. They plan to present future research on whether anti-inflammatory medications will help slow down the pace of the disease, Anton says.

"Anti-inflammatories could be an adjunct to antiretroviral medications," he adds.

Another research area that might benefit from studies about how HIV affects the gut is the development of microbicides to target mucosal cells, whether these are the cervical vaginal mucosa or rectal mucosa. ■

Researchers seek solutions to diarrhea, wasting

Research takes several different twists and turns

HIV-related diarrhea and cachexia are tremendously serious problems in developing countries where there is little access to antiretroviral medications. They also remain concerns for many AIDS patients in the United States, yet much needs to be proved with regard to treatments.

Patients who have these symptoms have a reduced quality of life and can have a shortened life span. One study has shown that 42% of HIV patients taking highly active antiretroviral therapy experienced clinical wasting, according to research presented last October at the American Dietetic Association annual meeting in Denver.

Studies on the incidence of wasting among HIV patients demonstrate that cachexia remains a problem despite antiretroviral treatments, says **Alvan Fisher**, MD, clinical associate professor of medicine at Brown University in Providence, RI.

Fisher says the most effective interventions now available for treating wasting and weight loss in HIV patients and cancer patients are anabolic agents and appetite stimulants.

One study using the appetite stimulant dronabinol (Marinol) vs. a placebo in 94 HIV / AIDS patients showed that patients taking dronabinol had a significant increase in appetite for up to 12 months, according to data presented at the ADA meeting.

Another study showed that most patients taking dronabinol had an improvement in symptoms of nausea and vomiting, according to data presented at the Fifth Congress on Drug Therapy in HIV Infection, held in October 2000 in Glasgow, Scotland.

Still, many researchers acknowledge that AIDS patients who have an adequate caloric intake still may suffer from wasting. This is why researchers from a variety of scientific backgrounds are seeking ways to reduce or eliminate this problem in HIV and cancer patients.

For example, investigators in the Carolinas and Virginia have studied the use of a glutamine-based oral rehydration solution (ORS) for treating HIV-related diarrhea and wasting.

The work is ongoing, but an interim analysis has demonstrated a favorable trend with respect to stool frequency and stool output, says **Nathan M. Thielman**, MD, MPH, assistant professor at Duke University Medical Center in Durham, NC.

There are two reasons for evaluating glutamine in an ORS, Thielman says.

"No. 1, ORS is a time-tested proven means of rehydrating patients with dehydrating diarrheal illnesses," he says. "It takes advantage of elegant physiological mechanisms in which glucose stimulates sodium absorption and hence absorption of fluid in the system, even in cases of cholera."

The second reason is that glutamine appears to have some nutritional benefit to the intestines and also is a major source of energy for enterocytes, Thielman adds.

The research involved observing patients in an inpatient unit for seven days in which stool samples were obtained.

Thielman also was involved in another study in which the quality of life of HIV patients who suffered from diarrhea and wasting was compared with patients who had diarrhea but no wasting and with patients who had neither diarrhea nor wasting. The quality of life of the patients who had neither diarrhea or wasting was significantly higher than the other two groups of patients, and the quality of life of the patients who had only diarrhea and no wasting was significantly higher than the patients who had both symptoms, Thielman says.

At the University of North Carolina in Chapel Hill, a separate avenue of research is being conducted into developing a better understanding of the mechanisms involved in cachexia.

"It was already known that cytokines were involved, and AIDS patients often have elevated cytokines, so cytokines are involved and muscle is involved," says **Albert S. Baldwin, Jr.**, PhD, professor and associate director at the Lineberger Cancer Center at the University of North Carolina in Chapel Hill. "But it wasn't known what was in between the two."

He notes that in addition to HIV-related cachexia, about 50% of late-stage cancer patients suffer from muscle wasting, and cachexia causes nearly one-third of their deaths.

Investigators now have an idea of what is going wrong to cause muscle wasting. Muscle cells normally go through constant loss and repopulation. Animal models suggest that with wasting disease, but the mechanism for replacing lost muscle cells is being blocked.

The first step in the process is to identify the culprit of the process that is downstream of the cytokines and that causes the muscle degeneration. Investigators believe they have found the cause of the block of repopulation, which is called NF-KappaB. Then researchers may identify a drug that could inhibit NF-KappaB and block its ability to cause the muscle degeneration.

The next step is to establish animal models for cachexia to determine whether the NF-Kappa B inhibitors will have an effect in these studies. Then it may be another year or longer before human trials can begin. ■

Feline research may help address thymic problems

AZT did not stop FIV damage to thymus

Researchers who have been working with the feline immunodeficiency virus (FIV) for years have recently concluded that while AZT will stop the virus from multiplying, it does not protect the thymus from physical damage.

"With FIV-infected cats and young humans, the thymus is one of the major target organs for infection, a massive depletion of lymphoid elements and inflammatory response that damages the thymus," says **Lawrence Mathes**, PhD, professor of immunology at The Ohio State University in Columbus and co-author of a recent study on FIV and thymic activity.[1]

Earlier research conducted by Mathes and other investigators has shown that the feline leukemia virus could be effectively stopped with the administration of AZT. If cats were treated fairly early in their infection, they could be cured. "We called the effect 'drug-induced vaccination,'" Mathes says.

"With HIV, the feeling was that early in the infection, the immune response was suppressing the virus because the viral load rises to a peak and then drops back down, but it wasn't actually clearing the infection," he adds. "The virus was getting around the normal way to clear the infection."

Then, when felines or humans are given antiviral drugs, the medications suppress their natural immune response.

"The toxicity you see is a suppression of the bone marrow's rapidly dividing cells, due to the biochemistry of the drug," Mathes says. "So if you suppress the replenishing of bone marrow cells, you'll see a drop in blood cell numbers and anemia develops."

Investigators found a dose of AZT that would induce the vaccine effect in cats with leukemia

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without suppressing the immune response to the point of anemia. Finding the right dose of AZT to use in FIV-infected cats was more difficult because the virus itself suppresses the immune system and the thymus undergoes a more rapid involution with FIV. The researchers used AZT with the felines because most of the other antiretrovirals would not work with cats.

When the FIV-infected felines were given AZT treatment, the thymus sometimes was damaged to the point of becoming dysfunctional and unable to produce new cells. The cats received AZT daily for 12 weeks, with treatment beginning two days before the cats were infected with the virus. Investigators compared the levels of T-cells in the infected and uninfected groups.

Felines receiving AZT treatment had a 75%-85% reduction in the levels of FIV in their blood and a 74% reduction in virus in their thymus. But they also had physical damage and inflammation in their thymuses similar to that of the untreated felines. Investigators concluded that the extent of inflammation, once initiated by FIV infection, was independent of thymus virus load. The threshold virus load needed to turn on the inflammatory response in the thymus was not determined in this study, but was predicted to be below the reduced virus load achieved by AZT monotherapy.

Mathes says the same effect could occur in human infants who are HIV-infected and are treated with AZT. Infants and children have fewer lymphocytes than do adults, meaning they have yet to develop the T-cells that defend their bodies against infection and disease. Thus, there are far worse health implications for a child's thymus to be damaged and unable to produce lymphocytes than for an adult's.

"It makes children more susceptible to opportunistic infections and major infections," he says.

"We have to be aware that the immune system is a two-edged sword, because on the one hand it can clear infection, and on the other hand it can cause collateral damage through inflammation," he adds.

This type of research may lead to ways to help HIV-infected children retain a healthy thymus despite antiretroviral treatment, Mathes says.

Reference

1. Hayes KA, et al. Antiviral therapy reduces viral burden but does not prevent thymic involution in young cats infected with feline immunodeficiency virus. *Antimicrob Agents Chemother* 2000; 44:2399-2405. ■

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. ■