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INSIDE

Special Coverage of the 6th Conference on Retroviruses and Opportunistic Infections

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A new HAART on the horizon says the proof is in the potency

Studies show a new regimen has better compliance

Research proving that HIV-1 originated in West African chimpanzees may have grabbed most of the national headlines at the recent 6th Conference on Retroviruses and Opportunistic Infections in Chicago. But some clinicians were more interested in studies that claim highly active antiretroviral therapy (HAART) need not involve protease inhibitors to achieve positive results.

The conference buzz over non-protease inhibitor therapies brings HIV treatment full circle, proving that protease inhibitors are not the magic bullet and it's potency that matters most.

"When there was all the hoopla two or three years ago with protease inhibitors, the point was we finally had extremely potent therapies that, in combination with existing ones, could suppress the virus below our ability to detect it," says **Daniel R. Kuritzkes**, MD, associate professor of medicine at the University of Colorado Health Sciences Center in Denver. Kuritzkes also is the co-director of the Colorado AIDS Clinical Trials Unit in Denver.

Protease inhibitors were never the only option

Although therapies with protease inhibitors quickly became the gold standard, they were never meant to be the only option, Kuritzkes says. "Even when they were introduced, people who were a little more forward-looking in their view were saying it's not the protease inhibitors per se, it's the potency," he says.

Other drug combinations — whether two, three, or more drugs — also should be able to succeed in suppressing HIV, he adds.

The latest research brings good news for clinicians, especially if they have patients who are having difficulty tolerating protease inhibitors, says **Kenneth Mayer**, MD, chief of the infectious disease division of Memorial Hospital in Pawtucket, RI. "Because there are all these metabolic side effects, clinicians have been concerned about [protease inhibitor] use, and now we have data on alternative regimens," Mayer says.

Researchers at the February retrovirus conference presented data showing successful results with an all-nucleoside reverse transcriptase

inhibitor combination of Ziagen (abacavir sulfate), Retrovir (zidovudine, AZT), and Epivir (lamivudine, 3TC). Ziagen, manufactured by Chicago-based Glaxo Wellcome, received accelerated approval by the Rockville, MD-based Food and Drug Administration (FDA) on Dec. 17, 1998, for use in combination with other antiretroviral agents for treatment of HIV-1 infection.

The Ziagen study showed a 74% probability of keeping a patient's viral load to undetectable levels for 48 weeks on the Ziagen triple-drug regimen. Also, 92% of the patients (48 out of 52) who remained on the Ziagen+Epivir+Retrovir arm for the entire 48 weeks achieved undetectable levels of HIV.¹

Abacavir combination holds promise

The abacavir study is encouraging because it provides clinicians with an option of a protease-sparing regimen that appears to have equivalent results, says **Joseph J. Eron**, MD, an associate professor of medicine at the University of North Carolina at Chapel Hill. Eron also is the co-investigator of the AIDS Clinical Trial Unit in Chapel Hill.

Also, a late-breaking session presented by **Karen Tashima**, MD, provided impressive data on the non-nucleoside reverse transcriptase inhibitor Sustiva, Eron says. "They had 48 weeks' data from their trial that showed very potent activity and a very low drop-out rate when compared with the control arm," Eron says.

Sustiva (efavirenz), manufactured by DuPont Pharmaceuticals in Wilmington, DE, was studied in a combination with zidovudine/AZT and 3TC. The combination was found to reduce viral load in 98% of patients, compared to reduced viral loads in 86% of patients on the protease inhibitor Crixivan plus AZT and 3TC.²

The Sustiva combination also had a lower discontinuation rate in a 48-week study, with 25% of patients discontinuing use, as compared with 42% of patients discontinuing use of the protease inhibitor Crixivan (indinavir) used with AZT and 3TC.

Sustiva, approved by the FDA on Sept. 18, 1998, was selected in December to be included in an update of "Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents," developed by the Panel on Clinical Practices for

Treatment of HIV Infection convened by the Department of Health and Human Services in Washington, DC, and the Henry J. Kaiser Family Foundation.

A Sustiva combination could be an effective alternative for patients who have become non-compliant with their HAART because of side effects caused by the protease inhibitor.

"Then we can use the protease inhibitors later on if needed, and avoid some of the side effects," says Tashima, who was a principal investigator in the Sustiva study and is an assistant professor of medicine at the Miriam Hospital of Brown University in Providence, RI.

"The drug itself is easy to take because it's just three pills at night with no food restrictions," Tashima adds. "Once-a-day drugs are the way we're going to improve patients' adherence to medications."

A British study of Sustiva found that patients who had experienced peripheral fat wasting (lipodystrophy) while on protease inhibitor therapy experienced various physical improvements after their regimen was changed to Sustiva plus two nucleoside reverse transcriptase inhibitors. These positive results included a significant weight gain at 12 and 24 weeks, a modest reduction in abdominal circumference, and a general improvement in appearance.³

48-week trial demonstrates durability

First introduced as a 24-week study at the 12th World AIDS Conference in Geneva in June 1998, the Sustiva study was expanded to 48 weeks, meaning its success rate has held up over nearly a year's time.

"The 48-week trial is important because one worry about the non-nucleoside class, such as efavirenz, is that, yes, they are potent, but how durable would they be, and how long would the potent activity last?" Eron says.

"This was the first time ever a large randomized study showed that a regimen without a protease inhibitor could be as successful as those with it," says **Laurent Fischer**, MD, senior vice president of the virology group at DuPont. "Using it once daily, Sustiva is a much more convenient and better tolerated drug," he says.

The protease inhibitor Crixivan reportedly has adverse effects of gastrointestinal intolerance,

nausea, headache, blurred vision, dizziness, rash, hyperglycemia, fat redistribution, and lipid abnormalities.

Research showed that Sustiva's most alarming side effects were a rare rash and central nervous system symptoms such as insomnia, vivid dreaming, confusion, and impaired concentration.⁴ Some patients also experienced dizziness. "Those side effects are seen early in treatment and disappear in a matter of weeks," he adds.

Also, pregnant women should not be given Sustiva because birth defects have been observed in animals that received the drug.

DuPont recommends that patients take the drug at night a few hours before they go to bed and to begin on a Friday night, so they have the weekend to adjust to it. Some physicians have been splitting the dose, having patients take half in the morning and half at night, although that has not helped to reduce the symptoms or affect the efficacy, Fischer says.

"We put a lot of emphasis on how it was important to educate patients about the side effects before they started treatment," Fischer says.

With a price tag of about \$3,900 a year, Sustiva is 28% to 38% cheaper than protease inhibitors, Fischer says.

A minor problem with the Sustiva study is that it was not a blinded study with a placebo, Kuritzkes and Eron note. Patients knew whether they were getting efavirenz or a protease inhibitor because the regimens are so different that patients would have known which drug they were taking in any event.

The analysis indicated that most of the patients who dropped out of the study did so because of drug-related toxicity. "But it's hard to evaluate toxicities objectively when patients know what drug they're on," Kuritzkes says.

Some additional Sustiva trials included the drug as part of a protease-inclusive or protease-sparing regimen, and found that 66% of patients given a combination of Sustiva and indinavir maintained undetectable levels of HIV at 108 weeks.

On the bright side, both the Sustiva and abacavir studies mean clinicians will have more choices for HAART, Eron says.

"I think we can tailor or adapt our treatment regimens to fit our patients even better now," Eron says. "And I think in general what we're

going to see over the next year is that more patients are started on treatments that do not contain protease inhibitors."

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Clinicians should check women with HPV for HIV

Research: Focus on female genital ulcer infections

Researchers at the recent 6th Conference on Retroviruses and Opportunistic Infections highlighted new studies that show why HIV prevention efforts should focus on women who have sexually transmitted diseases, such as genital human papilloma virus (HPV).

Research presented at the Chicago conference follows two other studies investigating the prevalence of genital ulcers in women who are infected with HIV.

The body of evidence indicates that when clinicians examine a woman who has HPV or a genital ulcer, they also should suggest she be tested for HIV.

“Some studies show that patients with genital ulcers are at higher risk for HIV, perhaps because the ulcer provides a portal of entry for the virus,” says **Kristen Mertz**, MD, medical epidemiologist with the Division of STD Prevention at the Centers for Disease Control and Prevention.

“Also we have a few studies that have detected HIV DNA in the ulcers, so we think HIV-positive patients with ulcers are more likely to transmit the virus,” Mertz says.

HIV prevention efforts should target all patients — male and female — who have genital ulcers, she adds. Clinicians also should become aware of which diseases cause ulcers most commonly in their areas. For example, clinicians in Jackson, MS, found an outbreak of chancroid in 1994, which typically is far less common than genital herpes and syphilis. Because chancroid is so rare, clinicians often misdiagnose it.

“They should know if there’s chancroid around, or if all ulcers are caused by herpes or syphilis,” Mertz advises. “It’s important to get the ulcers treated appropriately so they will heal quickly, and the message for patients is to abstain from sex when ulcers are present.”

Five studies presented at the retrovirus conference focused on HPV, and a sixth compared syphilis serology between HIV-positive and HIV-negative women.

HIV clinical trials traditionally have overlooked women, but recent research is reversing this trend, according to **Karin Nielsen**, MD, MPH, a clinical instructor in the department of pediatrics at the University of California – Los Angeles School of Medicine and an attending physician at the UCLA Children’s Hospital in Los Angeles.

Nielsen, in an article for *Medscape*,¹ describes the HPV and syphilis studies presented at the conference as follows:

Fifty-five percent of HIV-positive women in a study of vulvovaginitis had HPV, for a total of 171 out of 365 women studied. This compares to 33% of non-HIV infected women having HPV, for a total of 91 out of 335 seronegative women. Also, 26 or 7% of HIV-infected women had identifiable lesions at any site. Only two uninfected women had identifiable lesions. The study showed that risk factors for lesion development included CD4 absolute counts of less than 500 cells/mm³ and HPV seropositivity at entry.²

Another study of HPV persistence in HIV-infected women showed that 268 women who had been tested for HPV were re-evaluated. Of these, 22% had not had positive HPV tests at baseline. However, while 74% of non-HIV infected women cleared their HPV infection, only 16% of HIV-infected women with a CD4 T-cell count of less than 200 cells/mm³ were cleared of HPV infection.³

A study of 141 HIV-infected women conducted between March 1996 and January 1999 showed that HPV was more frequently detected in women with lower CD4 T-cell counts. As the women received more intensive antiretroviral therapy (ART), their CD4 T-cell counts increased and their HIV viral load decreased. The women were given Pap smears, and 45% had an abnormal Pap smear at their first visit. The study found that 82% of the women who had abnormal initial Pap smears had HPV, and half the women with normal Pap smears had the presence of HPV DNA.⁴

Study finds vitamin A deficiency

Another group of researchers found an association between vitamin A deficiency and HPV infection in HIV-positive women.⁵ Also, another study compared treating cervical lesions with topical 5-fluorouracil (5-FU). It found that using 5-FU as maintenance therapy for HIV-infected women with cervical lesions, class II or III, produced fewer incidents of recurrent dysplasia. Specifically, 50 women were given 5% 5-FU topical cream, 1 g every two weeks for six months. Another 51 women were observed as part of a control group. Local side effects were not significantly different from the treatment and control groups. But of the treated women, only 28% had recurrent dysplasia, as compared with 47% of the control group women observed.⁶

A sixth study involved a comparison of syphilis serology between 855 HIV-positive and 434 HIV-negative but at-risk women. Researchers tested for syphilis via nontreponemal antibody tests and confirmed with a fluorescent treponemal antibody absorption test. They performed 4,064 syphilis tests over 24 months; 91% of these were negative according to the screening test, 7% were true-positive, and 2% were false-positive. The rate was the same for both groups, and HIV

infection did not lead to an increase in false-positive syphilis serologies.⁷

Mertz and the CDC were involved in two studies, published last year in the *Journal of Infectious Diseases*, that looked at genital ulcers and HIV. Those studies' findings were as follows:

In 1994, clinicians in Jackson, MS, noted an apparent outbreak of atypical genital ulcers. Of 143 patients with ulcers, 56 (39%) were positive for *Haemophilus ducreyi* (the bacterium that causes chancroid); 44 (31%) had herpes simplex virus; 27 (19%) had *Treponema pallidum* (the bacterium that causes syphilis); 12 (8%) were positive for more than one organism. Clinicians tested 136 of these patients for HIV and found that 14 (10%) were HIV-seropositive, compared with none of 200 patients without ulcers. Plus, HIV-1 DNA was detected by a multiplex polymerase chain reaction (PCR) assay in ulcers of six of the HIV-positive patients.⁸

Another study was conducted in 10 U.S. cities to determine the etiology of genital ulcers and to assess the prevalence of HIV infection in ulcer patients. Clinicians collected ulcer and serum specimens from about 50 ulcer patients at a STD clinic in each city. Herpes simplex virus (HSV) was detected in more than 50% of specimens from all cities except Memphis, TN, which had 42%. HIV seroprevalence in ulcer patients ranged from 0% to 18%.⁹

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New supplement treats AIDS wasting successfully

Pilot shows weight gains in muscle

Wasting syndrome long has caused serious problems for about one in four AIDS patients, causing them to gain more fat mass while their overall body weight declines significantly. The syndrome robs them of lean body mass and sometimes leads to muscle weakness and organ failure.

Clinicians most commonly have treated AIDS wasting with testosterone injections or injections of a human growth hormone, such as Serostim, manufactured by Serono Laboratories in Norwell, MA. **(See story on AIDS wasting in AIDS Guide for Health Care Workers, inserted in this issue.)**

However, patients sometimes discontinue these treatments because of side effects. And the injections require prescriptions and careful medical oversight.

Now a new study presented at the 6th Conference on Retroviruses and Opportunistic Infections in Chicago suggests there might be an easier treatment that has no known side effects and does not need to be prescribed or injected. The treatment is a mixture of β -hydroxy β -methylbutyrate (HMB),

So how does the elixir work?

An over-the-counter supplement containing β -hydroxy β -methylbutyrate (HMB), arginine, and glutamine has a variety of potential health benefits that could greatly help people living with HIV/AIDS.

MTI BioTech of Iowa State University Research Park in Ames, IA, manufactures the orange-flavored drink, called Juven, and provides this guide to its ingredients:

- **HMB:** This biochemical is produced naturally in the body from proteins containing the amino acid leucine.

Earlier studies have shown evidence that HMB greatly increases the muscle-building and fat-reducing effects of resistance training in healthy men and women, and that it may be a critical element for increasing and preserving muscle size and function. It also may offer benefits to the cardiovascular system and accelerate fat loss while maintaining lean body mass during periods of caloric restriction.

Research also suggests HMB can support the body's natural immune system function during times of stress.

- **Arginine:** This is a semi-essential amino acid that can be used in protein synthesis and biosynthesis of other amino acids and plays a key part in elimination of excess protein nitrogen in the urea cycle.

Studies have shown that there is a greater demand for arginine during anabolism or growth, and researchers theorize that the demand for arginine may increase during periods of stress, such as injury and illness.

Also, arginine may increase lymphocyte response to immune system stimulation, especially in cancer, and it may enhance wound healing by increasing the amount of collagen deposited into the wound.

Research also shows that arginine may increase the total protein content at the wound site.

- **Glutamine:** Glutamine is the most abundant amino acid and can be synthesized by nearly all tissues. It's the primary carrier of nitrogen between tissues and organs in the human body.

The intestinal tissues use glutamine as a primary energy source rather than glucose, and it's needed to maintain muscle function and size.

Research suggests that during periods of excessive cellular turnover, such as tumor progression and recovery from trauma and infection, there tends to be a depletion of muscle glutamine stores, so a supplement of glutamine may be necessary.

For more information, contact MTI BioTech Inc., Iowa State University Research Park, 2625 North Loop Drive, Suite 2150, Ames, IA 50010; telephone: (877) 465-8836; Web site: www.juven.com. ■

arginine, and glutamine that patients take in the form of an orange-flavored drink mix. The mixture, called Juven, is made by MTI Biotech in Ames, IA, and is sold over the counter as a dietary supplement. (See description of Juven, above.)

A double-blind, placebo-controlled study targeting 68 AIDS patients who had lost more than 10% of their body weight had remarkable outcomes, says **Robert H. Clark**, MD, director of HIV clinical services for Nassau County Medical Center in East Meadow, NY. The clinic treats more than 900 AIDS patients, 600 of which are regular patients.

"It was a pilot study and it showed unbelievable results," Clark says. "We had a control group

and we had a group we gave the Juven to, and after eight weeks the Juven group gained more muscle than they would in just about any treatment regimen out there."

The Juven study group gained an average of 6.5 pounds over eight weeks, including a 5.5-pound gain of muscle weight. The placebo group continued to lose muscle at an average of 1.5 pounds during the eight-week period.

Clark's team saw no significant side effects with the supplement, and some patients reported that their diarrhea and bowel problems were reduced.

The study also found that the participants taking Juven had an increase in T-cells and their HIV

Improvement in Immune Status in Wasting AIDS Patient by Providing Muscle and Immune Tissue-Specific Nutrition

Parameter	Placebo Eight week change	HMB/Arg/Gln Eight week change	p<
Lymphocytes, 1000/mm ³	-0.31	0.29	0.007
CD3/mm ³	-2.46	211	0.01
CD4/mm ³	-49	17	0.10
CD8/mm ³	-188	167	0.02
VL, log copies/ml	0.40	-0.29	0.007
VL>400 (n=28), log copies/ml	0.64	-0.046	0.007

Source: PCP, wasting/protozoa, and other organ system complications (poster session #86). 6th Conference on Retroviruses and Opportunistic Infections. Chicago; Feb. 1-5, 1999.

viral loads decreased. The control group's viral load increased. (See chart detailing results, above.)

"The other exciting news was about lipodystrophy, where patients start to get fat in all the wrong places and start to look funny and complain horribly about it," Clark says. "With Juven, they tended to redistribute their fat back to a more normal distribution pattern."

Researchers found that change by measuring the patients' total body fat using a volume displacement machine and then measuring their arms and legs with circumference measurements and calipers, he explains. They also did a CT-scan of the patients' thighs.

"Here all they had was nutrients, and their fat seemed to distribute to a more normalized pattern, and they gained five pounds of muscle in eight weeks," Clark says.

Clark says clinicians should use Juven as a preventive measure and have AIDS patients take the supplement before they lose body weight from wasting. "You don't want to start after wasting begins; instead, just head them off at the pass."

The supplement, consisting of two amino acids and HMB, was developed at Iowa State University in Ames, where scientists were interested in the growth of muscle and preventing muscle breakdown. Clark says they isolated HMB and discovered its importance to muscle development. "It's been used by body builders to build more muscle, and it's been used in a lot of studies of animals

that have shown how to increase muscle mass in chicken breasts, for example."

The supplement comes in little packets and costs less than \$180 per month. Clark recommends patients take one package mixed into eight ounces of water twice a day. It has a pleasant orange taste, and the company is developing other flavors.

Clark and other researchers soon will conduct more studies with Juven, looking at whether AIDS patients taking the supplement have fewer emergency room admissions, fewer bouts with pneumonia, less diarrhea, and other problems.

"We'll follow patients over a longer period of time to see whether they sustain the weight gain and to see if they get a better response to decreasing infections," Clark says. "It seems pretty promising that I might get a decreased utilization of health care resources from these patients." ■

CDC stats show unsafe sex practices are increasing

AIDS group calls for greater HIV prevention focus

It's becoming clear that Americans are returning to unsafe sex practices, which could lead to a new statistical bump in the HIV infection python, a national AIDS advocacy group says.

"It's true we've done a good job on investing in AIDS research and treatment, and as a result the AIDS death rate is coming down dramatically,"

says **Daniel Zingale**, executive director of AIDS Action, a Washington, DC-based group that represents 3,200 community-based organizations that serve people with HIV/AIDS.

"But we haven't invested in prevention, so HIV infection rates are going up," Zingale says.

Zingale specifically refers to the recent Centers for Disease Control and Prevention *Morbidity and Mortality Weekly Report*¹, which shows an increase in the percentage of men engaging in anal sex without using condoms between 1994 and 1997.

The *MMWR* referred to an annual street survey conducted by The Stop AIDS Project in San

Francisco. The survey, taken of 21,000 men found in bars, neighborhoods, and at outdoor events in San Francisco, found that the percentage of men who have sex with men who reported having had anal sex increased from 57.6% in 1994 to 61.2% in 1997. Among those men, the percentage reporting that they always used condoms declined from 69.6% in 1994 to 60.8% in 1997. And the most pronounced decline in consistent condom use occurred among men in the 26-29 age group.

The same survey also found that the proportion of men who reported having had multiple sex partners and unprotected anal intercourse increased from 23.6% in 1994 to 58% in 1997. These increases occurred in all racial groups.

The CDC also reported that male rectal gonorrhea incidence declined from 1990 through 1993 from 42 per 100,000 adult men in 1990 to 20 per 100,000 adult men in 1993. However, the trend has been reversed. In 1997, the male rectal gonorrhea rate had increased to 38 per 100,000 adult men, and the rate was highest among men ages 25-34, with a rate of 83 cases per 100,000 men in that age group.

AIDS complacency takes a toll

The survey's findings suggest that Americans are beginning to lose their fear of HIV infection, Zingale says. "It confirms our fears about AIDS complacency taking a toll," he says. "I think in part it's driven by the misperception that the worst is over, and the good news about medical breakthroughs has raised some people's hopes beyond reason."

Zingale's group blames the trend partly on what they say is the federal government's lack of interest in HIV prevention. "For the past four years the Clinton administration has invested no new money for HIV prevention," he says.

Specifically, AIDS Action reports that CDC funding for prevention efforts was \$617 million in fiscal year 1997, \$634 million in fiscal year 1998, and \$657.8 million in fiscal year 1998, with \$666 million proposed in the 2000 fiscal year.

Another controversy is that some communities and states are resisting programs that allow injecting drug users to exchange dirty needles for clean ones. A recent *New York Times* article reported that New Jersey officials not only prohibit needle exchanges, but also arrest volunteers who engage in the practice.²

FY2000 Appropriations Levels for Federal AIDS Programs

(as of Feb. 1, 1999; increases or decreases from previous year are shown in parentheses)

PROGRAM	FY99 FINAL	FY2000 President's Budget Request 2/1/99
CDC: Prevention	\$657.8m	\$666m (+\$9m)
HRSA: Ryan White CARE Act Total	\$1,411.6m	\$1,511m (+\$100m)
Title I	\$505.2m	\$521m (+\$16m)
Title II: Care Services	\$277.3m	\$287m (+\$10m)
Title II: ADAP	\$461m	\$496m (+\$35m)
Title III	\$94.3m	\$130m (+\$36m)
Title IV	\$46m	\$48m (+\$2m)
Title V: AETCs	\$20m	\$20m (+0)
Title V: Dental Reimbursement	\$7.8m	\$8m (+\$0.2m)
NIH: AIDS Research	\$1,792.9m	\$1,833.8m (+\$40.9M)
SAMHSA (Substance Abuse Prevention & Treatment Blockgrant)	\$1,585m	\$1,615m (+\$30m)
HUD: HOPWA	\$225m	\$240m (+\$15m)

Source: AIDS Action, Washington, DC.

AIDS funding for 2000 falls flat, critics charge

President Clinton's FY2000 budget for federal AIDS programs is nothing to boast about, according to AIDS Action, an HIV/AIDS advocacy group based in Washington, DC.

Funding levels for prevention and care services have only small increases over the FY1999 budget, the group says. **(See AIDS Alert, December 1998, p. 135.)** For example, prevention funding increases only \$9 million to a total of \$666 million, in spite of recent studies showing that unsafe sex practices are on the rise. **(See story on unsafe sex, p. 43.)**

Also, the budget proposes no new funding for AIDS Education and Training Centers, and substance abuse treatment programs have only a 2% proposed increase.

AIDS activist Diana McCague, who had been distributing clean needles to drug addicts since 1994, has been arrested twice. Her last arrest in the fall of 1998 forced her organization, Chai Project in New Brunswick, NJ, to stop distributing syringes and resort to distributing condoms, brochures, and bleach kits to sterilize needles.

AIDS makes orphans of 9,100 NJ kids

Meantime, New Jersey has the nation's highest rate of HIV infection among women and children, including 9,100 orphans whose mothers have died of AIDS. And even the businessman who heads the state's Advisory Commission on AIDS has reached the conclusion that a needle-exchange program could cut the state's number of new HIV infections by as much as 50%.²

State officials, such as New Jersey Gov. Christine Todd Whitman, say distributing clean needles will encourage people to become drug addicts. Zingale disagrees. "It's the same mentality that making a condom available to a young person encourages them to have sex."

Adding to the controversy is the federal ban on needle-exchange funding, he adds.

AIDS Action has its own 10-point plan to reduce the HIV infection rate. The plan is as follows:

1. Increase federal HIV prevention funding by 25%.
2. Provide treatment on request to help stem the twin epidemics of drug abuse and AIDS.
3. Launch national roll-out of proven HIV prevention counseling with CDC grants and comprehensive HIV prevention programs for adolescents.
4. Make HIV testing safe, swift, and simple, including using CDC testing vans to reach people who might not go to a clinic or doctor's office.
5. Use state-of-the-art marketing to sell prevention efforts, including a new HIV prevention ad campaign; enlisting the help of adolescents to design and test ads intended for their generation; allowing condom ads on programs rated "S" for sexual content under the new TV rating system; and building comprehensive sexuality education curricula that are not limited to teaching abstinence.
6. Put the AIDS hotline on-line to reach young people, such as an HIV/AIDS Prevention Web Page with links from popular Web sites used by at-risk populations.

7. Launch an anti-stigma and healthy living campaign for people living with HIV.
8. Have the surgeon general launch a nationwide campaign for HIV prevention for women and people of color.
9. Promote physician patient dialogue about HIV risks, making grants available to AIDS Education and Training Centers to promote better HIV/AIDS knowledge in the medical community.
10. Make HIV vaccine development a top priority of the federal government.

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NIH study shows adult immune system rebuilds

You can teach old thymus gland new tricks

The thymus is functional and active well into adulthood, and this news holds great hope for HIV-infected patients who have seen their immune system beaten down by the virus.

While it's commonly known that highly active antiretroviral therapy (HAART) can stop HIV from causing further damage, no one knew whether the existing damage could be reversed. A new study suggests this is possible.

"Say HIV destroys some of your T-cells that are programmed to fight a certain infection," says **Richard Koup**, MD, chief of infectious disease at the University of Texas Southwestern Medical Center in Dallas. "Then with HAART treatment, the thymus should be able to recreate those T-cells that were lost." Koup and **Daniel C. Douek**, MD, PhD, led a research team that measured a genetic by-product of T-cell development in blood samples from 10 HIV-infected and 30 uninfected people.

"If the thymus wasn't active, you'd never be able to recreate those lost T-cells," Koup adds. "So it's a very positive message for HIV patients,

and it's just one more reason for them to stay on their antiretrovirals and keep the virus down."

The study belies commonly held beliefs that the thymus gland loses its ability to regenerate cells in adults.

"Previously, the thought was that the thymus was active when you were young, but there is a dramatic decline in size and function with age," says **Patricia D'Souza**, PhD, senior scientist with the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (NIH) in Bethesda, MD. NIH helped fund the study, which was published in *Nature*.¹

"Think of T-cells as alphabet soup, and then some pathogen comes along and wipes out ABC, and we never knew if there was a way to replace them," D'Souza explains.

Tracking the origin of new T-cells

Researchers set out to determine whether naive T-cells found in adults were from the thymus or were pre-existing cells standing in the periphery, Koup says.

If the T-cells came from the thymus, then it would mean they were new and therefore recently produced by an adult's thymus. The alternative would be that the cells arose through expansion of existing naive T-cells in the periphery.

However, determining whether the T-cells were new or existing was no easy feat.

"We had to develop an assay to tell us how the cells were coming out of the thymus," Koup says. "Other investigators had done the background work to address that question."

Before T-cells are released from the thymus, they generate circular fragments of DNA called T-cell receptor rearrangement excision circles (TRECs). Studies have shown that TRECs are stable and are not reproduced during subsequent cycles of cell division, so they're present in naive T-cells but not in memory T-cells, which are the cloned descendants of cells that have already encountered a specific antigen.

"As T-cells encounter a pathogen, they respond and then become a memory cell, and then they either die or they enter a memory department," D'Souza explains. "What we didn't know is if these T-cells lived so long if they were generated only in the young, or [because] they could regenerate as a person ages."

Koup's team hypothesized that through the presence or absence of TRECs, they could identify which T-cells had recently left the thymus. TREC quantity declines significantly with age.

"As the cells divide with age, TRECs get diluted," D'Souza says. "The more TRECs you have, the younger the cell is."

Also, an analysis of blood samples from HIV-infected people showed that their TREC levels were significantly lower than TREC levels in blood of healthy people of the same age groups. All but one of the HIV-infected individuals showed a rapid and sustained increase in TRECs after receiving HAART.

Children produce more new T-cells

The study showed that young people have many more of the TREC markers than older people, but even in people over age 70 there still were markers indicating freshly minted T-cells. For instance, children have 10 times the output from their thymus as do adults, Koup says.

"If you consider the rate of production of T-cells from the thymus, it's a slow trickle in an adult, and in a child it's a wide-open faucet," he adds.

This means children who have HIV should be able to recover their immune system potency much faster than adults. "With the treatment with HAART, what we hope is that the child's immune system will be reconstituted much more rapidly, and if we can keep the virus suppressed, then it might lead to a much more normal life for that child," Koup says.

But this discovery still holds promise for adults.

COMING IN FUTURE MONTHS

■ New behavioral change program causes greater AIDS drug compliance

■ Advanced-generation protease inhibitor has better tolerability

■ People who work with AIDS patients need not fear TB

■ Experts address long-term services for AIDS patients

■ AIDS epidemic sweeps India, Zambia

"The first message is, the thymus is active well into retirement age, and now we have a way of measuring thymic output," D'Souza says.

The research could lead to therapies that pump up the thymus' function and help it pump out more new T-cells in adults, as well. "One of our hopes is to measure thymus output, and that we can come up with therapies to increase the output of the thymus," Koup says.

These therapies could help HIV-infected patients and cancer patients after chemotherapy treatment. "Patients undergoing bone marrow transplants for whatever reason could benefit, so this is another example of how research in one area could benefit patients who have many different diseases," Koup adds.

In summary, the study's findings were the following:

- Thymic activity becomes less efficient as people age, and therapies that directly improve thymic function in adults may increase the rate of immune reconstitution after HAART.

- Changes in TREC levels occur early in HAART treatment and are indicative of thymic potential for reconstitution of naive T-cells.

- Thymic function in HIV-infected adults may be suppressed, and it can be improved by the reduction of viral load.

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Study: Virus may live up to four weeks in syringes

Researchers simulate illicit drug-use conditions

HIV-1 cells that are capable of reproducing can survive in syringes for up to four weeks, say researchers who claim the study highlights the importance of government-sponsored needle-exchange programs to reduce the spread of HIV through drug addicts sharing dirty needles.

If HIV-1 can survive for more than two weeks in a syringe, then it could be spread quickly among an addict community, as research has shown that people in some cities reuse and

share needles seven or more times, on average.¹ When states or cities ban needle-exchange programs, addicts may use needles for even longer periods of time.

"It tells us that needle-exchange programs are effective," says **Nadia Abdala**, PhD, a post-doctorate associate and researcher in the department of public health at Yale University School of Medicine in New Haven, CT. Abdala co-wrote the study, published in January in the *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*.

Needle-exchange programs reduce the circulation time of syringes and prevent people from sharing them, Abdala says. When needles were distributed, collected, and tracked by a New Haven syringe exchange program, investigators found that the average circulation time of syringes

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was seven days at the start of the exchange program, but it dropped to less than three days once the program was fully operational.¹

Previous studies have attributed three out of 10 cases of AIDS to the use of HIV-1-contaminated syringes during illicit drug use.^{1,2}

Drug users can contaminate needles when the plunger is withdrawn until blood becomes visible in the barrel of the syringe, which ensures that the syringe is inserted into a vein. In a worst-case scenario, which is what the study simulated, a drug user will pull up on the plunger a second time, introducing blood into the barrel of the syringe that mixes with the remaining drug solution.

Researchers worked on experiments and preliminary studies for two years, Abdala says. They found that infectious HIV can survive for as long as four weeks inside a syringe that contains one or two microliters of blood, Abdala says.

The study used a microculture assay that was sufficiently sensitive for the propagation of HIV-1 from small volumes of whole blood.

Study simulations based on field reports

“We worked with people who work in the field and have direct contact with injection drug users,” she says. “They report what practices drug addicts are using, and we used simulations in the lab to try to repeat what they were doing.”

The study also reported these findings:

- Syringes with detachable needles are riskier for HIV transmission because they harbor more blood between the plunger and the base, and when the needles are replaced it can extend the life of the syringes.

- Further studies should examine whether postinjection flushing with clean water may significantly lessen the chance of HIV-1 transmission when clean syringes and bleach are unavailable.

- The experiments showed that the likelihood of encountering a potentially infectious syringe decreased with time, and the risk increased if the volume of infected blood was larger.

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- 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. ■