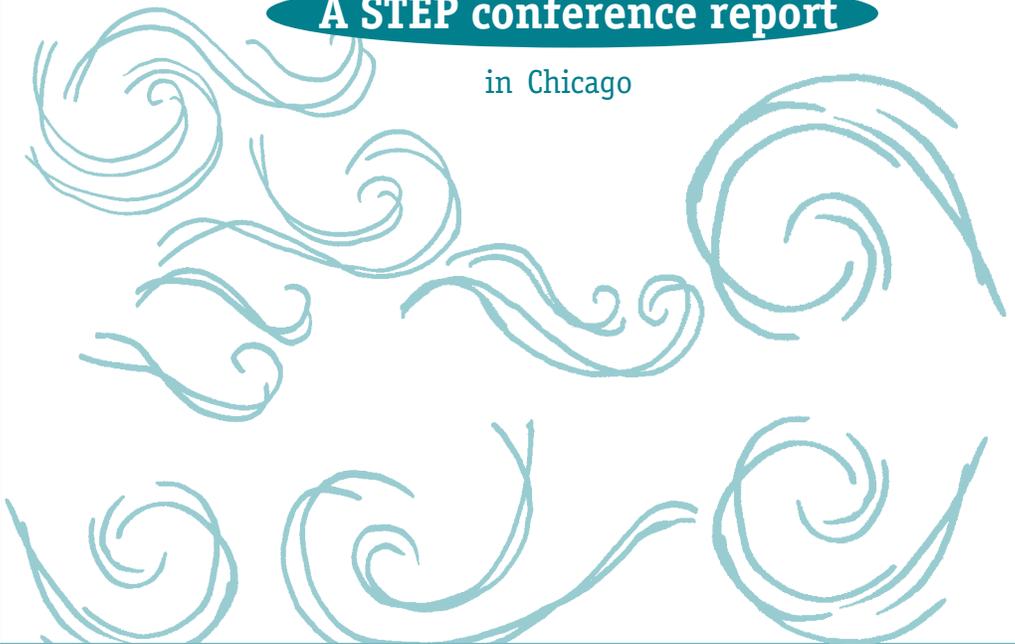


# The 8<sup>th</sup> Conference on Retroviruses and Opportunistic Infections

A STEP conference report

in Chicago



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# The 8<sup>th</sup> Conference on Retroviruses and Opportunistic Infections

## A STEP conference report

Reported by: Jeffrey T. Schouten MD, Quinten Welch, executive director, and Erica Didier, lead treatment educator, STEP

The 8<sup>th</sup> Annual Conference on Retroviruses and Opportunistic Infections (Retrovirus) met in Chicago from February 4-8, 2001. There were over 3,500 basic and clinical researchers, community scholarship recipients, and community press representatives from 58 countries in attendance. The purpose of the Retrovirus Conference is to bring together basic scientists and clinical researchers to facilitate translational research, moving laboratory findings into clinical trials.

Many of the lectures and symposia are available for viewing on the conference's website ([www.retroconference.org](http://www.retroconference.org)). Posters and abstracts, referenced and numbered in parentheses in this report, are also available on the website.

This year's conference highlighted the global impact of AIDS, and the lack of affordable, accessible treatment for the vast majority of people living with HIV, 90% who live in the developing world. In keeping with that emphasis, STEP will begin this conference report reviewing these issues.

## The African epidemic

The opening session included two very moving presentations, from Kevin DeCock of the Centers for Disease Control (CDC), and Jeffrey Sachs, an internationally prominent Harvard University economist. DeCock reviewed the devastating impact of AIDS in the developing world, most notably sub-Saharan Africa. He also noted the international response to Africa has been astonishingly small, asking the conference attendees to consider the following questions: What would we do if the United States faced African HIV infection rates? Are we accepting in Africa what would be unacceptable if it were in the US?

Professor Sachs began his talk by emphasizing that the only missing factor for addressing the African AIDS epidemic is money. Because of severe poverty in sub-Saharan Africa, even prevention efforts, let alone HIV treatments, are out of reach. Sachs estimated that the cost of controlling the African epidemic would be only \$2 billion. He pointed out that this is a "vanishingly small amount," trivial when compared to President Bush's proposed \$2 trillion tax cut in the US. He emphasized that two to three million lives could be saved in sub-Saharan Africa with a cost of only \$5 per person, per year, to developed countries.

The lack of world leadership has also hindered the process. Sachs noted that former President Clinton did not do enough for this issue, using the example of a pledge made last year to provide \$10 million in US aid during a presidential visit to Africa that cost \$25 million. Sachs noted that Clinton could have stayed home and sent all \$35 million. Another major obstacle has been the refusal of the World Bank to identify HIV treatment as a priority.

In addition, cooperation from the pharmaceutical industry is essential. For any plan to be effective, anti-HIV medications will need to be provided by the manufacturers at or near their production costs. Sachs predicted that the current lawsuits by drug companies attempting to prevent Uganda, South Africa, and Brazil from making cheap generic versions of anti-HIV drugs, as well as attempts by the World Trade Organization (WTO) to invoke sanctions against those countries,

will be a public relations disaster for the pharmaceutical industry. He also expressed his beliefs that intellectual property rights (patents) should not be enforced over human rights. Sachs was optimistic that the pharmaceutical industry may be more willing to cooperate with President Bush, feeling more secure that a Republican administration will protect their US markets, allowing them to maintain profits and recover research and development costs.

Sachs ended his talk with a five-fold call to action:

1. Conduct a trial of antiretroviral therapy (ART) in Africa.

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2. Make the World Bank commit to supporting these initial trials.
3. Make drug companies commit to providing the drugs *at cost*.
4. Have developing countries agree to support the plan
5. Emphasize that this plan would require only \$1 billion/year from the US.

At the closing session of the Retrovirus Conference, Dr. Anne-Valérie Kaninda, from Médecins sans Frontières (MSF, Doctors without Borders) addressed the conference and reiterated many of the above points. She also emphasized the secondary benefits of providing treatment, such as encouragement of testing, and battling discrimination and stigma. Commenting on the global response to the African AIDS epidemic, Kaninda criticized the WHO for refusing to list HIV medicines as essential medicines. Dr. Kaninda also announced that an Indian company had just agreed to make a generic three-drug antiretroviral regimen for MSF, containing stavudine/d4T (brand name Zerit), lamivudine/3TC (brand name Epivir), and nevirapine (brand name Viramune) for less than \$350 a year per person. This same regimen would cost about \$1,000 per year in the US. MSF is setting up clinics in 53 developing countries to treat HIV, but they have to rely on volunteers and have very few resources. Dr. Kaninda also noted the impossible task of deciding whom to offer treatment to when there are only enough resources to treat 1/10,000 people who need the treatment.

## Epidemiology and Transmission

### “Secondary” prevention aimed at HIV-positive people

A new concept that is gaining momentum nationally with the Centers for Disease Control and Prevention (CDC) is the idea of developing HIV/AIDS prevention programs aimed at HIV-positive,

rather than HIV-negative, individuals. A number of abstracts and discussions dealing with this topic, often called “secondary prevention,” were presented at Retrovirus. In particular, one symposium explained a new CDC program called the Serostatus Approach to Fighting the [HIV] Epidemic (SAFE). This initiative promotes interventions for HIV-positive people, to prevent transmission to sexual partners. SAFE focuses on (1) testing and diagnosing all HIV-positive individuals, (2) linking people to appropriate, high-quality care and prevention services, (3) helping individuals adhere to treatment regimens, and (4) supporting individuals in reducing HIV transmission risk behaviors.

### Early HIV diagnosis adds to prevention efforts

Evidence to support the idea of secondary prevention came from many abstracts. One of these dealt with the level of high-risk behaviors among people recently infected or newly diagnosed with HIV (Abstract 216). This study involved HIV-positive men and evaluated the factors associated with continued high-risk behavior. One hundred and sixteen individuals diagnosed with HIV, many during acute or primary infection were recruited within three months of their diagnosis for an interview study with 2-year follow up. Sixty-two of the individuals have completed both the interviewer-administered questionnaire given at baseline and the one given at 12 months post-diagnosis. Researchers looked at changes in HIV transmission behaviors and any associations between recreational drug use and high-risk behavior.

Many participants reported reducing recreational drug use following HIV diagnosis (84% at baseline and 58% at 12-month follow up). Most also reported a reduction in the number of sexual partners. At baseline, 74% of men who have sex with men (MSM) had more than 5 partners in the previous 6 months, while only 50% reported that many partners at 12 months. For men who have sex with women, the percentage reporting more than 5 partners in the previous 6 months dropped from 22% at baseline

to 0% at 12 months. Reductions in sex in bathhouses, sex clubs and other public sex environments among MSM also dropped (63% at baseline and 44% at 12 months).

Of the small number of participants who reported continued drug use after HIV diagnosis, there were increases in the percentage who reported that marijuana, speed or cocaine powder was their most frequently used drug (marijuana 10% to 67%, speed 10% to 30%, cocaine 4% to 16%). In MSM, marijuana use was associated with reports of sex with more than 5 partners in the previous 6 months.

The observed reductions in risk behavior among the majority of participants in the study, even in the absence of any targeted HIV prevention messages, emphasizes the importance of early HIV diagnosis as a means of preventing further transmission. The persistence of high-risk behavior in a significant proportion of respondents, however, points to the need for reinforcement of prevention messages among HIV-positive individuals. Prevention efforts could also be effective by targeting recreational drug use among MSM, which was associated with more risk behaviors.

### HIV rates and risk behaviors continue to increase among young MSM

Several presentations and posters at Retrovirus highlighted recent trends in HIV epidemiology. One study, in particular, received a great deal of attention from the popular press. The study, conducted by the CDC from 1998 to 2000 in Baltimore, Dallas, Los Angeles, Miami, New York and Seattle, found that the rates of HIV infection in men who have sex with men (MSM) aged 20-30 were alarmingly high (Abstract 211). In this ongoing study called the Young Men’s Survey (YMS), epidemiologists surveyed more than 2,400 men at bars and other places frequented by young MSM and conducted extensive interviews. The prevalence of HIV among MSM ranged from a low of 5% in Seattle to 18% in Dallas, and there was a high level of “risky” sexual behavior in all six-cities.

According to the most recent findings from YMS, 12% of MSM who were between 23 and 29 years old were HIV-positive. The incidence increased with age within this group, from 10% among 23- to 25-year-olds to 14% among 26- to 29-year-olds. The study found that among the men surveyed, 30% of African-Americans, 15% of Hispanics, 7% of non-Hispanic whites and 3% of Asian-Americans are infected with the virus.

Forty-six percent of participants said they had unprotected anal intercourse in the preceding six months. Of the 293 HIV-positive men in the study, only 29% knew they were HIV-positive before being tested as part of the study. This information has alarmed the prevention community and the CDC suspects that a substantial proportion of current HIV transmission is from people who do not know that they are infected. Although there is no direct evidence of rising HIV infections among MSM in most areas, this and earlier studies raise suspicions that such an increase may be occurring.

### Evidence of sexual transmission of Hepatitis C Virus in a study of MSM

Another interesting transmission issue is whether or not there is sexual transmission of the Hepatitis C virus (HCV), especially among MSM. Most transmission of HCV is thought to be through blood-to-blood contact such as needle sharing during drug use. The objective of this study was to determine HCV prevalence and identify risk factors for HCV infection (Abstract 561). This study screened for HCV antibodies in blood samples obtained from sexually active MSM in Vancouver B.C. between 1982 and 1998.

A total of 39 of the 662 participants (5.9%) were identified as HCV-positive. HCV prevalence was significantly higher among HIV-positive men compared to HIV-negative men (31/352 versus 8/310). HCV-positive men had higher numbers of male sexual partners in the previous year (more than 20 partners, 74% vs. 48%) and in their lifetime (more than 100 partners, 80% vs. 62%).

Not surprisingly, a history of injection drug use was a significant risk factor for HCV infection. However, 49% (19/39) of HCV-positive men in this study reported never using injected drugs. When these non-injection drug using (IDU) HCV-positive men were compared to other non-IDU, specific sexual practices were identified as significant risk factors for becoming HCV-positive. These were oral-anal contact and insertive fisting.



There are many potential antiretroviral drugs in development, but most are still a couple of years away from approval by the Federal Drug Administration (FDA). The nucleotide analogue reverse transcriptase inhibitor (NtRTI) tenofovir is the closest to FDA approval and manufacturer Gilead has begun an expanded access program. (See note in this issue of the *STEP Perspective*.) It is widely recognized that medications must be developed that are less toxic, easier to take, that work on HIV that is resistant to existing medications, or that target new sites. The expectation a few years ago was that medications that inhibit the HIV enzyme integrase would be the next class of medications to be available. However, due to unfavorable aspects of the early agents, medications in this class are only now entering the first human trials. A class known as entry inhibitors is developing much more quickly than the integrase inhibitors.

There were several presentations of new non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) that (at least in the test tube), appear to be effective against resistant strains of HIV. (Abstracts 11, 12, 13). But these agents are only just beginning, or have not yet begun, human testing. A new PI, **BMS 232632** (BMS) has the appealing characteristic that it can be dosed once a day. A study presented at Retrovirus compared three different doses of BMS (200, 400, and 500 mg), to a Viracept regimen

(dosed three times a day), all combined with Zerit and Videx. (Abstract 15). (However, because BMS is better absorbed with food, and Videx needs to be taken without food, this would not be a true once-a-day regimen.) All people in the study were treatment-naïve. The 400-mg dose and the 500-mg dose of BMS both showed a similar ability to suppress the HIV RNA viral load to undetectable after 48 weeks. The fact that this observed HIV suppression was not better than Viracept's, however, is of concern, especially because several other available agents, including Viamune and Sustiva, have performed better than Viracept in trials with people who were nucleoside reverse transcriptase inhibitor-naïve. BMS does, however, appear to have a unique resistance pattern. Trials of BMS in PI-experienced people are underway.

### Entry inhibitors: A new class of anti-HIV medications

The most exciting new drugs that are moving into clinical trials are entry inhibitors. These drugs are designed to block the ability of HIV to enter cells, which is required for it to make copies of itself in the body. There are three critical steps in the entry process. The first is the **attachment** of a receptor on the surface of HIV, glycoprotein 41 (gp41) to the CD4 receptor on the surface of the body's cells. This triggers the second, **chemokine co-receptor binding**. Following this there is a critical change in the shape of the gp41 protein, leading to the third step, **fusion**. This complicated process allows HIV to inject its genetic message, or RNA, into the cell, and begin the process of replicating and infecting new cells.

There are many compounds now in early development that have the ability to block HIV's entry into the cell. These compounds work at different points in the above-mentioned pathway. As reported last year by Dr. Marty Hirsch, and shown in several posters at Retrovirus, these compounds have a greater effect when used together in the test tube. The compounds currently in development include an inhibitor of the CD4 receptor

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site on the virus (one example is PRO 542), CCR5 chemokine receptor inhibitors (such as Schering Compound C), CXCR4 inhibitors (like AMD 3100), and fusion inhibitors (including T-20 and T-1249, discussed below).

**T-20 and T-1249** are very small proteins that block the fusion process. They must be injected under the skin, once a day for T-1249, and twice a day for T-20. At the Retrovirus Conference the first results of a randomized trial of T-20 were presented. (LateBreaker 5). People who had detectable viral loads on their current anti-HIV medication regimens, and who had never received an NNRTI, switched to a new regimen of Ziagen, Sustiva, Agenerase, and Norvir, plus either placebo injections or T-20 injections. All injections were twice a day, and doses of 50, 75 or 100 mg were given for T-20. The only problems observed for people on T-20 were some mild to moderate discomfort at the injection site. One person did develop an injection site abscess that required medical treatment. There were 71 people in the study, and 53 had completed 16 weeks of treatment at the time of this report. The results were as follows:

16 wks	Any dose of T-20	Placebo	
HIV RNA <50	48%	37%	Intent-to-treat analysis *
HIV RNA <400	71%	58%	On treatment analysis

*\*This was not a true intent-to-treat analysis as the authors excluded 7 people who did not get at least one HIV RNA measurement after beginning the trial. Nonetheless, T-20 appears to have improved the response rate to the new regimen in PI-experienced, NNRTI-naïve people.*

Further trials of T-20 are ongoing and it is anticipated that there will be an expanded access program beginning in a few months. Test tube studies have shown that it is possible to develop resistance to T-20 over time, but T-1249 and T-20 do not appear to be cross-resistant.

A different type of "entry inhibitor" was also widely discussed at the conference. This protein, called **DC-SIGN**, has

not yet been the target of drug development (LateBreaker 10). It is a new receptor, recently discovered, which appears to allow HIV to be picked up by cells in the skin or mucous membranes, and transported to lymph nodes where it can begin to attack the immune system. There are several significant aspects to this discovery. Not only will it provide some new targets to stop HIV replication, but it also could be a very effective target to use as a topical microbicide, which could be used intra-vaginally, or intra-rectally, to prevent HIV infection. (See also, the topical microbicide article in this issue of the *STEP Perspective*.)

## Structured treatment interruption: Novel strategy or oxymoron?

A session titled "Structured treatment interruption: Novel strategy or oxymoron?" summarized the current data on structured treatment interruptions (STI), or "supervised" treatment interruptions, as Dr. Bruce Walker prefers to call them. There were three types of interruptions described:

1. In people who began anti-HIV therapy during acute (or primary) infection
2. After successful anti-HIV therapy in people with chronic HIV infection
3. Prior to beginning a new regimen in people with a lot of drug resistance and a failing current regimen, referred to as salvage therapy

The first two categories are attempts to boost immune responses specific to HIV through a controlled burst of HIV replication, or auto-vaccination. The third type of interruption is used to allow non-resistant HIV, commonly called wild-type, to replace drug-resistant HIV in hopes of improving the response to the new regimen (Abstracts 288 to 293).

The only study showing significant results with STI was reported by Rosenberg and Walker in people treated during acute infection. (See the *STEP E-Zine* Vol. 1 Issue 16, [www.thebody.com/step/ezine\\_092900/interruptions.html](http://www.thebody.com/step/ezine_092900/interruptions.html).) The usefulness of STI in the setting of chronic infection remains totally unclear, as the only data available are from small, non-randomized studies with short follow-up. All presenters agreed that people who are interested in STI should participate in ongoing, randomized, clinical trials.

Steven Deeks, from the University of California at San Francisco, presented updated information on the use of STI in the salvage setting (Abstract 292). Twenty-one people who were failing PI-containing regimens had a treatment interruption of about 18 weeks. There was a genetic shift to HIV that was sensitive to PIs in 81% of the people, and 72% showed no resistance for NRTIs. After 24 weeks on the new regimen, which included Norvir, a second PI, 2 NRTIs and a NNRTI, there was an average decrease in viral load of 1,000-fold. Even though there were significant decreases in T-cells during the treatment interruption, 68% of the people had recovered to within 90% of their baseline T-cell count after 24 weeks on their new regimen. Half of the people in this study had a new class of drug available to use in the new regimen (an NNRTI), and they all had a decrease in viral load to less than 400 copies after 24 weeks, compared to only 3 of 11 people who were not naïve to any of the drug classes in their new regimen. Despite these fairly encouraging results, it is still important to emphasize that there is a risk of significant decreases in T-cell counts during treatment interruption. Also, this was not a randomized trial, so until a large randomized trial is completed that compares an immediate switch to treatment interruption with follow-up for at least 48 weeks, the efficacy of this strategy will remain unresolved.

### Intermittent or Pulse Therapy

There has been increasing interest in intermittent therapy, not only as a po-

tential immune-boosting approach, but to reduce drug side effects and the total cost of treatment. Two studies of interest were presented at Retrovirus. The first was a pilot study of 10 people who were switched from continuous anti-HIV therapy to taking their anti-HIV medications only every other week (one week on, one week off). These people all had HIV RNA viral loads below 50 copies and were on stable anti-HIV regimens before entering the trial. None of the subjects were on Sustiva, due to the concerns about the long time that Sustiva remains in the bloodstream after the subject stops taking it, which could lead to possible resistance (Abstract 354). All three of the people for whom 24-week data was available maintained HIV RNA viral loads below 50 copies after each week off of anti-HIV therapy. However, two people who delayed restarting medications for more than 1 week had viral rebound within 2 weeks.

Another study is evaluating continuous anti-HIV therapy versus cycles of 2 months on, 1 month off (Abstract 364). In this study, however, all people had viral rebound to detectable levels by the end of the monthly off cycles, and there is concern that this could lead to viral resistance over time, as well as a diminished improvement in the immune system.

## The phenomena formerly known as lipodystrophy

The phenomena formerly known as lipodystrophy were re-dubbed “metabolic complications” at the Retrovirus conference. The long-term side effects included under this title were:

- ▶ Elevated levels of lactate in the blood (lactic acidemia, lactic acidosis)
- ▶ Tingling, numbness, or pain in the arms or legs (peripheral neuropathy)
- ▶ Fat loss in the arms, legs, or face (lipoatrophy)

- ▶ Insulin resistance or high blood sugar and/or diabetes
- ▶ Fat accumulation inside the abdomen (visceral adiposity)
- ▶ Increased fat under the skin of the back or breasts
- ▶ Abnormal blood cholesterol or triglycerides levels (dyslipidemia)
- ▶ Decreased bone density and other bone disorders (osteopenia, avascular necrosis).

One of the reasons that these side effects are being separated is because they appear to have distinct sets of causes and correlations. Many of these problems (neuropathy, fat loss, decreased bone density) have been observed in HIV-positive people who have never taken therapy, and seem to be caused, at least in part, by HIV infection itself. Others (lactic acidemia, drug-related neuropathy, and fat loss in the face, arms, or legs) seem to be associated with damage to an energy-producing part of human cells called mitochondria, possibly correlated with NRTI treatment. Treatment with PIs is being investigated as a contributing factor to the alterations in fat and sugar metabolism that may lead to high cholesterol and triglycerides, insulin resistance, and high blood sugar (glucose).

Because of the growing appreciation of long-term side effects, over 60 abstracts were devoted to the subject. Most studies focused on defining and finding correlations or causes rather than on treatment. Some of the factors that were examined as possible correlations, other than HIV and anti-HIV medications, were age, physical inactivity, gender, race or ethnicity, and CD4 count.

### Incidence data from MACS

Abstract 538 presented data on the incidence of fat maldistribution in men-

who-have-sex-with-men (MSM) from the Multicenter AIDS Cohort Study (MACS). MACS is a long-term, observational cohort study of 5,000 MSM, both HIV-positive and HIV-negative. The study looked at the incidence of fat loss versus fat accumulation in a subset of 868 participants, (62% were HIV-positive and 38% were HIV-negative) using a survey and measurements. Because 73% of the HIV-positive men had taken “HAART” (highly active antiretroviral therapy with at least a 3-drug regimen, most including a PI) and 14% had never taken any anti-HIV medications, they also looked at differences in incidence based on anti-HIV therapy.

The results were that 25 to 35% of all the HIV-positive men had fat loss in the face, arms, or legs (lipoatrophy), com-

## The usefulness of STI in the setting of chronic infection remains totally unclear

pared to only 2% of the HIV-negative men. There was no statistically significant difference attributed to HIV, however, in central fat accumulation (35% of HIV-positive men versus 26% of HIV-negative men). When they looked at people who had a mixture of fat loss and fat accumulation symptoms, the differences were striking – 40% of the HIV-positive group had mixed symptoms, compared to only 1 to 2% of the HIV-negative group. They then looked at the differences according to the type of anti-HIV therapy in this group of people with mixed symptoms. Among people who had had no anti-HIV therapy, only 1 to 2% had moderate or severe mixed symptoms. For those who had taken mono or dual NRTI therapy, 8% had mixed moderate or severe symptoms, and 20% of those who had taken HAART fell into this category.

The MACS researchers also looked at changes in blood lipids (cholesterol and triglycerides). They found that a low level of “good cholesterol” (HDL less than 35 mg/dl) was associated with being HIV-

continued next page

positive, but did not vary with treatment history. In contrast, a high level of triglycerides (above 400 mg/dl) was associated only with HAART. Another interesting finding from this data set was that the incidence of peripheral fat loss and central fat accumulation rose steadily during the first 2 years of HAART, but appeared to stabilize after that. Although this study was not randomized, it did make good use of HIV-negative and untreated HIV-positive control groups to distinguish among side effects due to HIV, those due to treatment, and those due to aging.

### Lipoatrophy

Abstract 539 presented results from a small sub-study examining the differing effects of two NRTIs, Zerit and AZT, on both lipoatrophy and central fat accumulation. Both of the drugs were taken with Crixivan and Epivir for 30 months. None of the participants had ever used a PI, but a number of participants, evenly distributed between the groups, had already had mono or dual NRTI therapy with AZT, Videx or Hivid.

Similar to the MACS study, this study saw no differences between groups in central fat accumulation. The results did show a striking difference in fat atrophy. The type of fat loss, or lipoatrophy, most commonly found in people with HIV is a loss of subcutaneous (directly under the skin) fat in the face, arms, and legs. Using skin-fold measurements and physician and patient surveys, this study found that the percentage of people reporting fat loss in the face, arms, or legs after 30 months on therapy was twice as high in the group taking Zerit compared to the group taking AZT.

### Looking at lactate levels

Many studies concerning correlations between blood lactate levels, mitochondrial damage, and other metabolic side effects were also presented. Lactate is a normal by-product of human cells breaking down fats and sugars. Elevations in lactate levels, known as lactic acidemia, have been observed in people with HIV, especially in those taking NRTI therapy. It is also possible for a person to get "lactic acidosis," which indicates se-

verely elevated lactate levels above 5 to 10 mmol/l and the presence of symptoms. Lactic acidosis can be a very serious, although rare, condition that often involves symptoms such as unexplained severe fatigue, nausea, and/or abdominal pain.

A summarizing lecture was given by researcher Andrew Carr of Australia. Looking at several studies presented at Retrovirus and previously, he estimated that approximately 20% of HIV-positive people on NRTI medications had mild elevations in lactate, 2 to 5 mmol/l, with no accompanying symptoms. **He emphasized that routine measurements of lactate levels are not recommended, however, because these mild elevations do not appear to predict whether or not a person will progress to lactic acidosis or have symptoms.**

### Treatment for peripheral neuropathy

One of the few abstracts looking at treatment for metabolic side effects examined the use of aspirin for treatment of neuropathy (Abstract 601). Rather than having people take aspirin orally, these investigators crushed up 375 mg of aspirin, dissolved it in 7 ml diethyl ether, and applied it to the arms and legs where pain occurred. This was a rigorous, double-blind, placebo-controlled crossover study. Half of the participants applied the aspirin mixture topically, three times a day for 2 weeks, then, after a brief wash-out period, they switched to the placebo version (just the ether with no aspirin). The other half started with placebo and then switched to aspirin. Neither the participants nor the researchers knew which mixture was being used at any time. Throughout the study the participants assessed their level of pain relief with a survey known as the Brief Pain Inventory (BPI). When the results were unblinded, they showed that the aspirin mixture relieved pain 30% better than baseline measurements and 30% better than the placebo. In fact, some of the participants who were in the group that started with aspirin dropped out of the study when they switched to placebo because they were unwilling to give up the relief they found.



## Decreases in bone health

Data on decreases in bone health continues to be compiled. Although the interest in HIV and bone health is fairly new, it appears that these effects have been present for some time and are just now beginning to be noticed. One of the most common effects seen and reported on is osteopenia. Osteopenia is a decrease in bone mineral density. In its most severe form, this loss of bone mineral density can lead to osteoporosis and structural fragility in the bones. Studies presented at Retrovirus estimated the prevalence of osteopenia to be 21 to 45% among people with HIV (Abstracts 626 and 629). The

estimated prevalence of osteoporosis, 2 to 3%, was low, but still significantly higher than the rates for HIV-negative people of the same sex and age (Abstract 628).

Several studies also looked at a condition known as avascular necrosis (AVN). Avascular necrosis refers to the death of bone tissue, usually in the hip, due to a decrease in blood supply. Again, this condition is also very rare, but does appear to occur to a higher degree in people with HIV. A study from Johns Hopkins University (Abstract 637) found that the incidence rate for AVN of the hip among people with HIV was 48% higher than that of the general population (1.9 per 1000 person-years compared to 0.04 per 1000 person-years). The majority of bone health studies seemed to support the view that this is HIV related, rather than medication-related, although it is not yet entirely clear. One study (Abstract 631) did correlate osteopenia with elevated lactate levels, and possibly NRTI therapy. As with lactate levels, however, routine monitoring of bone mineral density is not yet recommended because the conditions are rare and their clinical significance is still not known. Like many of these metabolic side effects, the im-

pact of these findings may take on more significance as the population of people living with HIV ages.

### Increases in cardiovascular disease risk

Anti-HIV medications, particularly PIs, are known to increase total cholesterol, “bad” (LDL) cholesterol, and triglycerides. Before anti-HIV medications were available, it was shown that people with HIV already had low levels of “good” (HDL) cholesterol. All of these conditions increase a person’s risk of cardiovascular disease. Two large studies presented at Retrovirus tried to ascertain if this increase in risk actually translates to higher levels of cardiac problems in people living with HIV.

A retrospective study in French hospitals (Abstract 657) looked at the incidence of heart attacks in people with HIV and with varying lengths of exposure to PIs. They then compared these incidences to those found in the general French population. Of 19,795 HIV-positive men who had taken a PI, there were 54 heart attacks during an 18-month period. The researchers calculated the relative risk of heart attack for people with less than 18 months of PI use, with 18 to 29 months of PI use, and with over 30 months of PI use, compared to the general population. They found that the risk was no higher for those on PIs for less than 18 months, but did increase with longer duration of PI use (1.7 times higher for those on PIs for 18 to 29 months, and 3.1 times higher for those on PIs longer than 30 months). While the findings in this study were compelling, no examination of differences in other cardiac risk factors was done, so the conclusion that PI use accounted for all the difference can not be made.

Another large study was presented using data on patients at Kaiser Permanente of Northern California (Abstract 655). This is an ongoing, prospective observational study of coronary heart disease that began in 1996 and is following 4,500 HIV-positive and 41,000

age- and sex-matched HIV-negative people. This study found that the overall risk of hospitalization for coronary heart disease was 1.6 times higher among HIV-positive people, but that no differences in risk were attributable to PI use. These researchers did attempt to find differences in underlying cardiac risk factors by surveying the medical records of 264 HIV-positive people and 710 HIV-negative people. They found that people who were HIV-positive did tend to have higher cholesterol, but had lower blood pressure. They found no difference in rates of tobacco use or diabetes, both of which are significant risk factors.

### What can be done?

The growing list of known metabolic complications of HIV disease can seem overwhelming, especially because so little is known about the exact causes. The good news, however, is that a lot *is* known about the treatment of these conditions when they are not HIV-related. This means that there are many proven strategies that HIV-positive people can use to decrease their underlying risk. For instance, bones can be strengthened by maintaining good activity levels, supplementing calcium and vitamin D when needed, and avoiding the use of cigarettes and corticosteroids. It may

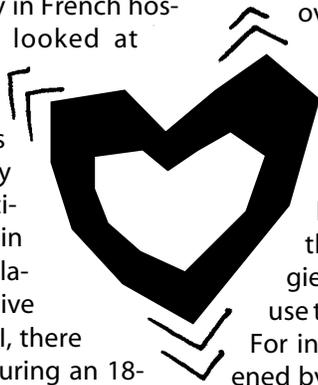
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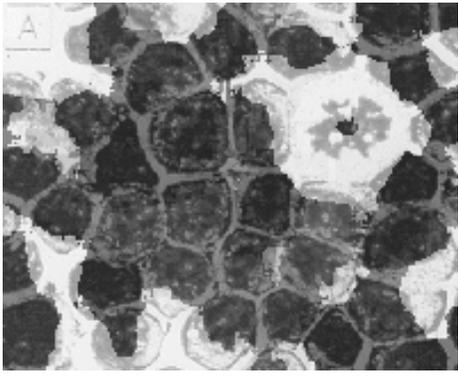
also be useful to monitor and supplement hormone levels, since hypogonadism (low testosterone or estrogen levels) is a known risk factor for osteoporosis. A healthy weight and a diet including low-cholesterol, low-fat, and low-sugar foods can help control cholesterol, triglyceride and blood sugar levels. In addition, cardiac risk can be lowered by stopping smoking, exercising and using cholesterol- and triglyceride-lowering drugs, if needed.

### Choosing anti-HIV therapy

Although very few of the symptoms show direct causation by specific anti-HIV therapies, many studies have looked at the effect of stopping or switching medications. In a few cases, stopping a given therapy is definitely warranted. One of these cases is symptomatic lactic acidosis. Lactic acidosis can require that a person interrupt the use of NRTIs and allow lactate levels to return to normal. It is also common to avoid certain PIs to attempt to control cholesterol levels. Many studies presented at Retrovirus also looked at switching from a PI to an NNRTI to alleviate metabolic symptoms (Abstracts 668-673).

These studies looked at people who had successful viral suppression (to undetectable viral loads) with a PI-based regimen, and then switched their PI for an NNRTI. In the vast majority of these studies, those who switched maintained viral suppression, suggesting that there is no negative health effect. However, few studies showed a clinically significant effect on cholesterol levels, triglycerides, or body-shape changes, such as facial and limb fat loss and central fat accumulation. ✕





# The Men's Anal Health Study

an interview with Paul Nelson, PA-C

Boyd Kravenas, contributing author

**STEP recently interviewed researcher Paul Nelson, certified Physician Assistant**, about his role as the Healthcare Specialist for the Men's Anal Health Study (MAHS). Some 365 gay or bisexual, HIV-positive men have volunteered to participate in this attempt to examine the links between HIV, the human papillomavirus (HPV), and anal cancer. Funded by a grant from the National Institutes of Health (NIH) and administered by the University of Washington (UW), the study began in July 1996 and closed March 31, 2001. Previously, the research group involved with MAHS conducted a study called "BeA Hero." That study compared the rates of anal disease in HIV-positive versus HIV-negative gay and bisexual men, to determine if HIV increases the risk of anal cancer. For more information on MAHS & upcoming studies, call (206) 731-8663.

**STEP: Why are you studying anal cancer in HIV-positive men-who-have-sex-with-men (MSM)?**

**PN:** Research for the past 20 years on anal cancer has shown that homosexual or bisexual men are at higher risk for anal disease. This is especially true if a person has had more than 10 sexual partners, practiced receptive anal intercourse, or has a history of genital warts or gonorrhea. In the "Be a Hero" study we compared HIV-positive men to HIV-negative men, and found that out of 781 men enrolled, 56 HIV-positive and 13 HIV-negative men had high-grade dysplasia [abnormal cell growth] on cytology [examination of the cells] and biopsy [small tissue sample]. We found that those patients with CD4 cells less than 500 were 7.5 times more likely to develop anal dysplasia than those who were HIV-negative. Gay and bisexual men who are HIV-negative still have the increased risk of anal cancer, but the progression rate from abnormal cells to cancer is very slow.

**STEP: Can you explain briefly what dysplasia is, and how it relates to cancer?**

**PN:** The word dysplasia means abnormal cell growth. The anal dysplasia we study is most commonly caused by HPV. This virus, with approximately 70 known types, is an extremely common communicable disease. These viruses cause genital warts or tissue changes, also known as dysplasia, that can cause normal tissue to become cancerous. Several of the types are known to cause warts that can target the hands and feet, while other types affect the face, and still others the genital tract. HPV is known to cause cervical cancer and can increase the risk of anal cancer. As a sexually transmitted disease (STD), it is thought to be transmitted by direct contact between infected skin on the penis, scrotum, vagina, vulva, or anus and uninfected skin in the same areas of the partner's body.

**STEP: How does a person know if they have dysplasia?**

**PN:** An anal pap smear is used to check for dysplasia in the anus. An anal pap smear is very

similar to a cervical pap smear. A pap smear is a few cells collected using a swab from the anus and placed on a slide. The slides are placed in a preservative and sent to a lab where they are stained and then read by a pathologist. The pathologist will look at the slide and can determine if abnormal cells are present, representing dysplasia. The amount of abnormal cells seen determines the rating of dysplasia. Low-grade dysplasia generally means that the current risk of cancer at this time is low but should be monitored in the future. High-grade dysplasia indicates the presence of severe abnormalities and the need for further evaluation. Specialists in this area have set no formal recommendations for how often anal pap smears should be done. We believe that any gay or bisexual male who has had sex with another male, is HIV-positive, and has a history of anal warts should have a pap smear and possibly a biopsy of tissue from the anal canal.

**STEP: Without an anal pap smear, is there any way to detect anal cancer?**

**PN:** Rectal bleeding is the most common initial symptom of anal cancer, but it only occurs in 45% of patients. Bleeding from the anus may have other causes, as well, such as hemorrhoids, tears, or infection. Thirty percent of patients have either pain or the sensation of a rectal mass. In 20% of cases of anal cancer there are no symptoms. Symptoms only occur when the cancer has begun to grow. People with anal cancer usually find out about it late in the disease when treatments are limited to surgery, chemotherapy, or radiation therapy, which do not have good recov-

## HPV: human papilloma virus

ery rates. In our study we are using anal pap smears to detect the early signs of anal cancer, namely the cell changes called dysplasia. We found that anal dysplasia can slow or revert to normal. Among HIV-negative people and those who had good control of their HIV infection, the percentage of people who will progress to cancer is as low as 1-3%.

**STEP: What is the treatment for a person who has HPV, anal warts, dysplasia, or cancer?**

PN: None of the men in our study have developed invasive anal cancer. Some had severe dysplasia with precancerous cells on biopsy, which can lead to cancer if not treated. None of the treatments for anal dysplasia are totally effective for treating HPV. Surgery is one option – removing only tissue that is abnormal, but it is only 50% effective in permanently preventing reoccurrence. The use of acids to burn warts or liquid nitrogen to freeze them has been used, but effectiveness has not been evaluated. Several drugs are being developed, and vaccines for HPV are starting to be evaluated in limited studies in the U.S. New chemotherapy treatments are being developed to treat anal cancer. The goal is to develop a better screening test than the pap smear, and begin screening programs to find those at risk for anal cancer.

**STEP: How important is screening?**

PN: Early detection is important. The earlier you find a cancer like prostate, testicular, or anal cancer, the less likely it is to invade other parts of the body. Men over the age of 40 should have their prostate examined annually, and men over the age of 20 should be doing testicular self-exams monthly. As with anal cancer, a person with any signs of problems or history of warts, STDs, or abnormal internal or external bumps should be screened by their provider. I tell my patients that it is their responsibility to get a complete physical exam with their healthcare provider, and they should not wait for problems to begin.

**STEP: How can someone obtain this type of exam, regardless of HIV status?**

PN: Most primary care providers can do an anal exam. We are trying to educate doctors on how to perform anal pap smears to provide the screening exam. We are also working with the Seattle-King County STD Clinic and Madison Clinic (at Harborview) to perform this type of screening exam. By the end of 2001, this program may be up and running. If you have concerns, simply talk with your doctor or ask for a referral to a colorectal specialist to perform this exam. There is little discomfort to having an anal pap smear and internal examination performed. It is also important to talk freely with your doctor about risk factors such as having receptive anal sex, using toys, fisting, drug use and HIV status.

**STEP: Is there anything a person can do to reduce his or her risk of developing anal cancer?**

PN: Certainly, one way is to reduce the risk of contracting the HPV virus by using condoms when having anal intercourse, reducing the number of sexual partners, and not sharing sex toys. We don't know how contagious the HPV viruses are, so the more you prevent exposure, the less your risk of contracting HPV. It may also help to eat healthily, more fruits and vegetables, to increase the fiber in your diet. It is also important to avoid irritants to the anal canal, such as lubricants with nonoxynol-9 spermicide.

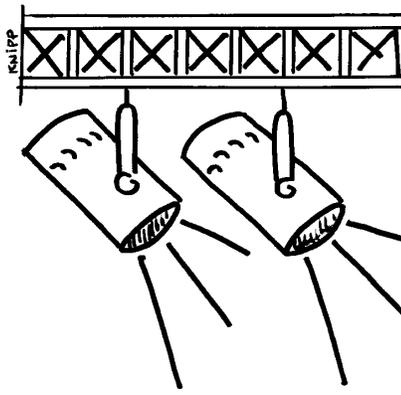
**STEP: Now that you are concluding your 4-year study on anal dysplasia, what are some of the tentative findings?**

PN: Although the study should be completed this year, the total conclusion will take several months to complete. Some interesting initial findings are that the rate of high-grade anal dysplasia is directly related to your overall health. HIV-positive patients who have gone on anti-HIV medications and keep

their CD4 counts above 500 are less likely to progress to anal cancer any faster than if they were HIV-negative. We have also found that two types of HPV are more likely to cause anal cancer. There are more than 70 different strains/types of HPV, and the two types (#16 and 18) that are known to cause cervical cancer are also suspected as the cause of anal cancer. We have noted differences between anal and cervical cancer in our latest research. The signs of cervical cancer in abnormal pap smears usually start at an early age and then progress with time. But with anal dysplasia, pap smear abnormalities can become high grade at an early age and then regress to low grade at middle age, and then possibly progress to high-grade abnormalities after the age of 40. HIV-positive patients, however, may not have this period of regression, and may progress to anal cancer more quickly. So staying in good health is proving to be very important. We won't have all the answers until all the data is evaluated.

**STEP: I understand that a new study is in the works that compares the incidence of anal cancer in gay and bisexual men, and includes both HIV-positive and HIV-negative participants.**

PN: Yes, this year we are writing a grant to look at better ways of detecting anal cancer. Since anal pap smears may be only 70% effective, we would like to develop new tests, and possibly look for new ways of treating anal dysplasia. This study may not begin until late in 2001 or early 2002. When we get the study going, we will begin a major advertising campaign and start recruiting patients for anal cancer screening. So watch your local newspaper or keep in touch with your doctor, because we will be sending information to local doctors when it becomes available.✎



# First Person

## Who cares about the dust bunnies?

Kris C. has been living with HIV since 1988. She's seen the ravages of the disease, and of the medications designed to treat the disease. As a woman living with HIV, she's in the minority in the Seattle area, but she does her part to make sure it is a vocal minority.

"When I first found out I was positive, the first thing I did was go to a STEP educational class. There was one other female there. I introduced myself, thinking 'I'm so glad she's here.' I said to her, 'Oh God, I can't even believe I have to be here. So, how did you find out?' She looked at me so strangely, and she said, really snotty, 'I'm a caregiver.' So I was the only positive female I knew for a long time." Since then, Kris has found support and camaraderie with other positive women, especially through the BABES Network in Seattle and Positive Women's Network in Snohomish.

"Now, there are more females out there, but often they're not talking. I'm not married and I don't have children. My heart goes out to the women who have to do all of that besides the full-time job of taking care of yourself and your body. I do have the house, the yard, the animal, but I still don't have kids. And when you've got children, they're your number one priority . . . and they should

be. It could very well be that somebody 'up there' was saying, 'I'm gonna keep her alive because she's verbal, she's vocal, she's one of the few females. She'll be talking, because she doesn't have to worry about the ramifications, the persecution, because she doesn't have kids.'"

Kris understands that this is a relatively new disease; that very little is actually known about HIV and its treatments. She participated in some of the early trials of anti-HIV medications and knows, first-hand, the ups and downs of HIV treatment and research.

"When you first start out with this disease, if you're not educated and proactive and an advocate for yourself, you're at the mercy of the medical community. And there are so few studies, they're not that long, they just don't know that much."

Some days, it seems like there is not a lot about this disease that is under anyone's control. Most days, however, Kris works very hard, using her energy and influence to improve the lives of people, especially women, living with HIV and AIDS.

Shortly before her 50th birthday, Kris retired from her job in sales. The transition from full-time work to disability was abrupt.

"The first six months were joyous, it's like vacation, but then the reality sets in – I have nothing to do! Since I own a house, a lot of the time was spent on gardening. I'd go out for eight hours at a time and weed. I would just sit there, there was no reason to rush; one day was the same as the next.

"I was spending a lot of time sitting at home, when a girl from Positive Women's Network said, 'Oh Kris, you should do *something*.' So I started volunteering. I joined the Region 3 Planning Council, thinking 'Oh, you can really make a difference.' And I'd never been politically active, except maybe during the Vietnam War, but if you're not doing anything, and you've got the time, it takes you out of yourself. You don't start thinking about your neuropathy, or how tired you are, or the possibility that you may not be around tomorrow. All those things are put on the back burner. It helps you live for the day, instead of worrying about what may be."

Kris often volunteers over 20 hours a week, contributing to various planning councils, community advisory groups, and AIDS care consortia. Sometimes the schedule seems like a lot of work and not much gain.

"Sometimes I feel like I'm just the token infected female, that there is so much crap going on, that I'm losing that passion, the disgust is taking over, and I don't want to get to that point. But then I think, 'If I don't do it, who will?' Besides, I'd rather be doing that than weeding any day, or cleaning the house. Who cares about the dust bunnies?"

One of Kris's priorities is speaking to young people.

"When I meet younger women who've been infected, the ones who got HIV education from 5<sup>th</sup> to 12<sup>th</sup> grade, I think, 'What the hell is going on here?'"

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# TREATMENT NEWS STEP

## Change in official “when-to-start” recommendations

On the same day as the opening of the 8<sup>th</sup> Annual Retrovirus Conference, the National Institutes of Allergy and Infectious Disease (NIAID, a division of the National Institutes of Health [NIH]) issued revised HIV treatment guidelines. The previous guidelines had advised that anti-HIV therapy should be considered, even when a person had no symptoms, if she or he had a T-cell count less than 500 or a viral load above 10,000 by bDNA or 20,000 by PCR.

A growing awareness of the long-term side effects of anti-HIV therapy, the evident inability of current medications to eradicate HIV, and the better-than-expected immune recovery observed in people who begin therapy with T-cell counts between 500 and 350 have led to the latest change in the guidelines. The guidelines now suggest that therapy be considered when the T-cell count is below 350, or the viral load is above 30,000 by bDNA, or 55,000 by PCR.

At the Retrovirus conference, there were three presentations evaluating the impact of when anti-HIV therapy is begun. One presentation from the Swiss HIV Cohort purportedly showed a beneficial effect from initiating anti-HIV therapy when the T-cell count was above 350 (LB 6). However, this was a very poor study which retrospectively compared two very different groups of people: those who began therapy during a 1-year period when their T-cells were above

350, and those who did not start therapy during that year, the majority of whom (82%) never received therapy. Obviously, the first group had fewer adverse clinical events such as AIDS-defining illness and death. The more appropriate comparison group would have been people who started anti-HIV therapy after more than a year, with T-cells below 350, but before they got sick. There was an interesting observation in this study that of the people who started therapy, 60% changed at least one drug in their regimen (29% due to side effects), and 20% stopped therapy completely. These findings illustrate the problems of tolerance and adherence with the regimens used during the period of this study.

There were two other presentations (Abstracts 519 and 520), also retrospective cohort studies, that showed that there is a definite survival advantage for people to be on anti-HIV therapy if their T-cell count is below 200. The studies also showed a trend towards better clinical outcomes in people starting therapy with T-cell counts between 200 and 350, but no difference in people on or off therapy when their T-cells are above 350.

In the study presented by Timothy Sterling of Johns Hopkins University, it was observed that once CD4 cell count was allowed for, viral load did not predict clinical outcome. This study also showed that disease progression rates were worse in men, compared to women, in the group with fewer than 200 T-cells. Dr. Sterling concluded that more emphasis should be placed on the T-cell count in determining when to start therapy and that it appears that anti-HIV therapy can be deferred until the T-cell count is “substantially lower than 500” (Abstract 519).

The other study was from the CDC’s Adult and Adolescent Spectrum of Disease Project, which includes data from over 5,000 people, from 11 cities in the United States, including Seattle (Abstract 520). They found that when anti-HIV therapy was deferred until after the T-

cell count was below 200, there were more deaths. They also saw a trend, which did not reach statistical significance, for better outcomes in the group that started therapy when the T-cell count was between 200 and 350. There was no benefit observed for the group that began therapy with T-cell counts above 350.

The bulk of the findings from these studies provide support for the change in the HIV treatment guidelines, but each one also shows the limitations in data acquired from retrospective analysis.

At the Retrovirus press conference, STEP asked Dr. Fauci, Director of NIAID, if he was concerned that insurers and HMOs might try to deny coverage for people who choose to begin anti-HIV therapy, or continue on therapy, when they have T-cell counts above 350. He said that the guidelines panel tries to make its recommendations on the best available data. The panel is aware of the possible misuse of the guidelines, but the guidelines clearly state that the decision to begin anti-HIV medications is a complex one and must be made on an individual basis, in consultation between the patient and their healthcare provider.

Coincidentally, the week before Retrovirus, NIAID apparently decided that it is not feasible to conduct a large, prospective, randomized “when-to-start” trial in the United States at this time. Rather, the NIH will be investigating the feasibility of gathering data from observational cohorts. These groups of people will be followed closely, over a long period of time (5 or 10 years), and evaluated based on the when they initiated anti-HIV therapy, and any clinical events, such as opportunistic infections or medication side effects, that occur.

To read the press release from the NIH regarding the change in guidelines, go to <http://www.niaid.nih.gov/newsroom/hivguidelines.htm>.

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# Topical Microbicides: Removing barriers to HIV prevention

Karin Christianson and Alisen Peterson Contributing authors

## The trouble with condoms

Ask a group of people to word associate the phrase “HIV prevention” and chances are you’ll hear a chorus of “condoms!” in return. Thanks to exhaustive safer sex educational campaigns, millions of people know that a properly used condom can successfully impede transmission of HIV and many other sexually transmitted diseases (STDs). Most people also know that infection with other STDs, such as gonorrhea, raises the possibility that a person will become infected with HIV.

Yet millions of people do not use condoms and continue to put themselves at risk every time they have sex. This knowledge/behavior disconnect is reflected in recent increases in infection rates of HIV and other STDs such as syphilis, gonorrhea and chlamydia. A recent estimate of HIV infection in young, gay, black men is a startling 30%.

Why, armed with condoms and information, do people continue to put themselves at risk? The reasons are many. Some of them are:

- Safe sex fatigue. Plainly put, people are tired of constantly being on guard against HIV.

- Some people regard condoms as a barrier to sexual pleasure and deep intimacy. Many studies suggest that only 20% of people in a stable relationship use condoms. Even those who use condoms with “outside” partners may be unwilling or unable to use them with

a primary partner. One study conducted at Columbia University showed that 43% of men-who-have-sex-with-men (MSM) reported inconsistent condom use.

- Women (and some men) often don’t have control over when and how they have sex. Asking a man to use a condom may result in a woman being beaten, threatened, or abandoned by her partner. The possibility of a violent response is especially high if a man believes that condoms imply a lessening of male pleasure, promiscuity or lack of fidelity, or a woman’s “inappropriate” knowledge of sexual practices.

Prevention methods based on condom use, monogamy, and abstinence have failed to keep millions of people from becoming infected with HIV and other sexually transmitted diseases. Each day sees as many as 16,000 new HIV infections globally. There are 34 million people in the world living with HIV/AIDS and 95% of infections occur in developing countries. More than 90% of these HIV infections are transmitted through unprotected sex and at least 5% of those infections are transmitted through anal sex. Adding to this bleak picture, UNAIDS reports (as it has every year for at least the last 5 years) that it will be 10 years or longer before an effective preventative vaccine is ready for use.

## Topical microbicides: New hope for HIV/STD prevention

There is no magic bullet solution to stop the spread of HIV and other STDs.

Complex issues including poverty, disenfranchisement, and powerlessness defy easy solutions. Meanwhile, people who do not or cannot use condoms need the tools to protect themselves now. As a convenient and practical method of prevention, topical microbicides represent such a tool.

## What is a microbicide?

A microbicide is any substance that can substantially reduce transmission of sexually transmitted infections, including HIV, when it is applied in the vagina or rectum. A microbicide could be produced as a gel, cream, film, suppository, sponge, vaginal (or rectal) rings or wipes.

Most of the microbicides being developed will probably also have some contraceptive effect — because it’s hard to make something that neutralizes viruses and bacteria but doesn’t affect sperm.

Some scientists are also working on products that may be microbicidal without being contraceptive. These will be useful to couples who want to conceive a child while still protecting themselves from infection. Non-contraceptive microbicides may also offer acceptable protection for those who choose not to use contraceptives for religious or cultural reasons.

It is hoped that some of the microbicides approved for distribution will be able to protect against multiple STDs, in addition to HIV.

## Microbicides currently under development work in several different ways:

► **Killing or inactivating STDs:** Detergent-like chemicals disrupt cells membranes of bacteria, and cover the surface of viral STDs. Compounds such as *nonoxynol-9*, *octoxynol-9* and *benzalkonium chloride*, *menfegol*, and *N-docosanol* are included in this category.

► **Preventing STDs from entering target cells:** These chemicals would prevent infection by blocking the attachment of infecting organism. Products include *PC-515*, *Pro 2000*, and *Dextran 2 Sulfate*.

► **Preventing STDs from replicating:** The anti-retroviral agents *PMPA gel* and *nevirapine gel/cream* are in this category.

► **Changing the vaginal/rectal environment to increase natural defense mechanisms:** Products like *BufferGel* and *Acidform* aim to maintain natural levels of acidity in the presence of semen and contain *lactobacillus*, which naturally resides in the healthy vagina, and which produces hydrogen peroxide to kill HIV and STDs.

► **Invisible condoms:** These products would prevent infection by forming a protective barrier after being inserted into the vaginal or rectal canal. One such product is liquid at room temperature and quickly turns into an impermeable gel inside the body.

Two or more of these approaches may be combined with a number of active ingredients to develop a successful microbicide. Right now there are no proven microbicides on the market, although there are at least 60 topical microbicides in development and 23 microbicidal products being tested in people. This is a promising increase compared to the dozen compounds that were being developed in 1994.

### How would a microbicide be used?

Topical microbicides could be used for anal or vaginal sex, along with

condoms for extra protection, or instead of condoms when condom use isn't possible.

Some have also suggested that a mouthwash-type product would also be useful for protection during oral sex. (The inside of the mouth is made up of the same type of mucosal cells as the vagina, so this isn't as far-fetched as it may seem.)

Microbicides may also help prevent HIV transmission from mother to baby during delivery by reducing the amount of HIV in an HIV-positive woman's vagina right before she gives birth. This might be especially important in very poor countries where women do not have access to anti-HIV therapy.

Because they are not actual physical barriers, microbicides will never be as good at stopping the transmission of STDs as a condom. However, the success of any method of prevention is a function of not only how effective it is, but how often it is correctly used. Because microbicides may be used more consistently than condoms, they may be more effective in the long run.

### How could microbicides benefit HIV-positive users?

There are several ways that microbicides could be useful to people who are HIV-positive. Since microbicides neutralize disease-causing organisms in both semen and vaginal secretions, they may give HIV-positive users a way of reducing their partner's risk of contracting HIV during sex. A microbicide could also reduce the risk of two HIV-positive partners being re-infected with different strains of HIV. They may also reduce an HIV-positive person's risk of getting other STDs, bladder infections, or yeast infections. For people with compromised immune systems, this could be an im-

portant advantage. It is important to note that condoms can also help with these issues.

Some products may be able to help HIV-positive women become pregnant without exposing her partner to HIV.

It might also be possible to develop products that would help an HIV-positive man to conceive a baby sexually, without infecting his partner if she were HIV-negative.

### What other advantages are there to using microbicides?

It is hoped that microbicides will be inexpensive and available over-the-counter like condoms. Successful use of the condom, however, requires the co-

operation of insertive sexual partners; successful microbicide use may not even require their knowledge. Microbicides could also offer increased sexual satisfaction while practicing safer sex. In addition to the lack of physical barriers, other characteristics of microbicides such as smell, taste, and viscosity may afford more choices in sexual pleasure.

### Microbicide Research

Interest in developing a form of STD prevention that could be used without a partner's knowledge or consent began in the early 1980s.

Many organizations advocating the development of microbicides, including the Alliance for Microbicide Development (AMD) in Takoma Park, Maryland, and Microbicides as an Alternative Solution (MAS) in Berkeley, California, were developed to organize the microbicide movement. Research and interest in microbicides has almost exclusively focused on vaginal use for two reasons. One is that worldwide, women make up the majority of those exposed to HIV. This is often because they do not have prevention methods that they can control. Furthermore, the number of women

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infected is the fastest-growing group of new HIV infections, and now represents 45% of HIV/AIDS cases worldwide, as compared to only 25% in 1992. In sub-Saharan Africa women represent more than 55% of adults living with HIV.

The second reason is that heterosexism has inhibited a broader discussion of anal sex practices and rectal microbicides. Dr. Connie Celum at the University of Washington is responsible for the only research of rectal microbicides on human subjects. She addresses the anal stigma of science, saying "Most of the researchers in this field aren't just homophobic, they are erotophobic."

Slowly, more interest and research has focused on finding a product that can be used both vaginally and rectally, although differences in the anatomy and environment may hinder such a formulation, making it necessary to create different products for vaginal versus anal sex. The open-ended rectal cavity makes it difficult to thoroughly coat and the acidity levels and bacterium ecology differ from those of the vagina. Unfortunately, these considerations are being ignored by many researchers, and funding of rectal microbicides is often being suppressed by conservative activists.

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**A barrier to microbicide research is lack of public awareness. People cannot demand what they have yet to imagine. By far the largest barrier, however, is lack of funding. Less than 1% of all federal AIDS funding goes towards finding a successful microbicide.**

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New drug development is usually funded primarily by major pharmaceutical companies that have the money to invest in large clinical trials. Unfortunately, none of the largest corporations are investing in microbicide research.

They are reluctant for a variety of reasons. Their main concern, however, is that microbicides may not be profitable enough to justify the cost of developing them. Those who need the product the most are the least able to afford it. According to Alliance for Microbicide Development, it costs about \$20 million to get one product from discovery through Phase II trials of safety. It can then cost up to \$20 to \$30 million more to get it through the huge Phase III efficacy trials, which

**The success of any method of prevention is a function of not only how effective it is, but also how often it is used correctly. Because microbicides may be used more consistently than condoms, they may be more effective in the long run.**

can involve as many as 3000 to 4000 participants per product. Right now, about \$35 million per year, at most, is being spent globally on microbicide research. The U.S. government is providing about \$26 million of that. Without additional funding, the money just isn't there to move potential microbicides efficiently through the research pipeline. Unless industrialized countries, including the United States, make microbicide research a higher priority, research will be delayed and even more lives will be lost during the wait for effective products. Effective microbicides might transform the HIV epidemic from a raging wildfire to a more controlled burn.

The Global Campaign for Microbicides is a broad-based, worldwide coalition of organizations working to engage individuals, community-based organizations and institutions in the advocacy needed to make microbicides a reality soon.

In addition to generating media coverage, speaking at conferences and lobbying legislatures, Global Campaign is collecting signatures in over 80 countries on a petition for greater investment in microbicides.

The goal is to amass 250,000 signatures calling for increased funding from the U.S. government, the European Union and other public donors. Global Campaign will present the completed petition at the 2002 international AIDS conference.

Global Campaign has also helped Maryland Representative Connie Morella write the Microbicide Development Act. If passed, the Act would increase federal microbicide research funding at the NIH to \$50 million in 2001, \$75 million in 2002, and \$100 million in 2003 — enough to get the first products through the research pipeline.

*More information on microbicide development is available at the website <http://www.microbicide.org>. You can help get safe, effective microbicides onto our drugstore shelves and into the hands of people who need them all around the world. Everyone who supports this issue may call their representatives and senators and ask them to sign on as a co-sponsor of the Microbicide Development Act as soon as it is re-introduced in congress. Congressional contact information is available, by state, on the website [www.congress.org](http://www.congress.org).*



And then I remember being a teenager. You experiment, maybe drugs, maybe alcohol, you get crazy, and who thinks about protected sex?"

Through speaking, Kris hopes to reach young heterosexual women and impress upon them that they are at risk.

"I just want to let them know about the possibility that they can be infected. I've known people who were infected after one time of unprotected sex. I want the girls to understand, that while they might think their partner is monogamous, maybe he's not. I know people who have been infected after being married 20 years. I know girls who were infected who thought their husband was heterosexual, and it turns out he was bisexual. I think when you're young, you don't think about that. Maybe more today, but it depends on what they're exposed to, and that's why I go out there."

"I also hope that the young ones go home and tell their parents about the discussion. A lot of parents are divorced. They're dating again. A lot of grandparents are widowed or widowers, and of course they're not in school. They don't get that kind of education. They rely upon the information they see in the newspaper, and that is sorely lacking. There is no message out there for older people. So I suppose that's part of why I do the speaking, too. Now, whether the kids actually end up in a discussion with their parents, I don't know. But if only one does, that's fine. It's worth it."

For more information about services for women living with HIV, the BABES Network can be reached at (888) 292-1912 and the Positive Women's Network can be reached at (360) 568-2888. ✈

### What do the new HIV treatment guidelines mean for those already on therapy?

People who began anti-HIV therapy with more than 350 T-cells and a viral load below 30,000 (bDNA), or 55,000 (PCR), may wonder how the new HIV treatment guidelines for when to start therapy apply to them. The decision of when to start anti-HIV medications, and subsequently when to stop them, remains very personal and is best addressed by an individual and their healthcare provider, using general recommendations as a guideline. For people who have had good suppression of HIV, with improvements in T-cells and minimal side effects, the risk of stopping therapy may outweigh the benefits. This is because almost everyone stopping anti-HIV medications has a very rapid rebound in viral load, and some people experience rapid losses in T-cells. So, the slowly gained benefits of anti-HIV therapy may be quickly lost. Additionally, there have been reports of people experiencing a primary-infection-like syndrome due to the rapid rise in viral load when medications are stopped. It is also important to emphasize that the revised guidelines attempted to balance the benefits of therapy against the potential long-term side effects. Long-term immune sup-

pression due to untreated HIV also has consequences. One of the long-term effects of immune suppression is the risk of lymphoma, or cancer of the lymph nodes. In general, while the incidence in people with HIV has declined in the last few years, there are more reports appearing of people with higher T-cell counts being diagnosed with lymphoma. Thus, if someone is tolerating therapy and not experiencing significant side effects, it may be beneficial to continue the medications in order to keep the immune system as strong as possible. On the other hand, people who *are* experiencing significant side effects that can not be addressed by switching drugs, and who started therapy with relatively high T-cells counts and low viral loads, may decide to stop therapy, while still closely following their T-cell and viral load measurements.

★ See also **Ask Dr. Jeff, on next page**

### Early access program opened for nucleotide analogue tenofovir

The makers of the new nucleotide analogue tenofovir have started offering the medication to people living with HIV through a limited early access program. Tenofovir is a compound that

looks to be of use for people with resistance to currently available nucleoside analogue drugs. The early access program is designed to make the medication available to people who have run out of other viable treatment options. To be eligible to participate in the program a person must be at least 18 years old, have a CD4 count at or below 100, and an HIV RNA viral load greater than or equal to 10,000 copies. The program is also limited to those who have had treatment failure with at two protease inhibitors (PIs) or one PI and one non-nucleoside reverse transcriptase inhibitor (NNRTI). If a person has between 100 and 200 CD4 cells, and has had an AIDS-defining illness in the last 90 days, they may also be eligible. It is hoped that these criteria will be expanded to include more people as the drug gets closer to FDA approval (expected in June).

For more information about the tenofovir early access program in the US, call (877) 226-8802, or visit the website [http://www.gilead.com/webpage/templates/frame\\_home.php3](http://www.gilead.com/webpage/templates/frame_home.php3). To enroll patients in the program, US physicians should call (800) Gilead-5. Patients will receive the investigational drug as a once-daily, 300 mg tablet. ✈

# Ask Dr. Jeff

Q:

I saw that the treatment guidelines have changed to say people should start anti-HIV therapy when they have less than 350 T-cells. I started meds when my T-cells counts were below 350, but now they are 525, should I go off therapy?

A:

First, it is important to note that the Public Health Service (PHS) HIV Treatment Guidelines are just that, guidelines. They clearly state that treatment should be individualized. To learn about the changes in the PHS HIV Treatment Guidelines see **page 13** in this issue of the STEP Perspective.] However, your question is one that is being asked by many people.

The first point to emphasize is that people tend to return to the viral loads and T cell values that they had before they started therapy, within a couple of months of stopping therapy. This seems to be because there appears to be viral load and T cell “set points” to which people return without therapy. Because of this, those people who gained the greatest number of T helper cells when they began anti-HIV therapy will generally lose the most when they stop medications. The other concern with stopping therapy is that some people may experience an acute HIV infection-like syndrome because of the rebound in viral load due to the large number of uninfected T helper cells available for the virus to infect.

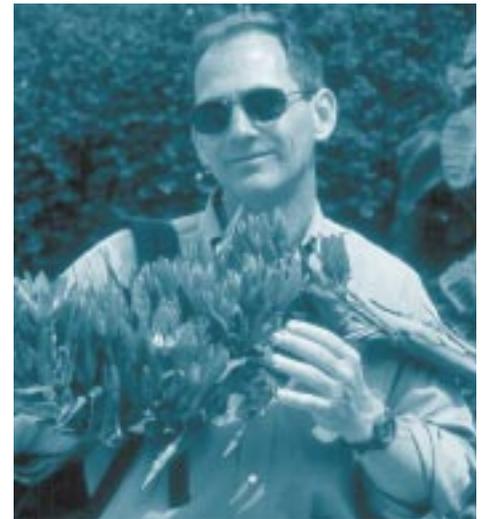
So, in general, I have some serious reservations about people stopping therapy. Especially if they started when they had T helper cell counts below 350 or viral loads above 30,000 (by bDNA) or 55,000 (by PCR), and are tolerating their treatment well. Again, this is because, on average, people will return to pre-treatment values within 3-6 months of stopping medications. Thus, the period off of medications is likely to be short, and the time to regain the lost T helper cells may likely be longer.

Q:

I began an anti-HIV medication regimen three years ago and have done well, maintaining an undetectable viral load and lots of T cells. Even before I started therapy, however, my T cell counts were still 450 and my viral load was only 25,000. I saw the change in the recent HIV Treatment Guidelines and I’m wondering if I should have ever started medications. Should I stop treatment now?

A:

This question is even more difficult than the previous question. First, it must be pointed out *again* the PHS HIV Treatment Guidelines emphasize the need to individualize therapy, and not just make choices based on numbers. There are many issues to consider when faced with this situation. On one hand, it makes sense to stop HIV from replicating in order to stop the damage to the immune system in all people with HIV infection. If we had drugs that were easier to take, with fewer side effects, the guidelines would probably still advise early therapy. On the other hand, one of the driving forces behind the change in the guidelines was increasing concern about the difficulties of staying on medication regimens for many years, and the long-term side effects that are being observed. Data showing the greatest benefit of anti-HIV therapy is still in people who start with T helper cell counts below 350, and especially in people



by Dr Jeff Schouten

## Ask Dr. Jeff your question!

Mail in your question  
or e-mail us at  
**dr@stepproject.org**  
We will answer all  
questions and print  
those that space allows.

Dr Jeff Schouten is a former general surgeon who has been living with HIV for over 10 years. He is chair of STEP’s Publications Advisory Committee and contributes regularly to the *STEP Perspective*. He has also earned a law degree from the University of Washington, so HIV-related legal questions, as well as medical, will be accepted.

with T helper cell counts below 200, also contributed to the change in recommendations.

It is important to consider both how effective the treatment is, and how well it is tolerated. Other factors to consider are the existence of other infections, such as chronic hepatitis B and C, whose course may be worsened by long-term immune suppression due to untreated HIV. Also, a large unknown variable is the long-term risk of developing cancer of the lymph glands, or lymphoma. HIV-positive people have significantly increased risks of lymphoma. While the overall incidence of lymphoma has decreased due to potent anti-HIV therapy, many clinics are reporting seeing lymphoma develop in people with T helper cell counts in the range of 200-300. It's possible that starting medications later may mean the improvements in the immune system will not completely reverse that risk. This is just one more variable to factor into the complex issues that people need to grapple with, both when deciding when to start anti-HIV therapy, as well as deciding if, and when, to stop therapy.

There is not a simple answer to your question, except to say that for people who are experiencing significant side effects from their therapy, and who started therapy when they had T cells well above 350, and relatively low viral loads, stopping medications (but continuing close monitoring) is a valid option to consider. At the other extreme would be people who are experiencing little or no side effects from medications, and have a good boost in immune function from therapy. Continuing therapy might be a reasonable choice in that situation. For the vast majority of people in between these two ends of the spectrum, a thorough discussion of your options with your healthcare provider, even seeking a second opinion, may be the best approach.

NOTE: The PHS HIV Treatment Guidelines are not meant to stop people who want to stay on medications from doing so. Insurers should not use the guidelines to stop paying for drugs. Already it is rumored that one state's AIDS prescription drug plan is considering stopping payment for drugs for people with more than 350 T helper cells. This was not the intent of the recent changes to the guidelines. Fortunately, in Washington State, the AIDS prescription drug plan is not even considering this option, and has never set any restrictions by lab values, or clinical conditions, on when approved drugs may be prescribed.

## STEP introduces "Ask Dr. Brad"

Naturopathic physician Brad Lichtenstein is now available to answer Perspective readers' questions regarding alternative medicine and complementary therapies for HIV/AIDS. Now you can send questions for either Dr. Jeff or Dr. Brad to [dr@stepproject.org](mailto:dr@stepproject.org). Dr. Brad's first column will appear in this summer's issue.

Dr. Ask  
Dr. Jeff

# Meet the staff



**Roberto Gonzalez**  
Treatment Educator  
& Outreach

Originally from Cuba, Roberto came to Seattle in 1993 and after a hiatus in San Francisco he's now back to stay. His love for people, his extensive experience in customer service coupled with his community activism activities helps to bring a unique and exciting perspective to STEP and all of its programs. Roberto will be coordinating all of our outreach activities, volunteers and the STEP TalkLine.

**Erica Didier**  
Lead Treatment Educator  
& Publications

I started working with STEP in June 1999 as the volunteer coordinator, and now edit and coordinate the *STEP Perspective* and *Ezine*. I am leaving in August to attend medical school at the University of Washington, but look forward to staying involved with STEP as a member of the Publications Advisory Committee.

**Adimika Meadows**  
Treatment Educator  
& Presentations

My name is Adimika Meadows; I was born and raised in the Seattle metropolitan area. I have an affinity for STEP and it's mission to provide treatment information and education to all communities involved in this epidemic "in my own backyard." I am taking time off from my medical school education and look forward to furthering my public health education. My role at STEP is to inform, equip, and galvanize community members affected or impacted by HIV/AIDS to begin addressing the epidemic in a coordinated and comprehensive campaign for overall health.

# Stepa