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# HIV Alerts

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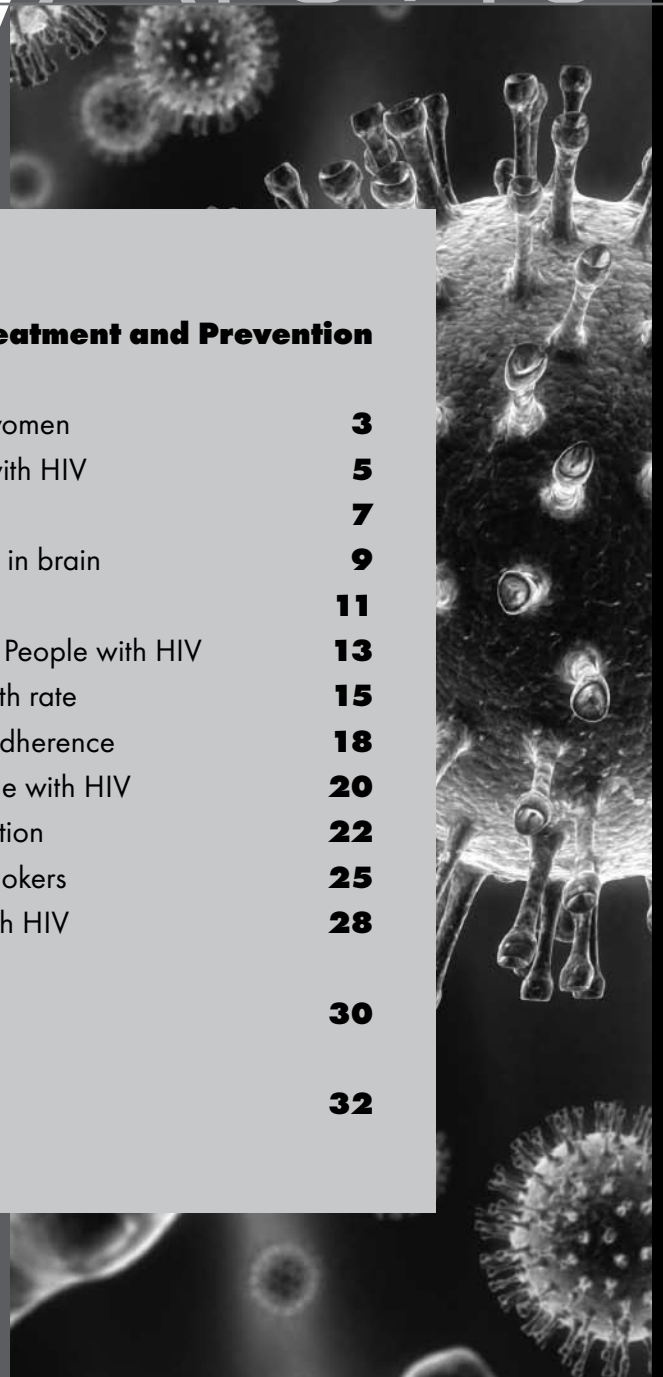
inside

## • Latest Studies on HIV Treatment and Prevention

- Low Pap test rate in HIV+ women **3**
- Anal sex risks in gay men with HIV **5**
- Prezista versus Kaletra **7**
- Isentress and Prezista levels in brain **9**
- HIV and artery damage **11**
- Stiffer Arteries in Untreated People with HIV **13**
- Impact of HBV/HIV on death rate **15**
- Alcohol and antiretroviral adherence **18**
- Non-AIDS cancers in people with HIV **20**
- Diabetes risk with HIV infection **22**
- Lung function worsens in smokers **25**
- Persistent lung problems with HIV **28**

**Definitions 30**

**Board and Staff 32**





## MISSION

The Center for AIDS Information & Advocacy empowers people living with HIV to make informed decisions about their health care by providing the latest research and treatment information and by advocating for accessible, affordable, and effective treatment options until there's a cure.



## About HIV Treatment Alerts!

*HIV Treatment Alerts!* is a publication of The Center for AIDS Information & Advocacy (The CFA). This newsletter is intended for those affected by HIV and their caregivers. The statements and opinions expressed in this newsletter do not imply recommendations or endorsement. Always consult your doctor before altering a prescribed drug regimen or taking any drug or supplement.

*HIV Treatment Alerts!* is published twice a year. The print version of the newsletter is available for free at The CFA's L. Joel Martinez Information Center, various AIDS service organizations, some physician offices and health clinics, or by mail. Access to the newsletter is available online from The CFA website ([www.centerforaids.org](http://www.centerforaids.org)).

The CFA also publishes *Research Initiative/Treatment Action!* (RITA!). RITA! is a literature-review journal that covers issues in HIV research and policy. This and other publications are available on The CFA website or can be requested by mail (see contact information below). CFA publications are supported in part with unrestricted funding from Abbott Laboratories, AIM Investments, CFP Foundation, GlaxoSmithKline, and The Arch and Stella Rowan Foundation.

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Article 1

## Nearly One Quarter of US Women With HIV Do Not Get Important Pap Test

A study of more than 2400 HIV-infected women in 18 states found that 23% did not have a Pap test in the past year.<sup>1</sup> HIV treatment guidelines recommend an annual Pap test to detect cervical cell changes that could lead to cervical cancer. In the year after women are diagnosed with HIV, they should have two Pap tests.

Women with HIV run a higher risk of infection with the virus that can cause cervical cancer than do women without HIV.<sup>2,3</sup> When cervical cell changes do lead to cancer, they do so faster in women with HIV.<sup>4</sup> Cervical cancer treatment fails more often in women with HIV than in those without HIV, and HIV-infected women have a shorter survival with cervical cancer than HIV-negative women.<sup>5</sup>

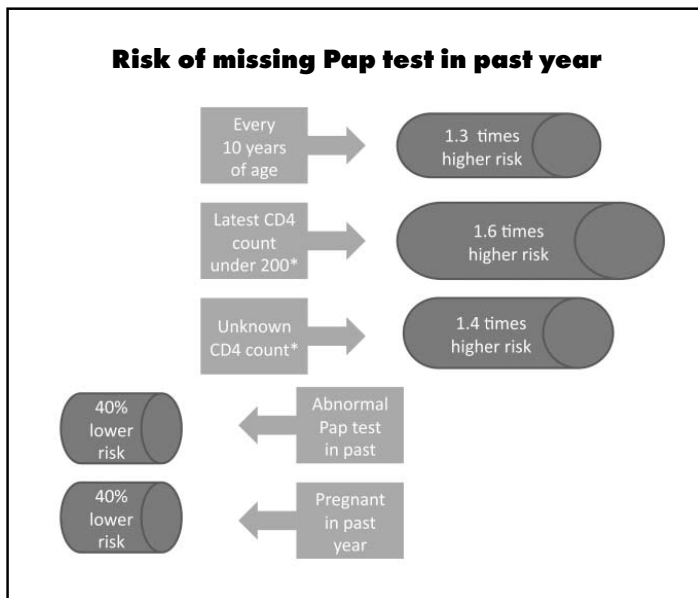
■ **How the study worked.** From May 2000 to June 2004, trained workers interviewed 2417 HIV-infected women in 18 states across the United States. Women answered questions about their social and economic status, gynecologic history, sexual behavior, HIV testing and treatment, and use of medical services. They also noted whether they ever had a pelvic exam and whether it included a Pap test. Women who did not have a Pap test at their most recent exam were asked if they ever had a Pap test and, if they did, the month and year of the test.

The researchers used standard statistical methods to analyze differences between women who had a Pap test and those who did not. They used a statistical method that considers several factors at the same time to pinpoint individual factors that predict which women did not have a Pap test in the past year.

■ **What the study found.** Of the 2417 women interviewed, about two thirds were African American and 15% Hispanic. **Median\*** age was 39 years, and 55% of women had a household income below \$10,000 per year. While 83% of women had health insurance, 74% received primary care at a community or public clinic.

Among the women interviewed, 556 (23%) had not had a Pap test in the year before the interview. Five factors affected the likelihood of having a Pap test, regardless of what other factors were involved (**Figure**).

HIV-infected women without AIDS but with a sexually transmitted disease were 40% more likely to have had a Pap test in the past year (when compared with women without a sexually transmitted disease). Women who had their last pelvic exam some place other than their usual HIV clinic had a higher risk of missing a Pap test in the past year. For these 1096 women,



**Figure.** Three factors independently raised the risk of missing a Pap test in the past year: (1) older age, (2) most recent CD4 count below 200 (\*versus over 200), and (3) unknown CD4 count (\*versus over 200). Two factors independently lowered the risk of missing a Pap test in the past year: (1) having an abnormal Pap test in the past and (2) being pregnant in the past year.

\*Please see the definitions on page 30 for **boldface** words.

the risk of skipping a Pap test in the past year varied with race or ethnicity:

- Hispanic women: 4.8 times higher risk of missing Pap test in past year (if their last pelvic exam was not at their usual HIV clinic)
- White women: 2.3 times higher risk of missing Pap test in past year (if their last pelvic exam was not at their usual HIV clinic)
- African-American women: 1.7 times higher risk of missing Pap test in past year (if their last pelvic exam was not at their usual HIV clinic)
- Women of other races: 2.1 times higher risk of missing Pap test in past year (if their last pelvic exam was not at their usual HIV clinic)

■ **What the results mean for you.** This important study of more than 2400 HIV-positive women across the United States found that a substantial minority of them—almost one quarter—had not had a Pap test in the past year. Pap tests detect abnormal cells in the cervix that can develop into cervical cancer. Early detection of abnormal cervical cells lets physicians begin treatment to prevent cervical cancer. HIV care guidelines call for two Pap tests in the year after a woman has a positive HIV test, then one test yearly after that. It is critical for women with HIV to get a Pap test regularly.

Women in this study and in an earlier study<sup>6</sup> who did not have their pelvic exams at their HIV clinic had a higher chance of missing a Pap test in the past year. This finding could point to poor communication between the HIV clinic and the gynecologic clinic where some women go for pelvic exams. Perhaps the gynecologic

clinics do not know the women have HIV, or perhaps they believe the women are getting Pap tests at their HIV clinic.

Hispanic women were the most likely to miss a Pap test if they got their pelvic exam outside their HIV clinic. Poor English language skills in some Hispanic women may explain why they are missing Pap tests. Physicians who care for Hispanic women with HIV should be especially careful to make sure these women are not missing Pap tests. And HIV physicians should make sure all women getting their pelvic exams outside the HIV clinic are not missing Pap tests.

Older women in this study were more likely to miss a Pap test in the past year. Older women may think they no longer run a high risk of cervical cancer. But older women with HIV have a higher risk of cervical cancer than older women without HIV, so they should not stop having Pap tests.

Another troubling finding of this study is that women with lower CD4 counts were less likely to have a Pap test in the past year. But women and men with lower CD4 counts have a higher risk of cancers and non-HIV infections. So women with low CD4 counts—and their doctors—should be especially sure that Pap tests are not missed.

A vaccine against human papillomavirus (HPV) infection is recommended for all girls and women from 9 to 26 years old. Preventing infection with certain types of HPV can prevent cervical cancer. However, girls and women already infected with types of HPV most likely to cause cervical cancer will not be protected by the HPV vaccine. And the vaccine does not protect against all types of HPV. So getting a regular Pap test is still important for women who have the HPV vaccine.

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## Worrisome Unsafe Anal Sex Rate Among US Gays With HIV

Although most HIV-infected gay men in a 30-study US analysis practice safe sex with all partners, 30% have unprotected anal sex with HIV-infected partners and 26% have unsafe anal sex with partners whose HIV status they don't know or partners without HIV.<sup>1</sup> The studies indicate that unsafe anal sex by HIV-infected gays has become more frequent since the year 2000. (Unprotected or unsafe anal sex in these studies means sex without a condom.)

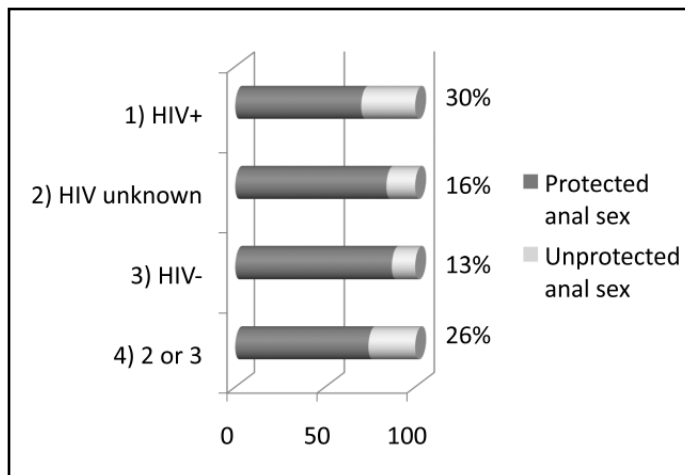
A five-city US study in 2005 found that 25% of gay men had HIV infection, and almost half of them did not know they carried the virus.<sup>2</sup> Discouraging people already infected with HIV from having unsafe sex is one of the surest ways to prevent further spread of HIV infection. When HIV-infected people have sex, they risk passing the virus to an uninfected person, passing a *second* virus to an already infected person, or getting other sexually transmitted infections themselves. Other infections can make HIV infection worse or make HIV care more difficult.

■ **How the study worked.** Centers for Disease Control and Prevention (CDC) researchers examined three online databases and other sources to find published US studies of HIV-infected gay men. The men knew whether they had HIV infection. All studies began after strong antiretroviral combinations came into wide use (late 1995 and early 1996). The researchers did not include studies that focused entirely on men very likely to have unsafe anal sex (for example, sex workers or men signed up for studies at gay bathhouses).

The CDC team used standard statistical methods to combine results from individual studies. This approach is an accepted way to get an overall look at results from studies addressing the same issue. The researchers aimed to figure the percentage of HIV-infected men who had unprotected anal intercourse with three types of partners: (1) partners they knew had HIV infection, (2) partners whose HIV status they did not know (HIV-unknown partners), and (3) partners they knew did not have HIV infection. The researchers also used standard statistical methods to answer questions about which personal factors or types of studies might make unprotected anal sex more likely.

■ **What the study found.** The 30 studies analyzed included 18,121 gay men diagnosed with HIV infection in the United States. The men had a **median** age of 38 years, and most men in half of the studies were black or Latino. In 15 studies that reported antiretroviral use, the proportion of men taking **antiretrovirals** ranged from 23% to 89%. In the 10 studies that reported **viral load**, proportions of men with an undetectable load ranged from 39% to 57%.

Overall, 43% of these gay men with HIV reported having insertive or receptive anal intercourse with any male partner. Rates of unprotected sex were highest with partners known to have HIV (30%) and lower with partners whose HIV status was not known (16%) or partners known to be HIV-negative (13%) (**Figure**). The rate of unprotected anal sex with HIV-unknown or HIV-negative partners combined was 26%.



**Figure.** A combined study of 18,121 gay men diagnosed with HIV infection found different rates of unprotected anal sex with male partners who had HIV, did not have HIV, or had an unknown HIV status.

During unprotected anal sex, the receptive partner (the “bottom”) is more likely to get infected than the insertive partner (the “top”). When HIV-diagnosed men had sex with an HIV-positive partner, the frequency of receptive versus insertive anal sex was almost equal (22% versus 21%). But with partners known to be HIV-negative, receptive anal sex was almost twice more frequent than insertive sex (9% versus 5%). Receptive anal sex was also more likely than insertive sex when the partner’s HIV status was unknown (12% versus 8%).

In the combined studies, treatment with antiretrovirals, **adherence** to antiretroviral therapy, and having an undetectable viral load did not affect rates of unprotected anal sex. Rates of unprotected anal intercourse were lower in five types of studies:

- Studies that gathered participants before the year 2000.
- Studies in which most participants were black and/or Latino
- Studies that signed up men in health care clinics
- Studies that did not use **convenience sampling**
- Studies in which interviewers asked questions (rather than having men answer questions on forms)

■ **What the results mean for you.** This large study found that most gay men diagnosed with HIV in the United States who continue to have sex practice safe anal sex with male partners. However, 30% of these men have unprotected anal sex with male partners known to have HIV infection, and 26% have sex with men they

know are HIV-negative or men whose HIV status they do not know.

Unprotected anal sex is dangerous for a person diagnosed with HIV and for that person’s partners. A person already diagnosed with HIV can get infected with another HIV strain during unprotected sex, and that new strain may be resistant to antiretrovirals. The already-infected person may also get infected with other viruses and bacteria that could worsen HIV infection or make HIV treatment more difficult.

For a partner not infected with HIV, unprotected anal sex carries the risk of infection with HIV or other harmful viruses or bacteria. Transmission of HIV is less likely when the infected partner has an undetectable viral load. But even then the transmission risk is not zero. And an undetectable HIV load has no impact on transmission of other viruses, like herpes viruses and hepatitis B or C viruses, or on transmission of bacteria.

This combined study did find strong evidence that most men diagnosed with HIV wear condoms during sex with other men to protect their partners—and to protect themselves. All HIV-infected men who continue to have sex should do the same. But the study also found that rates of unprotected anal sex have increased since the year 2000.

The first step in preventing HIV transmission is for all sexually active people to know whether they have HIV infection. The CDC recommends routine HIV testing for all adults who seek medical care. An earlier HIV diagnosis makes caring for HIV infection easier.

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## Response and Resistance With Prezista Versus Kaletra After Earlier Treatment



People who had tried earlier **antiretroviral** combinations controlled HIV better with Prezista/Norvir (darunavir/ritonavir) than with Kaletra (lopinavir/ritonavir) in a large trial comparing these two protease inhibitors.<sup>1</sup> When Prezista did fail to control HIV, fewer resistance mutations emerged than when Kaletra failed to control HIV.

In the United States, Prezista is approved for once-daily use by people starting their first antiretrovirals and for twice-daily use by people who have already taken antiretrovirals.

■ **How the study worked.** Researchers at centers around the world randomly assigned 298 people to switch their antiretroviral combination to Prezista/Norvir (plus other antiretrovirals) and 297 to switch to Kaletra (plus other antiretrovirals). Prezista and Kaletra are both protease inhibitors. This type of study, a randomized trial, is the best way to find similarities and differences between drugs. Everyone who entered the trial had a **viral load** above 1000 copies when the study began, and no one had taken Kaletra, Prezista, Aptivus (tipranavir), or Fuzeon (enfuvirtide) before. No one in this study could take Fuzeon.

The researchers defined treatment failure in two ways: First, never reaching a viral load below 400 copies during treatment. Second, reaching a viral load below 400 copies, but then having two viral loads in a row above 400 copies (or stopping treatment after one viral load above 400 copies). In anyone whose regimen failed and who had a viral load above 1000 copies, the researchers evaluated viral samples for resistance mutations and for how sensitive or resistant that virus was to the drugs being studied and to other antiretrovirals.

■ **What the study found.** About one third of study participants had never used a protease inhibitor, about one third had used just one protease inhibitor, and the remaining third had used more than one protease inhibitor. The Prezista group and the Kaletra group did not differ from each other in previous protease inhibitor use, starting CD4 count (**median** 232 CD4s), or starting viral load (average 20,000 copies). When the study began, the groups were almost identical in number of mutations making HIV resistant to Prezista, Kaletra, other protease inhibitors, and nucleosides. The nucleosides include drugs like Emtriva (emtricitabine), Epivir (lamivudine), Viread (tenofovir), and Ziagen (abacavir).

After 48 weeks of treatment, 90% of those who started Prezista and 79% of those who started Kaletra had a viral load below 400 copies. Even in people who began treatment with one or more mutations that make HIV resistant to Prezista, viral load response rates at 48 weeks were better in the Prezista group than in the Kaletra group.

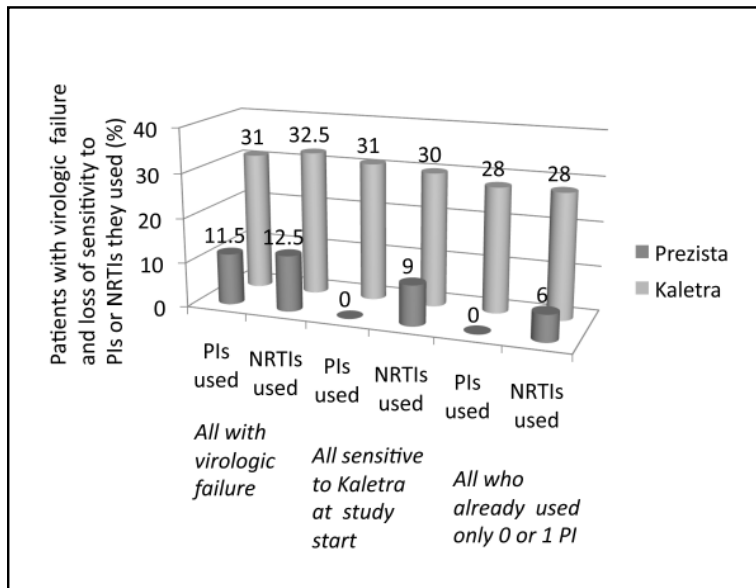
The researchers recorded 31 virologic failures in the Prezista group (10% of 298) and 65 failures in the Kaletra group (22% of 297). This difference was highly **statistically significant**. The research team was able to analyze mutations in 28 of the 31 people whose Prezista combination failed and in 56 of 65 whose Kaletra combination failed. Major protease inhibitor mutations developed in 6 of the 28 people (21%) taking Prezista versus 20 of 56 (36%) taking Kaletra. Mutations that make HIV resistant to nucleosides developed in 4 of 28 people (14%) taking Prezista and in 15 of 56 taking Kaletra (27%).

The investigators could measure changes in HIV sensitivity to antiretrovirals in 28 of 31 people whose Prezista combination failed and in 54 of 65 whose Kaletra combination failed. Among people with HIV sensitive to Prezista when the study began, 3 of 26 (11.5%) lost sensitivity to Prezista when their combination failed (**Figure**). In contrast, among 42 people with HIV sensitive to Kaletra when the study began, 13 (31%) lost sensitivity to Kaletra when their combination failed. People in whom Prezista failed also lost sensitivity to nucleosides at a lower rate than people taking Kaletra.

■ **What the results mean for you.** These findings indicate that for people like those in this trial, switching to Prezista offers a better chance of controlling HIV after 48 weeks of treatment than switching to Kaletra. Even when Prezista did fail in this study, virus resistant to protease inhibitors and nucleosides was less likely to develop than when Kaletra failed.

This study group had moderately advanced HIV infection, with CD4 counts averaging about 230 and viral loads averaging about 20,000 copies. No one had taken Prezista or Kaletra before. When the trial began, the Prezista group had a median of 0 mutations making HIV resistant to Prezista (range 0 to 5). At that point, the Kaletra group had a median of 1 mutation making HIV resistant to Kaletra (range 0 to 4). Median number of nucleoside-related resistance mutations was 2 in both the Prezista group and the Kaletra group. So people in this study did not have high-level resistance to protease inhibitors or nucleosides when the study started.

There is no doubt, though, that Prezista (plus low-dose Norvir) is a strong protease inhibitor. It is a good option for people who have tried other antiretrovirals, including other protease inhibitors, as long as resistance testing indicates that their HIV is still sensitive to Prezista. Prezista can also be a good choice for a first antiretroviral combination.<sup>2</sup>



**Figure.** Among people in whom Prezista failed, lower proportions lost sensitivity to protease inhibitors (PIs) or nucleoside reverse transcriptase inhibitors (NRTIs) they were taking when compared with people in whom Kaletra failed. This lower loss of sensitivity held true for people with HIV sensitive to Kaletra when the study started and for people who had taken no PIs or one PI before the study began.

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## Prezista and Isentress Can Get Into Nervous System and Brain to Attack HIV

Two powerful new antiretrovirals, Prezista (darunavir) and Isentress (raltegravir), get into the central nervous system in levels high enough to control HIV, according to results of separate studies by the same researchers.<sup>1,2</sup> Prezista, the newest protease inhibitor, may be used by people who have taken other antiretrovirals or by people starting their first antiretroviral combination. Isentress, the only integrase inhibitor approved by the Food and Drug Administration, may also be taken by people who have or have not used antiretrovirals before.

An ability to get into the central nervous system (the spinal cord and brain) is a benefit not shared by all antiretrovirals. HIV *does* get into the central nervous system. If someone with HIV takes only antiretrovirals that do not penetrate the central nervous system, HIV will continue to hide there and make new copies of itself. If only low levels of an antiretroviral get into the central nervous system, HIV may become resistant to that drug in the spinal cord and brain.

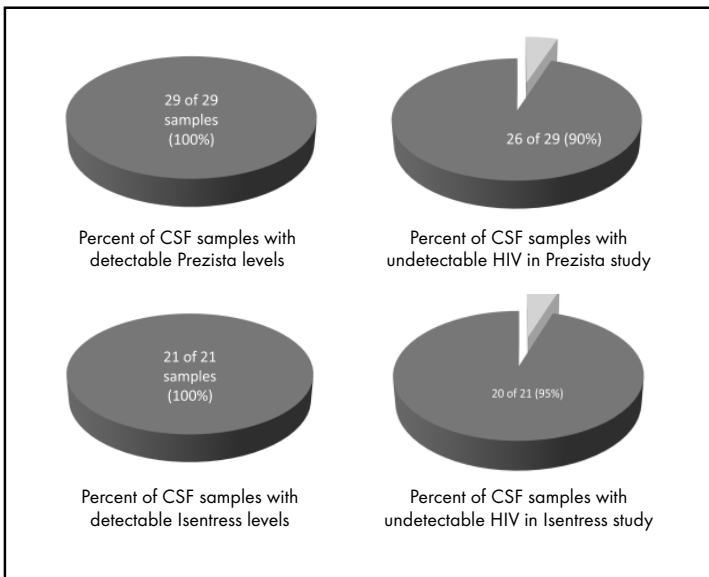
Confusion, forgetfulness, and other mental problems trouble some people with HIV, even though their **viral load** is undetectable when measured in blood outside their central nervous system. That could mean HIV remains poorly controlled in their central nervous system.

■ **How the studies worked.** The Prezista study involved 18 people taking this protease inhibitor who had stored blood samples and **cerebrospinal fluid (CSF)** samples in which Prezista levels could be measured.<sup>1</sup> Seventeen of these people were taking Prezista twice daily, and one was taking Prezista once daily. Researchers measured Prezista levels in 29 pairs of blood samples and CSF samples from these 18 people. Then they figured out how concentrations of Prezista in CSF compared with concentrations in blood.

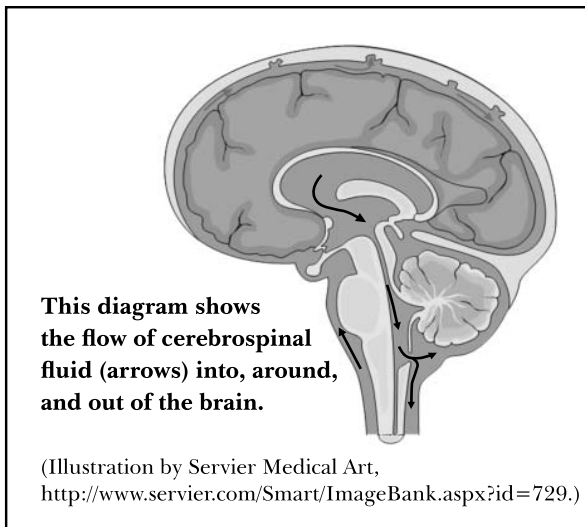
The Isentress study involved 18 people taking this antiretroviral who had stored blood and CSF samples in which Isentress levels could be measured.<sup>2</sup> Researchers measured Isentress levels in 21 pairs of blood and CSF samples from these people to compare Isentress concentrations in blood and CSF.

■ **What the studies found.** Everyone in the Prezista study had AIDS. Sixteen (88%) were men and 11 (62%) were white. **Median** CD4 count for the group was 197. These people had taken Prezista for a median of 7.5 months.

Prezista could be detected in all CSF samples at a median level of 56.9 ng/mL (**pie chart Figure**). Median total Prezista concentration in blood stood at 4094 ng/mL. Median concentration of Prezista in blood and



**Figure.** The protease inhibitor Prezista and the integrase inhibitor Isentress could be detected in all CSF samples analyzed in separate studies of people taking these antiretrovirals. HIV could not be detected in 90% of Prezista-treated CSF samples or 95% of Isentress-treated CSF samples.



not bound by protein was 542 ng/mL. Prezista levels in CSF were 9.4% of Prezista blood levels unbound by protein.

The 50% inhibitory concentration (IC<sub>50</sub>) of a drug is the amount of drug needed to stop 50% of HIV in a sample from making copies of itself. The IC<sub>50</sub> is a standard way to measure activity of drugs. As in many studies, the Prezista and Isentress studies calculated the IC<sub>50</sub> of the drug against virus not resistant to Prezista or Isentress.

Prezista levels in CSF were much higher than the IC<sub>50</sub> in all CSF samples tested. That means Prezista would probably help control HIV in the central nervous system of these people. Indeed, viral load was too low to measure in 26 of 29 CSF samples studied (90%) as well as in 18 of 29 blood samples (62%).

Seventeen of the 18 people in the Isentress study (94%) were men, 16 (89%) were white, and 15 (83%) had AIDS. Median CD4 count in these people was 276. Sixteen people had taken other antiretrovirals before they started Isentress, which they took for a median of 4.2 months.

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The researchers detected Isentress in all CSF samples at a median concentration of 14.5 ng/mL (pie chart Figure). Median Isentress blood concentration was 260.9 ng/mL. Isentress levels in CSF were 5.8% of levels in blood. Isentress levels were higher than the IC<sub>50</sub> in all CSF samples. Viral load could not be detected in 20 of 21 CSF samples (95%) or in 13 of 21 blood samples (62%).

■ **What the results mean for you.** The researchers conclude that Prezista should contribute to control of HIV in the central nervous system as a part of combination antiretroviral therapy. They reach the same conclusion about Isentress. In other words, either of these antiretrovirals should help rein in HIV in the brain. As a result, including Prezista or Isentress in an antiretroviral combination may help improve mental problems caused by HIV and may help prevent such problems.

Some of the researchers who worked on these studies helped create a score that rates individual antiretrovirals for how well they get into the central nervous system. One recent study showed that this CNS penetration effectiveness (CPE) score predicted better mental function: People taking an antiretroviral combination with a higher total CPE score had fewer problems detected by standard tests of mental function.<sup>3</sup> But an earlier study by the physicians who created the CPE score could not show that a higher score meant better mental function.<sup>4</sup> Differences in the methods used in these two studies may explain the different findings. The study that found that higher CPE scores reflected better mental functioning<sup>3</sup> included a larger number of people and used more accurate methods for measuring changes in mental function.

More work is needed to define the ability of individual antiretrovirals to reach the brain. But everyone agrees that controlling HIV in the central nervous system is a critical goal of antiretroviral therapy. Evidence that Prezista and Isentress enter the CSF at high levels is reassuring.

## HIV Infection Damages Arteries as Much as Smoking or Older Age

Compared with healthy adults not infected with HIV, people with HIV in a large US study had more extensive atherosclerosis (hardening of the arteries), even when researchers considered other atherosclerosis risk factors.<sup>1</sup> The worse atherosclerosis seen in people with HIV matched the degree of damage seen with every 5 to 9 years of age and the damage seen in smokers. Atherosclerosis can lead to heart attacks.

■ **How the study worked.** Researchers used ultrasound scans (a safe and painless technique) to measure carotid artery intima-medial thickness (CIMT) in two carotid artery regions (the common carotid and the internal plus bulb region) in two groups—one group with HIV and one without HIV. CIMT reflects early atherosclerosis.

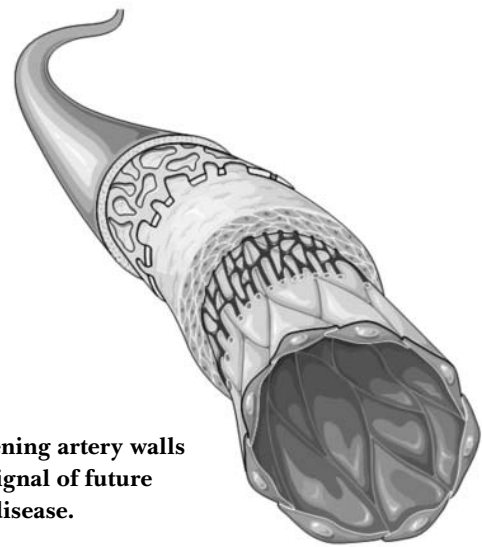
Trained technicians performed ultrasound of the right and left near and far walls of the common carotid artery and the internal carotid plus bulb region. The investigators calculated CIMT by averaging all readings for each person—up to four locations in the common carotid and up to 12 locations in the bulb region. Measuring CIMT is an accepted way to figure the risk of myocardial infarction (heart attack) and other **cardiovascular disease**. But studies evaluating CIMT in people with HIV have had conflicting results.<sup>2</sup>

HIV-infected people evaluated here were part of the study of Fat Redistribution and Metabolic Change in HIV (FRAM). The HIV-negative comparison group came from the Multi-Ethnic Study of Atherosclerosis (MESA) and the Coronary Artery Risk Development in Young Adults (CARDIA) study.

This analysis included 433 FRAM participants with HIV, 94% of whom had taken a potent **antiretroviral** combination, and 5749 people from CARDIA or MESA without an HIV diagnosis. All study participants were 37 to 78 years old and free of cardiovascular disease when CIMT was measured. All study participants answered questions about their personal and family medical history, smoking, current medications, and other factors that may affect heart disease risk. The researchers also measured height, weight, blood pressure, blood sugar (glucose), and blood fats (cholesterol and triglycerides).

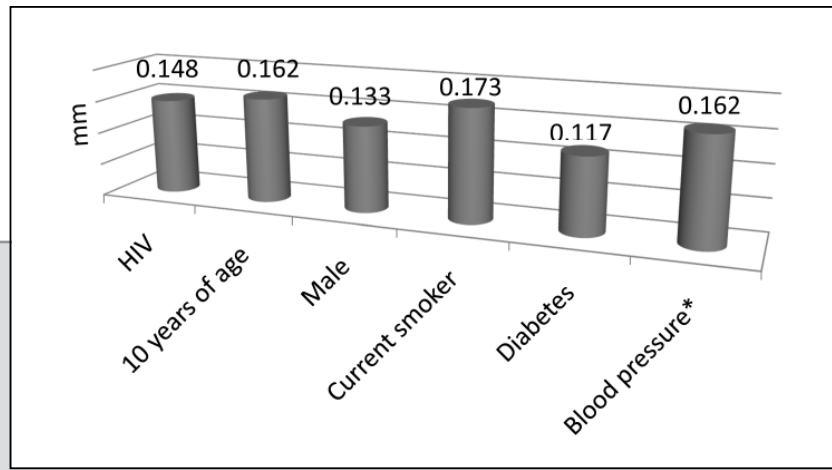
■ **What the study found.** The 433 HIV-infected study participants had a lower average age than the 5749 people without an HIV diagnosis (49 versus 61 years). While men accounted for 70% of the HIV group, the non-HIV group included equivalent proportions of men and women. The HIV group had a higher proportion of current smokers than the non-HIV group (36% versus 15%), higher average triglyceride levels (197.5 versus 130.4 mg/dL), lower “good” high-density lipoprotein (HDL) cholesterol (46.5 versus 51.1 mg/dL), and lower total cholesterol (188.2 versus 194.8 mg/dL).

The internal carotid region was 0.11 mm thicker in the HIV group, despite their much younger age. In a statistical analysis that accounted for the influence of age, gender, and race, the internal carotid remained **significantly** thicker in the HIV group (0.188 mm). The internal carotid also remained significantly thicker in the HIV group after further statistical adjustment for traditional heart disease risk factors (smoking, diabetes, blood pressure, total cholesterol, and HDL cholesterol) (0.148 mm). These analyses assured the researchers that being in the HIV group explains the thicker artery walls—regardless of whatever other risk factors a person may have.



**Thickening artery walls are a signal of future heart disease.**

(Illustration by Servier Medical Art, <http://www.servier.com/Smart/ImageBank.aspx?id=729>.)



**Figure.** A comparison of people with HIV and people without an HIV diagnosis found that HIV infection is similar to smoking, diabetes, and high blood pressure in its impact on internal and common carotid wall thickness, which is an indicator of early heart disease. This graph shows the relative impact of HIV and traditional heart risk factors on internal carotid wall thickness in millimeters (mm).

\*For every 30 mm Hg higher systolic blood pressure level.

Both women and men with HIV had thicker internal carotid walls than women and men without an HIV diagnosis (0.200 mm for women, 0.128 mm for men). However, the link between HIV infection and thicker carotid artery walls was stronger in women than in men.

Common carotid artery walls were also significantly thicker in people with HIV than in the non-HIV group, although the difference between the groups was not as great as with the internal carotid.

For the internal carotid, the impact of HIV infection on artery wall thickness (0.148 mm) was similar to the impact of several traditional heart disease risk factors—older age, male gender, current smoking, diabetes, and every 30 mm Hg higher systolic blood pressure (**Figure**). For the common carotid, the impact of HIV infection on artery wall thickness (0.033 mm) was similar to the impact of smoking (0.020 mm), diabetes (0.026 mm), and every 10-mm Hg higher systolic blood pressure (0.025 mm).

■ **What the results mean for you.** These findings add to the research showing that people with HIV have a higher risk of heart disease than people without HIV. In this study, the HIV group consisted almost entirely of people taking antiretrovirals.

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This study differs from many studies of heart disease risk with HIV because it compares HIV-related heart disease risk with traditional risk factors like smoking, diabetes, and high blood pressure. Several earlier studies could not record these risk factors. The impact of HIV on heart disease risk (measured by carotid artery thickness) was similar to the impact of several of these other risk factors (**Figure**). Unlike having HIV infection, many of the other risk factors can be controlled: With the help of your physician and others, you can stop smoking and prevent or control diabetes and high blood pressure.

“Although HIV infection and its therapies are associated with increases in several traditional cardiovascular risk factors,” these researchers write,

*“there is an additional effect of HIV infection beyond that of traditional cardiovascular risk factors.” Results of this study suggest that HIV infection affects heart disease risk as much as getting 5 to 9 years older.*

*“Now that patients with HIV infection are living longer,” the investigators propose, “these data suggest that clinicians should consider HIV infection as a candidate cardiovascular risk factor,” especially in people who already have a mid-level risk of heart disease because of other risk factors.*

## Stiffer Arteries in Untreated People With HIV Than in People Without HIV



Artery stiffness was much greater in people with HIV but not taking antiretrovirals than in people without HIV, according to results of a small comparative study.<sup>1</sup> Stiffness is a signal of early heart disease. The study adds to other evidence indicating that HIV itself, regardless of antiretroviral therapy, raises the risk of heart disease.<sup>2-5</sup>

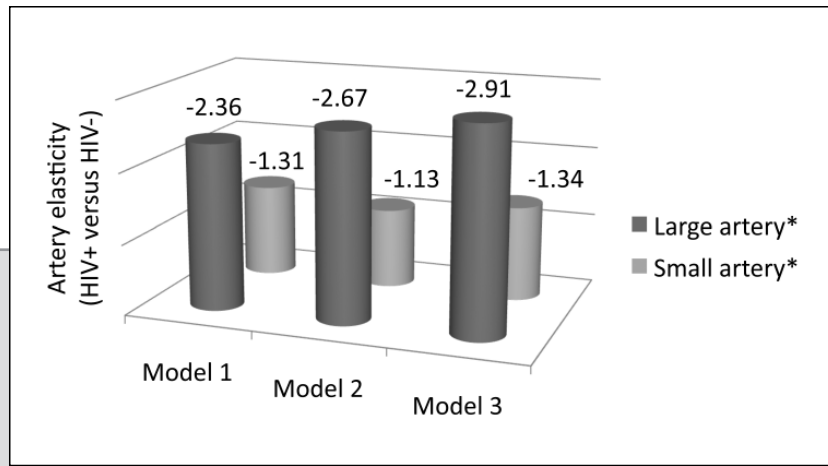
■ **How the study worked.** These researchers used a technique that analyzes waveforms created by pulse pressure at the wrist to estimate elasticity (the opposite of stiffness) of large and small arteries. They compared elasticity in 32 HIV-infected people not taking antiretrovirals for at least 1 year and 30 healthy people without HIV infection. None of these people ever had a myocardial infarction (heart attack) or angina (heart-related chest pain). The people without HIV were selected to reflect the HIV group in age, gender, race, smoking status, and a diabetes diagnosis.

Before being tested by the pulse waveform technique, study participants avoided alcohol and drugs that may affect test results. Each person had three waveform tests, and results of the three tests were averaged to give a single elasticity number for that person. The researchers also performed other blood tests to look for factors that may affect heart disease risk (such as blood fat levels). For each study participant, the investigators figured the 10-year risk of heart disease with an online tool (<http://hp2010.nhlbihin.net/atpii/calculator.asp>).

Finally, the researchers used standard statistical methods to estimate elasticity differences between people with and without HIV in three ways. *Model 1* factored in the calculated 10-year heart disease risk score. *Model 2* considered four factors that differed between the HIV group and the non-HIV group: smoking, injection drug use, hepatitis C virus infection, and “good” high-density lipoprotein (HDL) cholesterol. *Model 3* considered age, gender, race or ethnicity, smoking, injection drug use, hepatitis C, HDL cholesterol, and non-HDL cholesterol.

■ **What the study found.** The 32 people with HIV and the 30 without HIV did not differ much in age, gender, race or ethnicity, use of blood pressure-lowering drugs, or rates of high blood pressure or diabetes. People with HIV were more likely to have hepatitis C virus infection or to be a former injection drug user. The HIV group had a higher average heart rate, lower “good” HDL cholesterol, and lower creatinine (high creatinine may signal kidney disease). Only 4 people with HIV (13%) had a CD4 count under 200, indicating advanced HIV infection.

Both large-artery elasticity and small-artery elasticity were **significantly** lower in people with HIV. Average large-artery elasticity was 2.55 mL/mm Hg × **10** lower in the HIV group, and average small-artery elasticity was 1.50 mL/mm Hg × **100** lower in the HIV group. In the three statistical analyses that considered other heart risk factors, elasticity was significantly lower with HIV infection (**Figure on page 14**). Changing the sta-



**Figure.** Large-artery elasticity and small-artery elasticity were significantly lower in people with HIV (and not taking antiretrovirals) than in a comparison group of people without HIV. *Model 1* factored in 10-year heart disease risk score. *Model 2* considered four factors that differed between the HIV and non-HIV groups: smoking, injection drug use, hepatitis C virus infection, and “good” high-density lipoprotein (HDL) cholesterol. *Model 3*, the most complete model, considered age, gender, race or ethnicity, smoking, injection drug use, hepatitis C, HDL cholesterol, and non-HDL cholesterol.

**\*Note:** The large-artery bars cannot be directly compared with the small-artery bars in this chart because they are on a different scale. Large-artery elasticity is measured as mL/mm Hg × 10; small-artery elasticity is measured as mL/mm Hg × 100.

tistical analysis to eliminate 5 HIV-infected people who took antiretrovirals in the past did not greatly change these findings.

Further analysis indicated that CD4 count and viral load had no impact on the lower large-artery and small-artery elasticity in people with HIV. Infection with hepatitis C virus did partly explain lower large-artery elasticity in people with HIV. Also, in HIV-infected people a higher heart disease risk score tended to lower large-artery elasticity.

■ **What the results mean for you.** Along with other studies, this research shows that HIV infection itself can raise the risk of heart disease. Certain antiretroviral drugs may add to heart disease risk. But this study specifically shows that people who never took antiretrovirals—or did not take them for over 2 years—had lower artery elasticity than similar people without

HIV. Low artery elasticity is a sign that heart disease may develop.

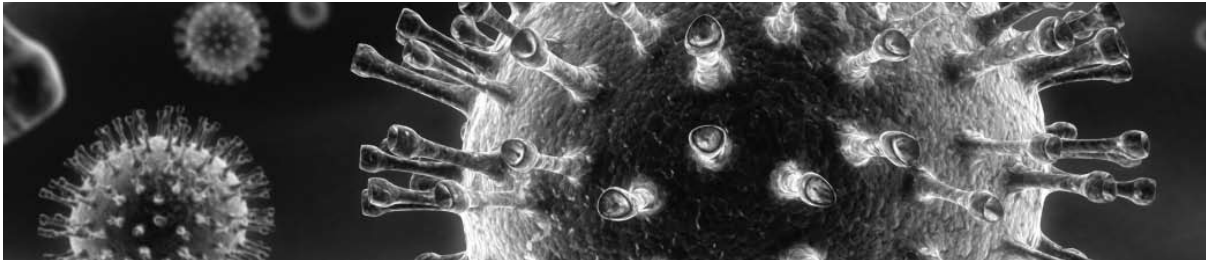
Because of these findings, people with HIV (including those not yet taking antiretrovirals) should do everything they can to lower their risk of heart disease. Factors that make heart disease more likely include smoking, being overweight, having diabetes, and having high blood pressure. All of these factors can be controlled with the help of your physician, other health professionals, and HIV support groups.

This study is the first to use the pulse waveform technique to measure artery elasticity in people with HIV. This test is safe and painless. It does not involve needles or any other device that penetrates the body. These researchers hope the method will be tested in larger groups of people with HIV.

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## Non-AIDS and AIDS Death Rates Higher With HBV Despite Antiretroviral Therapy



Men taking potent **antiretroviral** combinations had a 4 times higher risk of death from non-AIDS causes if they also had hepatitis B virus (HBV) infection.<sup>1</sup> Men with HBV and HIV also had nearly a 3 times higher death risk from AIDS causes. Like HIV, HBV can be picked up during sex or when drug users share needles. Between 5% and 10% of people with HIV also have HBV.

■ **How the study worked.** The study involved gay men in the Mulicenter AIDS Cohort Study (MACS), which has groups in Baltimore, Chicago, Los Angeles, and Pittsburgh. All men began combination antiretroviral therapy after they joined MACS. The earliest year in which men began treatment was 1996. MACS researchers kept track of these men until they died or until March 2006.

Everyone had at least two tests for HBV that had the same result, and at least one of the tests was done before antiretroviral therapy began. The MACS team divided the men into four groups according to their HBV status: (1) never infected, (2) past infection, (3) chronic (ongoing) HBV infection, and (4) isolated core.\*

The researchers classified deaths during the study period as related to AIDS or non-AIDS deaths. They also kept track of new AIDS illnesses, **viral load** drops below 400 copies, and CD4 count changes. They used accepted statistical methods to analyze the impact of HBV infection on death, new AIDS illnesses, viral load, and CD4 count in the first 6 months of therapy and later.

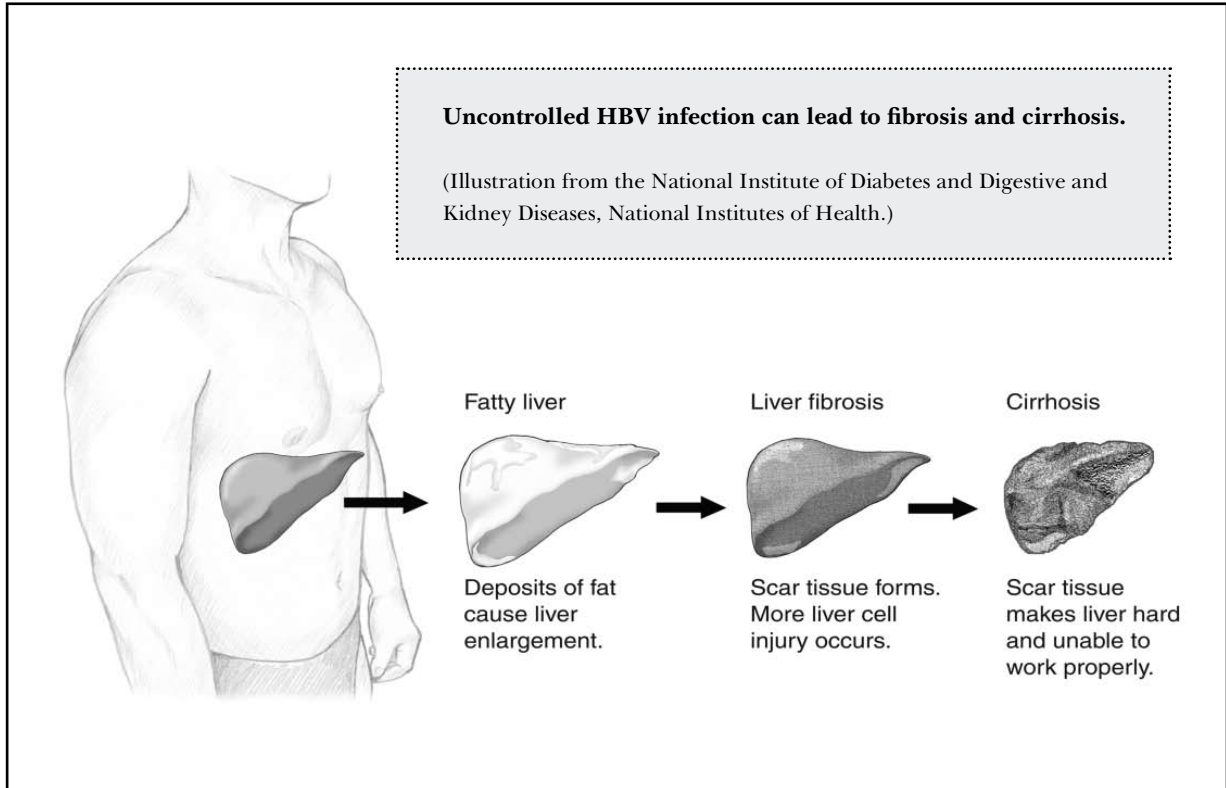
■ **What the study found.** The study focused on 816 men who started antiretrovirals in MACS and whose HBV status could be determined. Among these men, 350 never had HBV infection, 357 had past infection, 45 had chronic HBV, and 64 had isolated core HBV antibody. Compared with the other HBV groups, men with chronic HBV had the lowest CD4 counts when they began antiretrovirals and the highest levels of two liver enzymes that indicate liver damage. Almost all study participants took an antiretroviral active against HBV at some time during the study period: Epivir (lamivudine), Emtriva (emtricitabine), or Viread (tenofovir).

Eighty-seven people died during the study to give a death rate of 17 per 1000 person-years. Despite antiretroviral therapy, AIDS caused most deaths (43), while non-AIDS illnesses caused 30 deaths, and 14 people died of unrecorded causes. AIDS-related deaths were most frequent among men with chronic HBV infection and least frequent among those who never had HBV:

- Chronic HBV: 17 AIDS deaths per 1000 person-years
- Isolated-core HBV: 14 AIDS deaths per 1000 person-years
- Past HBV infection: 11 AIDS deaths per 1000 person-years
- Never infected with HBV: 2.9 AIDS deaths per 1000 person-years

The researchers then performed a statistical analysis to figure the impact of chronic HBV on AIDS-related deaths after taking into account the first measured CD4

\*Isolated core HBV means a positive test for anti-HBV core antibody but not for other anti-HBV antibodies. People with isolated core HBV do not have the standard signal of ongoing HBV infection (the hepatitis B surface antigen), but they can have low levels of detectable HBV DNA in their blood. Detecting HBV DNA is like detecting HIV RNA with the HIV **viral load** test. In people with isolated core HBV, the hepatitis virus probably keeps making new copies of itself at a low level. However, what this means for the patient's health is unclear.



count, proportion of study visits with a viral load below 400 copies, injection drug use, and starting antiretrovirals after 1996. In this analysis, chronic HBV raised the risk of AIDS deaths 2.7 times. This increased risk fell just short of statistical significance (which is explained in *What the results mean for you*, to the right).

The non-AIDS death rate was also higher among men with chronic HBV than among men in the other groups:

- Chronic HBV: 22 non-AIDS deaths per 1000 person-years
- Isolated-core HBV: 14 non-AIDS deaths per 1000 person-years
- Past HBV infection: 5.8 non-AIDS deaths per 1000 person-years
- Never infected with HBV: 2.4 non-AIDS deaths per 1000 person-years

In a statistical analysis that factored in age and first measured CD4 count, chronic HBV raised the risk of non-AIDS death 4.1 times, while isolated-core HBV raised the risk of non-AIDS death 3.6 times. These increased risks were statistically significant, meaning they almost certainly cannot be explained by chance alone. Among 6 people with chronic HBV who died from a non-AIDS cause, 4 died from liver disease.

The different HBV groups did not differ in rates of new AIDS illnesses, viral load control, or CD4-cell gains. These findings mean HBV infection does not affect the response to strong antiretroviral therapy.

■ **What the results mean for you.** This study shows that HIV-positive people with chronic (ongoing) HBV infection have a higher risk of dying from non-AIDS causes and from AIDS than people without HBV, despite treatment with strong antiretroviral combinations. Among the non-AIDS causes of death, liver disease was the most frequent. That probably means HBV infection was not completely controlled in these men.

Almost everyone in this study took at least one antiretroviral drug that also controls HBV infection. Taking only one anti-HBV drug can allow HBV to become resistant to that drug and other drugs. The risk of HBV resistance to Epivir is particularly high, if Epivir is the only anti-HBV drug being taken. (Epivir is part of the two-in-one combinations Combivir and Epzicom, and part of the three-in-one combination Trizivir.)

The Centers for Disease Control and Prevention (CDC) recommends that people with HIV and HBV take two drugs active against HBV.<sup>2</sup> People with chronic HBV should make sure they and their doctor know their HBV status, and they should receive therapy effective

against HBV. Even if Viread or Emtriva is no longer effective in controlling HIV, continuing these drugs may be important for controlling HBV.

The reasons behind the higher AIDS death rate in men with chronic HBV infection is not clear. This finding fell just short of statistical significance. Statistical significance usually means there is less than a 5% possibility that a result occurred by chance alone. In this study there was an 8% possibility that the higher AIDS death rate in people with chronic HBV resulted from chance alone.

All the people in this study were gay men living in or near a large city. In the United States, gay men often have better health insurance and get better medical care than some other groups with HIV, such as poor black and Hispanic people and people living in rural areas. That could mean the impact of HBV on the risk of death could be even greater in these other groups.

About one third of the people with chronic HBV infection were moderate, heavy, or binge drinkers of alcohol. Because alcohol can damage the liver, people infected with HBV or another hepatitis virus should get help to stop drinking. Heavy drinking and binge drinking are dangerous for anyone, with or without HBV or HIV. The National Institute of Alcohol Abuse and Alcoholism offers an interactive Web page that lets people check their drinking patterns, understand signs of problem drinking, and—if necessary—get help to make a change (<http://rethinkingdrinking.niaaa.nih.gov/>).

People with HIV should be tested for liver disease, which may be caused by hepatitis viruses. HIV-infected people without hepatitis A virus or HBV should be vaccinated against those viruses. There is no vaccine for hepatitis C virus.

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## Drinking Alcohol Makes Good Antiretroviral Adherence Up to 50% Less Likely

Compared with HIV-infected people who did not drink alcohol or drank relatively less, people who drank more were only 50% to 60% as likely to take their **antiretrovirals** on time.<sup>1</sup> Problem drinkers were the most likely to have poor antiretroviral **adherence** rates. These findings come from a study that considered results of 40 separate studies of alcohol drinking and antiretroviral adherence.

People taking antiretrovirals must be sure not to skip any doses and to take all medications exactly as their doctor instructs. Missing doses can let the **viral load** jump and allow development of HIV resistant to the drugs being taken. Resistant virus can lead to failure of the antiretrovirals being taken and can make related antiretrovirals useless.

Researchers planned this study to see how drinking alcohol affects steady pill taking (adherence). Several studies on how alcohol affects adherence have appeared, but results of these studies are not always consistent. Most studies found that drinking makes adherence more difficult, though a few studies did not. Some studies found similar adherence in moderate and heavy drinkers, though more studies found worse adherence in heavy drinkers. To get an overall picture of how drinking alcohol affects adherence, researchers examined all the results of earlier studies together.

■ **How the study worked.** This study is called a meta-analysis. In a meta-analysis, researchers select earlier studies on a certain topic that meet certain requirements. They compile the results of all selected earlier studies and analyze the total results. They can also compare results of different types of studies.

For this meta-analysis, the researchers selected studies published from 1996 through 2007 that examined the impact of alcohol on adherence to strong antiretroviral combinations. Selected studies had to measure adherence, they had to measure alcohol use, and they had to calculate the potential impact of alcohol use on adherence.

The researchers found 40 studies that met their requirements. They rated drinking in these studies as (1) problem drinking, (2) moderate drinking, or (3) any drinking. For men, the National Institute on Alcohol Abuse and Alcoholism defines problem drinking as more than

14 drinks weekly or more than 4 drinks daily. For women, problem drinking means more than 7 drinks weekly or more than 3 drinks daily. In this study the researchers defined moderate drinking as less intense than problem drinking, for example, drinking alcohol twice a week or having at least 10 drinks a month. Any drinking pattern that could not be rated as problem drinking or moderate drinking (for example, any alcohol in the past month) was called “any or global” drinking.

■ **What the study found.** The 40 studies analyzed took place from 1998 to 2007 and included more than 25,000 people. Most studies (33) took place in the United States, while others took place in France (3) or Canada, Brazil, India, or Italy (1 each).

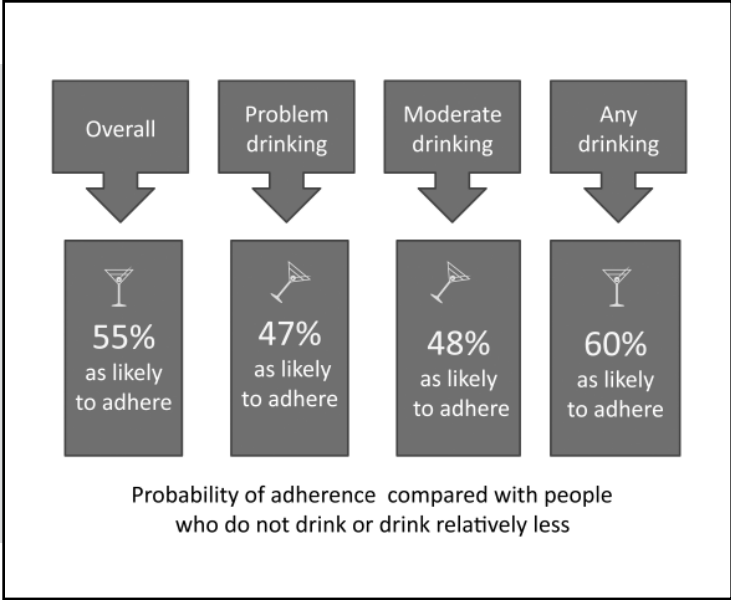
Overall results showed that people who drank alcohol were 55% as likely to be adherent as people who did not drink or who drank relatively less (**Figure on page 19**). People classified as problem drinkers were 47% as likely to be adherent as non-problem drinkers or people who did not drink at all. Moderate drinkers were 48% as likely to be adherent as people who drank less or did not drink at all. People who drank any alcohol were 60% as likely to be adherent as people who drank no alcohol.

■ **What the results mean for you.** Examining results of 40 studies involving over 25,000 people with HIV infection, this study shows that people who drink alcohol are less likely to take their antiretrovirals on time than people who do not drink at all or who drink relatively less. That finding held true not only for problem drinkers, but also for moderate drinkers and people who drank any alcohol. However, results of this study support earlier findings that the risk of poor adherence grows with more frequent drinking. Overall, people who drank were just a little over half as likely to be adherent with antiretrovirals as people who did not drink (or who drank relatively less).

The negative impact of alcohol on adherence was greater in studies that included a higher proportion of men than women. This finding contradicts two individual studies that suggested alcohol affects adherence by women more than men.<sup>2,3</sup>

Both men and women should take steps to ensure that drinking doesn't interfere with steady pill taking. If you drink heavily, you should get help to stop drink-

**Figure.** Combined analysis of 40 studies found that people who drink alcohol (far left) are 55% as likely to take their antiretrovirals on time as people who do not drink or drink relatively less. Problem drinkers and moderate drinkers were less than half as likely to take their antiretrovirals on time as people who did not drink or drank relatively less (middle two columns). Any drinking also lowered chances of good antiretroviral adherence (far right).



ing. Alcoholism is an illness that has many negative physical and mental effects far beyond poor antiretroviral adherence. The National Institute of Alcohol Abuse and Alcoholism offers an interactive Web page that lets people check their drinking patterns, understand signs of problem drinking, and—if necessary—get help to make a change (<http://rethinkingdrinking.niaaa.nih.gov/>).

If you are not a heavy drinker, you should make sure that social drinking does not prevent you from taking your antiretrovirals on time. For example, if you take your antiretrovirals at bedtime and you're going out

to a party where you will drink, you should put your pills in a place that will help you remember to take them when you get home.

Some people may deliberately stop taking their antiretrovirals when they drink because they believe drinking and taking antiretrovirals will make them ill. There is no evidence that alcohol and antiretrovirals interact in this way.

Very good adherence is essential to making your viral load undetectable and keeping it undetectable.

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## Non-AIDS Cancers Develop More Often With HIV Than Without HIV

New non-AIDS cancers were 60% more likely in people with HIV than in people without HIV in a large US veterans comparison.<sup>1</sup> For some (but not all) of these cancers, CD4 counts were lower in HIV-infected people who got the cancers than in HIV-infected people who did not. The findings support results of a recent large French study in which lower CD4 counts made non-AIDS cancers more likely.<sup>2</sup>

Development of three cancers in people with HIV—cervical cancer, Kaposi sarcoma, and certain lymphomas (which arise in lymph nodes)—mean a person has AIDS. But recent research shows that people with HIV infection run a higher risk of several cancers that do not lead to an AIDS diagnosis, the so-called non-AIDS cancers.<sup>3-6</sup> Rates of some non-AIDS cancers are higher in people with HIV than without HIV despite the availability of strong **antiretroviral** combinations that control HIV.

■ **How the study worked.** This study had two goals: (1) to see if people with HIV run a higher risk of non-AIDS cancers than similar people without HIV, and (2) to see if CD4 counts in HIV-infected people affect the risk of non-AIDS cancers. To answer those questions, researchers planned a case-control study. In a case-control study, people with a certain condition (in this study HIV infection) are compared with people without that condition. The people without the condition (the “controls”) are matched to the people with the condition (the “cases”). In this non-AIDS cancer study, researchers matched cases and controls according to age, race, gender, geographic location, and year of care.

Researchers examined electronic medical files of people diagnosed with HIV in the Veterans Affairs (VA) system from October 1997 to September 2004. The investigators then selected 2 matched controls for every person with HIV. None of the people with HIV had cancer before being diagnosed with HIV or before being matched to 2 controls. Non-AIDS cancers considered were any cancer except non-Hodgkin lymphoma, Kaposi sarcoma, cervical cancer, or poorly defined cancers.

Next the researchers calculated new diagnoses (incidence) of AIDS cancers and non-AIDS cancers per 100,000 **person-years**. They compared new diagnosis rates of non-AIDS cancers in people with HIV and controls without HIV. For people with HIV, they deter-

mined the earliest CD4 count recorded and compared counts in HIV-positive people with versus without a new cancer. The investigators were able to analyze records of HIV-infected people over a **median** of 5.1 years and of HIV-negative people over a median of 6.4 years.

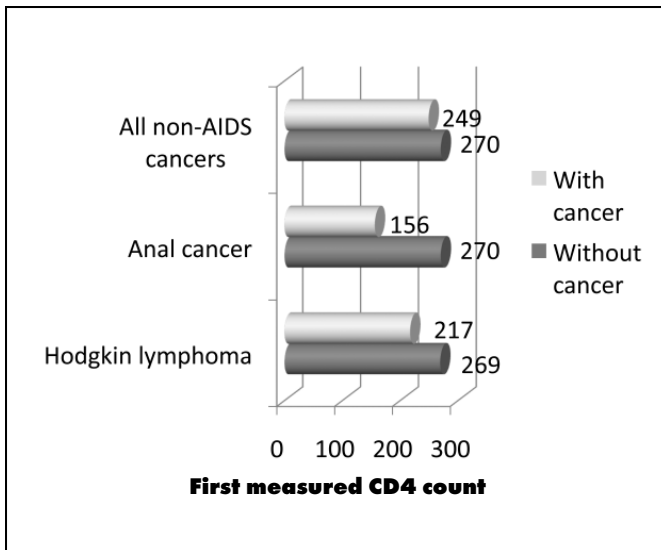
■ **What the study found.** The study focused on 33,420 people with HIV and 66,840 matched controls without HIV. About 46% of people in both groups were identified in fiscal year 1997, about a year after strong antiretroviral combinations came into use. Average age was similar in people with HIV (45.8 years) and people without HIV (46.1 years). Men made up 98% of both groups. The study population was 43% African American, 32% white, and 8% and Hispanic, with the rest having another or an unrecorded race or ethnicity. Hepatitis C virus infection (which may lead to liver cancer) was more frequent in the HIV group than the non-HIV group (36% versus 12%). Alcohol abuse or dependence was recorded in about 20% in each group.

The researchers counted 2128 new non-AIDS cancers in the HIV group and 3142 in the non-HIV group. Because there were half as many people in the HIV group, the new diagnosis rate was much higher in people with HIV: 1260.5 per 100,000 person-years versus 841.8 per 100,000 person-years in the non-HIV comparison group. Further analysis that factored in age, race, and gender showed that the risk of a new non-AIDS cancer was 60% higher in people with HIV.

The rate of new non-AIDS cancers fell from 1998-1999 to 2000-2001 in the non-HIV group but remained stable in the people with HIV. Compared with the HIV-negative comparison group, people with HIV were more likely to have five non-AIDS cancers: anal cancer, lung cancer, melanoma (a serious skin cancer), Hodgkin lymphoma, and liver cancer.

Looking only at people with HIV, the researchers found that **median** first-measured CD4 count was significantly lower in people with non-AIDS cancers than in those without cancer (249 versus 270) (**Figure**). The same was true in people with anal cancer (156 versus 270) and in people with Hodgkin lymphoma (217 versus 269).

Rates of new AIDS cancers were also much greater in people with HIV than in those without HIV. The new diagnosis rate for Kaposi sarcoma was 209.8 times



**Figure.** Median first-measured CD4 count was significantly lower in people with than without all non-AIDS cancers combined and in people with two individual non-AIDS cancers, anal cancer and Hodgkin lymphoma.

higher in people with HIV, the rate for non-Hodgkin lymphoma 8.0 times higher, and the rate for cervical cancer 12.8 times higher. In people with HIV, median first-measured CD4 was significantly lower in those with versus without Kaposi sarcoma (160 versus 272), non-Hodgkin lymphoma (171 versus 272), and cervical cancer (154 versus 340).

■ **What the results mean for you.** This large study involving over 100,000 people with and without HIV confirmed that people with HIV have a higher risk of non-AIDS cancers in general, and five non-AIDS cancers in particular: anal cancer, lung cancer, melanoma (a skin cancer), Hodgkin lymphoma, and liver cancer. The first CD4 count recorded in the study was significantly lower for HIV-infected people with any non-AIDS cancer than with no non-AIDS cancer. First CD4 count was also lower for HIV-infected people with two specific non-AIDS cancers—anal cancer and Hodgkin lymphoma—than in HIV-infected people without anal cancer or Hodgkin lymphoma.

These findings underline the importance of watching for non-AIDS cancers as well as AIDS cancers in peo-

ple with HIV, particularly people with lower current or past CD4 counts. The study also shows that AIDS cancers and certain non-AIDS cancers are more likely in HIV-infected people with lower CD4 counts than in those with higher counts. Antiretroviral therapy should begin well before CD4 counts fall as low as they fell in some of these study participants before their cancer diagnosis.

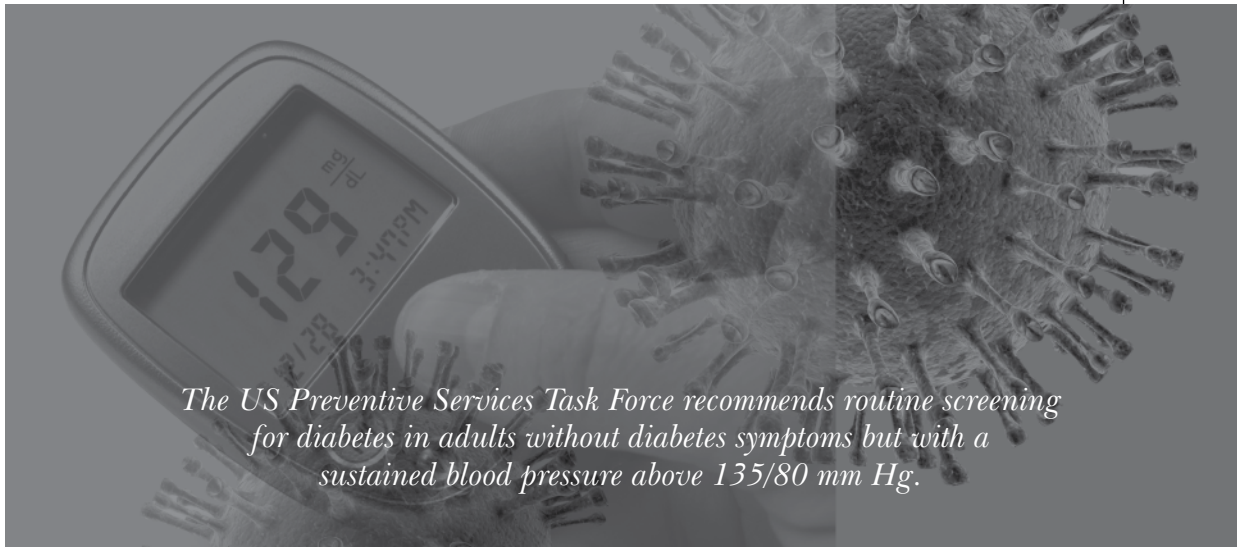
A recent French study, which involved more than 4000 people with HIV, found that longer time with a CD4 count under 200 raised the risk of a new non-AIDS cancer 13% for every year with a CD4 count that low.<sup>2</sup> Current CD4 count under 200 boosted the risk of a new non-AIDS cancer more than 6 times.

Human papillomavirus (HPV) causes anal cancer and is a particular risk in people who have anal sex—including men and women. Anal sex without a condom raises the risk of HPV infection. Some leading anal cancer experts believe people with HIV should be tested regularly for early signs of abnormal anal cell growth.

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## Some Risk Factors Make Diabetes More Likely in People With HIV



*The US Preventive Services Task Force recommends routine screening for diabetes in adults without diabetes symptoms but with a sustained blood pressure above 135/80 mm Hg.*

Three factors that raise the risk of diabetes—older age, heavier weight, and hepatitis C virus (HCV) infection—increased diabetes risk more in US veterans with HIV than in veterans without HIV.<sup>1</sup> But the overall risk of diabetes was lower in the HIV-infected veterans than in those without HIV. That last result suggests HIV itself does not make diabetes more likely, at least not in groups like these veterans. However, the effects of standard diabetes risk factors (like heavy weight), HCV infection, and **antiretroviral** therapy combine to yield a complex diabetes risk pattern in people with HIV.

Diabetes that begins in adulthood results from the body's resistance to the action of the hormone insulin. That leads to high sugar levels in their blood and urine. There is no doubt that diabetes poses a threat to people with HIV. This is especially true since people with HIV are living to an older age, because older age is a well-known risk factor for diabetes.

■ **How the study worked.** This study focused on veterans with and without HIV in the Veterans Aging Cohort Study (VACS), an ongoing study of people seen at eight Veterans Affairs (VA) centers across the country. Veterans who enter the VACS complete a survey covering many factors that could affect development of any disease, such as weight and tobacco and drug use.

The main goal of this study was to compare rates of diabetes between veterans with and without HIV when

they entered the VACS. The researchers determined which people had HCV infection, who drank alcohol or used illegal drugs, who took medications for diabetes or HIV infection, and numerous other factors that could help them figure what might raise the risk of diabetes in these people.

■ **What the study found.** The researchers compared 3227 HIV-infected people with 3240 HIV-negative people. Compared with veterans without HIV, those with HIV were somewhat younger: **Median** age was 49.6 in the HIV group and 50.8 in the non-HIV group. Veterans with HIV were more likely to be black, to be men, and to have HCV infection. The HIV group also had a significantly lower **body mass index** (a way to measure weight defined at the end of this issue). HIV-infected people used alcohol less but used illegal drugs more than people without HIV.

Diabetes rates were 14.9% in the HIV group and 21.4% in the non-HIV group, which is a statistically significant difference. In a statistical analysis that considered several diabetes risk factors at the same time, HIV infection lowered the risk of diabetes 16% regardless of any other risk factors.

In this analysis, older age and higher body mass index raised the risk of diabetes in veterans with and without HIV. But age and body mass index raised the diabetes risk more in people with HIV than in those without

**Table.** Factors that raised the risk of diabetes—regardless of other risk factors

Risk factor	Increased risk with HIV	Increased risk without HIV
Age 35 to 39	4.54*	1.25
Age 40 to 44	6.80*	1.97*
Age 45 to 49	8.43*	2.72*
Age 50 to 54	13.52*	3.88*
Age 55 to 59	13.75*	5.31*
Age 60 to 64	18.38*	6.81*
Age 65 to 69	22.53*	9.59*
Age 70 or more	17.04*	8.03*
Body mass index 20 to 24.9	1.68*	1.20
Body mass index 25 to 29.9	2.30*	1.70
Body mass index 30 or higher	5.35*	3.25*
HCV infection	1.36*	1.28

All age ranges are compared with under 35 years old. All body mass index ranges are compared with under 20 kg/m<sup>2</sup>. A person with a body mass index of 25 to 29.9 is considered overweight. Someone with a body mass index of 30 or more is considered obese.

\*These increased risk rates are **statistically significant**.

HIV (Table). For example, compared with people under 35 years old, HIV-infected people from 40 to 44 years old had almost a 7 times higher risk of diabetes (6.8), while HIV-negative people that old had only a 2 times higher risk of diabetes (1.97). Regardless of other risk factors, HCV infection raised the diabetes risk in veterans with HIV, but not in those without HIV.

Among people with HIV, those taking combination antiretroviral therapy had an 11% higher risk of diabetes than those not taking antiretrovirals. This was a statistically significant risk increase. Using nucleosides or protease inhibitors longer than 1 year raised the diabetes risk more than taking those drugs for 1 year or less.

■ **What the results mean for you.** Several studies of different groups in the United States and elsewhere, including this veterans study,<sup>1</sup> found that HIV by itself does not raise the risk of diabetes. US studies of women in the Women’s Interagency HIV Study<sup>2</sup> and of women and men in the Community Programs for Clinical Research of AIDS<sup>3</sup> found that equivalent proportions of people with and without HIV got diabetes during the studies. A study of gay men with and without HIV infection did find a slightly higher

diabetes rate in men with HIV but not taking antiretrovirals (7% versus 5% in men without HIV).<sup>4</sup> Among men taking antiretrovirals, the diabetes rate was 14%. A large international study including over 33,000 people with HIV found higher rates of newly diagnosed diabetes as time taking antiretrovirals grew longer.<sup>5</sup>

These findings do not mean diabetes poses little threat to HIV-infected people. The veterans study clearly shows that two common diabetes risk factors—older age and heavier weight—raise the risk of diabetes *more* in people with HIV than in people without HIV.<sup>1</sup> HCV infection, which can be transmitted sexually or by needle sharing, boosted the risk of diabetes in veterans with HIV but had a much lower impact on diabetes risk in veterans without HIV.

Almost everyone with HIV is taking antiretrovirals or will need to begin antiretroviral therapy. The veterans study,<sup>1</sup> the gay men’s study,<sup>4</sup> and the big international study<sup>5</sup> all showed that taking antiretrovirals makes diabetes more likely. However, the international study found the highest risk of new diabetes with three antiretrovirals that are used less and less—Zerit (stavudine, which is used hardly at all in the United States and Europe today), Retrovir (zidovudine, which is used mostly as part of the combination pill Combi-

vir), and Videx (didanosine). The researchers who ran the VA study<sup>1</sup> point out that the antiretroviral-related risk of diabetes may have changed as people with HIV started taking newer, safer antiretrovirals. But research has not confirmed that possibility.

The European AIDS Clinical Society says physicians trying to prevent or manage diabetes in people with HIV should rely on the same guidelines used in the general population.<sup>6</sup> The US Preventive Services Task Force recommends routine screening for diabetes in adults without diabetes symptoms but with a sustained blood pressure above 135/80 mm Hg.<sup>7</sup>

Besides controlling high blood pressure, people with HIV should also watch their weight because the veterans study found being overweight raises the risk of diabetes even more in people with HIV than in those without HIV. Being overweight means having a body mass index of 25 or more. A body mass index of 30 or more indicates obesity. You can check how your weight compares with others of your age, gender, and height by using an online body mass index calculator (<http://www.halls.md/body-mass-index/bmi.htm>). Overweight people should get help from their physician or other health professionals.

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## Lung Function Worsens in Smokers Despite Effective Antiretroviral Therapy

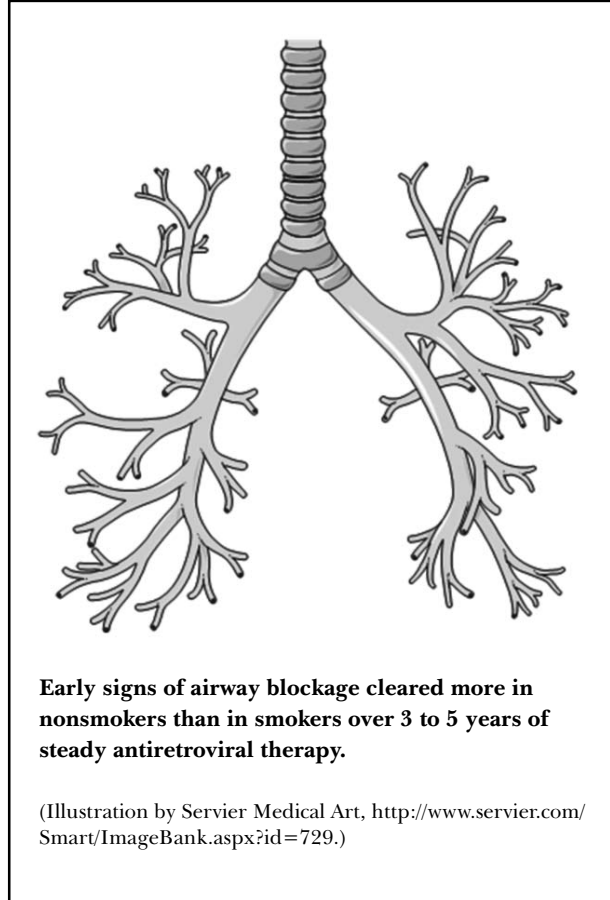
Sixty-three HIV-infected smokers and nonsmokers had signs of early lung disease, usually after several years of **antiretroviral** therapy.<sup>1</sup> After almost another 5 years of successful antiretroviral therapy, lung function improved in nonsmokers. But one measure of lung function got worse over that time in smokers, even though antiretrovirals controlled their HIV infection.

■ **How the study worked.** Physicians in Denmark performed a series of lung function tests on 63 people between October 2000 and November 2001. They repeated the tests between July 2005 and March 2007, after 3.8 to 5.7 years of successful antiretroviral therapy. The study group included 30 smokers and 33 nonsmokers. After the second set of lung function tests, the physicians compared results with the first set of tests to see if lung function improved, stayed the same, or got worse.

■ **What the study found.** At the first lung test visit, smokers and nonsmokers did not differ in average age (43.3 years overall), percentage of men (average 89%), length of HIV infection (**median** 105 months), CD4 count (average 520), **viral load** (median 45,500 copies), percentage already taking antiretrovirals (average 56%), or length of antiretroviral treatment (median 58 months). Nonsmokers weighed **significantly** more than smokers (average **body mass index** 24.0 versus 22.6 kg/m<sup>2</sup>) and had a significantly worse systolic blood pressure (average 133.1 versus 124.4 mm Hg).

During the first lung tests, 55 people (87%) were taking antiretrovirals, and 47 of these 55 (85%) had a viral load below 100 copies. During the second lung tests, 61 people (97%) were taking antiretrovirals, and 54 of these 61 (89%) had a viral load under 100 copies. Between the first set of lung tests and the second set, CD4 counts rose on average from 485 to 679 in smokers and from 548 to 737 in nonsmokers.

About one third of study participants were taking two nucleosides plus a nonnucleoside, one quarter were taking two nucleosides plus one or two protease inhibitors, and more than one third were taking another combination.



**Early signs of airway blockage cleared more in nonsmokers than in smokers over 3 to 5 years of steady antiretroviral therapy.**

(Illustration by Servier Medical Art, <http://www.servier.com/Smart/ImageBank.aspx?id=729>.)

The table shows the lung tests done and how results changed from the first set of tests to the second set. When people first had their lung function tested, both smokers and nonsmokers had test results suggesting early obstructive lung disease. FEV1/FVC and DLCO/VA (**see Table**) were both lower in smokers than in nonsmokers at the first lung function test, but the other measures were similar in smokers and nonsmokers.

For the whole study group, a **median** 4.5 years of successful antiretroviral therapy generally improved signs of early lung disease recorded at the first lung test visit. At the second lung test visit, DLCO/VA returned to normal in the nonsmokers. At the second visit, DLCO/VA in smokers returned to about the point measured in nonsmokers at the first visit. The researchers were surprised to see that the abnormally high RV (residual

**Table.** Lung function changes after 4.5 years of successful antiretroviral therapy

Test	What test measures	Change in smokers	Change in nonsmokers
<b>FEV1</b> (forced expiratory volume in 1 second)	Amount of air that can be forced out of lungs in 1 second after taking a deep breath)	↔ (No change)	↔ (No change)
<b>FVC</b> (forced vital capacity)	Amount of change in air in lungs between a full breath in and a full breath out	↑ (Improved)	↑ (Improved)
<b>PEF</b> (peak expiratory flow)	Greatest air flow in lungs measured during breathing out after a full breath in	↔ (No change)	↔ (No change)
<b>RV</b> (residual volume)	Amount of air left in lungs after a full breath out following a full breath in	↑ (Worsened)	↓ (Improved)
<b>TLC</b> (total lung capacity)	Amount of air in lungs after a full breath in	↓ (Improved)	↓ (Improved)
<b>DLCO/VA</b> (diffusing capacity divided by alveolar volume)	DLVO measures how well air passes from the lungs into the blood; VA is a measure of TLC (see above) that is very sensitive to breathing problems	↑ (Improved)	↑ (Improved)
<b>FEV1/FVC</b> (FEV1 as a percentage of FVC)	FEV1 (see above) divided by FVC (see above)	↓	↓

↑, increased; ↓, decreased; ↔, no change.

volume) recorded among smokers at their first visit got even worse by the second visit. In nonsmokers RV fell to normal levels between the first and second visit.

■ **What the results mean for you.** About 4.5 years of successful antiretroviral therapy reversed many of the carefully recorded lung problems seen in HIV-infected

nonsmokers. If these problems got worse, they could have led to serious breathing problems. The same benefits of antiretroviral therapy can probably be expected by HIV-infected nonsmokers similar to those in this Danish study—people in their late 30s or early 40s, usually with an undetectable viral load and a CD4 count between about 250 and 700.

The story is different for smokers. Compared with nonsmokers in this study, smokers had worse lung problems at the first lung test visit. After about 4.5 years of treatment, several signals of lung function did improve, but generally only to a level seen in nonsmokers at the first lung test visit.

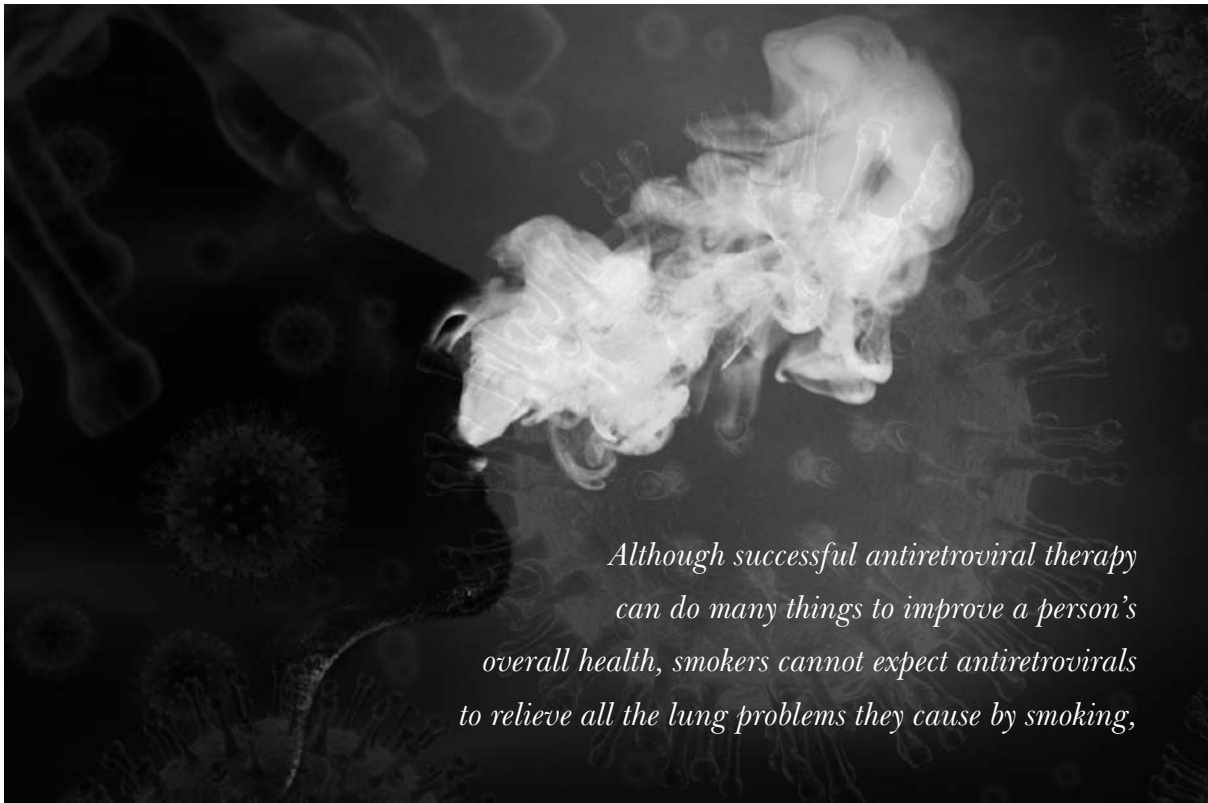
One signal of lung function (RV, residual volume) got worse in smokers during successful antiretroviral therapy. This finding suggests that smokers cannot expect antiretroviral therapy to relieve all the lung problems they cause by smoking. That is not a big surprise. Successful antiretroviral therapy can do many things to improve a person's overall health. But we cannot expect antiretroviral therapy to improve all lung problems in smokers any more than we can expect it to improve all liver problems in heavy drinkers.

Another recent study of lung problems in people taking effective antiretroviral therapy found that smoking almost tripled the risk of noticeable breathing difficulties.<sup>2</sup> Heavier smoking, older age, and a previous bout of pneumonia raised the risk of decreased FEV1/FVC, one of the lung function measures in the Danish study. The second study is reviewed next in this issue of *Treatment Alerts!*

People who smoke should get help trying to stop. Your physician can suggest stopping strategies that work. The Surgeon General's office provides online tips on quitting smoking (<http://www.surgeongeneral.gov/tobacco/#consumer>).

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*Although successful antiretroviral therapy can do many things to improve a person's overall health, smokers cannot expect antiretrovirals to relieve all the lung problems they cause by smoking,*

## Smoking Triples Risk of Lung Complaints in People Taking Antiretrovirals

Smoking cigarettes now or in the past almost tripled the risk of noticeable lung problems like coughing and shortness of breath in people taking strong antiretroviral combinations.<sup>1</sup> In this US study group, heavier smoking, older age, or bacterial pneumonia in the past each raised the risk of one common measurement of lung function.

Before HIV-infected people started taking effective antiretroviral combinations, research showed they had high rates of cough, shortness of breath, and difficult breathing during exertion (such as exercise). Emphysema (a serious lung disease marked by shortness of breath and a high risk of infection) developed more rapidly in people with HIV than in those without HIV before strong antiretroviral combinations became available. To see how often lung problems affect people taking antiretrovirals today, researchers performed lung tests in antiretroviral-treated people at the University of Southern California HIV clinic in Los Angeles.

■ **How the study worked.** The study involved 234 HIV-positive people who first came to the University of Southern California HIV clinic between September 2003 and September 2004. No one had new or worsening cough, shortness of breath, or fever in the 4 weeks before this study began. No one ever had asthma. Researchers interviewed all study participants and collected medical data from their clinic records. The researchers asked people specifically about lung symptoms including cough, shortness of breath, and shortness of breath on exertion.

Everyone completed standard lung function tests. For each patient, the research team determined FEV1, FVC, and FEV1 divided by FVC (see box). The researchers used standard statistical methods to pinpoint

factors that raised the risk of lung symptoms (cough or difficult breathing) or decreased FEV1/FVC.

■ **What the study found.** Of the 234 study participants, 193 (82.5%) were men. Age ranged from 26 to 70 years and averaged 44.1 years. There were 195 people taking an antiretroviral combination (83.3%) and 140 current or former smokers (60%). Time with HIV infection did not differ much between people taking or not taking antiretrovirals.

Almost one third of study participants had a lung complaint, usually cough (in 23%) or shortness of breath on exertion (in 16%); 3% had shortness of breath at rest. Current and former smokers were significantly more likely than nonsmokers to have cough, shortness of breath on exertion, or any lung problem. Three factors predicted lung complaints regardless of what other lung risk factors a person might have: current or former smoking, higher viral load, and lower FEV1/FVC (Figure).

Almost all study participants (93%) had normal lung test results. Both FEV1 and FVC were very close to levels predicted for HIV-negative people of the same age (99% and 94%). The researchers linked several factors to a lower (worse) FEV1/FVC: older age, the number of cigarettes smoked on average, and an earlier bout of bacterial pneumonia.

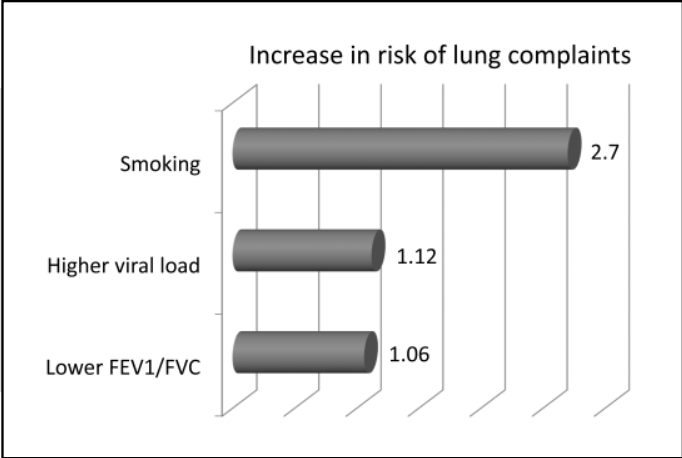
As a group, people taking an antiretroviral combination had a lower FEV1/FVC than people not taking antiretrovirals. The next section explores this finding in more detail.

■ **What the results mean for you.** This study shows that lung problems like cough and shortness of breath affect

- **FEV1:** Forced expiratory volume in 1 second, or the amount of air that can be forced out of the lungs in 1 second after taking a deep breath.
- **FVC:** Forced vital capacity, or the amount of change in air in the lungs between a full breath in and a full breath out.
- **FEV1/FVC:** FEV1 divided by FVC.

**Lower numbers mean more severe lung disease.**

**Figure.** Current or former smokers had almost a 3 times higher risk of some lung symptom (like cough or shortness of breath) than nonsmokers, regardless of other risk factors. People with a higher viral load or a lower FEV1/FVC (see box) also ran a higher risk of lung symptoms.



almost one third of people with HIV infection. Cough and shortness of breath may be early signs of serious lung disease.

Among these HIV-infected people in Los Angeles, three groups had a higher risk of lung complaints regardless of whatever other lung risk factors they had. Most notably, current or former smokers had almost a 3 times higher risk of lung problems. People with a higher viral load or a lower FEV1/FVC (a measure of lung function explained in the box on page 28) also ran a higher risk of lung complaints. Current or former smoking and smoking for a longer time made a lower FEV1/FVC more likely.

Another recent study (reviewed just before this one) found that lungs of nonsmokers generally returned to a healthy state as effective antiretroviral therapy continued over several years.<sup>2</sup> But one lung test in that study suggested lung function continued to get worse in smokers even though antiretrovirals did a good job controlling their HIV infection.

Smoking is an addictive habit that can be hard to break. But even people who have smoked for years do manage to quit. If you smoke, you should talk to your doctor about different approaches to help you

stop. The Surgeon General’s office provides online tips on quitting smoking (<http://www.surgeongeneral.gov/tobacco/#consumer>).

People taking combination antiretrovirals in the Los Angeles study had a lower FEV1/FVC than people not taking antiretrovirals.<sup>1</sup> This finding does not mean people with HIV should delay or stop antiretroviral therapy. The many benefits of antiretrovirals far outweigh any risk of a lower FEV1/FVC. As the other recent lung test study found, overall lung health improved in people taking antiretrovirals for several years.<sup>2</sup> And in the Los Angeles study,<sup>1</sup> people with a higher viral load were more likely to have lung symptoms.

Still, it is possible that airway blockage may be a long-term side effect of antiretroviral therapy. But it will take longer studies in larger groups to see if lung problems become more common in people taking antiretrovirals for years. The Los Angeles study evaluated lung function at a single point in time, and it is possible that other factors contributed to the lower lung function seen.<sup>1</sup> The other recent study compared lung tests at two points separated by about 4.5 years.<sup>2</sup> In that study, lung function improved in nonsmokers; some lung test results also improved in smokers, but one lung test result got worse.

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## Technical Word List

**Adherence** means taking all antiretrovirals your doctor prescribes and taking them at the right time of day.

**Antiretrovirals** are drugs used to treat HIV infection.

**Body mass index** calculates weight as kilograms divided by meters (in height) squared:  $\text{kg/m}^2$ . One kilogram equals 2.2 pounds; 1 meter equals 3.3 feet. To figure your body mass index and see how you compare with others of your gender and age, go to <http://www.halls.md/body-mass-index/bmi.htm>.

**Cardiovascular diseases** are those that involve the heart and major arteries and veins.

**Cerebrospinal fluid (CSF)** is the fluid that surrounds the brain and spinal cord. (See illustration on page 10.) Samples of CSF are taken from a space in the lower back during a spinal tap and can be tested for levels of HIV and antiretroviral drugs.

**Convenience sampling** means signing up anyone who meets study entry requirements and volunteers for a study. This is a less formal method than selecting study participants at random or according to a set system (such as every third person to come into a medical office). Convenience sampling can result in study groups that include unbalanced proportions of people with certain traits that can affect study results.

A **median** is the number above which half of all the numbers recorded lie, and below which half of all the numbers recorded lie. The median number differs from the average (or mean) number. For example, in the series 1, 3, 8, 9, and 14, the median is 8 because half of the other numbers lie above it and the remaining half lie below. But the average of 1, 3, 8, 9, and 14 is 7.

A **person-year** is a measure of time used in medical studies. A single person-year is 1 year lived by 1 person.

**Statistical significance** usually means there is less than a 5% possibility that a result occurred by chance alone.

**Viral load** is the number of HIV particles in a milliliter of blood or another body fluid, such as semen or cerebrospinal fluid.



# HIVAlerts

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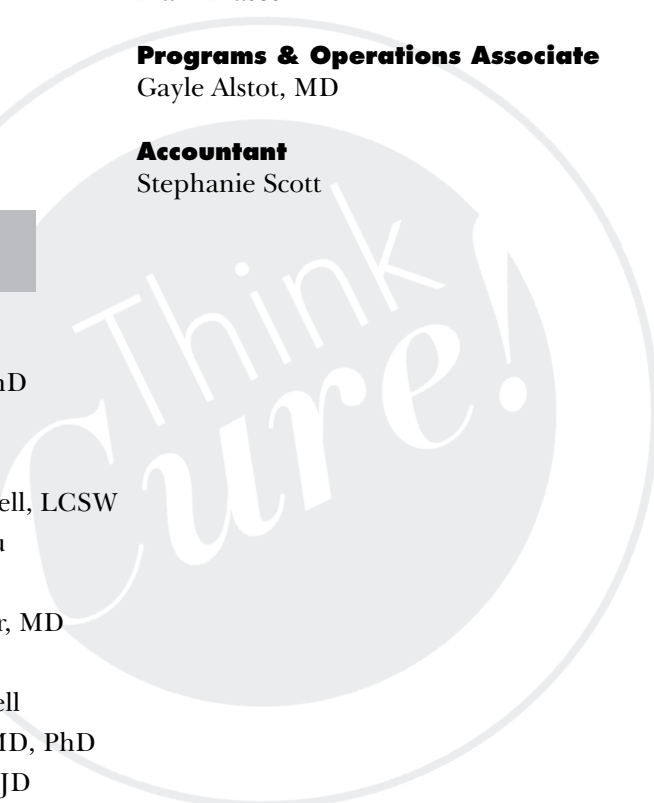
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