Articles

• Survival after age 50 with HIV doubles in nationwide Denmark study

• New HIV cases, death rate, and viral loads dropping in Seattle area

• New HIV resistance to antiretrovirals almost disappears in Switzerland

• People with HIV less likely to get treated for nine major cancers

• CT scans detect early lung cancer in middle-aged smokers with HIV

• Abnormal anal cells that could lead to cancer common in gays with HIV

• Proportion of deaths caused by heart disease rising in people with HIV

• Early artery thickening in middle-aged with HIV and low overall heart disease risk

• Osteoporosis and smoking raise fracture risk in people with HIV

• Liver disease signals more frequent in young people with than without HIV

• High HCV levels in 33% of semen samples from men with HIV and HCV

• Many factors—from marijuana to heart disease—tied to mental slowing with HIV

Definitions

Board and Staff
**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.

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The CFA also publishes Research Initiative/Treatment Action! (RITA!), a literature-review journal that covers issues in HIV research and policy. This and other publications are available on The CFA website ([www.centerforaids.org](http://www.centerforaids.org)).

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Among HIV-positive people in Denmark, estimated survival from age 50 almost doubled from 11.8 years in 1996-1999 to 22.8 years in 2006-2014. But HIV-positive people still had shorter estimated survival than people the same age and gender in the general population of Denmark.

Survival with HIV has increased dramatically in recent years, as people take stronger, safer, and more convenient antiretroviral* combinations. Some studies suggest that people with HIV are living almost as long as people without HIV. But analysis of projected survival is complicated, and not all studies find that people with HIV are close to surviving as long as HIV-negative groups. For example, a California study found that the gap in life expectancy between 24,768 people with HIV and 257,600 without HIV dropped from 44 years in 1996-1997 to only 12 years in 2011. But the gap persisted even in relatively healthy HIV-positive people who started antiretroviral therapy with a CD4 count above 500.

Because of increased survival with HIV, people 50 years old and older make up a growing proportion of HIV groups everywhere. Even less is known about survival with HIV in people 50 or older. To address that question, researchers in Denmark conducted a nationwide study of HIV-positive people matched by age and gender to people without HIV.

How the study worked. Everyone in care for HIV infection in Denmark goes to one of eight HIV centers, where care including antiretroviral therapy is free. Since January 1995, Denmark has kept electronic medical records of all these people, including data on antiretroviral treatment, CD4 count, and viral load. Other nationwide registries include regularly updated data on all Danish residents who have been admitted to a hospital in Denmark, plus data on deaths, emigration, and immigration.

This study focused on HIV-infected people who reached the age of 50 between January 1996 and May 2014 and lived for at least 1 year after testing positive for HIV. The researchers matched every HIV-positive person to 6 people the same age and gender in the general population. The research team also identified a group of “well-treated” HIV-positive people in care between 2006 and 2014 who (1) had taken antiretroviral therapy for at least 1 year, (2) had a viral load below 500 copies and a CD4 count at or above 350 after taking antiretrovirals for 1 year, and (3) had not been diagnosed with any AIDS illness or serious non-AIDS illness. The researchers matched each of these well-treated people with HIV to 6 people in the general population who did not have HIV infection or any other serious illness.

The research team used national registries to determine time from age 50 to (1) death from any cause, (2) date of leaving Denmark, (3) date of last recorded medical visit for HIV-positive people, or (4) May 31, 2014. They used a standard statistical method to determine survival of people who entered the study group in three periods: 1996-1999, 2000-2005, and 2006-2014. This analysis gave researchers an all-cause mortality rate. The researchers also calculated a mortality rate ratio comparing mortality in the HIV group and the general-population group.

What the study found. The study identified 2440 HIV-positive people 50 or older and 14,588 people in the general population matched to the HIV group by age and gender. In the overall HIV group, 530 people (21.7%) died during the study period, compared with 1388 people (9.5%) in the general population.

Among people with HIV, estimated median (midpoint) survival from age 50 rose from 11.8 years in 1996-1999 to 17.8 years in 2000-2005 and to 22.5 years in 2006-2014 (Figure 1). For the general-

*Words in bold are defined in the Technical Word List at the end of this issue of HIV Treatment Alerts.
Figure 1. HIV-positive people who turned 50 in 2006-2014 can expect to live longer than HIV-positive people who turned 50 in 2000-2005 or 1996-1999, according to results of a nationwide study in Denmark. But expected survival of people with HIV still falls short of survival in the general population.

population comparison group, median survival from age 50 was 30.2 years over the whole study period. To state those findings another way, an HIV-positive person 50 years old in 1996-1999 could expect to live to age 67.8, while an HIV-positive person 50 years old in 2006-2014 could expect to live to age 72.5. But by 2006-2014 the HIV group had not caught up to 50-year-olds in the general population, who could expect to live to age 80.2.

For the entire 1996-2014 study period, the researchers compared the chance of death from any cause with HIV versus without HIV in 5-year age groups, expressed as mortality rate ratio (Figure 2). Compared with matched people in the general population, 50-to-55-year-olds with HIV had a 3.8 times higher chance of death during the whole study period. That higher chance of death with HIV grew smaller in each older 5-year age group. But 75-to-80-year-olds with HIV still had a 1.6 times higher chance of death than matched people in the general population (Figure 2). Mortality rate ratio comparing death rates in people with versus without HIV were highest in 1996-1999 and fell in all 5-year age groups in 2000-2005 and 2006-2014. Next the researchers focused on 517 “well-treated” people with HIV who had not been diagnosed with an AIDS illness and had no serious non-AIDS illness 1 year after starting antiretroviral therapy. The investigators matched them by age and gender to 3192 people in the general population who did not have a serious illness.

Estimated median survival from age 50 in the HIV group was 25.6, compared with 34.2 years in the general-population comparison group. In other words, relatively healthy 50-year-olds with HIV could expect to live to age 75.6, compared with age 84.2 in the general population. Comparing death rates in HIV-positive people versus the general population, a mortality rate ratio of 1.7 meant these relatively healthy 50-year-olds with HIV had a 70% higher death rate.

What the results mean for you. This nationwide study in Denmark found that 50-year-olds with HIV can expect to live longer if they turned 50 in 2006-2014 than if they turned 50 in 2000-2005—and much longer than if they turned 50 in 1996-1999 (Figure 1). HIV-positive people 50 and older who avoided AIDS and serious non-AIDS illness because of antiretroviral therapy could expect to live even longer.
But the HIV groups never caught up to survival in people in the general population in Denmark who were the same age and gender. A recent comparison of 24,768 HIV-positive people in California and 257,600 people without HIV made similar findings.2

Large studies like these show that recent improvements in antiretroviral therapy and overall HIV care are helping people with HIV live much longer with their infection. But HIV-positive people still face more health challenges than people without HIV. These challenges include higher rates of some serious diseases like heart disease, cancer, diabetes, and liver or kidney disease. HIV-positive people should work with their healthcare providers to watch out for non-AIDS diseases that may pose a particular threat and take steps to lower chances of getting those diseases. HIV-positive people who already have one of these non-AIDS diseases can take steps to control them.

The most important thing you can do to live longer with HIV is taking all your antiretrovirals regularly, exactly as your provider instructs. If you have trouble taking your pills regularly, talk to your provider about finding ways to improve your pill taking. Sometimes it may be possible to switch to an antiretroviral combination that you find easier to take.

Taking good care of your overall health is important for everyone with HIV, but especially for people 50 and older. Whether a person has HIV or not, many serious diseases become more frequent as a person ages. This study found that people 50 and older who control their HIV infection and avoid AIDS and serious non-AIDS diseases can expect to live longer than people who acquire those diseases.

References


From 2004 through 2013 in King County, Washington State, the number of new HIV cases fell by 28%, and from 2006 through 2013 the proportion of HIV-positive people with an undetectable viral load* jumped from 45% to 86%. These two large changes may well be related because people with an undetectable viral load have a much lower chance of passing HIV to sex partners—and a lower number of sex partners getting HIV infection would translate into fewer new HIV infections.

The United States has a National HIV/AIDS Strategy with several aims, including (1) cutting the number of new HIV infections across the country, (2) improving access to care and the impact of care among people with HIV, and (3) lowering differences in HIV-related health measures between different groups with HIV, such as different racial and ethnic groups. The US Centers for Disease Control and Prevention (CDC) reported a recent drop in new HIV cases across the country, but that drop was not consistent across the different groups analyzed. In particular, new HIV cases remained steady among gay men and other men who have sex with men—and this group accounts for most new HIV infections in the United States.

King County, Washington, which includes Seattle, keeps detailed HIV and AIDS records, including the proportion of HIV-positive people with an undetectable viral load. Researchers in King County conducted this study to chart trends in HIV and AIDS numbers, including viral load, from 2004 through 2013. The investigators gathered US Census data to establish the age, race or ethnicity, and place of birth of people diagnosed with HIV infection. The researchers divided people into three HIV risk groups: heterosexuals, men who have with men, and people who inject drugs and are not men who have sex with men. They calculated death rates of HIV-positive people according to 10-year age groups. They defined HIV control as a viral load below 200 copies.

What the study found. The study included 9539 people who had HIV infection in King County at any point from 2004 through 2013, including 1036 women (11%), 8503 men (89%), and 6365 gays and other men who have sex with men (67%). Almost two thirds of these people (64%) were white, 18% black, and 11% Hispanic.

The proportion of HIV-positive people with a viral load below 200 copies rose from 45% in 2006 to 74% in 2009 and to 86% in 2013. This rising rate of viral control held true for both men and women, for all age groups, and for all HIV risk groups (heterosexuals, men who have sex with men, and people who inject drugs). From 2006 through 2013, the proportion of people with a viral load below 200 rose from 44% to 88% among whites, from 45% to 81% among blacks, and from 54% to 86% among Hispanics.

At the last CD4 count reported, the proportion of people with a CD4 count of 350 or higher climbed from 54% in 2006 to 79% in 2013. The proportion of people with a CD4 count of at least 350 over those years rose from 57% to 81% among whites, from 51% to 73% among blacks, and from 51% to 75% among Hispanics.

During the study period 3779 people tested positive for HIV. From 2004 through 2013, the new-HIV rate fell 28% from 18.4 to 13.2 cases per 100,000 people. The new-HIV rate fell in all HIV risk

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*Words in bold are defined in the Technical Word List at the end of this issue of HIV Treatment Alerts.*
groups—down 17% in heterosexuals, 26% in men who have sex with men, and 79% in people who inject drugs. Among MSM, the new-HIV rate dropped 16% in those younger than 30 years old, 51% in those 30 to 39 years old, and 44% in those 40 to 49 years old. The new-HIV rate fell 39% among blacks, 27% among whites, and 25% among Hispanics. The new-HIV rate dropped 26% from 6.2 to 4.6 per 1000 people in white men who have sex with men, 22% from 10.7 to 8.3 per 1000 people in Hispanic men who have sex with men, and 44% from 17.9 to 10.0 per 1000 people in black men who have sex with men.

From 2004 through 2013, new AIDS cases fell 42% from 12 to 7 per 100,000 people. The drop in new AIDS cases in this period measured 37% in men who have sex with men, 82% in people who inject drugs, and 35% in heterosexuals. Over the same period, the annual death rate fell 28% from 16 to 12 deaths per 1000 people with HIV/AIDS. The death rate fell 32% in men who have sex with men, 20% in people who inject drugs, and 21% in heterosexuals. The death rate dropped 33% among whites with HIV, 73% among blacks with HIV, and 33% among Hispanics with HIV.

Figure 1. In a study of 9539 HIV-positive people in King County, Washington State, a steadily rising proportion had a viral load below 200 copies from 2006 through 2013.

Figure 2. From 2004 through 2013 in King County, Washington State, the new HIV infection rate fell 28% overall, 17% in heterosexuals (Htx), 26% in men who have sex with men (MSM), 79% in injection drug users (IDU), 25% in Hispanics (His), 27% in whites, and 39% in blacks.
What the results mean for you. These encouraging findings show good progress in preventing and controlling HIV infection in Washington State’s King County. No group got left behind in these year-to-year measures of viral load, CD4 count, new HIV infections, new AIDS cases, and deaths: Rates improved in men and women; in blacks, whites, and Hispanics; and in heterosexuals, men who have sex with men, and people who inject drugs.

The individual measures analyzed are probably connected in several ways. For example, increasing proportions of people with an undetectable viral load and high CD4 count translate into fewer AIDS cases and fewer deaths among people with HIV. A growing proportion of HIV-positive people with an undetectable viral load means fewer people with HIV will pass HIV to sex partners or drug-injecting partners. As a result, the rate of new HIV infections should drop, and in turn the number of new AIDS cases and the number of deaths should fall.

People with HIV should remember that starting antiretroviral therapy, taking antiretrovirals consistently, and reaching an undetectable viral load have two major benefits: First, the individual benefits by returning to health and living a longer, productive life. And second, the community benefits because HIV-positive people with undetectable viral loads rarely pass HIV to uninfected people. That doesn’t mean HIV-positive people with an undetectable viral load can stop using condoms: Condoms remain important barriers to other sexually transmitted infections that might pass from one partner to another during sex.

Men who have sex with men account for the biggest share of HIV infections in the United States. Across the country the new HIV infection rate has begun to drop—but not among men who have sex with men. This study in the Seattle area shows that new HIV cases can fall sharply in men who have sex with men—26% in this analysis—in areas where public health officials, community-based groups, HIV providers, and individuals cooperate to limit new HIV infections. A recent study in San Francisco charted a 46% drop in new HIV infections among men who have sex with men—for some of the same reasons that this rate fell in the Seattle area.

This study in Seattle and surrounding King County shows that everyone can benefit from better HIV care, better viral load control, and other factors analyzed in this report. Everyone with HIV or at risk of HIV infection can benefit when a community works together to control HIV.

References

New HIV resistance to antiretrovirals almost disappears in Switzerland

New resistance to antiretrovirals* nearly disappeared from 1999 to 2013 in a nationwide study in Switzerland. Researchers calculated that 401 people taking antiretrovirals in 1999 had a new resistance mutation, compared with only 23 people in 2013.

The goal of antiretroviral therapy is to stop HIV from making new copies of itself in CD4 cells. Resistance happens when the genetic code of the HIV virus changes in a way that allows HIV to keep making new copies of itself when a person is taking a certain antiretroviral or group of antiretrovirals. Such a change in HIV’s genetic code is called a resistance mutation. If resistance mutations start piling up in the HIV of a positive person, fewer and fewer available antiretrovirals will be able to stop HIV from making copies of itself in CD4 cells.

Resistance mutations do not develop when a person is taking an antiretroviral combination that completely stops HIV from making copies of itself. But if a person starts skipping antiretroviral doses and lets HIV make new copies, resistance can emerge. If resistance to certain antiretrovirals develops, a person has to switch to different antiretrovirals to control HIV.

In the past 10 years or so, researchers have made many new, strong antiretrovirals and some new groups of antiretrovirals. New groups of antiretrovirals can usually control HIV that is already resistant to older groups of antiretrovirals. Providers can test HIV in blood with a resistance test to see which antiretrovirals will no longer be effective because of resistance and which new antiretrovirals can still control resistant virus. But a person has to take the new antiretrovirals steadily—without missing many doses—or HIV will become resistant to the new drugs. Eventually, a person who does not take antiretrovirals steadily will use up all the antiretrovirals that can control that person’s resistant HIV.

People who want to learn more about resistance to antiretrovirals can read an easy-to-understand Fact Sheet from the National Institutes of Health linked at reference 2 below.

Researchers in Switzerland conducted this study to see how development of new resistance mutations has changed since 1999.

How the study worked. The Swiss HIV Cohort Study (SHCS) is an ongoing analysis that includes 72% of HIV-positive people taking antiretroviral therapy in Switzerland. SHCS participants make study visits twice a year for testing and interviews, so researchers keep up to date on their health. As part of this ongoing study, researchers test blood samples to find out which antiretroviral resistance mutations developed over time. This information gets stored in a resistance database that can be analyzed at any time. The researchers also examined antiretroviral resistance findings in a national database that includes results of all resistance tests done in Switzerland from 2003 through 2013.

This analysis involved all SHCS members who had one or more study visits from January 1999 through December 2013. The researchers divided study participants into three groups, depending on when they started antiretroviral therapy:

1. Before January 1999, when people often started weak one- or two-drug therapies or poorly designed three-drug therapies that allowed resistance to develop quickly
2. January 1999 through December 2006, when people began taking stronger three-drug antiretroviral combinations
3. 2007 through 2013, when even stronger antiretrovirals that could often control resistant HIV became available

From 1999 through 2013, the investigators determined the yearly rate of antiretroviral resistance based on resistance test results and—when test results weren’t available—based on logical assumptions that classified

*Words in bold are defined in the Technical Word List at the end of this issue of HIV Treatment Alerts.
people as having a high risk of new resistance mutations, a low risk, or an unknown risk. The research team also estimated the rate of resistance to three of the four main antiretroviral groups—nucleosides, nonnucleosides, protease inhibitors, and integrase inhibitors.

Finally, for people in the SHCS in 2013 with a resistance test after starting ART, the researchers determined how many antiretroviral combinations would still be able to control each person’s HIV. To do this, the investigators used an antiretroviral resistance tool developed at Stanford University. This tool gives a resistance score that allows each antiretroviral to be classified as having (1) full activity, (2) intermediate activity, or (3) no activity against HIV with established resistance mutations.

What the study found. The study included 11,084 people, 29% of them women, and 19.5% nonwhite. Similar proportions of the study group became infected with HIV during sex between men (39.6%) or during sex between men and women (37.6%), and 18.8% became infected while injecting drugs. Median (midpoint) age of the study group was 47.

About one third of study participants started antiretroviral therapy before 1999, one third started between 1999 and 2006, and one third started between 2007 and 2013. The proportion of these antiretroviral-treated people with a resistance mutation ever detected fell from 56.2% in the group that started therapy before 1999, to 19.7% in the 1999-2006 group, and to 9.7% in the 2007-2013 group (Figure 1). The last group included 2092 people who had a resistance test before starting antiretroviral therapy; only 1.6% of people in this group acquired resistance during treatment.

Among study participants with resistant HIV in 2013, 59.8% had started antiretroviral therapy before 1999, 25.4% had started between 1999 and 2006, and only 14.8% had started between 2007 and 2013. Whereas 401 people acquired a new resistance mutation in 1999, only 23 did in 2013.

The proportion of people with HIV resistant to three antiretroviral groups fell from 10.7% in those who started therapy before 1999, to 1.6% in the 1999-2006 group, and to 0.2% in the 2007-2013 group.

Figure 1. In an 11,084-person study in Switzerland, the proportion of antiretroviral-treated people with one or more resistance mutations ever detected dropped sharply among people who started antiretrovirals in 1999 or later.
Among people who started antiretroviral therapy before 1999, the researchers determined that 33.8% no longer had a fully active nucleoside available and 14.4% no longer had a fully active nonnucleoside. (“Fully active” means very likely to control that person’s HIV regardless of any resistance mutations the virus may carry.) Among people who started therapy between 1999 and 2006, those proportions improved to 6% without a fully active nucleoside and 9.9% without a fully active nonnucleoside. And among people who started antiretroviral therapy between 2007 and 2013, only 0.7% no longer had a fully active nucleoside available and 8.2% no longer had a fully active nonnucleoside. Almost everyone who started therapy after 1999 had a fully active protease inhibitor and a fully active integrase inhibitor available.

**What the results mean for you.** All of the trends summarized in the preceding section reflect the impact of the stronger antiretrovirals that became available after 1999. The strength of these new antiretrovirals against resistant HIV—and the variety of different antiretrovirals available—mean chances of controlling HIV infection have improved over the years. As a result, fewer people are getting AIDS illnesses. Controlling HIV also helps prevent or control some major non-AIDS diseases.

In the Swiss study participants, this lower risk of AIDS and non-AIDS diseases has improved survival with HIV over the years. Proportions of people who died from AIDS fell from 4% in people who started antiretrovirals before 1999, to 2.4% in people who started therapy in 1999-2006, and to 0.5% in people who started in 2007-2013 (Figure 2). Proportions of people who died from any cause in those three periods fell from 18.6% to 10.3% to 2.1%.

Do resistance findings like these in Switzerland reflect what’s happening in other countries, including the United States? Switzerland differs from the United States in one important aspect of HIV care: Everyone...
in Switzerland receives free HIV care and free antiretroviral therapy. Some HIV-positive people in the United States still have no health insurance or poor insurance, and that impairs their access to antiretrovirals and care. But the antiretrovirals available and HIV treatment guidelines are very similar in the United States and Switzerland. A study in the United States tracked a drop in resistance among antiretroviral-treated people from 1999 through 2008. And a 1997-2008 study in 7 countries across Western Europe made similar findings.

There are two keys to avoiding resistance when taking antiretroviral therapy. First, everyone should have a resistance test before starting therapy to see if they have been infected with virus already resistant to some antiretrovirals. If a person has resistance before starting therapy, the HIV provider can pick an antiretroviral combination that should control that resistant virus. Second, once a person starts a well-selected antiretroviral combination, quickly reaching and maintaining an undetectable viral load will prevent resistant HIV from developing. Reaching and keeping an undetectable viral load depend on taking all your antiretrovirals every day exactly as your provider instructs.

For almost everyone living with HIV today in the United States, Switzerland, and countries with similar HIV epidemics, providers can find an antiretroviral combination that will control HIV—even if that person’s HIV already carries resistance mutations. Taking those antiretrovirals regularly is essential to reaching an undetectable viral load, preventing resistance mutations from developing, and living a long and productive life.

References

People with HIV less likely to get treated for nine major cancers

HIV-positive people proved less likely to get treated for nine major cancers—including lung, breast, and colon cancer—than people without HIV in a nationwide US study. The overall result held true regardless of what kind of health insurance people had and whether they had other illnesses besides cancer.

As people with HIV live longer thanks to antiretroviral therapy, cancer has become a more frequent cause of sickness and death. Among people with HIV, cancer is now the second-leading cause of death, according to results of a large international study. In the general population of the United States, cancer is also the second-leading cause of death, after heart disease. However, people with HIV and cancer do not live as long as cancer patients without HIV. And previous research found that people with HIV get treated for cancer less often than people without HIV. But those previous studies did not consider the possible impact of health insurance and noncancer illnesses on cancer treatment. Because lower treatment rates in people with HIV could contribute to shorter survival in cancer patients with HIV, researchers conducted this nationwide analysis.

How the study worked. The study used the National Cancer Data Base to identify people between 18 and 65 years old with cancer diagnosed for the first time from 2003 through 2011. This database includes information on patients from more than 1500 centers across the United States. The researchers focused on the 10 most common cancers in people with HIV: head and neck, upper gastrointestinal (pancreas, stomach, esophagus), colon and rectum, anus, lung, female breast, cervix, prostate, Hodgkin lymphoma, and diffuse large B-cell lymphoma (the most frequent non-Hodgkin lymphoma in people with HIV).

The research team used the database to determine (1) who had HIV infection, (2) which noncancer illnesses study participants had, and (3) which patients received cancer therapy (which could include surgery, radiotherapy, chemotherapy, or any combination of these therapies). The investigators used an accepted statistical method to determine the impact of HIV infection on lack of cancer treatment. This type of analysis determines the impact of HIV regardless of whatever other factors might affect lack of cancer treatment, including insurance status and other noncancer illnesses. (Other illnesses may make cancer therapy too risky to perform.) The researchers used a similar type of analysis to pinpoint factors that predicted lack of cancer treatment in people with HIV.

What the study found. The study involved 10,265 people with HIV and 2,219,232 without HIV. Compared with the HIV-negative group, people with HIV were younger (median age 47 versus 55 years) and more often men (77% versus 47.6%), black (41.1% versus 13.2%), Hispanic (14% versus 5.7%), using Medicaid (32.2% versus 10.1%), using Medicare (19.6% versus 8.4%), and without health insurance (10.3% versus 5.9%). Almost three quarters of the HIV-negative group (72.5%) had private health insurance, compared with only one third (35.5%) of the HIV group. A higher proportion of people with HIV than without HIV had at least one noncancer illness (23.5% versus 17.9%). HIV-positive people were more likely to have stage 4 (advanced) cancer (37.2% versus 18.9%), and people without HIV were more likely to have stage 1 or 2 cancer (57.2% versus 33.2%).

Chances of not getting treated for anal cancer were similar in people with and without HIV infection. But for the other nine cancers, HIV-positive people had a higher chance of not getting treated. This analysis found a higher chance of nontreatment with HIV regardless of several other nontreatment risk factors, including age, sex, race, insurance status, noncancer illnesses, year of cancer diagnosis, and cancer stage. In an analysis that included only stage 2 to 4 prostate cancer (eliminating the least advanced stage 1, which often requires no treatment), people with HIV had almost a doubled chance of not receiving treatment compared with HIV-negative people.

*Words in bold are defined in the Technical Word List at the end of this issue of HIV Treatment Alerts.
Figure 1. Compared with HIV-negative cancer patients, people with HIV and cancer had a higher chance of not getting treated for nine cancers: (A) Head and neck, upper gastrointestinal (GI), colon and rectum, lung, breast, and (B) cervix, prostate, Hodgkin lymphoma, and large B-cell lymphoma (a non-Hodgkin lymphoma).
Next the researchers focused only on HIV-positive and HIV-negative people who had private health insurance. Despite having private health insurance, people with HIV infection still had a higher chance of not getting treated for seven cancers than did HIV-negative people with insurance: upper gastrointestinal, colon and rectum, lung, breast, prostate, Hodgkin lymphoma, and B-cell lymphoma (Figure 2). As in the overall analysis, HIV-positive people ran a higher chance of not getting treated regardless of other nontreatment risk factors.

Finally, the researchers performed a statistical analysis to identify individual factors that predicted lack of cancer treatment in people with HIV—regardless of whatever other risk factors a person had. The research team performed this analysis separately for two groups of cancers: lymphomas (Hodgkin lymphoma and B-cell lymphoma) and solid tumors (all cancers studied except the two types of lymphoma). Two factors independently raised chances of nontreatment for both solid tumors and lymphoma: black race and lack of private insurance (Table 1). For solid tumors, advanced cancer stage (stage 4) also predicted lack of cancer therapy. For lymphomas, advanced cancer stage raised chances of getting treated. But two other factors lowered chances of treatment for lymphoma: older age and having noncancer illnesses.

Figure 2. Among HIV-positive and HIV-negative cancer patients with private health insurance, those with HIV had a higher chance of not getting treated for the seven types of cancer listed here. GI, gastrointestinal.
What the results mean for you. This large and well-planned US study shows that HIV-positive people with cancer run a higher risk of not getting cancer therapy than HIV-negative people with cancer. Because of the way the researchers designed the study, they showed that lack of health insurance or dependence on government health insurance (Medicaid or Medicare) did not explain why HIV-positive people had a lower chance of getting treated. Other factors that did not explain the lower chance of treatment with HIV versus without HIV were race, advanced cancer stage, or having another illness that might prevent cancer therapy. But when the researchers focused only on people with HIV, they found that being black raised chances of not getting cancer therapy about 40%. And having no health insurance or using Medicaid or Medicare raised chances of not getting treated even more.

The researchers who conducted this study stress that “improved access to cancer treatment is urgently needed, not only for uninsured patients but also for those with Medicaid and Medicare.” Many HIV providers and cancer specialists will probably read this study, and that could make them question whether they should recommend cancer therapy for more HIV-positive people.

If you have HIV infection and learn that you have cancer, work with your HIV provider and a cancer specialist to explore cancer treatment options. If your providers do not recommend treatment and you are not satisfied with that answer, you can get an opinion from other cancer specialists. Talk to your case worker, to someone at an AIDS service organization, or to another health professional you trust if you need help getting another opinion about cancer therapy.

If you do not have health insurance, you should know that insurance is available to everyone in the United States through the Affordable Care Act. (See https://www.healthcare.gov/) If you need help applying for medical insurance through the Affordable Care Act, talk to a case worker or social worker recommended by your HIV provider.

For several reasons, people with HIV infection may run a higher risk of getting cancer than HIV-negative people. Many cancers can be prevented by lifestyle choices (like quitting smoking) or by getting certain vaccines, like the vaccine against human papillomavirus (which can cause cervical cancer, anal cancer, and other cancers) or hepatitis B virus (which can cause liver cancer). A large

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*These factors raise chances of getting or not getting cancer therapy regardless of whatever other risk factors a person has.
†Includes the eight types of cancer studied other than Hodgkin lymphoma and B-cell lymphoma.
US study found that people who have a healthy lifestyle have a substantially lower risk of cancer. This study defined a healthy lifestyle by four factors:

- Smoking in the past or never smoking
- No or moderate alcohol drinking (1 or fewer drinks daily for women and 2 or fewer for men)
- Body mass index (weight) between 18.5 and 27.5 kg/m² (see reference 9)
- Weekly aerobic physical activity (at least 75 high-intensity minutes or 150 moderate-intensity minutes)

The researchers close their report by reminding readers that “cancer treatment not only extends survival from cancer, but also can improve quality of life, even for patients with advanced stage disease.”

References


If you have HIV infection and learn that you have cancer, work with your HIV provider and a cancer specialist to explore cancer treatment options.
CT scans (a simple and safe technique like an x-ray) detected lung cancer in 2% of HIV-positive smokers, most of them younger than 55 years old. Most lung cancers were still at an early stage, when treatment is usually more effective.

Lung cancer is the most frequent and deadly non-AIDS cancer in people with HIV. Smoking is the main cause of lung cancer in people with and without HIV, and more people with HIV than without HIV smoke. But people with HIV have higher lung cancer rates than the general population even in comparisons that take smoking rates into account.

Research in the general population shows that low-dose chest CT scans reduce the lung cancer death rate by detecting lung cancer in smokers 55 to 74 years old. Because of higher lung cancer rates in people with HIV than without HIV, it may make sense to use CT scans to look for lung cancer at an earlier age in HIV-positive smokers. But detecting possible cancer with chest CT carries some risk because procedures to confirm possible cancer may sometimes have harmful effects. Also, rates of false-positive CTs may be higher in people with HIV than without HIV. To see if chest CT detects lung cancer often enough in middle-aged smokers with HIV to justify this risk, French researchers conducted this nationwide study of early lung cancer diagnosis in HIV-positive smokers without active lung disease or AIDS.

How the study worked. The study focused on HIV-positive smokers at least 40 years old seen at one of 14 centers across France. Everyone had a lowest-ever CD4 count below 350 and smoked at least 20 pack-years (for example, 2 packs a day × 10 years = 20 pack-years). The study did not include people with active cancer, active AIDS disease, or lung infection in the past 2 months.

All study participants had a low-dose chest CT scan and returned for a study visit 2 years after the scan. If a CT scan showed something that might be lung cancer, clinicians followed the same set of steps to confirm a diagnosis. Those steps might include a biopsy, which involves taking a lung tissue sample. Lung cancer diagnosis depended on testing tissue from a lung biopsy. The main aim of the study was to determine the number of lung cancers confirmed by biopsy after the single chest CT scan.

What the study found. The study involved 442 HIV-positive smokers who had a chest CT scan in 2011 or 2012. The group had a median (midpoint) age of 49.8 years, and 82% were younger than 55. Most study participants (84%) were men. Almost everyone (98%) was taking antiretroviral therapy, and 90% had a viral load below 50 copies. Median lowest-ever CD4 count was 168, and median CD4 count at the time of the CT was 574. The study group smoked a median of 30 pack-years, which could mean, for example, 3 packs a day for 10 years or 2 packs a day for 15 years.

Clinicians diagnosed lung cancer in 10 people. Nine of these 10 people had a CT that indicated lung cancer (Figure 1). That means 2% of this group had lung cancer detected by CT. Six of the 9 cancers were at an earlier stage, which favors successful treatment. Two of 3 people with late-stage cancer had delayed procedures to establish a diagnosis after the CT scan showed possible signs of lung cancer. Three of the 9 people with CTs indicating lung cancer were younger than 50; another 4 were between 50 and 54; and the remaining 2 were 56 and 58. In the 9 people with CT evidence of lung cancer, smoking pack-years ranged from a low of 21 to a high of 60.

Eight of the 9 people with CT evidence of lung cancer had the cancer confirmed by lung tissue analysis. The ninth person probably had lung cancer, but she could not have the required procedure because she had severe pulmonary (lung) hypertension. Fifteen people had 18 procedures to establish lung cancer diagnosis, and none of these procedures led to serious complications.

Among 368 people who smoked at the time of their chest CT, 74 (20%) had quit by their last study visit.

What the results mean for you. This study of 442 HIV-positive smokers across France found that a single chest CT scan can detect lung cancer—often at an early
Previous research in the general population found that looking for lung cancer with CT scans lowers the lung cancer death rate in smokers 55 to 74 years old. The new study in people with HIV is too brief to measure the impact of chest CT on death. But the results show that CT scans can spot high numbers of lung cancer at an early stage in HIV-positive smokers in their 40s and 50s. And early-stage cancer is more likely to respond to therapy than late-stage cancer.

The French researchers propose that using CT scans to look for lung cancer could benefit HIV-positive smokers younger than 55 who once had a CD4 count below 350. In their study the French team detected one case of lung cancer in every 49 people who had a CT scan. A CT image indicating possible lung cancer may mean a person needs further procedures that take tissue from inside the lung. But none of the 18 procedures done in this study had serious harmful effects, partly because the study took place at a center with much experience doing these procedures.

Smoking is the main cause of lung cancer in people with and without HIV, and everyone in this study smoked—most of them for a long time. But it’s never too late to stop smoking. The risk of lung cancer falls by half in the 10 years after a person quits smoking. In this study group, 74 of 368 people (20%) who smoked at the time of their CT quit during the next 2 years. Other researchers figured that one third of HIV-positive smokers in the United States have quit. That rate could get higher as experts develop new ways to help HIV-positive smokers quit. For example, PositivelySmokeFreeMe, an online eight-session quitting program that can be completed by individual smokers, has had some success. If you smoke, talk to your HIV provider about making a plan to quit.


Four in 10 gay or bisexual men with HIV infection in a 1500-man US group had abnormal anal cells that may sometimes develop into anal cancer. In contrast, only one quarter of HIV-negative gay or bisexual men in the same study group had anal cell abnormalities.

Many anal cancers are caused by high-risk types of human papillomavirus (HPV), especially HPV-16. These high-risk HPVs often affect people who have anal intercourse, such as gays and other men who have sex with men. Research shows that anal cancer risk is 32 times higher in HIV-negative gay or bisexual men than in the general US population and 52 times higher in HIV-positive gay or bisexual men. From 2001 through 2005, almost one third of anal cancers detected in US men developed in HIV-positive men.

Cervical cancer, an AIDS cancer also caused by HPV, can be prevented or detected early by examining cells collected in Pap tests. Examining cells collected from the anus can detect abnormalities that may develop into anal cancer. But health authorities have not yet proposed a screening-and-treatment plan to test anal cells and treat precancer abnormalities. One reason for this uncertainty is the tendency of some risky abnormal cells and even some precancer cells to return to normal without treatment.

To get a better understanding of abnormal anal cell rates in gay and bisexual men with and without HIV infection, US researchers conducted this study.

How the study worked. The analysis involved men in the Multicenter AIDS Cohort Study (MACS), an ongoing study of HIV-positive gay or bisexual men and similar HIV-negative gay or bisexual men at risk of HIV infection. Men began entering the MACS group as early as 1984-1985 in four US cities. They make study visits twice a year to get a physical exam, give samples for study, and answer questions about their health and health-related behaviors (see http://aidscohortstudy.org/).

MACS men began having anal cell tests—called anal Pap tests—in 2010. Researchers invited men who had a first anal cell test to have a second test 2 years later. Trained health professionals collected anal cell samples with a swab inserted into the anus. A single lab analyzed anal cell samples collected at all MACS study sites. Cell experts rated the anal cell samples according to a standard system that starts with normal cells and progresses to high-grade squamous intraepithelial neoplasia (HSIL), which can lead to anal cancer (Figure 1). Among people with HIV infection, about 2% with HSIL have anal cancer within 5 years.

Figure 1. A study of 1511 US gay or bisexual men with or without HIV rated anal cells by a standard system starting with normal cells and ending in high-risk cells that could lead to anal cancer.
Men with abnormal anal cell results received information about high-resolution anoscopy, a procedure that allows a health professional to view the inside of the anus. The men were advised to see their primary provider to discuss whether they should have high-resolution anoscopy. During anoscopy an anal tissue sample (biopsy*) can be snipped off, and that sample can be used to confirm HSIL.

The researchers also tested anal cells for HPV type 16 (HPV-16), which is the HPV type most often linked to anal cancer.

- **What the study found.** The study involved 723 gay or bisexual men with HIV and 788 gay or bisexual men without HIV. Median (midpoint) age of the whole study group stood at 55 years. While 72% of study participants were white, 18% were black and 8% Hispanic. Most HIV-positive men in the study (91%) were taking antiretroviral therapy, 78% had an undetectable viral load, and median CD4 count was 583.

Among 1437 men with an adequate anal cell sample, 189 of 750 without HIV (25%) and 276 of 687 with HIV (40%) had abnormal anal cells (any cell type not normal in Figure 1). That large difference in abnormal anal cells between men with and without HIV is statistically significant, meaning the difference probably does not result from chance. Proportions of HIV-positive men with abnormal anal cells were higher in men with lower current CD4 counts: Among men with a CD4 count below 350, 47% had abnormal anal cells, compared with 41% of men whose CD4 count lay between 350 and 499 and 38% of men whose CD4 count lay above 499 (Figure 2).

*Words in bold are defined in the Technical Word List at the end of this issue of HIV Treatment Alerts.
The proportion of men with high-risk anal cell abnormalities detected in the anal Pap test (ASC-H or HSIL, see Figure 1) was low in men without HIV (3%) and only slightly higher in men with HIV (4%). The rate of lower-risk anal cell abnormalities (ASCUS or LSIL) was 22% in men without HIV and 28% in men with HIV. HPV-16 (the highest-risk human papillomavirus type) could be detected in anal cells of 16% of HIV-negative men and 20% of HIV-positive men.

Next the researchers analyzed anal cell samples from 447 men with HIV and 409 men without HIV who had two anal cell samples 18 to 30 months apart. None of these men received treatment for anal cell abnormalities between their two anal samples. Among all men who had normal anal cells in their first test, 29% with HIV versus 16% without HIV had abnormal anal cells in their second test. Most men with and without HIV who had abnormal anal cells on their first test had a lower-grade abnormality or normal cells on their second test. That probably means the abnormality was returning to normal on its own. Among men with HIV, 15% with a lower-grade abnormality (ASCUS or LSIL) on their first test had a higher-grade abnormality (for example, ASCUS → LSIL or LSIL → ASC-H or HSIL) on their second test. In contrast, only 5% of men without HIV went from a lower-grade abnormality to a higher-grade abnormality.

Among 1392 study participants who did not have HSIL confirmed by biopsy before the study, 220 (16%) had high-resolution anoscopy and biopsy during the study. Eighty-seven of these 220 men (40%) had HSIL confirmed by the biopsy. Among men with abnormal anal cells on their first test, 38 of 79 with HIV (48%) and 22 of 61 without HIV (36%) had HSIL confirmed by biopsy. One reason these proportions are so high is that men with more threatening Pap test results were the ones most likely to get follow-up testing. But some men with normal anal cells on their first test also had follow-up testing, and one of these men had HSIL confirmed by biopsy.

■ **What the results mean for you.** This large study of US gay and bisexual men found a higher rate of abnormal anal cell abnormalities in men with HIV than without HIV (40% versus 25%). Most men with HIV were taking antiretroviral therapy and three quarters of them had an undetectable viral load. Among men with HIV, abnormal anal cell rates were higher in men with lower CD4 counts (Figure 2).

This finding suggests that the better immune system health reflected by a higher CD4 count lowers chances of anal cell abnormalities. Starting antiretroviral therapy promptly after testing positive for HIV usually prevents the CD4 count from falling further.

About 1 in 50 HIV-positive people with HSIL—the most serious anal-cell abnormality (see Figure 1)—will go on to have anal cancer within 5 years. That may sound like a low proportion, but anal cancer rates are much higher in people with HIV than without HIV, especially among gay or bisexual men. Detecting abnormal anal cells could provide an early warning of developing anal cancer, just as abnormal cervical cells provide an early warning of cervical cancer. The researchers believe that the rate of biopsy-proved HSIL in gay men with or without HIV in this study “supports the need for effective screening methods in this population.”

A large trial has begun to see whether detecting and treating high-grade anal cell abnormalities will lower the anal cancer rate in people with HIV. Until we have results of this trial, however, the value of anal-cell testing in preventing anal cancer remains uncertain. If you are an HIV-positive man or woman 35 or older, you might qualify for this trial. If you are interested in participating, read about the trial at the link at reference 4 below and discuss the trial with your HIV provider.

The authors believe their study “underscores the increased risk of anal disease among [gay or bisexual men] in general and especially among HIV-infected [men].” Men and women who have anal sex should be aware that anal sex boosts the risk of anal cell abnormalities. Men and women can lower their risk of anal cell abnormalities and anal cancer in several ways:

1. Decrease contact with human papillomavirus (HPV) by using condoms during sex and by limiting the number of sex partners you have.
2. Get the HPV vaccine, which is recommended for women up to age 26, for gay or bisexual men with or without HIV up to age 26, and for other men up to age 21.
3. Quit smoking or don’t start smoking.
References


Among adults with HIV infection, cardiovascular* disease accounted for a growing proportion of all deaths over the past 15 years in a nationwide US study.\(^1\) In contrast, cardiovascular disease accounted for a decreasing (but still large) proportion of all deaths in the general population of the United States.

As people with HIV infection live longer thanks to antiretroviral therapy, they are more likely to acquire age-related diseases like cardiovascular disease (heart disease) and certain cancers. Research shows growing rates of cardiovascular disease in HIV groups compared with HIV-negative people. Reasons for higher rates of cardiovascular disease in people with HIV than in the general population include (1) high rates of heart disease risk factors like smoking and diabetes in people with HIV, (2) side effects from certain antiretroviral drugs, and (3) inflammation caused by HIV even when antiretroviral therapy makes the viral load undetectable.

Despite a growing understanding of cardiovascular disease in people with HIV, researchers had never analyzed patterns of death caused by cardiovascular disease in HIV groups compared with HIV-negative people. The research team recorded the proportion of all deaths caused by cardiovascular disease in three groups (1) people with HIV infection, (2) the general population, and (3) people with inflammatory polyarthritis (arthritis and related conditions that cause inflammation). The researchers included inflammatory polyarthritis because HIV infection is also an inflammatory disease and they wanted to compare death rates in people with HIV-related inflammation and non-HIV inflammation.

The analysis included all deaths in the United States from 1999 through 2013 among people 25 years old or older at the time of death. Within the three groups listed in the preceding paragraph, the researchers analyzed death rates by gender (male or female) and by race or ethnicity (black, white, or Hispanic). They used standard statistical methods to determine trends in cardiovascular death rates in these groups from 1999 through 2013.

\textbf{What the study found.} The study analyzed 140,661 HIV-positive people who died of any cause, including 4,104 who died of cardiovascular disease. In the general population, 18.2 million died of any cause, including 6.1 million who died of cardiovascular disease.

Total deaths among people with HIV fell from 15,739 in 1999 to 8,660 in 2013. But cardiovascular deaths rose from 307 in 1999 to 400 in 2013. Thus in people with HIV the proportion of all deaths caused by cardiovascular disease climbed from 1.95% in 1999 to 4.6% in 2013, more than a 2-fold increase (Figure 1). Cardiovascular disease accounted for a much higher proportion of all deaths in the general population across the study period. But the proportion of all deaths caused by cardiovascular disease in the general population fell from about 40% in 1999 to about 30% in 2013 (Figure 1). In the group with inflammatory polyarthritis, the proportion of all deaths caused by cardiovascular disease also fell from about 40% in 1999 to about 30% in 2013.

*Words in \textbf{bold} are defined in the Technical Word List at the end of this issue of \textit{HIV Treatment Alerts}.*
From 1999 through 2013, the cardiovascular death rate in people with HIV rose significantly in white men, black men, Hispanic men, and black women—but not in white women or Hispanic women. In this context, a “significant” increase in proportion of deaths means the increase probably cannot be explained by chance.

Then the researchers looked only at ischemic heart disease, which is heart disease caused by narrowing heart arteries, including angina and myocardial infarction (heart attack). Among people with HIV infection, the proportion of all deaths caused by ischemic heart disease rose from 0.8% in 1999 to 2.5% in 2013, more than a 3-fold increase. In the general population, the proportion of all deaths caused by ischemic heart disease fell from 22.8% in 1999 to 14.6% in 2013.

**Figure 1.** From 1999 through 2013 in a nationwide US study, the proportion of all deaths caused by cardiovascular disease rose from under 2% to above 4% among people with HIV. Over the same years, the proportion of all deaths caused by cardiovascular disease in the general US population fell from about 40% to about 30%.

- **What the results mean for you.** This analysis of all deaths in the United States from 1999 through 2013 among people 25 or older found that the proportion of deaths caused by cardiovascular disease fell in the general population while rising in people with HIV infection. The 15-year drop in the proportion of cardiovascular deaths in the general population probably reflects a growing awareness of heart disease risk in the United States and lifestyle changes (like more exercise and less smoking) that prevent cardiovascular disease and death. However, cardiovascular disease remains the leading cause of death in the United States, followed by cancer and lung disease.²

In the general population, cardiovascular disease caused about 40% of all deaths in 1999 and about 30% in 2013. In contrast, cardiovascular disease caused a much lower
proportion of all deaths among people with HIV, but that proportion rose from about 2% in 1999 to more than 4% in 2013. Cardiovascular disease probably causes a lower proportion of deaths in people with HIV than in the general population because people with HIV still face substantial threats from deadly diseases like AIDS illnesses, non-AIDS cancers, and non-AIDS infections.

But the growing proportion of deaths from cardiovascular disease in people with HIV provides a strong reminder that heart attacks, strokes, and other cardiovascular diseases pose a growing threat to HIV-positive individuals. People with HIV should be aware of heart disease risk factors, many of which can be avoided or changed (Table 1). The most important thing anyone can do to avoid heart disease is to avoid smoking or quit smoking.

Table 1. Factors that raise the risk of heart disease

<table>
<thead>
<tr>
<th>Changeable conditions</th>
<th>Changeable behaviors</th>
<th>Unchangeable factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>▶ High blood pressure</td>
<td>▶ Smoking</td>
<td>▶ Older age</td>
</tr>
<tr>
<td>▶ High cholesterol</td>
<td>▶ Unhealthy diet</td>
<td>▶ Family history of heart disease</td>
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<tr>
<td>▶ Diabetes</td>
<td>▶ Obesity</td>
<td></td>
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<tr>
<td></td>
<td>▶ Lack of physical activity</td>
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<td></td>
<td>▶ Too much alcohol</td>
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References

HIV-positive people in their 40s with low overall heart disease risk had higher rates of artery wall thickening than HIV-negative people the same age in a small but careful comparison.1 Everyone in the HIV group was taking antiretroviral therapy* and had an undetectable viral load.

Cardiovascular disease, which includes heart disease, has become an important cause of sickness and death among people with HIV infection. Traditional heart disease risk factors (like smoking and high cholesterol) contribute to higher rates of heart disease in HIV-positive people than in comparison groups without HIV. But continuing inflammation caused by HIV infection itself, even in people responding well to antiretroviral therapy, probably also contributes to cardiovascular disease risk. And certain antiretrovirals may boost chances of heart disease.

Previous studies using ultrasound scans of carotid arteries in the neck (Figure 1) found signals of atherosclerosis more often in HIV-positive people than HIV-negative comparison groups. But HIV-positive people in these studies usually had a high risk of cardiovascular disease because of traditional risk factors.

Researchers in London conducted a new study to see if middle-aged HIV-positive people with low cardiovascular risk also have more artery thickening than HIV-negative people with low cardiovascular risk. Instead of using ultrasound scans, which give a one-dimensional picture of the carotid artery, they used a scan called cardiovascular magnetic resonance, which gives a three-dimensional image.

How the study worked. Researchers invited adults who had been infected with HIV for at least 2 years to join the study. Everyone was taking combination antiretroviral therapy and had a viral load below 50 copies. No one had current or past cardiovascular disease, and no one in their immediate family had early artery disease. Study participants did not have certain traditional cardiovascular risk factors, including high blood pressure, high cholesterol, diabetes, or smoking (no one had ever smoked). The Framingham risk score, which predicts heart disease

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*Words in bold are defined in the Technical Word List at the end of this issue of HIV Treatment Alerts.
in the next 10 years, had to be 10% or lower. No one was taking any heart drugs, and no one abused alcohol or recreational drugs.

The research team created a comparison group of healthy HIV-negative people without the cardiovascular risk factors listed in the preceding paragraph. The investigators matched the HIV-negative people to the HIV-positive people by age and gender.

Everyone in the HIV-positive and negative groups had cardiovascular magnetic resonance to create three-dimensional images of the common carotid arteries 40 mm (1.6 inches) long. For each carotid artery image, the researchers calculated the wall-to-outer-wall ratio, which is a measure of artery wall thickening. A thicker wall indicates greater cardiovascular disease risk.

**What the study found.** The study included 33 people with HIV (19 men and 14 women) and 35 without HIV (19 men and 16 women). Age averaged 45.2 years in the HIV group and 46.9 years in the HIV-negative group. The HIV group included a lower proportion of whites than the HIV-negative group (48% versus 85%) and a higher proportion of blacks (42% versus 5%). The HIV-positive and negative groups did not differ much in total cholesterol, blood pressure, or body surface area. Ten-year cardiovascular risk by the Framingham score was very low in both groups—average 4% with HIV and 3.7% without HIV.

People with HIV infection had taken antiretrovirals for a median of 7 years, their CD4 count averaged 638.5, and everyone had a viral load below 50 copies.

Wall-to-outer-wall ratio, the measure of artery wall thickening, was significantly greater (worse) in people with HIV than in the comparison group without HIV: 36.7% versus 32.5% (Figure 2). In this context, “significantly” means a statistical test showed that chance probably did not explain the difference between the HIV group and the non-HIV group. This difference between groups was greater for women (36.4% versus 31.3%) than for men (36.2% versus 33.4%), but the differences were significant for both women and men.
Statistical analysis that weighs the impact of individual risk factors on wall-to-outer-wall ratio linked HIV infection itself to a greater (worse) ratio, regardless of whatever other risk factors a person had. Other factors—including ethnic background, CD4 count, years since HIV diagnosis, and years taking antiretroviral therapy—could not be linked to a greater ratio in this analysis.

What the results mean for you. Previous studies found higher rates of artery wall thickening in people with HIV than in HIV-negative comparison groups. The new study differs from these earlier reports in two important ways: First, the middle-age study participants with and without HIV had a very low cardiovascular disease risk as judged by traditional risk factors like smoking, high blood pressure, and family history of heart disease. Second, previous studies measuring thickness of the carotid artery wall used ultrasound scans, which create one-dimensional pictures. The new study used cardiovascular magnetic resonance, which creates more accurate and consistent three-dimensional images.

The new study is small, and the findings should be confirmed in larger investigations. Still, results of the new study warn that middle-aged men and women controlling HIV with up-to-date antiretroviral combinations—and with a low overall heart disease risk—still have thicker carotid artery walls than HIV-negative men and women the same age. Thicker carotid artery walls predict myocardial infarction (heart attack) and stroke. The artery wall difference between people with and without HIV was greater for women than for men. This finding underlines the need for HIV-positive women as well as men to be aware of cardiovascular disease risk and to take steps to lower their risk.

People in this study did not have some major cardiovascular risk factors: They did not smoke and they did not have high blood pressure, high cholesterol, or diabetes. Yet their carotid artery walls were thicker than those of a low-risk HIV-negative group the same age. That finding could mean that the inflammation and immune system activation seen even in people with an undetectable viral load and a high CD4 count raise their risk of cardiovascular disease.

Researchers are trying to find ways to control this ongoing inflammation and immune system activation in people responding well to antiretroviral therapy. HIV guidelines from the US Department of Health and Human Services suggest aspirin (an anti-inflammation drug) at a dose of 81 mg daily to prevent heart disease in HIV-positive people with a moderate to high risk of cardiovascular disease who can take aspirin safely. But whether daily aspirin helps people with a low cardiovascular risk—like those in this study—remains uncertain.*

People with HIV should certainly avoid heart risk factors or control any risk factors they already have. Two major risk factors—older age and family history of heart disease—cannot be controlled. Risk factors that can be avoided or controlled are high blood pressure, high cholesterol, diabetes, smoking, unhealthy diet, obesity, lack of physical activity, and too much alcohol (see Table 1 on page 27 of this issue).

References


*For the general population, the US Preventive Services Task Force recommends starting low-dose aspirin “for the primary prevention of cardiovascular disease and colorectal cancer in adults aged 50 to 59 years who have a 10% or greater 10-year cardiovascular risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.” (Bibbins-Domingo K; US Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: US Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2016 Jun 21;164(12):836-45. doi: 10.7326/M16-0577. Epub 2016 Apr 12.)
Osteoporosis and smoking raise fracture risk in people with HIV

Osteoporosis (very low bone density) raised the risk of broken bones 4 times in a study of 1006 middle-aged people with HIV infection in the United States. Smoking raised the bone fracture risk about 60%.

Several studies across the United States and Europe found that people with HIV infection fracture their bones more than people without HIV. Research also shows that HIV-positive people have lower bone density, which can be measured by DXA scans, than people without HIV. HIV bone experts in the United States recommend DXA scans for all HIV-positive men starting at age 50 and for all women after the menopause.

US researchers working with two large HIV study groups wanted to see whether bone mineral density measured by DXA scans predicts which HIV-positive adults would later fracture a bone. They also aimed to pinpoint other factors that might predict broken bones in people with HIV infection.

**How the study worked.** The researchers analyzed DXA bone density measurements in HIV-positive people from two US groups—the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (SUN) and the HIV Outpatient Study, Denver Infectious Disease Consultants (HOPS-DIDC). Most SUN study participants had a DXA during 2004-2006, while most HOPS-DIDC participants had a DXA during 2008-2010. The research team used those scans to determine who had normal bone density, who had osteopenia (low bone density), and who had osteoporosis (very low bone density) (**Figure 1**). They used the standard World Health Organization definitions of osteopenia and osteoporosis based on bone density levels.

**Figure 1.** In a study of 1006 middle-aged people with HIV infection, DXA scans showed normal bone in 61% (left), osteopenia in 36% (middle), and osteoporosis in 4% (right). Darker areas in thigh bone indicate bone loss. (Illustration from Servier PowerPoint Image Bank, [http://servier.com/Powerpoint-image-bank](http://servier.com/Powerpoint-image-bank)).

*Words in **bold** are defined in the Technical Word List at the end of this issue of *HIV Treatment Alerts*. 

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Then the researchers tracked people from the date of their DXA scan until (1) they had a fracture, (2) they stopped coming to study visits, or (3) a defined date in 2012. People who broke a bone before their DXA scan could participate in this analysis. The investigators used a standard statistical method to assess the impact of osteopenia or osteoporosis on having a fracture after the DXA scan. This method also identified other factors linked to a higher risk of a new fracture.

■ What the study found. The study included 1006 people, 837 of them (83%) men and 169 women. The median* (midpoint) age of the study group stood at 43, and about three quarters of study participants were younger than 50. As people grow older, risk of breaking a bone because of low bone density increases. But in the general population, people under 50 rarely break bones because of low bone density.

Two thirds of study participants were white, 21% were black, and 9% were Hispanic. About two thirds of the study group had become infected with HIV during sex between men. At the time of each person’s DXA scan, median CD4 count stood at 461, and three quarters of the group had a viral load below 400 copies. So these people were responding well to their antiretroviral therapy. Only 12% of the study group had HCV infection, a risk factor for low bone density. But 54% of study participants smoked or used to smoke; smoking is a well-established risk factor for low bone density. Sixty-seven people (7%) had a fracture before their DXA scan.

Among the 1006 people studied, 611 (61%) had normal bone density near the top of the thigh bone, 358 (36%) had osteopenia, and 37 (4%) had osteoporosis (Figure 1). Blacks made up a lower proportion of those with osteoporosis (19%) than whites (57%) or Hispanics (24%). People with osteoporosis were more likely to be older, to have a lower nadir (lowest-ever) CD4 count, to have a lower body mass index (a measure of weight), to have a previous fracture, and to have HCV infection. Previous research linked all of these factors to low bone density.

Median follow-up after the first DXA scan measured 3.2 years. During that time, 85 people (8%) broke a bone. Those numbers indicate the study group had a new fracture rate of 2 per 100 person-years, meaning 2 of every 100 people broke a bone every year. Twenty-two of the 85 fractures (26%) were considered major osteoporotic fractures, that is, fractures of the hip, spine, shoulder, or forearm. Among people with new fractures, median age stood at a young 44 years, and most were younger than 50 years old.

Statistical analysis singled out two factors that predicted a new fracture regardless of whatever other risk factors a person had. Osteoporosis detected by the first DXA scan raised the risk of later fracture 4 times. And current or prior smoking raised the risk 1.59 times, that is, it raised the risk by 59%. Osteopenia did not raise the risk of a new fracture. Neither did older age, current CD4 count, lowest-ever CD4 count, HCV infection, prior fracture, or treatment with certain antiretroviral drugs linked to low bone density in previous studies.

■ What the results mean for you. This study of 1006 HIV-positive US adults found that almost 1 in 10 broke a bone during 3 years of observation. The study showed that osteoporosis on a DXA scan of the thigh bone (femoral neck, Figure 1) predicts later fractures. Three quarters of people in this study, including most of those with fractures, were younger than 50 years old. Current US guidelines for bone disease in people with HIV recommend DXA scans for men 50 and older and for postmenopausal women (who are usually 50 or older). Results of this study suggest that HIV-positive people younger than 50 may benefit from DXA scans.

About 40% of people in this study had osteoporosis or osteopenia. Knowing which people already have low bone density would let HIV providers help those people take steps to avoid further bone density loss and fractures (Table 1).
The study also found that smoking makes fractures more likely. Throughout the United States and Europe, higher proportions of people with HIV than without HIV smoke. Avoiding smoking—or quitting smoking if you have started—can prevent not only fractures but also life-threatening heart disease, lung disease, and certain cancers. Quitting smoking usually requires a plan that your HIV provider can help you make. Such a plan often includes prescription medications such as Chantix, Zyban, or nicotine-replacement therapy. In the United States more people have quit smoking than still smoke.7

If you have osteoporosis risk factors (Table 1), talk to your HIV provider about whether you should have a DXA scan. Your provider can help you take steps to control osteoporosis risk factors that can be changed.

**Table 1.** Controllable and uncontrollable risk factors for osteoporosis

<table>
<thead>
<tr>
<th>Controllable risk factors</th>
<th>Uncontrollable risk factors</th>
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<tbody>
<tr>
<td>▶ Smoking</td>
<td>▶ Being over age 50 (or perhaps over 40 for people with HIV)</td>
</tr>
<tr>
<td>▶ Drinking too much alcohol</td>
<td>▶ Being a woman</td>
</tr>
<tr>
<td>▶ Substance abuse</td>
<td>▶ Being past the menopause</td>
</tr>
<tr>
<td>▶ Opioids or opioid substitution therapy</td>
<td>▶ Family history of osteoporosis</td>
</tr>
<tr>
<td>▶ Having an inactive lifestyle</td>
<td>▶ Broken bones or height loss</td>
</tr>
<tr>
<td>▶ Losing too much weight</td>
<td>▶ Being white or Asian</td>
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<tr>
<td>▶ Not getting enough calcium or vitamin D</td>
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<tr>
<td>▶ Not eating enough fruits and vegetables</td>
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<tr>
<td>▶ Getting too much protein, sodium, or caffeine</td>
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</tbody>
</table>

Sources: National Osteoporosis Foundation,4 Centers for Disease Control and Prevention,5 Mayo Clinic,6

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References

Liver disease signals more frequent in young people with than without HIV

A signal of early liver disease was 4 times more frequent in HIV-positive youth 15 to 20 years old than in HIV-negative people that age. In the group with HIV infection, liver disease signals got worse every year, especially in those with a low CD4 count, a detectable viral load, or not taking antiretroviral therapy. None of the young people in this study had hepatitis B or C infection (HBV or HCV).

HBV or HCV infection is common in people with HIV and can cause serious liver damage if left untreated. But HIV itself can cause liver damage even in people without HBV or HCV. HIV probably affects the liver because it causes inflammation. This inflammation can continue at a low level even in people whose antiretroviral therapy makes their viral load undetectable.

Simple blood tests can tell which people may have liver damage called fibrosis or cirrhosis (liver scar tissue). Using these tests could help HIV providers find out who may have fibrosis or cirrhosis and needs further studies. But these tests have not been closely analyzed in children, adolescents, or young adults with HIV. US researchers conducted this study to see if these tests indicate liver damage more in young people with HIV than without HIV, and to learn whether the tests show that liver damage gets worse over time.

How the study worked. The study focused on young people in the United States with blood samples available for liver function tests between the ages of 15 and 20 years. Study participants came from two previous study groups that included children with or without HIV infection. The children with HIV could have been infected around the time of their birth or later through sex or drug use. The study group included no one known to have HBV or HCV infection.

The researchers determined two established liver function markers in these young people, FIB-4 and APRI. In adults a FIB-4 greater than 1.45 or an
APRI greater than 0.5 suggests mild to moderate liver fibrosis. A FIB-4 greater than 3.25 or an APRI greater than 1.5 suggests advanced liver fibrosis.

First the researchers determined FIB-4 and APRI a single time in all study participants with and without HIV infection. Then the investigators focused only on HIV-infected young people who had two or more study visits and determined FIB-4 and APRI at each study visit to create FIB-4 and APRI records over time. Within this group of HIV-infected youth with two or more study visits, the researchers looked at young people with low initial APRI (at or below 0.5) and low initial FIB-4 (at or below 1.5) and determined how many people had higher (worse) scores over time.

■ What the study found. The 1785 young people in the study included 1612 with HIV and 173 without HIV. The 1612 people with HIV included 1042 infected around the time of birth and 570 infected later in life through sex or drug use. The overall group of young people with and without HIV had a median (midpoint) age of 17.3 years when FIB-4 and APRI liver tests were done, and 1055 people (59%) were women. While 57% of the study group were black, 27% were Hispanic, 13% white, and 3% in another racial or ethnic group.

The researchers measured an APRI score indicating mild to moderate liver fibrosis in 13% of young people with HIV versus 3% without HIV. This difference is statistically significant, meaning the difference probably cannot be explained by chance. FIB-4 indicating mild to moderate fibrosis was less frequent in young people with HIV (2%) and without HIV (1%).

In the whole study group, statistical analysis identified three factors that made mild to moderate fibrosis more likely regardless of whatever other fibrosis risk factors a person had: having HIV infection, being a man, and having low weight measured as body mass index. In an analysis focused just on people with HIV, three factors made mild to moderate fibrosis more likely regardless of whatever other fibrosis risk factors a person had: being a man, having a CD4 count below 350, and having a viral load above 400 copies/mL.

In the analysis of HIV-infected young people who had two or more liver function assessments, APRI indicated that 7.5% of the group went from no fibrosis to mild-to-moderate fibrosis every year. FIB-4 indicated that 1.6% went from no fibrosis to mild-to-moderate fibrosis every year. Rates of progression to advanced fibrosis were lower—1.4% per year with APRI and 0.3% per year with FIB-4.

Among all young people with HIV, FIB-4 rose by an average 6% every year. Among young people infected with HIV around the time of birth, APRI rose by an average 2% per year.

Finally, the researchers figured the impact of four factors on increases in FIB-4 and APRI over time in people with HIV (Figure 2). For FIB-4 the increase over time was 13% higher in men than women, 19% higher in people with a CD4 count below 350, 17% higher in people with a detectable viral load, and 12% higher in people not taking antiretroviral therapy. For APRI the increase over time was 24% higher in men than women, 21% higher in people with a CD4 count below 350, 23% higher in people with a detectable viral load, and 17% higher in people not taking antiretroviral therapy.

■ What the results mean for you. This large study of young people without hepatitis virus infection (HBV or HCV) found that a significantly higher proportion of youth with HIV than without HIV had mild to moderate liver damage (fibrosis) indicated by a liver test called APRI. This score rose 2% yearly in young...
people with HIV, and the score of another liver test called FIB-4 rose 6% yearly. Although those yearly increases sound small, they are concerning in a 15- to 20-year-old group that will probably live to old age thanks to antiretroviral therapy.

The study also found that yearly increases in APRI and FIB-4, indicating worsening liver health, were higher in young men than young women with HIV and in people with a low CD4 count, a detectable viral load, or not taking antiretroviral therapy. Those findings strongly suggest another advantage of starting and continuing antiretroviral therapy and taking antiretroviral pills regularly—better liver health throughout life.

About the size of a football in adults, the liver is crucial to the health of all people. It cleans the blood, makes an important digestive liquid called bile, stores energy in the form of a sugar called glycogen, and helps process many drugs in the body, including many antiretrovirals. This study underlines the importance of measuring liver function regularly in people with HIV, including young people. Your HIV provider may plug the results of liver function tests into the formula that calculates FIB-4 or APRI to get a closer look at your liver health. Although young people in this study did not have HBV or HCV infection, tracking liver health is especially important in people with those hepatitis viruses and in people whose liver might be threatened by other illnesses or by drugs that affect the liver.

Because this study shows that HIV poses a threat to the liver even in young people, everyone with HIV should avoid or control known risk factors for liver disease—drinking too much alcohol, high cholesterol and triglycerides, and obesity. People without HBV infection should get the HBV vaccine.

References


Aspartate aminotransferase-to-platelet ratio index (APRI) = (AST/AST upper limit of normal)/platelet count × 100 (http://www.hepatitis.uw.edu/page/clinical-calculators/apri).

One third of gay or bisexual men infected with HIV and hepatitis C virus (HCV) had detectable HCV in their semen. HCV levels in semen were high enough for these men to pass HCV to sex partners during anal sex without a condom.

HCV infection kills more people in the United States than any other infection, including HIV. Research over the past several years confirmed an epidemic of sexually transmitted HCV in HIV-positive gay and bisexual men in the United States, Western Europe, and other places. HIV and HCV can both pass from one sex partner to another in semen or blood, so people infected with one of these viruses often get infected with the other virus. Research in the United States established that receptive anal sex (being the bottom) without a condom is the main sexual risk factor for HCV infection in gay and bisexual men. Because the penis rarely bleeds during anal sex, it seems likely that HCV passes to an anal sex partner in semen, not in blood.

Researchers in the United States conducted this new study to see how often they could detect HCV in semen and blood of HIV-positive gay or bisexual men with HCV infection. They also wanted to see if HCV levels measured in semen were high enough to explain sexual transmission of HCV between men during anal sex without a condom.

How the study worked. The research team invited HIV-positive gay or bisexual men to enter the study. These men had either recent HCV infection (HCV antibody* first detectable in the past year) or chronic HCV infection (HCV antibody first detectable more than 1 year ago). Each man was asked to give semen and blood samples every 2 weeks for 6 weeks. At the end of this period, the researchers hoped to have 3 semen samples and 3 blood samples from each study participant. The research team tested each sample to see if they could detect HCV and to measure levels of detectable HCV.

What the study found. The study included 33 HIV-positive men, 21 (64%) with recent HCV infection and 12 (36%) with chronic (longer) HCV infection. Four men with recent HCV infection had become infected after anti-HCV drugs cured a previous episode of HCV infection. Median (midpoint) age was 36 in men with recent HCV infection and 52 in men with chronic HCV infection. About 60% of both groups were white, about 25% Hispanic, and the rest black. All but 1 man were taking antiretroviral therapy, but 15 men (45%) had a detectable HIV viral load.

All study participants said they had receptive anal sex without a condom. Fourteen men (42%) said they also injected drugs.

The researchers analyzed 59 semen samples. They detected HCV in 16 semen samples (27% of 59), which came from 11 men (33% of 33) (Figure 1). Median (midpoint) HCV viral load in semen with detectable HCV was about 30 IU (international units) per milliliter of semen. HCV viral load in blood samples was significantly higher when HCV could be detected in semen than when HCV could not be detected in semen. In the whole study group, HCV load in blood reflected HCV load in semen—the higher the blood HCV level, the higher the semen HCV level.

The proportion of semen specimens with detectable HCV did not differ significantly between men with recent HCV infection and men with chronic (longer) HCV infection. In the same way, HCV level did not differ significantly between men with recent HCV infection and men with chronic HCV infection.

Eleven men with recent HCV infection gave more than one semen sample. Four of those 11 men (36%) had HCV detectable in at least one semen sample, and 1 man (9%) had HCV detectable in all semen samples he gave. Six men with chronic HCV infection gave more

*Words in bold are defined in the Technical Word List at the end of this issue of HIV Treatment Alerts.
than one semen sample. Four of those 6 men (67%) had HCV detectable in at least one semen sample, and 3 men (50%) had HCV detectable in all semen samples.

**What the results mean for you.** One third of the HIV-positive and HCV-positive gay or bisexual men in this US study had HCV detectable in their semen. If these men were not wearing a condom during sex, they could expose anal sex partners to HCV whenever they had HCV in semen and ejaculated inside a partner. These findings help explain why there is an HCV infection epidemic in gay and bisexual men who have sex.²

On the basis of HCV levels measured in semen in this study, the researchers calculate that an average load of semen would allow between 50 and 6630 particles of HCV to pass into the rectum of the anal sex partner (Figure 2). Other research shows that as few as 10 to 20 HCV particles carried in blood can cause HCV infection in a person exposed to that blood. So the authors of this study believe 50 or more HCV particles in semen is enough to cause HCV infection in a male partner exposed to that semen during anal sex without a condom. They believe that changes in the rectal wall during anal sex—even if that sex is not bloody—may allow uptake of HCV carried in semen.

Some studies link rough, bloody anal sex to HCV transmission between gay men. But other studies do not confirm this link. The researchers who conducted the new study believe HCV carried in semen rather than blood largely accounts for the spread of HCV during sex between men. Just as health experts have long accepted that hepatitis B virus (HBV) carried in semen—not blood—explains sexual transmission of HBV, the authors of this study believe HCV also mainly uses semen—not blood—to pass from one partner to another during anal sex.

Wearing a condom during sex is the surest way to prevent a partner with a detectable HIV viral load from passing HIV to a sex partner. Condoms can also stop HCV from passing between sex partners. And condoms can block other infection-causing viruses and bacteria from passing between sex partners. Sometimes people with HIV feel safe not wearing a condom during sex if they have an undetectable HIV viral load. But those HIV-positive people can pass HCV and other
infection-causing agents to sex partners if they don’t wear a condom. And the partner with HIV can pick up other disease-causing viruses and bacteria during sex without a condom. HIV-negative people who use Truvada as PrEP to protect themselves from HIV may feel safe not using a condom during sex. But without a condom they expose themselves to HCV and other causes of infection, because Truvada PrEP protects only from HIV.

Finally, it’s important to note that 4 of 21 men (19%) with recent HCV infection in this study had been cured of an earlier HCV infection by anti-HCV drug therapy. One bout of HCV infection does not protect people from getting infected with HCV again. People who continue having sex without condoms or sharing drug-injecting equipment run a risk of another HCV infection regardless of how many times they were infected with HCV in the past.

References

Several diseases and behaviors are linked to decreased mental function in older HIV-positive men compared with older men without HIV, according to results of a careful comparison.\textsuperscript{1} Disease factors included cardiovascular disease, diabetes, and poor kidney function. Other factors were smoking marijuana and a wide waist. The study also linked a lower CD4 count before starting antiretroviral therapy to decreased cognitive performance.

Cognitive impairment can be defined as problems in memory, language, thinking, or judgment. These problems continue to affect many HIV-positive people who reach and maintain an undetectable viral load with antiretroviral therapy. Experts have different opinions on how to define cognitive impairment in people with HIV. Researchers in the Netherlands who conducted this new study believe one widely used method for identifying cognitive impairment in people with HIV is too broad because it classifies too many people with normal cognitive function as impaired.\textsuperscript{2} The Netherlands team worked with a new method (called multivariate normative comparison, or MNC) that appears to pinpoint cognitively impaired HIV-positive people more precisely.\textsuperscript{3}

The new study focused on HIV-positive and negative members of the AGEhIV study group in Amsterdam. The researchers aimed to identify factors linked to decreased cognitive function in these people.

How the study worked. The AGEhIV Cohort Study analyzes age-related diseases and conditions in HIV-positive people 45 years old or older and a highly similar group of HIV-negative people. Researchers select HIV-negative people from an Amsterdam sexual health clinic to create a group that matches the HIV-positive group in age, sex, sexual risk behavior, and other behaviors.\textsuperscript{4} At an initial visit and then every 2 years, all HIV-positive and negative AGEhIV members complete a series of tests to detect age-related conditions.

The cognitive performance study focused on HIV-positive men with a viral load below 40 copies for at least 12 months on antiretroviral therapy and a highly comparable set of HIV-negative men. Everyone in both groups was at least 45 years old. The study did not accept people who had evidence of previous or current severe problems that might cause cognitive (mental) problems, including stroke, multiple sclerosis, serious brain injury, major depression, or HIV-associated dementia. The study also excluded men who drank a lot of alcohol, injected illegal drugs, or used illegal drugs daily. Men who smoked marijuana daily could enter the study.

All study participants with and without HIV infection completed a set of standard tests that measure six areas of cognitive function—attention, information processing speed, memory, motor function (movement and coordination), executive function (ability to get things done), and fluency (ability to name as many things as possible in a category—like animals or fruits—in a set time).

The AGEhIV researchers used the method they had studied earlier (MNC) to compare the combined results of these cognitive tests (cognitive impairment) in men with versus without HIV. The research team compared cognitive function in the HIV-positive and negative groups in two ways: (1) a yes/no measure (either you have cognitive impairment or you don’t), and (2) a continuous measure (the degree to which each HIV-positive person differed from the whole HIV-negative group).

What the study found. The study involved 103 men with HIV and 74 men without HIV. As planned, the groups with and without HIV were similar in many ways. Both groups had a median (midpoint) age of 54 years, about 90% in each group were gay or bisexual, and more than 85% in each group were Dutch. Men with HIV had taken antiretroviral therapy for a median of 11.6 years and had a viral load below 200 copies for a median of 8.3 years. The group’s lowest-ever median CD4 count stood at 170 and their current CD4 count at 625.

About 15% of both groups smoked marijuana daily. About 5% in both groups had mild to moderate symptoms of depression, and no one had severe depressive symptoms. Waist-to-hip ratio was above normal in 85% of men with HIV versus 70% of men without HIV.\textsuperscript{†} About two thirds in each group had someone in their immediate family with

*Words in bold are defined in the Technical Word List at the end of this issue of HIV Treatment Alerts.
cardiovascular disease, but cardiovascular disease rates in the men themselves were low (partly because many men were middle-aged) and did not differ much between groups. About 5% of men in each group had diabetes. A lower proportion of men with than without HIV (81% versus 94%) had normal kidney function.‡

Seventeen of 103 men with HIV (17%) had cognitive impairment (reduced mental capacity), compared with 4 of 74 men without HIV (5%).

Comparing the degree to which cognitive performance in each HIV-positive person differed from the whole HIV-negative group, the researchers identified seven factors independently associated with worse cognitive function in the HIV group (Figure 1):

- Daily to monthly marijuana use
- Cardiovascular disease in the past
- Impaired kidney function
- Diabetes
- Above normal waist-to-hip ratio (wide waist)
- Symptoms of depression
- Lower nadir (lowest-ever) CD4 count

A separate analysis identified four factors that independently predicted whether or not an HIV-positive man had cognitive impairment:

- Marijuana use (raised odds of cognitive impairment about 28 times)
- Cardiovascular disease in the past (raised odds of cognitive impairment about 18 times)
- Poor kidney function (raised odds of cognitive impairment about 9 times)
- Diabetes (raised odds of cognitive impairment about 6 times)

What the results mean for you. This well-planned study linked a diverse group of factors to cognitive impairment or decreased cognitive performance (falling mental performance) in middle-aged and older men with HIV infection responding very well to antiretroviral therapy. The factors tied to worse cognitive performance included one HIV-related factor (lower lowest-ever CD4 count), one behavioral factor (smoking marijuana), one body size factor (above normal waist-to-hip ratio), and four non-HIV diseases or conditions (cardiovascular disease, diabetes, poor kidney function, and symptoms of depression).

Figure 1. A careful comparison of 103 middle-aged and older men with HIV and 74 similar men without HIV pinpointed seven factors related to worse cognitive function (mental ability) in the HIV group. Many of these individual factors may also be related to each other, as suggested by the lines (1) between depression symptoms and regular marijuana and (2) between the four conditions making up the bottom of the circle, which are traditional risk factors for cognitive decline. Because HIV or antiretroviral therapy may have a negative impact on these four traditional risk factors, these factors may influence the impact of HIV or antiretrovirals on cognition. (Cardio = cardiovascular).

† A normal waist-to-hip ratio is below 0.9, meaning waist width should be less than 90% of hip width.
‡ As judged by increased albumin-to-creatinine ratio.
Thus the study strongly suggests that different processes may contribute to cognitive impairment or decreasing cognitive performance in men with HIV. Some of these processes may be directly related to HIV infection (lowest-ever CD4 count) and some may be indirectly related or unrelated to HIV. In this way the study confirms that as people grow older with HIV infection (most men in this study were in their late 40s through early 60s), many aspects of their health and behavior are closely related to each other. For example, a person with diabetes runs a higher risk of poor kidney function and cardiovascular disease—three of the cognitive impairment risk factors in this study.

The researchers point out that all the factors they linked to cognitive impairment or performance in this study have been linked to cognitive problems in the general population and/or in people with HIV in previous studies. Most of these risk factors can be avoided, controlled, or reversed. Following your HIV provider’s advice to lead a healthy lifestyle can go a long way toward preventing or controlling cardiovascular disease, diabetes, kidney disease, and overweight or obesity (indicated here by a high waist-to-hip ratio). Elements of a healthy lifestyle that may affect all these conditions are quitting (or not starting) smoking, maintaining a steady level of physical activity, eating a balanced diet, and avoiding excessive alcohol or party drug use.

Depression affects many people with HIV. But providers often fail to notice or treat depression in people with HIV. If you think you have depression (feelings of persistent sadness or hopelessness), talk to your provider about it. Several medications, with or without short-course psychotherapy, can help people overcome depression.

Previous studies have linked smoking marijuana to cognitive problems in people with and without HIV. Some people smoke marijuana for health reasons (for example, to control neuropathy [foot pain], nausea, or mood problems), and some people smoke pot just because they like it. In either case, marijuana smokers should realize that too much pot can negatively affect cognitive performance and have other bad effects on their health. Medical marijuana is legal in many parts of the United States and Western Europe. If you think marijuana can help relieve physical problems you have, you should get advice from a health professional on using it—you should not try to treat yourself.

The researchers note that results of their study may not apply to everyone with HIV. All HIV-positive participants in this study were 45-year-old or older men in whom antiretroviral therapy had kept the viral load undetectable for many years. And 93% of HIV-positive study participants were gays or other men who have sex with men. The researchers also stress that this kind of study does not prove the identified factors cause cognitive problems—only that these seven factors are somehow linked to cognitive problems.

References

Angina is chest pain caused by low blood flow to heart muscle.

An antibody is a protein the immune system uses to identify invading bacteria or viruses. Detecting an antibody can indicate infection with the related bacterium or virus.

Antiretrovirals are drugs used to treat HIV infection.

Antiretroviral therapy (often abbreviated ART) usually means treatment with three or more antiretrovirals.

Atherosclerosis is build-up of plaque in arteries that can decrease blood flow and lead to heart attack or stroke.

A biopsy is a tissue sample taken from the body (for example, from the intestines or lung) for closer examination when an abnormality is suspected.

Cardiovascular is the term used to include the heart and blood vessels. Cardiovascular disease can include heart attacks and other heart diseases, stroke, and other blood vessel disease.

CD4 cells are one type of cell necessary to fight infection. HIV attacks CD4 cells, so CD4 counts fall when a person is not taking antiretrovirals to control HIV or when treatment fails.

CD4 count measures the number of CD4 cells in a cubic millimeter of blood. People with CD4 counts below 500 have a harder time controlling infections. The risk of uncontrolled infections gets higher as the CD4 count gets lower.

Cirrhosis is development of permanent nonfunctioning scar tissue in the liver.

Cognitive impairment involves problems in memory, language, thinking, or judgment.

Dementia is a decline in mental ability severe enough to interfere with daily life, according to the Alzheimer's Association. Memory loss is an example.

Diabetes is a lifelong disease in which there are high levels of sugar in the blood. Diabetes can be caused by too little insulin, resistance to insulin, or both.

Fibrosis is a high amount of scar tissue in the liver, which can result in cirrhosis.

The immune system is the collection of cells and organs that help the body fight infections and cancers.

Inflammation, marked by increased blood flow and fluid release, is the body's natural response to infection or injury. Ongoing inflammation can contribute to heart disease, certain cancers, liver disease, and other diseases.

A median is a midpoint—the number above which half of all the numbers in a series lie, and below which half of all the numbers in a series lie. A median age of 45 years means half of the people being studied are under 45 and half are over 45. 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.

Myocardial infarction, or heart attack, is heart cell damage or death caused by lowered blood supply to the heart. Artery blockage with plaques can lower blood supply to the heart.

Pack-years measure the number of packs smoked daily in a year. You can calculate pack-years by multiplying the number of packs smoked daily by the number of years the person has smoked. So 1 pack-year means smoking 1 pack per day for 1 year, or 2 packs daily for a half-year. Twenty pack-years means smoking 1 pack daily for 20 years or 2 packs daily for 10 years.

Plaques in arteries consist of built-up fat or calcium that can block the artery and cause myocardial infarction (heart attack).

A stroke occurs when blood stops flowing to part of the brain.

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

• Survival after age 50 with HIV doubles in nationwide Danish study

• New HIV cases, death rate, and viral loads dropping in Seattle area

• People with HIV now being treated for some other diseases

• CT scan detects early lung cancer in middle-aged women with HIV

• Abnormal anal cells that could lead to cancer common in gays with HIV

• Proportion of deaths caused by heart disease rising in people with HIV

• Early artery thickening in middle-aged with HIV and low overall heart disease risk

• Osteoporosis and smoking raise fracture risk in people with HIV

• Liver disease signals more frequent in young people with than without HIV

• High HCV levels in 33% of semen samples from men with HIV

• Many factors—from marijuana to heart disease—tied to mental slowing with HIV

Definitions  43

Board and Staff  44