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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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**Article 1  **

Antiretroviral-treated people lose more years of life to smoking than to HIV

Smoking doubled the death rate in a study of 17,995 antiretroviral-treated people with HIV in Europe and the United States.1 People who quit smoking had a death rate similar to that of people who never smoked. The researchers calculated that a 35-year-old HIV-positive smoker would lose 8 years of life because of smoking, compared with 6 years lost because of HIV infection.

Compared with the general population, a higher proportion of HIV-positive people smoke. The Centers for Disease Control and Prevention (CDC) calculates that 42% of HIV-positive people in care in the United States smoke, compared with 21% of the general US population.2 Smoking takes a tremendous toll on health. It can cause heart disease, stroke, lung cancer and other cancers, and lung disease—all of which can be deadly. In North America and Europe in 2010, smoking was the leading cause of disease in the general population.3

As people live to older ages thanks to antiretroviral therapy, age-related diseases like cardiovascular disease and cancer are becoming major causes of death. Different groups of risk factors can contribute to the risk of cardiovascular disease and cancer seen in people with HIV, including HIV itself (through inflammation and immune-system activation), certain antiretroviral drugs, and traditional risk factors (like smoking). Better understanding of which risks are the most important factors for specific diseases can help create strategies to prevent and manage those diseases in people with HIV.

Recent research involving all HIV-positive people in Denmark found that smoking contributed to more than 60% of deaths in these people.4 This study also found that a 35-year-old HIV-positive man who smokes would lose more years of life because of smoking than because of HIV infection. Researchers who conducted that study teamed up with researchers in other countries to see if the same findings held true throughout Europe and the United States.

How the study worked. This analysis combined findings from eight HIV study groups (cohorts) in Europe and the United States that had data necessary for an analysis of how smoking affects death rates in people with HIV. From each of these eight cohorts, individuals could be included in the analysis if they (1) started antiretroviral therapy between January 1996 and December 2008, (2) were alive 365 days after starting antiretroviral therapy, (3) had data on smoking status, and (4) did not inject illegal drugs.

The researchers determined who died during the study period by checking national death records, cohort records, and physician reports. They identified a cause for each death with a computer method developed by French HIV researchers. The research team attributed death to AIDS if a person had a serious AIDS illness or a CD4 count below 100 close to the time of death. They classified all other deaths as non-AIDS deaths. The investigators used cohort data to classify each individual as a smoker or a nonsmoker. In certain groups they could classify people as a current smoker, a former smoker, or a never smoker.

Follow-up time (the study period for each person) began when a person’s smoking status was determined or 365 days after antiretroviral therapy began, whichever came later. After 365 days of antiretroviral therapy, the CD4 count has usually risen substantially and death from AIDS has become rare. Follow-up time ended when (1) a person died or dropped out of care, (2) 180 days after the last medical visit, or (3) at the end of 2009, whichever came first.

The researchers used mortality rate ratios to compare death rates in smokers and nonsmokers. This type of analysis weighs the impact of standard death risk factors like age and sex (male or female) and HIV-specific risk factors (like CD4 count and time taking antiretroviral therapy). The research team used standard statistical techniques to calculate life expectancy (how long a person is expected to live) for men and to determine excess mortality caused by smoking. They did not figure life expectancy for women because too few nonsmoking women died during the study period to permit that analysis.

*Words in bold are defined in the Technical Word List at the end of this issue of HIV Treatment Alerts.*
The investigators compared mortality in HIV-positive men with mortality in the French general population of men.

**What the study found.** The study focused on 17,995 HIV-positive people from eight groups, two in France and one each in Italy, Switzerland, the Netherlands, Germany, the United Kingdom, and the United States. Men made up 71% of the entire study group, 71% had a viral load below 400 copies, and 56% had a CD4 count above 350. In three cohorts the researchers classified 9476 participants as smokers or nonsmokers, and in five cohorts they classified 8519 participants as current smokers, former smokers, or never smokers.

Smokers had a **median** age of 40 years, compared with 38 years among nonsmokers. Men made up 81% of smokers and 57% of nonsmokers. Gay or bisexual men made up a much larger proportion of smokers (45%) than nonsmokers (30%). Heterosexual women made up a smaller proportion of smokers (18%) than nonsmokers (40%).

Everyone had taken antiretroviral therapy for at least 1 year when follow-up began. During a median study period of about 4 years, rates of death from all causes were 7.9 per 1000 person-years among smokers and 4.2 per 1000 person-years among nonsmokers. (A rate of 7.9 per 1000 person-years means about 8 of every 1000 people died every year.) Statistical analysis comparing smokers with nonsmokers determined that smokers had a twice higher death rate (mortality rate ratio 1.94) (**Figure 1**). When the researchers focused on current smokers, former smokers, and never smokers, they determined that current smokers had a 70% higher death rate than never smokers (mortality rate ratio 1.70). But the death rate did not differ significantly between former smokers and never smokers.

The researchers classified 29% of deaths as AIDS deaths and 71% as non-AIDS deaths. Compared with nonsmokers, smokers had a 2.6 times higher rate of non-AIDS deaths (**Figure 2**). Smokers had more than a 3 times higher rate of death from non-AIDS cancers, more than a 6 times higher rate of death from cardiovascular disease, and almost a 9 times higher rate of death from liver disease (**Figure 2**). Thirty-four smokers and no nonsmokers died of lung cancer.

**Figure 1.** A 17,995-person analysis of HIV-positive people in Europe and the United States determined that smokers had almost a twice higher death rate than nonsmokers. In a separate analysis of current smokers, former smokers, and never smokers, current smokers had a nearly twice higher death rate than never smokers. But the death rate was similar in former smokers and people who never smoked.

**Figure 2.** Compared with HIV-positive nonsmokers, HIV-positive smokers in Europe and the United States had more than a twice higher death rate from all non-AIDS diseases over 4 years, a 3 times higher death rate from non-AIDS cancers (including lung cancer), more than a 6 times higher death rate from cardiovascular disease, and nearly a 9 times higher death rate from liver disease.
Compared with nonsmokers, smokers had an average 8-year shorter life expectancy. A 35-year-old man with HIV lost an average 5.9 years of life because of HIV infection compared with a 35-year-old man in the general population (Figure 3). Among 35-year-old HIV-positive men, smokers lost an average 7.9 years of life compared with nonsmokers. In other words, in this study population, smoking shortened life 2 years more than HIV infection in 35-year-old men \((7.9 - 5.9 = 2.0)\). Among 65-year-old men, smoking shortened life by 6.6 years, while HIV infection shortened life by only 2.9 years, almost a 4-year difference.

Finally, excess mortality related to smoking increased sharply with age—more than excess mortality related to HIV factors. This means that as HIV populations in Europe and the United States grow older, increases in smoking-related mortality can be expected.

**What the results mean for you.** This study of almost 18,000 HIV-positive people in Western Europe and the United States confirmed that smoking has a dramatic negative impact on survival. In fact, this 4-year analysis found that smoking shortens survival in these antiretroviral-treated people more than HIV itself. The study made these key findings:

- Smokers had a twice higher death rate than nonsmokers.
- People who quit smoking did not have a higher death rate than people who never smoked.
- Compared with nonsmokers, smokers had a 3 times higher death rate from cancer and a 6 times higher death rate from heart disease.
- Life expectancy was an average 8 years shorter in smokers than nonsmokers.
- A 35-year-old man with HIV can expect to lose 8 years of life because of smoking.
- A 65-year-old man with HIV can expect to lose more than 6 years of life because of smoking.
- Smoking shortens life more than HIV infection does in people taking antiretroviral therapy.

The finding that HIV-positive people who quit lived as long as people who never smoked is highly encouraging. It should motivate HIV-positive smokers to find a way to quit. No one pretends that quitting is easy, but many long-time smokers do manage to quit. Since 2002, the United States has had more people who quit than people who continue smoking.\(^5\) Visit the link at reference 6 below for more advice on how to quit smoking, including tips from former smokers. An Internet-based smoke-ending program, Positively Smoke Free, has helped HIV-positive people quit. Visit the link at reference 7 below.

According to the CDC, research shows that quitting smoking has the following health benefits:\(^5\)

- Lower risk of lung cancer and many other types of cancer
- Reduced risk of coronary heart disease within 1 to 2 years of quitting
- Reduced risk of stroke and peripheral blood vessel disease
- Reduced risk of chronic obstructive pulmonary disease, a leading cause of death in the United States
- Reduced risk of infertility in women

![Impact of smoking and HIV on life years lost in HIV-positive men](image-url)


7. Positively Smoke Free. [https://www.positivelysmokefreeme.com/](https://www.positivelysmokefreeme.com/)
More age-related illnesses in older people with HIV than comparable HIV-negatives

HIV-positive people 45 years old or older had more age-related illnesses than a comparable group of older adults without HIV in a 1000-person study in the Netherlands. The HIV group had high blood pressure, myocardial infarction (heart attack), peripheral arterial disease, and poor kidney function more often than the HIV-negative comparison group.

Thanks to antiretroviral therapy, people with HIV can now expect to live much longer. As people with and without HIV age, their chances of age-related illnesses like heart attacks and kidney disease climb. These illnesses may develop at an earlier age in people with HIV and they may be more severe with HIV infection. Understanding how often these illnesses develop in aging people with HIV and what factors make such illnesses more likely could help HIV-positive people avoid these problems. At the same time, learning about aging in people with HIV could improve overall understanding of the aging process.

Many studies have assessed rates of age-related conditions in HIV-positive people and risk factors for those conditions. But these studies are often limited by lack of an HIV-negative comparison group similar to the HIV group being studied. Researchers in the Netherlands aimed to remedy that shortcoming of previous studies by creating a large group of older people with HIV and a group of HIV-negative people similar in lifestyle and in factors such as age, gender, and ethnic origin. The study described here provides the first detailed comparison of these groups.

How the study worked. From October 2010 through September 2012, researchers created the AGEhIV Cohort, which includes people 45 or older with or without HIV infection. HIV-positive people come from the HIV outpatient clinic at a large Amsterdam hospital. HIV-negative people come from the sexual health clinic of the Municipal Health Center in Amsterdam and from another study group, the Amsterdam Cohort Studies on HIV/AIDS. The AGEhIV team adjusts recruitment of HIV-negative people so the HIV-negative group generally matches the HIV-positive group in age, gender, and ethnic origin. Everyone in the HIV group had a confirmed positive HIV test, and everyone in the HIV-negative group had a confirmed negative HIV test.

When people enter the study and every 2 years afterwards, they get tested for “age-associated noncommunicable comorbidities” (called age-related illnesses in this review) like hypertension, heart attack, and kidney disease. All study participants complete a detailed questionnaire on their medical history, the prescription drugs and nonprescription drugs they take, and on substance use, sexual orientation, intake of calcium and vitamin D, exercise, work, income, and other factors.

All study participants give blood and urine samples, and all get measurements of blood pressure and hip and waist width. Participants have several medical tests including electrocardiography (which measures heart rhythm) and tests of blood vessel stiffness, breathing, bone density, and mental function.

The main study goals were to count the number of age-related illnesses in all participants and to compare numbers in people with and without HIV. The researchers used standard statistical methods to identify risk factors for these illnesses. HIV infection could be one of those risk factors. This type of analysis pinpoints risk factors that affect chances of age-related illnesses regardless of whatever other risk factors a person has.

What the study found. This analysis involved 540 people with HIV and 524 without HIV. Median age of the entire study group was about 52 years; 88% with HIV and 85% without HIV were men. While 74% of the HIV group were gay or bisexual men,

* Words in bold are defined in the Technical Word List at the end of this issue of HIV Treatment Alerts.
† Peripheral arterial disease develops when fatty build-ups clog leg arteries. Clogged leg arteries can raise the risk of heart attack or stroke.
70% of the non-HIV group were gay or bisexual. The proportion of Dutch people was lower in the HIV group than in the HIV-negative group (72% versus 81%), and the proportion of people from Africa was higher in the HIV group (7% versus 1%).

About one third of HIV-positive people smoked, compared with one quarter of HIV-negative people. People with HIV had a lower median **body mass index** than those without HIV, but the HIV group included more people with an above-normal waist-to-hip ratio, 84% versus 62% (indicating wider waists in the HIV group). Compared with HIV-negative people, the HIV group had higher blood pressure and lower vitamin D levels. Fewer HIV-positive study participants were physically active.

Among people with HIV, 96% were taking antiretroviral therapy, most had an undetectable **viral load**, and median **CD4 count** stood at 565. Compared with the HIV-negative group, HIV-positive people had a higher average number of age-related illnesses—1.3 versus 1.0. That difference is statistically significant, meaning statistical analysis shows that chance alone does not explain the difference. The average number of these illnesses was higher among people with HIV than among those without HIV in every 5-year age group analyzed (*Figure 1*), and the difference was significant in three age groups: 50-54, 60-64, and 65 or older.

The proportion of people with one or more age-related illnesses was significantly higher in the HIV group than in the comparison group—69.4% versus 61.8%. Each individual illness analyzed affected a higher proportion of HIV-positive people than HIV-negative people. For individual illnesses, the difference between the HIV group and the HIV-negative group was statistically significant for four illnesses (*Figure 2*).

![Average number of age-related illnesses with or without HIV](image)

*Figure 1.* A comparison of 540 older adults with HIV and 524 without HIV found that the HIV group had higher average numbers of common age-related illnesses. In age groups marked with an **asterisk** the difference between the HIV group and the comparison group was statistically significant.
Statistical analysis that considered the potential impact of many disease risk factors determined that HIV infection—by itself—was linked to a 58% greater chance of having more of the age-related illnesses studied. The many factors considered in this analysis included age, gender, sexual orientation, Dutch origin, hepatitis B or C infection, a family history (of heart attack, high cholesterol, hypertension, or diabetes), smoking, alcohol use, use of cocaine, ecstasy, or marijuana.

Three other independent predictors of more age-related illnesses emerged in this analysis—a family history of these diseases, smoking, and older age. And older age was a stronger predictor in the HIV group than in the HIV-negative group.

Among people with HIV, the only HIV-related factor that predicted more non-AIDS illnesses was longer time spent with a CD4 count below 200.

- **What the results mean for you.** This large study made many important findings. The two most important findings are:
  1. HIV-positive adults 45 and older have more age-related illnesses than a comparable group of adults without HIV.
  2. HIV infection, by itself, raises chances a person will have more age-related illnesses by 58%.

These findings are especially notable because almost everyone in the HIV group had begun antiretroviral therapy and gained CD4 cells, and most had an undetectable viral load.

Four age-related illnesses developed significantly more often in older adults with HIV than without HIV—high blood pressure, myocardial infarction (heart attack), peripheral (leg) arterial disease, and impaired kidney function. Besides HIV infection, other independent risk factors for more age-related illnesses were (1) family history...
of these illnesses, (2) smoking, (3) older age, (4) above-average waist-to-hip ratio, and (5) longer time spent with a CD4 count below 200. That last finding means people who took longer to start antiretroviral therapy—for whatever reason—had a greater chance of getting diagnosed with an age-related disease later on.

This large study in the Netherlands is particularly valuable because of its unique design. Other large studies have compared HIV-positive people with HIV-negative people or mostly HIV-negative people in the general population. This AGEhIV report is the first analysis of an ongoing study that selects a group of HIV-negative people that generally matched the HIV-positive group in age, gender, and lifestyle. Many HIV-negative participants came from a sexual health clinic, so they reflected the HIV group in sexual activity. Because of this careful planning, the findings are convincing.

Among the several risk factors for more age-related diseases, three can be avoided or changed: smoking, wide waist-to-hip ratio, and time spent with a CD4 count below 200. A large HIV-group study summarized on page 3 of this issue of HIV Treatment Alerts found that smoking accounted for more life years lost than HIV infection itself. Smoking causes heart disease, lung disease, and several cancers. It contributes to bone loss, a growing problem in people with HIV. Your HIV physician can prescribe nicotine replacement or other therapies to help you quit smoking. The US National Heart, Lung, and Blood Institute has practical advice on strategies to quit smoking at the link in reference 3 below.

Longer time spent with a CD4 count below 200 raised chances of having more age-related illnesses in this study. Every year with a CD4 below 200 boosted the odds of more age-related illnesses 23%. Antiretroviral guidelines throughout the world call for starting antiretroviral therapy at CD4 counts above 200 and usually above 350. United States guidelines say everyone who tests positive for HIV should start antiretroviral therapy, whatever their CD4 count. People with a high risk of HIV infection—including sexually active people and those who inject drugs—should get tested regularly for HIV to avoid being diagnosed after the CD4 count has dropped to a low level.

A wide waist-to-hip ratio can be avoided or improved through exercise, diet, and perhaps other remedies your HIV clinician can recommend.

Taken together, results of this careful study provide strong evidence that people with HIV face a higher risk of common age-related illnesses than a comparable group of HIV-negative people—particularly heart disease, leg artery disease, kidney disease, and high blood pressure. Another study reviewed in this issue of HIV Treatment Alerts found evidence that an increased risk of heart disease with HIV may start in people as young as 20 years old. Everyone with HIV infection should be aware of cardiovascular disease risk factors (see Table 1 on page 26) and should work with their HIV clinician to avoid or control these risk factors.

References


Around 1996 antiretroviral therapy improved dramatically as HIV providers began combining three drugs from two antiretroviral classes. Treatment with three antiretrovirals has remained the standard approach since then, but new classes of antiretrovirals have become available and new antiretrovirals in each class have become safer and easier to take.

Because of these improvements, antiretroviral therapy today lowers viral loads to an undetectable level more consistently, and more people can continue the same regimen without interruption. Trials of new antiretrovirals and new strategies show that high proportions of trial participants now regularly reach an undetectable viral load. But these trials usually last only 1 or 2 years, and the trials often exclude people with advanced HIV infection or other illnesses like liver or kidney disease. As a result, antiretroviral success rates in these trials may not reflect what happens in the month-to-month care of everyone who starts treatment.

To get a better understanding of how response to antiretroviral therapy has changed over the years in treated people across an entire country, researchers in France conducted this study. The researchers also aimed to identify factors linked to success or failure of antiretroviral therapy over the years.

France is similar to the United States in antiretroviral combinations and strategies and in the general care of HIV-positive people. A key difference between the countries is that antiretroviral therapy and HIV care are free in France.

*Words in bold are defined in the Technical Word List at the end of this issue of HIV Treatment Alerts.
33% of study participants were gay or bisexual men, 18% were heterosexual men, 24% were heterosexual women, and 15% acquired HIV when injecting drugs. Across the study periods, 14% of the group came from sub-Saharan African countries. Slightly more than one quarter of the study population, 29%, had taken one or two antiretrovirals before starting a three-drug combination, which became the standard treatment around 1996.

Median age of the study group rose from 37.2 years in 1997-1998 to 46.6 years in 2009-2011. Over the same period, median CD4 count at the time of virologic failure climbed from 340 to 530, while viral load at failure fell from 7032 copies to 2536 copies (Figure 1).

The proportion of people with at least one virologic failure in any 2-year period dropped steadily from 61.5% in 1997-1998 to 9.7% in 2009-2011 (Figure 2). In the same period, proportions of people with a viral load of 500 to 999 copies dropped from 11.2% to 2.7% and the median viral load at the time of virologic failure fell from 7032 copies to 2536 copies.

Statistical analysis accounting for several factors that can affect virologic failure determined that chances of failure fell by 26% from 1997-1998 to 1999-2000, by 36% to 2001-2002, by 46% to 2003-2004, by 62% to 2005-2006, and by 79% to 2007-2009. Compared with people who had a CD4 count below 200 at the time of virologic failure, those with a CD4 count of 200 to 349 had a 34% lower chance of failure, those with a CD4 count of 350 to 499 had a 54% lower chance of failure, and those with a CD4 count of 500 or more had a 72% lower chance of failure.

For the years 2006 through 2011, the researchers conducted a separate analysis defining virologic failure beyond 6 months of treatment as (1) two consecutive viral loads above 50 copies or (2) one viral load above 50 copies followed by a switch in antiretrovirals. Defined this way, the virologic failure rate fell from 22.1% in 2006 to 18.5% in 2007, 16% in 2008, 13.7% in 2009, 12.1% in 2010, and 10.1% in 2011. Over that period, median viral load at virologic failure dropped from 528 copies to 171 copies.

*What the results mean for you.* This large and long study in France, where antiretroviral treatment practices and available antiretrovirals are similar to the United States, found that the proportion of people whose antiretroviral regimen failed fell steadily and consistently over the 15 years from 1997 to 2011. This continuing drop in the virologic failure rate confirms that antiretroviral therapy has been working better and better since
three-drug combinations became standard around 1996. The findings reflect results from other countries where the same antiretrovirals have been available—Canada, the United Kingdom, and Switzerland.

The French team also found that viral load at the time of virologic failure declined over the years. One reason for this change could be that in more recent years HIV clinicians stopped antiretroviral combinations faster and switched to a new combination when a treated person had a detectable viral load. That practice reflects French and US guidelines that recommend quick assessment of what caused the detectable viral load and a quick switch to new antiretrovirals if necessary. Continuing the same antiretroviral combination in a person who has a low but detectable viral load can make HIV resistant to drugs in the current combination and sometimes to other drugs—and resistant virus can be harder to treat.

Many factors could contribute to these improvements in virologic failure rates, including (1) availability of more antiretrovirals, (2) more antiretroviral classes that attack HIV in different ways, (3) stronger antiretrovirals, (4) antiretrovirals with fewer side effects, (5) antiretrovirals that are easier to take (because of once-daily dosing or combining two or more antiretrovirals in the same pill), (6) better pill-taking habits by people with HIV (often because of reasons 4 and 5), and (7) better understanding of how to treat HIV by providers.

A notable aspect of this study is that it included anyone taking antiretrovirals for 6 months or more, not just people starting their first antiretroviral combination. So the study group includes people in whom one or more antiretrovirals failed. Because no many new and different antiretrovirals became available in the 2000s, clinicians can often build a combination that will control HIV after one or more combinations have failed. An undetectable viral load should be the goal of treatment regardless of how many antiretrovirals have already failed.

The study also found that a higher current CD4 count lowered chances of virologic failure. That finding supports recent recommendations to start antiretroviral therapy before the CD4 count falls to a low level. Indeed, US guidelines say everyone with HIV should start antiretroviral therapy, no matter what their CD4 count.

Taken together, these findings are good news for people with HIV. The results should inspire confidence that today’s antiretroviral combinations and treatment strategies control HIV better than older combinations. To profit from these newer treatments, people with HIV should take their antiretrovirals regularly, exactly as instructed by their HIV providers.

References

Gradually accelerating heart disease risk with age in men with HIV

Risk of cardiovascular disease* grew somewhat faster with age in men with HIV than would be expected in the general population, according to results of a 24,000-man analysis.1 But risk of myocardial infarction (heart attack) did not rise faster with age in men with HIV than would be expected in men in the general population.

In the past several years much research has assessed rates of cardiovascular disease in people with HIV infection. For example, two other studies discussed in this issue of HIV Treatment Alerts found that US veterans with HIV and without major heart risk factors had a twice higher heart attack risk than veterans without HIV2 (see page 19) and that young adults infected with HIV early in life had significantly thicker coronary artery walls—a possible signal of future heart disease—than healthy HIV-negative adults3 (see page 23).

Older age is a major heart disease risk factor in people with and without HIV. Concern about the impact of aging on heart disease in HIV-positive people is growing because people with HIV are now living much longer than they did a few decades ago. But studies comparing cardiovascular disease rates in people with and without HIV can be difficult to interpret if the HIV-positive and negative groups are not similar in age and other key factors. And research has not determined whether the heart disease increase with age is more rapid in people with HIV than in the general population.

Besides traditional cardiovascular risk factors like aging and smoking, people with HIV face two other risk factors—antiretroviral therapy and the inflammation and immune-system activation caused by HIV itself.

To sort through these cardiovascular risk factors and get a better understanding of how older age adds to heart disease risk in people with HIV, researchers working with the DAD Study group of people receiving treatment for HIV infection conducted this study.1 Their main goal was to calculate the increased risk of cardiovascular disease with each additional year of age in men with HIV and to compare that increase with the age-related rate in men in the general population.

How the study worked. Researchers focused on men in the DAD group, which is an ongoing study of HIV-positive people taking antiretroviral therapy in Europe, the United States, Argentina, and Australia. Medical findings recorded during regular office visits are sent to the central DAD database. DAD researchers also collect basic data like age, gender, and smoking status—plus HIV-related data like CD4 count, viral load, and antiretrovirals taken.

The research team determined how many cases of cardiovascular disease developed during the study period. They classified each case into one of three groups:

- Myocardial infarction (heart attack)
- Coronary heart disease (myocardial infarction, an invasive cardiovascular procedure, or cardiovascular death)
- Cardiovascular disease (coronary heart disease or stroke)

The researchers limited their analysis to HIV-positive men because the low number of cardiovascular diseases that developed in these DAD women during the study period would not support reliable statistical analysis. All of the men had cardiovascular risk data available, and none of the men already had cardiovascular disease before the observation period began. The observation time for each man began when their cardiovascular risk data first got recorded and continued until that man had cardiovascular disease or died, until that man’s last study visit plus 6 months, or until February 2011, whichever came first.

*Words in bold are defined in the Technical Word List at the end of this issue of HIV Treatment Alerts.
The investigators measured age in several ways and used a standard statistical method to pick the measurement that would work best with this group of HIV-positive men. They compared this age-effect measure for HIV-positive men with several cardiovascular risk formulas used for the general population:

- Framingham Heart Study risk score (based on three studies involving more than 5500 US men 30 to 74 years old)
- CUORE risk score (based on 11 Italian groups of more than 6800 men 35 to 69 years old)
- ASSIGN risk score (based on more than 6000 men in Scotland between 30 and 74 years old)

Studies like this can measure two types of risk—absolute risk and relative risk. Absolute risk in a heart disease study is a group’s risk of getting heart disease in a given period. Relative risk is the risk of getting heart disease in one group (for example, men with HIV) compared with another group (for example, men without HIV). Because the absolute risk of cardiovascular disease differs by the population studied, the DAD researchers compared the relative increased risk of cardiovascular disease per year of age in DAD men versus the risk per year of age in the three general-population formulas. Specifically, the research team compared the DAD men with the general-population men by measuring the relative risk increase from the age of 40 to the age of 65.

Finally, the researchers calculated how the impact of age on relative risk of cardiovascular disease might be reduced by changing three other risk factors: (1) stopping smoking, (2) lowering cholesterol 18 mg/dL (1 mmol/mL), and (3) lowering systolic blood pressure by 10 mm Hg.

■ What the study found. The study included 24,323 men, 59% of them white, 6% nonwhite, and the rest with an unknown race or ethnic background. Median age of the study group stood at 41. Most of these men, 60%, became infected with HIV during sex with another man, 20% became infected during sex with a woman, and 15% became infected when injecting drugs. While 55% of these men smoked at the time of the study, 18% smoked in the past. As a group, these men had taken antiretroviral therapy for a median of 1.9 years.

During a median observation time of 6 years, the researchers counted 474 myocardial infarctions (heart attacks), 683 cases of coronary heart disease, and 884 cases of cardiovascular disease (as defined in the bullet list on page 14). The myocardial infarction rate rose from 2.3 per 1000 person-years in 40- to 45-year-old men to 6.5 per 1000 person-years in 60- to 65-year-old men. (A rate of 2.3 per 1000 person-years means about 2 of every 1000 men had a myocardial infarction every year). Coronary heart disease rates climbed from 3.1 per 1000 in 40- to 45-year-olds to 11.9 per 1000 in 60- to 65-year-olds, while cardiovascular disease rates rose from 3.7 per 1000 in 40- to 45-year-olds to 15.9 per 1000 in 60- to 65-year-olds.

The five best age-calculating methods all showed a similar impact of age on risk of heart disease in men with HIV. Compared with a 40-year-old man, a 50-year-old had about a doubled risk of cardiovascular disease (as defined in the bullet list on page 14), a 55-year-old had about a tripled risk, and a 65-year-old had about a 5 times higher risk.

When the researchers compared the age-related increasing risk of myocardial infarction in HIV-positive DAD men with the increasing relative risk in the general population formulas, they found no difference.

But compared with the general population, men with HIV had somewhat faster age-related increases in risk of coronary heart disease and cardiovascular disease. Compared with a 40-year-old HIV-positive man, a 65-year-old man with HIV had a 5.8 times higher relative risk of coronary heart disease (Figure 1). Compared with a 40-year-old man in the general population, a 65-year-old in the general population has a 3.3 to 4.9 times higher risk of coronary heart disease, depending on the general population formula used. Compared with a 40-year-old HIV-positive man, a 65-year-old man with HIV had a 5.8 times higher relative risk of cardiovascular disease. Compared with a 40-year-old man in the general population, a 65-year-old in the general population has a 4.2 to 4.7 times higher risk of cardiovascular disease, depending on the general population formula used.
In men with HIV, stopping smoking, lowering cholesterol, and lowering blood pressure at age 50 would each have a large impact on cardiovascular disease risk by age 65 (Figure 2). Compared with a 40-year-old HIV-positive man, a 65-year-old had a 5.8 times higher cardiovascular disease risk. That age-related increase dropped to 3.0 times if a man stopped smoking at age 50, dropped to 4.8 times if a man lowered his cholesterol 18 mg/dL at age 50, and dropped to 5.2 times if a man lowered his systolic blood pressure 10 mm Hg at age 50.

What the results mean for you. This large and careful study charted the increasing risk of cardiovascular disease in HIV-positive men from age 40 to age 65. Risk of myocardial infarction (heart attack), coronary heart disease, and cardiovascular disease (as defined in the bullet list on page 14) each rose with every additional year of age. The increase in myocardial infarction risk with each year of age was very similar in men with HIV and in formulas used to graph age-related risk in the general population of men. But compared with the general population formulas, the increasing risk with age was somewhat faster in men with HIV for coronary heart disease and cardiovascular disease (Figure 1).

The DAD researchers stress that their analysis found “only limited evidence” that cardiovascular risk increases faster with age in men with HIV than in the general population. They say “it remains difficult to conclude with any certainty” that aging has a greater relative impact on heart disease risk with HIV than without HIV.

The DAD team goes on to summarize results of several previous studies of heart disease risk with HIV infection. From these studies the DAD researchers conclude that HIV infection appears to increase the absolute risk of cardiovascular disease by about 1.2-fold (20%) to 2.0-fold (100%) compared with the general population. But these researchers believe the absolute risk difference between people with and without HIV will remain uncertain until a study compares an HIV group with an HIV-negative group well matched by age, gender, and other risk factors.
The study did not try to find reasons for these somewhat faster risk increases in men with HIV than in the general population. But the researchers did find that controlling three heart risk factors starting at age 50 would slow the increasing risk through age 65: Men who (1) stopped smoking, (2) cut their cholesterol level, or (3) lowered their blood pressure would slow the increasing risk seen with every year of age.

This is good news for men with HIV. It suggests that HIV-positive men in late middle age may be able to lower their heart disease risk by controlling traditional risk factors. Besides smoking, high cholesterol, and high blood pressure, other heart risk factors people can change are (1) being overweight or obese, (2) eating a diet high in saturated fats, cholesterol, or salt, (3) not getting enough physical activity, (4) drinking too much alcohol, and (5) failing to control high blood sugar (prediabetes or diabetes).\(^4\)

HIV-positive people with any of these cardiovascular risk factors should work with their HIV provider to change their lifestyle or get appropriate treatment for high cholesterol or triglycerides, high blood pressure, or high blood sugar. The American Heart Association has a great deal of information on ways to prevent heart disease, including advice on weight, exercise, diet, and smoking. Click on the link at reference 5 below.

The DAD researchers stressed the large impact smoking has on cardiovascular disease risk in people with HIV. Previous work by the DAD group found that cardiovascular disease risk fell more in every year since a person quit smoking.\(^6\) A European-US study reviewed on page 3 of this HIV Treatment Alerts found evidence that smoking shortens life more than HIV itself in people taking antiretroviral therapy.\(^7\)

This DAD study analyzed age-related heart disease risk only in men because the low number of cardiovascular diseases that developed in these DAD women would not support reliable statistical analysis. Other research does show that women with HIV run a higher heart disease risk than women in the general population.\(^8,9\) And in these studies the risk difference between HIV-positive and negative women was greater than the risk difference between HIV-positive and negative men. All of the risk factors that may contribute to heart disease in men with HIV also apply to women with HIV. So it makes sense for women with HIV as well as men to lower their heart disease risk.


5. American Heart Association. Prevent heart disease at any age. [http://www.heart.org/HEARTORG/GettingHealthy/GettingHealthy_UCM_001078_SubHomePage.jsp](http://www.heart.org/HEARTORG/GettingHealthy/GettingHealthy_UCM_001078_SubHomePage.jsp)


Among veterans without major heart disease risk factors, veterans with HIV had a twice higher risk of acute myocardial infarction* (heart attack) than veterans without HIV in a 6-year study. Among veterans who did have cardiovascular risk factors, veterans with HIV had a higher heart attack risk in every risk category analyzed.

In the early years of the HIV epidemic, before strong antiretroviral drugs became available, most HIV-positive people died of AIDS at an early age. Now that people are taking potent antiretroviral combinations, they are living to an older age and acquiring diseases common to old age, such as cardiovascular disease, diabetes, and bone disease. Finding ways to prevent and control those chronic diseases in people with HIV infection has become a research priority.

Many factors can contribute to a higher heart disease risk, starting with traditional risk factors like smoking, high cholesterol, high blood pressure, and diabetes. HIV-positive people also have cardiovascular risk factors seen only in HIV populations, such as certain antiretroviral drugs and HIV itself, which causes inflammation that can damage blood vessels.

Many studies of cardiovascular risk in people with HIV assess these risk factors one at a time. But research indicates that risk factors occur in clusters. Investigators working with the US Veterans Aging Cohort Study Virtual Cohort (VACS-VC) decided to compare heart attack rates in HIV-positive veterans with rates in HIV-negative veterans according to clusters of cardiovascular risk factors.

Understanding how much traditional heart risk factors contribute to acute myocardial infarction in people with HIV, the researchers noted, is essential for determining how much HIV and its treatment contribute to myocardial infarction risk.

**How the study worked.** This analysis involved US veterans who entered the VACS-VC study during or after 2003. VACS-VC compares HIV-positive veterans with HIV-negative veterans matched by age, gender, race or ethnicity, and study site. For the heart attack analysis, the researchers did not include anyone with current cardiovascular disease or cardiovascular disease in the past. People with abnormally low blood pressure (below 90/60) were also excluded from this analysis.

Researchers determined how many veterans had a myocardial infarction (heart attack) during the study period. The study period started at a veteran’s first study visit in 2003 or later and lasted until the veteran had a heart attack or died, until a veteran’s last study visit, or until the end of 2009.

![Four heart risk categories in US veterans study](image-url)
The study team created a cardiovascular risk profile that included diabetes, current smoking, total cholesterol, statin drug use for high cholesterol, blood pressure, and blood pressure drug use. With different combinations of these factors, the researchers created four heart risk factor categories: optimal, not optimal, elevated, and major (Figure 1). They defined these four categories in such a way that a veteran could be in only one category.

The VACS-VC investigators used medical records to determine basic personal information (like age, gender, and race or ethnicity), several health-related factors (like body mass index and kidney disease), and HIV-related factors (like CD4 count, viral load, antiretroviral use, and type of antiretrovirals used).

With standard statistical methods, the researchers determined the effect of (1) the cardiovascular risk profile and (2) HIV infection on the risk of a new heart attack. This type of analysis figures the risk associated with the risk profile or HIV infection regardless of whatever other risk factors a person might have.

■ What the study found. The study included 81,322 veterans, one third of them with HIV infection. Men made up more than 95% of the study group. Age averaged about 50 years. About 50% of study participants were black, nearly 40% were white, and most of the rest were Hispanic.

During a median follow-up period of 5.9 years, 858 veterans had a myocardial infarction (heart attack). Of the heart attacks recorded, 42% occurred in veterans with HIV, even though they made up only 33% of the study group.

Fewer than 2% of these veterans had optimal cardiac health (as defined in Figure 1), and only 12% of the study group had no major cardiovascular risk factors. Almost half of these veterans, 46%, had one major cardiovascular risk factor, 20% had two major cardiovascular risk factors, and 7% had three. Among veterans with only one major cardiovascular risk factor, that factor was usually smoking. Among veterans with two major factors, those factors tended to be smoking and diabetes. And among veterans with three major factors, those factors tended to be smoking, diabetes, and taking statins for high cholesterol.

Among veterans with HIV, 2.4% had optimal cardiac health, 7.1% fell into the nonoptimal group, 5.4% had elevated cardiac risk, and the rest had one, two, or three major cardiovascular risk factors as defined in this study.

Compared with veterans who had optimal cardiovascular health, those with one of more cardiovascular risk factors were more likely (1) to be older, (2) to be black, (3) to be obese, (4) to have a low-density lipoprotein (LDL) cholesterol (“bad cholesterol”) at or above 160, (5) to have triglycerides at or above 150, (6) to have kidney disease, (7) to have a history of cocaine use, and (8) to have a history of alcohol abuse.

Veterans with optimal cardiovascular health (Figure 1) had a low heart attack rate during the study period, 6.0 per 10,000 person-years. That rate means 6 of every 10,000 veterans had a heart attack each year. The heart attack rate climbed with each higher number of major cardiovascular risk factors: 18.5 per 10,000 with one major cardiovascular risk factor, 34.5 per 10,000 with two, and 42.5 per 10,000 with three.

Compared with HIV-negative veterans, HIV-positive veterans who fit in the same cardiovascular risk bracket had higher heart attack rates in each of the risk brackets. That analysis factored in the impact of age, race, and ethnicity on heart attack risk. Compared with HIV-negative veterans with no major risk factors, HIV-positive veterans with no major risk factors had a twice higher heart attack risk.

Compared with HIV-positive veterans with no major cardiovascular risk factors, (1) HIV-positive veterans with one major risk factor had almost a doubled heart attack risk, (2) HIV-positive veterans with two major risk factors had a 3 times higher heart attack risk, and (3) HIV-positive veterans with three or more major risk factors had a 4 times higher risk (Figure 2). This statistical analysis accounted for all risk factors considered in this study, including HIV-related factors.
Increase in heart attack risk with each additional risk factor in HIV+ veterans

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What the results mean for you. Previous studies found higher rates of heart attacks and other cardiovascular disease in people with HIV than in comparison groups without HIV.\(^5\) This new study in US veterans\(^1\) differs from previous studies because it compared HIV-positive and negative people according to how many cardiovascular risk factors they had. HIV-positive veterans with no major cardiovascular risk factors had a twice higher heart attack risk than HIV-negative veterans without risk factors. And HIV-positive veterans in every other risk group analyzed—with one, two, or three major risk factors—had a higher heart attack risk than HIV-negative veterans with the same number of risk factors.

Another notable finding of this study is that a tiny proportion of veterans with and without HIV—under 2%—had good heart health. In this study that meant they did not smoke, have diabetes, have high cholesterol (or take drugs for high cholesterol), or have high blood pressure (or take drugs for high blood pressure). This group of veterans—and many other people in the United States—clearly have lots of room for improvement in heart health.

Stopping smoking is one decisive step smokers can take to protect their heart—and to protect themselves from several cancers and lung diseases. Among veterans with one major cardiovascular risk factor in this study, that factor was usually smoking. Another study reviewed in this issue of \textit{HIV Treatment Alerts} found that HIV-positive people responding well to antiretroviral therapy lose more years of life from smoking than from HIV infection (see page 3).\(^7\)

If you smoke, work with your HIV provider to find the best way to quit. That may involve nicotine replacement strategies or drug therapies. The Centers for Disease Control and Prevention has plenty of online advice about quitting smoking, including tips from former smokers, other quitting pointers, and quit-smoking resources. Visit the link at reference 8 below.

The veterans study is limited in that almost all of these veterans were men. Thus it is not clear whether the results apply equally to women. However, other studies comparing HIV-positive women with HIV-negative women confirm higher heart attack risk in women with HIV.\(^4,5\)

The researchers concluded that preventing heart attack risk factors or lowering their number “may result in a substantial reduction in acute myocardial infarction risk among HIV-infected people.”\(^1\) Besides the risk factors considered in this study, other major heart disease risk factors are obesity, heavy alcohol drinking, physical inactivity, and diets high in saturated fats, cholesterol, or salt.\(^9\) Having a father, mother, brother, or sister with heart disease is another major risk factor. People with a close relative who has or had heart disease should work especially hard to control other risk factors.
References

Heart artery walls thicker in young adults with HIV than in HIV-negatives

Compared with healthy HIV-negative adults, young adults infected with HIV early in life had significantly thicker coronary artery walls—a possible signal of future heart disease.\(^1\) Statistical analysis determined that HIV infection itself—as well as more cigarette smoking and high cholesterol—raised the risk of greater coronary artery wall thickness regardless of a person’s other major risk factors. HIV-positive people in this study were 15 to 29 years old.

Several studies,\(^2,4\) including the one reviewed in the preceding pages of this issue,\(^5\) show a higher risk of cardiovascular\(^*\) disease in people with HIV than in comparison groups of HIV-negative people. Higher heart disease risk in people with HIV may be partly explained by traditional risk factors (like smoking, high blood pressure, and diabetes), long-term use of certain antiretroviral drugs, and ongoing inflammation and activation of immune system cells caused by HIV itself.

Previous comparisons of heart disease rates in people with and without HIV involved middle-aged and older adults, many of them approaching the age when people in the general population start having heart disease. Few heart risk studies have involved young adults with HIV, some of whom have had HIV infection and taken antiretrovirals all their life.

Young HIV-positive adults differ from other heart-risk study groups in that they usually do not have traditional cardiovascular risk factors like diabetes and high blood pressure. So studying young adults with HIV infection would fill an important gap in HIV heart disease research and could tell HIV providers what heart risk factors are most important in this young group.

To address these issues, researchers at the National Institutes of Health (NIH) conducted this comparison of young adults with HIV and healthy young adults without HIV. Because advanced heart disease is rare in young adults, the researchers used two scans that create images of the heart to look for three signals of future heart disease—heart artery wall thickness, plaque in the coronary arteries that supply blood to the heart, and fat around the heart.

- **How the study worked.** Researchers invited young adults infected with HIV early in life to join the study between April 2010 and April 2013. These people could not have inherited cardiovascular disease or cardiovascular disease that developed in their lifetime. To create a comparison group, the NIH team invited HIV-negative people at least 18 years old to enter the study. People in the HIV-negative group could not have any significant medical conditions.

Everyone in the study had two types of heart scans. First, coronary CT angiography assessed (1) artery blockage, (2) number of plaques, and (3) epicardial fat, which is fat surrounding the heart. Second, a sophisticated magnetic resonance imaging (MRI) scan called TRAPD measured thickness of the right coronary artery wall (Figure 1).

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*Words in **bold** are defined in the Technical Word List at the end of this issue of *HIV Treatment Alerts.*
Thickness was measured as the average distance between inner and outer boundaries of the right coronary artery wall. Coronary artery wall thickening is a possible early indicator or developing heart disease—earlier than development of plaques in arteries.

All study participants had a detailed physical exam and review of their medical records to find measures of possible interest to this study. The researchers used accepted statistical methods to identify predictors of coronary artery wall thickness. This type of statistical analysis finds predictors that affect artery wall thickness regardless of whatever other possible predictors a person might have.

What the study found. The study involved 35 people with HIV (19 men, 16 women) and 11 healthy people without HIV (3 men, 8 women). Age ranged from 15 to 29 years in the HIV group and from 22 to 29 in the HIV-negative group. Average age was significantly younger in the HIV group, 22 versus 25 years. In the HIV group, 48% were black, 34% were white, and the others were Hispanic or mixed race. These proportions did not differ significantly in the HIV-negative comparison group.

Average blood pressure was higher among young adults with HIV than among those without HIV, but the HIV group had lower body mass index (weight) and lower total cholesterol than the HIV-negative group. A higher proportion of people with HIV ever smoked, and they smoked more pack-years than people without HIV, but these differences were not statistically significant.

Among the 35 people with HIV, 25 (71%) were taking antiretroviral therapy but only 15 (43%) had an undetectable viral load. CD4 count averaged 502 among people with HIV, though 5 (14%) had a CD4 count below 200.

Epicardial fat volume did not differ significantly between people with HIV and those without HIV. Coronary CT angiography detected plaque in 6 people (19%) with HIV and in 5 (45%) without HIV. No plaques in any study participant caused significant artery narrowing.

Right coronary artery wall thickness averaged 1.32 millimeters (mm) in young adults with HIV, which was significantly greater than the average thickness of 1.09 mm in young adults without HIV (Figure 2). Because the HIV group was younger than the HIV-negative group, the researchers ran a separate analysis excluding HIV-positive people younger than 20. In this analysis, coronary artery wall thickness was still significantly greater in the HIV group than in the comparison group (1.31 versus 1.09 mm).

Smoking pack-years (the amount people smoked) correlated positively with coronary artery wall thickness in people with HIV—in other words, the more a person smoked, the thicker the artery wall. This correlation was not seen in people without HIV. Among all study participants, higher total cholesterol and higher low-density lipoprotein (LDL or “bad”) cholesterol correlated with detection of coronary artery plaque.

![Heart artery wall thickness in young adults with versus without HIV](image)

**Figure 2.** Coronary artery wall thickness, an indicator of possibly developing heart disease, was significantly greater in HIV-positive young adults than in a comparison group of HIV-negative people (left). Coronary artery wall thickness was also greater in the HIV group when the analysis excluded HIV-positive people younger than 20 (right). (Illustration of artery wall from Servier PowerPoint image bank, [http://servier.com/Powerpoint-image-bank](http://servier.com/Powerpoint-image-bank).)
Statistical analysis that considered the impact of age, gender, and body mass index on coronary artery wall thickness pinpointed three factors that predicted thicker walls regardless of these other risk factors:

- HIV infection
- More smoking pack-years
- Higher LDL cholesterol

An analysis focused only on people with HIV determined that a longer time taking antiretroviral therapy and a longer time taking any class of antiretroviral drugs correlated positively with coronary artery wall thickness. In other words, the longer a person took antiretrovirals, the thicker the coronary artery wall. But this correlation proved true for only one individual antiretroviral, stavudine (d4T), a drug no longer routinely prescribed in the United States or other Western countries. Among people with HIV, higher total cholesterol, LDL cholesterol, and triglycerides correlated with thicker coronary artery walls.

**What the results mean for you.** This is the first study to use the most up-to-date imaging scans to assess three indicators of potentially developing heart disease in young adults infected with HIV for most of their lives and in a comparison group of healthy HIV-negative young adults. The most important finding is that coronary artery wall thickness—a possible heart danger signal—was significantly greater in young adults with HIV than in those without HIV.

Statistical analysis that considered the impact of three heart risk factors—age, body mass index, and gender—identified HIV infection as an independent risk factor for thicker coronary artery walls. This analysis also pinpointed heavier cigarette smoking and higher LDL cholesterol (“bad cholesterol”) as independent predictors of thicker coronary artery walls.

The study linked longer time taking antiretrovirals to greater coronary artery wall thickness. This finding does not mean youngsters and young adults should avoid antiretroviral therapy to lower their risk of heart disease. The benefits of antiretroviral therapy far outweigh the potential heart disease risk possibly related to thicker coronary arteries. In this study the only individual antiretroviral linked to thicker coronary artery walls was stavudine, an old drug no longer prescribed in the United States.

Indeed, some studies have linked antiretroviral therapy to better heart health. For example, people who stopped antiretroviral therapy in a trial of treatment interruptions had more than a 50% higher risk of cardiovascular disease than people who never stopped their antiretrovirals. US antiretroviral guidelines for adults and adolescents stress that HIV control with antiretroviral therapy may decrease the inflammation and immune system cell activation that contribute to higher rates of cardiovascular disease in people with HIV.

Smoking and high LDL (“bad”) cholesterol also emerged as predictors of thicker coronary artery walls in this study. Both of these risk factors can be changed—smokers can stop smoking and people with high LDL cholesterol can lower their cholesterol through diet, exercise, or drug therapy, often with drugs called statins. (See the next two articles in this issue of *HIV Treatment Alerts* for findings on statin benefits in people with HIV.)

Abundant research links smoking to heart disease, lung cancer, other cancers, lung disease, and shorter life. Because HIV infection itself may raise the risk of heart disease, HIV-positive people should work hard to avoid or stop smoking. Quitting is not easy, but many long-time smokers do manage to stop. Your HIV provider can work with you to kick the smoking habit, perhaps by prescribing nicotine replacement therapy or other therapies, or perhaps through strategies like those described by the Centers for Disease Control and Prevention (visit the link at reference 8 below).

The researchers noted that their study is limited by its small size and by its snapshot design—it measured coronary artery walls and looked for plaque and heart fat at a single point in time. This kind of study cannot prove that HIV or smoking or high LDL cholesterol caused artery wall thickening in these young adults. But the findings do show possible links between these factors and coronary artery wall thickness. For this reason, people infected with HIV and treated for HIV from early in life should be aware that they may run a higher risk of heart disease than people without HIV. Therefore they
should work with their HIV provider to avoid or control heart disease risk factors throughout their life. **Table 1** lists heart disease risk factors that can be avoided or reversed.

**Table 1.** Heart disease risk factors that can be avoided or reversed

- Cigarette smoking
- Lack of physical activity
- Diet high in saturated fats, cholesterol, or salt
- Overweight or obesity
- Heavy alcohol drinking
- High blood pressure
- High cholesterol or triglycerides
- Diabetes


**References**

Article 7  
**Statin therapy reduces heart artery plaque size and number in people with HIV**

Treatment with atorvastatin, a drug aimed at lowering cholesterol, reduced coronary artery plaque* volume and number in HIV-positive people who took it for 1 year.1 Plaques are built-up fat and cholesterol deposits in arteries (Figure 1) that can eventually block the artery and cause myocardial infarction (heart attack). This is the first study comparing a statin to placebo (a dummy pill) that shows statin therapy can control plaque in people with HIV.

Heart disease, including coronary artery disease, has become a major cause of sickness and death in people with HIV infection. Recent studies show a higher rate of hidden atherosclerosis (plaque build-up) and potentially dangerous noncalcified plaque in people with HIV than in HIV-negative people.2-4 Finding ways to prevent and control coronary artery disease has become a priority in people with HIV.

In the general population, statins proved effective in lowering rates of cardiovascular disease5 and death. Research also shows that statins can slow or reverse coronary artery atherosclerosis.6-8 In studies of people with HIV infection, statins lowered cholesterol and triglyceride levels and reduced signals of inflammation. But no studies in HIV-positive people directly compared a statin with placebo to assess the impact of statins on coronary artery inflammation or plaque. Researchers in Boston conducted this study to address those questions.

- **How the study worked.** The research team recruited HIV-positive men and women between 18 and 60 years old who were not taking a statin and did not meet US guidelines for starting a statin. No one ever had cardiovascular disease, and no one had cardiovascular disease symptoms. All study participants did have evidence of symptom-free coronary artery atherosclerosis on coronary CT angiography, a type of scan. FDG-PET, another type of scan, indicated artery inflammation in all study participants.

Everyone had a low-density lipoprotein (“bad”) cholesterol level between 70 and 130 mg/dL (1.81 and 3.37 mmol/L), which are healthy levels. Everyone was taking antiretroviral therapy, and no one had changed antiretrovirals in the past 6 months.

The researchers randomly assigned 40 study participants to start atorvastatin or placebo (a dummy pill). No study participants or researchers knew which people were getting atorvastatin and which were getting placebo. This type of trial—a randomized, double-blind, placebo-controlled trial—is the strongest trial design for determining the impact of a treatment like statin therapy. People assigned to take atorvastatin started at a dose of 20 mg daily then increased the dose to 40 mg daily if they tolerated the drug well for the first 3 months. Participants took atorvastatin or placebo for 1 year.

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*Words in **bold** are defined in the Technical Word List at the end of this issue of *HIV Treatment Alerts.*
All study participants had an FDG-PET scan when the study began and after 1 year of atorvastatin or placebo to measure changes in inflammation of the aorta, the main artery coming out of the heart (Figure 1). Participants also had coronary CT angiography to assess changes in coronary artery plaque volume, number, and features. The researchers determined whether coronary artery plaques were calcified or noncalcified, because noncalcified plaques have a higher risk of rupture. They also determined whether plaques had other established high-risk features.

Changes in inflammation and plaque volume, number, and features were the main goals of the trial. The researchers used standard statistical methods to determine whether any of these changes differed significantly after 1 year in people taking atorvastatin compared with those taking placebo.

What the study found. The study ran from November 2009 to January 2014 at a single center in Boston. Researchers randomly assigned 21 people to take placebo and 19 to take atorvastatin. Thirty-two study participants (80%) were men, 26 (65%) were white, and 6 (15%) were black. Study participants averaged 51 years in age. They had an average CD4 count around 550, and everyone had an undetectable viral load or a very low viral load. The atorvastatin group and the placebo group were similar in age, gender, race, CD4 count, viral load, and other study-entry measures like cholesterol, hypertension, and signals of inflammation. The atorvastatin group and the placebo group did not differ in coronary artery inflammation or plaque volume; they did not differ in plaque danger signals.

During the study period, only two people dropped out of the atorvastatin group and one dropped out of the placebo group.

After 1 year of atorvastatin or placebo, average change in inflammation of the aorta measured by FDG-PET did not differ substantially between groups. Neither did average change in inflammation of the most diseased segment of the aorta. However, Lp-PLA, a marker of blood vessel inflammation, decreased significantly more after 1 year of atorvastatin than after 1 year of placebo.
A trial that randomly assigned HIV-positive people to a statin or placebo (a dummy pill) for 1 year found that the statin decreased total plaque volume in heart arteries and dangerous noncalcified plaque volume, while those volumes rose in people taking placebo. After 1 year people taking the statin had lower average numbers of low-attenuation plaques and positively remodeled plaques in heart arteries, while people taking placebo had higher numbers of those plaques.

Coronary CT angiography scans showed that average coronary plaque volume decreased in the atorvastatin group while increasing in the placebo group (Figure 2). This difference was statistically significant, meaning the difference cannot be explained by chance. Volume of dangerous noncalcified plaques decreased in the atorvastatin group while increasing in the placebo group, also a significant difference (Figure 2). The average number of two types of dangerous plaques (low-attenuation plaques and positively remodeled plaques) dropped among people taking atorvastatin while rising among those taking placebo (Figure 2), and these differences were also statistically significant.

Total plaque volume declined in 11 of 17 people taking atorvastatin for 1 year versus 4 of 20 taking placebo (65% versus 20%). Total plaque volume increased in 6 of 17 people taking atorvastatin and 16 of 20 taking placebo (35% versus 80%). These differences were statistically significant. Coronary arteries narrowed in a clinically meaningful way in 3 people taking placebo and none taking atorvastatin.

Total cholesterol and “bad” LDL cholesterol decreased significantly in people taking atorvastatin for 1 year while increasing slightly among people taking placebo. During the 1-year study period, changes in CD4 count, viral load, body mass index, or belly fat did not differ significantly between the atorvastatin group and the placebo group.

No study participants had treatment-related problems that forced them to drop out of the trial. Two people taking atorvastatin and 1 taking placebo had a serious adverse event during the study. Six people taking atorvastatin and 5 taking placebo had myalgia (muscle pain, a well-recognized statin side effect) during the study. One person in the atorvastatin group switched to a lower dose of atorvastatin because of myalgia, and 1 person in the placebo group switched to a lower dose because of a liver function test abnormality; both people completed the study. Atorvastatin did not cause blood sugar abnormalities in this study.
**What the results mean for you.** This well-planned trial produced strong evidence that 1 year of statin therapy can have a positive impact on coronary artery plaques and cholesterol in people with HIV. Plaque build-up and rising cholesterol can both lead to serious heart disease. Plaques shrank in two thirds of people taking atorvastatin for 1 year compared with only 1 in 5 people taking placebo, an inert pill made to look like atorvastatin. The results are strong because of the study design—having a comparison group taking placebo and not telling participants or providers who got atorvastatin and who got placebo.

The study did not find that atorvastatin lowered coronary artery inflammation measured by FDG-PET scans. But the researchers could measure inflammation changes in the same region of the aorta in only 21 people in this study. In contrast, they could measure plaque with coronary CT angiography in all 37 people who completed the study. Lp-PLA, a signal of blood vessel inflammation, did decrease significantly after 1 year of atorvastatin therapy.

Why are these findings important? Several studies show that people with HIV have higher rates of serious cardiovascular disease than people without HIV. Comparing almost 4000 HIV-positive people with 1 million HIV-negative people, the same Boston researchers who conducted the atorvastatin study found that HIV-positive men had a 40% higher heart attack rate than HIV-negative men, while HIV-positive women had a 3 times higher rate than HIV-negative women. A nationwide French study found remarkably similar results when comparing heart attack risk in people with and without HIV. Combined analysis of results from 20 individual studies figured that antiretroviral-treated people with HIV had a twice higher risk of cardiovascular disease than people in the general population.

The atorvastatin study suggests that statins could be one way to lower the risk of cardiovascular disease in people with HIV. Although participants had healthy LDL cholesterol levels when they entered this trial, they had atherosclerosis (plaque build-up) that had not started causing symptoms yet. Symptom-free atherosclerosis is not rare in people with HIV—more than half of the middle-aged HIV-positive adults screened for this trial had hidden atherosclerosis. Earlier study by the same researchers and by a British group also found high rates of hidden atherosclerosis in people with HIV.

US Health Resources and Services Administration 2014 guidelines for HIV care recommend statins as first-line therapy for HIV-positive people with (1) high LDL cholesterol alone or (2) high LDL cholesterol plus triglycerides between 200 and 500 mg/dL. Current general-population guidelines recommend statins for people over 20 years old with an LDL cholesterol at or above 190 mg/dL.

Researchers who ran this study cautioned that their findings do not prove that statins will prevent coronary heart disease, only that they have a positive impact on plaques and cholesterol. Larger, longer studies, they say, are needed to determine whether those positive effects translate into lower heart disease rates in people with HIV. But the Boston team believes evidence that atherosclerosis gets worse faster in people with HIV “suggests the need for more aggressive treatment with statins” in HIV-positive people.

Your HIV provider can explain whether statin therapy is right for you based on your cholesterol and triglyceride levels, your potential for responding to diet and exercise therapy, and the antiretrovirals you are taking. The next article in this issue of *HIV Treatment Alerts* describes a study that found improvements in hip bone density after 48 weeks of treatment with another statin, rosuvastatin.


HIV-positive people taking rosuvastatin for 48 weeks had significantly greater gains in bone mineral density than people taking placebo, according to results of a 150-person trial. Statins are used to treat high cholesterol in people with and without HIV, but this is the first comparative trial to show that statins have a positive impact on bone density in people with HIV.

HIV-positive people have higher rates of heart disease than people without HIV. Because statins lower “bad” low-density lipoprotein (LDL) cholesterol, they could help prevent heart disease in HIV-positive people. A recent study found that—besides lowering LDL cholesterol—a statin also cut the number and size of coronary artery plaques (fatty build-ups) in people with HIV (see the preceding article in this issue of HIV Treatment Alerts). That could be another way statins prevent heart disease in HIV-positive people.

Like heart disease, osteoporosis (low bone mineral density, Figure 1) has become more common in people with HIV as they grow older. Some studies of older people with HIV suggest that statins have a positive impact on bone mineral density and body composition, but research has not firmly established these benefits. To address those questions, US researchers planned a trial to compare daily rosuvastatin with placebo (a dummy pill) in HIV-positive adults.

How the study worked. The trial involved HIV-positive adults invited to join the study between March 2011 and August 2012. The researchers randomly assigned half of them to take 10 mg of rosuvastatin daily and half to take placebo, an inactive pill made to look like rosuvastatin. The prime use of rosuvastatin and all statins is to lower LDL cholesterol and thus prevent heart disease. Neither study participants nor study investigators knew which people got rosuvastatin and which got placebo. This is the strongest trial design for determining the impact of a treatment in a given group of people.

All study participants were at least 18 years old, were taking antiretroviral therapy for at least 6 months, and had a viral load below 1000 copies. Everyone had a “bad” LDL cholesterol at or below 130 mg/dL, which is a healthy LDL level. Everyone also had certain signals of inflammation or immune-cell activation.

No one had an active or ongoing inflammatory condition (except HIV infection), and no one had an earlier fracture suggesting low bone mineral density or an earlier heart attack. No one was taking bone therapy drugs, cancer chemotherapy, steroids, or more than 81 mg of aspirin daily (the low dose taken to prevent heart disease).

Healthy bone and osteoporosis

Healthy bone and osteoporosis

Figure 1. People with HIV infection may have several risk factors for severe loss of bone mineral density—osteoporosis. (Illustrations from Servier 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.*
When people entered the study and 48 weeks later, they had a DXA scan of their whole body, their lower spine, and their left hip. Researchers used initial DXA findings to see who had osteopenia (low bone density) or osteoporosis (very low bone density) and to measure limb fat, trunk fat, and lean mass. The researchers defined lean mass as DXA-measured mass not including fat or bone. They also measured blood markers of inflammation and immune-cell activation.

The main goals were to measure changes in bone mineral density, fat, and lean mass from study entry to week 48 and to compare changes in people taking rosuvastatin and people taking placebo. The research team used accepted statistical methods to make these comparisons.

This analysis of changes in bone mineral density, fat, and lean mass after 48 weeks was a planned part of the SATURN-HIV trial, which is also testing the impact of rosuvastatin on cholesterol, inflammation, and activation of immune system cells.4-7

■ What the study found. The researchers randomly assigned 72 people to take rosuvastatin and 75 to take placebo. The study group had a median age of 47 years, about three quarters were men, and about 70% were black. When the study began, median CD4 count stood at 613, and 78% of participants had an undetectable viral load. Almost one quarter of participants had osteopenia or osteoporosis when the study started.

After 48 weeks of treatment, average hip bone mineral density rose 0.6% in people taking rosuvastatin and fell 0.6% in people taking placebo (Figure 2). The difference between groups was statistically significant, meaning chance cannot explain the difference. At the trochanter (the top of the thigh bone), average bone mineral density rose 0.9% in the rosuvastatin group and fell 0.7% in the placebo group (Figure 2). This difference between rosuvastatin and placebo was also statistically significant. Average bone mineral density in the lower spine changed little through 48 weeks in either group.

The researchers then performed a statistical analysis that assessed the potential impact of age, race, sex, and smoking on hip bone mineral density. (Older age, white rate, female sex, and smoking can contribute to lower bone density.) In this analysis, the estimated average difference in hip bone mineral density between the rosuvastatin group and the placebo group was almost 1% (0.92%).

![Figure 2. In a trial that randomly assigned HIV-positive adults to take rosuvastatin or placebo (a dummy pill), people taking rosuvastatin for 48 weeks gained bone mineral density in the total hip and trochanter, while people taking placebo lost bone mineral density at these sites. (Bone illustration from Servier PowerPoint image bank, http://servier.com/Powerpoint-image-bank.)](http://servier.com/Powerpoint-image-bank)
Leg lean mass increased significantly by 1.5% in the rosuvastatin group, and there was a trend toward increased total lean mass with rosuvastatin (+0.8%). Changes in total, leg, or arm lean mass did not differ significantly between people taking rosuvastatin and people taking placebo. Total body fat, trunk fat, and limb fat did not change significantly during 48 weeks of treatment with rosuvastatin. And fat changes did not differ significantly between people taking rosuvastatin and people taking placebo.

- **What the results mean for you.** This well-planned trial of rosuvastatin versus placebo in people with HIV found that 48 weeks of statin therapy increased hip and trochanter bone mineral density, while bone density fell at those sites in HIV-positive people taking placebo (a dummy pill). Clinicians prescribe statins to lower dangerously high cholesterol. The relatively small gains in bone mineral density seen with rosuvastatin in this trial do not support use of statins for bone health alone. But the study suggests that HIV-positive people taking a statin to lower cholesterol could get the added benefit of small gains in bone mineral density—which is better than the continuing loss of bone density seen among people not taking statin.

The trial also showed that people taking rosuvastatin for 48 weeks gained total lean mass and leg lean mass. Fat mass also increased slightly but not significantly in people taking rosuvastatin. These findings suggest that statins may contribute to improved body composition in people with HIV.

Falling bone mineral density is a well-recognized problem in people with HIV infection. Bone density drops with age, and people responding well to antiretroviral therapy are now living as long or almost as long as people in the general population. HIV-positive people also have high rates of other risk factors for osteopenia and osteoporosis:

- Smoking
- Hepatitis C virus infection
- Low weight
- Physical inactivity
- Diet low in calcium

People with low bone density run a higher risk of fractures (broken bones), and several studies of HIV groups found higher fracture rates in people with HIV than in those without HIV. Therefore, finding ways to slow or reverse bone loss has become a priority in people with HIV. Combined analysis of eight studies in the general population found that statins protect against fractures. But statins did not lower fracture rates in a separate study of people with HIV or in a placebo-controlled trial including almost 18,000 men over 50 and women over 60 in the general population. The researchers who conducted the rosuvastatin study observed that larger and longer studies are needed to tell whether statin therapy helps people with HIV avoid fractures.

Statins can cause muscle pain in a few people. One person in this study stopped rosuvastatin because of muscle pain that required hospital admission; 2 people assigned to placebo dropped out of the study because of muscle pain.

US HIV care guidelines recommend statin therapy for HIV-positive adults with (1) high LDL cholesterol (at or above 190 mg/dL) or (2) high LDL cholesterol plus triglycerides between 200 and 500 mg/dL. Guidelines for bone health in people with HIV say providers should use FRAX (without DXA) to assess fracture risk in (1) all HIV-positive men 40 to 49 years old, and (2) all HIV-positive premenopausal women at least 40 years old. These guidelines recommend DXA scans for HIV-positive men 50 and older, postmenopausal women, people who have had a fragility fracture, people taking glucocorticoids (steroid hormones), and people with a high risk of falls.

**Statins are used to treat high cholesterol in people with and without HIV, but this is the first comparative trial to show that statins have a positive impact on bone density in people with HIV.**
A 6-year study of 3672 US adults with HIV infection linked missing three or more HIV clinic appointments to more than a tripled the risk of death from any cause. Two other methods of determining steady clinic attendance found a link between poor attendance and more than a doubled risk of death from any cause.

In recent years HIV researchers have begun to study the impact of steady HIV care on response to antiretroviral therapy and survival. For a person with HIV, the continuing interaction with healthcare professionals involves getting diagnosed with HIV infection, starting care for HIV, staying in care, starting antiretroviral therapy, and reaching an undetectable viral load. Of the 1.2 million HIV-positive people in the United States, the Centers for Disease Control and Prevention (CDC) estimates that only 25% are in care, started antiretroviral therapy, and reached an undetectable viral load. Other research shows that staying in care and keeping the viral load undetectable lowers chances of illness, death, and passing HIV to a sex partner.

To underline the importance of getting into care for HIV infection and staying in care, the US Department of Health and Human Services (DHHS) and the Institute of Medicine spelled out standards for HIV-positive people staying in care. Both of these sets of standards focus on the number of visits a person attends in a certain period. Researchers who conducted this new study wondered if measuring the number of scheduled appointments a person misses may also predict how well that person does in care and even how long that person lives.

To evaluate these two methods of measuring staying in care—visits made and visits missed—these researchers studied more than 3600 HIV-positive people starting antiretroviral therapy.

**How the study worked.** This analysis involved HIV-positive people in care at five US clinics that are part of a larger HIV study group, the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS). Every 3 months workers at the clinics send findings on the care and health of individual patients to a central database that collects this information for the whole CNICS network.

This study focused on people starting their first antiretroviral combination at one of the five CNICS clinics at any time from January 2000 through July 2010. All study participants were alive 24 months after starting antiretroviral therapy. From that 24-month point, the researchers used national health records to determine how many people died of any cause.

The research team used three methods to measure HIV care appointment keeping through 24 months by study participants (Table 1). Missed visits were those the patient or the provider did not cancel in advance.

**Table 1.** Three methods of measuring appointment keeping by people with HIV

<table>
<thead>
<tr>
<th>Method</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institute of Medicine</td>
<td>Two kept visits at least 90 days apart in a 12-month period. For this study, the researchers recorded kept visits over two consecutive 12-month periods.</td>
</tr>
<tr>
<td>Department of Health and Human Services (DHHS)</td>
<td>At least one kept visit in each 6-month period over a 24-month period, with at least 60 days between visits in each 6-month period.</td>
</tr>
<tr>
<td>Missed-visit definition</td>
<td>Missed visits over a 24-month period, grouped as 0 missed visits, 1 to 2 missed visits, or more than 2 missed visits.</td>
</tr>
</tbody>
</table>

*Words in **bold** are defined in the Technical Word List at the end of this issue of *HIV Treatment Alerts.*
Then the researchers used standard statistical methods to determine how the three measures of appointment keeping over 24 months affected the risk of death after that 24-month period. They performed a separate statistical analysis to see how the third definition—missed visits—affected risk of death in people classified by the first two methods as good appointment keepers. These statistical analyses considered the impact of other factors that might affect appointment keeping (age, race, sex, and initial viral load and CD4 count). As a result these analyses can determine how the three methods of appointment keeping affected risk of death regardless of whatever other risk factors a person had.

What the study found. The researchers assessed 3672 people, 2952 (80%) of them men, 1950 (53%) white, 1377 (38%) black, and the rest of other or unknown ethnic backgrounds. Age averaged 38 years, and CD4 count averaged 220 before people started antiretroviral therapy. Everyone was in care at one of five clinics in Birmingham, Alabama, Chapel Hill, North Carolina, Cleveland, San Diego, or Seattle.

Proportions of people who kept HIV care appointments were 64% by the Institute of Medicine definition and 59% by the DHHS definition (Figure 1). Similar proportions of study participants missed 0 visits (32%), 1 to 2 visits (39%), or more than 2 visits (29%). Study participants missed an average 2.1 visits.

Median observation time from when people started antiretroviral therapy was 6 years. From a point starting 24 months after antiretroviral therapy began, 332 people (9%) died to yield a death rate of 20.6 deaths per 1000 person-years (meaning about 20 of 1000 people died every year).

Death rates were lower in people who kept appointments by the Institute of Medicine definition (16.0 per 1000 person-years) or by the DHHS definition (15.3 per 1000). The death rate was even lower in people who missed no clinic appointments (11.5 per 1000). In contrast, death rates were higher in people who missed visits by the Institute of Medicine definition (29.5 per 1000) or by the DHHS definition (29.0 per 1000) and in people who missed 1 or 2 visits (20.4 per 1000) or more than 2 visits (30.9 per 1000).

Compared with people who met the Institute of Medicine definition for keeping HIV care appointments, those who did not had more than a doubled risk of death (Figure 2). Compared with those who met the DHHS definition for keeping appointments, those who did not also had more than a doubled risk of death (Figure 2). Compared with people who missed no visits, those who missed 1 or 2 had a doubled risk of death, and those who missed more than 2 had a tripled risk of death (Figure 2).

Figure 1. About 60% of adults kept clinic appointments in the 24 months after starting antiretroviral therapy, according to definitions by the Institute of Medicine (IOM) and the US Department of Health and Human Services (DHHS). (See Table 1 for definitions.) Similar proportions (about one third) missed 0 visits, 1 or 2 visits, or more than 2 visits in the 24 months after starting antiretrovirals.
Compared with whites, blacks had about a 50% higher risk of death after taking antiretrovirals for 2 years. Compared with people who started antiretroviral therapy with a CD4 count above 500, those who started with a count below 50 had more than a doubled risk of death after taking antiretrovirals for 2 years. Every 10 years of age raised the death risk about 50%. Death risk was similar in women and men.

Among people who met the Institute of Medicine definition or the DHHS definition of keeping HIV care appointments, about two thirds did miss at least 1 visit and one quarter missed more than 2 visits. Next the researchers conducted statistical analyses limited to people who met the Institute of Medicine and DHHS definitions for keeping appointments. Those who nevertheless missed 1 or 2 visits had about a 1.7 times higher death risk after the first 2 years of antiretroviral therapy. Those who missed more than 2 visits had a 3.6 times higher death risk after the first 2 years of antiretroviral therapy.

What the results mean for you. This study of almost 3700 people with HIV across the United States found strong evidence that missing HIV care appointments may be linked to a higher risk of death. The researchers measured appointment keeping in three ways. Missing visits during the first 24 months of antiretroviral therapy by each of those ways doubled or tripled the risk of death from a point starting 24 months after therapy began.

Once a person tests positive for HIV and begins care, keeping appointments regularly is the next crucial step to returning to health. Another study reviewed on page 45 of this issue of HIV Treatment Alerts found that missing appointments lowered chances of starting antiretrovirals and reaching an undetectable viral load. And the next study reviewed in this issue found that about three quarters of people who made two or more clinic visits at least 3 months apart had an undetectable viral load. People who keep their HIV care appointments have the best chance of getting all the benefits of care—starting antiretroviral therapy, reaching an undetectable viral load, gaining CD4 cells, and getting help avoiding or controlling the serious diseases that threaten people with HIV infection.

The definitions of appointment keeping developed by the Institute of Medicine and the US Department of Health and Human Services (DHHS) (Table 1) both predicted death in this study group. But the researchers found that some people counted as being in care by these definitions did miss one or more visits. Simply counting
missed visits—those not cancelled beforehand by the patient or provider—was the strongest predictor of death after the first 24 months of antiretroviral therapy.

HIV care experts in the United States developed guidelines to help HIV providers get HIV-positive people into care, stay in care, and take their antiretrovirals as scheduled.10 If you have trouble keeping medical appointments—for any reason—you should talk to your provider to plan ways to improve appointment keeping. Your provider may put you in touch with a case worker who can help you address problems that make appointment keeping tough.11 Some medical offices have community-based “patient navigators” who help HIV-positive people manage many complicated aspects of health care.12

Some problems that cause people to miss medical visits may be easy to solve. Other problems may have deep roots that are hard to get at. But people with HIV should find help addressing these problems. And your HIV provider or other professionals in the HIV care office can get you the help you need.

References

About three quarters of HIV-positive people who made two or more clinic visits at least 3 months apart in 2010 had an undetectable viral load* in a 339,000-person US study. Only about half of HIV-positive people who made fewer clinic visits had an undetectable viral load. This difference in rates of HIV control held true regardless of age, sex (male or female), race or ethnicity, or route of HIV infection.

Someone who has a positive HIV test should promptly begin care with an HIV provider, should make regular visits scheduled by the provider, and should start antiretroviral therapy. The main goal of antiretroviral therapy is to reach an undetectable viral load and to keep the viral load undetectable through steady treatment. Reaching and maintaining an undetectable viral load are the keys to regaining health and to avoiding passing HIV to sex partners.

Research by the Centers for Disease Control and Prevention (CDC) shows that many people diagnosed with HIV infection in the United States do not make regular visits to their HIV provider. A study of 338,959 HIV-positive people found that only half made at least two clinic visits at least 3 months apart in 2010. Of these 338,959 people with HIV, only 43% had an undetectable viral load. Among people who had at least one CD4 count or viral load test in that year, 69% had an undetectable viral load.

To get a better understanding of how making regular HIV clinic visits affects chances of reaching an undetectable viral load, CDC researchers conducted a new analysis of findings on these 338,959 people with HIV. This new study aimed to determine the impact of keeping clinic visits on viral load in the entire study group, in men and women, and in subgroups of different ages, races and ethnic groups, and routes of HIV infection.

How the study worked. CDC researchers used data on HIV-positive people collected by the National HIV Surveillance System through December 2012. These data came from 18 states and Washington, DC. All 19 areas report CD4 count and viral load results to city or state health departments.

The researchers used reports of CD4 counts and viral loads to determine how many people diagnosed with HIV were in care during the study period. All these people were 15 years old or older at the end of 2009. The CDC team considered three definitions of HIV care:

- **Engaged in care** meant having at least one CD4 count or viral load test during 2010
- **Retained in continuous care** meant having at least two CD4 counts or viral load tests done at least 3 months apart during 2010
- **Retained in care according to the US Health and Human Services (HHS) definition** meant having at least one CD4 count or viral load test in each 6-month period of a 24-month period, with at least 60 days between tests in two 6-month periods

The main goal of the study was to see how many people in each of these three care groups had an undetectable viral load, defined as a viral load of 200 copies or less on the most recent viral load test. The CDC investigators used standard statistical methods to analyze differences in undetectable viral load rates according to the different care definitions. They also analyzed undetectable viral load rates in various subgroups according to age, sex, race or ethnicity, and route of HIV infection (sex between men, sex between men and women, and injecting drugs).

What the study found. The first analysis involved 338,959 people diagnosed with HIV by the end of 2009 and alive at the end of 2010. Three quarters of this group were male and one quarter female. Nearly half of the group (45%) was black, 30% were white, 21% were Hispanic, and the rest had other racial backgrounds. Most of the group (51%) got infected during sex between men, while 24% got infected during sex between
men and women and 18% got infected while injecting drugs. Another 6% were gay or bisexual men who injected drugs.

Of the 338,959 HIV-positive people, 63% had any care in 2010 (at least one CD4 count or viral load test). Of these 214,734 people in care, 20% were considered engaged in care (at least one CD4 count or viral load test in 2010) and 80% were considered retained in continuous care (at least two CD4 counts or viral load tests at least 3 months apart in 2010). Proportions of people engaged in care and retained in care did not differ by sex, race or ethnicity, or HIV infection route. Compared with the overall group, a lower proportion of people 13 to 34 years old were retained in care (76%) and higher proportion of people 55 or older were retained in care (84%).

Slightly fewer than half of people engaged in care—48%—had an undetectable viral load in 2010, compared with 74% of people retained in continuous care (Figure 1). This sharp difference in proportions with an undetectable viral load held true for both males and females (Figure 1), for all five age groups considered (Figure 2), for all racial and ethnic groups (Figure 3), and for each HIV risk group (Figure 4).

In both the engaged in care group and the retained in continuous care group, proportions with an undetectable viral load climbed steadily from the youngest age group through the oldest group (Figure 2). But even the best viral load results in the engaged group (53.5% and 58.0% in the two oldest groups) did not measure up to the worst viral load results in the retained group (53.4% and 65.4% in the two youngest groups) (Figure 2).

In both the engaged group and the retained group, (1) males had better viral load results than females (Figure 1), (2) whites had better results than Hispanics and Hispanics had better results than blacks (Figure 3), and (3) gay/bisexual men had better results than other HIV risk groups (Figure 4).

The CDC investigators also assessed 173,870 people who (1) were diagnosed with HIV by the end of 2008, (2) made a clinic visit in the first half of 2009, and (3) were alive at the end of 2010. The aim was to see how many met the US Department of Health and Human Services (HHS) definition of retained in care (at least one CD4 count or viral load test in each 6-month period of a 24-month period, with at least 60 days between tests in two 6-month periods). Of those 173,870 individuals, 119,510 (69%) met the retained HHS definition.

![Undetectable viral load rates in 214,734 US residents with HIV](image)

**Figure 1.** A US study of 214,734 people diagnosed with HIV infection found lower rates of reaching an undetectable viral load in those engaged in care (at least one CD4 count or viral load test in 2010) than in those retained in continuous care (at least two CD4 counts or viral load tests done at least 3 months apart during 2010).
Figure 2. Regardless of age, HIV-positive people in 19 US regions who had evidence of more clinic visits (retained in care) proved more likely to reach an undetectable viral load than people with evidence of fewer visits (engaged in care). In both the retained group and the engaged group, undetectable viral load rates rose steadily with age.

Figure 3. Regardless of race or ethnic origin, people with HIV in a large US group reached an undetectable viral load more often if they kept more clinic visits (retained in care) than if they kept fewer (engaged in care). Undetectable viral load rates were lower in blacks than in other groups studied. This chart does not include findings on three other groups, American Indians/Alaska Natives, Native Hawaiian/other Pacific Islander, and multiple races. In all these groups, HIV control rates were higher among those retained in care.
Among these 119,510 people retained in care, 78% had an undetectable viral load (at or below 200 copies). Women had lower undetectable viral load rates than men (74% versus 80%). Again, the oldest age group, 55 and older, had the best undetectable viral load rate (85%), followed by 80% for 45-to-54-year-olds, 76% for 35-to-44-year-olds, 72% for 25-to-34-year-olds, and 59% for 13-to-24-year-olds. Asians had higher undetectable viral load rates than whites (90% versus 86%), followed by Hispanics (79%) and blacks (72%).

What the results mean for you. The key message of this large and thorough CDC study is that HIV-positive people who keep regular appointments with their providers are more likely to have an undetectable viral load than people who do not keep as many appointments.

This finding is not surprising. People who keep more appointments are often more concerned about their health and more organized, so they are more likely to start antiretroviral therapy and to take their antiretrovirals regularly—giving them the best chance to reach an undetectable viral load. Also, people who keep more clinic appointments get more support from their provider and other health professionals, who can help solve problems and relieve side effects that may arise during therapy.

What is surprising about this study is the big gap between rates of undetectable viral load in people retained in care by either study definition (74% or 78%) and the rate in people only engaged in care (48%). Reaching an undetectable viral load should be the main goal of everyone with HIV infection—because it will improve their own health and lower their chance of passing HIV to a sex partner. When only half of any HIV group has an undetectable viral load, the other half still has lots of work to do.

Just as striking was the finding that only two thirds of people diagnosed with HIV in these 18 states and Washington, DC had evidence of any HIV care (a CD4 count or viral load test) in 2010. The CDC investigators stress that this proportion of people in care “is far too low.”

The researchers also underline the findings that younger people (13 to 34 years old) and blacks had particularly low rates of achieving an undetectable viral load. Compared with people 55 or older, 13-to-24-year-olds had a 64% lower undetectable viral load rate, and 25-to-34-year-olds had a 40% lower rate. Compared with whites, blacks had a 37% lower undetectable viral load rate. These findings emphasize the need for all HIV-positive people—young and old, whatever their ethnic origin—
to get care, to keep clinic appointments, and to start and stick with antiretroviral therapy.

Results of this large study reflect recent findings in another CDC analysis. This previous study determined that starting care within 3 months of HIV diagnosis and making more clinic visits resulted in a faster time to reaching an undetectable viral load.\(^3\) The study reviewed just before this one in *HIV Treatment Alerts* linked missing three or more HIV clinic appointments to more than a tripled the risk of death from any cause.\(^4\)

An important limitation of the new study is that the CDC researchers did not have information on how many people were taking antiretroviral therapy or how faithfully they took their pills. So they could not consider the impact of pill-taking habits on how many people reached an undetectable viral load. Once a person starts antiretroviral therapy, taking all pills regularly is essential to controlling HIV.

### References

   [http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0084318](http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0084318)
Only one third of HIV+ young people in care have undetectable viral load

Only about one third of 2200 HIV-positive youth and young adults in care in the United States have an undetectable viral load, according to results of a 2009-2012 study.\(^1\) Consistent HIV care and more education were among the factors that raised chances of having an undetectable viral load.

Teens and young adults 13 to 24 years old made up 26% of new HIV infections in the United States in 2010.\(^2\) Detecting HIV infection early and starting antiretroviral therapy\(^*\) can prevent new infections because an HIV-positive person with an undetectable viral load has a much lower chance of passing HIV to a sex partner. Starting antiretroviral therapy and reaching an undetectable viral load are also essential steps in returning to health and ensuring a long and productive life.

Young people with HIV infection face several obstacles to reaching and keeping an undetectable viral load. Some research shows that low proportions of youth in care for HIV infection begin antiretroviral therapy, while other work indicates that younger people are less likely to achieve an undetectable viral load than older people. Recent research by the Centers for Disease Control and Prevention (CDC) found that young African Americans have the lowest undetectable viral load rate of any group studied, 18%.\(^3\)

Understanding how many teens and young adults enter care, start antiretroviral therapy, and reach an undetectable viral load is essential to planning care for this growing group of HIV-positive people. Understanding which factors favor reaching an undetectable viral load can help more youngsters and young adults achieve that target. With those goals in mind, researchers conducted the study described here.

**How the study worked.** From December 2009 to June 2012, researchers invited HIV-positive people from 12 to 26 years old to enter the study. All invited participants were in care at one of 20 clinics of the Adolescent Medicine Trials Network for HIV/AIDS Interventions across the United States and Puerto Rico. All participants had to be aware of their HIV infection and receiving care at one of the 20 clinics. The researchers classified each participant as either *perinatally* infected (infected with HIV in the womb or around the time of birth and called the “birth group” in this article) or *behaviorally* infected (infected with HIV through sex or drug use and called the “behavior group” in this article) (Table 1).

Table 1. Researchers divided study participants into two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>A birth group</strong></td>
<td>649 perinatally infected youth infected with HIV in the womb or around the time of birth</td>
</tr>
<tr>
<td><strong>A behavior group</strong></td>
<td>1547 behaviorally infected youth who got HIV during sex or when injecting drugs</td>
</tr>
</tbody>
</table>

All participants completed an extensive computer-assisted survey that covered (1) basic personal information (like age, gender, sexual orientation, and race or ethnic origin), (2) substance use, (3) mental health, (4) sexual behavior, and (5) adherence to antiretroviral therapy (taking all antiretroviral drugs as scheduled).

The researchers also determined whether each person was taking antiretroviral therapy and had an undetectable viral load at least 6 months after starting antiretroviral therapy. They classified a person as eligible for antiretroviral therapy if that person had a CD4 count at or below 500, which was the recommended CD4 starting level when this study was done. (Now US guidelines recommend antiretroviral therapy for everyone with HIV infection, whatever their CD4 count.)

The researchers used accepted statistical methods to identify factors linked to (1) taking antiretroviral therapy and (2) having an undetectable viral load. This type

*Words in **bold** are defined in the Technical Word List at the end of this issue of *HIV Treatment Alerts*.}
of analysis singles out individual factors that affect those two outcomes regardless of other factors (such as race, ethnic origin, and gender) that might affect the two outcomes.

**What the study found.** The study involved 649 youth infected at birth (the “birth group”) and 1547 infected via sex or drugs (the “behavior group”) (Table 1). Age averaged 17.9 in the birth group and 21.2 in the behavior group. Boys and men made up 44% of the birth group, while girls and women made up 55%. Proportions of boys/men and girls/women in the behavior group were 76% and 24%. Two thirds of both the birth group and the behavior group were black, about 12% were white, and the rest were mixed-race or Asian. Hispanics made up 20% of each group. Heterosexuals made up 88% of the birth group, while gays, lesbians, and bisexuals made up 11%. Heterosexuals made up 27% of the behavior group, while gays, lesbians, and bisexuals made up 69%.

A standard substance use survey classified 16% in the birth group and 43% in the behavior group as substance users. Proportions of people who had any sex without condoms were 14% in the birth group and 37% in the behavior group. Proportions who had condom-free sex with an HIV-negative partner or a partner with an unknown HIV status were 12% and 26%.

A large majority of the birth group—92%—had been diagnosed with HIV for 25 months or more, compared with 40% of the behavior group. Most people in the birth group—82%—were taking antiretroviral therapy, compared with 49% of the behavior group (Figure 1). More than half of the group not taking antiretrovirals, 56%, had a CD4 count at or below 500. A CD4 count at or below 500 meant they should be taking antiretrovirals, according to treatment guidelines in effect at the time of this study. More than a quarter of this untreated group, 28%, had a CD4 count at or below 350.

Proportions of study participants with an undetectable viral load were 37% in the birth group and 27% in the behavior group (Figure 1). Most people in both groups (85% or more) had taken their antiretrovirals for the past 7 days. The birth group missed an average 1.5 medical appointments in the past 12 months, while the behavior group missed an average 1.7.

People in the birth group who had been diagnosed with HIV 11 or more years earlier were 62% more likely to be taking antiretroviral therapy than people diagnosed more recently. Among youth in the behavior group, those who tested positive for HIV in the past 12 months were 70% less likely to be taking antiretrovirals than those with a longer time since their positive HIV test. People in the behavior group diagnosed with HIV for 5 or more years were 53% more likely to be taking antiretrovirals than people diagnosed more recently.

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**Figure 1.** A study of 2196 young people infected with HIV around the time of birth (Birth group) or later in life (Behavior group) found that only 59% were taking combination antiretroviral therapy (ART) and only 30% had an undetectable viral load. These rates were higher in the birth group than in the behavior group.
Statistical analysis that considered several factors at the same time singled out many factors individually linked to higher or lower chances of antiretroviral use in the birth group and the behavior group (Figure 2) and to higher or lower chances of an undetectable viral load in the two groups (Figure 3). Missing medical appointments lowered chances of antiretroviral use in the birth group and lowered chances of an undetectable viral load in both groups. In the behavior group, three factors were linked to higher chances of antiretroviral use: older age, completing high school, and employment.

In both the birth group and the behavior group, taking antiretroviral therapy for 6 or more months and taking antiretrovirals on time at least 90% of the time were tied to higher chances of an undetectable viral load. Completing high school was tied to doubled chances of an undetectable viral load in the behavior group.

Finally, the researchers found that almost one third of these young people had sex without condoms in the past 3 months. Three quarters of study participants who had sex without condoms had a detectable viral load, meaning they had a chance of passing HIV to their sex partner. And

![Factors linked to chances of antiretroviral use](image)

![Factors linked to undetectable viral load](image)

**Figure 2.** Seven factors predicted lower or higher chances of taking antiretroviral therapy in young people infected in the womb or around the time of birth (Birth group) or later in life, usually through sex (Behavior group).

**Figure 3.** In a study of young people in care for HIV infection, four factors predicted lower chances of having an undetectable viral load, while five factors predicted higher chances. Participants were infected with HIV in the womb or around the time of birth (Birth group) or later in life (Behavior group). ART, antiretroviral therapy.
three quarters of this group had condom-free sex with an HIV-negative partner or did not know if their partner had HIV.

**What the results mean for you.** This study of almost 2200 HIV-positive youngsters and young adults in the United States found that fewer than two thirds of them (59%) were taking antiretroviral therapy at the time of this study and fewer than one third (30%) had an undetectable viral load. Antiretroviral treatment guidelines in the United States recommend antiretroviral therapy for all teens and adults with HIV infection, whatever their CD4 count. And the goal of treatment for everyone is an undetectable viral load. This study shows how far young people across the United States are from reaching those goals.

Many reasons may lie behind the low antiretroviral treatment rate in these teens and young adults. They may not be able to afford antiretrovirals, or they may feel taking antiretrovirals will show others they have HIV. At the same time, their HIV providers may feel some of these people are not emotionally ready to make the commitment needed to begin and stick with antiretroviral therapy. With current antiretrovirals, once treatment starts, it must continue for life.

But some findings in this study indicate that young people can continue taking their antiretrovirals year after year. The researchers divided study participants into 649 people infected in the womb or around the time of birth (the birth group) and 1547 infected later in life, usually through sex (the behavior group). A much higher proportion in the birth group than the behavior group was taking antiretroviral therapy at the time of this study (82% versus 49%). Three quarters of them had taken antiretroviral therapy more than 6 months, and 85% of them took their antiretrovirals regularly over the last 7 days. On the other hand, only 58% of the birth group took their antiretrovirals on time at least 90% of the time, and only 63% of the behavior group did so.

Taking all antiretrovirals in your treatment combination on time every day is the surest way to reach and maintain an undetectable viral load and to avoid AIDS illnesses. Never stop any of your antiretrovirals unless your HIV provider tells you to. If you think your antiretrovirals are causing side effects, contact your provider right away. Side effects sometimes go away after a short time. Side effects that persist can often be relieved by changing the drug dose or by switching to another drug. In this study people who took their antiretrovirals at least 90% of the time had almost doubled chances of having an undetectable viral load.

Keeping all HIV care visits is also very important in reaching and maintaining an undetectable viral load. In this study young people missed an average of more than one visit in the past 12 months. Missing one or more visits in this study cut in half a person’s chances of having an undetectable viral load.

Another important study finding is the high rate of sex without condoms by these young people. Almost one third of the whole group said they had condom-free sex. And almost 75% of young people with a detectable viral load had condom-free sex with an HIV-negative partner or did not know if their sex partner had HIV. Using a condom during sex usually prevents the HIV-positive partner from passing HIV to the negative partner. At the same time, condoms can protect both partners from other serious sexually transmitted infections, like herpes, hepatitis viruses, and cancer-causing human papillomavirus.

**References**


HIV therapy not linked to more risky sex or sexual infections

Taking antiretroviral therapy* did not lead people to have more condom-free sex, to pick up more sexually transmitted infections (STIs), or to practice unsafe drug-injecting behavior, according to results of a 58-study analysis.\(^1\) In fact, people taking antiretrovirals proved less likely to have risky sex and possibly less likely to pick up STIs than HIV-positive people not taking antiretroviral therapy.

Antiretroviral therapy usually restores the health of HIV-positive people. And because therapy lowers viral load—typically to an undetectable levels—it also cuts the risk that treated people will pass HIV to sex partners. Because people feel better after treatment begins and often understand that they have a reduced chance of passing HIV to partners, there is concern that they will resume having sex without condoms or return to risky needle-sharing practices. Countries where people have easy access to antiretroviral therapy have reported increases in new HIV infections,\(^2\,3\) sex without condoms,\(^4\,5\) and STIs.\(^6\,7\)

Previous analyses of 16 studies\(^8\) and three studies\(^9\) found no evidence that antiretroviral use increased rates of sex without condoms. But these analyses are 8 to 10 years old, they did not address drug-injecting behavior, and they had other limitations. Researchers in Australia conducted a new study of research addressing not only sex without condoms, but also STI rates and unsafe injecting behavior, comparing people taking antiretrovirals with HIV-positive people not taking antiretrovirals.

**How the study worked.** The investigators searched electronic databases for studies that appeared through April 1, 2012 and compared HIV-positive people taking antiretroviral therapy with HIV-positive people not taking antiretrovirals. The investigators compared the treated and untreated people for three outcomes (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Three outcomes in a comparison of treated and untreated HIV-positive people</th>
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<tbody>
<tr>
<td><strong>Proportion of anal or vaginal sex acts without a condom</strong></td>
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<tr>
<td><strong>New sexually transmitted infection (STI), including chlamydia, gonorrhea, and early syphilis</strong></td>
</tr>
<tr>
<td><strong>Proportion of unsafe drug-injecting behaviors—lending, borrowing, or reusing any needle, syringe, or injecting equipment</strong></td>
</tr>
</tbody>
</table>

Within past 6 months

(Drawings of bacterium and syringe 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.*
Reviewers read each article that addressed these issues to determine whether it could be included in their analysis and—if it could—to record findings of interest. The reviewers also evaluated each selected study for potential biases that could affect study results.

The researchers combined results of studies that evaluated each of the three outcomes listed in Table 1. Then they used accepted statistical methods to determine whether taking antiretroviral therapy increased, decreased, or had no impact on chances of the three outcome behaviors. When possible, these analyses tried to account for the impact of other factors that may affect sexual or drug-taking outcomes, such as gender, sex practices, casual versus regular partners, and viral load.

What the study found. The researchers found 58 studies involving 52,278 people that addressed the three target behavioral outcomes listed in Table 1. The studies included findings collected between 1992 and 2011. Forty studies (69%) were done in high-income countries, including 24 in the United States. The remaining 18 studies were done in low- and middle-income countries.

Fifty-six of the 58 studies involving 32,857 people evaluated rates of sex without condoms. Twenty-one studies found that people taking antiretrovirals had a lower chance of reporting condom-free sex than people not taking antiretrovirals. Thirty-two studies found no clear difference in condom-free sex between people taking and not taking antiretrovirals. Only 3 studies linked antiretroviral therapy to a greater chance of sex without condoms.

Analysis of the combined data from all 56 studies determined that people taking antiretroviral therapy had a 27% lower chance of reporting condom-free sex than people not taking antiretrovirals (Figure 1). Gender, sex practices, or geographic location did not affect the impact of antiretroviral therapy on condom-free sex. In 38 studies in high-income countries (such as the United States), people taking antiretroviral therapy had a 15% lower chance of sex without condoms. In 18 studies in low- and middle-income countries, antiretroviral-treated people had a 43% lower chance of sex without condoms.

![Antiretroviral therapy impact on chances of condom-free sex](image)

**Figure 1.** Combined analysis of 56 studies determined that, compared with people not taking antiretroviral therapy, those taking antiretrovirals had 27% lower chances of reporting condom-free sex. Chances of reporting sex without condoms was 15% lower in antiretroviral-treated people versus untreated people in high-income countries, 43% lower in treated people in low- and middle-income countries, and 36% lower in antiretroviral-treated people who knew their partner was HIV-negative or did not know if their partner had HIV.
When the researchers combined studies that assessed condom-free sex with an HIV-negative partner or a partner with an unknown HIV status, the analysis linked taking antiretrovirals to a 36% lower chance of sex without condoms. The impact of antiretroviral therapy on sex without condoms grew smaller as the proportion of people who knew they had an undetectable viral load rose.

The research team found 11 studies including 16,138 people that assessed rates of new STIs. Combining findings from all these studies, the analysis linked taking antiretroviral therapy to a 42% lower chance of getting a new STI (Figure 2). This 42% reduction did not quite reach the traditional level of statistical significance, meaning there is a very small possibility that chance could explain the result.

Only 1 of the 11 studies tied antiretroviral therapy to a higher chance of getting a new STI. This San Francisco study involved mostly women, and relatively few of them took antiretroviral therapy. When the researchers eliminated this study from the analysis, combined results of the remaining 10 studies indicated that taking antiretroviral therapy lowered chances of a new STI by 52%, and this result was statistically significant (not explained by chance).

The researchers combined results of four studies of drug-injecting behavior involving 1600 people. This combined analysis determined that taking antiretroviral therapy did not affect chances of risky injecting practices one way or the other. The four studies used different definitions of unsafe injecting practices, but risk-taking rates did not differ much from study to study.

**What the results mean for you.** This large and careful analysis combining results from 58 studies found evidence linking taking antiretroviral therapy to (1) a lower rate of sex without condoms, and (2) possibly a lower rate of new sexually transmitted infections (STIs). Among people who inject drugs, evidence indicated that those taking antiretrovirals did not have riskier drug-injecting behavior (like sharing needles) than those not taking antiretrovirals. But the authors caution that “too few studies exist [four] for meaningful comment on the effect of antiretroviral therapy on injecting behavior.”
The findings on sexual risk are reassuring because some individual studies did find evidence suggesting people who took antiretroviral therapy had sex without condoms more than untreated people. Some experts proposed that people might adopt riskier behavior when they start taking antiretrovirals because they know treatment will lower their viral load and thus lower the chance of passing HIV to a partner. This new 58-study analysis found strong indications that this is not happening. In fact, antiretroviral-treated people reported sex without condoms less often than untreated people. And these self-reports of sexual behavior are backed up by the lower STI risk in antiretroviral-treated people.

The researchers suggest that people may have less risky sex when they take antiretrovirals because they “receive regular monitoring and ongoing medical care, including ongoing counseling, have more opportunities for reinforcement of preventive health messages, and this could fortify decisions to reduce risk.”

Still, the study did find a weaker link between antiretroviral therapy and condom-free sex in people who knew they had an undetectable viral load. People with HIV should certainly use condoms when having sex, even if antiretroviral therapy has made their viral load undetectable. Having an undetectable viral load does nothing to protect a person from picking up (or passing along) other sexually transmitted infections that condoms might block. If HIV-positive people do not use condoms during sex, they also run the risk of picking up a second HIV strain from an HIV-positive partner.

People who inject drugs should work with their HIV provider and other professionals to find a way to stop, possibly through opioid substitution therapy with methadone or buprenorphine. Injecting drugs carries many risks besides HIV infection, notably infection with hepatitis C virus and serious bacterial heart disease.

The researchers note that their multistudy analysis is limited because most of the individual studies analyzed measured sexual behavior within the first year of starting antiretroviral therapy. Thus longer studies are needed to determine whether the overall positive impact of antiretroviral therapy on sexual risk persists beyond 1 year.

The bottom line, the authors suggest, is that findings of this study should ease concerns that expanding antiretroviral therapy to more people who need it will undermine HIV prevention programs.

References

Adherence means taking medications, such as antiretrovirals, according to the schedule set by your healthcare provider.

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.

Body mass index, or BMI, is a measure of weight often used in medical studies. BMI equals weight in kilograms divided by height in meters squared. A BMI below 18.5 is underweight, 18.5 to 24.9 is normal, 25 to 29.9 is overweight, and 30 or higher is obese. You can find a BMI calculator at http://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm

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.

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.

DXA scans use low-dose x-rays to create images of internal body parts, including bone, fat, and lean mass. They measure both bone mineral density and body composition.

Hypertension is high blood pressure against artery walls as blood circulates through the body. Blood pressure below 120/80 mm Hg (millimeters of mercury) is considered normal; 120-139/80-89 is considered prehypertension; and 140/90 or higher is considered hypertension.

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

...continued
A **median** is 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.

**Osteoporosis** is “a condition characterized by progressive loss of bone density, thinning of bone tissue and increased vulnerability to fractures,” according to the National Institutes of Health.

**Pack-years** measure the number of packs smoked daily in a year. One pack-year of smoking means smoking 1 pack per day for 1 year, or 365 packs.

**Peripheral arterial disease** develops when arteries in your legs become clogged with plaque. Clogged arteries in the legs mean you are at risk for having a heart attack or stroke.

**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.

**Virologic failure** means failure of an antiretroviral combination to keep viral load below a certain level, often 200 copies per milliliter of plasma.
If you have HIV, what are the **25** most important things to know? **And do!**

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Articles

1. Antiretroviral-treated people lose more years of life than smoking to HIV.
2. More age-related illnesses in older people with HIV than comparable HIV-negatives.
3. Antiretroviral failure rate falls from over 60% to under 10% in France.
4. Gradually accelerating heart disease risk with age in men with HIV.
5. Heart attack rates twice as high with HIV among veterans at low risk.
6. Heart artery walls thicker in young adults with HIV than in HIV-negatives.
7. Statin therapy reduces heart artery plaque size and number in people with HIV.
8. Statin therapy for 1 year linked to gains in bone density in people with HIV.
9. Missed clinic visits linked to tripled risk of death in US HIV group.
10. Undetectable viral load more likely in people who receive steady HIV care.
11. HIV therapy not linked to more risky sex or sexual infections.

Definitions

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