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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 impy recommendations or endorsement. Always consult your doctor before altering a prescribed drug regimen or taking any drug or supplement.

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HIV-positive people with a recent **CD4 count** above 500 had a **myocardial infarction** (heart attack) rate similar to that of a matched group of HIV-negative people, according to results of a quarter million-person analysis in California.1 People with a lowest-ever (nadir) CD4 count above 500 also had a heart attack rate similar to the HIV-negative comparison group.

Several large studies have found higher heart attack rates in men and women with HIV than in HIV-negative people.2-5 Many factors probably contribute to this higher heart attack rate with HIV, starting with inflammation caused by HIV, which can damage arteries in the heart and throughout the body. Also, people with HIV often have traditional heart disease risk factors, like smoking, high blood pressure, and high cholesterol and triglycerides.

Certain antiretrovirals used to treat HIV infection may also contribute to a higher heart disease risk in people with HIV, though the overall impact of antiretroviral therapy on the heart is probably positive. Effective antiretroviral therapy lowers the level of HIV in the body and thus limits inflammation and its damaging effects. Antiretroviral therapy also raises CD4 counts and so helps the body regain its infection-fighting ability. But the impact of a high or low CD4 count on heart disease risk remains incompletely understood. Some studies found little or no evidence that CD4 count affects heart disease rates,6-10 while other studies have found such evidence.11-15

To learn more about how CD4 count may influence heart attack risk in people with HIV infection, researchers at California’s Kaiser Permanente healthcare system conducted the large comparison described here.

**How the study worked.** The study involved people in care in two large, related healthcare systems: Kaiser Permanente Northern California and Kaiser Permanente Southern California. The analysis started with all HIV-positive adults who were members of the Northern California group for some period between 1996 and 2009 or members of the Southern California group for some period between 2000 and 2009. All these HIV-positive people had at least one CD4 count recorded during the noted study periods.

For every 1 HIV-positive person, the researchers selected 10 HIV-negative people matched to the HIV patient by age, male or female sex, medical center, and calendar years in care. The investigators also identified a smaller group of HIV patients with complete records of the antiretrovirals they took. The observation period for each study participant continued until that person had a heart attack, died, or left the Kaiser Permanente health plan, or until December 31, 2009.

The research team checked medical records of all study participants to gather basic information that might affect health—and particularly heart disease risk. Such information included age, race, smoking, overweight or obesity, alcohol or drug abuse, and an index of social and economic status that includes factors such as income, occupation, and education.

For people with HIV infection, the researchers recorded CD4 count and **viral load** over time. They also determined each HIV-positive person’s lowest-ever (nadir) CD4 count. The researchers divided recent and nadir CD4 counts into three groups: under 200, 200 to 499, and 500 or over. They also divided viral loads into three groups: under 500 copies, 500 to 9999 copies, and 10,000 copies or more. Next they determined how many people in each of the CD4 brackets and each of the viral load brackets had a heart attack.

Then the research team used accepted statistical methods to determine differences in heart attack rates between HIV-positive people and HIV-negative people. This type of statistical analysis can take into account differences between the HIV-positive and negative groups in numerous heart risk factors, such as age, use of anti-cholesterol drugs, diabetes, and high blood pressure. The researchers also used standard statistical methods to determine how heart attack rates differed by recent CD4

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*Words in **bold** are defined in the Technical Word List at the end of this issue of *HIV Treatment Alerts.*
count, lowest-ever CD4 count, and recent viral load. For the subgroup of people with a complete antiretroviral treatment history, the researchers determined whether length of treatment with protease inhibitors or nonnucleosides affected heart attack risk.

■ What the study found. The study focused on 22,081 people with HIV and 230,069 without HIV. Most people in both groups (91%) were men, about 36% were between 30 and 39 years old, and about 34% were between 40 and 49 years old. Compared with the HIV-negative group, the HIV group had a higher proportion of whites (55.9% versus 45.8%), a higher proportion of blacks (18% versus 9.7%), a lower proportion of Hispanics (21.1% versus 28.2%), and a lower proportion of Asians and Pacific Islanders (4.2% versus 14.9%). The observation period for all study participants averaged 4.5 years.

A higher proportion of people with than without HIV had ever smoked (43.3% versus 29.0%) and ever had an alcohol or drug abuse diagnosis (20.3% versus 8.4%). A lower proportion of people with HIV were overweight or obese (39.0% versus 44.3%) or had prior high blood pressure (7.3% versus 8.1%). Similar proportions in both groups had prior diabetes (about 3%) or had used anti-lipid therapy for high cholesterol or triglycerides (about 5%).

Among people with HIV, 74.5% became infected with HIV during sex between men, 16.4% during sex between men and women, and 7.1% while injecting drugs. CD4 counts averaged 400 when HIV-positive people entered the study period, and their viral loads averaged 55,272 copies. Almost half of study participants with HIV (48.7%) had started antiretroviral therapy before they entered the study period, and most (79.8%) took antiretrovirals at some point during the study period.

During the study period, heart attacks were diagnosed in HIV-positive people at a higher rate than in HIV-negative people: 283 versus 165 per 100,000 person-years. The rate in the HIV group means 283 of every 100,000 people (or about 3 of every 1000) had a heart attack every year. Statistical analysis comparing the heart attack rate in people with versus without HIV determined that HIV-positive people had a 44% higher heart attack rate. In other words, HIV infection resulted in a 44% higher heart attack rate that was not explained by whatever other heart risk factors a person had (such as older age and diabetes).

Statistical analysis that weighed the impact of many heart attack risk factors determined that people with a recent CD4 count below 200 had a 76% higher risk of a heart attack than HIV-negative people in the Kaiser Permanente healthcare system (Figure 1). People with a recent CD4 count between 200 and 499 had a 59% higher heart attack risk than HIV-negative people. But people with a recent CD4 count of 500 or more did not have a higher heart attack risk than HIV-negative people.

People with a lowest-ever CD4 count below 200 had a 74% higher heart attack risk than HIV-negative people (Figure 1). And people with a lowest-ever CD4 count between 200 and 499 had a 30% higher heart attack risk. But people with a lowest-ever CD4 count of 500 or more had about the same heart attack risk as HIV-negative people. Differences in recent viral load did not affect heart attack risk.

**Figure 1.** Compared with HIV-negative people in the same California healthcare system, HIV-positive people with (1) a recent or lowest-ever CD4 count below 200 or (2) a recent or lowest-ever CD4 count between 200 and 499 had higher heart attack risks. But that risk was similar in HIV-negative people and HIV-positive people with a recent CD4 count or lowest-ever CD4 count of 500 or higher. (The 18% higher risk with a recent CD4 count above 499 is not statistically significant, meaning chance alone could explain the finding.)
Next the researchers used this type of statistical analysis only in people with HIV to identify factors that raised their heart attack risk independently of any other factor. Every 100-cell higher lowest-ever CD4 count lowered the heart attack risk 12% (Table 1). No other HIV-related factor affected heart risk in this analysis, but several traditional heart risk factors did: Being a woman, being black or Hispanic rather than white, and entering the study group more recently all lowered the heart attack risk (Table 1). Factors that raised the risk were older age, smoking, diabetes, high blood pressure, and abnormal cholesterol or triglycerides.

What the results mean for you. This large study comparing people with and without HIV in the same California healthcare system found that HIV infection raises the risk of heart attacks 44%. That increased risk is very similar to the 48% higher risk seen in US veterans with HIV compared with HIV-negative veterans in an earlier study. Both of these studies are strong because they compared large numbers of HIV-positive and negative people with equal access to care and matched to each other by age and sex. So the similar finding of about a 45% higher heart attack risk with HIV is convincing.

The newer study in California found, however, that heart attack risk does not differ between certain HIV-positive people and HIV-negative people: HIV-positive people with (1) a recent CD4 count of 500 or more or (2) a lowest-ever (nadir) CD4 count of 500 or more had a heart attack risk similar to people without HIV. Those findings are good news for people taking antiretroviral therapy who reach a CD4 count of 500 or more—and for people whose CD4 count never falls below 500 because they start antiretroviral therapy at a CD4 count above 500.

The researchers who conducted this study believe their findings "argue for increased efforts to diagnose and treat HIV as early as possible." The results also mean that people taking antiretrovirals should try their best to take all their pills on time—exactly as their HIV provider instructs. Taking your antiretrovirals without missing doses is the surest way to get your CD4 count above 500 and keep it there.

Length of treatment with protease inhibitors or nonnucleosides did not affect heart attack risk in analyses that factored in other heart disease risks.

<table>
<thead>
<tr>
<th>Lowered heart attack risk:</th>
<th>Raised heart attack risk:</th>
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<tbody>
<tr>
<td>Every 100-cell higher lowest-ever CD4 count</td>
<td>12% lower</td>
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<tr>
<td>Women versus men</td>
<td>47% lower</td>
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<tr>
<td>Black versus white</td>
<td>40% lower</td>
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<tr>
<td>Hispanic versus white</td>
<td>38% lower</td>
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<tr>
<td>Entered study 2005-2009 versus 1996-1999</td>
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</tr>
<tr>
<td>65 or older versus 18-39</td>
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<tr>
<td>50-64 versus 18-39</td>
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<tr>
<td>40-49 versus 18-39</td>
<td>3.20 times higher</td>
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<tr>
<td>Ever smoked</td>
<td>2.21 times higher</td>
</tr>
<tr>
<td>Prior diabetes</td>
<td>1.53 times higher</td>
</tr>
<tr>
<td>Prior high blood pressure</td>
<td>1.99 times higher</td>
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<tr>
<td>Abnormal cholesterol or triglycerides</td>
<td>1.61 times higher</td>
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</table>
Boosting the CD4 count with antiretroviral therapy can be particularly effective in preventing heart attacks if people with HIV and their providers work together to avoid or limit the impact of other heart disease risk factors. Many already well-known heart disease risk factors are common in people with HIV. And this study pinpointed several such factors that boosted the heart attack risk in these HIV-positive people (Table 1).

Some of these well-known risk factors—like gender, race, and age—cannot be changed. But some of the behaviors or illnesses linked to heart attacks in this study can certainly be avoided or reversed: smoking, poorly controlled diabetes (high blood sugar), poorly controlled hypertension (high blood pressure), or high cholesterol or triglycerides. Table 1 on page 13 of this issue of HIV Treatment Alerts! lists all well-known heart disease risk factors in people with HIV and highlights those that can be avoided or changed.

Probably the single most important thing HIV-positive people can do to avoid heart disease (and to avoid lung disease and many cancers) is to avoid or quit smoking. People who already smoke should work with their HIV provider to find a way to stop. Many successful approaches to quitting smoking are available. Find the approaches that work for you, and keep trying until you stop. Many smokers try to stop several times before they finally succeed. So keep trying even if you fail a few times.

This study produced another piece of good news: HIV-positive people who began care in this California healthcare system from 2005 through 2009 had almost a 60% lower heart attack risk than people who began care from 1996 through 1999. That could mean providers in this healthcare system are getting better at working with HIV-positive people to treat or control heart risk factors—and that HIV-positive people are getting better at working with their providers on heart disease risk. The finding of a lower heart attack risk in more recent years could also reflect the greater heart safety of antiretroviral drugs that came into use in more recent years.

References

High blood pressure adds to heart attack risk in people with HIV

Compared with HIV-negative people with normal blood pressure, HIV-positive people with moderately higher or much higher blood pressure ran an increased risk of **myocardial infarction*** (heart attack) in a large comparison of HIV-positive and negative US veterans.1 High blood pressure added to the increased myocardial infarction risk already linked to HIV itself.

Several previous studies found that people with HIV infection run a higher risk of myocardial infarction than people without HIV.2-4 HIV infection may contribute to a higher risk of myocardial infarction because HIV causes inflammation that can damage arteries. Certain **antiretrovirals** (anti-HIV drugs) may also contribute to myocardial infarction risk.

At the same time, many people with HIV have traditional heart disease risk factors, such as smoking, high cholesterol, and hypertension (high blood pressure). Some research shows that even moderately higher blood pressure raises the risk of heart disease in the general population. To get a better understanding of how different levels of hypertension may contribute to heart attack risk in people with HIV, researchers conducted this study.

**How the study worked.** This study involved US veterans in the Veterans Aging Cohort Study virtual cohort (VACS VC). Every HIV-positive person in this study group is matched to 2 HIV-negative people by age, race/ethnicity, and VACS VC study site. Everyone in the blood pressure analysis was alive and continuously enrolled in VACS VC on or after 2003. The researchers did not include veterans with heart disease or stroke before or up to 6 months after the study baseline date. Baseline date was a veteran’s first medical visit on or after April 1, 2003. Follow-up continued from the baseline date until a veteran had a heart attack or died, or until January 1, 2010.

The VACS team calculated blood pressure for each veteran as the average of three measurements made during routine medical visits closest to the baseline date (defined above). They separated blood pressure results into several standard categories:

- Normal: systolic† 90-120 mm Hg, diastolic† 60-80 mm Hg and taking no blood pressure drugs
- Prehypertension: systolic 120-139 mm Hg, diastolic 80-89 mm Hg and no blood pressure drugs
  - Low prehypertension: systolic 120-129 mm Hg or diastolic 80-84 mm Hg
  - High prehypertension: systolic 130-139 mm Hg or diastolic 85-89 mm Hg
- Hypertension: systolic at or above 140 mm Hg, diastolic at or above 100 mm Hg and no blood pressure drugs
- Treated hypertension: taking blood pressure drugs
- Very low blood pressure: systolic below 90 mm Hg, diastolic below 60 mm Hg

*Blood pressure is usually recorded as two numbers, for example, 120/80 mm Hg (millimeters of mercury). The first (higher) number is the systolic pressure; the second (lower) number is the diastolic pressure.*

By checking medical records, the researchers determined how many veterans had a myocardial infarction (heart attack) during the study period. The investigators also recorded many other factors that could affect heart attack risk. These other factors included age, gender, race/ethnicity, and standard risk factors (like diabetes, high cholesterol, smoking, cocaine use, alcohol use, and weight calculated as body mass index). For HIV-positive veterans, the research team recorded **CD4 count, viral load**, and current use of antiretroviral therapy.

The VACS investigators used standard statistical methods to determine the risk of myocardial infarction according to (1) HIV status (positive or negative) and (2) blood pressure category (bullet list above).

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*Words in **bold** are defined in the Technical Word List at the end of this issue of *HIV Treatment Alerts.*
**What the study found.** The study included 81,026 veterans, 27,059 (33%) with HIV and 53,967 (67%) without HIV. Proportions of veterans in the HIV-positive and negative groups with normal blood pressure were 21% and 14%, with prehypertension 45% and 43%, with hypertension 33% and 42%, and with low blood pressure 1% and 1%. Half of participants with prehypertension had high prehypertension.

More than 90% of study participants were men. Average age ranged from 46 to 53 years across the different blood pressure categories. About 45% of HIV-positive veterans were taking antiretroviral therapy. Veterans with hypertension were older than those without hypertension, and veterans with prehypertension or hypertension had higher rates of diabetes, high triglycerides, high body mass index, and poor kidney function.

Through a median follow-up of almost 6 years, 860 veterans had a heart attack. In a statistical analysis that factored in age and race, the heart attack rate was higher in each higher blood pressure group (Figure 1). And within each blood pressure group, the heart attack rate was always higher in veterans with HIV than in those without HIV (Figure 1).

**Figure 1.** In a study of 81,026 US veterans, the rate of myocardial infarction (MI, heart attack) rose with each higher blood pressure level. In each blood pressure group, the rate was always higher in veterans with HIV than in those without HIV. Veterans with abnormally low blood pressure (far right) had a higher heart attack rate than veterans with normal blood pressure.3

Compared with HIV-negative veterans with normal blood pressure, HIV-positive veterans with low prehypertension, high prehypertension, untreated hypertension, or treated hypertension had higher heart attack rates, even after the researchers accounted for the possible impact of age, race, gender, and medical factors that may affect myocardial infarction risk:

**Compared with HIV-negative veterans with normal blood pressure:**

- HIV-positive veterans with low prehypertension had a 1.6 times higher heart attack risk
- HIV-positive veterans with high prehypertension had a 1.81 times higher heart attack risk
- HIV-positive veterans with untreated hypertension had a 2.57 times higher heart attack risk
- HIV-positive veterans with treated hypertension had a 2.76 times higher heart attack risk

In the whole study group, every 10 mm Hg higher blood pressure raised the heart attack risk 12%.

**What the results mean for you.** This large and well-planned study found that high blood pressure raised the risk of myocardial infarction (heart attack) in veterans with and without HIV infection. Among veterans with HIV, even “low prehypertension” (120/80 to 129/84 mm Hg) and “high prehypertension” (130/85 to 139/89 mm Hg) raised the heart attack risk regardless of what other risk factors a person had. This study found for the first time that HIV infection alone and high blood pressure alone each made heart attacks more likely.

The researchers stress that even HIV-positive people with an undetectable viral load have a higher heart attack risk than people without HIV.2 The investigators emphasize that traditional heart disease risk factors such as high blood pressure add to the heart attack risk, which is already higher because of HIV infection. They caution that all their findings may not apply to women with HIV because fewer than 10% of veterans in this study were women.
One out of every 3 people in the United States has high blood pressure—68 million people in all. Hypertension (high blood pressure) does not necessarily make a person feel sick, so the best way to detect hypertension is to measure blood pressure. Your HIV provider probably measures your blood pressure every time you make a visit. You can also measure blood pressure yourself with the machines often found in drug stores. Blood pressure measured by yourself should always be double-checked in your provider’s office.

Research has identified several risk factors for hypertension in people with and without HIV (Table 1). Knowing these risk factors is important because many of them can be avoided or changed. The US Centers for Disease Control and Prevention lists seven hypertension risk factors that can be avoided or changed: too much salt in diet, too little potassium in diet, being overweight, smoking, drinking too much alcohol, not getting enough physical activity, and having poorly controlled diabetes. Your HIV clinician can work with you to avoid or control these risk factors.

Smoking can cause or contribute to hypertension and heart disease. At the same time, smoking raises the risk of several cancers and serious lung diseases. Your HIV provider can help you stop smoking by prescribing nicotine-replacement products or recommending other methods. If you tried to quit smoking and failed, try again. Many people try several times before eventually breaking their smoking habit.

<table>
<thead>
<tr>
<th>Risk factors you can change</th>
<th>Risk factors you can’t change</th>
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</thead>
<tbody>
<tr>
<td>• Diabetes</td>
<td>• Older age</td>
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<tr>
<td>• Too much salt in diet*</td>
<td>• Black race</td>
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<tr>
<td>• Not enough potassium (from fruits and vegetables) in diet</td>
<td>• Hypertension in father, mother, brother, or sister</td>
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<tr>
<td>• Overweight</td>
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<tr>
<td>• Physical inactivity</td>
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<tr>
<td>• Smoking</td>
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<tr>
<td>• Drinking too much alcohol</td>
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What you can do to prevent or control high blood pressure:

1. Eat a healthy diet.
2. Maintain a healthy weight.
3. Be physically active.
4. Don’t smoke.
5. Limit alcohol use.

For details see: Centers for Disease Control and Prevention. High blood pressure. How to prevent high blood pressure. [http://www.cdc.gov/bloodpressure/what_you_can_do.htm](http://www.cdc.gov/bloodpressure/what_you_can_do.htm)

References

Middle-aged HIV-positive women with no heart disease symptoms had more noncalcified (or “soft”) heart artery plaques* than a comparable group of women without HIV.1 Noncalcified (soft) plaques are dangerous because they have a higher chance of bursting than harder, calcified plaques (Figure 1). Artery narrowing caused by plaques can lead to heart attacks, stroke, or death. In this new study, the difference in noncalcified plaque rate was greater in women with versus without HIV than in men with versus without HIV.

People with HIV infection have a 2 times higher rate of cardiovascular (heart and blood vessel) disease than people without HIV.2 Previous studies in the United States3 and France4 found that HIV-positive women have higher rates of myocardial infarction (heart attack) than HIV-negative women.

Several factors probably contribute to this higher cardiovascular disease risk in people with HIV, including (1) higher rates of traditional heart disease risk factors like smoking and diabetes, (2) the impact of antiretroviral therapy on risk factors like cholesterol and triglycerides, and (3) inflammation and activation of the immune system by HIV.

Researchers are still trying to figure out exactly why women and men with HIV run a higher risk of heart disease than HIV-negative people the same age. A prior study identified one possible explanation in men with HIV: They had a higher rate of noncalcified coronary artery plaques than men without HIV.3

Further study of these HIV-positive and negative men found that men with HIV had higher levels of soluble CD163 (sCD163), which is a signal that immune system cells are activated.6 Activated cells could mean the body is still fighting HIV infection, even if a person has an undetectable viral load.

To learn more about coronary artery plaques and immune cell activation in women with HIV, researchers at Boston’s Massachusetts General Hospital conducted the study described here.

■ How the study worked. Researchers invited HIV-positive women from Boston-area HIV clinics and community health centers to enter the study. They also invited HIV-negative women from the same communities to participate. All women were 18 to 60 years old, and none had heart disease or signals of current or past heart disease. No women had kidney disease or indicators of kidney disease. HIV-positive women taking antiretrovirals had taken the same antiretroviral combination for more than 3 months.

All women had cardiac CT imaging, which uses a powerful x-ray machine to make images of coronary arteries in slices. Technicians then put these slices together to make a complete picture of a coronary artery segment. Women also gave blood samples so the research-

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*Words in bold are defined in the Technical Word List at the end of this issue of HIV Treatment Alerts.
The researchers collected detailed information about each woman, including their medical history and smoking and recreational drug-taking habits.

The Massachusetts General team also reviewed findings from a previous study of HIV-positive and negative men in the Boston area who had cardiac CT imaging. The aim was to compare artery findings in four groups: HIV-positive women, HIV-negative women, HIV-positive men, and HIV-negative men.

The researchers used standard statistical methods to compare findings in the four groups of women and men. This type of analysis can consider the impact of several factors at the same time, such as age, gender, and HIV status. As a result, the researchers could identify factors that affect plaques and immune-cell activation independently of all other factors.

**What the study found.** The study included 60 women with HIV and 30 without HIV. Both groups averaged 47 years in age, and similar proportions were nonwhite (75% with HIV, 67% without HIV). About half of the women in both groups smoked, but both groups had a low overall risk of heart disease as calculated by the Framingham 10-year risk score (average 2% in both groups, meaning 2 of 100 women with that risk would probably have a heart attack in the next 10 years).

HIV-positive women had been infected for an average 15 years, and 59 of these 60 women were taking antiretroviral therapy. Length of antiretroviral treatment averaged 8 years, and 84% of women had an undetectable viral load. CD4 counts averaged 597 in women with HIV.

Similar proportions of women with and without HIV had some type of coronary artery plaque (37% versus 38%). But women with HIV had a 3 times higher rate of dangerous noncalcified (soft) plaques, which are plaques with a tendency to burst (35% versus 12% in women without HIV). Compared with HIV-negative women, those with HIV had a higher average number of artery segments with noncalcified plaques (0.92 versus 0.40) and a higher percentage of coronary artery segments with noncalcified plaques (74% versus 23%). The number of artery segments affected by noncalcified plaque remained significantly higher in HIV-positive women than in HIV-negative women when the researchers limited the analysis to HIV-positive women with an undetectable viral load.

Seven markers of immune system activation were significantly higher in HIV-positive women than in HIV-negative women, including levels of sCD163. HIV-positive women with noncalcified (soft) plaques were more likely to have higher sCD163 levels than HIV-positive women without noncalcified plaques.

HIV-positive women had a higher average percentage of coronary artery segments affected by noncalcified (soft) plaques than did HIV-negative women, HIV-positive men, or HIV-negative men. Noncalcified plaques are more likely to burst than harder calcified plaques.

Finally, the researchers conducted statistical analyses to see if being HIV-positive, being a woman, or being older affected the percentage of noncalcified (soft) plaques or levels of sCD163 in HIV-positive women and men and HIV-negative women and men. These analyses yielded the following findings:

- HIV infection by itself—regardless of other risk factors—was significantly related to a higher percentage of noncalcified plaques in these people.
The percentage of noncalcified plaques was increased more in women with HIV than in men with HIV.

HIV infection by itself—regardless of other risk factors—was significantly related to higher sCD163 levels.

Being a woman by itself was significantly related to higher sCD163 levels.

Being older by itself was significantly related to higher sCD163 levels.

sCD163 levels increased more with age in women than in men.

**What the results mean for you.** This careful study showed that middle-aged HIV-positive women with no signals of heart disease and with an undetectable viral load had a higher rate of noncalcified (soft) coronary artery plaques than a comparable group of women without HIV. Activation of immune system cells—a signal that HIV is still affecting the body—was significantly higher in HIV-positive women than in HIV-negative women. And both of these findings—a higher rate of soft plaques and more immune-cell activation—were increased more in HIV-positive women than in HIV-positive men compared with HIV-negative groups. The soft noncalcified plaques affecting these women with HIV are more likely to break than harder calcified plaques, and as a result they are more likely to raise the risk of a heart attack.2

Men are generally thought to run a higher risk of serious heart disease than women. But that may not be true when comparing HIV-positive women and men with HIV-negative women and men. Previous research found that HIV-positive women have a higher risk of myocardial infarction (heart attack) than HIV-negative

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**Table 1. Possible heart disease risk factors in people with HIV**

<table>
<thead>
<tr>
<th>General risk factors</th>
<th>Conditions</th>
<th>Behaviors</th>
<th>HIV-related factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age</td>
<td>• Abnormal cholesterol or triglycerides</td>
<td>• Smoking</td>
<td>• Treatment with protease inhibitors or abacavir†</td>
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<tr>
<td></td>
<td>• Diabetes</td>
<td>• Physical inactivity</td>
<td>• Higher viral load ‡</td>
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<td></td>
<td>• Poor kidney function</td>
<td>• Excessive alcohol use</td>
<td>• Lower CD4 count ‡</td>
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<td>• Low vitamin D</td>
<td>• Hormonal contraceptive use</td>
<td>• HCV infection*</td>
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<tr>
<td></td>
<td></td>
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<td>• Cocaine use</td>
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Risk factors in **bold** can be changed.

*HCV infection can be avoided by avoiding sex without condoms or sharing drug-injecting equipment. The impact of HCV infection in HIV-positive people can be lessened by anti-HCV therapy.

†The impact of abacavir on heart disease risk is controversial. When considered in the context of other heart disease risk factors, most experts do not advise avoiding abacavir or protease inhibitors as a way to prevent heart disease.

‡Some studies have found links between lower CD4 count or higher viral load and heart disease. Other studies have not found these links.
women, and that increased risk in women is greater than the increase seen when comparing HIV-positive men with HIV-negative men. The higher noncalcified plaque rate in HIV-positive women than HIV-positive men in the new study^4 may explain why HIV-positive women had a higher relative increase in heart attacks than HIV-positive men in the previous study.

Taken together, these findings should alert HIV-positive women and their providers that women as well as men with HIV run a higher risk of heart disease than people without HIV. HIV-positive people should know the risk factors for heart disease (Table 1). Most of these risk factors (written in bold in Table 1 on page 13) can be avoided or changed. Probably the single most important thing anyone can do to prevent heart disease is to avoid smoking or to quit if they already smoke.

HIV providers should check current HIV care guidelines for advice on evaluating HIV-positive people for cardiovascular risk. The 2013 guidelines from the Infectious Diseases Society of America (IDSA) and the HIV Medicine Association (HIVMA) make the following recommendations:^8

- At an HIV-positive person’s first visit, perform a comprehensive cardiopulmonary exam including assessment for chest pain, shortness of breath, palpitations, wheezing, peripheral pulses, and edema.
- Check fasting lipid levels every 6 to 12 months, before starting antiretroviral therapy, and 1 to 3 months after starting a new antiretroviral combination. Manage abnormal lipids according to the National Cholesterol Education Program Guidelines.
- Check blood pressure annually in all patients.

Complete IDSA/HIVMA guidelines are online at the link following reference 8.

References


http://cid.oxfordjournals.org/content/58/1/e1.long
**Article 4**

**Diabetes, hypertension, smoking, low CD4 count predict advanced kidney disease**

Well-known kidney disease risk factors—diabetes,* hypertension (high blood pressure), and smoking—were linked to development of advanced kidney disease and end-stage kidney disease in a 6-year study of 35,000 people with HIV. This large and long analysis also linked lower CD4 count to advanced and end-stage kidney disease risk. But past or current use of Viread (tenofovir)—or any other antiretrovirals—was not associated with kidney risk in this study. Overall the study found a low rate of advanced chronic kidney disease (CKD) or end-stage kidney disease (requiring dialysis or kidney transplant) in this large group of HIV-positive people.

HIV-positive people run a higher risk of kidney disease than people without HIV for several reasons. HIV infection itself, other infections common in people with HIV, and a weakened infection-fighting immune system may all raise the risk of kidney disease. People with HIV have high rates of traditional kidney disease risk factors, including diabetes, hypertension, and smoking. And HIV-positive people often take drugs—including certain antiretrovirals—that may affect the kidneys.

But previous research suggests that HIV-positive people who start combination antiretroviral therapy maintain healthy kidneys better than HIV-positive people not taking antiretrovirals. Combination therapy has also been tied to decreased development of HIV-associated nephropathy (a form of kidney disease), and stopping antiretrovirals has been linked to development of end-stage kidney disease.

Much research on kidney disease in people with HIV involves people with African ancestry. Because of certain genetic traits seen in Africans and their descendants, they run a higher risk of kidney disease than non-Africans. To get a better understanding of kidney disease risk in HIV-positive populations of diverse ancestry, researchers working with the Data collection on Adverse events of Anti-HIV Drugs Study (DAD) conducted this analysis.

**Figure 1.** The two kidneys filter about 200 quarts of fluid daily, eliminating waste through the bladder. Chronic kidney disease affects 26 million US adults with and without HIV infection, especially African Americans. (Illustration from Servier Medical Art. [http://www.servier.co.uk/medical-art-gallery/])

*Words in **bold** are defined in the Technical Word List at the end of this issue of *HIV Treatment Alerts.*
How the study worked. Begun in 1999, the DAD study involves more than 49,000 HIV-positive people in Europe, the United States, and Australia. At regular office visits, HIV providers collect information on these people—including antiretroviral use, CD4 count, and conditions like end-stage kidney disease. All of this information gets sent to the central DAD database so DAD researchers can analyze various health trends in this large HIV-positive group over time.

The kidney study involved all DAD members who had at least three measurements of estimated glomerular filtration rate (eGFR, an indicator of kidney function) after February 2004. Nobody had advanced CKD or end-stage kidney disease before their first eGFR measurement. DAD researchers tracked each person until (1) they had advanced CKD or end-stage kidney disease, (2) 6 months after their last clinic visit, or (3) February 2012. DAD researchers defined advanced CKD as two consecutive eGRFs at or below 30 mL/min. They defined end-stage kidney disease as dialysis (mechanical blood filtering) for at least 3 months or kidney transplantation.

The researchers determined how often advanced CKD or end-stage kidney disease developed in the HIV group they studied. The DAD team used accepted statistical methods to identify factors that raised the risk of advanced CKD or end-stage kidney disease. This kind of analysis considers an array of personal factors (like age, gender, and race), HIV-related factors (like CD4 count and viral load), and traditional kidney risk factors (like diabetes and high blood pressure). The study focused particularly on antiretrovirals linked to possible kidney problems in previous research—Viread (tenofovir, also in the combination pills Atripla, Complera, and Truvada), Reyataz (atazanavir), Reyataz plus Norvir (ritonavir), and Kaletra (lopinavir plus Norvir). By considering the impact of many factors at the same time, this kind of statistical analysis can pick out individual factors that affect kidney disease risk regardless of whatever other risk factors a person has.

What the study found. The study involved 35,192 people with a median age of 41 at their first eGFR measurement. About three quarters (74%) of these people had a normal initial eGFR, and median CD4 count stood at 436. Almost half of the study group (48%) were white, and 7% were African; the researchers did not know the race of 43% because several study groups that contribute to DAD do not report race.

About one third of study participants (31%) had never taken antiretrovirals. At participants’ first eGFR measurement, rates of diabetes (4%) and hypertension (9%) were low. More than half of these people (59%) were current or former smokers, 26.5% never smoked, and smoking status was not known for 14%.

During a median observation time of 6.2 years, advanced CKD or end-stage kidney disease developed in 155 people (0.4% of 35,192). The rate of new advanced CKD or end-stage kidney disease was 0.67 per 1000 person-years, meaning advanced kidney disease developed in fewer than 1 of every 1000 people every year. Among people classified as having a low risk of kidney disease (because they had an initial eGFR above 60 mL/min, did not smoke, and did not have hypertension or diabetes), the rate of new advanced CKD or end-stage kidney disease was even lower—0.16 per 1000 person-years. Among people who already had moderate CKD (initial eGFR at or below 60 mL/min), 6.6% had advanced CKD or end-stage kidney disease after 5 years of observation.

Statistical analysis that considered multiple kidney disease risk factors determined that the risk of advanced CKD or end-stage kidney disease was the same in people who never took Viread and in those who took Viread in the past but stopped.* Compared with people who never took Viread, those taking Viread at the time of their severe kidney impairment had about a 75% lower rate of advanced CKD or end-stage kidney disease.† This statistical analysis found no links between current or former use of other antiretrovirals and development of advanced CKD or end-stage kidney disease.

The study also showed that people stopped taking Viread, Reyataz, and Kaletra at increasing rates as kidney function declined (as measured by decreasing eGFR). This finding indicated that HIV providers were aware that these antiretrovirals may affect the kidneys and appropriately switched to other antiretrovirals in patients whose eGFR fell. These preventive actions may explain why the study found no link between use of these drugs and advanced CKD or end-stage kidney disease.

*Adjusted incidence rate ratio 1.00, 95% confidence interval 0.66 to 1.51.
†Adjusted incidence rate ratio 0.23, 95% confidence interval 0.13 to 0.41.
Statistical analysis did identify five factors that predicted a higher rate of advanced CKD or end-stage kidney disease regardless of whatever other risk factors a person had (Figure 2): (1) Diabetes more than tripled the rate. (2) Hypertension (high blood pressure) more than doubled the rate. (3) Every 10 mL/min lower initial eGFR doubled the rate. (4) Current smoking almost doubled the rate. (5) Every one-half lower current CD4 count raised the rate about one third.

The rate of newly developing advanced kidney disease was low in this study—2 to 24 times lower than previous estimates in HIV groups in the United States. Several factors probably contribute to this lower rate of advanced kidney disease in the new study: Most people studied were relatively young, and the proportion of people with known African ancestry was relatively low. (Compared with whites, blacks have a higher risk of kidney disease, partly because of genetic factors.) In addition, this study group had low rates of two prominent kidney disease risk factors—diabetes and hypertension (high blood pressure).

More than half of the people in this study smoked at the time of the study or in the past, and smoking boosts the risk of kidney disease. Many people took antiretrovirals linked to moderate kidney disease in previous studies—Viread, Reyataz, and Kaletra. But the new study found that HIV providers appropriately switched away from these antiretrovirals in people with lower eGFR, a signal of poor kidney function. And the study produced no evidence that other antiretrovirals raise the risk of advanced kidney disease. However, the researchers cautioned that advanced kidney disease takes a long time to develop, so a longer study may be needed to fully understand the long-term impact of antiretrovirals on kidney disease.

Also, the study highlights the importance of a continued checking of kidney function to identify and take action against possible risk factors (such as eGFR decline related to antiretroviral drug use) before severe kidney impairment develops.

The study also found a low rate of progression from moderate kidney disease to advanced kidney disease in these HIV-positive people. Still, the progression rate in HIV-negative people studied for a similar period is more than 5 times lower than in this large HIV group. And the study found strong evidence that HIV-positive people with certain conditions and behaviors have higher rates of advanced kidney disease than people without these conditions (Figure 2): Having diabetes or hypertension, smoking, having a lower current CD4 count, and having worse kidney function measured by eGFR each independently raised the rate of advanced kidney disease.

**What the results mean for you.** This is the largest multiyear study to analyze development of advanced chronic kidney disease (CKD) and end-stage kidney disease in people with HIV. These people in Europe, the United States, and Australia were all studied at some point between February 2004 and February 2012, so they were taking many of the antiretroviral combinations widely used today.
Other research in people with and without HIV has identified other kidney disease risk factors (Table 1). Some of the risk factors found in this study or in earlier research can be avoided or reversed:

- Diabetes
- Hypertension
- Heart disease
- Smoking
- Lower current CD4 count

The link between lower current CD4 count and advanced kidney disease leads the researchers who conducted this study to stress the importance of good antiretroviral pill-taking habits to ensure that treatment raises the CD4 count and maintains it at a high level.

The US National Institute of Diabetes and Digestive and Kidney Diseases emphasizes three things people can do to maintain kidney health: (1) Choose foods with less salt (sodium). (2) Keep your blood pressure at the level set by your healthcare provider. (3) Keep your blood glucose in the target range, if you have diabetes.

<table>
<thead>
<tr>
<th>Table 1. Risk factors for chronic kidney disease</th>
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<tbody>
<tr>
<td><strong>Family background:</strong></td>
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<tr>
<td>• Kidney disease in a close relative (parent, brother, or sister)</td>
</tr>
<tr>
<td>• African Americans</td>
</tr>
<tr>
<td>• Hispanics</td>
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<tr>
<td>• Pacific Islanders</td>
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<tr>
<td>• Native Americans</td>
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<tr>
<td><strong>Other illnesses:</strong></td>
</tr>
<tr>
<td>• Diabetes</td>
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<tr>
<td>• Hypertension</td>
</tr>
<tr>
<td>• Heart disease</td>
</tr>
<tr>
<td><strong>Other factors:</strong></td>
</tr>
<tr>
<td>• Older age</td>
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<tr>
<td>• Cigarette smoking</td>
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Source: National Kidney Foundation.³


Certain groups of antiretroviral*-treated HIV-positive people in the United States and Canada can expect to live almost as long as people in the general population, according to results of a 23,000-person study.1 Among the HIV-positive groups with the longest life expectancies are gay or bisexual men, people who started antiretroviral therapy with a CD4 count above 350, and whites.

Antiretroviral therapy prolongs the lives of HIV-positive people by slowing progression of HIV infection to AIDS and by reducing development of new AIDS and non-AIDS diseases. One study of HIV-positive people in two large trials found that those with a recent undetectable viral load and a CD4 count of 500 or more had a death rate similar to that of the general population.2 Recent studies of large HIV groups in the Netherlands,3 France,4 and across Europe5 found evidence that survival of certain people with HIV is similar to survival in the population at large. (See the first article in the August 2013 issue of HIV Treatment Alerts! at http://centerforaids.org/pdfs/ta0813final.pdf.)

But life expectancy has not been closely studied in large HIV groups across the United States and Canada. And as HIV-positive people live longer by avoiding AIDS, some non-AIDS diseases have become more common in HIV groups and have accounted for a growing number of deaths. As a result, experts are unsure of long-term survival in HIV-positive North Americans today.

To examine life expectancy in greater detail among HIV-positive residents of the United States and Canada, researchers working with NA-ACCORD, a large collaboration of HIV study groups, conducted the study described here.

**How the study worked.** This study involved HIV-positive adults in the NA-ACCORD collaboration. NA-ACCORD consists of several smaller HIV study groups throughout the United States and Canada. At regular intervals, these smaller study groups send information on their members to NA-ACCORD. This information includes basic personal data (like age, gender, and race), what antiretrovirals each person is taking, laboratory findings like viral load and CD4 count, and whether each person is living or has died.

This analysis included HIV-positive people at least 20 years old who began combination antiretroviral therapy and had a CD4 count recorded when they began therapy or within 6 months of starting. The study period began in January 2000 and ran through December 2007. The researchers divided that time into three smaller periods—January 2000 through December 2002, January 2003 through December 2005, and January 2006 through December 2007. They divided study participants into four age groups—20 to 34, 35 to 44, 45 to 54, and 55 or older.

The main goal of the study was to estimate life expectancy, defined as the average number of additional years that a 20-year-old person will live if the death rate remains constant over that person’s lifetime. The researchers used death rates recorded in the NA-ACCORD database to estimate life expectancy. Observation of each study participant continued until death, until they dropped out of their study group, or until December 31, 2007, whichever came first. The NA-ACCORD team estimated mortality for each of the study periods and each of the age groups defined in the previous paragraph. They also estimated mortality according to:

- Gender (male or female)
- Race (nonwhite or white)
- HIV transmission group (gay or bisexual men, injection drug users, or other transmission groups)
- CD4 count above or below 350 when antiretroviral therapy began or within 6 months of starting therapy

**What the study found.** The study included 22,937 people starting combination antiretroviral therapy for the first time. About three quarters of study participants (77%) were men, and almost three quarters (72%) started antiretroviral therapy with a CD4 count below 350. Most study participants (62%) were nonwhite, 39% became infected with HIV during sex between men,
20% became infected while injecting drugs, and the remaining 41% became infected during sex between men and women or in other ways.

During the study period, 1622 people died to yield a mortality of 19.8 per 1000 person-years, meaning about 20 of every 1000 people died each year. Mortality was similar in men and women (20.0 and 19.1 deaths per 1000), higher in injection drug users than in other groups (34.5 deaths per 1000 versus 12.5 in gay/bisexual men and 19.1 in other HIV transmission groups), higher in nonwhites than whites (22.4 versus 16.0 deaths per 1000 person-years), and higher in people who started antiretroviral therapy with fewer than 350 CD4 cells than in those who started with a higher CD4 count (23.3 versus 11.3 deaths per 1000 person-years). Mortality fell across each of the three study periods, being highest in 2000-2002, lower in 2003-2005, and lowest in 2006-2007.

Using a statistical analysis that accounted for people who dropped out of their study group, the researchers determined that a 20-year-old could expect to live to age 62.7 (Figure 1). Life expectancy was similar for 20-year-old women (63.9 years) and men (62.4 years). Twenty-year-old injection drug users had a much lower life expectancy (49.1 years) than men infected during gay sex (77.3 years) or people infected during sex between men and women or in other ways (70.1 years). While a 20-year-old white person could expect to live to 72.1, a 20-year-old nonwhite could expect to live only to 58. A 20-year-old starting antiretroviral therapy at a CD4 count below 350 could expect to live to 58.8, while a 20-year-old starting treatment at a CD4 count above 350 could expect to live to 74.6.

An HIV-positive 20-year-old who started antiretroviral therapy at a CD4 count above 350 would have a life expectancy about 2.5 years shorter than that of a US man in the general population and about 7 years shorter than that of a US woman in the general population (Figure 2). Life expectancy for a 20-year-old man who became infected with HIV during sex with another man was almost identical to life expectancy of a 20-year-old man in the general population of the United States. Life expectancy of a 20-year-old HIV-positive white person was about 5 years shorter than life expectancy of a US man in the general population and about 10 years shorter than life expectancy of a US woman in the general population.

Overall life expectancy for an HIV-positive 20-year-old rose from 56.1 years in 2000-2002 to 65.2 years in 2003-2005 and to 71.4 years in 2006-2007. Over these three periods life expectancy rose steadily for all groups stud-

What the results mean for you. This is the first study to estimate life expectancy in a large, diverse group of HIV-positive people across the United States and Canada. The study group included large numbers of men and women, whites and nonwhites, and people who became infected with HIV by injecting drugs, by sex between men, or by sex between men and women. The main finding of this large study is that life expectancy increased steadily for HIV-positive people throughout the study period, from 2000 to 2007. This is good news for HIV-positive people taking an antiretroviral combination. It means many people with HIV can expect to live as long—or almost as long—as people without HIV.

But life expectancy differed between certain HIV subgroups studied. Life expectancy was longer in gay and bisexual men than in past or current injection drug users, longer in whites than in nonwhites, and longer in people who started antiretroviral therapy at a CD4 count above 350 than in those who started antiretrovirals at a lower CD4 count.

Of all these groups, injection drug users were the only group whose life expectancy did not improve over the study period. Compared with gay and bisexual men, injection drug users face a number of problems that could explain their shorter life expectancy. For example, the researchers observe that current or former injection drug users often have more non-HIV illnesses than gay/bisexual men, they often have unstable employment and housing, and their antiretroviral pill-taking habits may be poor.

Compared with whites, nonwhites may also face certain disadvantages that contributed to their shorter life expectancy than whites: poorer access to health care, less education, lower income, and lack of good health insurance. Health coverage is free to everyone in Canada, but at the time of this study many poor and unemployed people in the United States could not afford health coverage. In the United States, the Affordable Care Act has already extended health coverage to thousands who did not have health insurance. Uninsured people in the United States can learn how to apply for insurance through the Affordable Care Act from their HIV provider, community groups, or others who understand the US healthcare system.

Life expectancy was similar in HIV-positive men and women in this study. In the general population of the United States and Canada, women live an average 4 years longer than men, so a similar life expectancy in HIV-positive women and men indicates that women are not gaining life years as much as one would expect. The researchers suggest several possible reasons for this slowed improvement in survival among women: HIV-positive women may be starting HIV care with more serious disease than men. Women with HIV may be at a disadvantage because of lower education or income than men. And other social factors may make it harder for HIV-positive women to get good health care.

The three groups with lower life expectancy—injection drug users, nonwhites, and women—should do their best to start and continue regular HIV care. They should get whatever help they need from government agencies and community groups to overcome obstacles to care, such as getting help with child care, breaking a drug habit, or taking advantage of government assistance programs. HIV providers can help people with these challenges to contact government agencies or other healthcare professionals who can help with specific needs.

In this study people who started their first antiretroviral combination with a CD4 count below 350 had a much shorter life expectancy than people who began antiretrovirals with a higher CD4 count. That finding supports advice from US experts that people with HIV and HIV providers should not wait until CD4 counts fall below a certain level to start antiretroviral therapy. These experts say people with HIV and their providers should strongly consider starting antiretrovirals regardless of CD4 count.

The researchers who conducted this study make an important point about their findings. As a group, people with HIV differ in many ways from the general population in the US and Canada. For example, they include much higher proportions of blacks and other nonwhites, more current and former injection drug users, and more gay and bisexual men. All of these groups may face economic and social challenges or may have lifestyle habits that raise their risk of poor health. At the same time, HIV-positive people have higher rates of certain non-HIV diseases than people in the general population, such as heart disease and hepatitis C virus infection. For these and other social and health rea-
sons, people with HIV may be expected to die earlier than people without HIV. In other words, HIV-positive people may be expected to have a shorter life expectancy than the general population for reasons not directly related to HIV infection. So the steadily increasing life expectancy of many people with HIV in this study seems all the more impressive.

This study assessed life expectancy based on death rates through the end of 2007. It is possible that life expectancy in HIV-positive people changed after 2007. Life expectancy could have improved between 2007 and today because of newer antiretrovirals that are easier to take and cause fewer side effects. These newer antiretrovirals probably make it easier for people to take their pills without interruption and thus keep HIV under control year after year. But some studies show that people with HIV die from certain non-HIV diseases at an earlier age than people without HIV. If that holds true for a large number of HIV-positive people taking effective antiretroviral therapy, their life expectancy may have improved as much as it can, or it may even start decreasing.

The bottom line for people with HIV is that antiretroviral therapy—especially therapy begun at a higher CD4 count—is giving them the chance to live as long as people without HIV. That news should encourage HIV-positive people to take their antiretrovirals on time every day to keep HIV under control. And it should encourage people with HIV to avoid or get good care for non-HIV diseases like heart disease and diabetes.

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   http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0081355


US HIV-positive men and women who started combination antiretroviral therapy at a CD4 count above 350 had a non-AIDS death risk almost exactly the same as that of HIV-negative men and women with similar lifestyles and disease risk factors. People who started antiretrovirals at a CD4 count under 350 had a higher non-AIDS death risk than the comparison group of HIV-negative people.

Combination antiretroviral therapy greatly lengthens the lives of people with HIV infection. It does so by preventing or reversing AIDS diseases and some non-AIDS diseases as well. A study reviewed just before this one in HIV Treatment Alerts! found that people who started antiretroviral therapy with a CD4 count above 350 and some other groups with HIV can now expect to live as long as people in the general population of the United States and Canada. Other recent studies also found normal or nearly normal life expectancy in some people with HIV.

Several recent studies found health advantages for starting antiretroviral therapy at higher CD4 counts, before allowing HIV to do more damage. As a result, US antiretroviral experts now recommend that everyone with HIV should consider starting therapy, whatever their CD4 count.

But how starting antiretrovirals at a higher CD4 count will affect survival with HIV remains uncertain. It will take a long time to see if people starting current antiretroviral combinations at a high CD4 count will live as long as people without HIV, and to figure out which HIV-positive people have the best chance of living longer. Studies addressing these questions so far have not separated AIDS deaths from non-AIDS deaths in making these predictions. And these studies have compared survival in people with HIV with survival of people in the general population—not in people with economic backgrounds, lifestyles, and disease risks similar to people with HIV.

To learn more about how antiretroviral therapy begun at different CD4 counts affects chances of death with AIDS and non-AIDS diseases, researchers working with two large study groups in the United States conducted this new analysis. The groups they studied include HIV-positive men and women as well as HIV-negative men and women with similar social and economic backgrounds and similar habits. In addition, the researchers analyzed AIDS death risk and non-AIDS death risk separately.

**How the study worked.** The study involved HIV-positive and negative men in the Multicenter AIDS Cohort Study (MACS) and HIV-positive and negative women in the Women’s Interagency HIV Study (WIHS) (Table 1). MACS and WIHS are ongoing studies that include HIV-positive people and HIV-negative people with similar health habits and economic backgrounds. All men in MACS are gay or bisexual. Members of MACS and WIHS make regular visits for check-ups and interviews. Information from those visits is available for studies like this one.

**Table 1.** Two HIV study groups in the US: MACS and WIHS

- **MACS:** The Multicenter AIDS Cohort Study is an ongoing assessment of the health and behavior of HIV-positive and negative gay and bisexual men in four US cities.
- **WIHS:** The Women’s Interagency HIV Study is an ongoing assessment of the health and behavior of HIV-positive and negative women in six US cities.
- Men and women in MACS and WIHS make regular visits to study sites to have medical checkups and to answer questions about personal behavior and other factors that may affect their health.

*Words in bold are defined in the Technical Word List at the end of this issue of HIV Treatment Alerts.*
This analysis involved two groups of men and women—those without HIV and those with HIV who had started antiretroviral therapy. The researchers recorded how many men and women in each group died during the study period, which ran from age 35 for each person up to January 1, 2011. The research team used death certificates and data from the National Death Index to determine whether people died from an AIDS disease or a non-AIDS disease. The analysis did not include deaths due to accident or poisoning.

HIV-positive people in the study were divided into three groups:

1. People who started antiretroviral therapy at a CD4 count below 201, or late starters
2. People who started antiretroviral therapy at a CD4 count of 201 to 350, or intermediate starters
3. People who started antiretroviral therapy at a CD4 count above 350, or early starters

The researchers used sophisticated statistical methods to determine the risk of AIDS death or non-AIDS death in each of these CD4-count groups compared with the risk of death in HIV-negative men and women in MACS and WIHS. This type of analysis can simultaneously weigh the impact of several factors that affect the risk of death. For their statistical analysis, the researchers weighed the potential impact of study group (MACS or WIHS), infection with hepatitis B or hepatitis C, hypertension, depression, smoking, and employment (full time, part time, student, or unemployed).

What the study found. The study involved 6699 people, including 3854 without HIV. Compared with HIV-positive people, those without HIV were more likely to be younger, in MACS, white, high school and college graduates, employed, nonsmokers, and heavy drinkers. HIV-negative people were less likely to have depression and more likely to have hypertension.

During the study period, 165 people without HIV died, 341 people with HIV died of AIDS, and 199 with HIV died of non-AIDS diseases. Among people without hepatitis B or C infection, the most common causes of non-AIDS death were heart disease (38%), non-AIDS cancers (27%), lung disease (10%), and liver disease (5%). In people with hepatitis B or C infection, the most common causes of non-AIDS death were liver disease (28%), non-AIDS cancer (24%), heart disease (15%), kidney disease (8%), and lung disease (7%).

Among people with HIV, the proportion dying from a non-AIDS disease was highest in early starters of antiretroviral therapy (78%), followed by intermediate starters (74%), and late starters (49%). (See numbered list in preceding section for definitions of early, intermediate, and late starters.) In other words, people who started antiretroviral therapy at a higher CD4 count tended to die of non-AIDS diseases rather than AIDS diseases; and people who started therapy at a lower CD4 count tended to die of AIDS diseases rather than non-AIDS diseases.

Early starters of antiretroviral therapy died of non-AIDS diseases at an older median age (72.0) than intermediate starters (68.6) or late starters (65.7). So people who started antiretroviral therapy at a higher CD4 count were less likely to die of an AIDS disease and more likely to live longer before dying of a non-AIDS disease. But all three HIV-positive groups tended to die of non-AIDS diseases at younger ages than HIV-negative people. Median age when HIV-positive people died of AIDS was also highest in early starters of antiretroviral therapy (54.4), lower in intermediate starters (52.4), and lowest in late starters (47.4). However, this part of the analysis did not consider the possible impact of other risk factors.

Starting antiretrovirals at a CD4 count below 200 or between 201 and 350 raised the risk of death regardless of whatever other death risk factors a person had. Among these other risk factors, infection with hepatitis B or C, smoking, depression, unemployment, and hypertension each independently raised the risk of non-AIDS death compared with HIV-negative people (Figure 1). HIV-positive women in the WIHS study group had a 41% higher risk of non-AIDS death than HIV-negative people. But early antiretroviral starters had almost exactly the same risk of non-AIDS death as people without HIV.

Statistical analysis that did consider the impact of several other death risk factors determined that late starters of antiretroviral therapy had more than a doubled risk of non-AIDS death compared with people without HIV (Figure 1). Intermediate antiretroviral starters had a 66% higher risk of non-AIDS death than HIV-negative people. But early antiretroviral starters had almost exactly the same risk of non-AIDS death as people without HIV.

People who started antiretroviral therapy at a CD4 count above 350 died of non-AIDS diseases at a later age than people who started therapy at a lower CD4 count in a large US study.
What the results mean for you. This large and carefully planned study reached several important conclusions about risk of death in HIV-positive men and women starting antiretroviral therapy compared with HIV-negative men and women in the same study groups. Perhaps most importantly, statistical analysis indicated that HIV-positive people who start combination antiretroviral therapy at a CD4 count above 350 have a risk of dying from non-AIDS diseases very similar to that of HIV-negative people in the comparison groups. In contrast, people who started antiretrovirals at lower CD4 counts had higher risks of dying from non-AIDS diseases than comparison groups without HIV.

These results add to earlier findings indicating that antiretroviral therapy does more than lower the risk of dying from AIDS: If treatment begins at a higher CD4 count, it also lowers the risk of dying from non-AIDS causes—like heart disease, cancer, and kidney disease. Partly because of findings like these, experts working with the US Department of Health and Human Services now recommend that everyone with HIV infection should consider starting antiretroviral therapy, whatever their CD4 count.6

Another important finding of this study is that HIV-positive women in the WHIS study group had a 40% higher risk of dying from non-AIDS diseases than HIV-positive men in the MACS group. This finding is particularly disturbing because women in the general US population usually live longer than men in the general population. The researchers suggest that the high death risk in these HIV-positive women may mean the social and economic disadvantages suffered by these women remain strong enough to affect their survival above and beyond those risk factors considered in the statistical analysis.

The study found that HIV-positive men and women also infected with hepatitis B virus or hepatitis C virus (1) died of AIDS more often than people without hepatitis and (2) died of non-AIDS diseases 15 years earlier than people without hepatitis. Infection with a hepatitis virus adds greatly to the health problems faced by people with HIV. HIV-positive people not already infected with hepatitis B should get the vaccine that prevents this infection. There is no vaccine for hepatitis C. Sharing drug-injecting equipment and having sex without condoms allow hepatitis viruses to pass from an infected person to an uninfected person.

People already infected with hepatitis B or C should work with their HIV provider to get proper treatment for these infections. (See the article on hepatitis C starting on page 36 of this issue.) Several stronger and easier-to-take drugs to treat hepatitis C infection recently became available. With proper treatment, HCV infection can be cured in most people.

Figure 1. A CD4 count under 201 when starting antiretroviral therapy more than doubled the risk of death from a non-AIDS disease in HIV-positive US men and women compared with HIV-negative men and women. A CD4 count between 201 and 350 when starting antiretrovirals raised the non-AIDS death risk 1.66 times (66%). But people who started antiretrovirals with a CD4 count over 350 had a non-AIDS death risk almost exactly the same as that of people without HIV. Six other factors also independently raised the risk of non-AIDS death in men and women with HIV.
The study identified four other factors that raised the risk of a non-AIDS death in people with HIV: smoking, depression, hypertension, and unemployment. Smoking can cause or contribute to heart disease, cancer, lung disease, and other diseases that greatly raise the risk of death. For antiretroviral-treated people who smoke, quitting is probably the single most important thing they can do to live longer. There are many effective treatments for hypertension and depression, including drug therapies and nondrug therapies.

Researchers who conducted this study went to great lengths to make their statistical analyses as accurate as possible. Still, factors they did not consider could affect the results. But the study has many strengths, including its large size, the long observation time of people with and without HIV, and HIV-negative comparison groups similar to the HIV-positive groups in many ways. The results should encourage HIV-positive people to start antiretroviral therapy if they have not already done so. And the findings should encourage people already taking antiretrovirals to take their medications faithfully, without skipping doses.

References


African Americans in five US clinical trials had a 40% higher risk of antiretroviral* treatment failure than whites after statistical analysis accounted for many personal and medical factors that might affect treatment failure. The failure rate remained consistently higher in blacks than whites for all antiretroviral combination regimens studied.

AIDS Clinical Trials Group (ACTG) researchers noted that blacks account for almost half of all new HIV infections in the United States and that HIV-positive blacks have a 9 times higher death rate than HIV-positive whites. Numerous studies show that African Americans stop antiretroviral therapy sooner than others and that antiretroviral therapy fails more often in blacks.

Difficulties in steady access to antiretroviral therapy could be one factor explaining these differences between US blacks and whites. But two studies of HIV-positive people in the US military—where everyone has equal access to antiretroviral therapy—also found differences in treatment response between minority racial and ethnic groups and whites.

The ACTG researchers who conducted this new study suggested several other reasons why African Americans may have a worse response to antiretroviral therapy than whites, including differences in income, living circumstances, medical conditions, behavior, and attitudes about HIV and antiretroviral therapy.

To get a better understanding of these issues, the ACTG team analyzed responses to antiretroviral therapy in five trials whose primary goal was to assess antiretroviral failure (failure to achieve or maintain an undetectable viral load) with various antiretroviral combinations.

**How the study worked.** The analysis involved five ACTG trials that compared various antiretroviral combinations and took place between 1998 and 2006. No one had taken antiretrovirals before they entered these trials. The new analysis focused on people who identified themselves as black (and not Hispanic) or white (and not Hispanic). The researchers did not analyze people who took a combination of three nucleoside analogs in one trial, because that combination did not control HIV well.

Participants in these five ACTG trials made study visits at least every 8 weeks for measurement of their viral load and CD4 count. Most study participants (92%) regularly reported whether they missed any antiretroviral doses over the past 4 days.

The main goal of the combined five-trial analysis was time to virologic failure regardless of whether people changed their original antiretroviral combination. The researchers defined time to virologic failure as the time between entering the study and (1) having two consecutive viral loads above 1000 copies (with the first between study week 16 and week 24), or (2) having two consecutive viral loads above 200 copies (with the first at or after study week 24).

To identify factors that predicted time to virologic failure, the researchers used a type of statistical analysis that simultaneously considers several factors that may affect failure. By weighing the impact of these individual factors at the same time, this type of analysis can single out factors that affect chances of failure by themselves—regardless of whatever other risk factors a person has. The factors included in this analysis were age, viral load, CD4 count, having a positive blood test for hepatitis C virus, self-reported mode of HIV infection, highest education level, depression, number of children in household, perceived social support, perception of how well antiretroviral therapy works, alcohol use, marijuana use, and self-efficacy (belief in your ability to meet certain goals).

**What the study found.** The 5-study analysis involved 2495 people starting their first antiretroviral combination: 1151 (46%) were black and 1344 (54%) were white. The study group included 473 women (19% of 2495), with 331 blacks (70% of 473) and 142 whites (30%). The whole group had a median age of 37 years, a median pretreatment viral load of 100,000 copies, and a median pretreatment CD4 count of 210. Compared with whites, blacks were more likely to have a lower pretreatment viral load and a lower pretreatment CD4 count.

*Words in **bold** are defined in the Technical Word List at the end of this issue of HIV Treatment Alerts.*
Study participants took 15 different antiretroviral combinations in these trials. They participated in the study at 55 research clinics across the United States.

Similar proportions of blacks and whites believed they had good support from family or friends. One third of black men lacked confidence that antiretrovirals have positive health benefits, compared with one quarter of white men, white women, and black women. White men had more education than black men or white or black women.

About 80% of all study participants reported taking all their antiretrovirals in the preceding 4 days at study weeks 4, 12, 24, 48, 72, 96, and 120. But whites consistently reported missing fewer antiretroviral doses than blacks over the preceding 4 days.

Median observation time for everyone in the 5 ACTG trials was 129 weeks (2.5 years), with no major differences between blacks and whites. Antiretroviral treatment failed in 854 study participants (34% of 2495), including 468 blacks (41% of 1151) and 386 whites (29% of 1344). The 3-year failure rate was 45% in blacks and 32% in whites.

Statistical analysis that considered many factors that may affect antiretroviral failure determined that blacks had a 40% higher risk of failure than whites (Figure 1). In other words, this analysis determined that blacks had a higher risk of treatment failure regardless of whatever other risk factors they had (such as less education or missing antiretroviral doses). This higher risk among blacks did not vary from one antiretroviral combination regimen to the next.

Six other factors independently raised the risk of antiretroviral treatment failure: younger age, higher pretreatment viral load, testing positive for hepatitis C virus (HCV), two measures indicating less education, and not taking all antiretroviral doses in the past 4 days (Figure 1). All of these factors except younger age and higher viral load were more common in blacks than whites. Missing antiretroviral doses in the past 4 days raised the risk of treatment failure more than any other single factor, including black race.

What the results mean for you. The main finding of this large and well-planned study is that blacks starting antiretroviral therapy in the United States had a 40% higher risk of treatment failure than whites in studies conducted between 1998 and 2006. Other factors linked to a higher risk of failure—like age, education, and pill-taking habits—did not explain this difference between blacks and whites.

The study does offer a hint at why blacks had a higher treatment failure rate than whites in these five trials: The higher risk of failure among blacks held true regardless of which combination study participants took, and there were 15 different combinations. That probably means biological factors do not explain the response difference between blacks and whites. Such biological differences may include differences in antiretroviral levels and tolerability that depend on genetic differences between blacks and whites.
If biological differences cannot explain the higher failure risk in blacks, social and economic factors not measured in this study probably do explain that difference. Although the study considered a great many social and economic factors—like education and belief that antiretrovirals have benefits—no study can include every factor that may affect antiretroviral treatment response. For example, these researchers did not have information on income or housing of study participants.

A critical finding of this study is that missing antiretroviral doses had the strongest impact on antiretroviral failure risk. Statistical analysis indicated that people who missed doses had a 2.5 times higher risk of treatment failure. In comparison, the other risk factors (listed in Figure 1) raised chances of failure 1.2 times to 1.5 times.

The strong link between missing antiretroviral doses and treatment failure emphasizes the importance of taking all antiretroviral doses exactly as your HIV provider directs. If you have trouble taking your antiretrovirals on time, talk to your provider about it. There are many methods to help people remember when they’re supposed to take medications. If you think the antiretrovirals you’re taking are causing side effects (like nausea, rash, or sleep problems), tell your provider right away. Side effects can often be controlled. Don’t stop an antiretroviral drug on your own because you think it may be causing side effects.

The higher antiretroviral failure rate found in blacks than whites in this study does not mean blacks should lose faith in the benefits of antiretroviral therapy. Millions of blacks, whites, and Asians across the world—including African Americans—are avoiding AIDS and non-AIDS diseases and living longer because they’re taking antiretrovirals. Most blacks in the 5 studies analyzed here had good responses to their antiretrovirals—including good CD4 count gains—for the 3 years that these studies lasted. And since these 5 studies ended, many new antiretrovirals have become available. These new antiretrovirals are often stronger and cause fewer side effects than older antiretrovirals. And several new antiretrovirals are combined with others in tablets that can be taken once a day.

US experts on antiretroviral therapy recommend treatment for everyone with HIV, regardless of CD4 count.16 If you have not started antiretroviral therapy, or if you started and stopped, talk to your HIV provider about finding an antiretroviral combination that will work for you. Other research discussed in this issue of HIV Treatment Alerts! found that many HIV-positive people taking antiretrovirals can now expect to live as long as people without HIV. (See the articles starting on pages 20 and 24.)

References

In the United States, black gay and bisexual men take antiretroviral therapy less often than white gays, and a lower proportion of blacks reach an undetectable viral load. Those findings from a nationwide comparison of black and white gay and bisexual men could explain why black men run a higher risk of passing HIV to sex partners than white men.

Black gay and bisexual men bear a heavy burden of HIV infection in the United States. Compared with white gays and bisexuals, blacks have a 6 times higher rate of new HIV infections. The overall HIV rate is almost 4 times higher in black gays and bisexuals than in white gays and bisexuals. One study estimated that up to half of all US black gay/bisexual men will have HIV infection by age 35.

Reasons for these differences between black and white gay/bisexual men are not well understood. Several studies found no evidence that black gays differ from white gays in sex practices that may increase their risk of HIV infection. But researchers from the US Centers for Disease Control and Prevention (CDC) suggested two factors that may contribute to the higher HIV risk in black gays and bisexuals:

1. Because black gays tend to have sex with other blacks, and because blacks already have a higher HIV rate than whites, HIV-negative blacks stand a higher chance of picking up HIV infection during sex.
2. Some research shows that lower proportions of HIV-positive black than white gays take antiretrovirals and thus fewer blacks have an undetectable viral load. People with an undetectable viral are less likely to pass HIV to sex partners than people with a detectable viral load.

To get a better understanding of why black gay and bisexual men have higher HIV rates than whites, CDC researchers conducted the study described here. Specifically, they aimed to compare three factors in sexually active black and white gays: risk taking during sex, antiretroviral use, and rates of reaching an undetectable viral load.

How the study worked. The study involved HIV-positive people at least 18 years old in care across the United States and involved in the CDC’s Medical Monitoring Project. The CDC runs the Medical Monitoring Project to study behavior and medical information in a group of HIV-positive adults who represent people with HIV across the United States and its territories. This particular study focused on HIV-positive people who made at least one medical visit from January through April 2009.

Everyone involved in this study completed a face-to-face interview and had medical records checked from June 2009 through May 2010. All participants were in care at one of 461 healthcare centers in California, Delaware, Florida, Georgia, Illinois, Indiana, Michigan, Mississippi, New Jersey, New York, North Carolina, Oregon, Pennsylvania, Puerto Rico, Texas, Virginia, or Washington state.

This analysis involved 1010 interviewed men who reported having oral or anal sex with another man in the past 12 months. All men described themselves as black (and not Hispanic) or white (and not Hispanic). The CDC team used standard statistical methods to calculate that these men represented 102,300 HIV-positive adults receiving care in the United States from January through April 2009.

The researchers determined three sexual behaviors for each study participant: (1) anal sex without a condom with a male partner who was HIV-negative or whose HIV status was unknown, (2) condom-free anal sex with such a partner while having a detectable viral load, and (3) number of anal sex partners in the past 12 months. Men reported whether they were currently taking antiretroviral therapy. The researchers checked medical records to determine whether each man had (1) a most recent viral load at or below 200 copies, and (2) all viral loads in the past 12 months below 400 copies.

The CDC team used accepted statistical methods to figure which HIV transmission risk factors (sexual behavior, antiretroviral use, and viral load) differed significantly between black and white men.

*Words in bold are defined in the Technical Word List at the end of this issue of HIV Treatment Alerts.*
What the study found. The study focused on 1010 sexually active gay or bisexual men, 314 of them (31%) black and 696 (69%) white. The researchers calculated that these men represent 30,477 HIV-positive black gay/bisexual men and 71,823 HIV-positive white gay/bisexual men across the United States. Compared with white men, black men were younger, less educated, poorer (35% versus 15% living in households below the US poverty level), more likely to have a lapse in health insurance or coverage in the past 12 months (39% versus 18%), and more likely to have tested positive for HIV within the last 5 years (34% versus 23%).

Risky sex was no more likely among black men than white men: Blacks and whites did not differ in proportions who had anal sex without a condom or who had anal sex when they did not have an undetectable viral load. A significantly lower proportion of black than white men had 4 or more male sex partners in the past 12 months (21% versus 30%).

But significantly lower proportions of sexually active black men than white men were taking antiretroviral therapy (80% versus 91%). And fewer blacks than whites had a current viral load at or below 200 copies (64% versus 79%) or had all viral loads below 400 copies in the past 12 months (48% versus 69%).

Statistical analysis identified five factors linked to lower chances of black or white men taking antiretroviral therapy (Figure 1).

When the researchers included these factors in a statistical analysis of antiretroviral use in black and white men, the proportion of white men using antiretrovirals stayed at 91% while the proportion of black men using antiretrovirals rose from 80% to 84% (Figure 2, left).

Figure 1. A study of 1010 black or white HIV-positive men representing 102,300 gay/bisexual men in care for HIV across the United States identified five factors that affect whether men use antiretroviral therapy: younger age, lapse in health insurance, poverty, shorter time since HIV diagnosis, and less advanced HIV disease.

Figure 2. Statistical adjustment for factors that can influence antiretroviral use (younger age, lapse in health insurance, poverty, shorter time since HIV diagnosis, less advanced HIV disease stage) or maintaining an undetectable viral load for 12 months (younger age, lapse in health insurance, poverty, shorter time since HIV diagnosis, less education) gives a more precise estimate of how much black gay/bisexual men differed from white gay/bisexual men in these two measures (back row versus front row). Even after statistical adjustment, lower proportions of black men used antiretrovirals or maintained an undetectable viral load. But the impact statistical adjustment had on estimates in black men indicates that the factors considered (age, insurance, etc) explained some of the difference between black men and white men.
The resulting 7 percentage point difference in antiretroviral use between white and black men (91% compared with 84%) was still statistically significant, meaning that chance does not explain the difference. But the narrowing difference between white and black men after statistical analysis accounted for these five factors means those factors partly explain the difference in antiretroviral use between black and white men.

Statistical analysis identified five factors linked to lower chances that antiretroviral-treated men would keep their viral load below 400 copies for 12 months (Figure 3):

- Younger age
- Lapse in health insurance
- Poverty
- Shorter time since HIV diagnosis
- Less education

When the researchers included these factors in a statistical analysis of maintaining an undetectable viral load for 12 months, the proportion of white men with a 12-month undetectable load fell slightly from 74% to 72% while the proportion of black men with a 12-month undetectable viral load rose from 58% to 65% (Figure 2, right). The resulting 7 percentage point difference in a 12-month undetectable viral load between white and black men (72% compared with 65%) was not statistically significant. This loss of statistical significance after statistical analysis accounted for these five factors means these factors largely explain the difference in viral suppression between black and white men.

- What the results mean for you. This important study offers the first look at sexual behavior, antiretroviral use, and viral loads in black and white gay or bisexual men in care for HIV infection across the United States. Because of the way CDC researchers planned this study, the 1010 men analyzed represent more than 100,000 gay or bisexual men with HIV across the country.

Black gay/bisexual men in the United States have a much higher rate of new HIV infection than white gay/bisexual men. This study found that differences in sexual behavior between black and white men probably do not explain the higher HIV rate in black men. Black men in this study did not have anal sex without condoms more than white men, and they had fewer anal sex partners in the last year than white men. So among people receiving care, something other than sex practices must explain the differing HIV rate between black and white gay/bisexual men.

Almost 90% of HIV-positive men in this study were taking antiretroviral therapy. And high proportions of treated men had an undetectable viral load for a span of 12 months. But the CDC found that lower proportions of black men than white men (1) were taking antiretroviral therapy, (2) had a current undetectable viral load, or (3) had an undetectable viral load for 12 months.

These differences could partly explain higher HIV rates in black than white gay/bisexual men across the United States. Only a few rare individuals have an undetectable viral load without taking antiretroviral therapy. And people with a detectable viral load run a much higher risk of passing HIV to sex partners than people with an undetectable viral load. Since more black than white men in this study group had a detectable viral load, black gay/bisexual men probably run a higher risk of spreading HIV to sex partners than do white gay/bisexual men.

The study also identified factors that could explain why fewer black than white men take antiretroviral therapy in the United States, and why fewer black men have an undetectable viral load. Four factors—younger age, periods without health insurance, poverty, and shorter time since HIV diagnosis—partly explained both the lower antiretroviral use and the lower undetectable viral load rate in black men than in white men. Less advanced HIV disease helped explain lower antiretroviral use by black men, and less education helped explain why a
lower proportion of black men kept their viral load undetectable for 12 months.

The Affordable Care Act offers a way for all uninsured people in the United States to get health insurance. Black gay and bisexual men—and anyone with HIV—who doesn’t have regular health insurance should get help applying for insurance through the Affordable Care Act. HIV providers, other healthcare workers, and community groups can tell people with HIV where to get help applying for health insurance at the following website: https://www.healthcare.gov/

This study confirms that, as a group, black gay/bisexual men are younger than white gay/bisexual men. And younger gay or bisexual men in this study were more likely not to use antiretroviral therapy and not to have an undetectable viral load. Other research shows that younger people are less likely to seek care for HIV infection and less likely to take their antiretrovirals consistently. Young people should realize that they are not invulnerable to the serious ill effects of HIV infection. Untreated HIV infection can result in lifelong negative health consequences that are difficult to treat.

Men in this study who tested positive for HIV more recently were less likely to take antiretrovirals and less likely to have an undetectable viral load. These findings reflect other research showing that people with a more recent HIV diagnosis are less likely to be in care for their infection. Beginning care for HIV infection is the crucial first step to controlling HIV and living a long and healthy life with HIV infection. Other research described in this issue of HIV Treatment Alerts! indicates that certain groups of HIV-positive people in the United States—including those who start antiretroviral therapy at a CD4 count above 350—can live as long or almost as long as people without HIV. (See the articles starting on pages 20 and 24.)

The CDC researchers who conducted this study suggest that other factors they did not measure could contribute to lower antiretroviral use by black gay/bisexual men than by white men: HIV provider prescribing practices and differences in acceptance of antiretroviral therapy by blacks versus whites. HIV experts working for the US Department of Health and Human Services recommend antiretroviral therapy for everyone with HIV infection, whatever their CD4 count. Besides improving the health of individuals who start antiretrovirals, these experts note, treatment also lowers the chance that a person will pass HIV to a sex partner. People with HIV and their providers should work together to overcome obstacles preventing a person from starting antiretroviral therapy.

Poverty and limited education—which contributed to lower antiretroviral use and/or a lower chance of having an undetectable viral load—are difficult problems to overcome. Both require planning and a long-term effort. The CDC team who conducted this study suggests that job training and community development programs can help low-income people with less education improve their lot. Case workers whom HIV-positive people meet in social welfare programs and community groups can recommend available programs and help people get enrolled.

References

HIV-positive people who also had hepatitis C virus (HCV) infection had a worse response to their first antiretroviral* combination than HIV-positive people without HCV, according to results of a 3041-person study.\footnote{Words in \textit{bold} are defined in the Technical Word List at the end of this issue of \textit{HIV Treatment Alerts.}} The group infected with both HCV and HIV had a worse \textit{viral load} response to antiretrovirals, a worse \textit{CD4 count} response, and a doubled risk of AIDS or death. The researchers who conducted the study believe their findings support an earlier start to antiretroviral therapy in people also infected with HCV.

Almost one third of HIV-positive people in the United States also have HCV infection. These two viruses often infect the same people because they are both carried in blood and thus can pass between people who share drug-injecting equipment or who have sex together. HCV infects the liver and can cause serious liver damage and death if left untreated. People who study HIV and HCV agree that HIV can worsen HCV infection.\footnote{Words in \textit{bold} are defined in the Technical Word List at the end of this issue of \textit{HIV Treatment Alerts.}} But researchers still disagree on how HCV affects the course of HIV infection. Studies on how HCV affects HIV infection have reached conflicting conclusions, possibly because many of these studies were small, involved differing groups of people with HIV and HCV, and assessed different antiretroviral combinations, many of which are no longer used today.

To get an up-to-date look at how HCV affects people with HIV infection, AIDS Clinical Trials Group researchers combined the results of four studies of antiretroviral therapy. They compared the impact of antiretroviral treatment in people infected only with HIV and in those infected with both HIV and HCV.

\textbf{How the study worked.} The AIDS Clinical Trials Group (ACTG) studies HIV infection and its complications, often comparing leading antiretroviral combinations. For this analysis of how HCV affects response to antiretroviral therapy, an ACTG team combined findings from four clinical trials.\footnote{Words in \textit{bold} are defined in the Technical Word List at the end of this issue of \textit{HIV Treatment Alerts.}} All of these trials studied key antiretrovirals, most of which are still widely used today. All trials accepted people with HCV infection and tested people for HCV when they entered the trial.

Trial participants returned regularly to the study clinic—usually every 12 weeks—for measurement of HIV viral load, CD4 count, and other medical data typically collected in trials of this kind. Every 24 weeks, study participants reported whether they took all their antiretroviral doses in the previous 7 days.

This new analysis focused on three racial/ethnic groups: black non-Hispanics, white non-Hispanics, and Hispanics. By comparing HIV-plus-HCV-positive people with HIV-only trial participants, the researchers aimed to learn how HCV affected four results:

\begin{enumerate}
  \item Virologic failure, defined as two consecutive viral loads of (1) at least 1000 copies at or after study week 16 and before week 24, or (2) at least 200 copies at or after week 24
  \item Change in CD4 count and \textit{CD4 percent}
\end{enumerate}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{HCV_and_liver_fibrosis.png}
\caption{Hepatitis C virus (HCV) infects the liver and can cause serious liver damage, including fibrosis or cirrhosis (scarring), if left untreated. Almost one third of HIV-positive people in the United States also have HCV infection. (Images of liver from Servier Medical Art, http://www.servier.co.uk/medical-art-gallery/. Image of HCV from Wikipedia Commons.)}
\end{figure}
3. Time to a new AIDS illness or death, or time to death alone
4. Time to first serious (grade 3 or 4) signs or symptoms or laboratory abnormalities

The researchers used accepted statistical methods to determine how HCV affected response to antiretrovirals measured by these four results. By simultaneously considering several factors that can affect these results, this type of analysis can pinpoint individual factors that affect results regardless of whatever other risk factors a person has.

What the study found. This analysis involved 3041 people, including 1197 whites (39%), 1117 blacks (37%), and 727 Hispanics (24%). Most study participants (81%) were men. Of these 3041 people with HIV, 279 (9%) also had HCV infection. Compared with HIV-only people, those with HIV and HCV were older (median 44 versus 37), more likely to be black (47% versus 36%), and more likely to inject drugs currently or in the past (52% versus 5%).

Depending on the measure used, 10% to 13% of HIV/HCV-infected people had signals of severe liver scarring called fibrosis (Figure 1).

Compared with people infected only with HIV, those infected with HIV plus HCV had a significantly shorter time to treatment failure after starting antiretroviral therapy. The estimated time when 20% of people in each group had virologic failure (defined at number 1 in the preceding section) was 112 weeks in people infected only with HIV, compared with only 48 weeks in people with HIV and HCV. Statistical analysis that weighed the impact of many treatment failure risk factors determined that people with HIV and HCV had a 43% higher risk of failure than people with only HIV (Figure 2). The worse viral load response in people with HIV plus HCV did not differ according to which antiretroviral combination people took.

People with HIV and HCV gained fewer CD4 cells after starting antiretrovirals in these four trials than did people infected only with HIV. After 48 weeks, CD4 counts were an average 32.8 cells lower in the HIV-plus-HCV group than in the HIV-only group. At that point the average CD4 gain in people with HIV and HCV was 27.8 cells smaller than the average gain of people infected only with HIV. The lower CD4-cell gain in the HIV-plus-HCV group persisted through 144 weeks of antiretroviral therapy. And the worse CD4-cell response in people with HIV plus HCV held true when the researchers limited the analysis to people in whom antiretrovirals were not failing to control viral load. Finally, the lower CD4 gains in people with HIV plus HCV did not differ according to which antiretroviral combination people took.

During the study period, 11% of people with HIV plus HCV had a new AIDS disease or died, compared with 5% of people with HIV alone. Statistical analysis that considered several factors that may affect chances of death or development of an AIDS illness determined that people with HIV plus HCV had a doubled risk of AIDS or death compared with the HIV-only group (Figure 2). The same kind of analysis figured that people with HIV plus HCV had a 5 times higher risk of death compared with people infected only with HIV, those infected with HIV plus HCV had higher rates of virologic failure (detectable viral load), AIDS or death, death alone, or serious safety concerns in a 3041-person study. (For providers: 95% confidence intervals around these point estimates were 1.07-1.91 for virologic failure, 1.42-3.13 for AIDS or death, 2.48-10.67 for death alone, and 1.26-1.81 for safety concerns.)
alone (Figure 2). Among people who died, death could be attributed to accidents, suicides, or substance abuse in 41.2% of the HIV-plus-HCV group versus 20.6% of the HIV-only group.

A higher proportion of people with HIV plus HCV than with HIV alone had a serious (grade 3 or 4) safety concern (65% versus 53%). Most of this difference could be explained by a higher rate of liver enzyme elevation, a signal of poor liver function, in the HIV-plus-HCV group (14% versus 3%). Statistical analysis considering multiple factors that may affect serious safety concerns determined that people with HIV and HCV had a 51% higher risk of such concerns than people with HIV alone (Figure 2).

After 24 weeks of antiretroviral therapy, people infected with both HIV and HCV reported 100% antiretroviral pill-taking more often than people infected only with HIV. At that point the HIV-plus-HCV group had a 73% higher chance of perfect pill-taking. After 48, 72, and 96 weeks of antiretroviral therapy, rates of perfect pill-taking were similar in people with HIV plus HCV and in those with HIV alone.

**What the results mean for you.** This large and well-planned analysis of HIV-positive people with and without HCV infection in four antiretroviral treatment trials made several important findings. Compared with people infected only with HIV, those infected with HIV plus HCV before starting their first antiretroviral combination had:

- A faster time to antiretroviral treatment failure measured by viral load response
- A lower increase in CD4 count and CD4 percent
- A higher risk of a new AIDS illness or death
- A higher risk of death alone

The researchers who conducted this study suggest these results support starting antiretroviral therapy earlier in HIV-positive people who also have HCV infection. Earlier treatment might help people with HIV plus HCV reach and maintain an undetectable viral load, gain more CD4 cells, and avoid new AIDS illnesses and death. Antiretroviral experts working with the US Department of Health and Human Services recommend early antiretroviral therapy for people also infected with HCV or hepatitis B virus, including people who have high CD4 counts or cirrhosis (liver scarring).13

The worse antiretroviral treatment outcomes in people with HCV also suggest that HIV clinicians should check viral loads, CD4 counts, and possible safety concerns very closely in such people to catch the earliest hints of trouble.

Another important finding of this study is that people with HIV plus HCV took their antiretrovirals on time after 24 weeks of antiretroviral therapy, people infected with both HIV and HCV reported 100% antiretroviral pill-taking more often than people infected only with HIV. After that, the HIV-plus-HCV group and the HIV-only group did not differ in how faithfully they took their antiretrovirals through 96 weeks of observation. The researchers who conducted this study observe that people who had injected drugs before entering the original four trials may have been evaluated very closely by trial physicians to exclude people with bad pill-taking habits. As a result, HCV-positive former drug injectors who entered these trials may have been a select group with particularly good pill-taking habits.

But even if that’s true, the good pill-taking by HIV-plus-HCV people in this study demonstrates that such people—including people who have injected drugs—can take their antiretrovirals on time. Taking your antiretrovirals exactly as your HIV provider directs is critical to achieving the best possible response to antiretroviral therapy, whether you have HCV or not.

Finally, the ACTG team that ran this study points out that treatment for HCV infection in changing rapidly right now. New, stronger, easier-to-take anti-HCV drugs are becoming available, and they are improving results of anti-HCV therapy. Improved responses to anti-HCV drugs could have a big impact on how HCV infection affects the response to antiretroviral therapy in people with HIV.


Having a viral load between 50 and 199 copies for 6 months doubled chances that antiretroviral* therapy (ART) would eventually fail, when compared with always keeping the viral load below 50 copies.1 Risk of ART failure (defined as a viral load above 1000 copies) was even higher in people whose viral load stayed between 200 and 499 copies or 500 to 999 copies for 6 months.

Today’s antiretroviral combinations can usually make a person’s viral load undetectable, even if several combinations have already failed in that person. The goal of antiretroviral therapy for anyone receiving treatment is to reach and maintain an undetectable viral load, which means fewer than 25 to 75 HIV RNA copies per milliliter of blood, depending on which viral load test is used. When the viral load stays that low, HIV cannot change its genetic code to become resistant to antiretrovirals, although some HIV does remain in the body.

From time to time, the viral load will bounce back into the detectable range and then fall back below the limit of detection again. Isolated viral blips like this do not pose a threat that antiretroviral-resistant HIV will develop or that the antiretroviral combination will fail to keep HIV under control. But little is known about the risk of resistance or treatment failure when the viral load bounces into the low but detectable range and stays there for several months. Before this study, HIV experts couldn’t predict what will happen if a person’s viral load bounces to between 50 and 200 copies, or to between 200 and 400 copies, and stays there for several months.

To answer that question, researchers in Montreal, Canada, compared rates of virologic failure in people who always kept their viral load below 50 copies and people whose viral load rose to between 50 and 999 copies for 6 to 12 months.

Researchers divided study participants into four groups: (1) people whose viral load always remained undetectable, that is, below 50 copies, (2) people with a viral load between 50 and 199 copies for 6, 9, or 12 months, (3) people with a viral load between 200 and 499 copies for 6, 9, or 12 months, and (4) people with a viral load between 500 and 999 copies for 6, 9, or 12 months. The observation period continued until virologic failure, defined as a viral load above 1000 copies, or until the most recent visit in which viral load was measured.

The analysis did not include (1) people whose viral load never fell below 1000 copies and (2) people with repeated viral load blips, defined as a viral load of 50 to 999 copies followed by a viral load below 50 copies.

The Montreal researchers used standard statistical methods to measure associations between viral load status (defined two paragraphs above) and virologic failure. These analyses considered the potential impact of several factors on virologic failure: age, gender, date of HIV diagnosis, sexual orientation, monthly income, type of employment, CD4 count, injection drug use, and any antiretroviral use.

**What the study found.** The study included 1860 people with a median age of 40.8 years at their first study visit. Most study participants were men (94%), gay or bisexual (86%), white (92%), and born in Canada (88%). About one quarter of study participants (28%) had injected drugs. Median observation period for this study was 7.1 years, and median number of viral load measurements was 14 for the 6-month analysis and 13 for the 9- and 12-month analyses.

The rate of virologic failure (a viral load above 1000 copies) was lowest for people who kept their viral load below 50 copies through 6 months: 4.9 failures per year. In contrast, people whose viral load stood between 50 and 199 copies for 6 months had a failure rate of 13.7 per year, and people whose viral load stood between 200 and 499 copies for 6 months had a failure rate of 13 per year. People with a viral load between 500 and 999 copies for 6 months had the highest failure rate: 29 per 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.*
HIV Treatment Alerts

Four years of observation, the failure rate remained significantly lower in the group who always maintained a viral load below 50 copies for 6 months than in those with a viral load of 50 to 199, 200 to 499, or 500 to 999 copies for 6 months (Figure 1). Results were similar when the researchers measured viral loads over 9 months or 12 months. The failure difference between the group with a viral load always below 50 copies and the other groups was always statistically significant, meaning the difference cannot be explained by chance alone.

Three-year failure rates after persistent low-level viral loads (50 to 199, 200 to 499, or 500 to 999 copies) did not change much when the researchers looked at three periods in which low-level loads developed: 1999-2000, 2000-2004, and 2004-2008. In all three study periods, people who kept their viral load below 50 copies always had a statistically lower rate of treatment failure than people with a persistently detectable low-level viral load.

Statistical analysis that weighed the impact of several factors that can affect treatment failure determined that—compared with a viral load below 50 copies for 6 months—a load of 50 to 199 copies for 6 months more than doubled the risk of virologic failure, a viral load of 200 to 499 copies for 6 months also more than doubled the risk of virologic failure, and a viral load of 500 to 999 copies for 6 months raised the failure risk almost 5 times:

- A viral load of 50 to 199 copies for 6 months raised the risk of treatment failure 2.22 times
- A viral load of 200 to 499 copies for 6 months raised the risk of treatment failure 2.15 times
- A viral load of 500 to 999 copies for 6 months raised the risk of treatment failure 4.85 times

**What the results mean for you.** This large Canadian study found that having a low but detectable viral load for 6, 9, or 12 months raised the risk of antiretroviral treatment failure (reaching a viral load above 1000 copies), regardless of whatever other failure risk factors a person had. Even people with a viral load of only 50 to 199 copies for 6 months had a doubled risk of treatment failure when compared with people who always kept their viral load below 50 copies for 6 months.

Six previous studies all found that a low but detectable viral load made antiretroviral failure more likely. But none of these previous studies evaluated the impact of three levels of low detectable viral load (50 to 199 copies, 200 to 499 copies, and 500 to 999 copies) maintained for 6, 9, and 12 months, as in the new Canadian study.

These findings are important because treatment failure indicated by a viral load above 1000 copies can affect a person’s health and can limit the number of antiretrovirals that will remain effective in a person after treatment failure.

**Figure 1.** In a 1860-person Montreal study, people who kept their viral load below 50 copies for 6 months had significantly lower treatment failure rates (viral load above 1000 copies) than people whose viral load stayed between 50 and 199 copies, 200 and 499 copies, or 500 and 999 copies for 6 months. The lower failure rate in people with a viral load below 50 copies held true after 1 or 5 years of observation.
HIV providers face a difficult challenge when deciding whether to advise switching antiretrovirals in a person who has a low but detectable viral load. Tests that detect resistance are not reliable when a person's viral load lies between 50 and 999 copies, so providers can't be sure that resistance is developing in a person with a steady low viral load. But some research shows that low but detectable viral loads sometimes let HIV change its genetic code to become resistant to one or more antiretrovirals. A viral load above 1000 copies raises the chance of resistance farther. When HIV becomes resistant to an antiretroviral, that drug can no longer stop HIV from multiplying in a person's body.

The researchers who conducted this new study suggest that the higher risk of treatment failure at viral loads between 50 and 999 copies means providers should consider certain steps when a person has a low but detectable viral load. Such steps may include (1) reinforcing advice on taking all antiretrovirals as scheduled, (2) measuring antiretroviral levels in blood, (3) considering antiretroviral interactions with other antiretrovirals or other drugs, (4) checking viral load more frequently, or (5) trying resistance testing.

For HIV-positive people taking antiretrovirals, the goal of treatment should always be to reach and maintain an undetectable viral load. Taking all antiretrovirals on time, as your HIV provider directs, is the best way to ensure that your antiretroviral combination will make your viral load undetectable and keep it there. People taking antiretrovirals should never start other drugs—even nonprescription drugs and supplements—without consulting their HIV provider first. Your provider should give you instructions on what to do if you miss one or two antiretroviral doses. If you forget that advice and you do miss doses, check with your provider about what to do.

References

Among 244 HIV-positive people cared for at a North Carolina clinic, 30 (12%) had sex without a condom when they had a detectable viral load* and carried a strain of HIV resistant to one or more antiretrovirals. As a result, this 12% placed sex partners at high risk of infection with HIV that may not be controlled by certain antiretrovirals (anti-HIV drugs).

HIV can change its genetic code to become resistant to individual antiretrovirals or groups of antiretrovirals. Once HIV is resistant to a certain antiretroviral, that drug can no longer stop HIV from multiplying inside the body. HIV cannot become resistant to antiretrovirals when a person keeps his or her viral load undetectable by taking antiretrovirals regularly. HIV has to be multiplying (indicated by a detectable viral load) for resistance to develop.

If a person has HIV resistant to antiretrovirals, that person can pass the resistant HIV to a sex partner or a needle-sharing partner. In this way some people have resistant HIV from the moment they become infected. Of the 48,600 people who became infected with HIV in the United States in 2006, about 7100 (15%) became infected with antiretroviral-resistant HIV. The proportion of newly HIV-infected people who become infected with resistant virus has remained stable at 10% to 20% in North America and Europe for many years. People who get infected with resistant HIV and do not get tested for resistance may start treatment with one or more antiretrovirals that cannot control the resistant HIV.

Research shows that almost three quarters of people with HIV continue having sex after they become infected. Some studies show that many people begin using condoms more regularly after they become infected with HIV, but after a few years many stop using condoms consistently. A certain small percentage of people never use condoms after they pick up HIV infection.

To get a better understanding of sexual risk patterns in people with HIV and to pinpoint factors that may help identify people with a high risk of transmitting resistant virus, researchers at the University of North Carolina at Chapel Hill conducted this study.

- **How the study worked.** Everyone 18 or older receiving HIV care at the University of North Carolina Infectious Diseases Clinic is invited to join an ongoing study of people with HIV, and more than 95% do. When people join the study group and every 6 months after that, researchers record basic information like age, gender, and race, as well as relevant medical information. Study participants may also complete a face-to-face interview that includes information on antiretroviral adherence, sexual activity, and use of alcohol and other drugs.

The researchers were particularly interested in people with a high risk of infecting sex partners with antiretroviral-resistant HIV. People with that risk would have (1) sex without a condom, (2) a detectable viral load (above 400 copies), and (3) evidence of resistant HIV in blood samples. To help determine which people had the greatest risk of transmitting resistant HIV, the researchers constructed a flow chart that included (1) number of recent sex partners, (2) condom use, (3) detectable viral load, and (4) one or more detectable resistance mutations.

Finally, the investigators used standard statistical methods to identify factors that raised the risk of transmitting resistant HIV.

- **What the study found.** The study involved 244 HIV-positive people who had face-to-face interviews between 2000 and 2011. The group included 153 men (63% of 244), 91 women (37%), 171 blacks (70%), 52 whites (21%), and 21 people (9%) of other racial or ethnic backgrounds. While 142 people (58%) had a high school education or less, 102 (42%) had more than a high school education. The study group included 92 gay or bisexual men (38%). About one fifth of the study group (21%) reported being homeless at some point since learning they had HIV infection.

A median of 8 years had passed since people in this group were diagnosed with HIV infection. Median CD4 count stood at 426, and 59% of the group had a viral load below 400 copies. Most study participants, 84%, were taking antiretroviral therapy for their HIV infection at the time of their interview. Only 8 people (3%)
had never taken antiretrovirals. Among people taking antiretrovirals, 44% had taken more than four antiretroviral combinations, 11% reported missing one antiretroviral dose in the past 4 days, and 8% reported missing two or more doses. Regularly missing antiretroviral doses can allow antiretroviral-resistant virus to develop.

The study revealed several factors that distinguished people who had antiretroviral-resistant HIV from those who did not: They were significantly more likely to have depression, to have a history of homelessness, and to use powder cocaine. People with resistant HIV had HIV infection longer than those who did not have resistant HIV, had taken antiretrovirals longer, and had taken more antiretroviral combinations. People who reported excellent adherence to their antiretroviral pill-taking schedule were significantly less likely to have resistant HIV than those who reported poor adherence. Race, gender, and sexual identity did not differ significantly between consistent and inconsistent condom users.

Statistical analysis that considered many risk factors at the same time identified two factors that raised the risk of being in the group with a high risk of transmitting antiretroviral-resistant HIV. Using any illegal substance or heavy alcohol use in the last year more than tripled chances of being in the high-risk group. Being homeless at any time since HIV diagnosis more than doubled the risk.

**High risk of transmitting resistant HIV during sex**

- **70%** One or more sex partners in last 6 months
- **39%** Did not use condoms regularly
- **18%** Had detectable viral load
- **12%** Had detectable resistance mutation

Of the 244 study participants, 172 (70%) had one or more sex partners in the past 6 months (Figure 1). Of those 172, 94 (39% of 244) said they did not use condoms regularly during sex, 18% had a detectable viral load, and 12% had detectable antiretroviral-resistant HIV. Because this 12% had resistant HIV and a detectable viral load during sex without a condom, they had a high risk of passing antiretroviral-resistant HIV to their sex partner.

Several factors distinguished study participants who reported having vaginal or anal sex without a condom from people who used condoms regularly: They were more likely to be younger, to be gay or bisexual, and to use drugs including alcohol. Study participants with an AIDS disease were significantly less likely to report sex without condoms, and viral loads were lower in people who used condoms regularly. Neither race nor gender differed significantly between consistent and inconsistent condom users.

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Several factors distinguished study participants who reported having vaginal or anal sex without a condom from people who used condoms regularly: They were more likely to be younger, to be gay or bisexual, and to use drugs including alcohol. Study participants with an AIDS disease were significantly less likely to report sex without condoms, and viral loads were lower in people who used condoms regularly. Neither race nor gender differed significantly between consistent and inconsistent condom users.
These consistent findings emphasize the importance of always taking antiretrovirals on schedule and always using a condom during vaginal or anal sex. Taking antiretrovirals exactly as your HIV provider directs will help you reach an undetectable viral load as quickly as possible once treatment begins and will keep your viral load undetectable. When your viral load is undetectable, it means HIV is not multiplying in your body. HIV must multiply to become resistant to antiretrovirals, so keeping your viral load undetectable prevents development of resistant virus. At the same time, people with an undetectable viral load are less likely to pass HIV to a partner during sex because their body contains very little HIV.

Always using a condom during sex is the surest way to avoid passing HIV to a sex partner. Wearing condoms has other benefits beyond preventing HIV transmission to an HIV-negative partner. Condoms also block transmission of other sexually transmitted infections, such as herpes and syphilis.

The researchers who conducted this study point to other studies in which people who did not take their antiretrovirals regularly were more likely to have sex without condoms or in which antiretroviral-resistant HIV developed often in people who have sex without condoms. Studies like these show that condom-free sex with multiple partners, poor pill-taking habits, and development of resistant HIV often involve the same people. The North Carolina researchers urge HIV providers to consider these overlapping patterns and to help their patients (1) limit the number of sex partners, (2) wear condoms regularly, and (3) take their antiretrovirals as directed.

This study also found heavy use of alcohol and illegal drugs more than doubled chances that a person would run a high risk of passing resistant HIV to a sex partner. Heavy drinking and heavy use of party drugs pose many health risks. (The next article in this issue of HIV Treatment Alerts! describes a link between heavy drinking and skipping antiretroviral doses.) Drinking and drug use are especially risky just before or during sex. Being high makes people forget to use condoms and take other sexual risks they might otherwise avoid. People with out-of-control alcohol or drug habits should talk to their HIV providers or other healthcare professionals about getting treatment for substance abuse.

References

**Article 12**  
**Heavy alcohol drinking more than doubles risk of HIV treatment interruption**

Compared with HIV-positive people who do not drink alcohol or drink lightly, heavy alcohol drinkers (defined as "severe health-risk drinkers") ran more than a doubled risk of antiretroviral treatment interruption in a large Swiss study. Treatment interruptions can lead to treatment failure, to development of antiretroviral-resistant HIV, and to AIDS or non-AIDS diseases.

Heavy alcohol drinking is associated with a severe health risk and can cause or worsen several medical conditions often seen in HIV-positive people, including liver disease, heart disease, and bone disease. Drinking before or during sex can raise chances of risky sex without condoms, and that could result in sexual transmission of HIV and other infections. Pregnant women who drink face a risk of miscarriage or stillbirth.

Studies in human cells and animal research suggest that alcohol can have a negative impact on the course of HIV infection by lowering **CD4 counts** or raising **viral loads**. Previous research found heavy drinking in 8% to 35% of people in different HIV-positive groups. But the impact of risky drinking has not been closely studied in HIV-positive people over a period of time.

To determine how different levels of alcohol drinking may affect CD4 counts, viral loads, and antiretroviral treatment interruptions in people with HIV, Swiss researchers studied HIV-positive people participating in the Swiss HIV Cohort Study. To assess the effect of alcohol on CD4 counts and viral loads with and without the influence of antiretroviral therapy, the researchers focused on two groups: (1) people who had not started antiretroviral therapy, and (2) people starting their first antiretroviral combination.

### How the study worked
The Swiss HIV Cohort Study (SHCS) is an ongoing analysis of more than 17,000 HIV-positive people representing about 70% of all HIV-positive people in Switzerland. Begun in 1988, the SHCS enrolls HIV-positive people 16 years old or older and asks them to make twice-a-year visits for check-ups and interviews. At those visits healthcare professionals (1) gather basic information on health-related behavior and antiretroviral treatment, and (2) perform blood tests including measurement of CD4 count and viral load.

In August 2005 HIV-positive people in the SHCS started answering questions about alcohol drinking. If they drank alcohol in the past 6 months, they were asked how much alcohol they drank daily. On the basis of how many grams of alcohol people drank daily, researchers described them as (1) nondrinkers or drinkers with a light health risk, (2) drinkers with a moderate health risk, or (3) drinkers with a severe health risk (**Table 1**).

### Table 1. Classification of light, moderate, and severe health risk alcohol drinkers

<table>
<thead>
<tr>
<th>Grams (ounces*) of alcohol daily</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondrinkers/light-risk drinkers</td>
<td>Under 40 (under 1.4)</td>
<td>Under 20 (under 0.7)</td>
</tr>
<tr>
<td>Moderate-risk drinkers</td>
<td>40 to 60 (1.4 to 2.1)</td>
<td>20 to 40 (0.7 to 1.4)</td>
</tr>
<tr>
<td>Severe-risk drinkers</td>
<td>Over 60 (over 2.1)</td>
<td>Over 40 (over 1.4)</td>
</tr>
</tbody>
</table>

*1 ounce is 0.125 (one-eighth) cup, so 0.7 ounce is 0.0875 cup, 1.4 ounces are 0.175 cup, and 2.1 ounces are 0.2625 cup. A 12-ounce beer, 8 ounces of malt liquor, 5 ounces of wine, and 1.5 ounces of 80-proof liquor contain 0.6 ounces of alcohol.*

*Words in **bold** are defined in the Technical Word List at the end of this issue of *HIV Treatment Alerts.*
The researchers considered two separate groups of HIV-positive individuals: (1) people who began their first antiretroviral combination between August 1, 2005 and October 1, 2012 and answered at least one alcohol questionnaire in the first 12 months of antiretroviral therapy, and (2) people who did not take antiretrovirals, had a known date of their first positive HIV test between August 1, 2005 and October 1, 2012, and answered at least one alcohol questionnaire in the first 12 months after their positive HIV test.

The Swiss investigators were mainly interested in how different levels of alcohol drinking affected (1) CD4 count over time, (2) antiretroviral treatment failure (failure to reach an undetectable viral load or reaching an undetectable viral load and then having two detectable loads), and (3) antiretroviral treatment interruption (stopping antiretroviral therapy for more than 7 days without a medical reason).

The SHCS researchers used reliable statistical methods to identify factors that affected CD4-count change, antiretroviral failure, and antiretroviral interruption. This type of statistical method considers the possible impact of numerous personal and health factors at the same time. By doing so, the method can identify factors that have an impact on the three outcomes independently of all other factors considered.

What the study found. This analysis of alcohol use involved 2982 people starting their first antiretroviral combination. Researchers followed changes in CD4 count, viral load, and antiretroviral pill taking of these people for a median of 30 months. There were 2085 people who had not started antiretroviral therapy, and researchers tracked their CD4 counts for a median of 2 months after their positive HIV test.

Three quarters of antiretroviral-treated and untreated people were men, and three quarters in each group were white. About half of the people in each group became infected with HIV during sex between men, about one third became infected during sex between men and women, and fewer than 10% became infected while injecting drugs. Median age stood at 39 years in the antiretroviral-treated group and 37 years in the untreated group. Median CD4 count stood at 269 in the treated group and 355 in the untreated group.

More than 90% of people in both groups were nondrinkers or light health-risk drinkers (Figure 1). Moderate health-risk drinkers accounted for fewer than 5% in each group, and severe health-risk drinkers made up about 2% of each group.

Of 2982 antiretroviral-treated people, 449 (15%) interrupted treatment. Statistical analysis that considered several factors that may affect treatment interruption determined that severe health-risk drinkers had more than a doubled risk of interrupting treatment when compared with nondrinkers and light health-risk drinkers (Figure 2). When the statistical analysis also considered whether people took their antiretrovirals regularly, severe health-risk drinkers still had more than a doubled risk of interrupting treatment.
Antiretroviral therapy failed in 241 of 2982 treated people (8%). Statistical analysis that considered several factors that may affect treatment failure found no link between drinking level and failure. However, when the statistical analysis included people who interrupted antiretroviral therapy, severe-risk drinkers had a 66% higher risk of treatment failure than nondrinkers and light-risk drinkers (Figure 2).

Level of alcohol drinking had no impact on CD4-count change over time in either the antiretroviral-treated group or the untreated group.

What the results mean for you. This study from Switzerland is among the largest assessing the impact of severe versus light health-risk alcohol drinking on people with HIV infection. The Swiss study did not find a direct link between severe health-risk drinking and antiretroviral treatment failure or CD4 counts. But the study did find that severe health-risk (heavy) drinkers had more than a doubled risk of interrupting antiretroviral therapy than nondrinkers and light health-risk drinkers. That doubled risk did not change when the researchers considered whether study participants took their antiretrovirals regularly (Figure 2).

Previous work by the Swiss researchers found that the more HIV-positive people drink, the more often they miss antiretroviral doses. Other studies found that moderate to heavy alcohol drinkers had a 3 times higher risk of missing antiretroviral doses than nondrinkers.

Repeatedly missing antiretroviral doses can allow HIV to become resistant to the antiretrovirals a person is taking. Eventually those antiretrovirals will no longer be able to control HIV, and treatment will fail. Stopping antiretroviral treatment entirely (for more than 7 days in this study) can have serious health consequences. Without treatment, your viral load will climb and you will become more vulnerable to AIDS diseases and some non-AIDS diseases. A large international study found that even planned antiretroviral interruptions can result in a higher risk of death, AIDS, and serious non-AIDS diseases—including heart, liver, and kidney disease.

For these reasons, you should never stop one or more antiretrovirals unless your HIV provider tells you to. If you think the antiretrovirals you’re taking are causing side effects (like nausea, rash, or sleep problems)—or if you fear alcohol drinking may cause a problem with taking antiretrovirals—you should tell your provider immediately. Side effects can often be controlled by changing the dose of an antiretroviral, switching to another antiretroviral, or by other measures.

The Swiss study did not find a direct link between heavy drinking and antiretroviral treatment failure. But in a statistical analysis that included people after they interrupted antiretroviral therapy, heavy drinking raised the risk of treatment failure 66% (Figure 2).

Besides its impact on antiretroviral interruption and possibly treatment failure, heavy alcohol drinking poses many other threats to people with HIV and to their sex partners. Drinking before or during sex raises chances that people will have sex without condoms, and that could lead to sexual transmission of HIV and other bacterial and viral infections (such as hepatitis C, syphilis, and herpes).
Drinking alcohol can also cause or worsen many non-HIV health problems faced by HIV-positive people. The Centers for Disease Control and Prevention (CDC) lists several immediate and long-term health risks of heavy drinking (Table 2).

How can you tell if you have an alcohol problem? The CDC offers this simple assessment: “Drinking is a problem if it causes trouble in your relationships, in school, in social activities, or in how you think and feel.”

If you think you have an alcohol problem—or if friends or family members say you drink too much—there are several ways to get help: Ask for advice from your HIV provider, from another health professional, or from someone at an HIV community group. For people in the United States, another alternative is to call the National Drug and Alcohol Treatment Referral Routing Service at 1-800-662-HELP. There are many successful approaches to controlling a drinking problem.

Table 2. Immediate and long-term health risks of heavy drinking

<table>
<thead>
<tr>
<th>Immediate health risks</th>
<th>Long-term health risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Risky sexual behavior including sex without condoms and with unknown partners</td>
<td>• Heart problems, including hypertension and heart attacks</td>
</tr>
<tr>
<td>• Miscarriage and stillbirth</td>
<td>• Cancer of the mouth, throat, esophagus, liver, colon, or breast</td>
</tr>
<tr>
<td>• Injuries including traffic accidents and falls</td>
<td>• Liver disease, including hepatitis and cirrhosis (liver scarring)</td>
</tr>
<tr>
<td>• Violence including violence to sex partners and child abuse</td>
<td>• Stomach and pancreas inflammation</td>
</tr>
<tr>
<td>• Alcohol poisoning, which can result in loss of consciousness, coma, or death</td>
<td>• Mental problems including depression, anxiety, and suicide</td>
</tr>
<tr>
<td></td>
<td>• Neurologic problems including stroke, dementia, and neuropathy (foot or hand numbness)</td>
</tr>
<tr>
<td></td>
<td>• Social problems including job loss</td>
</tr>
</tbody>
</table>

Source: Centers for Disease Control and Prevention

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.

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 infection gets higher as the CD4 count gets lower.

CD4 percent is the proportion of CD4 cells relative to other infection-fighting cells in the body. A CD4 percent above 29% is considered healthy. A CD4 percent below 15% reflects advanced HIV infection.

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.

Estimated glomerular filtration rate (eGFR) is a reliable measure of kidney function that incorporates age, race, gender, level of creatinine in blood, and other factors. It requires a small blood sample.

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.

A median is the number above which half of all the numbers recorded lie, and below which half of all the numbers recorded lie. A median age of 45 years mean 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.

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

Viral load is the number of HIV particles in a milliliter of blood or another body fluid, such as semen or cerebrospinal fluid.
If you have HIV, what are the 25 most important things to know? And do!

The Center for AIDS Information & Advocacy
(a program of Legacy Community Health Services)
answers those questions
in an easy-to-read booklet
prepared with the help of
some of the best HIV
providers working today.

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