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INTERVIEW WITH:

James H. Stein, MD

Pointers on cardiovascular disease risk, screening, and management in patients with HIV

Articles by **Mark Mascolini**

Cardiovascular risk factors with HIV infection: a long and motley list

Antiretroviral therapy: from heart risk factor to heart protector?

When and how to screen for cardiovascular disease risk in people with HIV

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Cardiovascular risk factors with HIV infection: a long and motley list

By Mark Mascolini

Abstract: Cohort studies show that cardiovascular disease affects HIV-positive people more often than HIV-negative comparison groups. People with HIV carry a heavy burden of classic and HIV-specific cardiovascular risk factors. HIV itself and combination antiretroviral therapy (cART) appear to inflate cardiovascular risk about 50% in adults and children. At the same time, cART eases cardiovascular disease risk in various ways. Hypertension is highly prevalent in HIV populations and has a profound impact on cardiovascular and overall mortality. A Mediterranean diet rapidly cut rates of MI, stroke, and cardiovascular death in a randomized trial of high-risk people in the general population of Spain. But studies of this diet in small HIV-positive groups have yielded mixed results. Smoking prevalence stands twice higher in HIV-positive than HIV-negative US residents, and smoking may account for one quarter of all deaths and new diagnoses of cardiovascular disease, non-AIDS cancer, and bacterial pneumonia in people with HIV. US research shows that many HIV providers do not even know if their patients smoke. Some evidence suggests heavy alcohol drinking may boost cardiovascular risk in HIV-positive men more than in HIV-negative men. More than 7% of HIV-positive people in the United States have stage 3 or worse chronic kidney disease, which has a great impact on risk of cardiovascular events and heart failure.

When someone fashioned the handy acronym HAART in 1996, it seemed an apt and mnemonically friendly way to name the triple-drug strategy that wondrously reversed the course of AIDS. But it took only 2 years of HAART use to discover what a ruefully sardonic moniker HAART would be. In May 2008, fewer than 24 months after the watershed Vancouver AIDS Conference, Keith Henry and colleagues in Minnesota reported "severe premature coronary artery disease" in two men taking protease inhibitors—one 26 years old and the other 37.[1] Looking at 124 people taking PIs, Henry discovered that a third of them had high lipids. He urged colleagues "to be aware that patients receiving protease inhibitors have the potential for accelerated atherosclerosis." (This watershed report appeared as a 1-page letter in *The Lancet*, after the journal rejected a full-length article with angiograms.)

Everyone knows now that Henry's two young men were no anomalies, but instead harbingers of a heart disease surge that dogs HIV clinicians and disables or kills their patients to this day. In March 2013 a PubMed search for "cardiovascular disease" and "HIV" returned 5225 entries in a remorseless crescendo more than doubling from 163 citations in 1998, the year of Henry's study, to 389 in 2012 (**Figure 1**).

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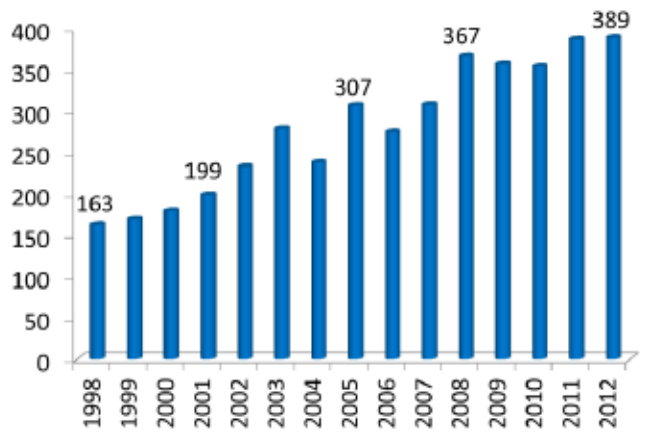

Figure 1. Published reports on cardiovascular disease (CVD) and HIV swelled from 163 in 1998, only 2 years after the introduction of HAART, to 389 in 2012.

Today only the most forbearing experts mapping the interlacings of HIV and cardiovascular disease can resist the heart/HAART homophone. But whatever their rhetorical indiscretions, after 15 years these experts—and allied pathophysiologists, epidemiologists, and statisticians—have offered some solid answers to questions posed by Keith Henry's 1998 case reports:[1] Did HIV infection cause heart disease in these young men? Or was it the protease inhibitors? Or both? Or something else? Unfortunately for those preferring clean causal pathways, the answer to all four questions seems to be yes.

At the same time, HIV heart experts hasten to caution, a causal relationship between HIV or combination antiretroviral therapy (cART) and cardiovascular disease can be established only in a randomized controlled trial, and such a trial—were it even feasible—would have to be large and long.[2] This particular HIV/heart brain trust propose that HIV and antiretrovirals can flick the risk of cardiovascular disease (CVD) in three ways (**Figure 2**)[2]:

- HIV may be a marker of a subgroup in the general population that has a heightened prevalence of one or more risk factors unrelated to HIV or cART per se, such as smoking and drinking alcohol.
- HIV or cART may sway the risk of traditional risk factors, such as abnormal lipids.
- HIV or cART may affect the pathogenic process via nonclassic routes, such as relentless immune activation and smoldering inflammation.

"Importantly," these authorities add, "there is substantial evidence to suggest that all 3 mechanisms are in operation and affect the risk of cardiovascular disease in patients infected with HIV."[2] In other words, it's hard to figure out what's going on. But steadfast research since those first case reports has afforded HIV clinicians a firm footing from which to evaluate, test, counsel, and treat people with HIV who may be headed for heart trouble. The thousands of studies addressing these issues can hardly be boiled down to tidy take-home ABCs, but several points—discussed in detail throughout this issue—are clear:

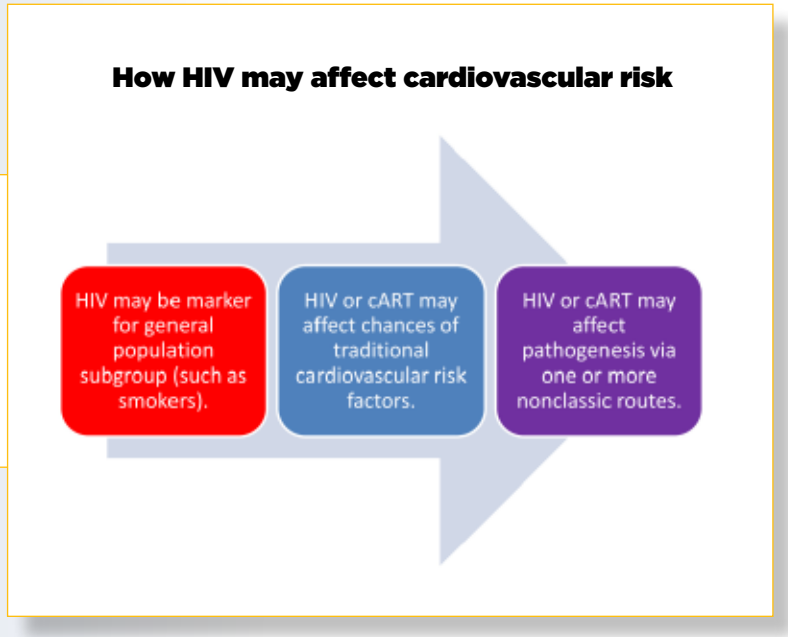

Figure 2. An international panel of experts on heart disease in HIV-positive people outlined three routes by which HIV, its treatment, or both may contribute to development of cardiovascular disease.[2]

- Cardiovascular disease has emerged as a leading cause of non-AIDS death in large international and US cohort studies.
- Cardiovascular disease affects HIV-positive people more often than HIV-negative comparison groups.
- People with HIV carry a heavy burden of classic and HIV-specific cardiovascular risk factors.

Heart disease mortality in people with HIV

Cardiovascular disease kills more people in the United States than any other malady, felling 600,000 people a year,[3] a number higher than the population of Luxembourg. For every 3 people in the United States who die of something else, 1 dies of heart disease. So maybe we shouldn't be surprised that so many Americans with HIV get heart disease and die from it. But when one considers the grisly array of mortal threats people with HIV face—still led by AIDS in most analyses—heart disease exacts a stunning toll in the United States and Western Europe.

A EuroSIDA study with follow-up starting in January 2001 tracked death rates and causes in 12,844 HIV-positive people.[4] During follow-up AIDS arose in 1025 people and 339 (33%) of them died. In the same period 1058 people had a serious non-AIDS diagnosis and 462 (44%) died. Of the 1058 non-AIDS diagnoses, heart disease accounted for 384 (36%), more than attributed to non-AIDS cancer (380), liver-related disease (183), pancreatitis (81), or end-stage renal disease (35).

The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study gathers and deciphers stats on more than 49,000 HIV-positive people in Europe, the United States, and Australia. Parsing input from 33,308 cohort members with data culled up to February 2008, the DAD team counted 2482 deaths, with AIDS causing the highest proportion (29.9%).[5] Cardiovascular deaths accounted for 11.6% of the tally, just behind liver-related deaths (13.7%) and ahead of deaths from non-AIDS cancer, invasive bacterial infection, kidney disease, and pancreatitis.

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The HIV Outpatient Study (HOPS) has tracked HIV-positive people in 10 US cities since 1993. An analysis of 6945 patients seen from 1996 through 2004 logged 702 deaths.[6] In 2004 cardiovascular disease, liver disease, and non-AIDS cancers each accounted for 23.5% of non-AIDS deaths. Rates of cardiovascular death did not rise significantly over the study period. And in one analysis figuring non-AIDS diseases as primary or secondary causes of death with or without an AIDS disease, the cardiovascular death rate fell significantly from 1996 through 2004 ($P = 0.01$).

In contrast, French researchers canvassing a larger, national HIV cohort charted a burgeoning trend in heart deaths.[7] Surveys in 2000, 2005, and 2010 saw the proportion of deaths caused by heart trouble balloon from 8% to 10% to 14%, a highly significant jump ($P < 0.0001$). In 2010 AIDS retained its top mortality ranking, accounting for 25% of deaths, followed by non-AIDS nonliver cancers (22%) and cardiovascular disease (14%). Heart disease vaulted from fourth place in 2005 to third in 2010, swapping spots with liver disease.

Cardiovascular risk with HIV: how different and why?

On its website the CDC lists nine heart risk factors grouped into four categories (**Table 1**).[8] Besides leaving out a personal history of heart disease, the list omits at least 11 risk factors closely studied in people with HIV, many of which apply to the general population as well (**Table 1**). The following review considers most of these risk factors, one by one, with special emphasis on variables probed in studies with clinical endpoints.

This review leaves out male gender and older age, virtually certain predictors of higher heart disease risk in any study including men and women across a range of ages. This analysis also sets aside the knotty question of whether heart disease arises at a younger age in HIV populations. (A recent Veterans Aging Cohort Study audit found it does not.[9]) This review also excludes analysis of many individual biomarkers because clinicians are unlikely to measure things like D-dimer and sCD14 when reckoning a patient's cardiovascular risk.

A spate of DAD Study analyses piqued interest and stirred controversy with their findings that certain protease inhibitors, abacavir, and didanosine upped the risk of myocardial infarction in people with HIV. But these studies, and countless others, consistently show that classic risk factors weigh heavily in the risk equations of people with HIV. A 2007 DAD inquest found, for example, that age, male gender, a previous cardiovascular event, smoking, diabetes, and dyslipidemia each strongly and independently inflated the risk of myocardial infarction.[10]

Yet classic cardiovascular risk factors do not hold true across studies of all HIV populations—they vary with the make-up of the study group and the methods applied. For example, a comparison of 1525 HIV-positive veterans and 843 HIV-negative veterans found that the HIV group shouldered a heavier burden of prevalent cardiovascular disease, hypertension, diabetes, obesity, hazardous drinking, and renal disease.[11] But veterans without HIV were more likely to smoke and to have HCV infection and out-of-line lipids.

Table 1. Cardiovascular risk factors in the general population and in people with HIV

CDC list of risk factors[8]	*Risk factors studied in people with HIV*
Older age*[F]	**Older age*[F]** **Male gender*[F]**
Conditions Abnormal lipids[F] High blood pressure[F] Diabetes	**Conditions** Abnormal lipids[F] High blood pressure[F] Diabetes Personal history of heart disease* Poor kidney function HCV coinfection Vitamin D deficiency or insufficiency Inflammation
Behaviors Tobacco use[F] Poor diet Physical inactivity* Obesity Excessive alcohol use	**Behaviors** Tobacco use[F] Poor diet Physical inactivity* Obesity Excessive alcohol use Cocaine use Hormonal contraceptive use
Family history*	**Family history***
	HIV-specific factors Antiretroviral therapy† Lower CD4 count† Higher viral load†

* Not considered in this review article.

† Considered in a separate review article in this issue.

[F] The Framingham tool for estimating 10-year risk of myocardial infarction considers age, gender, total cholesterol, high-density lipoprotein cholesterol, smoking, systolic blood pressure, and antihypertensive therapy in people who do not already have heart disease or diabetes.

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Statisticians working with the French Hospital Database on HIV figured in 2010 that HIV-positive men have a 40% higher risk of myocardial infarction (MI) than men in the general population, and HIV-positive women have almost a tripled MI risk compared with other women.[12] In the United States a comparison of 3851 HIV-positive people in a Boston healthcare system and over 1 million people without HIV also found that HIV-positive men had a 40% higher MI risk than the comparison group, while women again had a 3-fold higher risk.[13]

A study comparing all 3953 HIV patients in Denmark from 1995 through 2004 and a general-population group of 373,856 people yielded similar results.[14] Compared with the general population, HIV-positive people who had not begun combination antiretroviral therapy had a 39% higher risk of getting admitted to the hospital for ischemic heart disease, though this difference stopped short of statistical significance (adjusted relative risk, 1.39, 95% confidence interval [CI] 0.81 to 2.33). After people with HIV started antiretroviral therapy, they had a doubled (and significant) risk of hospital admission for heart disease (adjusted relative risk 2.12, 95% CI 1.62 to 2.76). But this risk did not grow through the first 8 years of antiretroviral treatment.

Although analyses like these[12-14] try to account for the impact of critical risk factors, heart disease adepts who scrutinize such studies urge caution in parsing the results. The University of Wisconsin's James Stein, among the top authorities in this field, counsels that most data suggesting heightened heart disease risk with HIV come from observational studies "with important methodological limitations, including short durations of follow-up, low CVD event rates, incomplete ascertainment of risk factors and events, and a lack of HIV-negative controls."[15] The Massachusetts study, for example, had an HIV-negative comparison group and adjusted calculations for age, gender, race, hypertension, diabetes, and lipids but couldn't account for one cardinal cardio factor—smoking.[13] Danish investigators were also unable to adjust for smoking in their hospital admission study.[14]

Meta-analysis of studies assessing heart disease risk in HIV-positive people compared with HIV-negative groups determined that antiretroviral-naive people with HIV ran a 61% higher risk (relative risk [RR] 1.61, 95% CI 1.43 to 1.81).[16] Antiretroviral-treated people had a doubled risk of cardiovascular disease compared with the general population (RR 2.00, 95% CI 1.70 to 2.37) and a 52% higher risk than treatment-naive HIV-positives (RR 1.52, 95% CI 1.35 to 1.70).

After considering this study, US antiretroviral guideline writers echoed James Stein in noting that such comparisons of HIV-positive groups and the general population must typically omit a few critical factors like smoking and often cannot tame a statistical bugbear called competing risks.[17] Competing risks can skew statistical analyses when people in a study group succumb to some illness or outcome other than the one being analyzed. For example, an HIV group being assessed for incident myocardial infarction may die first from kidney failure (the competing risk), whereas if they had lived they may have ended up in the group with a new MI.

Researchers working with the Veterans Aging Cohort Study (VACS) tried to conjure a relatively unbiased estimate of myocardial infarction risk with HIV by comparing HIV-positive veterans with an age- and race-matched HIV-negative group behaviorally similar to the HIV group.[18] Rates of drinking and cocaine use, for example, were similar in vets with and without HIV, and the Framingham risk score was 6 (low risk) in both groups. None of these veterans had heart disease when they joined the study

group, and all were in care at some point between April 2003 and December 2009.

Through a median follow-up of 5.9 years, 82,459 veterans had 871 acute MIs, and MI incidence proved consistently higher in vets with HIV in three age brackets ($P < 0.05$ for all comparisons):

MI incidence (per 1000 person-years) in veterans with and without HIV:

- 40 to 49 years: 2.0 with HIV versus 1.5 without HIV
- 50 to 59 years: 3.9 with HIV versus 2.2 without HIV
- 60 to 69 years: 5.0 with HIV versus 3.3 without HIV

After statistical adjustment for Framingham risk factors (see **Table 1** footnote), comorbidities, and substance use, veterans with HIV had almost a 50% higher MI risk (adjusted hazard ratio [aHR] 1.48, 95% CI 1.27 to 1.72). When the researchers focused only on veterans with a viral load below 500 copies/mL, this HIV-positive subgroup still had almost a 40% higher MI risk than veterans without HIV (aHR 1.39, 95% CI 1.17 to 1.66).

Despite the clever plan of this VACS study,[18] like all efforts to reckon whether HIV-positive people run a higher risk of heart disease, it falls short in several ways underlined by the authors. From their list of five possible limitations, the most important is that 97% of study participants were men, so the results do not apply to women. Another limitation they do not mention, perhaps because it is so obvious, is that these veterans have ready access to free care for life. So the results may not hold for the many HIV-positive US men who fall in and out of care and have trouble paying for it.

Myocardial infarction and other heart maladies are hardly the only cardiovascular diseases that seem to affect HIV-positive people more than coevals without HIV. A comparison of HIV-positive and negative people in a Boston healthcare system figured that those with HIV had about a 20% higher risk of ischemic stroke (resulting from clots rather than ruptured vessels).[19] The study focused on HIV-positive and matched HIV-negative people seen between 1996 and 2009. Over that period stroke incidence measured 5.27 per 1000 person-years in the HIV group and 3.75 in the non-HIV group. After statistical adjustment for demographics and stroke risk factors, people with HIV had about a 20% higher ischemic stroke risk (aHR 1.21, 95% CI 1.01 to 1.46, $P = 0.043$). The study linked a higher viral load to a heightened stroke risk.

Some evidence suggests swifter vascular disease progression in people with than without HIV. Using noninvasive ultrasonography to measure carotid intima-media thickness (cIMT), a sturdy marker of subclinical atherosclerosis, offers a safe way to track such changes (**Figure 3**). A cIMT at or above 0.9 mm is abnormal. cIMT is especially useful in HIV populations, James Stein notes, because most HIV groups studied are relatively young and have a low short-term risk of cardiovascular disease.[15]

Meta-analysis of 19 cross-sectional studies confirmed significantly higher cIMT in people with HIV than in HIV-negative comparison groups.[20] A longitudinal comparison of cIMT in people with and without HIV found that 148 HIV-positive people had an abnormal average baseline cIMT (0.91+/-0.33 mm), significantly higher than the average 0.74+/-0.17 mm in 63 age- and sex-matched controls.[21] Comparing 121 HIV-positive and 27 HIV-negative people with a second cIMT a year later showed significantly greater progression in the HIV group (0.074+/-0.13 mm versus -0.006+/-0.05 mm). A nadir CD4 count

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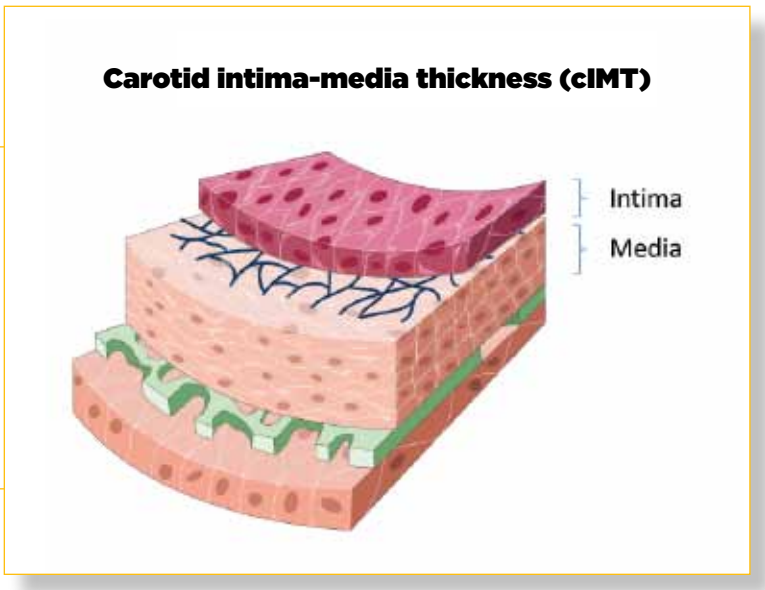

Figure 3. Carotid intima-media thickness (cIMT) measures the two inner layers of the carotid artery, the intima and the media, and offers a noninvasive look at subclinical atherosclerosis and progression. (Illustration from Servier Medical Art. http://www.servier.co.uk/medical-art-gallery/)

at or below 200 cells/mm^3 tended to predict cIMT progression (P = 0.082).

Age averaged a relatively young 45 years in this longitudinal comparison.[21] Another longitudinal study tracked cIMT over time in HIV-positive children and young adults from 2 to 21 years old.[22] Even at these tender ages, the 35-person HIV group had a significantly higher (and already abnormal) baseline cIMT than did 37 matched controls in both the internal carotid artery (0.90 versus 0.78 mm, P = 0.01) and the common carotid artery (1.00 versus 0.95 mm, P = 0.05). After 48 weeks of follow-up, though, cIMT of both arteries decreased significantly in the HIV group (–0.23 mm and –0.15 mm, P = 0.01 for both). Over those 48 weeks, CD4 percent rose and low-density lipoprotein (LDL) cholesterol fell in people with HIV, findings leading the authors to suggest that "lipid control, immune restoration, and viral suppression with continuous antiretroviral therapy" may prevent cIMT worsening in children and young adults.

Still, the prospect of nearly lifelong HIV infection and cART poses special concerns for children infected at birth or early in life. A 3035-child US study found that cardiomyopathy developed in 99 of them through a median 5.5 years of follow-up.[23] Cardiomyopathy incidence stood at 5.6 per 1000 child-years, a rate 40 times higher than in the general population. Triple antiretroviral therapy halved the risk of cardiomyopathy, but taking zidovudine boosted cardiomyopathy risk 90%. (US pediatric antiretroviral guidelines list zidovudine as a preferred first-line antiretroviral for infants, children, and adolescents through puberty.[24]) Ongoing research on cardiovascular disease in HIV-positive children deserves special attention not only from pediatricians, but also from clinicians who will start caring for these youngsters when they reach their late teens and 20s.

Given the added heart risk burden HIV groups tote, can clinicians rely on risk formulas devised for the general population, like the Framingham Risk Score? The short answer seems to be no—because the Framingham index does not account for important HIV-specific variables. The DAD Study group fashioned three HIV-specific risk tools—one for myocardial infarction, one for coronary heart disease, and one for a composite endpoint.[25] All three models proved more accurate than Framingham in a 22,625-person analysis. The final article in this issue of RI*TA!* details differences between the Fram-

Table 2. Antiretrovirals linked to abnormal lipids

Nucleoside analogs	Nonnucleosides	Protease inhibitors	
Stavudine > zidovudine > abacavir	Efavirenz	All ritonavir-boosted PIs	LPV/r > DRV/r >ATV/r
↑ LDL and TG	↑ TG, LDL, and HDL	↑ LDL, HDL, and TG	↑ TG

Source: Panel on Antiretroviral Guidelines for Adults and Adolescents.[17]
ATV, atazanavir; DRV, darunavir; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; LPV, lopinavir; r, ritonavir; TG, triglycerides

ingham and DAD tools. And in an interview in this issue, James Stein advises HIV clinicians on what they can learn from a Framingham score

Whether and when to treat lofty lipids

Like heart disease itself, aberrant lipids trouble a high fraction of all US residents, not just people with HIV. CDC head counters figure that one third of American adults have high LDL ("bad") cholesterol.[26] That rate tops the 27% prevalence of high non-HDL cholesterol charted by HIV Outpatient Study (HOPS) investigators among US men in a survey of 3166 cART-treated men and women in care in 2006-2010.[27] But 81% of these men had some sort of dyslipidemia, 41% had low HDL cholesterol, 32% had high triglycerides, and their median age was only 47. Among women in this study group, 67% had dyslipidemia of some sort, including 27% with low HDL cholesterol. More than half of these women had hypertension, 32% were obese, and their median age was only 45.

The HOPS study group had taken cART for a median of 6.8 years, and treatment almost certainly contributed to their bad lipid numbers. Current US antiretroviral guidelines list all ritonavir-boosted PIs, efavirenz, and abacavir (but not integrase inhibitors or the CCR5 antagonist maraviroc) as lipid mischiefmakers (**Table 2**).[17] But HIV itself, in antiretroviral-naive people, can send lipids off on wayward paths, boosting triglycerides and cutting HDL cholesterol.[28] And studies comparing HIV-positive and negative groups consistently find worse lipid scores in people with HIV.[2]

Lofty triglycerides do heighten myocardial infarction risk in people with HIV, according to a 33,308-person DAD Study analysis.[29] The DAD team figured that the overall impact of high triglycerides on MI risk is small—though still independent of other factors—when the analysis included those other factors.

This DAD analysis followed people enrolled in this European-American-Australian cohort at some point from 1999 through 2008. During 178,835 person-years of follow-up, the investigators recorded 580 MIs. Every triglyceride doubling upped the MI risk 67% in an unadjusted analysis. Layering on one statistical adjustment after another, the DAD team found that relative risk fell with each adjustment but remained independent of other risk factors:

MI risk per triglyceride doubling with HIV:

- Unadjusted relative risk (RR): 1.67, 95% CI 1.54 to 1.80
- Plus adjustment for latest total and HDL cholesterol: RR 1.33, 95% CI 1.21 to 1.45
- Plus adjustment for other cardiovascular risk factors: RR 1.17, 95% CI 1.06 to 1.29
- Plus adjustment for HIV and treatment risk factors: RR 1.11, 95% CI 1.01 to 1.23

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Because the relative MI risk dwindled when the analysis considered other risk factors, the DAD team questions whether drugs that cut triglyceride levels would make a dent in MI incidence among people with HIV.[29] These investigators note that European AIDS Clinical Society Guidelines do not recommend niacin or fibrates to treat high triglycerides in people with HIV.[30] In a review of cardiovascular risk and capricious lipids in people with HIV, US cardiologist James Stein suggests high triglycerides should become a target of lipid-lowering therapy only if levels exceed 500 mg/dL, when pancreatitis poses a threat.[31] (Stein's review, accessible online, is loaded with advice on managing dyslipidemia in people with HIV. He also addresses lipid control in the interview in this issue.)

Of course lipid values other than triglycerides sway MI risk. In the DAD analysis considering triglycerides, total cholesterol, and HDL cholesterol at the same time (second bullet above), every mmol/L (39 mg/dL) higher total cholesterol boosted MI risk 26% (RR 1.26, 95% CI 1.20 to 1.32, $P < 0.001$) and HDL cholesterol below 0.9 mmol/L (35 mg/dL) doubled the risk (RR 2.02, 95% CI 1.39 to 2.95, $P < 0.001$).[29]

US HIV/heart guidelines from the HIV Medicine Association and allied groups are a decade old, but little has changed to affect bedrock management principles: measure fasting lipids before people start cART and within 3 to 6 months after starting a new combo.[28] If changing diet, exercise, and smoking habits doesn't control lipids, start statins (that don't interact with prescribed antiretrovirals) for high LDL or non-HDL cholesterol and fibrates for lofty triglycerides. These guidelines are linked at reference **28** below.

In his 2012 lipid review, James Stein opines, "if there is a single take-home message about treating dyslipidemia to reduce [coronary heart disease] risk [in people with HIV], it is to put patients on statin therapy."[31] Simply stated, Stein observes, statins saves lives: A meta-analysis of statins versus no statins in 160,000 people in the general population found that every 39-mg/dL (1 mmol/L) drop in LDL cholesterol with statins over 5 years trimmed all-cause mortality 10%, coronary heart disease (CHD) mortality 20%, MI and CHD mortality 26%, and major cardiovascular events 21%.[32]

Recent research links statin therapy to a higher risk of diabetes in the general population[33,34] and in people with HIV.[35] In all these studies the statin-related diabetes risk was small and apparently outweighed by the cardiovascular benefits of these drugs. Another recent study tied statin use to lower all-cause mortality in 25,884 people with cART-induced virologic suppression.[36]

How well do US clinicians follow lipid therapy guidelines in people with HIV? The report card features some high marks and some low marks, at least for clinicians seeing people in the HIV Outpatient Study cohort from 2002 through 2009.[37] Among more than 1300 cohort members who had their 10-year cardiovascular risk figured, 28% had less than a 10% 10-year risk, 18% had a 10% to 20% risk, and 20% had a 10-year risk above 20%. Using National Cholesterol Education Program Adult Treatment Panel III (NCEP) guidelines as the standard, the HOPS team found that 81% to 87% of eligible patients got treated for high LDL/non-HDL cholesterol and 56% to 91% got prescriptions for high triglycerides. But only 2% to 11% took lipid drugs for low HDL cholesterol, and only 46% to 69% who needed antihypertensives got them. The investigators concluded that "a large percentage of at-risk patients who were eligible for pharmacologic treatment did not receive recommended interventions and did not reach recommended treatment goals."[37]

Rates and impact of hypertension and diabetes

Abnormal lipids—and what to do about them—have preoccupied HIV clinicians and researchers since the first report of coronary artery disease in cART-treated people.[1] But early on it became clear that flaring lipids are hardly the only heart worry in people with HIV—and hardly the only trigger for vascular "events." Among classic cardiovascular risk factors, hypertension and diabetes represent two of the most treatable conditions.

The CDC estimates that one third of Americans have high blood pressure.[38] An HIV Outpatient Study analysis logged even higher rates in US men and women with HIV.[27] The 3166 people studied had a median age of 47 years and had taken cART for a median of 6.8 years; 21% were women and more than half smoked or used to smoke. Similar high proportions of women (57.4%) and men (54.4%) had hypertension. Almost one third of these women were obese.

Untreated or inadequately treated hypertension has a profound impact on morbidity and mortality (and not only cardiovascular mortality) in people with HIV. A DAD Study analysis of 33,308 HIV-positive cohort members figured that current hypertension doubled the risk of cardiovascular death (adjusted relative rate [aRR] 2.04, 95% CI 1.57 to 2.66) and more than doubled the risk of liver death (aRR 2.34, 95% CI 1.83 to 2.99).[5] Hypertension also independently hoisted chances of all-cause mortality and AIDS mortality.

Meta-analysis of 2242 HIV-positive people in 11 studies determined that hypertension independently magnified the odds of left ventricular dysfunction almost as much as 10 years of age.[39] The adjusted odds ratio for hypertension stood at 2.3 (95% CI 1.2 to 4.5), compared with 2.5 (95% CI 1.70 to 3.6) for every decade of age.

A Swiss HIV Cohort Study analysis of 2595 people with HIV and confirmed hypertension calculated that every 10 mm Hg higher systolic blood pressure boosted the risk of cardiovascular disease 18% (hazard ratio 1.18, 95% CI 1.06 to 1.32).[40] "Insufficient control of hypertension was associated with increased risk for cardiovascular events," the Swiss team noted, "indicating the need for improved management of hypertension in HIV-infected individuals."

Diabetes affects 11.3% of US residents 20 years old or order, according to a 2011 CDC estimate.[41] In contrast, big HIV cohort studies in Europe record much lower diabetes prevalence: 2.5% of 17,852 DAD Study members (from Europe, Australia, and Israel),[42] 2.7% of 8033 Swiss HIV Cohort Study participants,[43] and 3% of 394 HIV-positive people at a London hospital.[44]

Compared with these European cohorts, US studies tabulate much higher diabetes prevalence in HIV-positive people—perhaps reflecting the older age in these US groups than the European groups (**Figure 4**) and the high diabetes rate in the US population at large.[41] A Multicenter AIDS Cohort Study (MACS) comparison of 534 men with HIV and 322 at-risk men without HIV charted an 11.4% diabetes prevalence in the HIV group and an 8.0% rate in the HIV-negative group, a nonsignificant difference ($P = 0.16$).[45] But average age was significantly younger in the HIV group (48.9 versus 52.6, $P < 0.0001$).

A Veterans Aging Cohort Study of 3227 vets with HIV and 3240 without HIV found a significantly lower diabetes prevalence in the HIV group (14.9% versus 21.4%, $P < 0.0001$),[46] though prevalence in

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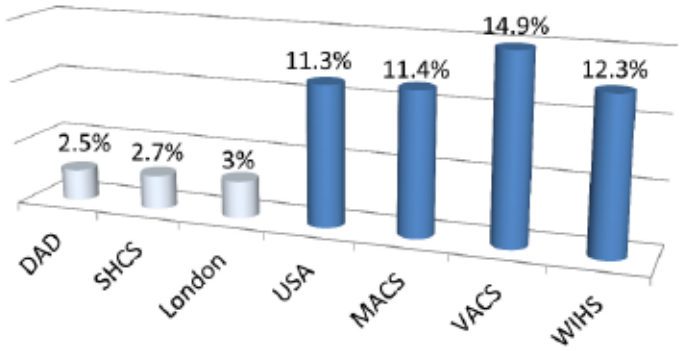
Diabetes prevalence in 3 European and 3 US HIV cohorts



DAD	SHCS	London	USA	MACS	VACS	WIHS
n = 17,852	n = 8033	n = 394	—	n = 534	n = 3227	n = 1797
76% M	69% M	85% M	~50% M	100% M	97.5% M	100% F
39 y	39 y	34 y	≥20 y	49 y	49.6 y	39 y

Figure 4. Diabetes prevalence was much lower in three European HIV cohorts[42-44] than in three US HIV cohorts[45-47] or the US population at large.[41] Younger age in the European groups than the US groups could partly explain the difference between cohorts, but US national data[41] indicate that diabetes is highly prevalent throughout the US, at a rate of 11.3%. In comparison, Diabetes UK estimates that 2.5 million people in England had diabetes in 2012, or 4.7% of the 53 million people in England.[48] (DAD data from Europe, Israel, Australia; SHCS, Swiss HIV Cohort Study; London, Chelsea and Westminster Hospital; MACS, Multicenter AIDS Cohort Study; VACS, Veterans Aging Cohort Study; WIHS, Women's Interagency HIV Study. Ages are medians, mean, or range [for USA]. USA national estimate from CDC.[41])

this largely male HIV-positive contingent was higher than among HIV-positive men in the MACS analysis.[45] Ages averaged 49.6 in the veterans HIV group and 50.8 in the HIV-negative group ($P < 0.001$). A recent Women's Interagency HIV Study (WIHS) survey logged a diabetes prevalence of 12.3% in 1797 women with HIV and 14.0% in 679 without HIV.[47] These HIV-positive and negative women had median ages of only 39 and 35 and a collective body mass index in the overweight range.

Whether HIV and cART confer a higher diabetes risk remains open to question—at least for men. MACS and WIHS studies from the mid-2000s differed in

determining the impact of HIV on diabetes risk—MACS findings a higher diabetes risk with HIV in men[49] and WIHS finding no higher diabetes risk with HIV in women.[50] The Veterans Aging Cohort Study discerned a *lower* diabetes prevalence with HIV than without HIV in a mostly male population.[46]

At least two factors contribute to these seemingly contradictory results—what antiretrovirals people are taking and how the researchers define diabetes. For example, a nationwide French study of 1046 HIV-positive people charted a diabetes incidence of 14.1 per 1000 person-years.[51] Incidence peaked in 1999-2000 at 23.2 and fell afterwards, a turnaround at least partly reflecting abandonment of indinavir, stavudine, and didanosine, all of which heightened diabetes risk in this analysis. CD4 count, CD4/CD8 ratio, and viral load did not affect diabetes risk, but traditional risk factors did (older age, overweight, and waist-to-hip ratio).

The French team defined diabetes by a *confirmed* high blood glucose and/or starting antidiabetic medication.[51] The two US studies that found a higher diabetes risk with than without HIV in men[49] but not in women[50] relied on a single blood glucose level (or antidiabetic medication or a clinical diagnosis). The 97.5% male veterans study that discerned a lower diabetes risk with HIV relied on a confirmed high blood glucose (or other dual clinical criteria).[46] And a Swiss HIV Cohort Study analysis, which used confirmed fasting glucose to define diabetes, observed similar age- and gender-specific diabetes incidence in HIV-positive cohort members and in a population-based cohort of HIV-negative people.[52]

When WIHS researchers updated their diabetes incidence analysis using multiple confirmed diagnostic criteria, they found an independently higher incident diabetes risk in HIV-positive women when diagnosis depended on a confirmed high blood glucose.[47] HIV doubled the diabetes risk in these women after statistical adjustment for age, body mass index, and other variables. The WIHS investigators cautioned that relying on an unconfirmed blood glucose can result in an overestimate of diabetes incidence.

The Swiss study buttressed earlier work linking incident diabetes to nucleosides with or without protease inhibitors—but not to nucleosides plus nonnucleosides.[52] Among protease inhibitors the association held true for the first-generation protease inhibitor indinavir, but not for atazanavir or lopinavir. Three nucleoside combinations—none used routinely today—upped the risk of incident diabetes: didanosine/stavudine, stavudine/lamivudine, and didanosine/tenofovir. Reviewing all recent antiretroviral data, US guidelines list diabetes or insulin resistance as a side effect of three nucleosides (zidovudine, stavudine, and didanosine) and two protease inhibitors (indinavir and lopinavir/ritonavir).[17]

Regardless of whether HIV makes diabetes more likely in women, men, or both, no one doubts the potentially deadly impact of this chronic and often poorly controlled disease. The 33,308-person DAD study analysis that linked current hypertension to higher death rates from cardiovascular disease, liver disease, AIDS, and all causes also found that current diabetes independently raised the risk of death in those four categories.[5]

Obesity compounds cardiovascular risk with HIV

One reason HIV-positive people in the United States have high rates of hypertension and diabetes (see preceding section) is the growing girth of the populace at large. Besides causing or contributing to hypertension and diabetes, obesity heightens the risk of wanton lipids, coronary heart disease, and stroke.[53] The CDC figures more than one third of US adults

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and 17% of children are obese. In 2000, the CDC reports, no state had an obesity prevalence topping 30%; in 2010, 12 states had crossed that line.[54]

In fact, a recent CDC analysis found a higher obesity prevalence in the general US population than in a nationally representative sample of people with HIV.[55] This study focused on 4040 HIV-positive adults in 23 health departments across the United States, comparing them with people in the 2009-2010 National Health and Nutrition Examination Survey (NHANES). Obesity (body mass index above 30 kg/m^2) affected 35.7% of NHANES participants and 22.8% of people with HIV. Age-adjusted obesity prevalence in HIV-positive women exceeded the general population rate (40% versus 36%), but HIV-positive men had an obesity rate less than half that of general-population men (17% versus 36%). Nearly half of HIV-positive women under 40 years old (45%) were obese.

Obesity prevalence fell with age in women with HIV and rose with age in the general population **(Figure 5**).[55] Women with HIV ran a twice higher risk of obesity than HIV-positive men (adjusted prevalence ratio 2.12, 95% CI 1.87 to 2.41). Less education and less advanced HIV infection also made obesity more likely.

Cohort studies verify the savage impact of high weight and visceral fat on cardiovascular risk in people with HIV. FRAM study investigators com-

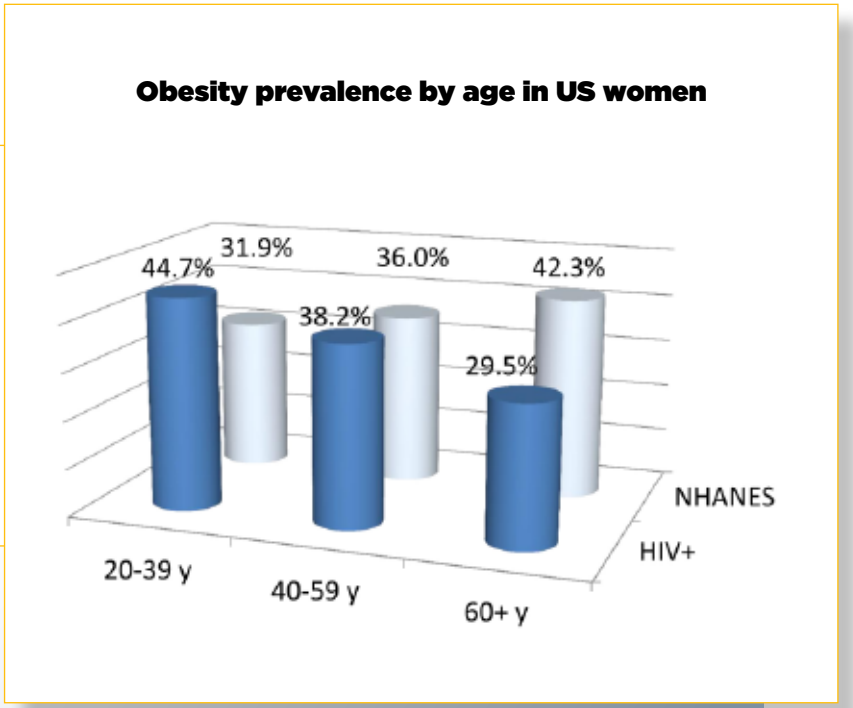

Figure 5. CDC analysis of a nationally representative sample of people with HIV found that obesity prevalence dwindled with age in HIV-positive women but rose with age in women in the general population (NHANES).[55] Linear trend for age $P < 0.01$ for both groups.

pared 586 HIV-positive men and women with 280 HIV-negative controls, calculating regional body fat by whole-body magnetic resonance imaging and figuring heart risk with the Framingham Risk Score.[56] Splitting visceral adipose tissue (VAT) levels into four quartiles, they found that the median Framingham score rose with higher VAT quartiles in people with and without HIV. But in each VAT quartile the Framingham score was significantly or nearly significantly higher in the HIV group than in the HIV-negative group. "Increased VAT is associated with cardiovascular disease risk" with or without HIV infection, the FRAM team concluded, "but the risk is higher in HIV-infected individuals relative to controls at every level of VAT."[56]

Overweight and obese people with HIV also heft a heavier burden of other morbidities familiar to HIV clinicians, according to a 1833-person study at the University of Alabama at Birmingham.[57] Earlier work by this team uncovered a 45% prevalence of overweight and obesity (>25 kg/m^2) among HIV-positive men and women before they began cART in this clinic.[58] The newer study classified participants as underweight, normal weight, overweight, or obese and grouped 15 common non-HIV conditions into three clusters—metabolic, behavioral, and substance use. While 35% of participants were underweight or normal weight, 36% were overweight and 29% obese. Obesity independently predicted having one or more conditions in at least two of the disease clusters (adjusted odds ratio 1.52, 95% CI 1.15 to 2.00). The University of Alabama team urged colleagues to "embrace HIV care as complex chronic disease management of multiple overlapping conditions within the context of primary care."[57]

Italian and Canadian researchers proposed one step toward that daunting goal. They devised a simple tool combining triglycerides (TG) and waist circumference (WC) that predicted a higher Framingham Risk Score—as well as higher VAT and rates of metabolic syndrome and type 2 diabetes—in 1481 men and 841 women with HIV in an Italian study group (**Figure 6**).[59] Researchers divided people into four groups: low WC/low TG, low WC/high TG, high WC/low TG, and high WC/high TG using cutoffs of ≥90 cm and ≥2.0 mmol/L (177 mg/dL) for men and ≥85

A four-box tool to predict CVD risk

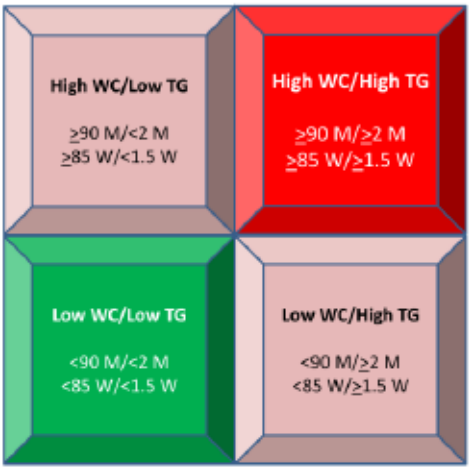

Figure 6. A foursquare tool dividing HIV-positive men (M) and women (W) into four groups according to high or low triglycerides (TG) plus high or low waist circumference (WC) predicted Framingham Risk Score, type 2 diabetes, hypertension, metabolic syndrome, and visceral adipose tissue in a 2322-person study.[59] (Waist circumference in cm; triglycerides in mmol/L; 2 mmol/L = 177 mg/dL; 1.5 mmol/L = 133 mg/dL).

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cm and ≥1.5 mmol/L (133 mg/dL) for women. Men in the high TG/high WC group had the most VAT (208 cm^2), the highest Framingham score (10.3), and the highest prevalence of metabolic syndrome and type 2 diabetes, when compared with other groups of men. Women in the high TG/high WC box also had elevated VAT (average 150 cm^2) as well as the highest Framingham score (2.9) and the highest rates of metabolic syndrome, hypertension, and type 2 diabetes, when compared with other groups of women.

A North Carolina comparison of 92 HIV-positive adults and 92 age-matched HIV-negative people found that overweight/obesity prevalence in the HIV group climbed from 52% to 66% during the first 12 months of cART, a relative increase of 27% ($P = 0.002$).[60] HIV-positive women gained significantly more weight than men, and people starting a protease inhibitor regimen gained significantly more than those starting other regimens. People who began cART with fewer than 200 CD4 cells/mm^3 added significantly more pounds than those starting at higher CD4 counts. Nearly everyone in the HIV-negative group, 93%, was overweight or obese at the start of follow-up, and that rate did not change during the study.

Time for an extended Mediterranean vacation?

Diet and exercise—or at least supplanting a sedentary lifestyle with some vigorous pursuits—offers the surest path to weight reduction while often tempering cardiovascular risk. Research shows that structured exercise programs can cut fat and build lean body mass. But because most exercise studies in people with HIV are small and completion rates often modest, this article focuses on diet and its impact on heart disease.

Whether obese, overweight, or normal weight, many American have bad diets, a failing glaringly reflected in a study of 265 men and 56 women with HIV in Boston and Providence.[61] About 3 in 10 women and 1 in 10 men were obese, while one third of women and 40% of men were overweight. Figuring dietary intake by 3-day food records, the researchers found that total fat and saturated fat intakes exceeded US recommendations for both men and women in all body mass index categories.

Heavier people did not eat more than normal-weight people, but they ate worse, wresting less energy from every kilocalorie (kcal) gulped: average energy intake per kilogram waned significantly from normal weight to overweight to obese in women (33 to 25 to 19 kcal) and in men (40 to 33 to 28 kcal) (**Figure 7**).[61] Diets of overweight and obese people contained significantly less fiber than diets of normal-weight people among both women (11.3 to 9.3 to 6.9 g for normal, overweight, and obese women) and men (13.2 to 12.8 to 11.7 g) (**Figure 7**). A low-fiber diet bespeaks a lack of whole grains, fruits, vegetables, nuts, and seeds.

Worse diets in heavier people in this study probably contributed to three factors intimately linked to cardiovascular risk—significantly worse insulin resistance in both men and women (**Figure 8**), and significantly higher triglycerides and total cholesterol in men.[61]

A study comparing 356 HIV-positive adults with 162 HIV-negative people in the same community determined that, despite consuming similar shares of calories, the HIV group ate significantly more total fat, saturated fat, and cholesterol.[62] Using 4-day food records or 24-hour recall, this Boston study of 197 men and 159 women with HIV also found that

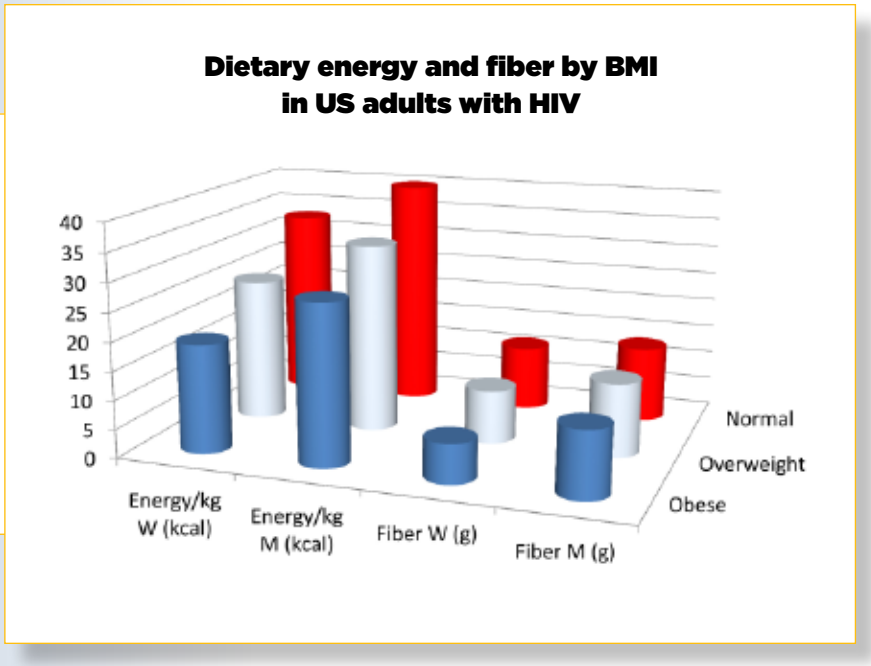

Figure 7. As body mass index (BMI) category rose from normal, to overweight, to obese in a study of 265 men (M) and 56 women (W) with HIV, (**1**) average energy intake per kilogram fell significantly, and (**2**) median fiber content dipped significantly.[61] (See text for exact values.)

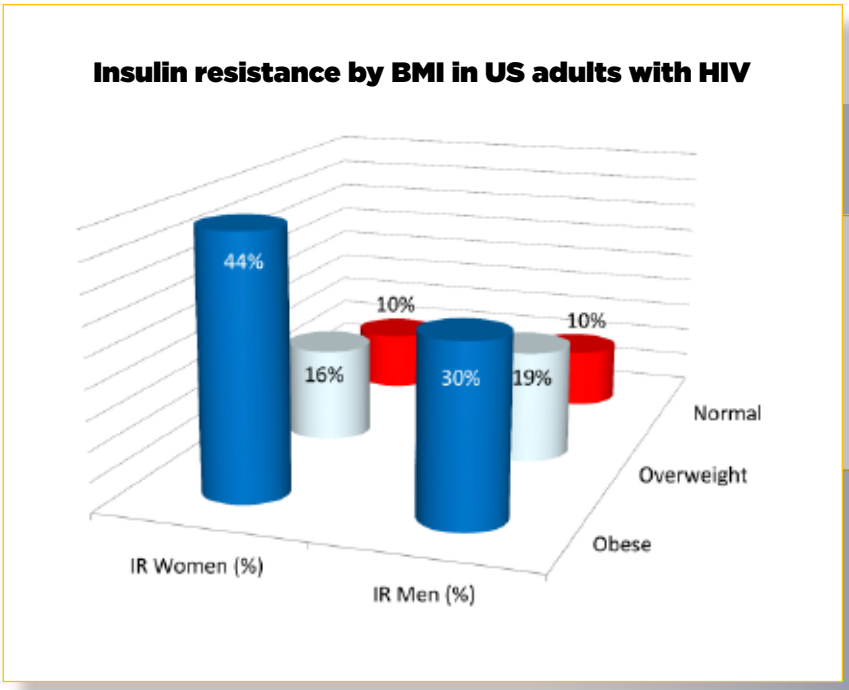

Figure 8. HIV-positive women and men in each higher body mass index (BMI) category had a higher prevalence of insulin resistance (HOMA IR >3.5).[61]

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the HIV group derived a significantly higher percentage of calories from saturated fat and trans fat than the 73 men and 89 women in the HIV-negative group. Triglycerides rose 8.7 mg/dL for each gram of fat an HIV-positive person swallowed ($P = 0.005$).

People who improve their diets reap health benefits, plentiful research attests. Anyone who had occasion to browse the internet or scan a newspaper in the past few months will know results of the randomized clinical-endpoint PREDIMED trial pitting a Mediterranean diet against advice to eat a low-fat diet: People in the two Mediterranean diet groups (supplemented by extra-virgin olive oil or additional nuts) had a 30% lower risk of myocardial infarction, stroke, or death from cardiovascular disease than the low-fat group after only 4.8 years of follow-up.[63]

Adherence to the Mediterranean diet prescribed in this trial (**Table 3**) was good. The PREDIMED researchers believe their striking results "are particularly relevant given the challenges of achieving and maintaining weight loss."[63] Earlier, a systematic review rated a Mediterranean diet the type of diet most likely to ward off coronary heart disease in the general population.[64]

This widely lauded study may have special pertinence for people with HIV because study participants had a high risk of heart disease but a clean cardiovascular slate when they entered the trial. A comparison of risk factors shows, though, that PREDIMED participants were a whole lot closer to a heart attack than 33,308 antiretroviral-treated DAD Study participants in 2010:[5] The PREDIMED contingent ran a higher heart risk by age (67 versus 39 in DAD), body mass index (29 versus 23 kg/m^2), hypertension prevalence (82% versus 14%), and diabetes prevalence (48% versus 3%). The DAD cohort had a twice higher proportion of current smokers (35% versus 14%). More than half of PREDIMED study participants, 57%, were women, and 97% were white Europeans. In the DAD study 26% were women and 54% white. So whether the profound cardio-

Table 3. Mediterranean diet prescribed in the Spanish PREDIMED trial[63]

Recommended	Discouraged
Olive oil	Soda drinks
Tree nuts and peanuts	Commercial bakery goods, sweets, pastries
Fresh fruits	Spread fats
Fish (especially fatty fish), seafood	Red and processed meats
Legumes	
Sofrito (tomato and onion sauce)	
White meat	
Wine with meals (only for habitual drinkers)	

vascular benefit seen with a Mediterranean diet in PREDIMED would hold true in contemporary HIV populations—at least over the short term—remains an open question.

A few studies have appraised Mediterranean fare in people with HIV. A pilot randomized trial in HIV-positive Hong Kong patients found pluses and minuses with a 12-month Mediterranean diet versus a low-fat, low-cholesterol diet.[65] Of the 48 people randomized to one diet or the other, 36 (75%) completed 12 months of follow-up, which included regular dietary consultation. Dietary adherence was good, and use of specific nucleosides and protease inhibitors was similar between study arms. People in the low-fat/cholesterol crew had unfavorable body fat changes in triceps skinfold, hip circumference, and waist-to-hip ratio. Triglycerides rose in the low-fat/cholesterol group while remaining unchanged in the Mediterranean group. The Mediterranean arm had significant jumps in total cholesterol at 9 months ($P = 0.03$) and 12 months ($P = 0.01$), whereas the low-fat group did not. Because of missing data, the researchers did not analyze HDL and LDL cholesterol, so the total cholesterol findings are hard to interpret.

A larger cross-sectional US study linked Mediterranean eating habits to improvements in three heart disease indicators—insulin resistance, triglycerides, and HDL cholesterol.[66] This study involved 247 HIV-positive people with abnormal fat distribution seen at a Boston center, all of whom had complete metabolic profiles available. Researchers figured how closely their diet fit a Mediterranean plan by calculating a Mediterranean Diet Score (MedDietScore).[67] A higher MedDietScore meant (**1**) a lower rate of insulin resistance (standardized beta –0.15, $P = 0.03$), (**2**) marginally lower triglycerides (standardized beta –0.16, $P = 0.13$), and (**3**) higher "good" HDL cholesterol (standardized beta 0.15, $P = 0.01$).

Two studies in Croatia gauged the impact of a Mediterranean diet and other variables on lipids and body fat in the first year of cART.[68,69] Both studies relied on a 150-item questionnaire to rank people in a low Mediterranean adherence group (below 4 points on a 0-to-9 scale) or a moderate to high adherence group (4 to 9 points). Analysis of 117 people interviewed between May 2004 and June 2005 discerned no link between Mediterranean diet and serum lipids.[68] Notably, people in this study were still taking lipid-malefic antiretrovirals such as indinavir and stavudine, both of which were associated with higher total cholesterol.

A similar questionnaire-based dietary analysis of 136 Croatians in the first year of cART during the same period focused on lipoatrophy and lipohypertrophy assessed by self-report and physical exam.[69] Compared with nonsmoking participants with a moderate to high Mediterranean diet score, nonsmokers with a low diet score had nonsignificantly higher odds of lipoatrophy (adjusted odds ratio 4.53, 95% CI 0.86 to 23.92, $P = 0.076$), while smokers with a low diet score had significantly higher lipoatrophy odds (adjusted OR 3.42, 95% CI 1.21 to 9.67, $P = 0.014$), as did smokers with a moderate to high diet score (adjusted OR 4.39, 95% CI 1.35 to 14.26, $P = 0.021$). People with a moderate to high Mediterranean diet score had 70% lower odds of lipohypertrophy (adjusted OR 0.3, 95% CI 0.1 to 0.7, $P = 0.012$).

Although these small studies[65,66,68,69] hint that Mediterranean meal planning can score cardiovascular pluses for people with HIV, hints are all they provide

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(**Table 4**). Results of the randomized PREDIMED trial[63] strongly suggest that HIV-positive people with a heart risk as high as people in this trial can ward off ischemic heart disease by eating more olive oil, nuts, fish, and fresh produce.

But will other healthy diets, leavened with a little exercise, do as well? A small randomized US trial found heart marker benefits with a 6-month low-fat/high-fiber diet plus 3 hours of physical activity weekly.[70] This trial randomized 34 HIV-positive adults with metabolic syndrome to physical activity plus counseling that emphasized a diet low in saturated, polyunsaturated, and trans fat and high in omega 3 fatty acids and fiber or to a control group whose members got monthly counseling sessions on healthy eating. After 6 months the intervention group did significantly better on measures of waist circumference, systolic blood pressure, hemoglobin A1C, lipodystrophy score, and activity measured by the Modifiable Activity Questionnaire. Lipids did not improve significantly in the intervention group compared with the control group. And as in many studies of diet and/or exercise, getting people to stick to the program was not easy. Four people dropped out of the intervention arm and 2 left the control arm for an overall 6-month dropout rate of 18%.

When healthy heart hopes go up in smoke

"Aside from having a history of cardiovascular disease," write HIV heart expert James Stein and colleagues, "current cigarette smoking is the most powerful predictor of CVD events among patients with HIV."[71] Everyone knows that lots of people with HIV smoke more than the most leather-lunged film noir antihero, and everyone knows tobacco sears a deeply corrosive path through many a major organ. The data are so uniform and unequivocal they hardly bear repeating. But this article will detail some of these dreary numbers—and offer a few suggestions on getting people to quit—in hopes that some clinician readers will pluck out a fact or two that will

Table 4. Impact of Mediterranean diet on heart risk factors in HIV studies

Body fat	Triglycerides	Cholesterol	Insulin resistance
▶ No body fat changes (RCT) ▶ Less lipoatrophy (in nonsmokers) (XC Cr) ▶ Less lipohypertrophy (XC Cr)	▶ Triglycerides unchanged (RCT, XC Cr) ▶ Lower triglycerides (XC US)	▶ Total cholesterol up (RCT) ▶ Cholesterol unchanged (XC Cr) ▶ Higher HDL cholesterol (XC US)	▶ Less insulin resistance (XC US)

RCT, 12-month randomized controlled trial in Hong Kong[65]; XC US, cross-sectional study in United States[66]; XC Cr, cross-sectional studies in Croatia.[68,69] See text for study details.

scare patients into stopping, or that some clinician readers will recommit themselves to the difficult chore of helping patients quit.

Why so many HIV-positive people smoke remains unclear. An unadorned hunch is simply that the groups most likely to get infected with HIV include a high fraction of smokers. There seems to be no evidence that people start smoking because they learn they have HIV infection.

The first nationally representative estimate of smoking prevalence in US residents with HIV, unveiled in 2013 by the CDC, found that 42% of HIV-positive people in care smoke, compared with 21% of the US general population.[72] While 37% of people with HIV never smoked, 58% of the general population never lit up. Men made up the biggest proportion of current HIV-positive smokers (72%), while women accounted for 27% of that group and transgenders for 1%. Blacks accounted for 43% of current HIV-positive smokers, followed by whites (36%), Hispanics (16%), and others (5%). Statistical analysis adjusted for age determined that HIV-positive people in care have a twice higher smoking prevalence than the general population (standardized prevalence ratio 1.9). The prevalence ratio stayed near that mark after individual adjustment for gender (1.9), race/ethnicity (2.1), education level (2.0), and poverty level (1.7).

SMART trial investigators recorded a current smoking rate of 40.5% in 5472 HIV-positive participants from 33 countries[73]—nearly the same as the CDC's US estimate.[72] SMART researchers tallied a 24.8% former-smoker rate in this group, compared with 20% in the CDC study. The SMART analysis went on to address a bigger question: what does smoking do to people with HIV? To find an answer they (**1**) figured hazard ratios for major clinical endpoints by comparing SMART participants who smoked at study entry with participants who never smoked and (**2**) calculated population-attributable risk percentages (see note **74**) for the same endpoints.

Compared with SMART enrollees who never got a nicotine high, current smokers ran more than a doubled risk of dying from any cause (adjusted hazard ratio [aHR] 2.4, $P < 0.001$), a doubled risk of incident major cardiovascular disease (aHR 2.0, $P = 0.002$), more than a doubled risk of bacterial pneumonia (aHR 2.3, $P < 0.001$), and almost a doubled risk of non-AIDS cancer (aHR 1.8, $P = 0.008$).[73] **Quitting made a difference.** Comparing former smokers with current smokers, the SMART team found significantly higher adjusted hazard ratios for all-cause mortality (1.5, $P = 0.04$), major cardiovascular disease (1.6, $P = 0.02$), AIDS-related disease (1.6, $P = 0.03$), non-AIDS cancer (2.3, $P < 0.001$), and bacterial pneumonia (1.5, $P = 0.01$) in current smokers.

Comparing current smokers with former and never smokers indicated that 24.3% of all deaths could be attributed to smoking, as could 25.3% of major cardiovascular diagnoses, 30.6% of non-AIDS cancer diagnoses, and 25.4% of bacterial pneumonia diagnoses (**Figure 9**).[74] The SMART team warns that "significant reductions in morbidity and mortality among HIV-infected patients achieved by advances in HIV therapy may be undercut by increases in adverse clinical outcomes attributable to smoking."[73]

In a group 6 times bigger than the SMART population, DAD Study investigators linked current smoking to a 2.2 times higher rate of death from non-AIDS cancers, a 90% higher rate of cardiovascular death, and a 44% higher rate of death from any cause.[5] Unlike the SMART analysis, the DAD team found that former smokers matched current smokers in adjusted death rates for non-AIDS cancer, cardiovascular disease, or any cause. "Studies in the general population suggest that although smoking cessation leads to decreased risk" of death, the DAD

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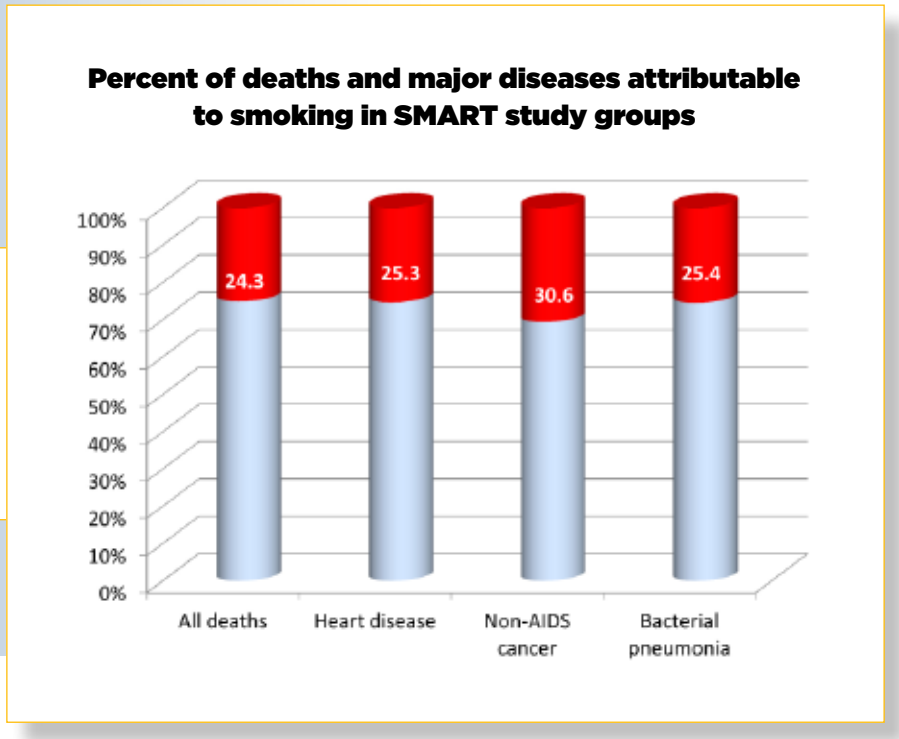

Figure 9. Among START trial participants who died or got diagnosed with a major disease, smoking explained about one quarter of deaths or new diagnoses.[73]

team noted, "ex-smokers remain at an excess risk for a number of years after cessation, with the risk of malignancy in particular remaining raised for up to 10 years."[5]

How many years do risks of heart disease and death stay elevated after a person stops smoking? Another DAD analysis suggested not too many.[75] This study involved 27,136 HIV-positive people with a reported smoking status, divided into never, previous, and current smokers. None had a history of heart disease. The researchers counted how many people had (**1**) a myocardial infarction, (**2**) coronary heart disease (MI plus invasive coronary artery procedure or death from other coronary heart disease), (**3**) cardiovascular disease (coronary heart disease plus carotid artery endarterectomy or stroke), and (**4**) death from any cause. Poisson regression analysis to determine how quitting affected these endpoints factored in cohort, calendar year, age, sex, family heart disease history, time-updated diabetes and lipids, cumulative cART, cumulative indinavir, cumulative lopinavir, and current abacavir. Every additional year without smoking trimmed the risk of the three cardiovascular endpoints significantly (or nearly significantly, $P < 0.06$) (**Figure 10**). This analysis found a nonsignificant trend to lower all-cause mortality with time since quitting.

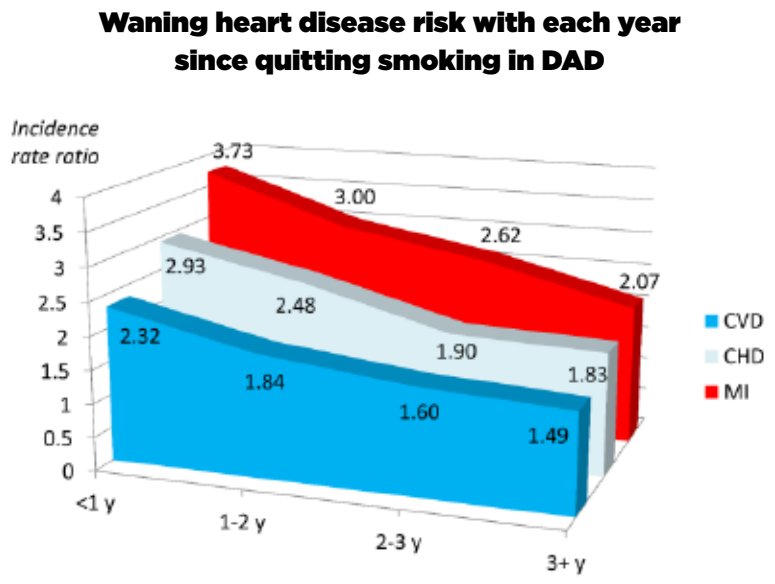

Figure 10. With each year since DAD Study participants quit smoking, incidence rate ratios for myocardial infarction (MI), coronary heart disease (CHD), and cardiovascular disease (CVD) (see text for definitions) declined significantly or nearly significantly.[75]

A nationwide study of everyone in Denmark with diagnosed HIV infection and a matched group of HIV-negative people figured that a 35-year-old smoker with HIV could expect to live to the age of 62.6, whereas a 35-year-old HIV-positive nonsmoker would probably celebrate his 78th birthday.[76] These researchers calculated a much higher death risk due to smoking than figured in the SMART study (61.5% versus 24.3%). Among people without HIV in the Danish study, smoking could explain 34.2% of all deaths. HIV-positive people who smoked had more than a 4.4 times higher risk of death than HIV-positive people who never lit up. The death risk was only 1.7 times higher in HIV-positive former smokers than in people who never smoked.

Smoking appears to abuse arteries more in people with HIV than in HIV-negative people, according to results of a study comparing carotid intima-media thickness (cIMT, **Figure 3**) in 166 men and women with HIV and 152 healthy HIV-negative people.[77] Multivariate regression modeling that considered gender, race, and classic heart risk factors identified a significant three-way interaction between age, smoking burden, and HIV status with respect to cIMT ($P < 0.01$). This interaction indicated that more smoking and older age had a bigger negative impact on cIMT in people with than without HIV.

How to make HIV-positive smokers ex-smokers

Many a clinician will attest familiarity with the foregoing dizzying data—or similar findings that crowd the medical literature. And most HIV-positive smokers say they're already thinking of quitting.[78] Yet HIV providers in a US veterans study were less likely than non-HIV providers even to know if their patients smoked.[79] This 143-provider analysis determined that infectious disease specialists were almost 3 times more likely than generalists not to know whether a patient smoked. If findings like these hold

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true for HIV providers outside the Veterans Affairs system, educating providers seems a good place to start a smoke-ending campaign in people with HIV.

HIV heart maven James Stein and coauthors advise colleagues to take the 5A approach to encouraging patients to break the smoking habit (**Figure 11**).[71] Because effective medications have become available, Stein and colleagues believe "pharmacotherapy is the preferred approach to smoking cessation." Nicotine replacement products now come in gum, lozenges, transdermal patches, inhalers, and sprays.[73] In the interview in this issue, Stein notes that dual pharmacologic therapy—with a nicotine patch and lozenge—proved most effective in one randomized trial. Bupropion or varenicline may work for people who have no success with nicotine replacement. SMART investigators caution, though, that these drugs may interact with antiretrovirals, so consulting an HIV pharmacologist or a reliable drug interaction website is prudent.[73]

Figure 11. HIV heart sages recommend the 5As for getting patients to conquer their nicotine habit.[71]

Clinicians may not realize that the Department of Health and Human Services rounded up 24 physicians and scientists who assembled 276 pages of guidelines on treating tobacco use and dependence.[80] Providers who prefer not to scour every page of that report would do well to scan the "ten key guideline recommendations" on pages 6 through 8, accessible at the link in the reference list.[80] The National Heart Lung and Blood Institute offers a straightforward online patient-directed guide, "Strategies to quit smoking."[81]

SMART investigators stress that smokers often make many attempts to stop before succeeding.[73] Smokers with HIV should know this so they can muster the resolve to try again after one or a few futile tries. And clinicians should know this so they don't quit supporting would-be quitters. Stein and colleagues observe that the best time to campaign against smoking is before a patient starts.[71] Avoiding nicotine is easier than subduing the addiction, and years of cumulative damage can be sidestepped. Clinicians caring for adolescents with HIV, take note.

5A approach to prompting smoking cessation

Ask about tobacco use

Advise to quit

Assess willingness to quit

Assist with quit attempt

Arrange for follow-up

Alcohol, cocaine, and coronary heart disease

Besides tobacco use, two other substance problems figure mightily in cardiovascular risk. The CDC lists one of them, alcohol,[8] but not the other, cocaine.

▶ ***Alcohol abuse.*** Getting drunk boosts chances of transmitting or acquiring sexually transmitted infections, including HIV. The CDC offers a sobering list of long-term health risks from drinking, including dementia, stroke, and neuropathy; depression, anxiety, and suicide; liver, colon, mouth, throat, and esophageal cancer; alcoholic hepatitis and cirrhosis; pancreatitis and gastritis; miscarriage and stillbirth; and cardiovascular disease—including myocardial infarction, cardiomyopathy, atrial fibrillation, and hypertension.[82]

Research in the general population shows that, compared with abstinence, low to moderate drinking (20 g daily) eases the risk of coronary heart disease, while heavy drinking (70 g daily) hikes the risk.[83] This J-shaped curve describing the relation between alcohol volume and heart risk starts its upward swing into the danger zone between 25 and 50 g daily. Five ounces of wine, 12 ounces of beer, and 1.5 ounces of 80-proof liquor contain about 14 g (1.2 tablespoons) of alcohol,[82] so routinely downing four drinks puts one on the road to perdition.

The most illuminating study of alcohol and heart disease in people with HIV found that heavy drinking boosts cardiovascular risk in HIV-positive men—perhaps more than in HIV-negative men.[84] This Veterans Aging Cohort Study (VACS) analysis involved 4743 HIV-positive and negative (and demographically similar) veterans. The analysis excluded women and lifetime abstainers. The VACS team defined infrequent or moderate drinking as 14 or fewer drinks weekly and no binge drinking; hazardous drinking meant more than 14 drinks weekly or binge drinking. The VACS team defined cardiovascular disease by self-report survey and ICD-9 codes. The 2422 HIV-positive and 2321 HIV-negative men both averaged about 50 years in age; about two thirds were black and one quarter white.

Compared with HIV-negative vets, the HIV-positive group had higher proportions of infrequent or moderate drinkers (45.9% versus 42.9%) and current hazardous drinkers (33.2% versus 30.9%), but a lower proportion who ever had an alcohol dependence diagnosis (20.9% versus 26.2%) ($P < 0.001$). The HIV-positive group included significantly lower proportions with key heart risk factors—hypercholesterolemia, diabetes, hypertension, current smoking, and high body mass index.

Among HIV-positive vets, hazardous drinking and alcohol abuse and dependence each independently boosted the odds of cardiovascular disease prevalence about 50%, compared with infrequent or moderate drinking, after adjustment for age, race/ethnicity, traditional heart risk factors, HCV and liver disease, kidney disease, exercise, education, CD4 count, and adherence to cART:

- Hazardous drinking: adjusted odds ratio 1.43, 95% CI 1.05 to 1.94
- Alcohol abuse or dependence: adjusted odds ratio 1.55, 95% CI 1.07 to 2.23

Notably, the links between heavy drinking and heart disease did not hold true in HIV-negative vets, a finding "suggesting the effect of alcohol may be more pronounced among those infected with HIV."[84]

In HIV-positive vets, a familiar list of classic risk factors also hoisted odds of heart disease in this analysis, including older age, high cholesterol, diabetes, hypertension, and current smoking. Kidney disease

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(defined as glomerular filtration rate below 30 mL/min) more than doubled chances of cardiovascular disease (aOR 2.39, 95% CI 1.24 to 4.61). Regular exercise lowered odds of heart disease almost 20%, though that association fell short of statistical significance (aOR 0.81, 95% CI 0.62 to 1.05).

▶ ***Cocaine use.*** More than a few gay and bisexual men, injection drug users, and other substance abusers use cocaine. Some clinicians may not realize that many HIV-positive US women also use cocaine and crack cocaine. A study of 1686 HIV-positive women enrolled in the Women's Interagency HIV Study in 1996-2004 found that 29% used crack during the study period.[85] An analysis controlling for other risk factors figured that persistent crack users ran more than a 3 times higher risk of AIDS death than nonusers. Persistent crack users also lost more CD4 cells and had higher viral loads than women who did not use crack.

A longitudinal study of 736 gay and bisexual men in San Francisco found that cocaine, methamphetamine, and popper use declined over 48 months in older men but rose during the same period in younger men.[86] Compared with men who did not use these drugs, those you used them less than weekly or at least weekly were more likely to have condom-free anal sex with an HIV-positive or status-unknown partner.

HIV clinicians who care for youngsters should realize cocaine habits can start in high school. The national Youth Risk Behavior Survey found that more than 1 in 20 youngsters in the 9th to 12th grades used cocaine at least once in 1993.[87] That rate rose to almost 1 in 10 in 1999, then drifted down to about 7% in 2011.

Cocaine is not kind to the heart. A general-population study of 479 people 50 and younger admitted to the coronary care unit at a Barcelona hospital found that cocaine use prevalence vaulted from 6.8% in 2001 to 21.7% in 2008 ($P = 0.035$).[88] People younger than 30 had more than a 4 times higher cocaine use rate by urine testing than people 45 to 50 (18.2% versus 4.1%, $P = 0.035$). Cocaine users had bigger MIs (by troponin I level) than did nonusers, and more cocaine users died in the hospital (8.3% versus 0.8%, $P = 0.030$).

Two studies of HIV-positive cocaine users at Johns Hopkins University uncovered evidence linking both HIV and cocaine use to coronary artery calcification, an early stage in plaque development that can culminate in coronary heart disease. A cross-sectional study of 192 African Americans in the Baltimore area found a higher prevalence of coronary calcification (measured by computed tomography) in HIV-positive cocaine users (37.6% of 85) than in HIV-negative people who used cocaine (29.8% of 47), HIV-positive people who did not use cocaine (28.6% of 28), or HIV-negative people who did not use cocaine (18.8% of 32).[89] These people averaged about 38 years in age and had no symptoms of cardiovascular disease.

Statistical analysis to reckon the impact of HIV and cocaine use (alone and together) on coronary calcification factored in age, body mass index, LDL cholesterol, triglycerides, mean corpuscular volume, and systolic blood pressure. Compared with total calcification volume in HIV-negative nonusers, the total value was higher in HIV-negative cocaine users (regression estimate [RE] 2.59), higher still in HIV-positive nonusers (RE 2.92), and highest in HIV-positive cocaine users (RE 3.49). Compared with

HIV-negative nonusers, the other three groups all had a significantly higher number of lesions and a significantly higher total calcium score.

Later work by this Johns Hopkins team involved 165 HIV-positive African Americans from 25 to 54 years old and recruited from August 2003 through June 2007.[90] Median age stood at 44 years, and 36% were women; nobody had cardiovascular symptoms. Computed tomography detected significant (50% or greater) coronary artery stenosis in 24 people (15%). Among people who used cocaine at least 15 years and took antiretrovirals for at least 6 months, that rate reached 42%. Regression analysis determined that using cocaine at least 15 years hoisted the odds of significant stenosis almost 8 times (aOR 7.75, 95% CI 2.26 to 31.2), while cART for at least 6 months more than quadrupled the odds (aOR 4.35, 95% CI 1.30 to 16.4).

Duration of stavudine or Combivir drove the association between longer cART and significant stenosis. At least 6 months of stavudine boosted the odds 18 times, while at least 6 months of Combivir raised the odds almost 6 times. Antiretrovirals not associated with significant stenosis in this 6-month duration analysis were zidovudine or lamivudine alone (that is, not as part of Combivir), didanosine, efavirenz, nevirapine, nelfinavir, indinavir, lopinavir, and atazanavir. Odds for abacavir could not be calculated because not many people had used it. Long-term cocaine use, these researchers concluded, "imposes an alarming risk of coronary artery disese."[90]

Faltering kidneys and cardiovascular risk

Kidneys, the fist-sized filters facing each other across the spine, do much more than remove waste (and drugs) from the body: they also balance bodily fluids, release hormones that regulate blood pressure, produce vitamin D, and help make red blood cells.[91] Every day 200 quarts of fluid sluice through the kidneys, percolating through a million nephrons (**Figure 12**). The kidneys extract 2 quarts of fluid daily and return 198. The National Kidney Foundation estimates that 26 million adults in the United States have chronic kidney disease, which poses a high threat of heart disease.[92]

In a nationally representative sample, the CDC recently estimated that 7.6% of HIV-positive adults in care in the United States have stage 3 or worse chronic kidney disease, defined as estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73m^2.[93] Among 20- to 39-year-olds, HIV-positive people had more than a 4 times higher rate of chronic kidney disease than the general population (prevalence ratio [PR] 4.6); among 40- to 59-year-olds, people with HIV had an 80% higher rate (PR 1.8). Among people 60 and older, the general population had a higher rate, probably partly because more HIV-negative than HIV-positive people with chronic kidney disease survive past 60. In HIV-positive adults in care, the CDC identified five factors associated with chronic kidney disease—older age, female sex (adjusted PR 1.4), HIV duration longer than 10 years (adjusted PR 1.4), an AIDS diagnosis, and a CD4 count under 350 cells/mm^3 (adjusted PR 1.6).

Recent cohort studies link poor kidney function—measured as eGFR, albuminuria, or proteinuria—with cardiovascular disease in people with HIV. Persistent albuminuria indicates that a damaged kidney is spilling albumin into urine. Researchers at the San Francisco Veterans Affairs Medical Center parsed records of 17,264 HIV-positive people in the Veterans Health Administration to catalog newly diagnosed cardiovascular disease (defined as coronary, cerebrovascular, or peripheral arterial disease) and new cases of heart failure.[94]

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In this national sample the 1194 cohort members with eGFR below 60 mL/min averaged 52 years in age, compared with 46 in the 16,070 members with an eGFR at or above 60 mL/min. About 45% of study participants were black, about 35% white, and only 3% women. Through a median 7 years of follow-up, the investigators counted 370 heart failures and 833 atherosclerotic cardiovascular events.

People with an eGFR below 30 mL/min and albuminuria at or above 100 mg/dL had about a 6-fold higher rate of new cardiovascular disease than people with an eGFR at or above 60 mL/min and no albuminuria. Incidence of atherosclerotic cardiovascular events and albuminuria grew progressively as albumin levels rose (from 0 to 30 to 100 or more mg/dL) and as eGFR waned (from 60 or higher to 30 to 59 to under 30).

A full multivariate model adjusted for age, sex, race, and time-updated hypertension, diabetes mellitus, chronic obstructive lung disease, dyslipidemia, smoking, CD4 count, viral load, and antiretroviral therapy. In this analysis albuminuria above 30 mg/dL and eGFR below 60 mL/min each independently raised the risk of an atherosclerotic cardiovascular event and the risk of heart failure (**Figure 12**). When a person had both albuminuria and a sub-60 eGFR, the risk of an atherosclerotic cardiovascular event and the risk of heart failure were even higher.

These investigators believe their results "are clinically relevant because they may help providers to identify HIV-infected persons at high risk for CVD events."[94] The National Kidney Foundation recommends screening for albuminuria in people with chronic kidney disease risk factors, including dia-

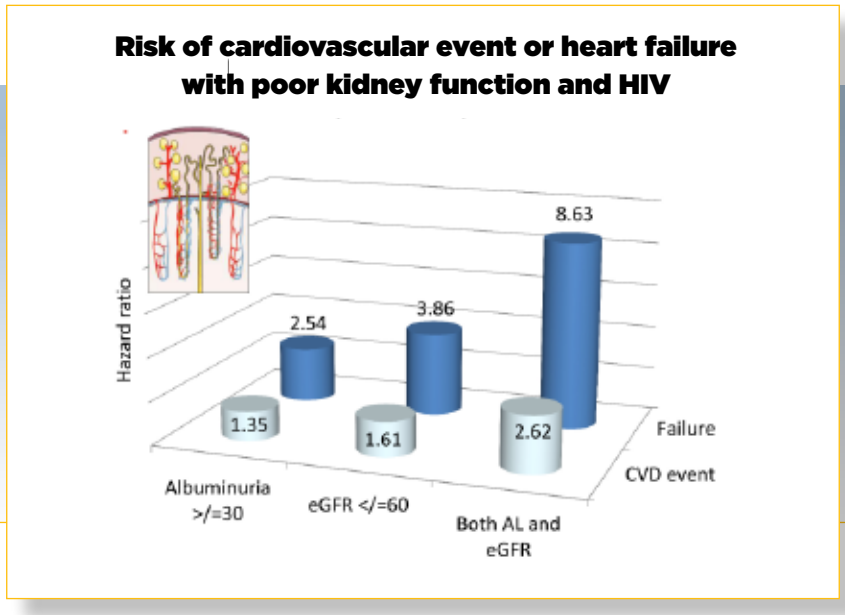

Figure 12. Analysis of 17,264 veterans with HIV—more than 95% of them men—found that two indicators of poor kidney function independently raised the risk of a new atherosclerotic cardiovascular event or heart failure.[94] When a person had both indicators of poor kidney function, risks for these two outcomes were considerably higher. Kidney nephron shown at upper left, from Servier Medical Art. ***http://www.servier.co.uk/medical-art-gallery/***. (See text for variables in model.)

betes, hypertension, systemic illnesses, age over 60, and family history of chronic kidney disease.[95] The Foundation advises confirming a positive test with a second urine test.

A case-control study at the Johns Hopkins HIV Clinic confirmed the graded impact of worsening kidney function on cardiovascular risk.[96] This study involved 315 HIV-positive adults, 63 who had a myocardial infarction or a cerebrovascular accident and 252 who did not. The 252 randomly selected control patients had no history of heart disease and matched the 63 case patients by age, race, and sex. Age averaged 49.5 in both groups, 63.5% were men, and 84% were black.

Multivariate analysis (adjusted for diabetes, hypertension, previous cardiac events, dyslipidemia, viral load, and CD4 count) linked every 10 mL/min lower eGFR to 20% higher odds of a cardiovascular event (aOR 1.2, 95% CI 1.1 to 1.4, $P = 0.009$). In the same analysis proteinuria, defined as a urine dipstick reading at least above 1+, nearly tripled the odds of a cardiovascular event, though that association stopped short of statistical significance (aOR 2.9, 95% CI 0.9 to 9.0, $P = 0.070$). In a separate analysis, proteinuria compounded the impact of low eGFR on cardiovascular risk.

The Johns Hopkins investigators noted that their findings reflect results in the general population but assume greater importance in people with HIV, who have a 3- to 5-fold higher kidney disease prevalence than people without HIV.[93,97,98] They proposed that their findings "suggest the potential value of early screening and treatment of chronic kidney disease in HIV-1-infected patients, particularly those with other cardiovascular risk factors."[96]

In its report on chronic kidney disease prevalence with HIV, the CDC recommends (**1**) routine screening for chronic kidney disease, (**2**) aggressive management of related conditions including diabetes, hypertension, and obesity, and—among people who do have chronic kidney disease— (**3**) avoidance of nephrotoxic drugs and referral to a nephrologist.[93]

HCV and other flamethrowers

HIV infection is an inflammatory disease marked by ongoing immune activation. Even when cART corrals HIV replication, low-level inflammation and immune activation may persist and tweak up the risk of cardiovascular disease. How? HIV heart guru James Stein explains that relentless inflammation, immune activation, and viremia hamper a blood vessel's ability to dilate and generate an anticoagulant surface.[31] And clumpy cells are a big enemy of cardiovascular health.

The literature on inflammation, immune activation, and heart health in people with HIV has ballooned to Brobdingnagian proportions. Searching for cardiovascular disease + HIV + inflammation on pubmed returned 371 articles in April 2013. The same search on Google Scholar gives you "about 52,000" returns. Most of these studies point in the same direction: inflammation is bad for your heart. But James Stein cautions that pinning down the precise inflammation-linked risk, and figuring which markers predict best, "likely will require several thousand subjects, more than a decade of follow-up, reliable biomarker/imaging tests, and strict endpoint adjudication."[31]

One place to start through the thicket of research on inflammation and HIV-related heart disease is with HCV infection, an overtly inflammatory illness that often coexists with HIV infection. Meta-analysis of 12 studies linked HCV infection to a higher risk of coronary artery disease in the general population.[99] Of the 6 best studies analyzed, three found a significant association between HCV and

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coronary artery disease, two found a nonsignificant association, and one figured HCV *protects* against coronary artery disease.

Six recent studies on HCV, HIV, and cardiovascular risk yielded divergent results reflecting the different study populations, methods, and endpoints.

Women's Interagency HIV Study (WIHS) investigators measured cIMT and carotid plaque in 1865 HIV-positive women in 2004 and 2005.[100] Median cIMT was similar in HCV-infected and HCV/HIV-coinfected women, and higher than in HIV-monoinfected women. But after statistical adjustment for other cardiovascular risk factors, HCV infection was not associated with cIMT or with carotid plaque.

A DAD Study analysis involved 33,347 HIV-positive men and women in Europe, the US, and Australia who had 517 myocardial infarctions during follow-up for an incidence of 3.3 per 1000 person-years.[101] Incidence was marginally lower in HCV-seropositive people than HCV-negative people (2.7 versus 3.3 per 1000 person-years). After statistical adjustment for relevant variables, HCV seropositivity was not associated with incident myocardial infarction (rate ratio 0.86, 95% CI 0.61 to 1.19). There were 295 strokes during the study period (1.47 per 1000 person-years with HCV and 1.91 without HCV), and HCV positivity did not affect stroke risk after statistical adjustment. Active HBV infection did not affect rates of MI or stroke.

But a large Veterans Affairs study did link HCV/HIV infection to a higher risk of cerebrovascular disease (stroke and transient ischemic attack) and to a trend toward a higher MI rate.[102] This analysis involved 19,424 HIV-positive veterans, 32% of them coinfected with HCV and HIV and 97% of them men. The investigators identified HCV infection by diagnostic codes and HCV-antibody positivity. There was no HCV/HIV-negative control group. After statistical adjustment for potentially confounding factors, HCV/HIV coinfection was linked to a 20% higher risk of cerebrovascular disease compared with HIV alone (adjusted hazard ratio 1.20, 95% CI 1.04 to 1.38, $P = 0.013$), while coinfection was nonsignificantly associated with a 25% higher risk of acute MI (adjusted hazard ratio 1.25, 95% CI 0.98 to 1.61, $P = 0.072$).

Another US veterans study did find an independent (though small) association between HCV infection and acute myocardial infarction in a comparison of HIV-positive and negative veterans.[18] This Veterans Aging Cohort Study involved 27,350 HIV-positive and 55,109 age-, race-, and site-matched HIV-negative veterans, 97% of them men. No one had a history of cardiovascular disease. The researchers defined HCV infection by ICD-9 code or positive HCV antibody. During 5.9 years of follow-up, 871 veterans had an acute MI. Statistical analysis adjusted for multiple risk factors associated HCV infection with about a 20% higher MI risk when compared with HCV-negative vets (adjusted hazard ratio 1.19, 95% CI 1.01 to 1.40).

A medical record review at the University of Rochester compared 239 people with HIV, 167 with HCV, and 182 with both HIV and HCV with gender-, race-, and age-matched uninfected people in the NHANES database.[103] After statistical adjustment for confounders, HCV/HIV-coinfected people had a 2% higher Framingham Risk Score than the general population ($P = 0.03$) and a 4.1-year older vascular age ($P = 0.01$). People infected with HCV but not HIV had a 2.4% higher Framingham Risk Score than the general population ($P < 0.001$) and

a 4.4-year older vascular age ($P < 0.001$). But HIV infection alone did not confer a higher Framingham score or an older vascular age.

Comparing 18 HCV/HIV-coinfected people with 22 HIV-monoinfected people, French investigators recorded a significantly higher prevalence of subclinical carotid plaque in the coinfected group, even though LDL cholesterol and blood pressure were lower in coinfected people.[104] Chronic HCV infection was associated with 10-fold higher odds of plaque (OR 10, 95% CI 1.5 to 72, $P = 0.02$).

The French team suggested that "HCV infection might be considered as not only a liver infection but also as a metabolic disease in HIV patients, justifying regular cardiovascular surveillance."[104] The VA team observed, though, that HCV may inflate rates of some cardiogenic conditions, including metabolic syndrome and diabetes, while it appears to lower levels of total cholesterol, LDL cholesterol, and triglycerides.[102] Of the three studies that assessed HCV impact on clinical endpoints, the two predominantly male VA studies uncovered evidence implicating HCV in MI and stroke,[18,102] but the DAD study (with 74% of participants men) saw no HCV tie to MIs (**Table 5**).[101]

The DAD team tabulated results of 18 previous general-population studies assessing cardiovascular disease risk with HCV: eight found an association and 10 did not. Nailing down whether HCV substantially inflates an already high cardiovascular risk in people with HIV requires further study.

Two recent studies saw links between markers of inflammation and all-cause mortality in people with HIV, and one of them extended that association to atherosclerotic cardiovascular disease and heart failure. Albumin levels fall in the face of inflammation, providing an inverse marker of the inflammatory process.[105] To gauge the impact of serum albumin on mortality and heart disease in people with HIV, University of California San Francisco researchers turned to a national veterans database, the HIV Clinical Case Registry.[106] This analysis included 25,522 HIV-positive veterans enrolled between 1986 and 2007 who

Table 5. Cardiovascular disease risk with HCV in clinical endpoint studies

Study	n (% men)	Comparison groups	Study years (follow-up)	Endpoints	HCV association
VACS[18]	27,350 (97%)	55,109 matched HIV-negative veterans	2003-2009 (median 5.9 y)	Acute MI	19% higher MI risk
Veterans[102]	19,424 (97%)	6136 HIV/HCV+ vs 13,288 HIV+ only	1996-2004 (mean 3.9 y)	Acute MI, cerebrovascular disease (CVD)	25% higher MI risk;* 20% higher CVD risk
DAD[101]	33,347 (74%)	5084 HCV/HIV+ vs 16,731 HIV only†	1999-2007	MI, stroke	No association

VACS, Veterans Aging Cohort Study.
*Not significant.
†11,532 had unknown HCV status.

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had serum albumin, serum creatinine, and urine dipstick measures between 1986 and 2007. The three primary outcomes were time to death, atherosclerotic cardiovascular disease, and hospital admission for heart failure. The investigators broke serum albumin levels into five brackets: at or above 4.0, 3.5 to 3.9, 3.0 to 3.4, 2.5 to 2.9, and under 2.5 g/dL.

Compared with the highest albumin bracket, each lower bracket independently boosted chances of mortality—both with baseline albumin and (even more so) with time-updated albumin. Lower baseline albumin did not affect chances of atherosclerotic cardiovascular disease, but lower updated albumin did. Both lower baseline and lower updated albumin hoisted hazard ratios for heart failure:

Hazard ratios (and 95% CIs) for mortality:

Baseline albumin 3.5 to 3.9 vs >4.0: 1.34 (1.27 to 1.40)
Baseline albumin 3.0 to 3.4 vs >4.0: 1.68 (1.58 to 1.78
Baseline albumin 2.5 to 2.9 vs >4.0: 2.27 (2.14 to 2.42)
Baseline albumin <2.5 vs >4.0: 3.00 (2.67 to 3.37)

Time-updated albumin 3.5 to 3.9 vs >4.0: 1.65 (1.54 to 1.77)
Time-updated albumin 3.0 to 3.4 vs >4.0: 3.37 (3.15 to 3.61)
Time-updated albumin 2.5 to 2.9 vs >4.0: 7.02 (6.58 to 7.50)
Time-updated albumin <2.5 vs >4.0: 15.1 (14.0 to 16.4)

Hazard ratios (and 95% CIs) for atherosclerotic cardiovascular events:

Time-updated albumin 3.5 to 3.9 vs >4.0: 1.35 (1.16 to 1.58)
Time-updated albumin 3.0 to 3.4 vs >4.0: 2.36 (1.98 to 2.82)
Time-updated albumin 2.5 to 2.9 vs >4.0: 3.15 (2.58 to 3.86)

Hazard ratios (and 95% CIs) for heart failure:

Baseline albumin 3.0 to 3.4 vs >4.0: 1.45 (1.09 to 1.93)
Baseline albumin 2.5 to 2.9 vs >4.0: 1.53 (1.10 to 2.11)
Time-updated albumin 3.0 to 3.4 vs >4.0: 6.07 (4.31 to 8.55)
Time-updated albumin 2.5 to 2.9 vs >4.0: 11.7 (8.3 to 16.5)

The associations between low albumin and mortality were strongest in the first year of follow-up, though still usually significant after 2 or 3 years.

The investigators[106] acknowledged the difficulty in explaining why low serum albumin (versus high *urine* albumin in the just-described study[94]) predicts dire clinical outcomes. Serum albumin levels can fall because of poor nutrition, liver disease, kidney disease, and chronic inflammation. But a sensitivity analysis that excluded people with liver and kidney dysfunction found nearly identical associations between low serum albumin and the three endpoints. That result suggested to the investigators "that a more transient process such as inflammation is responsible for the lower levels of albumin."[106] They proposed that "serum albumin captures a dynamic

process of inflammation in HIV infection that has clinical importance in the short-term."

A prospective study of 327 HIV-positive people at Boston's Tufts University found significantly higher risks of all-cause mortality with higher high-sensitivity C-reactive protein (hsCRP), a classic marker of inflammation, and with cIMT, a verified signal of subclinical atherosclerosis.[107] The study involved 242 men and 85 women, 52% of them white, with an average age of 44 years. None of them had overt cardiovascular disease. Through a median follow-up of 3.1 years, 38 people (12%) died. Five of these deaths (13%) had primary or secondary cardiovascular causes, and one was sudden and unexplained.

Statistical analysis adjusted for age, gender, race, body mass index, cigarette smoking, CD4 count, viral load, LDL cholesterol, HDL cholesterol, and hsCRP determined that cIMT above versus below 0.655 mm almost tripled the risk of death (adjusted hazard ratio 2.74, 95% CI 1.26 to 5.97, $P = 0.01$). In a similar analysis adjusted for cIMT, hsCRP at or above versus below 3 mg/L more than doubled the risk of death (adjusted hazard ratio 2.38, 95% CI 1.15 to 4.90, $P = 0.02$). hsCRP was almost 3 times higher in people who died than in those who did not (3.2 versus 1.3 mg/L, $P < 0.001$), and a significantly higher proportion of people who died had hsCRP above 3 mg/L (51% versus 25%, $P < 0.001$). An earlier study of 209 HIV-positive US women identified baseline CRP as an independent predictor of mortality through a median 45 months of follow-up.[108]

In Boston's Partners HealthCare System, elevated CRP and HIV each independently doubled chances of acute myocardial infarction.[109] This analysis involved 487 HIV-positive patients and 69,870 HIV-negative people in care between January 1997 and December 2006. Everyone had CRP measured in the past 3 years and more than 1 week before an acute MI. A statistical model adjusted for age, sex, race, hypertension, diabetes, dyslipidemia, elevated CRP, and HIV status determined that high CRP and HIV each independently doubled the odds of acute MI (**Figure 13**). People with HIV and elevated CRP had quadrupled odds of acute MI compared with HIV-negative people with normal CRP levels. At the end of the third review article in this issue of RI*TA!*, this study's principal investigator, Steven Grinspoon, offers his insights on when measuring CRP in people with HIV may pay off in practice.

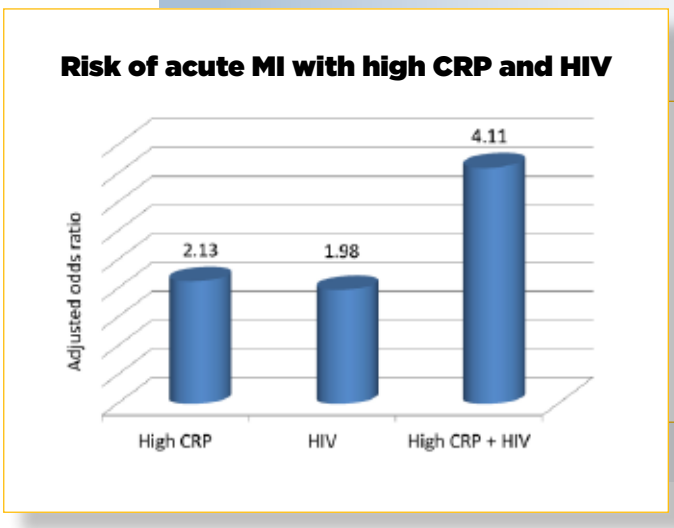

Figure 13. In 487 HIV-positive and 68,870 HIV-negative people in care in Boston, elevated CRP and HIV infection each independently doubled the odds of acute MI.[109] People with HIV and elevated CRP had quadrupled odds of acute MI compared with HIV-negative people with normal CRP.

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Vitamin D and hormonal contraceptive conundrums

Research links low vitamin D to cardiovascular disease in the general population, but so far studies of vitamin D and cardiovascular risk in people with HIV are small, rely on surrogate markers, and yield mixed results. All of these studies weigh vitamin D in relation to cIMT, a marker of atherosclerosis, and some examine other cardiovascular proxies.

The largest heart-related vitamin D study involved 139 HIV-positive adults in a San Francisco group, all of whom had vitamin D measured as 25-hydroxyvitamin D [25(OH)D], the standard way to measure this vitamin.[110] The study group averaged 45 years in age, 84% were men, 54% white, and 32% black. Half of these people (52%) had vitamin D insufficiency, defined as a level at or below 30 ng/mL. A statistical model adjusted for classic heart risk factors and HIV variables determined that average cIMT increased (worsened) significantly from about 0.8 mm in people with normal vitamin D (above 30 ng/mL) to about 1.0 mm in those with deficient vitamin D (15 to 30 ng/mL) and to about 1.1 mm in those with vitamin D below 15 ng/mL ($P = 0.021$). cIMT was an average 0.13 mm greater in people with 25(OH)D below 30 ng/mL than in people with normal 25(OH)D. The authors observe that research in the general population links every 0.10-mm greater cIMT to a 15% higher MI risk and an 18% higher stroke risk. The study is limited by its cross-sectional nature and the inability to account for the possible impact of individual antiretrovirals. Other work, for example, links efavirenz to low vitamin D.

In three smaller cross-sectional analyses of vitamin D and cIMT, one study tied lower 25(OH)D to greater cIMT but two studies did not. The study that found a link involved 56 adults with HIV.[111] Median age stood at 49, and most participants were men (85%) and white (52%). Although this analysis did not tie 25(OH)D to inflammatory or endothelial markers, lower 25(OH)D conferred a 10 times higher risk of common carotid IMT above the median for the study group ($P < 0.01$). The association was not significant for internal carotid IMT.

An analysis in the Hawaii Aging With HIV-Cardiovascular Cohort Study involved 100 people with a median age of 52, most of them male (86%) and white (60%).[112] Analysis of 50 cIMT measurements found a significant correlation between 25(OH)D and brachial artery flow-mediated dilation but not cIMT ($r = -0.05$, $P = 0.76$). A third cross-sectional study involved 30 HIV-positive children and young adults with a median age of 11, three quarters of them black and 37% male.[113] These researchers found no significant correlation between 25(OH)D and cIMT, inflammatory markers, or lipids. But 25(OH)D correlated inversely with insulin resistance—the lower the 25(OH)D, the greater the insulin resistance.

A recent review of randomized trials, meta-analyses, and other evidence in the general population concluded that adequate vitamin D may protect against cardiovascular disease—as well as musculoskeletal maladies, infectious diseases, autoimmune diseases, type 1 and type 2 diabetes, several cancers, neurocognitive dysfunction, and mental illness.[114] This mega-analysis also tied low vitamin D to all-cause mortality. With such a catalog of benefits-in-waiting, checking HIV-positive people for vitamin D and supplementing those deficient may seem a sensible hedge. But randomized trials in the general population—and in people with HIV—show that swallowing high doses of vitamin D3 does not ipso facto translate into sounder health. A double-blind,

placebo-controlled trial of 45 HIV-positive adults who took 4000 IU of vitamin D daily or placebo for 12 weeks found that supplementation modestly improved vitamin D status and non-HDL cholesterol but did not change endothelial function and worsened insulin resistance.[115]

A Women's Interagency HIV Study of 885 HIV-positive and 408 HIV-negative women linked progestin-only hormonal contraceptives to lower HDL cholesterol (–3 mg/dL, 95% CI –5 to –1 with HIV, –6 mg/dL, –9 to –3 without HIV) and greater insulin resistance (HOMA-IR +0.86, 95% CI 0.51 to 1.22 with HIV, and +0.56, 95% CI 0.12 to 1.01 without HIV).[116] Estrogen/progestin hormonal contraceptives were associated with higher HDL. The WIHS investigators suggested that combined hormonal contraceptives may be preferred for women with HIV, but they cautioned clinicians to check for interactions with antiretrovirals.

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Pointers on cardiovascular disease risk, screening, and management in patients with HIV

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Heart risk attributable to HIV and antiretrovirals

Mascolini: Many people with HIV carry a high burden of classic cardiovascular risk factors. How much do HIV infection and antiretrovirals add to that risk?

Stein: The impact of traditional cardiovascular disease risk factors—smoking, abnormal lipids, diabetes—outweighs the impact of HIV infection itself and antiretroviral therapy. In people with HIV and a low overall risk of cardiovascular disease, HIV and antiretrovirals will not greatly increase their risk of heart disease. In HIV-positive people at moderate or higher risk, the excess risk associated with HIV and antiretrovirals can put them over the edge for having a heart attack or developing heart disease.

Data indicating that there's an increased risk of cardiovascular disease with HIV infection have only recently been appreciated. The kind of research studies that we do in the HIV community aren't really optimally designed to determine how much excess cardiovascular disease risk HIV infection confers.

In the HIV community we do a great job conducting antiretroviral studies and looking at how effective a new drug is in treating HIV. We also do a good job assessing the complications of antiretroviral therapy. But because cardiovascular disease takes decades to develop and manifest itself, the HIV community is only now starting to appreciate that risk and starting to study it in a really robust way.

Most of these studies suggest that the excess cardiovascular risk with HIV infection is about 50%.[1-4]

Although 50% sounds high, it's a relative risk. If you're at low risk—let's say your MI risk over the next decade is 2%—and your risk goes up 50% to 3% over

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a decade, that's a pretty small increase. But if your 10-year risk is 20% or higher because you smoke and have high cholesterol, then that 50% increase with HIV raises your risk to 30% or more. At that point that excess risk with HIV becomes very important.

Mascolini: What about specific antiretrovirals? Should clinicians shy away from lopinavir or abacavir, for example, in people with an already high cardiovascular risk?

Stein: I don't think so. Taking care of patients with HIV infection is very complicated. But one principle overrides everything—getting optimal viral suppression. And getting optimal control of HIV is the most important predictor of long-term survival. So as a cardiologist I would never tell an HIV treater or a patient with HIV infection that they can't start an antiretroviral because it raises their heart disease risk so much that it will overshadow the risk of uncontrolled HIV infection. There's no drug for treating HIV that I think is prohibitive from the standpoint of heart disease.

Having said that, I will add that there are certain protease inhibitors (ritonavir-boosted lopinavir and perhaps indinavir) and certain nucleoside reverse transcriptase inhibitors (abacavir and perhaps didanosine) that have been associated with heart disease. If everything is equal and the same amount of viral suppression can be obtained using a different agent, I would recommend staying away from those agents. But again the most important thing is to suppress the virus.

We and others have shown that obtaining adequate viral suppression is good for endothelial function—it improves the ability of blood vessels to relax.[5,6] When you look at the overall data for cardiovascular disease risk in people with HIV, some data suggest that uncontrolled viremia or inadequate treatment of HIV increases cardiovascular risk.[7-9] Start with controlling the virus; then we can address cardiovascular disease risk factors.

Cardiovascular risk screening in adults and children

Mascolini: Should everyone with HIV be screened regularly for cardiovascular disease?

Stein: All patients with HIV should be regularly screened for modifiable risk factors for cardiovascular disease, specifically smoking, high blood pressure, high cholesterol, diabetes mellitus, and poor lifestyle choices. In addition to smoking, those poor choices include not getting enough exercise and eating a diet of low nutritional quality. I don't think the next step of screening people with imaging tests usually is indicated. I don't think HIV-positive people routinely need stress tests or calcium scans or carotid ultrasounds. There are very specific indications for those tests.

Mascolini: Unlike US experts, the European AIDS Clinical Society (EACS) does recommend an annual ECG for people with HIV.[10] What do you think about that?

Stein: We don't recommend screening electrocardiograms in the United States, mainly because they're not very sensitive in picking up disease. And whenever you screen people there's a chance that you'll falsely mislabel someone as having disease. So we try not to screen people with an ECG unless there's a reason. If a patient is having symptoms that are suggestive of heart disease—shortness of breath or chest discomfort—doing a 12-lead electrocardiogram would absolutely be indicated. But for someone who doesn't have any symptoms, doing a 12-lead ECG doesn't really have any benefits and has the potential for some harm.

Mascolini: Should HIV-positive children and adolescents be screened?

Stein: First a caveat: I don't treat children and teens because I'm an adult cardiologist. I do recommend that kids with HIV be screened for cardiovascular disease risk factors. Although there's even less data in children with HIV than in adults, it looks like traditional risk factors—along with uncontrolled HIV—do predict most of the blood vessel dysfunction seen in kids with HIV. I think controlling the virus is critical in children, then making sure they live a healthy lifestyle.

I would default to the general population recommendations for screening of blood pressure, cholesterol, and blood sugar. For kids probably the more important points are making sure they don't start smoking and making sure they get adequate exercise and eat a healthy diet. Although HIV infection seems to cause vascular damage, I don't think having HIV accelerates blood vessel damage so quickly that we need to treat a 12-year-old as if that child is 40.

Interpreting the Framingham score in HIV patients

Mascolini: Some research suggests the Framingham equation lacks sensitivity in predicting cardiovascular disease in HIV-positive people.[11,12] Should HIV clinicians use it or take a modified approach?

Stein: The Framingham risk score does a very good job at what it's meant to do, which is predicting 10-year risk of cardiovascular disease in otherwise healthy, predominantly white, young and middle-aged patients.[13] It's a little less accurate with certain ethnic minorities, and a European group has found that it's less accurate in patients with HIV. [11,12] But it's hard to know what to do with that information because the Framingham risk score is less accurate when used in Europeans because their lifestyle and genetic make-up are different from people in America.

What I say to patients and physicians is that the Framingham score is a good starting place for discussion and it tells you what's going to happen over 10 years. But it's not very precise and it doesn't tell you what's going to happen over your lifetime. We're developing lifetime cardiovascular risk calculators that I think will be more useful for clinicians, and we hope to see them within the next year. Updated lipid guidelines should also be coming out soon.

For now, clinicians should not hang their hat too much on any one number. If the MI risk over the next 10 years is 5%, that's a starting point for discussion. But then ask yourself what it is about the patient that might put them at higher or lower risk. With HIV, for example, that 5% risk over 10 years may be more like 7% or 8%. If a patient smokes 3 packs a day, the risk is probably higher than the Framingham score suggests because the score just counts a person as a smoker or a nonsmoker. On the other hand a patient may have a very healthy lifestyle—may be lean and exercise regularly and have no one in the family with any heart problems. That profile moves a patient a little bit lower on the risk scale.

The Framingham score should be thought of as a starting point for discussion with recognition that there's error in it and that it's not perfect in people with HIV. It's also not perfect when you move away from the typical young or middle-aged white adult in the United States. For minorities and people of European, Asian, or South American descent, it becomes less accurate.

Lipid targets: how low should you go?

Mascolini: How aggressive should HIV clinicians be in pharmacologic management of abnormal lipids?

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Stein: Let me start with what we know. We know that dyslipidemia predicts cardiovascular disease in patients with HIV. And we know that certain antiretroviral therapies and certain lifestyle habits add to that risk. Treating dyslipidemia in HIV patients is complicated because of the drug interactions between statins and antiretrovirals. Newer antiretroviral agents have less dyslipidemic effects, and some of these newer antiretrovirals have fewer drug interactions—and that could make prescribing easier.

The question is how low you should go with lipid targets, and I think the answer depends on the patient's baseline cardiovascular disease risk. Patients with higher risk—people who already have coronary disease, people with multiple risk factors—need to be treated more aggressively. People who are younger and have a lower risk factor burden can be treated less aggressively.

I think clinicians treating people with HIV can default to the regular US guidelines for treating dyslipidemia[14] but be a little bit more aggressive because of that excess risk with HIV infection. With someone at high risk, you're already going to treat them more aggressively, aiming at an LDL cholesterol below 100 mg/dL or even 70 mg/dL if they already have coronary disease. A patient who is solidly at low risk is still at low risk with HIV. It's those people in the middle—those intermediate-risk patients—where I'm inclined to be a little bit more aggressive, simply because they have HIV and that increases the risk by about 50%. That may put them over the threshold for treating them more aggressively.

Caution with aspirin and counsel on smoking

Mascolini: Should HIV clinicians consider primary prevention with aspirin?

Stein: Again I would default to the regular recommendations for people without HIV infection [see box].[15] Aspirin is not a benign drug. It can prevent heart attacks, especially in men. It seems to prevent more strokes in women than heart attacks. If your patient already has cardiovascular disease, aspirin is already indicated. And if your patient has diabetes mellitus, aspirin is probably indicated.

For everyone else you really have to look at the balance of bleeding and cardiovascular disease prevention. I think defaulting to the usual guidelines is the way to go—use the Framingham risk score and look at the age and sex of your patient to determine if aspirin is needed. GI bleeding is a real problem. The rare but more feared complication is intracranial bleeding. We can't just give patients aspirin and think it's a completely benign drug.

Mascolini: Everyone knows smoking has a huge impact on cardiovascular risk, but physicians often throw up their hands in despair when you suggest they get their patients to quit. How do you recommend HIV clinicians approach this challenge?

Stein: The first way they approach the challenge is by doing an attitude adjustment. If the clinician doesn't think it's going to work, the patient will pick up on that. Then you go through this empty ritual of telling the patient to quit smoking when you don't think it's going to work and they don't think it's going to work. And when they leave the office and fail to quit you have a self-fulfilling but very dysfunctional prophesy.

Cigarette smoking is the single most powerful modifiable risk factor for cardiovascular disease. It's incontrovertible. We're fortunate enough to live in an era in which we have multiple options for help with smoking cessation, ranging from counseling and lifestyle

Main USPSTF recommendations on aspirin for prevention of cardiovascular disease*

- The USPSTF recommends the use of aspirin for men age 45 to 79 years when the potential benefit due to a reduction in myocardial infarctions outweighs the potential harm due to an increase in gastrointestinal hemorrhage.
- The USPSTF recommends the use of aspirin for women age 55 to 79 years when the potential benefit of a reduction in ischemic strokes outweighs the potential harm of an increase in gastrointestinal hemorrhage.
- The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of aspirin for cardiovascular disease prevention in men and women 80 years or older.
- The USPSTF recommends against the use of aspirin for stroke prevention in women younger than 55 years and for myocardial infarction prevention in men younger than 45 years.

*For the complete report: US Preventive Services Task Force. Aspirin for the Prevention of Cardiovascular Disease. March 2009. ***http://www.uspreventiveservicestaskforce.org/uspstf/uspsasmi.htm***

intervention through dual pharmacologic therapy. I'm not going to say it's easy to quit smoking. It's not easy for patients; it's not easy for clinicians working with patients. But for all our worry over nutritional supplements and LDL targets and baseline ECG screening, the single most important thing would be to help people quit smoking.

I recommend that clinicians approach smoking cessation with a positive attitude and realize that it takes the average patient six or seven quit attempts before they're successful. Clinicians have to work with patients to develop a strategy for quitting based on how addicted to cigarettes they are, previous experiences with quit attempts, and concurrent medications, because polypharmacy is an issue for people with HIV.

In our research in people without HIV we have found that dual nicotine replacement therapy with a nicotine patch supplemented with a lozenge is the most effective strategy.[16] But of course it has to be personalized. If someone has failed nicotine replacement therapy they could use bupropion (Wellbutrin, Zyban) or they could use varenicline (Chantix). But there's some art in dealing with the drug interactions.

If a physician doesn't have the time or interest in working with patients on smoking cessation, they should refer patients to a preventive cardiology clinic, or to a smoking cessation clinic, or to a clinical trial that will enroll people with HIV infection.

I think that smoking cessation in people with HIV is an untapped research need. I would much rather see some research money invested in helping people with HIV quit smoking than in worrying more about LDL cholesterol targets. That's how important it is.

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Antiretroviral therapy: from heart risk factor to heart protector?

By Mark Mascolini

Abstract: Multiple studies indicate that certain antiretrovirals raise chances of cardiovascular morbidity and mortality. At the same time, diverse research indicates that combination antiretroviral therapy lowers cardiovascular risk. Studies addressing this question have been pooled in several systematic reviews and meta-analyses. One meta-analysis of recent observational studies determined that recent abacavir or protease inhibitor use approximately doubled chances of myocardial infarction. Every additional year of lopinavir or indinavir therapy also independently raised MI risk. A second meta-analysis determined that HIV-positive antiretroviral-naive people had a 60% higher risk of cardiovascular disease than did HIV-negative people, while antiretroviral-treated people had a doubled risk compared with the HIV-negative group. Antiretroviral-treated people had about a 50% higher cardiovascular disease risk than did treatment-naive HIV-positive people. This analysis could not factor in other cardiovascular risks, such as smoking, which may be more prevalent in people with HIV and have nothing to do with cART. In this second meta-analysis, each year of treatment with protease inhibitors, nucleoside reverse transcriptase inhibitors, or nonnucleoside reverse transcriptase inhibitors added to cardiovascular disease risk. Studies are divided on whether a lower viral load or higher CD4 count cuts cardiovascular risk.

In 2010 EuroSIDA investigators found that a lower CD4 count inflated chances of every non-AIDS event analyzed, except one—cardiovascular disease.[1] Bolstering their finding with results of two other studies,[2,3] the EuroSIDA team noted "there is, to date, no strong evidence linking cardiovascular disease with immunodeficiency." But even as the EuroSIDA team steered their paper into print, a small army of other researchers was amassing data pointing in the opposite direction.

If a low CD4 count tips the scales toward cardiovascular disease, one would expect combination antiretroviral therapy (cART) to ease cardiovascular risk by boosting CD4 tallies—and maybe via other mechanisms. Yet studies from the United States,[4] France,[5] and the international Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group[2] from the early 2000s all implicated cART—and specifically protease inhibitor (PI)-based cART—in surging cardiovascular rates seen in people with HIV. Other research tied certain nucleoside reverse transcriptase inhibitors (NRTIs) to heart disease. Ten years later, however, the French team found evidence that a viral load above 50 copies/mL hiked the risk of myocardial infarction 50%.[6]

A stockpot of other data simmered throughout these years, as researchers refined their multivariate recipes. Sometimes data implicating cART in heart matters bubbled to the top; sometimes cART emerged as an essential ingredient of a heart-healthy recipe. So where are we today, in 2013? Does antiretroviral therapy inflate chances of cardiovascular morbidity and mortality? Or does cART help HIV-positive people trim their coronary risk? The answers to those two questions would be yes and yes.

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The Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents believes stavudine, zidovudine, abacavir, efavirenz, and all ritonavir-boosted PIs can send lipids awry and so pose a cardiovascular threat to people taking those drugs (see Table 2 in the first review article in this issue).[7] Franck Boccara, an HIV cardiology expert at Saint Antoine University Hospital in Paris, and colleagues suggest "the 2 most important and recent observational cohorts[8,9] with a sufficient duration of exposure to PIs showed that the duration of exposure was associated with an increased risk for MI."[10]

Yet suspending cART in the SMART treatment interruption trial hoisted hazards of cardiovascular events more than 50% compared with taking steady cART.[3] And when AIDS Clinical Trials Group (ACTG) investigators randomized antiretroviral-naive people to NRTIs plus efavirenz, NRTIs plus lopinavir/ritonavir, or efavirenz plus lopinavir/ritonavir, they found that all three regimens rapidly improved endothelial function (measured as brachial artery flow-mediated dilation), and that improvement persisted through 24 weeks of follow-up.[11] Only one factor appraised predicted improved arterial function—viral suppression. (For details of this study, see below under the subhead "Low viral load: low cardiovascular risk (usually).")

Cardio meta-analyses with (slightly) different outcomes

When matters get this messy, who can resist a meta-analysis? But meta-analyses can get murky, too: Because they ask different questions, use different methods, and examine different studies, they can reach different conclusions. The earliest such effort—already a decade old—focused on 30 randomized double-blind trials involving the first four PIs: indinavir, ritonavir, saquinavir, and nelfinavir.[12] Comparing trial participants who took a PI with those who took only NRTIs, these researchers found no higher MI risk with PIs (relative risk [RR] versus NRTIs 1.69, 95% confidence interval [CI] 0.54 to 7.48). The absolute difference in MI risk in PI takers was +0.77 per 1000 person-years, meaning an excess MI rate below 1 MI per 1000 people each year.

Three meta-analyses focused solely on abacavir,[13-15] the NRTI famously yoked to higher MI risk in a DAD study.[9,16] These three studies came from the FDA,[13] the ACTG,[14] and abacavir's maker, GlaxoSmithKline.[15] None of them turned up any evidence that abacavir predisposes people to heart attacks.

A team from Stanford University offered the latest meta-analysis of cardiovascular risk with cART[17] and compared their findings with those of the most comprehensive abacavir analysis[13] and the early PI analysis.[12] The Stanford group criticized both of these meta-analyses, noting they did not assess study quality or the likelihood of publication bias. These investigators winnowed a field of 1458 articles to 27 studies published through June 2011, only one of them a randomized controlled trial.

The Stanford researchers could combine data from only a handful of these studies for each of the risk profiles they explored.[17] Two studies of cumulative exposure to NRTIs reached opposite conclusions on whether abacavir or didanosine magnifies MI risk, DAD saying those NRTIs did,[9] the French national team saying they did not.[8] Pooled analysis of two studies[16,18] determined that abacavir use within the last 6 months almost doubled MI risk (RR 1.91, 95% CI 1.50 to 2.42) (**Figure 1**). Three studies of recent didanosine use[8,16,19] could not be combined by meta-analysis, but together they indicated a "harmful association" between didanosine and MI risk. No studies yielded evidence that other NRTIs imperil heart health.

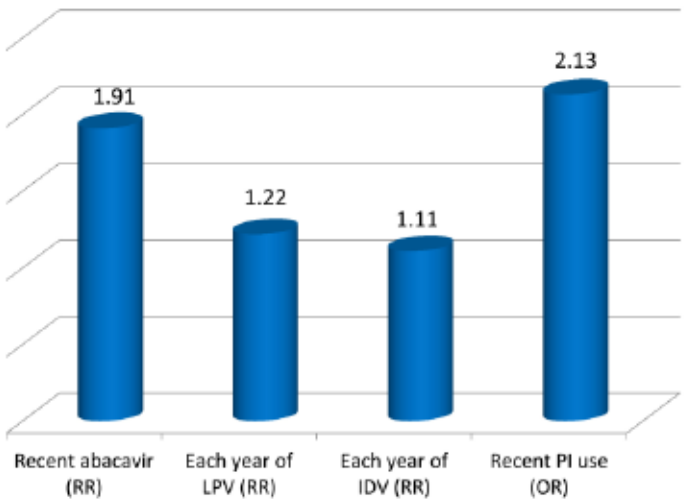

Figure 1. Meta-analysis of recent observational studies determined that recent abacavir or protease inhibitor (PI) use approximately doubled chances of myocardial infarction (MI).[17] Every additional year of lopinavir or indinavir therapy also independently raised MI risk. (Risks for abacavir, lopinavir, and indinavir calculated as relative risk (RR); risk for recent PI use calculated as odds ratio (OR). See text for 95% confidence intervals.)

The Stanford team melded data from a DAD study[9] and a French study[8] to determine that every additional year of lopinavir use boosted MI chances more than 20% (RR 1.22, 95% CI 1.01 to 1.47) (**Figure 1**). Every additional year of indinavir use inflated MI chances a little more than 10% (RR 1.11, 95% 1.05 to 1.17). Another DAD analysis figured that every additional year of exposure to PIs as a class significantly raised MI risk.[20] Combining three studies[21-23] that calculated odds ratios for recent PI use, the Stanford statisticians reckoned a doubled MI risk with recent PI use (OR 2.13, 95% CI 1.06 to 4.28). Combining 6 studies[21-26] by a different method, they confirmed a significantly higher MI risk with recent PI use ($P = 0.003$).

The Stanford group does a good job not only sifting through these hazards, odds, and oddities, but also explaining what they mean:[17]

- Evidence from observational studies implicated both PIs and abacavir in myocardial infarction risk.
- Evidence from randomized trials did not.
- Randomized trials offer the least biased approach to reckoning cardiovascular risk.
- But none of the clinical trials analyzed was designed for that purpose, and none lasted very long.
- Observational studies include a much larger and more representative patient sample than clinical trials.
- But observational studies are fraught with confounders that cannot be adjusted away by savvy statisticians.
- Also, combining evidence from several studies is hard because the studies differ in design and analytical plan.

Keeping all those caveats in mind, the Stanford investigators "believe there is still uncertainty whether ART leads to increased cardiovascular risk, and if so, the magnitude of that risk."[17] But the observational studies analyzed yield enough good data "to warrant further study in prospective studies designed to assess cardiovascular risk from ART."

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People dissatisfied with "uncertainty" after all these numbers get crunched down to bite-sized portions can consult yet another meta-analysis of studies weighing cardiovascular risk with cART.[27] Of course this second meta-analysis, by researchers at the University of New South Wales, catechizes mostly the same studies as the first meta-analysis,[17] so the findings are largely concordant. But the Australian team asked some different questions and used somewhat different methods, so their findings do not perfectly mirror those of the Stanford team.

The Australian meta-analysis focused on 23 studies, including 2 randomized trials, published before August 2010.[27] Unlike the Stanford group,[17] the Australian investigators combined studies with different risk metrics (odds ratios, relative risks, or hazard ratios). While myocardial infarction was the outcome in the Stanford study, the main Australian outcome was "cardiovascular disease," meaning coronary artery atherosclerosis. Whereas both groups assessed the impact of individual antiretrovirals and antiretroviral classes, the Australians also compared outcomes in antiretroviral-naive people, antiretroviral-treated people, and HIV-negative people. In that analysis, the antiretroviral-naive group had about a 60% higher cardiovascular disease risk than people without HIV (RR 1.61, 95% CI 1.42 to 1.83) and antiretroviral-treated people had a doubled risk (RR 2.00, 95% CI 1.70 to 2.37). cART-treated people had about a 50% higher cardiovascular disease risk than treatment-naive HIV-positive people (RR 1.52, 95% CI 1.35 to 1.70). Notably, though, this analysis could not factor in other cardiovascular risks, such as smoking, which may be more prevalent in people with HIV and have nothing to do with cART.

In the Australian meta-analysis, every added year of PI therapy upped the cardiovascular disease risk 11% (RR 1.11, 95% CI 1.05 to 1.17)[27] (**Figure 2**), about the same as each year of lopinavir therapy jacked MI risk in the Stanford inquest[17] (**Figure 1**). Each year of NRTI therapy boosted cardiovascular disease risk 4%, a relative risk just beyond the confines of statisti-

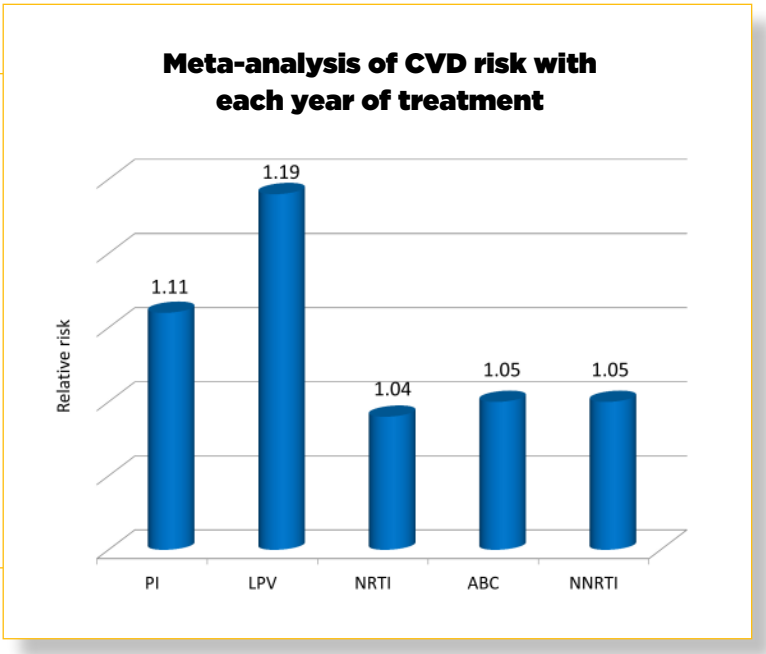

Figure 2. Meta-analysis of studies assessing cardiovascular disease (CVD) risk in antiretroviral-treated people found that each year of treatment with a protease inhibitor (PI), lopinavir (LPV), a nucleoside reverse transcriptase inhibitor (NRTI), abacavir (ABC), or a nonnucleoside reverse transcriptase inhibitor (NNRTI) raised that risk.[27] The association with NRTIs fell just short of statistical significance. See text for 95% confidence intervals.

cal significance (RR 1.04, 95% CI 0.99 to 1.09). Each year of nonnucleoside therapy budged cardiovascular risk 5%, a statistically significant impact (RR 1.05, 95% CI 1.01 to 1.10). DAD saw the same per-year MI risk with NNRTIs, but the association stopped short of statistical significance: relative rate 1.05, 95% CI 0.98 to 1.33.)[20]

Every year taking lopinavir inflated chances of cardiovascular disease 19% (RR 1.19, 95% CI 1.03 to 1.39), and each year of abacavir boosted chances 5% (RR 1.05, 95% CI 1.02 to 1.16).[27] The lopinavir and abacavir risks of cardiovascular disease diverge from the lopinavir- and abacavir-linked MI risks in the Stanford study[17] (**Figure 1**). In the Australian analysis, people who took a PI regimen ran about a 40% higher risk of cardiovascular disease than people taking a non-PI combo (RR 1.41, 95% CI 1.21 to 1.65).

The Australian team stresses that cART has improved the "quality and length of life" in people with HIV.[27] And "it is possible," they caution, "that the use of ART increases life expectancy and hence increases the average age of those taking ART in comparison to the reference group, which may lead to confounding of results."

cART and cardiology: a balancing act

So what's the bottom line? No one suggests stopping or delaying or interrupting cART to trim the risk of heart disease, even in people with an otherwise foreboding risk profile. When US antiretroviral guideline writers began recommending cART for everyone with HIV, regardless of CD4 count, the first reason they listed is the higher risk of AIDS, cardiovascular disease, and other non-AIDS diseases with untreated infection or uncontrolled viremia.[7]

But what about avoiding or switching from PIs or abacavir in people with an otherwise high risk? Certainly one would not want to avoid all PIs when considering cardiovascular risk. A big DAD analysis sniffed out not a whiff of evidence that cumulative atazanavir treatment boosts MI or stroke risk.[28]

A comparable analysis has not weighed the impact of darunavir/ritonavir on cardiovascular risk. But a review of trials involving two NRTIs plus a ritonavir/boosted PI as first-line therapy found darunavir/ritonavir comparable to atazanavir/ritonavir in 48-week lipid readings, and superior to lopinavir/ritonavir or amprenavir/ritonavir in triglyceride or total cholesterol results.[29] A 13-person study tracked lipids and cystatin C in people who switched from lopinavir/ritonavir or amprenavir/ritonavir to darunavir/ritonavir.[30] Total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides all improved through 12 months of follow-up, as did cystatin C. (High levels of cystatin C have been linked to cardiovascular disease, kidney disease, and death.)

What about abacavir in people with a high background cardiovascular risk? US antiretroviral advisors demoted abacavir/lamivudine from a "preferred" to an "alternative" NRTI backbone[7] because of some evidence indicating worse virologic outcomes with abacavir/lamivudine than with tenofovir/emtricitabine.[31,32] But after reviewing studies of cardiovascular risk with abacavir, these experts concluded that "to date [in February 2013], no consensus on the association between abacavir use and MI risk or the mechanism for such an association has been reached."[7]

The DAD Study Group, whose two big analyses first turned the spotlight on abacavir as a possible MI risk factor,[9,16] stressed in their later report that the overall MI rate in this population was low—3.2 events per 1000 person-years.[9] In other words, 3 of 1000 people in the DAD cohort (0.3%) died of an MI every year. And "any toxicities of antiretroviral drugs must always be interpreted in the context of the benefits that these drugs provide," the DADmasters added.[9]

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A team of top-drawer HIV researchers distilled HIV-related cardiovascular risk variables into a list of seven—three that raise risk and four that lower risk (**Figure 3**).[33] Antiretroviral therapy figures in most of these risk factors in one way or another. On the increased-risk side of the equation, cART can contribute to dyslipidemia, insulin resistance, and body shape changes. And because cART prolongs survival with HIV, it paradoxically favors the higher risk of cardiovascular death that comes with older age. On the decreased-risk side of the equation, all four factors involve cART.

In an interview in this issue, the University of Wisconsin's James Stein stresses that viral suppression remains the overriding principle of antiretroviral. "As a cardiologist," he says, "I would never tell an HIV treater or a patient with HIV infection that they can't start an antiretroviral because it raises their heart disease risk so much that it will overshadow the risk of uncontrolled HIV infection." But if two drugs are good candidates for viral control and one carries some cardiovascular disease risk, he would opt for the antiretroviral with a cleaner cardiovascular risk profile in someone with an already high risk of cardiovascular disease.

Current US antiretroviral guidelines lean toward favoring cART-induced viral control as one way to cut cardiovascular risk, citing multiple lines of evidence suggesting "that early control of HIV replication with ART can be used as a strategy to reduce risk of CVD, particularly if drugs with potential cardiovascular toxicity are avoided."[7] But no study demonstrates that cART prevents heart disease, these experts caution. And "for HIV-infected individuals with a signifi-

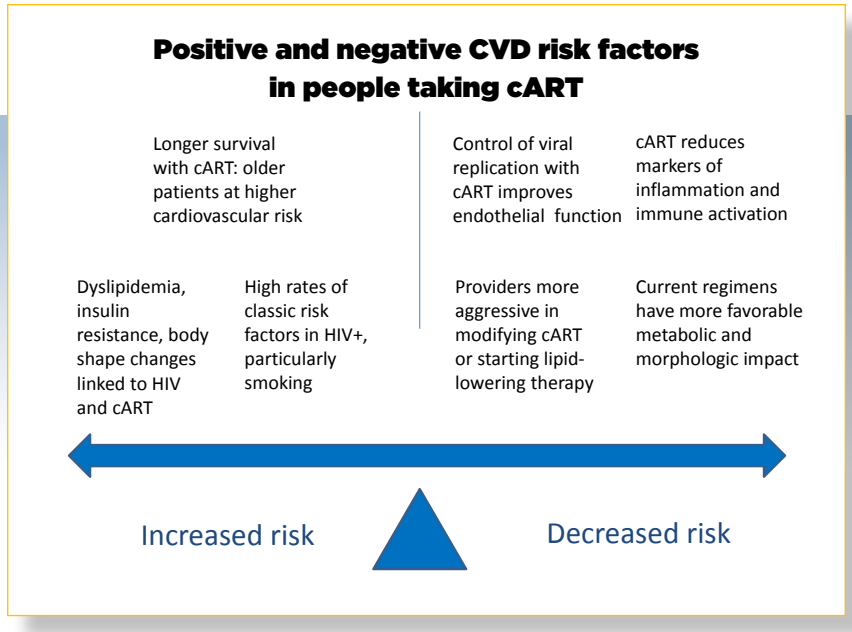

Figure 3. Top HIV clinicians, cardiologists, and epidemiologists proposed this scheme summarizing the balance between decreased and increased cardiovascular risk in people with HIV.[33] Most factors on both sides of the equation involve cART.

cant risk of CVD, as assessed by medical history and established estimated risk calculations, risk of CVD should be taken into consideration when selecting a specific ART regimen."[7]

Low viral load: low cardiovascular risk (usually)

A well-planned cART regimen usually boosts CD4 tallies and curbs HIV replication. Abundant research addresses whether those responses directly affect cardiovascular risk. By and large the answer seems to be yes, though several key studies say no. Sorting out the reasons for these divergent results is tough, but close analysis offers some clues.

Recent French and US studies appraised the impact of viral replication on a clinical endpoint—myocardial infarction,[6,34] and a European-Canadian-Australian cohort study gauged the impact of viral load on cardiovascular death.[35] A case-control study within the French Hospital Database on HIV determined that a viral load above 50 copies/mL upped chances of incident myocardial infarction 50%.[6] This study involved 289 people with a new MI between January 2000 and December 2006, matched by age, sex, and clinical center to 884 HIV-positive people with no MI history.

Median age was 47 in people with an MI and 46 in those without an MI. A higher proportion of control patients had a body mass index in the overweight range, but otherwise classic cardiovascular risk factors were more prevalent in the case group, including current smoking (64% versus 40%, $P = 0.028$), family history of premature coronary artery disease (18% versus 7%, $P < 0.001$), hypertension (20% versus 12%, $P = 0.001$), current cocaine or injection drug use (13% versus 9%, $P = 0.041$), and diabetes (16% versus 10%, $P = 0.036$). Fasting glucose and lipid measurements were significantly worse in people who had an MI.

Statistical analysis that considered antiretroviral exposure, CD4 and CD8 counts, and a mélange of classic risk factors determined that a current viral load above 50 copies/mL (versus below) independently raised the odds of a new MI 51% (adjusted odds ratio 1.51, 95% CI 1.09 to 2.10). Cumulative exposure to PIs more than doubled MI odds in this analysis (adjusted odds ratio 2.23 per 10 years, 95% CI 1.17 to 4.24), but abacavir exposure did not.

A study of 6517 HIV-positive people in two tertiary-care Boston hospitals found links between higher viral load and incident MI in statistical models that did not include CD4 count, but not in the models that did factor in CD4 tallies.[34] The Boston team checked records of HIV-positive people in care sometime between December 1998 and February 2008 to see how many suffered an acute MI. Age averaged 53.7 years in the 273 people who had an MI and 45.7 in the 6244 who did not. Women made up almost one third of the study group; 55% were white, 24% black, and 18% Hispanic. Half of these people smoked (55% with an MI and 50% without an MI). Classic cardiovascular risk factors were consistently more prevalent in the MI group.

Statistical analysis accounting for classic risk factors, antiretrovirals, CD4 count, and viral load determined that a load above 100,000 copies/mL predicted acute MI, but not significantly (adjusted odds ratio [aOR] 1.63, 95% CI 0.91 to 2.93, $P = 0.10$). In statistical models not including CD4 count, a higher viral load invariably altered odds of acute MI:

- Above 100,000 copies: aOR 2.16, 95% CI 1.26 to 3.69, $P = 0.01$
- Every 10-fold higher viral load: aOR 1.23, 95% CI 1.04 to 1.44, $P = 0.01$
- Every 10-fold higher peak viral load: aOR 1.23, 95% CI 1.04 to 1.44, $P = 0.02$
- Less than 400 copies: aOR 0.60, 95% CI 0.38 to 0.93, $P = 0.02$

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More HIV RNA may also inflate prospects of cardiovascular death, according to a 23-cohort European-Canadian-Australian CASCADE collaboration analysis involving 9858 people with an estimated date of HIV seroconversion.[35] Compared with people whose viral load lay below 100,000 copies/mL while not on cART, those with a load above that level while not on cART had almost a 6 times higher risk of death from cardiovascular disease (adjusted hazard ratio 5.81, 95% CI 1.59 to 21.24) and those with a viral load above 100,000 copies/mL while on cART had almost a 5 times higher risk (adjusted hazard ratio 4.70, 95% CI 1.25 to 17.73). However, the study group included only 36 people who died from heart disease. And this analysis uncovered no link between CD4 count and death from cardiovascular disease.

Not all big studies tie viral load to cardiovascular disease or death. Two notable exceptions are the SMART study[3] and a big DAD analysis.[20] SMART randomized 5472 adults with a CD4 count above 350 cells/mm^3 to continuous cART or to CD4 count-guided interruptions. During follow-up a major cardiovascular condition developed in 79 people, with more than a 50% higher risk in the interruption arm (hazard ratio 1.57, 95% CI 1.00 to 2.46, $P = 0.05$). With an expanded definition of major cardiovascular events, that risk reached statistical significance (hazard ratio 1.58, 95% CI 1.12 to 2.22, $P = 0.009$). But statistical analysis considering age, gender, use of antihypertensives, smoking, and total cholesterol found no evidence that being off cART at the time of the cardiovascular event or in the past 6 months made the event more likely. Every 10-fold higher most recent viral load also failed to implicate viral replication in incident cardiovascular events in several analyses.

People who interrupted cART during SMART had a worse total-to-high-density lipoprotein (HDL) cholesterol ratio than steadily treated people.[3] That difference, the SMART team suggested, "could offer a partial explanation" for the higher cardiovascular event rate in the interruption arm. The researchers also acknowledged the hypothesis that inflammation kicked off by a "sudden burst of high level HIV replication" when a drug break began could trigger an MI or a stroke. Perhaps, the authors surmised, the trial did not measure viral load often enough to capture these viremic flares. Or maybe viral load simply is not a good way to measure inflammation and immune activation. The SMART team also suggested their analysis may have suffered from low statistical power because of the scant cardiovascular events recorded (79).

DAD investigators focused only on MIs,[20] as the French[6] and Boston[34] studies did. The DAD team counted 345 MIs in 23,437 HIV-positive people monitored through February 2005 for an incidence of 3.65 per 1000 person-years. Median age at last follow-up was 43 years overall and 49 in people who had an MI. Three quarters of cohort members (78%) were white, and almost everyone (94%) had taken antiretrovirals. The DAD team found no link between peak viral load and MI risk (relative rate for each 10-fold higher peak viral load 1.06, 95% CI 0.95 to 1.18) or between CD4 count and MI risk (relative rate for each 50-cell higher count 0.98, 95% CI 0.95 to 1.01). But the investigators did not reckon the impact of other viral load measures on MI risk—such as latest viral load or viral load at MI.

Why would a low viral load cut chances of cardiovascular disease or death? Uncontrolled viral replication means prodigious inflammation and immune activation, both of which threaten the heart and its vascular tributaries. But a subgroup analysis of an ACTG antiretroviral trial suggests another reason: endothelial function improves when cART curbs viral

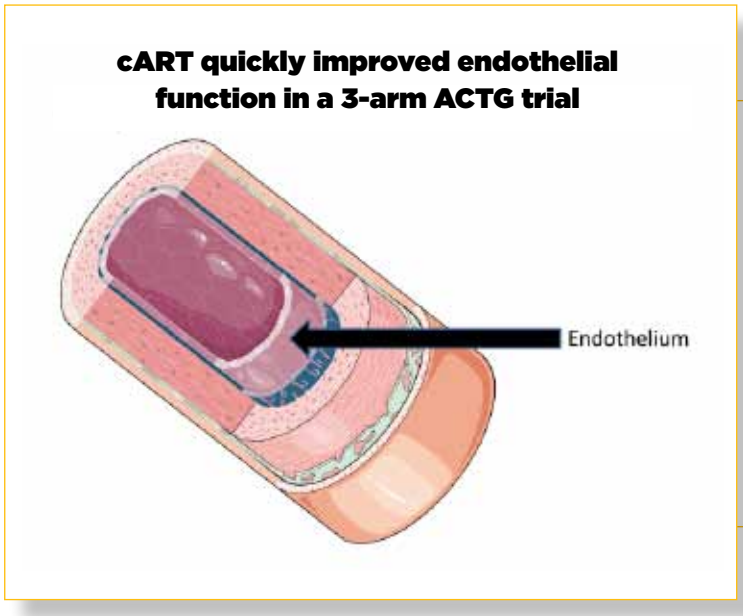

Figure 4. Combination antiretroviral therapy (cART) may lower the risk of cardiovascular disease by improving arterial endothelial function, measured as flow-mediated dilation, according to results of an ACTG trial substudy.[11] Arteries must be able to dilate readily to generate an anticoagulant surface.[36] (Illustration from Servier Medical Art. ***http://www.servier.co.uk/medical-art-gallery/***)

replication.[11] ACTG investigators found that starting either a standard PI or NNRTI regimen—or lopinavir plus efavirenz without NRTIs—swiftly improved endothelial function reckoned as brachial artery flow-mediated dilation. This 82-person analysis charted significant improvements in flow-mediated dilation with all three regimens (**Figure 4**).

Study participants were young (median 35 years, interquartile range 30 to 40), and 91% were men.[11] As in many HIV populations, a high percentage, 44%, smoked. Median body mass index just crossed the overweight threshold (25.1 kg/m^2), but group blood pressure was good (119/74 mm Hg). Except for low HDL cholesterol, other lipid, glucose, and insulin values were within the normal range. The group had a median pre-cART CD4 count of 245 cells/mm^3 and a median viral load around 66,000 copies/mL.

After 24 weeks of treatment, 67% of study participants had a viral load below 50 copies/mL and another 18% had between 50 and 100 copies/mL. After only 4 weeks of treatment, flow-mediated dilation rose (improved) 0.74% overall (IQR (– 0.62% to +2.74%, P = 0.003), with no difference between study arms. After 24 weeks of treatment flow-mediated dilation continued to improve in every study arm, increasing by 1.48% overall (IQR –0.20% to +4.30%, P < 0.001). Change in flow-mediated dilation from baseline to week 24 correlated with only two factors—adiponectin and change in viral load. (Adiponectin is an adipocyte-specific protein that may play a role in insulin resistance and atherosclerosis.) The correlation with viral load was inverse (– 0.30, P = 0.017), meaning the bigger the drop in viral load, the greater the improvement in endothelial function. The ACTG team suggests their findings support the hypothesis that controlling HIV replication improves endothelial function, but they note that follow-up was short and the study group young.

Disentwining diverse CD4 impacts on cardiovascular risk

Two DAD Study analyses,[2,20] a EuroSIDA review,[1] the SMART cardiovascular endpoint dissection,[3] and a combined analysis of the ESPRIT and SILCAAT interleukin 2 (IL-2) trials[37] discerned no link between

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CD4 count (measured various ways) and risk of cardiovascular disease (also measured various ways) (**Table 1**). But since the last of those reports in 2010,[1,37] five other cohort studies,[6,34,38-40] including a new DAD analysis,[40] did yoke CD4 count to cardiovascular endpoints (**Table 2**). Two other studies tied lower CD4 counts to subclinical signals of arterial disease,[41,42] and one linked lower CD4 nadir to sustained hypertension.[43]

Table 1. Studies finding no association between CD4 measures and cardiovascular endpoints

Study (years)	n (% male)	Age, CD4 count	Study group	CD4 measure	CVD endpoint	Main results
EuroSIDA[1] (2001-2009)	12,844 (73.2%)	BL 39 y Nadir 178, BL 403	Prospective cohort from Europe, Israel, Argentina	Doubling of current CD4 count	MI, stroke, CABG, coronary angioplasty, carotid endarterectomy (n = 384)	Every doubling of current CD4 count predicted lower risk of 4 non-AIDS illnesses, but not CVD
DAD[2] (1999-2002	23,468 (75.9%)	BL 39 y Nadir 226, BL 418	Prospective cohort from Europe, United States, Australia	Per 50-cell higher nadir CD4 count and BL CD4 count (at enrollment)	MI (n = 126)	Every 50-cell higher nadir CD4 count or BL CD4 count had no impact on MI risk
DAD[20] (1999-2005)	23,437 (75.9%)	BL 39 y, last FU 43 y BL 420, last FU 461	Prospective cohort from Europe, United States, Australia	Per 50-cell higher nadir CD4 count	MI (n = 345)	Every 50-cell higher nadir CD4 count had no impact on MI risk
SMART[3] (2002-2006)	5742 (73%)	BL 44 y BL 267	People randomized to continuous or interrupted cART	Per 100-cell higher current CD4 count	Clinical or silent MI, nonfatal stroke, CAD requiring surgery or invasive procedure (n = 79)	Every 100-cell higher current CD4 count had marginal impact in interruption arm (P = 0.08) and no impact in combined trial arms

Study (years)	n (% male)	Age, CD4 count	Study group	CD4 measure	CVD endpoint	Main results
ESPRIT and SILCAAT[37] (NR)	3012 (82.3%)	BL 41 y Nadir 167, BL 400	People randomized to standard cART (no IL-2) in two IL-2 trials	Per doubling of latest CD4 count	MI, stroke, CAD requiring procedure, other fatal heart/vascular events, sudden death (n = 95)	Every doubling of latest CD4 count had no impact on rate of fatal or nonfatal CVD events

BL, baseline; CABG, coronary artery bypass graft; CAD, coronary artery disease; CVD, cardiovascular disease; FU, follow-up; IL-2, interleukin 2; MI, myocardial infarction; NR, not reported.

Table 2. Studies finding an association between CD4 measures and cardiovascular endpoints

Study (years)	n (% male)	Age, CD4 count	Study group	CD4 measure	CVD endpoint	Main results
FHDH[6] (2000-2006)	289 cases, 884 controls (89%)	BL 47 y Nadir 135, BL 427	Case-control study of HIV+ with first MI or no MI	Doubling of nadir CD4, highest tertile CD8	MI (n = 289)	Every doubling of CD4 nadir cut MI risk 10%; highest (vs lowest) CD8 tertile raised risk 48%
Boston[34] (1998-2008)	6517 (69.4%)	46 y 26% < 200	HIV+ in two large Boston hospitals	Current CD4 count <200, every 50-cell higher CD4 count	MI (n = 273)	Current CD4 count <200 raised MI odds 74%; every 50-cell higher current CD4 lowered MI odds 7%
HOPS[38] (2002-2009)	2005 (76%)	42 y Nadir 197, BL 395	Prospective cohort from 10 US centers	BL CD4 count <350 vs >500, every 100-cell lower BL CD4 count	MI, stroke, CAD, angina, PAD (n = 148)	BL CD4 count <350 raised CVD risk 58%; every 100-cell lower BL CD4 count raised risk 8%

BL, baseline; CABG, coronary artery bypass graft; CAD, coronary artery disease; CVD, cardiovascular disease; FHDH, French Hospital Database on HIV; HOPS, HIV Outpatient Study; MI, myocardial infarction; PAD, peripheral arterial disease.

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Study (years)	n (% male)	Age, CD4 count	Study group	CD4 measure	CVD endpoint	Main results
ATHENA[39] (2000-2009)	3068 (83.4%)	41 y Nadir 170, BL 360	Prospective cohort on cART in Netherlands	CD4 count <200, 200-350, 351-500, >500 2 years after starting cARTt	MI, CABG, coronary stenting and/ or angioplasty, cerebrovascular attack (n = 57)	CD4 count of 200-350 (vs <200) 2 years after starting cART cut CVD risk 66%
DAD[40] (1999-2008)	33,308 (74.1%)	BL 39 y BL 408	Prospective cohort from Europe, United States, Australia	Every 50-cell higher current CD4 count	Cardiovascular death (n = 289)	Every 50-cell higher current CD4 count cut CVD death risk 3%

BL, baseline; CABG, coronary artery bypass graft; CAD, coronary artery disease; CVD, cardiovascular disease; FHDH, French Hospital Database on HIV; HOPS, HIV Outpatient Study; MI, myocardial infarction; PAD, peripheral arterial disease.

In a EuroSIDA analysis of 12,844 HIV-positive people (**Table 1**), every doubling of current CD4 count independently predicted a lower incidence of AIDS, all non-AIDS events combined, non-AIDS malignancies, end-stage renal disease, pancreatitis, and liver-related events, but not cardiovascular events (incidence rate ratio 0.98, 95% CI 0.85 to 1.12, $P = 0.78$).[1] The EuroSIDA team proposed that cardiovascular disease risk depends less on CD4 status than on lipid changes, lifestyle, and inflammation.

Two DAD analyses (**Table 1**) determined that every 50-cell higher nadir CD4 count[2,20] or every 50-cell higher baseline CD4 count[2] had no impact on MI risk in prospective follow-up of more than 23,000 people. But the DAD team acknowledged "the possibility that other unmeasured immunologic effects may exert an influence on the development of cardiovascular disease."[20] For example, time-updated CD4 count, CD4 count at MI diagnosis, or CD4/CD8 ratio could have an impact in this population. In an updated DAD analysis involving 33,308 people (**Table 2**), higher latest CD4 count did predict a slightly lower risk of cardiovascular *death* (see below).[40]

In the SMART analysis of 79 cardiovascular events in that trial, every 100-cell higher current CD4 count marginally boosted chances of cardiovascular disease (adjusted hazard ratio 1.11 per 100 cells, 95% CI 0.99 to 1.25, $P = 0.08$) in the cART interruption arm.[3] But that CD4 yardstick had no impact on cardiovascular risk in the combined study arms (adjusted hazard ratio 0.99, 95% CI 0.90 to 1.07, $P = 0.74$).

ESPRIT and SILCAAT randomized antiretroviral-naive adults to standard cART or to standard cART plus IL-2 (**Table 1**).[37] To analyze the impact of various CD4 metrics on AIDS and non-AIDS endpoints, the investigators focused on 3012 people randomized to the standard-cART control arms. Every doubling of the latest CD4 count

had no impact on the rate of fatal or nonfatal cardiovascular events (adjusted hazard ratio 1.05, 95% CI 0.77 to 1.43). Among all these analyses (**Tables 1** and **2**), the ESPRIT/SILCAAT study involved the smallest number of HIV-positive people and only 95 cardiovascular endpoints. The investigators surmised higher rates of cardiovascular and other non-AIDS diseases in people with HIV could reflect a "subtle ongoing inflammatory process stimulated by residual viral replication or the treatment" and "subclinical inflammation may not be best reflected by latest CD4+ count."[37]

French Hospital Database on HIV investigators planned a case-control study specifically to scrutinize the impact of viral load and CD4 count on risk of first myocardial infarction (**Table 2**).[6] The French team matched 289 HIV-positive people who had a first MI in 2000-2006 to 3 controls of the same age, sex, and clinical center who had not had an MI. A current viral load above 50 copies/mL (versus below) independently raised chances of a new MI 51% (adjusted odds ratio 1.51, 95% CI 1.09 to 2.10).

In the same analysis, which adjusted for antiretroviral exposure and classic risk factors, two T-cell variables swayed MI risk: every doubling of CD4-cell nadir trimmed MI risk 10% (adjusted odds ratio 0.90, 95% CI 0.83 to 0.97), and being in the highest current CD8 count tertile (above 1150 cells/mm^3) versus the lowest tertile (at or below 760 cells/mm^3) hoisted MI odds almost 50% (adjusted odds ratio 1.48, 95% CI 1.01 to 2.18). Current CD4 count did not predict MI, but CD4 nadir/CD8 ratio did. The CD4/CD8 ratio was significantly lower (worse) in cases than controls (0.42 vs 0.50, $P < 0.001$). A higher CD8 count reflects ongoing immune activation to control HIV, indicated in this study by the parallel link between a detectable viral load and heightened odds of myocardial infarction. Previous studies have also linked MI or cardiovascular disease markers to CD4/CD8 ratio[44] or other immune activation markers.[44-46]

The Boston study described in the preceding section found ties between several viral load measures and acute MI when the analysis excluded CD4 count.[34] A multivariate regression model adjusted for viral load, age, gender, race, hypertension, diabetes, dyslipidemia, chronic kidney disease, smoking, years since first cART use, and antiretroviral medications individually associated with MI determined that a current CD4 count under 200 cells/mm^3 boosted MI odds almost 75% (adjusted odds ratio 1.74, 95% CI 1.07 to 2.81, $P = 0.02$). Further analysis determined that every 50-cell higher current CD4 count cut MI risk 7% (adjusted odds ratio 0.93, 95% CI 0.89 to 0.97, $P = 0.002$). Every 50-cell higher CD4 nadir pared MI risk 5%, but that association did not reach statistical significance (adjusted odds ratio 0.95, 95% CI 0.89 to 1.01, $P = 0.09$). Thus in this analysis, the impact of CD4 measures on MI appeared to outweigh the impact of viral control, because viral load associations proved significant only when statistical models did not include CD4 count.

An HIV Outpatient Study (HOPS) analysis of 2005 HIV-positive people counted 148 new cardiovascular diagnoses (defined in **Table 2**) from 2002 through 2009.[38] A multivariate model accounting for traditional risk factors determined that a baseline CD4 count below 350 cells/mm^3 (versus at or above 500) boosted cardiovascular disease risk 58% (adjusted hazard ratio 1.58, 95% CI 1.09 to 2.31, $P = 0.017$). Every 100-cell lower baseline CD4 count upped the cardiovascular event risk 8% (adjusted hazard ratio 1.08, 95% CI 1.01 to 1.14). Additional adjustment for baseline injection drug use, frequency of alcohol use, and baseline viral load did not change these results. The HOPS team also calculated that about 20% of cardio-

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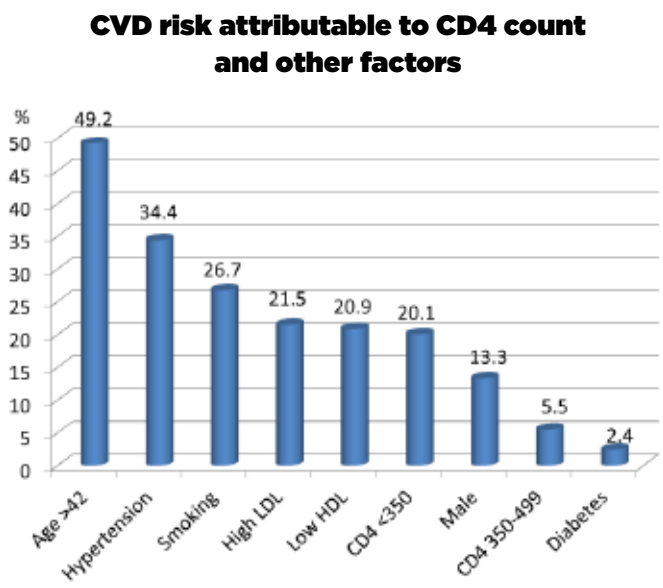

Figure 5. A 2005-person HIV Outpatient Study (HOPS) analysis figured that cardiovascular disease risk attributable to a baseline CD4 count below 350 cells/mm^3 (versus above 499) was similar to risk attributable to classic risk factors like current or former smoking, high LDL or non-HDL cholesterol, low HDL cholesterol, and male gender.[38] The HOPS team cautioned that this analysis may not apply to HIV populations with cardiovascular risk factor rates unlike those in these HOPS cohort members.

vascular disease risk could be attributed to a sub-350 baseline CD4 count (versus above 499), an attributable risk similar to those seen with several classic risk factors (**Figure 5**).

In the Netherlands ATHENA cohort investigators focused on 3068 people who had taken cART for at least 2 years and reached a viral load below 500 copies/mL, dividing them into 2-year CD4 brackets of below 200, 200 to 350, 351 to 500, and over 500.[39] A multivariable model to pinpoint predictors of a new cardiovascular diagnosis (see **Table 2**) adjusted for age, gender, family history of heart disease, cardiovascular event before baseline, smoking, and alcohol abuse. Compared with a CD4 count below 200 cells/mm^3 after 2 years of cART, a count of 200 to 350 cut the cardiovascular event risk by two thirds (adjusted hazard ratio 0.34, 95% CI 0.14 to 0.86, P= 0.02). People who reached a CD4 count above 500 had almost a 50% lower risk of reaching a composite endpoint including death, AIDS, malignancies, liver cirrhosis, and cardiovascular events (adjusted hazard ratio 0.54, 95% CI 0.33 to 0.87, P = 0.01). Because older age, a lower nadir CD4 count, and a higher pre-cART viral load independently predicted poor CD4 recovery, the ATHENA team suggested that "starting HAART at higher CD4 cell counts, especially in older aged patients, may be beneficial."[39]

DAD investigators offered the biggest study to address CD4 impact on the ultimate cardiovascular endpoint—death.[40] They considered latest CD4 count in six brackets, under 50, 50 to 59, 100 to 199, 200 to 349, 350 to 499, and 500 or higher. Cardiovascular death rates were 3.11 per 1000 person-years for people in the lowest CD4 bracket and 1.16 per 1000 for those in the highest bracket. Every 50-cell higher current CD4 count trimmed the risk of cardiovascular death 3% (adjusted relative rate 0.97, 95% CI 0.95 to 0.99).

What CD4 and viral load measure—and what they don't

Why do some cohort studies find no link between CD4 measures and cardiovascular disease (**Table 1**) while others do (**Table 2**)? Comparing features of the two groups of studies in these tables yields no easy answer, but perhaps some hints. The no-association studies were generally bigger, but the biggest analysis, the 1999-2008 DAD study,[40] did find an link between latest CD4 count and cardiovascular disease, and it had the sternest endpoint—death. The only case-control study, from the French Hospital Database on HIV, identified ties between both CD4 and CD8 counts and MI risk.[6] Median or mean age tended to be older in the positive-association studies (**Table 2**). Older age would yield more cardiovascular endpoints and so may beef up the statistical power needed to show an association. But two no-association studies, EuroSIDA[1] and DAD,[20] had the highest number of endpoints.

DAD investigators who worked on the no-association 1999-2005 analysis[20] noted that a CD4 metric other than the one they used could have found a link between CD4s and cardiovascular events. Both of the DAD studies that found no link between CD4 count and cardiovascular trouble used a 50-cell higher CD4-nadir measure,[2,20] and one of those studies used cohort baseline CD4 count.[2] The French study that found a CD4-heart link was the only other analysis to use nadir CD4 count, and they used a doubling of CD4 nadir.[6] The 1999-2008 DAD analysis that found a CD4 association with cardiovascular death used latest CD4 count as the yardstick. Perhaps every 50-cell higher CD4 nadir is too fine a gauge to identify an association.

The French team suggested another reason why results of these 10 big studies differ. Their case-control probe showed that a viral load above 50 copies/mL upped the MI risk by half.[6] Two other studies reviewed above tied a lower viral load to a lower heart disease or death risk.[34,35] In the studies evaluating CD4 impact on cardiovascular disease, the French investigators proposed, "the differences between the studies could be explained by differences in the proportion of patients with controlled viral load."[6]

Why would lower or higher CD4 count affect risk of cardiovascular disease? On an elementary level, a higher CD4 count indicates better overall health, and healthier people are less likely to get diagnosed with any number of non-AIDS diseases, including heart disease. But there are probably more precise mechanisms. A climbing CD4 count typically mirrors falling numbers of CD8s—the T cells recruited to kill infected cells and tumor cells. Fewer CD8s in circulation mean less HIV in circulation, in other words, less inflammation and immune activation.

This is not just airy hypothesis. A handful of studies address this issue in one way or another. During untreated HIV infection, CD4s wane and CD8s surge, an immunologic seesaw that sends a normal CD4/CD8 ratio (about 2) into the abnormal range (under 1). A study of 78 HIV-positive men with an average age of 46.5 and no history of coronary artery disease used computed tomography coronary angiography to assess indicators of atherosclerosis.[44] Lower (worse) CD4/CD8 ratio was significantly associated with both number of plaque-bearing coronary artery segments and plaque volume. Notably, the relationship between CD4/CD8 ratio and plaque volume proved stronger than the association seen with CD4 count or viral load and plaque volume—a result suggesting CD4 count and viral load may be relatively blunt instruments for assessing cardiovascular risk.

Two studies in San Francisco found higher levels of CD4 and CD8 activation with lower CD4 counts.[47,48] The first study correlated CD8-cell activation with poor CD4 gains despite good virologic control with antiretroviral therapy.[47] The 99 adults evaluated kept

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their viral load at or below 1000 copies/mL for a median of 21 months on cART. Although they had lower levels of CD8-cell activation than untreated HIV-positive people, they had higher levels than HIV-negative controls. Every 5% higher proportion of activated (CD38+/HLA-DR+) CD8 cells meant a 35-cell lower CD4 gain during therapy. The same researchers analyzed CD4- and CD8-cell activation in a cross-sectional study of 30 elite controllers—people who maintain an undetectable viral load without cART.[48] This study linked lower CD4 counts to higher levels of activated CD4s and CD8s (rho = –0.52, $P = 0.003$ for activated CD4s and rho = –0.37, $P = 0.047$ for activated CD8s).

HOPS investigators[38] noted that lower CD4 counts mean higher activated CD4 numbers, and activated CD4 cells turn up in atherosclerotic lesions in the general population.[49] The HOPS team also observed that the chronic inflammation seen in advanced HIV infection is driven by "the same inflammatory cells and proinflammatory cytokines that destabilize atherosclerotic plaques,"[38] resulting in plaque rupture and coronary artery thrombosis.[49-51]

Does cART prevent heart disease?

Does the evidence tying higher viral loads and lower CD4 counts to a bigger heart disease risk mean clinicians should consider cART a component of cardiovascular disease prevention? That one might even ponder such a proposition is remarkable. Just over a decade ago, SMART trial investigators planned that seminal study to test the hypothesis that *avoiding* cART for planned intervals would ease the burden of major cardiovascular, kidney, or liver disease.[52] In other words, plenty of HIV luminaries thought cART should be shunned when possible to trim the risk of heart disease—and lots of clinicians felt the same way. SMART demolished that strategy. But do the data reviewed above mean clinicians should start cART earlier—as soon as possible, US guidelines say[7]—not only to thwart AIDS but also to ward off cardiovascular disease and other portentous afflictions? Some of the researchers who ran the studies reviewed here think so:

Summing up their 6500-person study of CD4 and viral load impact on MI, Steven Grinspoon, Paul Sax, and other Boston researchers wrote that "treatment of HIV infection to improve immunologic function is likely to be an important component of cardiovascular prevention for HIV patients" and that "cardiovascular risk reduction might therefore be an additional benefit of earlier initiation of ART."[34]

The HOPS team believes their findings "support prior observations that HIV infection in itself is a risk factor for cardiovascular disease not dissimilar in magnitude to some traditional risk factors for cardiovascular disease events," and they call for "randomized controlled trials to assess whether earlier initiation of antiretrovirals and avoidance of treatment interruptions will reduce the incidence of cardiovascular events."[38]

In February 2013 antiretroviral guidelines, US experts maintained that "increased risk of cardiovascular events with treatment interruption, the effects of ART on markers of inflammation and endothelial dysfunction, and the association between cardiovascular disease and CD4 cell depletion suggest that early control of HIV replication with ART can be used as a strategy to reduce risk of cardiovascular disease, particularly if drugs with potential cardiovascular toxicity are avoided."[7] But they stress that research has yet to prove that cART prevents cardiovascular disease, and "therefore, a role for early ART in preventing cardiovascular disease remains to be established."

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When and how to screen for cardiovascular disease risk in people with HIV

By Mark Mascolini

Abstract: HIV groups in the United States and Europe—including pediatric experts—have promulgated largely concordant guidelines on screening people with HIV infection for cardiovascular disease risk. These guidelines recommend some form of regular cardiovascular risk assessment for everyone with HIV infection. European guidelines call for annual screening including an ECG in men over 40 and women over 50, but US authorities do not recommend routine ECG screening. A National Heart, Lung, and Blood Institute panel considers pediatric HIV infection a moderate risk factor for accelerated atherosclerosis and recommends assessing cardiovascular risk factors in all children with HIV infection. The Framingham Risk Score overestimates or underestimates 10-year cardiovascular risk in some people with HIV, depending on individual risk factors and geographic origin. The DAD cardiovascular risk tool may offer a more precise gauge for populations like the DAD cohort. US HIV/heart experts suggest guidelines on when HIV patients need further noninvasive or invasive testing.

Guidelines for cardiovascular disease (CVD) screening in people with HIV are profuse yet elementary[1-4] (**Table 1**). And pediatric solons have devised a transparent algorithm for sizing up cardiovascular risk in children with HIV[5] (**Table 2**). But as with any facet of HIV medicine, the deeper you dig, the bigger the hole you can find yourself in. As the first two articles and the interview with James Stein in this issue make clear, cardiovascular risk with HIV infection is fraught with confounders ranging from parental chromosomes to pernicious lifestyle choices. Not to mention antiretroviral picks.

For adults, the HIV Medicine Association (HIVMA) and collaborating groups,[1,2] the European AIDS Clinical Society (EACS),[3] and the US Health Resources and Services Administration (HRSA)[4] all recommend routine assessment of cardiovascular risk factors with a standard heart risk calculator when people enter care, start antiretroviral therapy (ART), switch antiretroviral regimens, and at regular intervals depending on calculated risk (**Table 1**). The EACS takes a more aggressive stance than the US groups, also calling for yearly electrocardiograms (ECGs) in men over 40 and women over 50.[3] Lipids, blood pressure, and glucose also need regular checking (**Table 1**).

In 2011 an expert panel assembled by the National Heart, Lung, and Blood Institute (NHLBI) issued "Integrated guidelines for cardiovascular health and risk reduction in children and adolescents," which includes some HIV-specific screening advice (**Table 2**).[5] The panel figures that HIV itself poses a moderate risk of accelerated atherosclerosis in children. Indeed, the Bogalusa Heart Study famously found that atherosclerotic changes can begin brewing in childhood.[6] The NHLBI recommends assessing heart risk factors in children with HIV and—in those with two or more risk factors—taking steps to control weight, blood pressure, lipids, and glucose.

Table 1. Screening adults with HIV for cardiovascular disease risk and related conditions

	HIVMA*[1,2]	European[3]	HRSA[4]
Cardiovascular disease	For every adult on ART, count CHD risk factors;† if 2 or more perform 10-year risk calculation‡[1]	For every adult risk assessment‡ before ART, then annually; for men over 40 and women over 50, ECG annually	For every adult, determine whether patient has established CHD or a CHD risk-equivalent state; if 2 or more risk factors, perform 10-year risk calculation‡
Lipids	For every adult, every 3 to 6 months, and consider 1 to 3 months after starting or modifying ART[2]	For every adult, fasting lipid profile at HIV diagnosis, before ART, then annually unless otherwise specifically indicated	For every adult, fasting lipid profile at baseline and when starting ART; within 3 to 6 months after starting ART and sooner for patients with abnormal values; then annually for patients with normal values and more often for patients with abnormal values
Hypertension	For every adult, blood pressure annually[2]	For every adult, blood pressure at HIV diagnosis, before ART, then annually unless specifically indicated	Assess when evaluating cardiovascular risk (above)
Diabetes	For every adult, fasting glucose every 6 to 12 months; consider 1 to 3 months after starting or modifying ART[2]	For every adult, fasting glucose at HIV diagnosis, before ART, then annually unless specifically indicated	For every adult, fasting glucose at baseline and within 3 to 6 months of starting or changing ART if baseline results normal; more often if abnormal

ART, antiretroviral therapy; CHD; coronary heart disease; ECG, electrocardiogram; HIVMA, HIV Medicine Association.

* Recommendations of the HIV Medicine Association (HIVMA), Infectious Diseases Society of America, and Adult AIDS Clinical Trials Group.

† Risk factors are cigarette smoking, hypertension, low high-density lipoprotein (HDL) cholesterol, family history of premature coronary heart disease, and age older than 45 in men and 55 in women.

‡ Framingham 10-year risk calculator or DAD 5-year estimated risk calculator, both at ***www.cphiv.dk/tools.aspx***.

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Table 2. Screening children with HIV for cardiovascular disease[5]

Children with HIV are considered as having moderate risk of accelerated atherosclerosis and early CVD*
Assess cardiovascular risk factors: ▶ Family history of early CVD ≤ 55 male or ≤ 65 female ▶ Fasting lipid profile ▶ Smoking history ▶ Blood pressure ▶ Height, weight, body mass index ▶ Fasting glucose ▶ Diet, physical activity/exercise history
If 2 or more risk factors, consider child at high risk and establish following targets: ▶ Body mass index ≤ 85th percentile for age and sex ▶ Blood pressure ≤ 90th percentile for age and sex ▶ Lipids ≤ 100 mg/dL for LDL, < 90 mg/dL for TG, <120 mg/dL for non-HDL ▶ Fasting glucose <100 mg/dL, HgbA1C<7%
Use intensive lifestyle management plus condition-specific management. For details see source linked in footnotes.

CVD, cardiovascular disease; HbgA1C, hemoglobin A1C; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglycerides.
Source: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Integrated guidelines for cardiovascular health and risk reduction in children and adolescents. The report of the expert panel. 2011.[5]
http://www.nhlbi.nih.gov/guidelines/cvd_ped/summary.htm
Thanks to George K. Siberry, MD, MPH, Eunice Kennedy Shriver National Institutes of Child Health and Human Development, for help in identifying pediatric guideline sources.
* High-risk children include those with chronic kidney disease or diabetes type 1 or 2.

Does Framingham reliably frame CVD risk with HIV?*

Is the Framingham score an accurate cardiovascular risk predictor for people with HIV? Studies that address this question agree that the Framingham risk-reckoner does a decent job in HIV-positive people but may underestimate 10-year risk in some subgroups and overestimate risk in others—depending on risk factors and geographic origin. And no wonder. As the first two articles in this issue of RI*TA!* make clear, people with HIV tote an ample burden of classic heart risk factors. On top of that they have a chronic inflammatory infection and may take cardiotoxic drugs to treat it. So compared with the general population, HIV-positive people face a more ramified array of risk mediators that may sway the prediction one way or the other.

The Framingham tool figures 10-year risk of "hard coronary artery disease," meaning myocardial infarction or coronary death, in adults without coronary heart disease, diabetes, or intermittent claudication (leg or arm pain caused by inadequate blood flow).[7] It does so by assigning points for six variables: age, total cholesterol, HDL cholesterol, systolic blood pressure, antihypertensive therapy, and smoking status for men or women (**Figure 1**). A 10-year risk score below 10% indicates low risk, 10% to 20% signals intermediate risk, and 21% or higher signifies high risk. These 10-increment cut points are arbitrary.

An HIV-specific cardiovascular risk calculator engineered by the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study leaves out antihypertensive therapy but adds five others factors to the equation—number of years taking indinavir or lopinavir; current treatment with indinavir, lopinavir, or abacavir; previous smoking; diabetes; and family history of cardiovascular disease (**Figure 1**).[8] Unlike Framingham, the DAD tool predicts *5-year* risk of coronary heart disease (in people without a heart disease history). The DAD team considers a 5-year CHD risk below 1% low, 1% to 5% moderate, 5% to 10% high, and above 10% very high. The Framingham and DAD calculators are online at the links following references **7** and **8**.

DAD researchers stress the big differences between their study group and the Framingham cohort.[8] The HIV-negative US-based Framingham population included 2590 men and 2983 women from 30 to 74 years old followed for 12 years from a baseline date of 1968 to 1975. The DAD cohort was bigger (16,765 men and 5860 women), younger (median 40 years), and mostly European, and follow-up was shorter (4.8 years starting in the year 2000) than in Framingham. Everyone in DAD had HIV infection and most were taking antiretrovirals. The DAD investigators cite previous research indicating that the Framingham equation overpredicts cardiovascular disease risk in European populations. They note that the limited number of cardiovascular endpoints in DAD women prevented them from developing sex-specific prediction models.

Thanks to Nina Friis-Møller, MD, PhD, DMSc, Copenhagen HIV Programme, University of Copenhagen, for reviewing this section of this article.

How can these differences in variables and study populations affect risk calculations? Say your patient is a 52-year-old male smoker with a total cholesterol of 237, an HDL of 42, a systolic blood pressure of 138, and naive to antihypertensives. Feed those numbers into the Framingham brain and you come away with a 10-year risk of 20%, right at the cusp of high risk. That 20% means 20 of 100 people with this risk will have a heart attack in the next 10 years. Not happy odds.

Now you turn to the DAD decoder and add that this same patient took lopinavir for 3 years and is still taking lopinavir with abacavir. He's a current smoker, does not have diabetes, but has a family history of heart disease. Click the CALCULATE button. In the next 5 years, this man runs a 14.1% risk of coronary heart disease. But if he stopped lopinavir and is not on abacavir, this 5-year risk shrinks to 7.1%. If he quit smoking, the 5-year risk dwindles to 4.2%. If you take smoking out of the Framingham calculation detailed above, the 10-year risk falls to 9%. Thus, depending on the patient subgroup involved, the DAD tool would predict a greater or lesser coronary heart disease risk than Framingham.

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Comparison of Framingham and DAD cardiovascular risk calculators

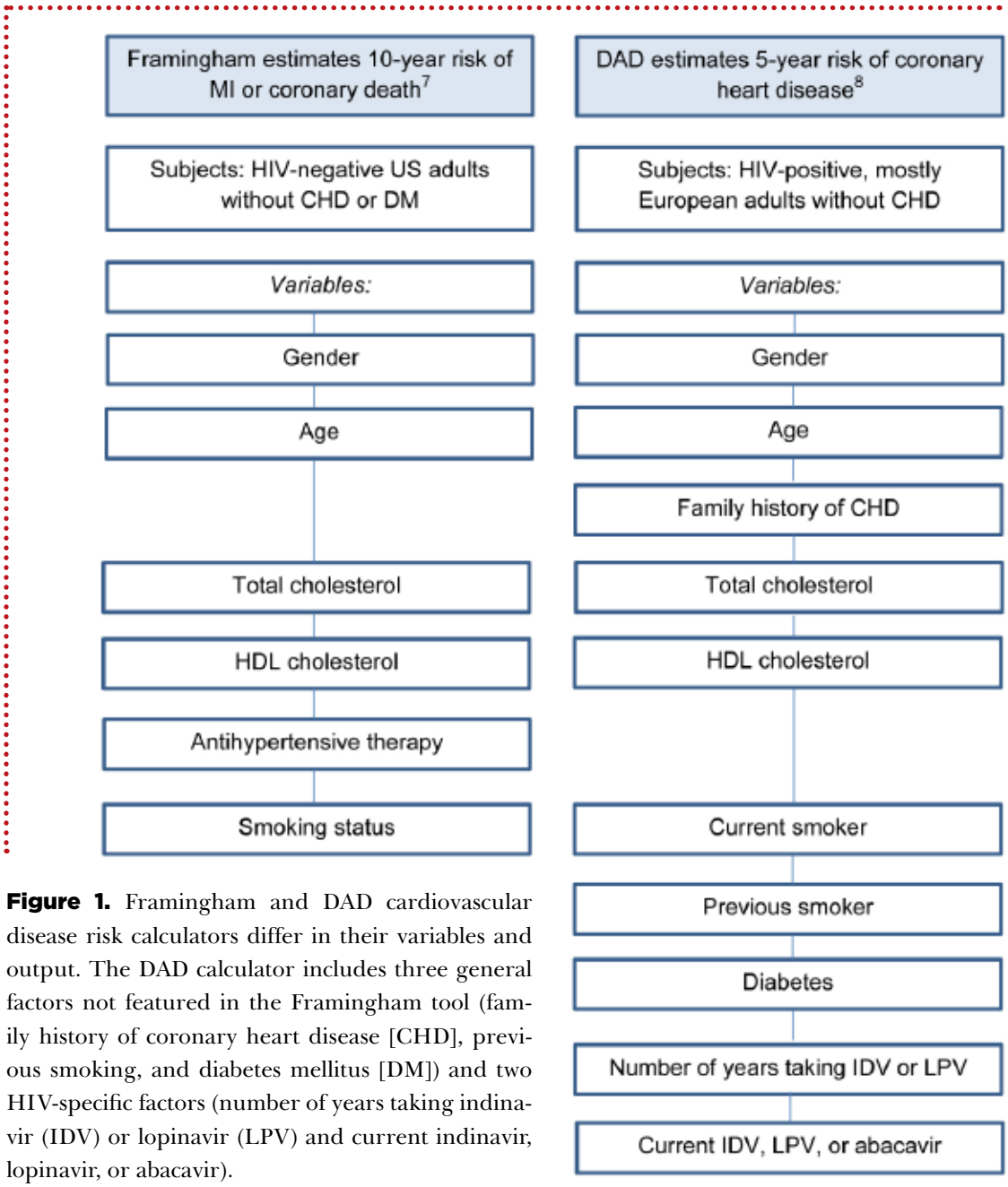

Figure 1. Framingham and DAD cardiovascular disease risk calculators differ in their variables and output. The DAD calculator includes three general factors not featured in the Framingham tool (family history of coronary heart disease [CHD], previous smoking, and diabetes mellitus [DM]) and two HIV-specific factors (number of years taking indinavir (IDV) or lopinavir (LPV) and current indinavir, lopinavir, or abacavir).

In the study in which DAD investigators developed their risk calculator, it proved more accurate than the Framingham equation in estimating cardiovascular disease risk in the overall (largely European) cohort and in certain subgroups.[8] In the DAD cohort, the Framingham model underpredicted risk compared with the DAD model when forecasting myocardial infarction or coronary heart disease in women, former smokers, and people with diabetes. On the other hand, Framingham overpredicted risk in people who never smoked.

"Although pending external validation," DAD collaborators note, "our models are intended for clinical usage to inform doctor-patient discussions on CVD risks and interventions,"[8] as well as for research applications.

Before DAD investigators devised their risk calculator, they analyzed the accuracy of the Framingham formula in predicting myocardial infarction.[9] Among European, US, and Australian DAD participants taking antiretrovirals, Framingham underpredicted actual MI incidence (9 observed MIs versus 5.5 predicted). But among antiretroviral-naive people, Framingham overpredicted actual incidence (3 observed MIs versus 7.6 predicted).

In an interview in this issue, cardiologist James Stein counsels that HIV clinicians should consider the Framingham model "as a starting point for discussion," recognizing that it's not perfect in people with HIV or people who differ from the young to middle-aged white US population in the Framingham cohort.

Which patients need deeper probing?

When should you refer a patient with HIV for further cardiovascular workup? HIV/heart experts advise first figuring the pretest probability that a person has CHD.[10] They suggest several tools for doing this (like the one in **Table 3** on page 76), cautioning that these formulas remain unvalidated in people with HIV.

In the **Table 3** model, a score of 0 to 8 indicates low risk, 9 to 15 indicates intermediate risk, and 16 or higher signals high risk. People in the intermediate-risk stratum are the best candidates for a noninvasive stress test such as an exercise ECG, the HIV experts advise.[10] People in the high-risk group often get false-negative results and thus are not great candidates for a noninvasive stress test. Instead, they should be referred for invasive coronary arteriography. People with a low-pretest probability of CHD tend to have false-positive test results, so they are not ideal candidates for noninvasive stress testing. Instead, they may be candidates for a stress test with nuclear perfusion imaging or wall motion imaging with echocardiography, but only if they have an intermediate global CHD risk or have a high-risk job, like flying airplanes.

This thoughtful review probes the ins and outs of noninvasive testing and cardiovascular markers, including high-sensitivity C-reactive protein (hsCRP), apolipoprotein (apo)B and apoA-1, carotid intima-media thickness (cIMT), and coronary calcium scores.[10] Although these markers see routine use in cohort studies and trials, their value in individual patients remains uncertain.

For the general population at least, hsCRP may have clinical value, according to a Centers for Disease Control and Prevention (CDC) panel—but not for everyone who walks through the door.[11] Instead, these experts suggest that hsCRP in people with a 10% to 20% CVD risk over 10 years may pick out those who would benefit from medical inter-

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Table 3. Tool for estimating pretest probability of coronary heart disease

Variable	*Score*	*Example: 52-year-old woman*
Age (male/female):		
—Under 40/under 50	3	
—40 to 50/50 to 64	6	6
—55 or older/65 or older	9	
Estrogen status positive (F)	–3	–3
Estrogen status negative (F)	3	
Angina history typical*	5	
Angina history atypical	3	
Angina history nonanginal	1	1
Diabetes	2	2
Hyperlipidemia	1	1
Hypertension	1	
Smoking (any)	1	
First-degree family history of coronary artery disease	1	1
Obesity (BMI >27 kg/m^2)	1	1
	Total score	9
Risk according to total score		
Low: 0 to 8	Intermediate: 9 to 15	High: 16 or greater

Source: Morise AP, Jalisi F. Evaluation of pretest and exercise test scores to assess all-cause mortality in unselected patients presenting for exercise testing with symptoms of suspected coronary artery disease. *J Am Coll Cardiol.* 2003;42:842-850.
*Diamond method.

vention, for example, with antilipid agents, antiplatelets, or cardioprotective drugs. (See note **11** for details of this panel's advice on clinical use of hsCRP in the general population.)

But because hsCRP reflects inflammation, and because HIV-positive people have so many potential inflammation inciters (including HIV itself), the HIV/heart panel says "the role of hsCRP in clinical [HIV]

practice is less clear" and suggests the need for hsCRP studies that control for traditional risk factors.[10] One study published after this panel wrote did control for traditional risk factors when measuring the impact of CRP and HIV—independently and together—on acute myocardial infarction risk.[12] In this analysis of 487 people with HIV and 69,870 HIV-negative people seen from January 1997 through December 2006, people with HIV and high CRP had 4-fold higher odds of an acute MI than HIV-negative people with normal CRP. (See **Figure 13** in the first review article in this issue of RI*TA!*)

In a 2010 issue of RI*TA!*, HIV metabolics maven Steven Grinspoon, who headed this study in Boston's Partners HealthCare System, addressed the question of CRP use in the HIV clinic.[13] "If you have a patient with a short duration of HIV and no other risk factors," he suggested, "measuring CRP early in the process is probably not useful. At the other end of the spectrum, in someone with severe dyslipidemia and diabetes, the additive value of CRP is probably irrelevant. But perhaps in borderline patients who have had chronic HIV for a long time and borderline dyslipidemia, much like the patients in this study,[12] measuring CRP may be useful because having HIV and a high CRP would raise the MI risk 4-fold. I couldn't say specifically whether the predictive value of CRP in such patients is entirely independent of other markers. Our study would suggest this is the case, but further studies need to be done."[13]

Should HIV-positive men over 40 and women over 50 have an annual ECG, as EACS guidelines recommend?[3] A 4518-person SMART study analysis lends credence to this advice,[14] but some authorities voice reservations about routine ECGs. One in two people in the SMART analysis had a minor ECG abnormality, and 1 in 13 had a major abnormality. During a median follow-up of 28.7 months, 155 people (3.4%) got diagnosed with cardiovascular disease. A statistical model adjusted for study arm, demographics, cardiovascular risk factors, and HIV variables figured that a major ECG abnormality almost doubled the risk of a new cardiovascular diagnosis (hazard ratio 1.83, 95% confidence interval 1.12 to 2.97, $P < 0.015$), but major and minor abnormalities combined did not. The SMART investigators believe these findings "suggest that the ECG could provide a convenient risk-screening tool in HIV-infected patients."[14]

But in an interview in this issue, HIV/heart expert James Stein explains that screening ECGs are not recommended in the United States because they lack sensitivity in identifying cardiovascular disease and because they may yield false-positive results. ECGs, Stein believes, should be reserved for people with heart disease symptoms, like shortness of breath and chest discomfort.

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    a. Of current inflammatory markers identified, hsCRP has the analyte and assay characteristics most conducive to use in practice. (Class IIa, Level of Evidence B)
    b. Measurement of hsCRP is an independent marker of risk and, in those judged at intermediate risk by global risk assessment (10 to 20% risk of CHD per 10 years), at the discretion of the physician, may help direct further evaluation and therapy in the primary prevention of CVD. The benefits of such therapy based on this strategy remain uncertain. (Class IIa, Level of Evidence B)
    c. Patients with persistently unexplained, marked elevation of hsCRP (>10mg/L) after repeated testing should be evaluated for noncardiovascular etiologies. (Class IIa, Level of Evidence B)
    d. In patients with stable coronary disease or acute coronary syndromes, hsCRP measurement may be useful as an independent marker of prognosis for recurrent events, including death, MI, and restenosis after PCI. The benefits of therapy based on this strategy remain uncertain. (Class IIa, Level of Evidence B)
    e. Measurement of markers should be done twice (averaging results), optimally two weeks apart, fasting or nonfasting in metabolically stable patients. If hsCRP level is >10 mg/L, test should be repeated and patient examined for sources of infection or inflammation. (Class IIa, Level of Evidence B)
    f. hsCRP levels, using standardized assays, categorize patients as follows:

Relative risk category	Average hsCRP level
Low	**<1 mg/L**
Average	**1.0 to 3.0 mg/L**
High	**>3.0 mg/L**

(Class IIa, Level of Evidence B)

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