

RESEARCH INITIATIVE

Treatment Action!

What speeds aging with HIV - and what can be done about it?

By Mark Mascolini

Interviews with:

Steven Grinspoon, MD:

Hidden heart disease and other non-AIDS risks in HIV patients

David E. Vance, PhD, MGS:

Hardiness, cognitive function, psychological support

Carl Grunfeld, MD, PhD:

A challenge to the concept of accelerated aging with HIV

A publication of AIDS Research Consortium of Houston dba

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*“Do not regret growing older.
It is a privilege denied to many.” — Unknown*

Dear reader,

In this issue of *RITA!*, editor Mark Mascolini and his collaborators explore what was nearly unimaginable just 15 years ago: growing old with HIV.

The exploration is timely. According to [a report](#) by CBS News, half of those living in the U.S. with HIV/AIDS will be over 50 only five years from now. Already [more than half](#) are over 40.

Unlike those who were diagnosed in the therapeutically desolate 1980s, today people with HIV can expect to live not for years, but for decades. In fact, if the antiretrovirals now on the market had become available in [an earlier era](#), they might have been looked on as a de facto cure. People are, after all, *supposed* to get old.

Still, all the news isn't happy. Even as people with HIV are living longer, they aren't living a normal lifespan. Mascolini cites data showing that HIV infection may shave off as much as a third of average life expectancy. What's more, "aging with HIV is fraught with more peril than aging without the retrovirus" (p. 29). In addition to the risk of cardiovascular disease – [the leading killer](#) of all Americans, regardless of serostatus – people with HIV face, among other things, a heightened risk of diabetes, cancer, liver failure, and broken bones. HIV infection remains an infection with clinical consequences.

With his usual belt-and-suspenders approach to detail, Mascolini examines the causes and mechanisms of early mortality and morbidity in people with HIV. What is it, for example, about this virus that causes a 50-year-old to have the brain of a 65-year-old?

In the youth-worshipping gay male subculture where I live, it's hard to remember that *aging itself isn't a disease*. Helping people to age has long been the goal of organizations like The Center for AIDS and of HIV treatment activism, even if the activists themselves didn't always realize it. But sitting, at just 46, as James L. did, in a screening of *Syriana* and [realizing halfway through](#) that you'd seen it two weeks earlier ... well, that's accelerated aging, and it's rightly the subject of both alarm and inquiry.

Until there's a cure,

A handwritten signature in red ink that reads "Paul". The signature is written in a cursive, slightly slanted style.

Paul Simmons, RN, ACRN
Executive Director



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Hidden heart disease and other non-AIDS risks in HIV patients

An interview with **Steven Grinspoon, MD**

*Professor of Medicine, Harvard Medical School
Director, MGH Program in Nutritional Metabolism and
Clinical Director, Neuroendocrine Clinical Center
Massachusetts General Hospital
Boston, Massachusetts*



An ever-growing mound of research suggests that people with HIV—even those with well-controlled viral replication—face a torqued-up risk of premature aging. This precipitate progress to old age seems especially apparent when considering metabolic and cardiovascular diseases, as well as bone thinning. Because Steven Grinspoon ranks among the leaders in research on these maladies in people with HIV, *RITA!* invited him to discuss aging and HIV in the context of some of his recent work.

Subclinical coronary artery disease in “low-risk” patients

Mascolini: Your use of computed tomography (CT) angiography to compare subclinical coronary atherosclerosis in men with and without HIV found that 5 men with HIV and none without HIV had critical coronary stenosis.¹ Can you describe the design and major findings of this study?

Grinspoon: We recruited 78 HIV-infected men and 32 HIV-negative men similar in age and weight. The two groups had similar cardiac risk factors and Framingham scores, and none of the men had prior cardiac symptoms or car-

diovascular disease. We compared these groups using a very sensitive method that detects not only coronary artery calcium, but also plaque. Standard cardiac CT looks only at coronary artery calcium, and studies with that endpoint have had mixed results—some showing increased calcium in HIV-infected people and others showing no increase. To our knowledge, no one had used 64-slice coronary CT angiography to look at plaque. This type of scan is like a virtual angiogram. It’s not a real angiogram in that a catheter is not inserted, but the slices are so thin that they can be reconstructed to yield a virtual angiogram of the major vessels in the heart.

The percent of patients who had any coronary artery calcium was 46% in the HIV group versus 25% in the control group, and that was statistically significant. But even more impressive was that this newer technique determined that 59% of men with HIV versus 34% without HIV had prevalent coronary atherosclerosis. The number of coronary lesions was higher in men with HIV, as was plaque volume per lesion.

We decided that more than a 70% luminal narrowing would be clinically significant. While 5 of the HIV patients (6.5%) had more than 70%

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narrowing, none of the non-HIV controls did. In fact the very first patient in the study had to have coronary artery bypass grafting based on our findings and further testing. We thought it was quite striking that this asymptomatic group of HIV patients similar in age and cardiovascular risk factors to men without HIV and without known cardiovascular disease had a significant prevalence of coronary artery disease.

Mascolini: Had these men with HIV controlled their virus with antiretroviral therapy?

Grinspoon: Most of them had. The vast majority, 95%, were on antiretroviral therapy, the average CD4 count was 523 cells/mm³, and 81% had an undetectable viral load.

Mascolini: What do your findings add to other observational evidence on cardiovascular risk in people taking effective antiretroviral regimens?

Grinspoon: Our findings add to earlier data because we were very careful to recruit populations that were similar with respect to cardiovascular risk factors.¹ Prior studies were often criticized because HIV-infected patients had more dyslipidemia or glucose intolerance than control groups, and that may have explained why they had a higher rate of cardiovascular disease. In our study we took great pains to recruit patients with similar cardiovascular risk factors and without a known history of cardiac disease. Even after leveling the playing field in that way, we saw a significantly higher rate of cardiovascular disease in men with HIV.

I think this study adds to the literature by suggesting that patients who would not ordinarily be screened for cardiovascular disease (because

they're young—on average 45—without symptoms, and with reasonable cholesterol levels and other risk factors) may have subclinical cardiovascular disease.

Does the HIV explain the higher rate of subclinical disease? Multivariate modeling showed that duration of HIV infection was one of the most significant characteristics contributing to the subclinical atherosclerosis.

Is CRP a good marker in HIV populations?

Mascolini: Your group also found an independent association between elevated C-reactive protein (CRP) or HIV and acute myocardial infarction (MI).² What are elevated markers like CRP telling us about HIV-infected people today?

Grinspoon: The issue of CRP as a marker of cardiovascular risk is controversial in general, not just in people with HIV, for two reasons. First, does CRP add more to risk calculations than traditional risk factors like lipids? And second, is it a marker or is it somehow causal?

The question of causality has been answered fairly well through Mendelian genetic studies showing that elevated CRP does not cause cardiovascular disease. Most people would agree that it's a good marker in the general population. It may not add that much more to traditional markers, but it does have independent associations as a marker.

In the HIV population this is a particularly critical question because HIV-infected patients have a chronic inflammatory disease, so one would anticipate higher CRP levels in HIV patients. Our study and others show that that's the case. Some people may be skeptical that CRP would be associated with myocardial infarction in a

group of patients in whom CRP is potentially always elevated or more often elevated because of their primary infectious disease and all the infectious comorbidities that go with it. What we attempted to do was to use a very large database at Massachusetts General Hospital to assess the association between elevated CRP and acute MI in HIV-infected and HIV-uninfected individuals.

Our analysis suggested, first, that HIV itself is associated with MI, which supports results of our prior study using a bigger database.³ Second, we found that elevated CRP also predicts MI. These effects were independent and additive: There is a 2-fold increase in MI risk if you have HIV, a 2-fold increase in risk if you have elevated CRP, and a 4-fold higher risk if you have HIV and elevated CRP.

Those findings told us that CRP may be a useful biomarker in patients with HIV and that this chronic elevation in inflammatory pathways due to HIV may itself be contributing to premature cardiovascular disease in HIV-infected people. The infectious hypothesis of cardiovascular disease is an old hypothesis that has been investi-

gated in other infectious models. According to this hypothesis, the presence of infection per se may cause inflammation and lead to endothelial dysfunction and other processes. I think our data tend to support the idea that the inflammatory pathway may be related to MI in patients with HIV.

Mascolini: Do we know enough to support CRP monitoring in people with HIV?

Grinspoon: The clinical utility of CRP is another story. Our study doesn't answer the question of how useful CRP is given the other markers clinicians can evaluate, for example, low-density lipoprotein (LDL) cholesterol. In fact, no study has been done to query whether CRP predicts MI independently of a low LDL. But in our study the final models corrected not only for HIV status, but also for age, race, gender, diabetes, hypertension, and dyslipidemia—which is not an LDL level but is a surrogate (**Table 1**). Even in that model elevated CRP remained associated with an approximately 2-fold increase in MI risk.

Table 1. Risk of acute MI in multivariate modeling: people with versus without HIV and with high versus normal CRP

- Model 1 (CRP): for high CRP OR 2.51 (95% CI 2.27 to 2.78), $P < 0.0001$
- Model 2 (HIV): for HIV OR 2.07 (95% CI 1.31 to 3.10), $P = 0.0009$
- Model 3 (CRP, HIV): for HIV OR 1.74 (95% CI 1.10 to 2.61), $P = 0.0122$; for high CRP OR 2.50 (95% CI 2.26 to 2.77), $P < 0.0001$
- Model 10 (CRP, HIV, age, sex, race, hypertension, diabetes, dyslipidemia): for HIV OR 1.93 (95% CI 1.21 to 2.93), $P = 0.0035$; for high CRP OR 2.13 (95% CI 1.92 to 2.37), $P < 0.001$

Source: Triant VA, et al.²

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My guess—and this is still a hypothesis—is that CRP may have independent associations with cardiovascular disease and may be a useful marker beyond traditional markers. But that specific question has not been answered. If the question is how would one use CRP in patients with HIV, I would answer it this way: People with HIV may have chronically elevated CRP due to different processes. Whereas in the past some dismissed elevated CRP as being related to various infections and morbidities, I believe our study shows that elevated CRP, albeit from an infectious process, may mark more severe cardiovascular disease processes in patients with HIV.

I think it's reasonable to look at CRP levels in patients who have a borderline elevated risk of cardiovascular disease. If you have a patient with a short duration of HIV and no other risk factors, 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, 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.

Low growth hormone and metabolic disarray

Mascolini: In another case-control study, you found an independent association between reduced growth hormone secretion and dyslipi-

demia and higher glucose in HIV patients with excess abdominal fat.⁴ What are the clinical implications of those findings?

Grinspoon: In this study we were comparing people with and without HIV, looking at the relationship of growth hormone to metabolic disarray within the HIV group particularly. We planned this study because we know from non-HIV populations that viscerally obese people and obese people in general have reduced growth hormone. The question has always been whether the reduced growth hormone comes first and leads to visceral obesity, or whether the visceral obesity comes first and leads to reduced growth hormone.

Studies of weight loss in people without HIV suggest visceral obesity comes first, then growth hormone levels fall. But in fact low growth hormone itself further contributes to the visceral obesity in a vicious cycle. So a person may have excess visceral adiposity for many reasons—perhaps including antiretroviral medications—leading to relatively low growth hormone. In this particular study we showed that relatively low growth hormone itself is associated with metabolic parameters, such as high glucose and dyslipidemia. So the paper describes a further mechanism by which excess visceral fat may contribute to metabolic disarray.

In the FRAM study, for example, excess truncal fat was very significantly associated with dyslipidemia.⁵ The mechanism explaining that association may relate in part to the relatively low growth hormone levels seen in viscerally obese HIV patients.

We showed that the peak growth hormone level in response to a standardized stimulation testing was inversely related to various metabolic

parameters including elevated glucose. That relationship held in an analysis controlling for race, age, gender, weight, and antiretroviral use, suggesting there is a direct significant relationship between low growth hormone and glucose and triglycerides. The results suggest the mechanism by which visceral adiposity could be contributing to those parameters and suggest that strategies to reduce visceral adiposity through augmenting growth hormone may help, particularly with the lipids.

Work on a growth hormone-releasing substance to increase endogenous growth hormone is ongoing with promising results to date.^{6,7} However, a growth hormone-releasing factor is not yet approved by the FDA, and growth hormone itself should not be used for this purpose as it is not FDA approved for this indication.

A shift in the age-bone density curve

Mascolini: You were the first to confirm a higher fracture prevalence—not just osteopenia or osteoporosis—in a large study of people with versus without HIV.⁸ What's contributing to this high fracture rate in HIV-infected people?

Grinspoon: Prior large studies had not assessed fracture prevalence in patients with HIV. A few small studies had, but there was nothing close to the size of our study, which included 8500 people with HIV and over 2 million people without HIV. We saw approximately a 2-fold higher relative risk of certain fractures among men and women with HIV.

These were relatively young patients. We did see the anticipated association with age, so the data are behaving as one would expect in a large

epidemiological study. An increased prevalence of fracture with age would be anticipated in women. What's interesting is that we also saw an increase in fracture prevalence among men with age that was not seen in the control male population (**Table 2** on page 10).

Other studies show that bone density is 0.5 to 1 standard deviation lower in people with HIV, which is consistent with the increased fracture rate. In other words, a mild reduction in bone density is associated with a relatively moderate increased risk of fracture.

What contributes to that elevated fracture risk? Postulates include antiretroviral therapy, but this study did not assess that. Other factors could be low weight, which is a concern when people initially get HIV—they're catabolic and that may contribute to future bone loss. Cigarette smoking is highly prevalent among people with HIV and may contribute to fracture risk, as may use of steroids for HIV-related diseases. But the truth is we're not entirely sure what's contributing to that increased fracture risk.

Although I can't venture a further guess on causality, I think the important message of this study is that the age-bone density curve appears to be shifted in HIV populations: The anticipated effect of aging on bone is occurring at an earlier stage in HIV-infected patients, both for women and for men.

Screening for non-AIDS disease in people with HIV

Mascolini: Which non-AIDS diseases occur at high enough rates in HIV-infected people to merit more intense screening than in the general population?

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Table 2. Fracture prevalence by age in women and men with versus without HIV

Age	Prevalence per 100 persons (95% CI)	
	Women with HIV	Women without HIV
30 to 39	2.52 (1.40 to 3.64)	0.63 (0.59 to 0.66)
40 to 49	1.50 (0.75 to 2.26)	0.80 (0.77 to 0.84)
50 to 59	2.68 (1.38 to 3.97)	1.41 (1.36 to 1.47)
60 to 69	5.59 (1.83 to 9.39)	2.15 (2.07 to 2.22)
70 to 79	6.58 (1.01 to 12.15)	3.47 (3.35 to 3.59)
	Men with HIV	Men without HIV
20 to 29	3.23 (0.87 to 5.58)	2.45 (2.35 to 2.54)
30 to 39	2.19 (1.26 to 3.12)	1.72 (1.65 to 1.78)
40 to 49	3.29 (2.53 to 4.05)	1.72 (1.66 to 1.79)
50 to 59	4.03 (3.05 to 5.00)	1.72 (1.65 to 1.79)
60 to 69	5.76 (3.61 to 7.92)	1.58 (1.51 to 1.65)

Source: Triant VA, et al.⁸

Grinspoon: HIV-infected menopausal women absolutely need bone density screening because the effects of menopause may be shifting to an even earlier age in these women. I think some HIV-infected men may also merit bone density testing, particularly if they have traditional risk factors like low weight, smoking, and prior fractures. Although I view HIV itself as a risk factor for bone loss, I would not recommend global screening of all HIV-infected patients. I think clinicians should look for the traditional risk factors and perhaps consider HIV as an additional risk factor. So in patients with other risk factors, you might consider relatively earlier testing for bone loss, particularly around menopause in women.

I think cardiovascular disease merits more intensive screening in patients with HIV because the preponderance of the evidence suggests an increased risk of cardiovascular disease in this population. Our data from the original cohorts published in the *Journal of Clinical Endocrinology and Metabolism* showed about a 1.75-fold elevated risk of MI with HIV versus without HIV.⁵ Patients with increased cardiovascular risk factors should definitely be screened. Our study of subclinical atherosclerosis¹ would suggest that even patients without significant risk factors may merit screening.

I don't want to suggest that every HIV-infected patient should get screened for cardiovascular disease. You have to use judgment. Screening is not necessary in very young patients or in those who have absolutely no risk. But our study suggested that, in HIV-infected patients progressing through middle age, HIV itself may be a cardiovascular risk factor. I would add HIV to the list of risk factors when one assesses patients for cardiovascular disease.

I would also encourage HIV clinicians to use traditional risk stratification paradigms in HIV-infected patients. For example, I would encourage physicians to use the Framingham risk paradigm.^{9,10} It's not perfect, but the DAD research group assessed the Framingham model in people with HIV and found it reasonably accurate.¹¹ I would also consider CRP testing for patients with an indeterminate or moderate cardiovascular risk to try to add to that predictive power.

The jury is still out on definitive screening guidelines for cardiovascular disease in people with HIV infection. But if you're suspicious and you're looking at an HIV patient with chronic long-standing disease in their early to mid 50s or beyond, even if they're asymptomatic, that patient may have subclinical cardiovascular disease. I think it's critical to develop specific guidelines on how to test and treat that person. I personally would consider increased cardiovascular disease screening to be relevant in that population.

Lifestyle interventions and research priorities

Mascolini: In a small randomized trial, you found that intensive lifestyle modification improves waist circumference, blood pressure, and other metabolic variables in HIV-infected people with metabolic syndrome.¹² How practi-

cal are interventions like this outside the context of a clinical trial?

Grinspoon: Interventions like the one in our trial can be done in the context of a research study. But they are very difficult to achieve in the general population. In our study patients exercised intensively 3 times a week based on the Diabetes Prevention Program¹³ algorithm. They had intensive dietary counseling and individualized coaching. These are very difficult paradigms to export out to the general population.

Having said that, I believe our goal should be to help all our patients achieve a healthy lifestyle. Cigarette smoking is the number one thing to address. We should encourage more exercise, such as daily walking, and an adequate mixture of fat, carbohydrates, and protein. I think those things are important, but it is difficult to generalize the results of studies like ours to a wider patient population. If you just tell HIV patients to go out and improve their lifestyle, you're not going to see these kinds of results.

Mascolini: What are the top research priorities for aging-related issues and non-AIDS diseases in people with HIV?

Grinspoon: The top priorities include determining the specific mechanisms of cardiovascular disease in people HIV and whether there is a significant inflammatory component. Also, we need to address when and how to assess HIV-infected patients for cardiovascular disease. Our research should assess specific treatments to improve the cardiovascular risk profile in our patients, such as improvements in glucose tolerance, visceral adiposity, and dyslipidemia. For bone disease, research should focus on

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mechanisms of bone loss and optimal treatment and screening strategies.

Other diseases that we haven't touched on include kidney disease. Chronic kidney disease is more common than we previously thought in HIV-infected patients, and kidney disease can be a major contributor to both bone and cardio-

vascular disease. So I think kidney disease holds an important place on the research agenda.

Finally, determination of the optimal method to improve quality of life in HIV-infected patients is a very important question.

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Hardiness, cognitive function, psychosocial support:

Overlooked factors in slowing HIV-related aging?

An interview with **David E. Vance, PhD, MGS**

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Understanding hardiness, aging, and HIV

Mascolini: Please explain the concept of hardiness and describe how it may affect aging and longevity in people with HIV.

Vance: When we talk about hardiness, we're referring to one's commitment to life, one's sense of control, and the ability to see obstacles as a challenge instead of as obstacles.¹ Hardiness means looking at what you can do instead of what you can't do. It relates to aging because hardiness entails both the cognitive and the emotional sides of looking at life in a positive way, despite how we're feeling and the knowledge that life may not be the way we want it to be.

Aging can exacerbate HIV-related problems, and HIV can exacerbate aging issues. Many changes and challenges can tax one's coping resources or compromise one's ability to age successfully with HIV infection. An HIV-infected person may become more discouraged and more likely to engage in behaviors that do not promote successful aging. If someone is not feeling well and doesn't have a sense of hardiness, they may resort to negative adaptations, such as substance use, not get-

ting out of bed, not taking their medications, not exercising, not taking care of themselves, not socializing, and so forth. We want to promote hardiness as much as possible, so people keep living their lives the best they can, and keep reaching for goals, because it's important to get out of bed and do something with your life.

Aging with HIV is fraught with all sorts of problems, not just medical problems, but also psychosocial problems. When some people are diagnosed with HIV, they feel like they're damaged goods. Because we live in a youth-oriented culture, aging people also feel damaged. So HIV-infected aging people have a double whammy: You're older *and* you have HIV.

If you haven't been working, you may compare yourself with contemporaries who are going on with their lives and looking to retirement some time in the near future. But someone older with HIV may not have a complete work history because of their illness and so cannot realistically plan for a quality retirement. So an older person with HIV may have a more difficult time adjusting to the developmental social aspects of where they think they should be in their lives.

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Social isolation is another important issue for aging people, and especially those with HIV. Shippy and Karpiak found that many older adults with HIV report not having their emotional needs met, and many of them report not being in a committed relationship.² We know from the literature that being in a committed, intimate relationship buffers you from a whole host of problems.

Can hardiness be measured and learned?

Mascolini: How objectively can hardiness be measured?

Vance: There are instruments that measure hardiness, such as the Proactive Coping Inventory.^{3,4} But these instruments don't have a cutoff score; they don't say "you're hardy and you're not." It's a continuum.

To judge hardiness, I listen to attributions people make. That's where the Proactive Coping Inventory comes in handy because such attributions are imbedded in the scale.³ One attribution people might make is, "I can manage most things, given enough time." Or they might say something like, "I always try to find a way to work around obstacles; nothing really stops me." Those are positive affirmations—what we call hardiness. We want to hear people say those things because these are people who are going to be taking their medication, they're going to be exercising, they're going to be looking for ways of investing in their life.

Other people may make negative attributions, such as this one from the Proactive Coping Inventory: "I often see myself failing, so I don't get

my hopes up too high." If you believe that, you're not going to try any more. You'll think, "Why bother? I'm older, I have HIV, I probably have some other comorbidity. I'm going to just be." It doesn't have to be that way.

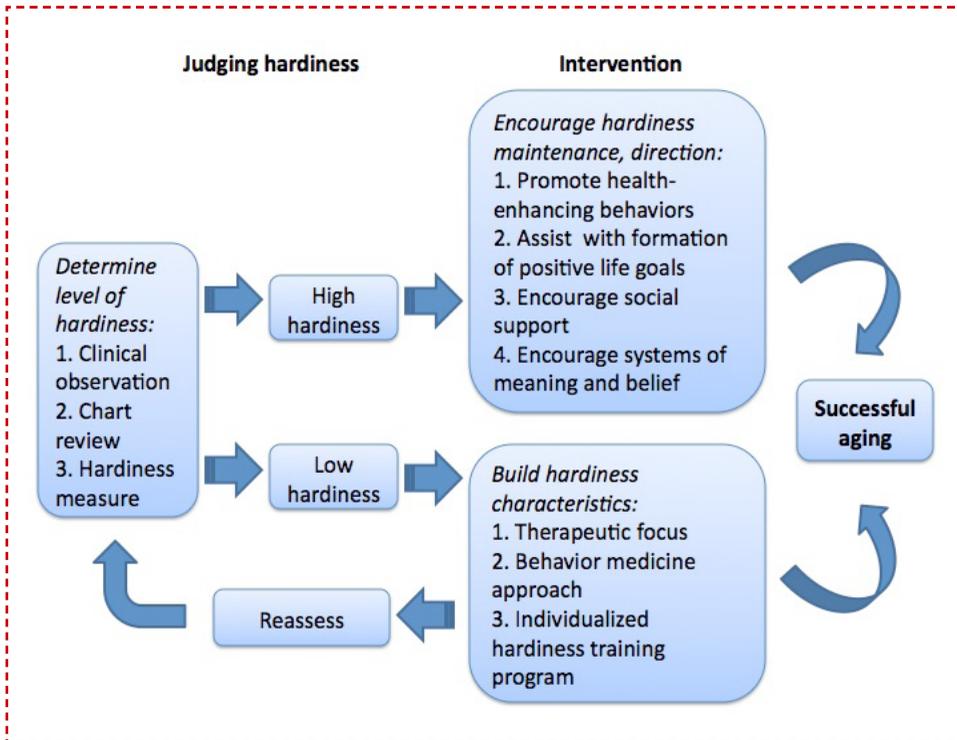
But there isn't an objective measure that will tell you who's hardy and who's not. I think the important thing when clinicians are working with patients—whether it be nurse practitioners, nurses, social workers, physicians, or clergy—is to pay attention to the little statements people make. These statements are also clues to depression, and we know that depressed people have a harder time coping with HIV infection and aging. A lot of studies suggest that people who are more depressed don't adhere to their medications as well and generally don't take as good care of themselves. That could lead into a downward spiral of suicidal ideation and all those stress hormones that are not friends of the immune system. Some research shows that people who score high on hardiness actually have better immune systems.⁵

Mascolini: Is hardiness something that health workers can help people attain or strive for?

Vance: I would like to think so. I haven't done any pilot work on this yet, but I want to. In the literature some people say hardiness is a trait and it can't be changed. I don't believe that. Even in terms of my own life, I see that on some days I feel like I can take on the world, and at other points I feel that everything's against me and I don't know how I can take one more thing.

These reactions are both emotional and cognitive, and I think they can be changed (**Figure**).

FIGURE. A method to foster hardiness in people with HIV begins with a simple evaluation. The Proactive Coping Inventory^{3,4} is one tool to assess hardiness. (Adapted from Vance et al.¹)



I have proposed a cognitive-behavioral approach to hardiness that relies on an individualized hardiness training program.⁶ You could also call it an individualized depression program or an individualized resilience training program. The nomenclature doesn't really matter; whatever you call it, the point is to focus on what you can do and not on what you can't do.

As an example, I wrote one such program for myself. The goal is to become more hardy in my daily affairs, and there are specific steps to accomplish this goal. Those steps might include: Every day I'll get out of bed and take at least 5 minutes to visualize what being hardy means to me: never

giving up; taking care of myself physically, emotionally, socially, and spiritually; not focusing on things I can't change, but focusing on what I can; and reminding myself that the wise never wish to be younger, just wiser.

I also have some mantras to repeat because, when you're feeling down, it's important to put positive thoughts back in your head. Here are some of my favorites: perseverance is the ornament of the strong; falling down is fine, staying down is not; even the strong get tired, but that does not mean they're not strong; and (my personal favorite) I am not my circumstances.

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A third thing I do is actively seek out positive energy, which means listening to upbeat music, listening to comedians and laughing, and watching movies and TV shows that emphasize hardiness and can-do attitudes. One of my personal favorites is “Star Trek” because they just never give up. An individualized hardiness program for me would include watching “Star Trek” as part of my routine. Another favorite is the movie “Secondhand Lions,” which includes the line, “Die with your boots on.” In other words, just keep trying till you can’t. There’s a movie called “Flawless” in which a drag queen says, “*Can’t* lives on *won’t* street.” It’s not that you can’t do it; it’s that you won’t do it.

There are other steps in the individualized program that I developed, including visualizing, aspects of spirituality, prayer, doing good deeds, and so forth. It’s basically a way of investing in your own life. It’s not rocket science. But when people are down and discouraged, they need to hear about how to focus on the good stuff in their life while minimizing the bad stuff.

Recognizing psychosocial factors that affect aging

Mascolini: In an overview of aging with HIV, you mention several factors that can negatively affect successful aging, such as social isolation, HIV-related stigma, and suicidal ideation.⁷ What should HIV physicians do to recognize and address psychosocial issues like these?

Vance: I think many physicians are fully aware of these issues. But they may not always remember that older adults with HIV are more vulnerable to these problems of social isolation. Karpik’s study found that 71% of their HIV population

50 and over were living alone.² The doctor may say, “I need you to take your pills at this time of day and to monitor this and monitor that.” If you have a partner, they’re going to help you take your pills on time and monitor yourself.

Physicians may sometimes forget that they’re barking a lot of orders at patients but the patients may be absorbing only a little bit of this. For most patients it would help if physicians wrote down this kind of medical advice and also inquired about a partner and whether that partner can help remind them about things they should be doing to care for themselves. When a patient lives alone, the physician can ask how they are you going to remember these things. Some people with HIV also have memory problems, and those problems may grow worse with age.

If the doctor only *tells* patients what to do, it can go in one ear and out the other, especially if they get bad news. The patient may focus only on the bad and might not necessarily focus on how to deal with it, especially if they’re already depressed or discouraged.

Mascolini: You’ve written about the synergistic effect of aging and HIV on cognitive impairment.⁸ How can health workers prevent or delay cognitive impairment in aging people with HIV?

Vance: It’s the same as in people without HIV. We can start with stressing a healthy lifestyle, and that includes sleep hygiene because sleep is important for cognitive functioning. We know that our sleep patterns become degraded with aging. We also know that depression interferes with sleep, whether that depression is due to social isolation or being diagnosed with HIV or the comorbidities common with HIV.

We also want to focus on emotional stabilization by reducing depression and anxiety. And we should emphasize good nutrition, physical activity, and social stimulation. Many studies at our center have focused on these issues in HIV-negative older adults, and I'm trying to turn that focus on older adults with HIV.

At our center we also do cognitive remediation training, which involves a computerized program that helps older adults improve their "useful field of view" so they can take in more visual information at a moment's glance. That's especially useful for older drivers. We know this training works in older adults without HIV. A pilot study of cognitive remediation training in older people with HIV is already showing that it improves their useful field of view as well. I don't know what mechanisms cause some of these declines in HIV, but this intervention is working. I'm hoping to use these pilot data to obtain funding for a long-term study in people with HIV.

We do know that cognitive simulation—whether it's being socially engaged or having intellectual pursuits or using a computerized cognitive training program—all are probably effective.

Sharpening the focus on psychosociologic issues

Mascolini: Are HIV clinicians giving neuropsychological issues in aging patients the attention they deserve?

Vance: I don't think so. Not yet. Of course physicians take steps to address very marked changes, but they may overlook more subtle changes or minor cognitive complaints because of the limited amount of time physicians have to spend with patients. At our center we've been discussing how to

integrate a sharper focus on neuropsychological issues into our own database.

Before HAART we saw a lot of concern about these problems because HIV-related dementia was much more common. But as the incidence of dementia decreased with HAART, more attention turned to other HIV-aging-related issues, such as heart disease, liver disease, and kidney disease. I don't think we're focusing enough on the neurological aspect. But because more of our HIV patients are 50 and over, that focus will have to increase in the next 5 to 10 years in order for us to provide more holistic care.

Mascolini: What are the biggest research priorities on questions of psychosocial factors, aging, and HIV?

Vance: One of the main priorities is diminishing cognitive ability and how that impacts everyday functioning, whether that means driving, the ability to do your job, medication adherence, or other aspects of daily living.

There are also many psychosocial aspects that need more research, such as fatigue. Are older people with HIV tired because they're older or because of their HIV? It's probably both. If you don't feel well, if you don't have a lot of energy, you're not going to be as socially engaged as you normally would be. A lot of that's related to medication toxicity and interactions between HIV medications and medications for age-related comorbidities. Many HIV medications were tested in younger adults and they haven't been tested well in older adults living with the disease. We're just putting the pieces together right now and extrapolating based on the HIV literature and the aging literature and trying to figure out how all these drugs interact.

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A challenge to the concept of accelerated aging with HIV

An interview with **Carl Grunfeld, MD, PhD**

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From his endocrinologic perch in San Francisco, Carl Grunfeld has repeatedly jarred accepted wisdom on how HIV riles the metabolic and lipogenic pathways that give this infection its often unprepossessing, often portentous phenotype. As head of the FRAM study, he famously rocked the HIV world by identifying lipoatrophy—not fat buildups—as the distinguishing feature of the lipodystrophy syndrome.¹ To glean his insights on the non-AIDS conditions now under increasing scrutiny in clinics and labs across the globe, *RITA!* interviewed Grunfeld about these issues from the vantage of his own research.

Weighing non-AIDS illnesses with an eye toward screening

Mascolini: What are the major non-AIDS threats in aging people responding well to antiretroviral therapy?

Grunfeld: The major non-AIDS threats are a group of diseases that are common in the non-HIV population and that may be accelerated by factors like immunodeficiency, an imbalanced immune system, or inflammation in patients with HIV. I prefer to look at this issue in terms of individual diseases rather than grouping them as accelerated aging.

For instance, if you look at some of the malignancy data, you certainly see some malignancies that are clearly accelerated with HIV infection. Rates of other malignancies have improved in the era of HAART. Therefore I would look at individual malignancies. I'm not a cancer expert, so I don't want to pontificate. But that's a very good model for what's going on in HIV.

We should be concerned in HIV about any comorbidity that's known to be more prevalent than usual with other diseases marked by inflammation or immune abnormalities. In addition to malignancies, obviously cardiovascular disease comes to the forefront. There's a long list of diseases that are infections and inflammatory disorders, which increase cardiovascular disease risk. HIV infection has squarely joined that group.

With regard to HIV infection and cardiovascular disease, however, the basic treatments are the same as treatments for any person with cardiovascular disease. The key issues, I believe, are not issues like whether statins work in HIV infection—they certainly work in HIV infection. Rather, what we have to be wary of are drug-drug interactions and understanding why a particular

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drug in a group may not work in someone with HIV infection who has polypharmacy. There are abundant data to indicate that this should be one of our major concerns, not just the increased incidence of cardiovascular disease alone.

Mascolini: Which non-AIDS diseases occur at high enough rates in HIV-infected people to merit more intense screening than in the general population?

Grunfeld: We have to worry about liver disease, and particularly coinfection with HCV, which is not uncommon in people with HIV. We definitely have to worry about kidney disease because all the markers for kidney disease are increased in people with HIV. At this meeting [the 17th Conference on Retroviruses and Opportunistic Infections] there are a number of reports suggesting that progression of kidney disease in the long run will be a problem in people with HIV. As a metabolic person, that's what I would focus on.

There's also the issue of bone disease, and that's a complicated issue because picking a control group in bone disease isn't as easy as in some other diseases. HIV lipoatrophy and decreased body mass index account for a major part of the decrease in bone mineral density among patients with HIV. What one has to begin looking for is the extent to which the fracture rate is up for a given bone mineral density, and that to my knowledge has not been done.

Having said all that, I think we need to focus on trying to figure out which particular subset of patients with HIV are more prone to some of the many complications, whether with regard to their immune status or their therapy.

Ranking HIV with traditional cardiovascular risk factors

Mascolini: If you focus just on cardiovascular disease and look at all the possible mechanisms of increased incidence in people with HIV, which of those mechanisms do you see as most important and most deserving of further research?

Grunfeld: There are two areas I think we have to focus on.

First, it's clear that traditional cardiovascular disease risk factors still play the most important role in patients with HIV infection. On the other hand, HIV itself is the equivalent of one of the many traditional risk factors, like smoking or diabetes (**Figure**).² Reduction of the traditional risk factors should be of prime importance in people with HIV infection. I would advocate more liberal treatment to address these risk factors, depending on the guidelines. For example, the NCEP [National Cholesterol Education Program] guidelines say definitely treat, think about it, or no strong need to treat.³ "Think about it" might be moved up into the treat range in people with HIV.

A simple way to look at it might be to multiply the Framingham risk score⁴ by something like 1.5, maybe 2, and *then* look at the score and determine whether you would treat a person with that score if that person didn't have HIV infection. We can argue about the exact score, but that's the principle: The major cardiovascular risk factors are still dominant, but the risk is accelerated in HIV and we should take that into account in terms of how we normally treat.

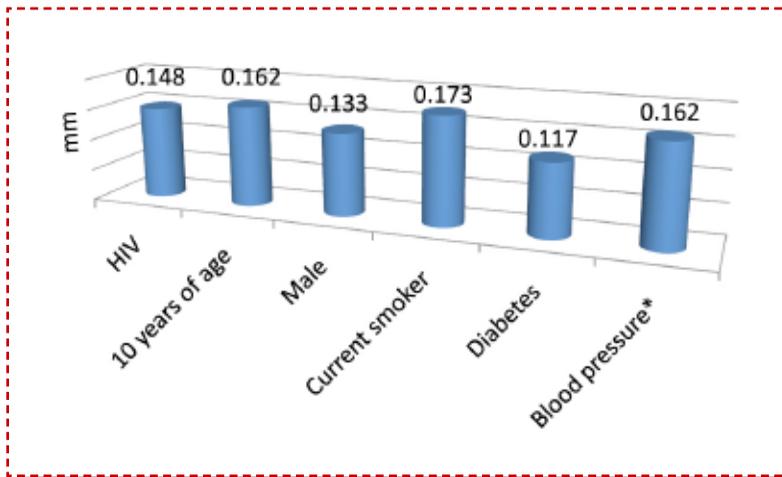


Figure. A FRAM study comparison of people with HIV and people without an HIV diagnosis found that HIV infection is similar to smoking, diabetes, and high blood pressure in its impact on internal and common carotid wall thickness, which is an indicator of early cardiovascular disease. This graph shows the relative impact of HIV and traditional heart risk factors on internal carotid wall thickness in millimeters (mm). (Source: Grunfeld C et al.²)

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

Second, I think the most worrisome area that should be focused on in research involves clotting factors. Several groups have shown that there is increased evidence of clotting or decreased evidence of anticlotting factors in people with HIV, and the major myocardial infarctions are caused by plaque rupture followed by clot. Serious thought needs to be given to considering HIV a reason to be on aspirin to prevent clots and to try to understand in particular how antiretroviral drugs as well as HIV infection itself might be accelerating clotting.

Mascolini: A lot of research is looking at inflammation markers in relation to cardiovascular disease risk in people with HIV. Has the time come for HIV clinicians to consider measuring markers like C-reactive protein (CRP) in their patients with a borderline risk?

Grunfeld: In most of the studies in which HIV-infected patients on antiretroviral therapy are compared to controls, the increment in CRP is not dramatic or it doesn't exist at all. So we have to step back and look at CRP, as opposed to some of the other markers, as a marker that you use the same way you would in a patient not infected with HIV.

The increment that an elevated CRP gives you is clear, but it is a small increment in terms of predictability. You could equally argue that the increment in risk from HIV infection is at least in the same ballpark, if not more predictive. By that reasoning, you don't have to measure CRP. You can say that HIV infection could give the extra nudge toward treating patients who are in the middle ground or who are ambivalent about therapy. You could tell those middle-ground pa-

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tients with HIV that they should really consider treatment of dyslipidemia. As a matter of fact that's what I do in practice because, although I'm an endocrinologist, one third of my patients have HIV infection.

Mascolini: What about other markers?

Grunfeld: There are two types of inflammatory markers—inflammatory markers that are not known to play a direct role in atherosclerosis, and inflammatory markers that *are* in the causal pathway. In some camps many of the clotting factors are viewed as inflammatory markers. Since clotting factors have the potential to be in the causal pathway—for example, by predisposing to a clot when there is a plaque rupture—they deserve special attention. Unfortunately, they are not as easily measured as some other markers and not as easily used in predicting cardiovascular disease. For instance, a meta-analysis across several large populations of HIV-uninfected people looked at the increment in fibrinogen levels for its ability to predict cardiovascular disease.⁵ But I don't think we have enough data to know how helpful those markers would be above and beyond the risk conferred by HIV infection.

I think we have to pay real attention to the upcoming NCEP guidelines. I don't know what they're going to say, but the presumption is that they're going to move the thresholds down and recommend treating at even lower levels of low-density lipoprotein (LDL) cholesterol and/or treating to reach lower levels of LDL. Now, LDL is not the major problem in HIV infection. If anything, LDL tends to be a little bit lower in people with HIV.⁶ In HIV infection, high-density lipoprotein (HDL) cholesterol is lower; HDL protects against cardiovascular disease, so protection

is lower in HIV infection. In addition, although LDL is lower, non-HDL cholesterol is higher than normal. Non-HDL cholesterol is total cholesterol minus HDL cholesterol and represents the sum of the bad cholesterol that causes cardiovascular disease. In the original NCEP guidelines, if you look at Table 9 it gives you the LDL goal and it gives you the non-HDL cholesterol goal, which is 30 mg/dL above the LDL goal. That advice is by and large ignored, not just in the HIV literature, but in the non-HIV literature. But it gives you an idea of how rigorous you should be and what targets you should aim for.

Reverse cholesterol transport is one of the ways in which HDL protects. Many of the steps in reverse cholesterol transport are inhibited during infection and inflammation. In an animal model we showed that nearly all the steps in reverse cholesterol transport, are affected by infection and inflammation.⁷ Now two groups have shown in similar animal models that the acute phase response induced by infection, inflammation, trauma, and malignancy affects the total reverse cholesterol transport process,^{8,9} and we have an editorial explaining each of the steps involved.¹⁰ Reverse cholesterol transport is pulling cholesterol out of the macrophages in the artery and excreting it through the liver into the bile, which goes into the intestine. If your macrophages become too loaded with cholesterol, they die, and that's how you get fat plaques. "Good" HDL scavenges a lot of the cholesterol that ends up there and gets rid of it. That's how HDL protects.

Very little work addresses HDL in people with HIV, and low HDL remains a major problem in HIV infection. HDL cholesterol levels are a crude marker of HDL function. We can't measure HDL function adequately in the clinical laboratory, so

I don't have recommendations in that area. But understand that for a given amount of HDL in an inflammatory disease, it's known that the HDL doesn't work as well as the same HDL level in healthy people.

Encouraging practical—but difficult—lifestyle interventions

Mascolini: You mentioned low-dose aspirin as one measure HIV clinicians might consider recommending to prevent cardiovascular disease.

Grunfeld: It's not been tested in HIV, but there's no reason to believe it won't work. Understand that there are things that do block the activity of aspirin, like certain NSAIDs. So if you're taking indomethacin for your joint pain, that decreases the protective effects of aspirin.

Mascolini: Are there other practical interventions that HIV clinicians should start thinking about in patients at high risk of cardiovascular disease?

Grunfeld: The same things we recommend for everybody at risk of cardiovascular disease, which are very hard to do: diet and exercise. A diet rich in monounsaturated fats, omega-3 fatty acids, fiber, minimizing saturated fat, and exercising, which is tougher as you get older. And of course getting smokers to quit.

Let's talk more about smoking. Risk factors are usually additive, and sometimes they're synergistic. The more risk factors you have, the worse off you are. If HIV is a risk factor for cardiovascular disease and certain malignancies, and if smoking is a risk factor for cardiovascular disease and certain malignancies—and the answer of course is yes for all of those ifs—then they add or syner-

gize. We know we can suppress HIV, but at the moment we can't eradicate it. Therefore we're at our limits with what we can do in controlling HIV as a risk factor in the current era.

But we can modify smoking as a risk factor. And I would urge HIV-infected patients and care providers to work hard on what can be modified.

Let me give you another analogy. Diabetes predisposes you to kidney disease. There's a particular type of kidney disease that occurs with diabetes, and that's high-proteinuria kidney disease. Hypertensive kidney disease doesn't have protein in it. If you take the patients who have diabetic kidney disease and treat their hypertension, you decrease the slope to renal failure. You protect them from diabetic renal disease even though hypertensive renal disease is different from diabetes-related kidney disease. The problem is that if you've got hypertension and you've got diabetes, they add together to increase your kidney disease risk.

I think that analogy should be an example in HIV. If HIV is a risk factor for something, and there are other treatable risk factors, you'd better be very aggressive in treating the other risk factors. That includes smoking.

Mascolini: One of your FRAM study analyses found that current smoking almost tripled the risk of all-cause mortality in people with HIV.¹¹ What do you do with your patients who smoke?

Grunfeld: Beg them. Hound them. Tell them that their smoking is more likely to kill them than their HIV infection at this stage. I'm delighted we've reached this stage. But it's very difficult to get people to stop smoking. I have had patients

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tell me it's easier to kick heroin than to kick smoking. But it's also possibly easier to kick smoking than to kick overeating. I bring it up every single time. I smell their clothes; I smell their breath; I walk into the examining room and I say, "You're still smoking, aren't you?"

I have the attitude that Winston Churchill had. Churchill made his last public speech when he spoke to the graduating class at Eton. He was very frail. When the time for his talk came, he got up, he slowly walked across to the podium—it took a long time. He then surveyed the class at Eton—and that took a while. People were waiting, wondering what had happened to the old man. Then he said, so the story goes, "Never give up. Never, ever, ever give up."

I don't know if the story's true or apocryphal, but that's been my attitude with things like smoking, with diet, with other risk factors that we know we need to reverse but are difficult to change. Many physicians try to get people to quit smoking once or twice and give up. I address these risks at every session. If you look at some of my progress notes, they say, "Smoking—address each time" or "Alcohol—address each time." I go down my list, and I do it. I don't succeed all the time. No one succeeds all the time. But I don't give up.

Understanding pluses and minuses of releasing growth hormone

Mascolini: You've done a lot of research on growth hormone in people with and without HIV.¹²⁻¹⁵ What's your appraisal of the research on both growth hormone and growth hormone-releasing hormone^{16,17} in HIV-infected people with excess central fat?

Grunfeld: Both growth hormone and growth hormone-releasing hormone clearly reduce visceral fat and have beneficial effects on lipids. The problem with growth hormone is that it has a tendency to have adverse effects on glucose metabolism, while growth hormone-releasing hormone does not.

Given that growth hormone and growth hormone-releasing hormone have not been compared head to head, we cannot tell whether the overall effect in reducing visceral fat is less with growth hormone-releasing hormone. But one can infer that at similar levels of IGF-1, which is one mediator of growth hormone action but not the sole mediator, you get more complications with growth hormone than you get with growth hormone-releasing hormone. Growth hormone-releasing hormone probably has a beneficial effect because it results in pulsatile hormone release. The body likes pulsatile hormone release rather than flat and sustained levels.

I think the question that's going to arise is "at what cost?" We have no idea what the cost is going to be for growth hormone-releasing hormone. We have a pretty good idea of what the cost of growth hormone would have been for this indication because we can predict that cost on the basis of its current use. Growth hormone would have a very high cost for a small effect that is definitely positive. If growth hormone-releasing hormone is priced reasonably, then it will be a valuable adjunct. Why? Because it's very difficult to reduce triglycerides in people with HIV infection because there are multiple factors that affect triglycerides. So growth hormone-releasing hormone could become another drug in the armamentarium if reasonably priced.

Exploring genetic correlates of non-AIDS conditions

Mascolini: You've started studying possible genetic correlates of atherosclerosis in people with HIV.¹⁸ Is that something that may one day move into the clinical arena, or is this purely a research initiative?

Grunfeld: Let's start with what I think we should be looking for in genetic correlates in general. There are very well-known genetic correlates of atherosclerosis, diabetes, total cholesterol, HDL cholesterol, and triglycerides. What we don't want to do is spend a lot of research effort finding that those same genetic correlates affect people with HIV infection. We published that paper¹⁸ without accruing thousands of patients because it was a novel gene that was not linked to atherosclerosis in people without HIV, but you could infer why it might be linked once the study showed an association. It's a protein that affects endothelial function, and it's a protein whose class is affected by HIV infection.

That's where I think this type of research should be going: What is there in HIV infection that should be determined? Where can that take us? I'll begin by saying I don't know, but I think it opens up possibilities. First of all it opens up understanding causal pathways better. For example, if this protein does get confirmed as a genetic factor, and if it is involved in endothelial function, and if we find factors in HIV infection or drugs that affect endothelial function, understanding that interaction is important. And what the consequences of this protein are may open up new areas to look at in terms of proteins or functions.

In addition, we don't often have useful targets that work directly on processes like clotting or

endothelial function. If you hit clotting factors with a sledgehammer, you bleed. We do know that aspirin and clopidogrel, through their antiplatelet actions, do decrease recurrent heart disease or, in the case of aspirin, prevent heart attacks. Knowing that platelets are involved, a lot of people think about aspirin as a target. If our findings on this gene are confirmed, then we can begin to look at whether we can develop a drug that affects the bad part of this function and, if so, take it into clinical trials.

Do I think there's a short-term yield from this kind of research? No. But I think that such fundamental investigations may open up things for HIV infection.

And, by the way, we don't know yet whether that gene is involved in increased atherosclerosis in other infectious or inflammatory diseases. That possibility needs to be investigated. I think the infectious diseases field needs to be paying more attention to other infections and inflammatory diseases in terms of comorbidities to understand what's in common and what's different.

Questioning the concept of accelerated aging

Mascolini: What do you think are the major unmet research needs in this area of non-AIDS complications and premature aging in people with HIV?

Grunfeld: From my arena, I think the two that I haven't already discussed are what affects lean body mass and physical function. I don't like looking at things in terms of "accelerated aging." I know that's very much in fashion, but I believe you need to look at individual diseases and indi-

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vidual processes, some of which get worse with aging and some of which can be a problem when you're young.

I'll give you an example. Patients with familial hypercholesterolemia have very high LDL levels. If you're a homozygote for familial hypercholesterolemia, you get cardiovascular disease as a child. If you're a heterozygote, you get cardiovascular disease prematurely. The rest of your body doesn't age—until you have enough myocardial infarctions to go into congestive heart failure. I would not call that premature aging. If you look at cardiovascular disease, I can compare the effect of HIV to the effect of years of age, but I can also compare it to smoking or diabetes. I don't think it's helpful to call that premature aging.

I really think we need to focus on specific diseases. In the context of aging, we have to worry about the diseases that are known to be associated with poor aging. But we should focus on them as that specific disease.

It turns out that physical functioning is a major predictor of how well you age. So we should be paying attention to that in treated HIV-infected patients. We should be paying attention to body composition. In data that we're analyzing now on lean body mass, the predictors of not doing well in lean body mass are the predictors of not doing well with HIV infection. We're not done with the analysis. But I can tell you now that if your HIV is not well controlled or if your CD4 count is not restored optimally despite viral suppression, you are at risk of having less lean body mass.

I would turn this whole issue on its head. I would ask, what processes and what diseases lead to unhealthy aging. We should see how those processes and diseases are affected by HIV.

Mascolini: Can you explain more precisely what you mean about impaired physical functioning in this context?

Grunfeld: There are many different tests of physical functioning used in aging research. Most of them predict decline, if results are poor. Let me give you one example. You ask people to walk a walking course at the pace they find comfortable. That sounds pretty general, but it's fairly repeatable and very predictable. The people who walk faster do better in terms of survival than the people who walk slower. We can't talk about the precise causality of this because these are cross-sectional studies. You can't conclude that walking faster prevents decline. It may be that there are factors that prevent you from walking faster, not that walking faster predicts decline. It's an association. But some of the aging studies are striking in this way. If it turns out that slow walking is causal, then obviously exercise would make a difference and should be recommended. We do know that exercise improves brain function in general.

I think we have to begin asking how well HIV-infected people are functioning physically, not how well they feel. I'm aging, I run more slowly than I did 10 years ago, I don't do stairs as well as I did 10 years ago. But I'm healthy and, compared to most people my age, I do stairs and I

run very well. But at my age I can see the downhill slope. So we have to keep in mind that the degree of physical functioning is relative to the norm that we're comparing it to. We also have to keep in mind that we know some of the predictors of poor aging, and those are things we should be looking at.

But I like to look at it as individual processes, trying to understand them and pick them apart,

and put them together at the end. I don't presume that there's global accelerated aging with HIV infection. I don't believe we're going to find that. I believe we're going to find that certain aspects are changed with HIV and certain are not, just as we find that certain malignancies are increased and certain are not.

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What Speeds Aging With HIV— And What Can Be Done About It?

By Mark Mascolini

A 50-year-old with HIV infection has the brain and blood vessels of a 65-year-old without HIV.^{1,2} Compared with an uninfected person of the same age, a person with HIV runs a higher risk of heart disease, diabetes, liver failure, kidney failure, broken bones, and a swarm of “non-AIDS” cancers.³ Someone with HIV can expect to die 11 to 21 years sooner than a person without HIV.⁴

Those comparisons come with a carload of caveats about the perils of comparing diverse populations and the covert confounders that haunt cohort studies. But no one doubts that people with HIV face stiffer odds than their HIV-free coevals in reaching their 60th, 70th, or 80th birthday. By bucking up the immune system, antiretroviral therapy helps most people outrun death from AIDS; but already battered immune cells, or ongoing inflammation, or risky behavior, or antiretroviral therapy itself, or some combination of those factors makes infected people more prone to non-AIDS killers and perhaps to faster progression of those diseases.

Why aging with HIV is fraught with more peril than aging without the retrovirus has inched toward the higher echelons of HIV research priorities. Understanding those studies—and the speculation they inspire—poses a plethoric challenge to HIV clinicians, but one they can ill afford to ignore as their patients advance steadfastly through middle and old age with a virus that may remain unmeasurable for life.

By one estimate, half of all HIV-infected people in the United States will be 50 or older only 5 years from now.⁵ Even 5 years ago, the Centers for Disease Control (CDC) figured, US residents who passed the half-century mark accounted for almost one quarter of all HIV-infected people and more than one third of those who died with AIDS.⁶ In the 50-and-over set, HIV rates were 12 times higher in blacks and 5 times higher in Hispanics than in whites (51.7 and 21.4 versus 4.2 per 100,000).

This issue of *RITA!* wades into the swelling stream of HIV aging research with an eye toward understanding the clinical import of these new (and not always pellucid) data. Interviews with three clinical researchers who spend time plumbing these issues aim to fathom their tricky crosscurrents. And a table summarizes current advice on screening HIV-positive people for the non-AIDS diseases that pose the gravest threats to a long and healthy life.

How long can antiretroviral responders live with HIV?

Two things are clear: First, today’s antiretroviral medleys let people live longer with HIV than they did 20 or even 10 years ago. Second, this extended longevity falls short of life expectancy without HIV. The first of these HAART era denouements kindled gleeful acclaim; the second is a sour disappointment. In 1999, only 4 years

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after people started taking three antiretrovirals together, CHORUS cohort researchers floated the mellifluous prospect that “people with HIV in clinical care may be approaching a normal life expectancy.”⁷

From August 1997 through June 1999, Amy Justice (University of Pittsburgh) and CHORUS colleagues prospectively tracked 4524 HIV-positive people living in New York City, San Francisco, Beverly Hills, or Nashville. Most people, 93%, were taking antiretrovirals, though only 62% were taking a protease inhibitor (PI)-based combination, and only 30% had fully suppressed HIV. During the study span, 135 people died to yield a 3% mortality.

People who joined the cohort with fewer than 200 CD4 cells/mm³ could expect to live 10 more years. People who already had an AIDS disease could soldier on for another 15. And people over 39 could expect to live another 31 years. For men that meant a 39-year-old with HIV in the United States could count on living almost as long as his contemporary without HIV, because life expectancy for a 39-year-old man at that time averaged 77.

The investigators cautioned that their findings might be marred by survivor bias: the cohort might not include people who died quickly and thus might overrepresent survivors. And the results might not apply to every US resident with HIV. Nine in 10 cohort members were men, most of them gay or bisexual, and three quarters were Caucasian. Follow-up lasted only 2 years. Considering the brevity of this study, Justice offered this argus-eyed forecast:

“It is likely that over very long intervals of time, competing risks of mortality, comorbid disease, and aging will play an increasingly important role.”

But no one could predict what toll those comorbid Minotaurs would take on survival. In a 2009 review of non-AIDS threats that may afflict people with HIV more than uninfected people, Steven Deeks (University of California, San Francisco) and Andrew Phillips (University Medical College London) unrolled this list:³

- Hypertension
- Pulmonary hypertension
- Cardiovascular disease
- Diabetes mellitus and insulin resistance
- Cancer
- Osteopenia and osteoporosis
- Liver failure
- Kidney failure
- Peripheral neuropathy
- Frailty
- Cognitive decline and dementia

And more recent life expectancy studies paint a dimmer picture of survival prospects for people with HIV (**Figure 1**). In 2009 Elena Losina (Massachusetts General Hospital) and colleagues compared the general US population with simulated cohorts of HIV-positive people and HIV-negative people who have similar demographic traits.⁸ Thirty-three-year-olds in the HIV-negative but demographically similar group can count on living to 67, a full 8 years fewer than the general population. People with HIV lose an *additional* 12 years compared with the general population, even if their doctors follow up-to-date guidelines.

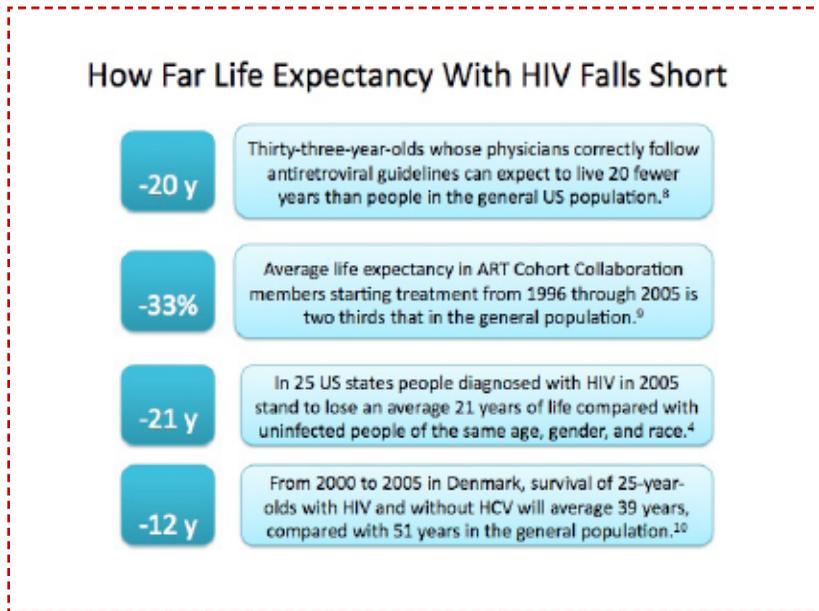


Figure 1. Four recent life expectancy studies in Europe and North America found that people with HIV could die one to two decades earlier than same-aged people without HIV.

HIV-infected people who start antiretrovirals late lose another 2.6 years.

In 2008 Antiretroviral Therapy Cohort Collaboration researchers figured that 20-year-olds starting their first antiretrovirals could expect to see another 36 years of life if they began treatment in 1996-1999 and 49 more years if they started in 2003-2005.⁹ Twenty-year-olds who started therapy with more than 200 CD4 cells/mm³ could look forward to another 50 years, while those who started with a lower CD4 count could expect only another 32. Overall average life expectancy in these 14 cohorts was only about two thirds of life expectancy in the general population.

A 25-state CDC study reckoned that people diagnosed with HIV in 2005 stand to lose an average 21.1 years of life compared with people of the same age, gender, and race in the general popu-

lation.⁴ Remarkably, this life deficit persists even into old age. Compared with the general population, 60-year-olds with HIV will lose an average 11 years and 70-year-olds an average 8 years.

The 21-year shortfall for people diagnosed with HIV in 2005 marked a hefty improvement from the 32.9 years of life lost among people diagnosed in 1996 but still bespoke a staggering gap in life expectancy between people with and without HIV. And the analysis may soften the bad news because the CDC did not include New York and California, where AIDS morbidity is high. The CDC audit differs from some longevity studies because it looks at everyone diagnosed with HIV, not everyone treated. Thus the estimates probably offer a more accurate overall look at life expectancy but do not fully reflect the benefits of antiretroviral therapy.

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Danish HIV cohort studies afford a unique slant on treatment and survival trends because they often include *every* registered infected person on the slender Scandinavian peninsula. And that population has long reaped the rewards of universal antiretroviral access and enlightened treatment guidelines. A recent case-control comparison of 3900 people with HIV and 379,872 controls matched by gender, date of birth, and place of residence included everyone receiving care for HIV from 1995 through May 1, 2005.¹⁰

Median overall survival for 25-year-olds measured 51.1 years in the general population and 19.9 in the HIV group. This 31-year gap nearly mirrors the 33-year difference gauged by the CDC among people diagnosed in 1996.⁴ But by 2000-2005, survival with HIV improved to 32.5 years in Denmark, and to 38.9 years in people without hepatitis C virus (HCV) infection.

Together these studies show that HIV shortens the lives of Europeans and North Americans by a decade or more. Early HAART-era prognoses that triple therapy would hike life expectancy with HIV into the normal range proved illusory. Antiretrovirals—even today’s safer and stronger antiretrovirals—do not restore health to the level one can expect in an HIV-negative person of the same age. In the United States, a 2010 case-control comparison showed, HIV-infected adults have a three times higher risk of dying than contemporaries without HIV, even if you subtract heart risk and demographic factors from the equation.¹¹

Looking at 29,935 people who started antiretrovirals and survived 6 months, the Antiretroviral Therapy Cohort Collaboration figured in

2009 that gay men who did not have AIDS and reached a CD4 count of at least 350 cells/mm³ and a viral load under 501 copies/mL after 6 months of therapy had virtually the same death rate as HIV-negative people of the same age, gender, and country.¹² Overall, though, 54% of gay men, 58% of heterosexually infected people, and *everyone* infected by injecting drugs had more than twice the death risk of the general population.

HIV alone certainly does not explain the higher death rate and curtailed lifespan of infected people. Compared with the population at large, the CDC team notes,⁴ the US HIV cohort includes more smokers, more drinkers, more drug abusers, and more people with hepatitis virus infection. Sometimes survival and mortality studies can account for these behavioral asymmetries, and sometimes they can’t. Research has a long way to go in explaining why most people with HIV die before their time. But work in the past few years has at least defined the categories of concern and begun to compile critical data in each, as detailed in the following sections of this article.

Why people with HIV age (and die) faster

There are lots of answers to this question, though they fall into six broad categories:

- Antiretroviral toxicity
- T-cell activation
- Inflammation
- Immunodeficiency
- Neurocognitive decline
- Frailty

The SMART study established that taking antiretrovirals—without pause—is much better than not taking them or taking them only when the CD4 count falls.¹³ Steady antiretroviral therapy in

this randomized trial warded off not only AIDS, but also major heart, kidney, and liver disease—and all-cause mortality as well. But no one suffers from the illusion that antiretrovirals are benign life extenders. PIs and abacavir heighten the risk of heart disease, tenofovir imperils kidney function, and PIs and nonnucleosides can pommel the liver. Perhaps worse, over a lifetime antiretrovirals may not completely reverse the ill effects of T-cell activation, HIV-fanned inflammation, immunodeficiency, neurodegeneration, and frailty. Here's what's known so far:

■ T-cell activation

Relentless T-cell activation during chronic HIV infection “may result in eventual immunologic ‘exhaustion’ and premature aging of the immune system,” suggests Steven Deeks, who has spent more than a little time studying aging in people with HIV and pondering the literature.¹⁴ To underpin this proposal, he cites two studies—an *ex vivo* analysis and *in vitro* model of CD8 cells showing close correlation between activation level and CD8 cell differentiation (as an indicator of “replicative senescence”)¹⁵ and a comparison of CD4- and CD8-cell markers in 20 fast progressors and 40 slow progressors linking “a shift in the T-cell population toward an aged conformation” in people with more advanced infection.¹⁶ These latter investigators note that, “in cell culture, [T cells] inevitably reach a state of replicative senescence after repeated antigen-driven cell divisions, with loss of proliferative capacity and other striking functional changes.”¹⁶

Deeks also notes similarities in T-cell changes in people with untreated HIV infection and elderly people without HIV,¹⁴ such as low CD4/CD8 ratios, low naive/memory ratios, blunted T-cell repertoire, weak response to vaccines, and ex-

pansion of CD28-negative effector T cells.^{17,18} He cites one of his own studies to note that up to half of peripheral CD8 cells remain on active patrol during untreated HIV infection (versus fewer than 10% in people without HIV) and that antiretroviral therapy does not completely halt this systemic hopscotch, at least not in the first years of therapy.¹⁹ More CD4- and CD8-cell activation in these 99 patients (figured as cells positive for CD38 and HLA-DR) correlated with a briefer period of HIV suppression, frequent low-level viremia, HCV infection, and a lower nadir CD4 count. T cells bearing activation markers declined steadily, but slowly, through 1 year of viral suppression (defined in this study as a viral load under 1000 copies/mL).

A more recent study by Deeks's group compared CD4- and CD8-cell activation in 30 HIV-infected people with an undetectable viral load despite lack of therapy (so-called elite controllers), 187 antiretroviral-treated people with an undetectable load, 66 untreated people with a detectable load (under 75 copies/mL), and 47 people without HIV.²⁰ Although most elite controllers had normal CD4 counts and no clinical signs of HIV infection, they had significantly higher CD4- and CD8-cell activation than people without HIV and more CD8-cell activation than people who used antiretrovirals to attain an undetectable load. T-cell activation levels were also higher in antiretroviral-treated controllers than in people without HIV.

In all four study groups, women, people with HCV, and older people had more activated CD4s or CD8s. Finally, higher T-cell activation correlated with lower CD4 counts in elite controllers, a finding suggesting that stirred-up T cells spur a drop in CD4s even among people with an undetectable HIV load.

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In Chicago a comparison of 10 antiretroviral responders (viral load below 50 copies/mL, median age 56 years, median CD4 count 724 cells/mm³), 10 older HIV-negative people (median age 88), and 5 younger HIV-negative people (median age 27) documented significantly higher CD8-cell activation (CD38 positive, HLA-DR positive) in the HIV group than in the 10 older people without HIV ($P < 0.01$).²¹

The elite controller study²⁰ ranks as the most revealing because it shows that people who shut down HIV replication for years (the elite controllers were infected for a median of 16 years²²) still had riled-up T cells. Other studies confirm that a zesty response to antiretrovirals does not necessarily reorder T cells into a normal array.²³⁻²⁵ The question none of these studies answers is whether T cells roused to the levels recorded in these people have unhappy clinical consequences. Higher activation levels did correlate with lower CD4 counts in the elite-controller study,²⁰ but whether constantly mobilized T cells mean premature aging, faster progression to AIDS, heightened susceptibility to other diseases, or earlier death remains poorly defined.

The study that found more upregulated T cells in fast progressors than in slow progressors defined fast progression as AIDS within 4 years of enrollment in the Multicenter AIDS Cohort Study (MACS) and slow progression as remaining AIDS-free for 8 years after entering the cohort.¹⁶ But a correlation between T-cell activation and HIV disease progression does not mean the activation explains faster progression.

Analysis of MACS blood samples collected from 1986 through 1994 found that T-cell activation

predicted death better than viral load—but the study involved men with fewer than 50 CD4 cells/mm³ in these early days of HIV care.²⁶ Another MACS study found that higher quotients of activated (CD38-positive) CD8 cells predicted progression to AIDS better than CD4 count, but researchers collected these cell samples from January through June 1992, in the days of one- and two-drug therapy.²⁷ A recent study found that CD8-cell activation and senescence correlate with early carotid intima-media thickness in HIV-infected people without clinical heart disease,²⁸ but a correlation does not denote cause-and-effect, and intima-media thickness is an atherosclerosis marker, not a clinical endpoint.

Despite the missing link between ever-excited T cells and HIV disease progression, non-AIDS disease, early aging, or death in people taking contemporary antiretroviral combos, taxing one's T cells for decades surely can't be salubrious and may indeed "exhaust" these critical components of the immune system.

■ Inflammation

The tie between ongoing inflammation and morbidity or mortality in people on current anti-HIV combinations is stronger than the link between T-cell activation and clinical endpoints. Researchers who ran the SMART treatment interruption trial have mined the richest lode of data on inflammation and morbidity in people with HIV.

In SMART higher readings of two inflammation markers (interleukin 6 [IL-6] and high-sensitivity C-reactive protein [hsCRP]) and a coagulation marker (D-dimer) at study entry independently predicted a higher risk of death from any cause in a case-control comparison.²⁹ The impact of these markers on all-cause mortality held true when the SMART team analyzed the treatment-inter-

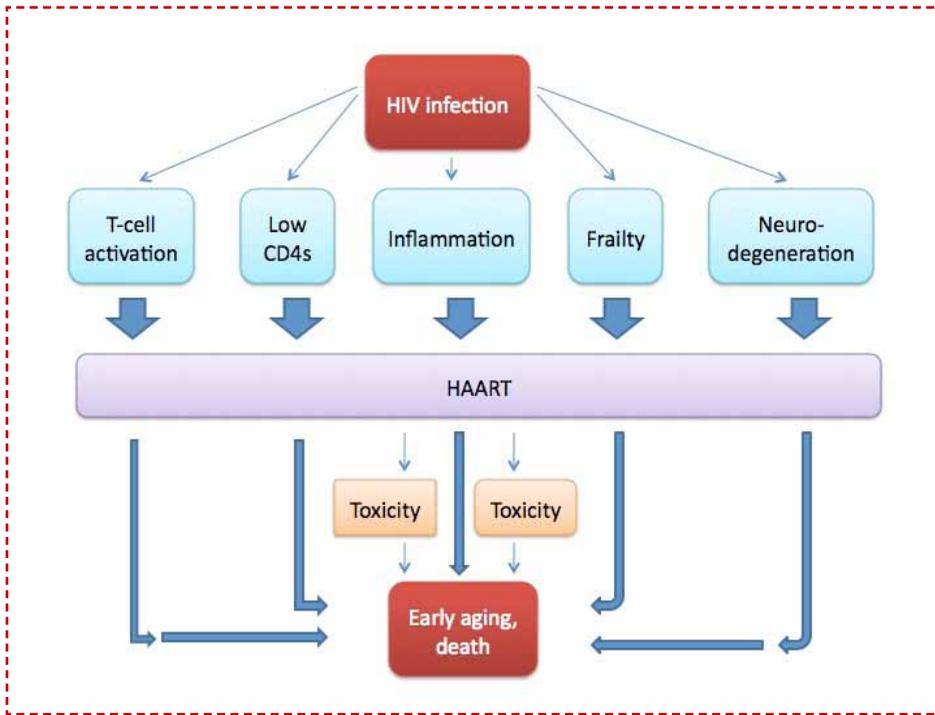


Figure 2. A model of early aging and death in HIV-infected people posits several pathways, which antiretroviral therapy (HAART) may limit but not block. Antiretroviral toxicities may speed the overall process.

ruption and continuous-therapy groups separately and when they measured the latest levels of these mortal harbingers. IL-6 and D-dimer levels rose during drug breaks.

Later, SMART investigators compared trial participants with two control populations—287 SMART enrollees aged 33 to 44 years compared with 3231 CARDIA members of the same age, and 494 SMART enrollees 45 to 76 years old compared with 5386 MESA study members of the same age.³⁰ None of the SMART participants had a record of cardiovascular disease, and most were taking antiretrovirals. Levels of hsCRP, IL-6, and D-dimer were 50% to more than 100% higher in SMART participants than in the control populations. Cystatin C (a kidney

function marker) was 27% higher in SMART than in MESA. Levels of hsCRP, IL-6, D-dimer, and cystatin C remained higher in SMART participants than in the control groups when the investigators looked only at nonsmokers. And the differences held constant after statistical adjustment for cardiovascular risk factors. The SMART team proposed that “the magnitude of the differences in these markers... [is] clinically relevant considering the prognostic importance of these markers in the general population.”

Another SMART comparison of 91 people with a new opportunistic disease during the study and 182 people without a new opportunist found that higher levels of hsCRP and IL-6 at study entry in-

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dependently predicted a new diagnosis.³¹ Higher readings of hsCRP, IL-6, and amyloid A (another inflammatory marker) at latest follow-up also hiked the odds of a new opportunistic disease.

Priscilla Hsue and Steven Deeks's group assessed carotid intima-media thickness, hsCRP, and other variables in 33 elite HIV controllers (untreated people with a viral load below 75 copies/mL and a stable CD4 count), 96 untreated noncontrollers with a detectable load, 180 antiretroviral responders with an undetectable viral load, 92 antiretroviral nonresponders with a detectable load, and 93 HIV-negative controls.³² Even after statistical adjustment for heart risk factors, the elite controllers had significantly higher intima-media thickness than the HIV-uninfected controls, as did all the other HIV groups (0.91 mm overall with HIV versus 0.72 mm without HIV, $P < 0.001$).

Median hsCRP in all HIV-infected groups nearly doubled the value in people without HIV (2 versus 1.1 mg/dL, $P < 0.001$), even after statistical correction for other risk factors. Notably, elite controllers had as much hsCRP as the other groups, so keeping HIV under wraps with or without antiretrovirals did not ease levels of this inflammation marker. But Hsue cautions that hsCRP "did not appear to explain the difference in intima-media thickness between the controllers and the HIV-seronegative persons since inclusion of hsCRP in the multivariable model changed the adjusted difference between HIV controllers and HIV-seronegative persons by less than 10% and the difference between controllers and HIV-seronegatives remained significant ($P = 0.003$)."

The same caveats noted in the T-cell activation studies apply to this inflammation research: in-

flammation markers are not disease, and neither is carotid intima-media thickness. Correlations between markers and death²⁹ or a new opportunistic disease³¹ in SMART do not mean these markers triggered disease progression or death. Indeed, the role of inflammatory markers like hsCRP in general medicine remains controversial (see the interview with Steven Grinspoon).

But most observers would agree that high levels of these markers may bode ill, and physicians would be happier treating people in those control groups with lower hsCRP and thinner carotid artery walls. Finally, tight HIV control does not reverse abnormal inflammation marker readings. Indeed, levels of hsCRP climbed significantly in women throughout 96 weeks of suppressive efavirenz therapy in one AIDS Clinical Trials Group study, and levels did not fall in men.³³

■ Immunodeficiency

Suppressive antiretroviral therapy boosts CD4 counts *toward* the normal range, but CD4s take a long time to reach a tally most would call normal,^{34,35} and both CD4s and CD8s remain functionally flawed long after the viral load falls off the RNA radar.²³⁻²⁵ Does the initial T-cell insult of untreated HIV infection and the incomplete return to full function with therapy accelerate aging or pose clinical risks for other reasons?

Yes.

A small case-control study determined that aging HIV-infected people (median 56 years) with a good CD4 count (median 724 cells/mm³) and long-term viral suppression with antiretroviral therapy have CD4 and CD8 cells similar to those of a substantially older HIV-negative comparison group (median 88 years) and utterly unlike those of a younger HIV-negative group (median

27 years).²¹ The HIV group had significantly more CD8 cells rated senescent (CD57 positive and CD28 negative) than did non-HIV comparison groups.

In the FIRST trial, which compared three antiretroviral strategies in previously untreated people, 149 people (18%) gained fewer than 50 CD4s in the first 8 months of suppressive therapy (viral load below 400 copies/mL).³⁶ These slow CD4 responders lagged faster responders by about 100 cells/mm³ through 5 years of follow-up. Every 10 years of age raised the risk of tardy CD4 recovery 34% ($P = 0.003$).

Compared with people who gained at least 50 CD4s in the first 8 months of treatment, those with sluggish CD4 gains ran a doubled risk of reaching a composite endpoint of AIDS, a non-AIDS disease, or death (adjusted hazard ratio 2.24, $P < 0.001$). People with slow CD4 recovery had a lower risk of reaching this endpoint if they started therapy at a higher CD4 count ($P < 0.01$). Non-AIDS complications included non-AIDS cancer and cardiovascular, kidney, or liver disease. The FIRST team proposed that “ART treatment strategies that minimize time spent at lower CD4+ levels are important in reducing risk for HIV-related morbidity and mortality, including both AIDS and non-AIDS diseases.”

Another analysis of FIRST study participants confirmed a higher risk of AIDS and non-AIDS diagnoses with blunted CD4 gains through 5 years of follow-up.³⁷ AIDS and non-AIDS event rates per 100 person-years were 13.8 and 2.1 with a latest CD4 count under 200 cells/mm³, 2.0 and 1.7 with a latest count between 200 and 350 cells/mm³, and 0.7 and 0.7 with a latest count above 350 cells/mm³. Every 100 CD4-cell gain lowered the risk of AIDS 44% and the risk of non-AIDS maladies 14%.

A 23-cohort analysis of 9858 adults with an estimated date of HIV seroconversion determined that every additional 100 CD4 cells/mm³ in the latest CD4 count yielded a 32% reduction in deaths from non-AIDS infections, a 33% drop in deaths from end-stage liver disease, and a 34% fall in deaths from non-AIDS cancers.³⁸ Lower nadir CD4 count and longer immunosuppression before antiretroviral therapy also inflated the risk of non-AIDS death. Several cohort studies discussed in the review of non-AIDS cancers (page 56) also traced links between immunodeficiency and non-AIDS malignancies.

A DAD cohort study scrutinized correlates of liver-related death in more than 23,000 people with HIV, most of them taking antiretrovirals.³⁹ A latest CD4 count below 50 versus above 500 cells/mm³ hiked the risk of death from liver disease 16 times, and every 5 years of age swelled the death risk 30%. The liver-related death rate (per 100 person-years) was 1.33 with fewer than 50 CD4 cells/mm³, 1.23 with 50 to 99, 0.73 with 100 to 199, 0.34 with 200 to 349, 0.12 with 350 to 499, and 0.06 with 500 or more. Injection drug use, HCV infection, and active HBV infection also independently raised the risk of death from liver disease.

Together these studies leave little doubt that a lower CD4 count before antiretroviral therapy, longer time with a lower CD4 count, and a lower current count make HIV-infected people more liable to an array of non-AIDS ailments, and of course to AIDS as well. As the FIRST study showed,^{36,37} slower CD4 gains during successful therapy—over a median 5-year follow-up—heightened the risk of AIDS, non-AIDS diseases, and death. In some of these studies, older age (a frequent correlate of slower CD4 gains) also boosted the odds of morbidity and mortality.

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■ Neurocognitive decline

Aging and ebbing brain power are confederates in decrepitude, and HIV only makes things worse. A proton magnetic resonance spectroscopy comparison of 61 people with HIV dementia, 39 HIV-infected people without neurologic symptoms, and 37 HIV-negative controls found that HIV infection and aging had additive effects on brain metabolites associated with inflammation that could heighten the risk of cognitive slippage.⁴⁰ The study documented glial activation during neurologically asymptomatic stages of HIV infection that spread to basal ganglia and white matter as dementia developed.

Work from before and during the HAART era uncovered a link between older age and higher risk of HIV dementia as the first AIDS diagnosis.⁴¹⁻⁴⁴ A study published in 2004 involved 202 people assessed on entering the Hawaii Aging With HIV Cohort—106 of them 50 or older and 96 of them 20 to 39 years old.⁴⁴ As one would expect, older people had a longer HIV infection duration. One quarter of the older group had HIV dementia, compared with 14% of the younger group. Statistical analysis that factored in race, education, substance abuse, antiretroviral status, viral load, CD4 count, and Beck Depression Inventory score figured that the 50-plus group had more than a tripled risk of dementia (odds ratio 3.26).

Older age and HIV infection both stymied cerebral blood flow in a comparison of people with and without HIV.¹ These investigators surmised that differences between groups with and without HIV “do not correlate with existing markers of HIV disease and could reflect ongoing inflammation and oxidative stress that continue to oc-

cur despite relatively good virologic control by antiretroviral therapy.”

To test the impact of HIV and aging on the brain, University of Washington (St. Louis) researchers gauged cerebral blood flow with arterial spin labeling magnetic resonance imaging in 26 people with HIV and 25 uninfected controls. The HIV group averaged 39 years in age (+/- 12 years standard deviation), compared with 41 (+/- 12 years) in controls, a nonsignificant difference. Education level and gender distribution were also equivalent in the two groups. HIV-infected people had a median CD4 count of 486 cells/mm³, a median CD4 nadir of 278 cells/mm³, and a median plasma load around 1000 copies/mL. Fifteen people with HIV (58%) were taking antiretrovirals.

Baseline cerebral blood flow slackened significantly with age in both the HIV group and controls ($P < 0.001$) but was slower in HIV-infected people at every age ($P < 0.001$). Functional blood oxygen level-dependent changes in response to visual stimuli fell significantly with age ($P = 0.001$) and when comparing the HIV group with the non-HIV group ($P = 0.048$). Whether a person took a protease inhibitor or a nonnucleoside regimen did not affect magnetic resonance imaging results.

The researchers calculated that HIV infection adds 15 to 20 years in brain age. They speculated that HIV-spurred drops in endothelial function or platelet function could lead to decreased cerebral blood flow.

■ Frailty

Everyone knows a frail person when they see one, but the many variables that add up to frailty make defining it difficult. HIV clinician and researcher

Keith Henry (University of Minnesota) suggests defining frailty as “a syndrome involving loss of muscle mass, weight, and energy; slower muscle performance; and low levels of physical activity.”⁴⁵ Those factors make up a “frailty phenotype” that some researchers try to pin down by tallying certain physical markers.^{46,47} The first of these two studies found that 55-year-old men with HIV for 4 or fewer years have the frailty phenotype as often as HIV-negative men 65 years and older in the Multicenter AIDS Cohort Study (MACS).⁴⁶ The second study correlated a lower CD4 count and a higher viral load with an enhanced risk of frailty.⁴⁷

How did these researchers define the frailty phenotype? They began with a definition proposed by other investigators,⁴⁸ who rated people frail if they had three of the following five markers:

- Physical shrinking (unintentional weight loss)
- Exhaustion (self-reported)
- Low physical activity level (measured by a weighted score of kilocalories expended per week)
- Slowness (time to walk 15 feet)
- Weakness (grip strength)

By these measures only 2% of 65-to-70-year-old men and 3% of 71-to-74-year-old men in the Cardiovascular Health Study were frail. Loic Desquilbet and coworkers modified this definition in MACS members—gay men with or without HIV infection in Baltimore/Washington, Chicago, Los Angeles, and Pittsburgh.⁴⁶ Without a ready way to measure weakness, the MACS team defined frailty as three of the other four factors as determined by record review and participants’ answers to nine questions (**Table 1**). Follow-up of these men ran from 1994 through 2004.

Table 1. Questions on frailty components asked in the MACS study⁴⁶

Physical shrinking

Since your last visit, have you had unintentional weight loss of at least 10 pounds?*

Exhaustion

During the past 4 weeks, as a result of your physical health, have you cut down the amount of time you spent on work or other activities?

Since your last visit, have you had persistent fatigue (feeling tired all the time) for at least 3 consecutive days?

During the past 4 weeks, as a result of your physical health, have you had difficulty performing your work or other activities (for example, it took extra effort)?*

Slowness

Does your health now limit you in walking more than 1 mile?

Does your health now limit you in walking several blocks?*

Low physical activity level

Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?

Does your health now limit you in bathing or dressing yourself?

Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?*

*Included in final definition of frailty-related phenotype. Source: Desquilbet et al.⁴⁶

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The first analysis involved 1977 men ranging in age from 24 to 79 (median 42) when uninfected with HIV. Frailty prevalence ranged from 1.0% in 45-to-49-year-old men to 4.4% in men older than 65. White, non-Hispanic men with a college education and older than 65 had a frailty prevalence of 3.4%.

The second part of the study compared 1905 men consistently free of HIV and 245 men who got infected during follow-up. Thirty-four HIV seroconverters (13.9%) had the frailty phenotype at least once during the study, compared with only 28 men (1.5%) who did not pick up HIV ($P < 0.01$). A multivariate model that considered age, ethnicity, and education determined that HIV-infected men were 11 times more likely to have the frailty phenotype (odds ratio [OR] 10.97). Because weight loss is common in people with HIV, the researchers eliminated weight as a variable and found that HIV infection still more than quadrupled the risk of frailty (OR 4.49, $P < 0.001$). Frailty risk rose with increasing age and longer HIV duration. Lack of association between age and HIV duration suggested these two factors independently raise the risk of frailty. A CD4 count under 350 cells/mm³ versus over 350 made frailty almost 3 times more likely (OR 2.75), while a viral load above 50,000 copies/mL versus a lower load also nearly tripled the risk (OR 2.91).

A more recent MACS analysis by the same investigators found that a lower CD4 count predicted the frailty phenotype independently of antiretroviral use.⁴⁷ This study focused on 1046 HIV-infected men enrolled in MACS before 1996 and seen twice yearly from April 1994 through April 2005. Non-Hispanic whites accounted for 80% of the study group, half of whom had gone to col-

lege. Median age on January 1, 1994 was 39 and ranged from 22 to 65, and median HIV duration stood at 9.2 years.

Although median current age rose over three treatment periods (1994-1995, 41 years; 1996-1999, 43 years; 2000-2005, 48 years), frailty prevalence fell from 7.6% in the pre-HAART era to 5.2% in the early HAART era and to 4.5% in the later HAART era. HAART use over those periods climbed from under 0.1% to 52.0% to 68.7%.

Multivariate models to predict frailty phenotype included variables that might affect frailty plus (1) CD4 count, (2) viral load, or (3) both CD4 count and viral load. The investigators modeled CD4 count quantitatively to assess the impact of five specific CD4 counts on frailty phenotype: 750, 500, 350, 200, and 100 cells/mm³. In all models, the reference CD4 value was 500 cells/mm³ (OR 1.0).

In the confounders-plus-CD4 model, a CD4 count of 750 cells/mm³ on the previous visit lowered the risk of frailty 41% (OR 0.59) at the next visit, whereas a count of 350, 200, or 100 cells/mm³ on the previous visit raised the risk 1.47 times, 2.36 times, or 3.65 times on the next visit ($P < 0.01$ for all comparisons). In the model including both CD4 count and viral load, a CD4 count of 750 cells/mm³ cut the frailty risk 34%, while counts of 350, 200, or 100 cells/mm³ upped the risk 1.36 times, 1.98 times, or 2.80 times ($P < 0.01$ for all comparisons). An AIDS diagnosis or AIDS wasting did not affect the CD4-related risk of frailty. Also, the frailty phenotype proved more likely in men with a viral load above 50,000 copies/mL versus 400 copies/mL or lower ($P < 0.01$).

In the CD4-only model, every 10 years of age inflated the risk of frailty 1.48 times. In the viral load-only model, aging 10 years hiked the risk

1.54 times. And in the CD4-plus-viral load model, aging 10 years made frailty 1.52 times more likely. Desquilbet and colleagues figured that in the current treatment era a 10-year increase in age matched a 250-cell drop in CD4s in upping the odds of frailty.

The investigators cautioned that their studies did not determine whether frailty heightened the risk of morbidity or mortality. But longitudinal studies in people without HIV in Sweden linked a weakened immune system (marked by an inverted CD4/CD8 ratio and T-cell activation) with mortality in elderly people.^{49,50} Desquilbet and colleagues suggested their findings “provide evidence that the [frailty-related phenotype] is etiologically related to a compromised immune system as associated with HIV infection.”⁴⁷

Tactics to slow premature aging with HIV

Suggestions for slowing overhasty aging almost outnumber posited mechanisms. They run the gamut from the obvious (exercise) to the abstruse (zinc), from the mundane (aspirin) to the heroic (thymus grafts). As the authors of one prolix yet probing review of antiaging therapies put it, because aging itself is not a disease, the elderly “do not require adventurous therapies with unpredictable side-effects.”⁵¹ But aging people with HIV might more readily countenance adventure.

■ Restyling lifestyles

Encouraging lifestyle change is the soundest, simplest, and probably most effective way to retard time’s remorseless scythe. It’s probably also the hardest. If getting people to lose weight and stop smoking were easy, the Big Men’s Shop and Philip Morris would be out of business. When

randomized trials compare diet-and-exercise programs with “standard of care,” better-eating people who exercise always end up significantly healthier after 6 months. Everyone knows these interventions take more time and money than many harried clinicians can readily afford (a difficulty discussed by Steven Grinspoon in the accompanying interview). But these realities are no reason to stop trying. The list of malleable risk factors bears repeating:

- Smoking
- Overweight
- Lack of exercise
- Injection drug use
- “Recreational drug” use
- Alcoholism
- Hypertension
- Dyslipidemia

A small but insightful study by researchers in France (where smoking comes right after liberté and égalité on the bill of rights) divided 254 smokers into four groups according to reasons for smoking and found they also differed in how much they smoked and how much they felt like quitting.⁵² For example, people who smoked to lose weight proved most motivated to quit, even though they tended to smoke more than people who inhaled for enjoyment or to forget their worries. People who claimed they smoked “automatically” had the strongest tobacco dependency and the least inclination to quit.

Clinicians looking for fresh ideas on helping people quit might consult two less-than-obvious online aids. The US Surgeon General’s Website offers copious advice plus clinical guidelines on treating tobacco dependence and patient-directed material in English and Spanish.⁵³ The Vet-

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erans Administration's comprehensive guide on HIV care includes ample sections on smoking, injection drug use, and alcohol.⁵⁴

■ Retooling antiretroviral plans

Hardly a month goes by without the release of some new study showing that people who started antiretrovirals earlier in the course of infection ended up with better T-cell recovery^{34,35} or even longer survival.^{55,56} US antiretroviral guideline writers took these findings under advisement and now say clinicians should recommend treatment in people with 350 to 500 CD4 cells/mm³, and half the panel thinks treatment should start with counts above 500 cells/mm³.⁵⁷

For people who have already begun treatment, clinicians have long shaped and reshaped regimens to avoid drugs that may worsen underlying conditions or add to existing risks. This tactic takes on added urgency as non-AIDS maladies muscle their way to the top of HIV mortality charts.

In a review article on accelerated aging with HIV,⁵⁸ clinician/researcher Steven Deeks cites evidence showing that regimens including the protease inhibitors lopinavir/ritonavir⁵⁹ or the CCR5 antagonist maraviroc⁶⁰ may hold an edge over nonnucleoside combos in boosting CD4 counts faster. However at the 2010 Conference on Retroviruses, ACTG researchers reported that adding maraviroc to a virologically effective but immunologically underachieving regimen did not boost stalled CD4 counts.⁶¹ Only 2 of 34 people gained more than 50 CD4s in 24 weeks. And of course hurrying CD4 gains is only one of many factors to weigh in picking antiretrovirals.

“In an era in which more than 25 therapeutic options are available” for people with HIV, Deeks cautions elsewhere,¹⁴ “it is more important than ever that all patients have access to a clinician with expertise in managing antiretroviral therapy.” And because older patients take more non-HIV drugs than younger patients, that clinician should count on an HIV pharmacologist for help in avoiding drug interactions. Several often-updated online tools unspool reliable guidance in this labyrinthine arena.⁶²⁻⁶⁴

■ Rethinking antiinflammatory and adjunctive tactics

If, as most believe, inflammation is a prime culprit in speedy aging with HIV, clinicians might consider more aggressive management of other flame-throwing maladies common in this population, including hepatitis, chronic kidney disease, and the long list of sexually transmitted conspirators. For people still free of these inflammatory afflictions, prevention—by vaccination or other means—should be a priority. The CDC offers an online vaccination schedule for all adults by age, HIV status, CD4 count, and other variables.⁶⁵ Vaccinations against HBV, pneumonia, and tetanus/diphtheria/pertussis are recommended for everyone with HIV, and the HPV vaccine is recommended for HIV-infected women. The CDC contraindicates varicella, zoster, and measles/mumps/rubella vaccines in people with a CD4 count under 200 cells/mm³.

Aside from disease-specific treatment and vaccinations, should clinicians consider regular aspirin or nonsteroidal antiinflammatories (NSAIDs) for people with HIV? The US Preventive Services Task Force advises *against* routine aspirin or NSAIDs to prevent colorectal cancer *in individuals at average risk for colorectal cancer*.⁶⁶ Although the Task Force doesn't say so, people

Short List of Antiaging Strategies for People With HIV

Strategy	Aim	Pluses	Minuses
Get people to stop smoking	Lower risk of CVD, cancers, and other threats to longevity	Benefits certain; reversible weight gain only side effect	For many patients requires steady commitment; cost
Start ART earlier	Shorter time at low CD4, high RNA, which may threaten longevity	Risks, benefits of long-term ART becoming better understood	Cost; long-term adherence to avoid resistance
Aspirin every other day	Lower risk of all-cause mortality in people with high CVD risk	Simple; direct; side effects reasonably well understood	Adds to pill burden; risk of GI bleeding
Vitamin E supplements	Promote stronger bones and possibly immune function	Simple; direct; low risk of toxicity	Adds to pill burden; immune benefit not clear
Encourage “hardiness”	Promote mental health, coping skills in people of any age	Side effects non-existent; benefits apply to many aspects of life	Cost; commitment; benefits not established

Figure 3. Several straightforward, relatively safe strategies will or may slow accelerated aging in people with HIV. For an explanation of “hardiness,” see the final section of this article and the interview with David Vance. ART, antiretroviral therapy; CVD, cardiovascular disease; GI, gastrointestinal.

with HIV may have a higher than average risk,⁶⁷ and colorectal cancer may be more aggressive in people with HIV.⁶⁸ The Task Force says “clinicians should continue to discuss aspirin chemoprophylaxis with patients who are at increased risk for coronary heart disease,” adding that “aspirin use by patients at increased risk for coronary heart disease has been shown to reduce all-cause mortality.”⁶⁶

Five years ago the INSIGHT research group (which planned SMART) proposed a placebo-controlled trial of a preventive “polypill” in people with HIV.^{69,70} In an idea perhaps ahead of its time (funders could not be found), the quadruple prophylactic would attack diverse

cardiovascular risk factors by melding low-dose pravastatin, aspirin, hydrochlorothiazide, and lisinopril. Analyzing meta-analyses of published trials, INSIGHT strategists projected that the superpill could cut ischemic heart disease diagnoses by 88% and stroke by 80%, while causing side effects in 8% to 15%.⁷⁰ They proposed a “vanguard study” in 400 people with HIV to assess changes in cholesterol, blood pressure, and other risk factors.⁶⁹ But the group has abandoned active planning for such a trial.

What about vitamins? An avalanche of population-based research indicates that a surprising proportion of people with HIV may be moder-

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ately to severely deficient in vitamin D, a micronutrient essential for bone health and perhaps healthy immune function.⁷¹ For the general population, the US Preventive Services Task Force concludes (in its latest, 2003, vitamin update) “that the evidence is insufficient to recommend for or against the use of supplements of vitamins A, C, or E; multivitamins with folic acid; or antioxidant combinations for the prevention of cancer or cardiovascular disease.”⁷² The Task Force advises against beta-carotene supplements, alone or in combination, to prevent cancer or heart disease in the general population.

Most vitamin supplementation trials in people with HIV involve pregnant women and their newborns, usually in poor countries, or adults with TB. However, more than a decade ago, French researchers pitted selenium or beta-carotene against placebo to address the hypothesis that antioxidant loss contributes to endothelial dysfunction with HIV.⁷³ Ten people got 100 μg of selenium daily, 11 got 30 mg of beta-carotene twice daily, and 15 got no supplements. One year later the people taking no supplements had significantly increased von Willebrand factor and soluble thrombomodulin ($P < 0.01$ for both), a result the investigators interpreted as implying increased endothelial damage. These indices did not change in the two supplemented groups.

A small open-label study at the Veterans Affairs Medical Center in Los Angeles found no evidence that 4 weeks of beta-carotene supplementation boosted CD4 counts in HIV-infected people with normal baseline levels of beta-carotene and vitamin A.⁷⁴ These 21 people entered the study with 100 to 300 cells/ mm^3 while taking a single antiretroviral or none.

Taking vitamins E and C daily for 3 months significantly reduced oxidative stress and marginally lowered viral load in a 49-person placebo-controlled trial.⁷⁵ CD4 counts averaged 269 cells/ mm^3 in the intervention group, and none of these people were taking more than two nucleosides.

A double-blind placebo-controlled trial of multivitamins plus selenium in 400 HIV-infected non-pregnant Kenyan women found that supplementation significantly boosted CD4 and CD8 counts but—defying expectation—significantly *increased* vaginal shedding of HIV.⁷⁶

Taking daily vitamins and minerals with or without arginine and omega-3 fatty acids did not improve CD4 count, CD8 count, or viral load in a double-blind trial of 55 Swiss patients.⁷⁷ Most of these people were not taking antiretrovirals; a few were taking zidovudine, didanosine, or both.

A double-blind, placebo-controlled, community-randomized trial of 331 Canadian adults *with advanced AIDS* gave vitamin A and trace elements to everyone and natural mixed carotenoids to one group.⁷⁸ Mortality was higher in people who did not get the carotenoids, but the difference from the intervention group fell short of statistical significance (hazard ratio for time to death 1.76, 95% confidence interval 0.89 to 3.47, $P = 0.11$).

Daily calcium plus vitamin D for 48 weeks tended to increase bone mineral at the lumbar spine, total hip, and femoral neck in a placebo-controlled trial of adults with low bone density while on stable antiretroviral therapy, but improvements were significant only with once-weekly alendronate plus the two supplements.⁷⁹

Two Tanzanian micronutrient trials in the past 5 years involved people with pulmonary tuberculo-

sis, with or without HIV. A placebo-controlled trial of vitamins A, B complex, C, and E plus selenium in 471 Tanzanian adults with HIV and 416 without HIV found a marginally significant 64% reduction in mortality, but only in the HIV-negative group.⁸⁰ The vitamins lowered the incidence of peripheral neuropathy in people with and without HIV. A trial of multivitamins and minerals plus zinc recorded significantly lower mortality after 8 months in HIV/TB-coinfected people who got both the multivitamin and zinc.⁸¹

Last year BITE study researchers unveiled results of an international trial that randomized 340 antiretroviral-naïve adults to a nutritional supplement or no treatment in an effort to promote gut integrity, corral baneful bacteria, and quell CD4-cell activation.⁸² The supplement combines oligosaccharides (simple sugars that promote healthy gut bacteria and suppress harmful bacteria while decreasing systemic CD4 activation), n3-PUFAs (polyunsaturated fatty acids that decrease inflammation and gut permeability), bovine colostrum (nutrient-rich milk that enhances gut integrity), N-acetyl cysteine (an amino acid that improves glutathione status), and a vitamin/mineral mix (to prevent micronutrient deficiencies).

BITE's Data and Safety Monitoring Board recommended halting the trial early because people taking the supplement gained significantly more CD4s in a year—68 cells/mm³ versus 28 cells/mm³ in the control group. But because some might call the *P* value for this difference borderline (*P* = 0.03), not everyone agreed with the investigators' decision to stop.

With IL-2 officially off the immune-enhancing candidate list for people with HIV, work continues on IL-7, which expanded CD4 and CD8 populations in a placebo-controlled trial of peo-

ple taking suppressive antiretroviral therapy.⁸³ As with IL-2, however, advocates must still determine whether these better counts foster better health.

Outside-the-box balms that may counter aging can—and do—get more arcane than that. Tesamorelin, a growth hormone-releasing factor, significantly reduced visceral adipose tissue and other central fat measures in people with HIV.^{84,85} But the benefits faded when treatment stopped. Want to keep telomeres long and vigorous? TAT2 (GRN163L), a small-molecule telomerase activator, “modestly” retarded telomere shortening while enhancing antiviral activity of CD8 cells collected from people with HIV.⁸⁶ This agent has entered phase I trials in people with cancer, but not in people with HIV.

For the general aging population, intrepid scientists eye an array of novel and not-so-novel agents that may tinker with T-cell function, restore thymic output, or decrease antigenic load.⁵¹ Many of the HIV-specific strategies discussed above (IL-7, statins, selenium, vitamin D, omega-3 fatty acids) make this list, as do still-untested high-risk tactics (caloric restriction, stem cell transplants) that probably interest researchers more than aging people with HIV.

■ Reimagining the intangibles

After all the screening, testing, counseling, preventing, and treating, there's still that ill-defined knack for survival we all recognize but can't name, unless we are a social worker, in which case we call it hardiness. Hardiness embraces all those traits that combine to promote successful aging “despite traumatic life events and chronic diseases,”⁸⁷ explains David Vance, who studies har-

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diness, aging, and HIV at the University of Alabama. Hardy people “perceive the changes and problems in their lives as challenges and opportunities for growth and further development.”⁸⁷

Among hardy attributes, Vance lists confronting problems head-on, social connectedness, working hard, curiosity, purpose in life, and adopting nontraditional—even maverick—behavior. Everyone can think of long-term HIV survivors who answer to those requirements (the playwright Larry Kramer, the novelist Edmund White), but did hardiness help them live long, or did living long make them hardy?

In an interview starting on page 13, Vance fields the two toughest questions about hardiness—

whether it can be measured and whether it can be learned—offering a qualified yes in both cases. Two small studies in people with HIV did test programs that promote hardiness—or something like it. One suggested that hardiness can be bolstered,⁸⁸ the other didn’t.⁸⁹ In the interview Vance outlines an individualized hardiness intervention he thinks can work.

Of course even if hardiness can be learned, hardiness-enhancing sessions mean sluicing money and time away from something else, possibly with less return than smoke-ending programs, for example. But perhaps a hardy person would insist that getting people to think positively is easier than getting them to forswear cigarettes, burn calories, and eat broccoli.

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Recent Non-AIDS Disease Screening Guidelines for People With HIV Infection

(The US Preventive Services Task Force offers comprehensive screening advice for the general population at <http://www.ahrq.gov/clinic/pocketgd.htm>.)

<p>Cardiovascular disease</p>	<p>DHHS: Fasting lipid profile at entry into care, annually if normal before ART; at ART initiation or switch; 2 to 8 weeks after ART initiation or switch; consider after starting new ART; every 6 months if borderline or abnormal when last measured, every 12 months if normal when last measured, and if clinically indicated.</p>	<p>EACS: Framingham score, ECG at HIV diagnosis for every man over 40 or woman over 50 without CVD; Framingham score before starting ART, every 12 months on or off ART. Total cholesterol, HDL, LDL, TG at HIV diagnosis, before starting ART, every 12 months on or off ART; repeat in fasting state if used for medical intervention. Blood pressure at HIV diagnosis, before starting ART, every 12 months on or off ART.</p>
<p>Anal cancer</p>	<p>EACS: Digital rectal exam with or without Pap test for gay men every 1 to 3 years; anoscopy if Pap test abnormal.</p>	<p>VA: For women, annual Pap test for anal carcinoma.</p>
<p>Breast cancer</p>	<p>EACS: Mammography for women age 50 to 70 every 1 to 3 years.</p>	<p>VA: Mammography for women age 40 to 69 every 1 to 2 years; clinical breast exam and breast self-exam may be incorporated into screening according to patient and provider preference.</p>

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<p>Cervical cancer</p>	<p>EACS: Pap test for sexually active women every 1 to 3 years; longer screening interval if tests repeatedly negative.</p>	<p>VA: Pap test at HIV diagnosis and 6 months thereafter; if initial results normal, rescreen annually if CD4 count >200 or every 6 months if CD4 count <200.</p>
<p>Colorectal cancer</p>	<p>EACS: Fecal occult blood test for men and women age 50 to 75 every 1 to 3 years.</p>	<p>VA: Men and women at average risk (CD4 count >350 or undetectable viral load) screened starting at age 50 with fecal occult blood testing (FOBT), flexible sigmoidoscopy with or without FOBT, colonoscopy, or double-contrast barium enema.</p> <p>Office-based digital rectal examination plus FOBT should not be used.</p>
<p>Prostate cancer</p>	<p>EACS: Digital rectal exam with or without PSA for men over age 50 every 1 to 3 years (“controversial”).</p>	<p>VA: Counsel patients annually about risks and benefits of screening for prostate cancer by PSA and digital rectal exam; screening may be performed if patient desires.</p>
<p>Vaginal cancer</p>	<p>VA: Regular vaginal cuff Pap test after hysterectomy for women with history of high-grade CIN or invasive cervical cancer.</p>	
<p>Cognitive function</p>	<p>EACS: Questionnaire* at HIV diagnosis, before starting ART, every 12 to 24 months on or off ART.</p>	

<p>Diabetes</p>	<p>DHHS: Fasting glucose at entry into care, annually if normal before ART, at ART initiation or switch, every 3 to 6 months if borderline or abnormal when last measured, every 6 months if normal when last measured, if clinically indicated.</p>	<p>EACS: Fasting glucose at HIV diagnosis, before starting ART, every 6 to 12 months on ART; consider oral glucose tolerance test if repeated fasting glucose 6.1 to 6.9 mmol/L (110 to 1250 mg/dL).</p>
<p>Liver function</p>	<p>DHHS: HAV and HCV serology at entry into care; HBV serology at entry into care; may repeat if not immune and if HBsAg negative at baseline, at treatment failure, and if clinically indicated.</p> <p>ALT, AST, bilirubin at entry into care, every 6 to 12 months before ART, at ART initiation or switch, 2 to 8 weeks after ART initiation or switch, every 3 to 6 months on ART.</p>	<p>EACS: ALT, AST, ALP at HIV diagnosis, before starting ART, every 3 to 6 months with ART, every 6 to 12 months without ART; more frequent monitoring before starting and on treatment with hepatotoxic drugs.</p>
<p>Kidney function</p>	<p>DHHS: Urinalysis at entry into care, at ART initiation or switch, every 6 months in patients with HIVAN, every 12 months if on TDF, if clinically indicated.</p> <p>EACS: eGFR (MDRD) at HIV diagnosis, before starting ART, every 3 to 6 months with ART, every 6 to 12 months without ART; more frequent monitoring with CKD risk factors and/or before starting and on treatment with nephrotoxic drugs.</p>	<p>IDSA/HIVMA:</p> <ol style="list-style-type: none"> 1. Urinalysis for proteinuria and calculated estimate of renal function at HIV diagnosis. 2. If no proteinuria at initial evaluation, annual screening for high-risk patients (African Americans, CD4 count <200, viral load >4000, diabetes mellitus, hypertension, or HCV). 3. If proteinuria grade >1+ by dipstick or GFR <60 mL/min per 1.73 m², additional evaluation (quantification of proteinuria, renal ultrasound, potentially renal biopsy) and referral to nephrologist.

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	Urine dipstick at HIV diagnosis, before starting ART, every 12 months on or off ART, every 6 months if eGFR <60 mL/min; if proteinuria >1+ and/or eGFR <60 mL/min, perform UP/C or UA/C.	
Osteopenia and osteoporosis	DHHS: Consider assessment of bone mineral density with DEXA scan at entry into care and follow up if abnormal; proper interval not determined in people with HIV.	EACS: FRAX in patients >40 years at HIV diagnosis, before starting ART, every 2 years on or off ART; if not using FRAX, consider DEXA of spine and hip in specific patients.

*According to the US Preventive Services Task Force, “the Mini-Mental Status Examination (MMSE) is the best-studied instrument for screening for cognitive impairment [in the general population]. When the MMSE is used to screen unselected patients, the predictive value of a positive result is only fair.” Recommendations of the US Preventive Services Task Force. The guide to clinical preventive services. 2009. <http://www.ahrq.gov/clinic/pocketgd.htm>.

Guideline abbreviations:

DHHS, Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. December 1, 2009. <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>.

EACS, European AIDS Clinical Society. Guidelines: prevention and management of non-infectious co-morbidities in HIV. November 2009. <http://www.europeanaidscinicalsociety.org/guidelinespdf/EACS-EuroGuidelines2009FullVersion.pdf>.

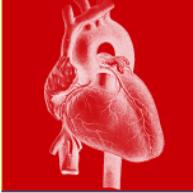
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VA, Veterans Health Administration. Primary care of veterans with HIV. April 2009. <http://www.hiv.va.gov/vahiv?page=pcm-00-00>.

General abbreviations:

ALP, alkaline phosphatase; **ALT**, alanine aminotransferase; **ART**, antiretroviral therapy; **AST**, aspartate aminotransferase; **CIN**, cervical intraepithelial neoplasia; **CKD**, chronic kidney disease; **CVD**, cardiovascular disease; **ECG**, electrocardiogram; **eGFR**, estimated glomerular filtration rate; **FRAX**, a fracture risk tool; **HAV**, hepatitis A virus; **HBsAg**, hepatitis B surface antigen; **HBV**, hepatitis B virus; **HCV**, hepatitis C virus; **HDL**, high-density lipoprotein cholesterol; **HIVAN**, HIV-associated nephropathy; **LDL**, low-density lipoprotein cholesterol; **MDRD**, modification of diet in renal disease method; **PSA**, prostate-specific antigen; **TDF**, tenofovir; **TG**, triglycerides; **UA/C**, urinary albumin creatinine ratio (mg/mmol) predominantly detects glomerular disease (use in patients with diabetes mellitus); **UP/C**, urinary total protein creatinine ratio (mg/mmol) detects total protein secondary to glomerular and tubular disease.





Two Top “Non-HIV” Threats to Aging Survivors: Heart Disease and Cancer

By Mark Mascolini

As the first and second leading causes of death in the United States,¹ heart disease and cancer also rank as the prime non-AIDS causes of morbidity and mortality in people with HIV. Researchers who study these diseases have long proposed simmering inflammation as a crucial factor in the genesis of heart disease, and many non-AIDS cancers can be traced more specifically to hepatitis viruses, Herpesviruses, and human papillomavirus (HPV). A persistently low CD4 count also apparently plays a role in both conditions.

Analyzing studies of cancer and heart disease risks and rates in people with HIV could be a full-time job. This brief review outlines some of the key issues and details results of some recent studies on immunodeficiency and risk of heart disease and non-AIDS cancers.

HIV clinician and researcher Keith Henry (University of Minnesota) considers three risk factor clusters for heart disease, with some overlap between clusters (**Table 1**).²

Table 1. Cardiovascular disease risk factors in people with HIV

Traditional factors	Antiretroviral-related factors	HIV-related factors
<ul style="list-style-type: none"> → Increased lipids → High blood pressure → Aging → Diabetes → Smoking 	<ul style="list-style-type: none"> → Lipid abnormalities → Glucose and insulin-related abnormalities 	<ul style="list-style-type: none"> → Decreased high-density lipoprotein cholesterol → Increased triglycerides → Immune activation → Increased thrombosis and fibrinolysis → Endothelial dysfunction
		Source: Henry K. ²

An array of studies found that people with HIV run a higher risk of heart disease than the general population.³⁻⁶ In the interview starting on page 5 of this issue, Harvard's Steven Grinspoon describes his rigorous and cogent case-control study assessing covert coronary artery disease in men with and without HIV, all of whom appeared to have a low heart disease risk according to Framingham score and other signals.⁷ Computed tomography angiography, which builds a "virtual angiogram" of major coronary arteries, found that 59% of the HIV group versus 34% of the non-HIV group had prevalent coronary atherosclerosis. Defining clinically significant coronary artery disease as luminal narrowing above 70%, Grinspoon uncovered serious coronary artery trouble in 5 men with HIV (6.5%) and none without HIV.

Using carotid intima-media thickness as an atherosclerosis indicator, a recent analysis of the FRAM trial cohort found significantly thicker internal and common carotid arteries in people with HIV than in a general population control group.⁸ Multivariate analysis showed that HIV itself raised the risk of carotid wall thickening as much as smoking, diabetes, or high blood pressure. FRAM investigators reckoned that HIV caused as much carotid wall damage as another 5 to 9 years of age.

Two recent studies yielded evidence that a lower latest CD4 count inflates the risk of cardiovascular disease. DAD cohort investigators determined that every 50-cell higher current CD4 count independently cut the risk of cardiovascular disease 3%.⁹ A smaller US study found a 14% lower risk of non-AIDS disease, including heart disease and non-AIDS cancers, with every 100-cell higher latest CD4 count.¹⁰

In his non-AIDS condition review,² Keith Henry sorts cancer risks into three bins in people with HIV: behavioral factors (including smoking, alcohol, and drug abuse), exposure to sexually transmitted oncogenic viruses (HBV, HCV, HPV, Epstein-Barr virus, and HHV-8), and immune deficiency resulting from decreased immune surveillance. A useful Veterans Administration handbook on caring for people with HIV lists eight non-AIDS cancers seen more in people with than without HIV:¹¹

- Anal squamous cell carcinoma
- Non-small-cell lung carcinoma
- Melanoma
- Colorectal carcinoma
- Hepatocellular carcinoma
- Oropharyngeal cancer
- Hodgkin lymphoma
- Vaginal cancer

In 2008 the US Adult and Adolescent Spectrum of Disease Project and HIV Outpatient Study investigators added leukemia and renal cancer to that list.¹² Last year a meta-analysis of 18 non-AIDS cancer studies charted a higher incidence in people with HIV versus the general population for infection-related cancers (anal, liver, Hodgkin lymphoma) and smoking-related cancer (lung, kidney, laryngeal).¹³

In the DAD study mentioned above,⁹ every 50-cell higher current CD4 count cut the risk of non-AIDS cancer 14%. French Aquitaine cohort investigators found that every year spent below a CD4 count of 500 cells/mm³ boosted the non-AIDS cancer risk 13%, while a current CD4 count below that mark doubled the risk.¹⁴ A Veterans Administration study recorded significantly lower first CD4 counts in HIV-infected people with

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anal cancer, Hodgkin lymphoma, and all non-AIDS cancers combined.¹⁵ The DAD team also found that a lower CD4 count independently predicted death from AIDS cancers and non-

AIDS cancer, as did older age, earlier calendar year, longer combination antiretroviral treatment, active HBV infection, and current or former smoking.¹⁶

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