Perspective

Immune Dysfunction, Inflammation, and Accelerated Aging in Patients on Antiretroviral Therapy

Patients receiving long-term antiretroviral therapy are at increased risk of age-associated non–AIDS-related morbidity and mortality compared with HIV-seronegative persons. Despite suppressive antiretroviral treatment, inflammation remains elevated and CD4+ count often remains low, with both measures predicting age-associated events. Several factors likely contribute to persistent inflammation and suboptimal gains during therapy. These include residual HIV replication, persistent virus expression, loss of immunoregulatory cells, collagen deposition, microbial translocation, chronic coinfections, and thymic dysfunction. How these factors influence disease outcomes and how chronic inflammation should be managed during therapy are the focus of intense ongoing investigation. Currently, the most practical advice is to start antiretroviral therapy early and to manage traditional risk factors for non–AIDS-related conditions aggressively. This article summarizes a presentation made by Steven G. Deeks, MD, at the International AIDS Society–USA continuing medical education program in Chicago in May 2009.

The most commonly stated goal of therapy is to prevent AIDS-related complications and prolong life. It might be argued, however, that the real goal of therapy should be to fully restore health and to prolong life in a manner that is not distinguishable from HIV-uninfected persons. The fact that we are now considering such a goal illustrates how successful antiretroviral therapy has been for those patients who can access and adhere to treatment with these drugs.

Current treatment provides the ability for patients to achieve and maintain undetectable levels of plasma HIV RNA and can successfully prevent AIDS-related morbidity and mortality, resulting in increased lifespan for HIV-infected patients. However, it has become evident that patients taking otherwise effective antiretroviral drugs remain at increased risk of non–AIDS-related morbidity and mortality. Many of these conditions are classically associated with the normal aging process but appear to be occurring at an earlier age in HIV-infected persons. These conditions include premature onset of cardiovascular disease, neurocognitive disease, bone disease, and cancer.

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Poorer Life Expectancy and Increased Risk of Non–AIDS-Related Conditions in Treated Patients

Depending on when antiretroviral therapy is started, life expectancy for HIV-infected persons in the modern treatment era is approximately 10 years to 30 years less than that for uninfected persons. For example, the number of additional years of life expectancy at age 20 is estimated to be 32 in patients with a CD4+ count nadir of less than 100 cells/µL, 42 years in those with a nadir of 100 cells/µL to 200 cells/µL, and 50 years in those with a nadir of greater than 200 cells/µL (Antiretroviral Therapy Cohort Collaboration et al, *Lancet,* 2008; Lohse et al, *Ann Intern Med,* 2007; Lewden et al, *JAIDS,* 2007). According to a prospective study from France, a normal life span can be expected only once a patient has been on effective therapy for several years and obtained a "normal" CD4+ count (> 500 cells/µL; Lewden et al, *JAIDS,* 2007).

Why are treated patients dying earlier than their non–HIV-infected peers? Numerous reports have indicated higher rates of non–AIDS-related conditions and events in patients treated for HIV disease than in age-matched control subjects, including cardiovascular disease, cancers, bone fractures and osteopenia, left ventricular dysfunction, liver failure, kidney failure, cognitive decline, and frailty (Klein et al, *JAIDS,* 2002; Hsue et al, *Circulation,* 2004; Mary-Kraus et al, *AIDS,* 2003; Grinspoon et al, *Circulation,* 2008; Triant et al, *J Clin Endocrinol Metab,* 2008; Arnsten et al, *AIDS,* 2007; Odden et al, *Arch Intern Med,* 2007; McCutchan et al, *AIDS,* 2007; Desquilbet et al, *J Gerontol A Biol Sci Med Sci,* 2007). In addition, there are many reports in the popular press regarding vague but not-uncommon complaints about long-term-treated patients feeling "older" than they should. These concerns are difficult to quantify epidemiologically, and may apply to only a small subset of treated patients, but they clearly represent a growing concern among some patients and their advocates (Deeks and Phillips, *BMJ,* 2009).

Contributing Factors

The poorer health and sense of health among patients receiving long-term suppressive antiretroviral therapy is likely related to several factors. Although many of the studies that have examined non–AIDS-related morbidity and mortality have controlled for age, the age of the population of HIV-infected patients is increasing, as is the frequency of age-related conditions. By the year 2015, it is expected that more than 50% of the HIV-infected population in the United States will be over the age of 50 years. Between 2001 and 2005, there were dramatic shifts in the age distribution of HIV-infected persons in the United States, with a reduction in the proportion below age 40 and an increase in the proportion above this threshold (Effros et al, *Clin Infect Dis,* 2008; Figure 1). The real concern, however, is not that the HIV-infected population is getting older (a natural outcome of effective

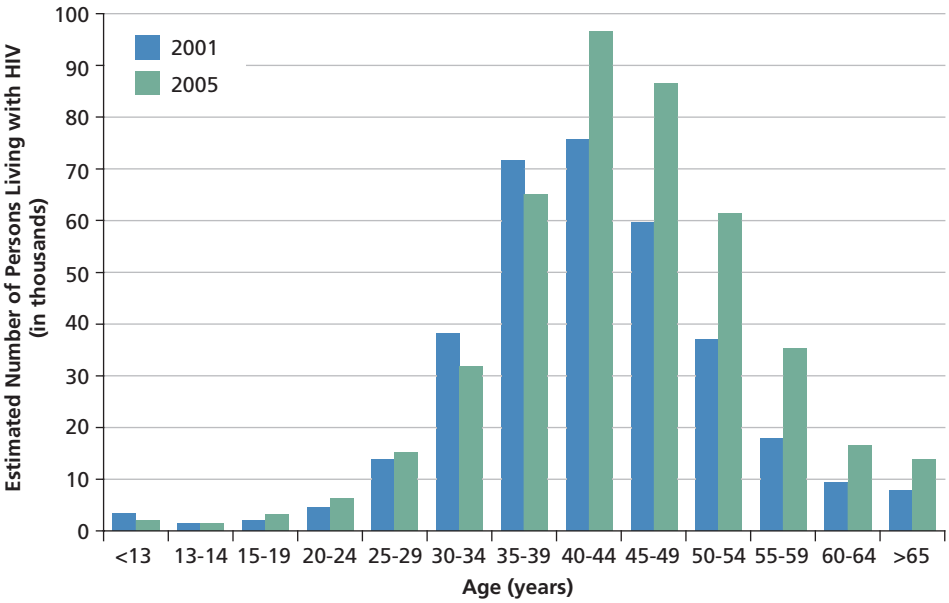

Figure 1. Age distribution of HIV-infected individuals living in the United States. Adapted from Luther and Wilkin, *Clin Geriatr Med,* 2007.

therapy), but that for any given age, HIV-infected persons are at increased risk of age-associated complications.

Also contributing to age-associated complications are the direct toxicities of antiretroviral drugs. A clear example of such effects was provided by the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study, which showed that long-term exposure to protease inhibitor (PI) treatment was independently associated with higher risk of cardiovascular disease (DAD Study Group et al, *N Engl J Med,* 2007). Other antiretroviral drugs may contribute to the aging process by causing renal dysfunction (eg, tenofovir) or heart disease (eg, abacavir).

Another major factor contributing to the non–AIDS-related, age-associated morbidity in treated HIV disease is the high prevalence of traditional health-related risk factors. For example, analysis of the MACS/WHIS (Multicenter AIDS Cohort Study/Women's Interagency HIV Study) population showed higher prevalence of risk factors such as low levels of high-density lipoprotein cholesterol, elevated levels of triglycerides, and smoking in HIV-infected patients than in their uninfected counterparts (Kaplan et al, *Clin Infect Dis,* 2007). Although many cohort studies have attempted to control for the increased prevalence of these factors, it is nearly impossible to fully address this concern. Hence, how much of the risk of age-associated complications can be attributed to traditional risk factors remains unclear. This question is important, as most of these risk factors are clearly modifiable, whereas most of the HIV-associated factors (immunodeficiency, inflammation) may be difficult to reverse.

It has become increasingly likely, however, that these non–AIDS-related events are more common in HIV disease, after adjustments are made for age, exposure to antiretroviral therapy, and traditional risk factors. An independent role of HIV disease in causing accelerated aging is suggested by findings that levels of inflammation do not normalize during antiretroviral therapy and that elevated inflammation levels and lower on-treatment CD4+ counts both predict risk of non–AIDS-related events.

Inflammation Is Elevated in Treated HIV Disease

Data from the SMART (Strategies for Management of Antiretroviral Therapy) study showed higher levels of the inflammatory or coagulation markers high-sensitivity C reactive protein (hs-CRP), interleukin-6 (IL-6), D-dimer, and cystatin C in patients with treated HIV disease than in uninfected control subjects (Neuhaus et al, CROI, 2009). Among patients on stable antiretroviral therapy in the SMART study compared with uninfected control subjects, the risk of any-cause mortality was statistically significantly increased for elevated IL-6 levels (odds ratio [OR], 2.4; $P = .03$). There were also nonsignificant trends suggesting an association between risk of all-cause mortality and elevated levels of hs-CRP (OR, 2.7; $P = .08$) and D-dimer (OR, 7.1; $P = .08$) (Kuller et al, *PLoS Medicine,* 2008).

Low On-Therapy CD4+ Counts Predict Mortality and Age-Related Events

A robust and growing series of studies indicate that suboptimal CD4+ cell gains in patients receiving antiretroviral

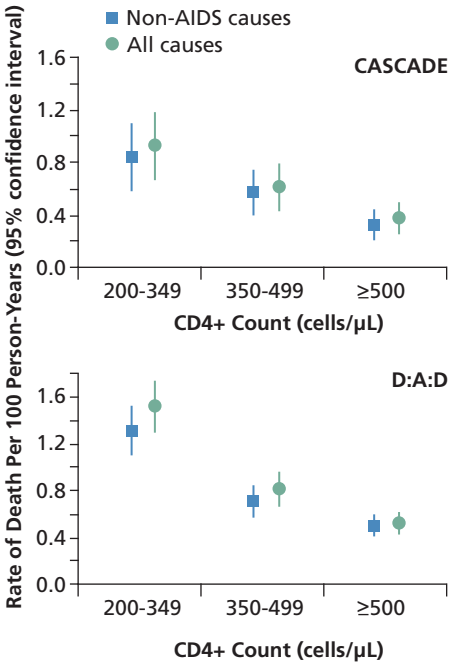

Figure 2. Rate of non–AIDS-related death and all-cause death, with 95% confidence intervals, according to on-treatment CD4+ count in the CASCADE (Concerted Action on Seroconversion to AIDS and Death in Europe) and D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) studies. Adapted from Phillips et al, *AIDS*, 2008, based on Smit et al, *JAIDS,* 2008, and Neaton and Grund, *Curr Opin HIV AIDS,* 2008.

therapy are associated with a higher risk of morbidity and mortality. For example, the risk of heart disease, liver disease, and non–AIDS-related cancer is higher in treated patients with lower CD4+ cell counts (Weber et al, CROI, 2005; Weber et al, *Arch Intern Med,* 2006; Phillips et al, *AIDS,* 2008; Baker et al, *AIDS,* 2008). Data from both the CASCADE (Concerted Action on Seroconversion to AIDS and Death in Europe) study in antiretroviral-naive patients and the D:A:D study indicate higher risk of death due to non–AIDS-related causes in patients with lower on-treatment CD4+ counts than in those with counts of 500 cells/μL or higher (Figure 2; Phillips et al, *AIDS,* 2008). Although an on-treatment CD4+ count below 500 cells/μL increases risk of non–AIDS-related events, whether risk of such events becomes comparable with the uninfected population if the CD4+ count is increased to and maintained above 500 cells/μL is still unknown.

Suboptimal CD4+ Count Gains Are Common in Treated Patients

Although most patients who start therapy with a CD4+ count above 200 cells/μL eventually achieve a "normal" CD4+ count (generally defined as > 500 cells/μL, considered on the low end of "normal"), many patients who defer therapy until late in disease fail to achieve a robust CD4+ cell gain. For example, recent data from the Center for AIDS Research Center Network of Integrated Clinical Systems (CNICS) indicate that 40% of patients starting treatment with a CD4+ count below 200 cells/μL failed to reach a count of 500 cells/μL over the course of 10 years of suppressive antiretroviral therapy (Kelley et al, *Clin Infect Dis,* 2009; Figure 3). A typical clinical observation is that patients starting treatment at a CD4+ count below 200 cells/μL tend to have a count that plateaus in the 200 cells/μL to 350 cells/μL range.

These findings should be considered in the context that antiretroviral treatment routinely is started at a CD4+ count below 200 cells/μL in developed areas of the world, including the United States. Data from 176 sites in 42

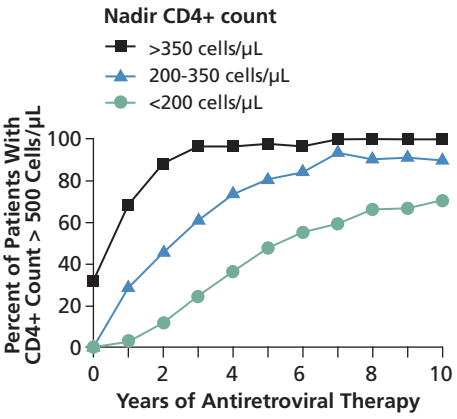

Figure **3**. Percentage of patients reaching a CD4+ count in the "normal" range (> 500 cells/μL) over 10 years of treatment, stratified by CD4+ count before initiation of therapy. Adapted from Kelley et al, *Clin Infect Dis,* 2009.

countries for 2003 to 2005 showed that compared with data from 2000, the CD4+ count at which antiretroviral therapy was started remained at approximately 150 cells/μL to 200 cells/μL in developed areas (187 cells/μL in the United States). The starting count was lower in resource-poor areas, although it had increased from 50 cells/μL to 100 cells/μL in sub-Saharan Africa (Egger, CROI, 2007).

Thus, the emerging picture of the health of HIV-infected patients who are being treated successfully with antiretroviral therapy in terms of viral suppression is as follows: lifespan is not normalized by antiretroviral treatment; the risk of age-associated diseases is higher than expected; inflammation remains elevated and predicts age-associated events; and CD4+ count often remains low and predicts age-associated events.

Inflammation and Immunosenescence in HIV Infection

Immunosenescence is a vague and poorly defined concept, but it generally refers to the well-known effects of aging on function of the adaptive immune system. The immune system of the very old (> 70 years of age) is characterized by increased populations of terminally differentiated effector CD8+ cells (which appear to be resistant to apoptosis), reduced levels of naive CD8+ cells, a reversed ratio of CD4+ to CD8+ cells, increased T-cell activation, increased levels of many inflammatory markers, and reduced T-cell proliferation. Most of these outcomes are accelerated by the presence of chronic persistent infections, with cytomegalovirus (CMV) infection most consistently implicated in the "aging" process. This picture of immunosenescence closely resembles observations in patients receiving long-term antiretroviral therapy, suggesting that ongoing HIV-related immune dysfunction and inflammation during antiretroviral treatment underlies premature aging in HIV-infected persons.

Collectively, these observations support an emerging model that posits that residual inflammation and suboptimal CD4+ count gains along with a hypercoagulable state can result from several ongoing factors. These include residual viral replication, persistent viral expression, the loss of immunoregulatory cells that should dampen immune activation, increased lymphoid fibrosis, and microbial translocation (Figure 4). Other factors contributing to ongoing inflammation may include chronic infection with CMV, hepatitis C virus

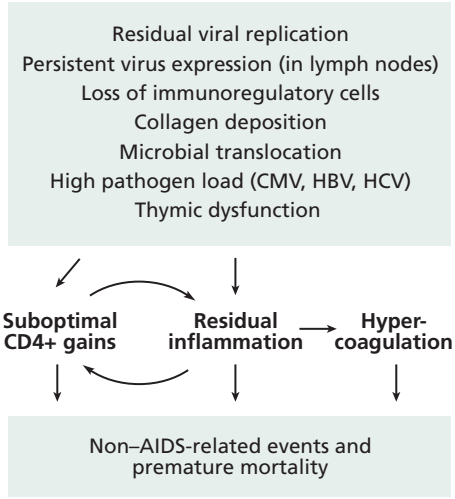

Figure **4**. Factors involved in increased risk of premature age-associated non–AIDS-related events in treated HIV disease. CMV indicates cytomegalovirus infection; HBV, hepatitis B infection; HCV, hepatitis C virus infection.

Table 1. Approaches to the Management of "Immunologic Failure" in HIV-Infected Patients

Start antiretroviral treatment early
Aggressively manage traditional risk factors (eg, incorporate use of statins, aspirin, others)
In addition:
Avoid offending antiretroviral medications (including the combination of tenofovir and didanosine)
Treat coinfections (hepatitis C virus, hepatitis B virus)
Consider a ritonavir-boosted, protease inhibitor–based regimen
Consider treatment intensification
Consider immune-based therapies (research studies): CC chemokine receptor 5 (CCR5) inhibitors, interleukin-7, growth hormone

(HCV), or hepatitis B virus (HBV), and thymic dysfunction. How these factors combine to affect CD4+ cell gains, immune function, and early morbidity and mortality is not known.

Can We Prevent or Reduce Inflammation and Accelerated Aging?

What can be done about ongoing inflammation, suboptimal CD4+ count gains, and "accelerated aging" during antiretroviral therapy? Although there are several potential approaches, most are still theoretical and should remain the focus of clinical research studies (Table 1). For now, the most practical approaches may be to start antiretroviral therapy early to prevent potentially irreversible immune dysfunction, including CD4+ loss, and to institute aggressive management of traditional risk factors—for example, use statins, aspirin, or other preventive antiinflammatory treatments. Perhaps antiretroviral therapy–treated HIV disease should be considered an important cardiovascular risk factor like smoking and diabetes that should prompt aggressive risk-factor treatment, irrespective of whether elevated lipid levels or other traditional cardiovascular risk markers are present.

With regard to the other potential approaches to reducing risk of non–AIDS-related morbidity and mortality, there is strong evidence that switching to the combination of tenofovir plus didanosine is associated with CD4+ count declines, apparently reflecting intercellular toxicity in T cells (Negredo et al, *AIDS,* 2004; Barreiro and Soriano, *J Antimicrob Chemother,* 2006). Some practitioners advocate dose modification when this combination is used, whereas others avoid use of the combination.

As certain coinfections may accelerate the aging process (or exacerbate the inflammatory state), consideration should be given to their treatment. This is particularly true for HBV and HCV infections. Unfortunately, no safe therapy is available for CMV, which is the major persistent infection associated with immunosenescence and age-associated morbidity.

Use of ritonavir-boosted (/r), PI-based regimens might be considered to achieve higher CD4+ counts during treatment. Many reports indicate greater increases in CD4+ count with PI/r regimens than with non–PI-based regimens, even when virologic response rate with the PI-based regimen is lower. For example, in ACTG (AIDS Clinical Trials Group) 5142, increases in CD4+ count at 96 weeks were 287 cells/μL with lopinavir/r plus 2 nucleoside analogue reverse transcriptase inhibitors (nRTIs), 273 cells/μL with the nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) efavirenz plus lopinavir/r, and 230 cells/μL with efavirenz plus 2 nRTIs (P = .001 across treatments) despite the finding that the proportion of patients with plasma HIV RNA levels below 50 copies/mL was lower in those receiving the PI-based regimens (Riddler et al, *N Engl J Med,* 2008). Although the strategy has not been examined in a clinical trial, it may make sense to consider switching patients with "stagnant" CD4+ counts from NNRTI-based regimens to PI/r-based regimens to attempt to achieve additional gains in the CD4+ count.

Similar findings have been made with the entry inhibitor maraviroc in the MERIT (Maraviroc Versus Efavirenz Regimens as Initial Therapy) trial, in which the combination of maraviroc plus fixed-dose zidovudine/lamivudine produced a statistically significantly greater increase in CD4+ count (169 vs 142 cells/μL) and CD8+ count at 48 weeks than did efavirenz plus zidovudine/lamivudine, despite a lower virologic response rate (Saag et al, IAC, 2007). Possibly, by blocking the CC chemokine receptor 5 (CCR5) coreceptor on T cells, maraviroc acts to prevent T cells from migrating to gut lymphoid tissue, where they may be killed by HIV. The strategy of intensified therapy including maraviroc is now being evaluated in patients with poorer CD4+ responses with antiretroviral therapy.

The phenomenon of ongoing viral production under suppressive antiretroviral therapy is also being investigated. Use of a super-sensitive assay in a University of California San Francisco cohort of patients achieving undetectable viral load on a standard assay during antiretroviral treatment showed that over years of follow-up, virus was detectable at approximately 80% of the measurement time points (Hatano et al, CROI, 2009). This evidence of ongoing viral production, and perhaps replication, suggests that adding another drug to current regimens may be a rational strategy for further reducing viral expression and potentially reducing inflammation. This strategy is being examined using the integrase inhibitor raltegravir.

A strategy of increasing CD4+ count that has not proved successful in improving clinical outcomes is the use of interleukin-2 (IL-2), which has long been recognized to boost CD4+ counts. The large-scale ESPRIT (Evaluation of Subcutaneous Proleukin [aldesleukin] in a Randomized International Trial) showed that although treatment including IL-2 produced an average 160-cell/μL

increase in CD4+ count versus control treatment over 7 years of follow-up ($P < .001$), there was no difference in rates of opportunistic conditions or death in the 2 groups (Losso et al, CROI, 2009). The CD4+ cells produced under IL-2 treatment are of an unusual phenotype, are long-lived, and may not be normal, characteristics that may account for the absence of benefits observed with IL-2 treatment.

The definitive proof of the failure of IL-2–induced CD4+ count boost to improve clinical outcome should not affect investigation of interleukin-7 (IL-7). Phase I trials of IL-7 have also shown impressive, rapid increases in CD4+ count (Levy et al, *J Clin Invest,* 2009). The CD4+ cells produced with IL-7 treatment include central memory cells and naive cells, deficits in which are thought to account for a major portion of the immune dysfunction in many patients treated long-term.

Growth hormone has also been shown to increase CD4+ count, apparently by stimulating thymic production of naive cells (Napolitano et al, *J Clin Invest,* 2008). However, growth hormone is not being used widely in patients receiving antiretroviral treatment, in part because of its toxic effects and expense.

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