Perspective

When to Start Antiretroviral Therapy: A Swinging Pendulum?

Although early initiation of antiretroviral treatment has long been associated with some benefit over later initiation, the magnitude of the benefit is becoming better defined with longer follow-up of large numbers of patients in cohort studies. These benefits have become more evident in part because of improvements in efficacy, tolerability, and convenience of antiretroviral treatment regimens. The benefits also reflect growing recognition of the effect of such treatment in reducing risk of both HIV-related and non-HIV-related complications that are not associated with low CD4+ cell count. On balance, currently available information supports using a CD4+ count of 350 cells/µL as a general threshold for initiating treatment, with immediate treatment warranted for selected patients, including those with conditions for which antiretroviral therapy is the best or only treatment. This article summarizes a presentation on when to initiate antiretroviral therapy made by Joel E. Gallant, MD, MPH, at an International AIDS Society–USA Continuing Medical Education course in New York in October 2007. The original presentation is available as a Webcast at www.iasusa.org.

Since the advent of antiretroviral treatment, the recommended CD4+ cell count threshold for starting therapy has steadily declined, with 2006 recommendations of the US Department of Health and Human Services (DHHS), the International AIDS Society–USA, and the British HIV Society all generally indicating a threshold of 200 cells/µL for initiating treatment in asymptomatic patients. The rationale for later treatment included the acknowledgment that eradication of HIV is not a realistic goal of antiretroviral therapy and recognition of both the long-term toxicities of treatment and the absence of data indicating that earlier treatment provided marked benefits. More recently, however, accumulating information on the effects of earlier versus later treatment has resulted in a shift toward earlier initiation of antiretroviral therapy.

Easier, More Potent, Less Toxic Therapy

Newer antiretroviral regimens are less complex, better tolerated, and more potent than older regimens. This combination of factors appears to be reflected in the higher rates of achievement and maintenance of plasma HIV RNA levels below 50 copies/mL at 48 weeks in more recent clinical trials. As shown in Figure 1, outcomes with ritonavir-boosted protease inhibitors (PIs) and nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs) as part of triple therapy (ie, newer regimens) are more effective than those with older regimens that used unboosted PIs and nucleoside analogue reverse transcriptase inhibitors (nRTIs) (Bartlett et al, *AIDS*, 2006). Similar information has come from observational cohorts. For example, data from patients in 5 clinic cohorts in Europe and Canada beginning treatment from 1996 to 2002 show greater increases in median CD4+ cell count and reduced frequency of virologic failure during the first year of treatment over this period (Figure 2); most cases of virologic failure in the more recent years resulted from loss to follow-up or treatment discontinuation rather than loss of antiviral efficacy (Lampe et al, *Arch Intern Med,* 2006).

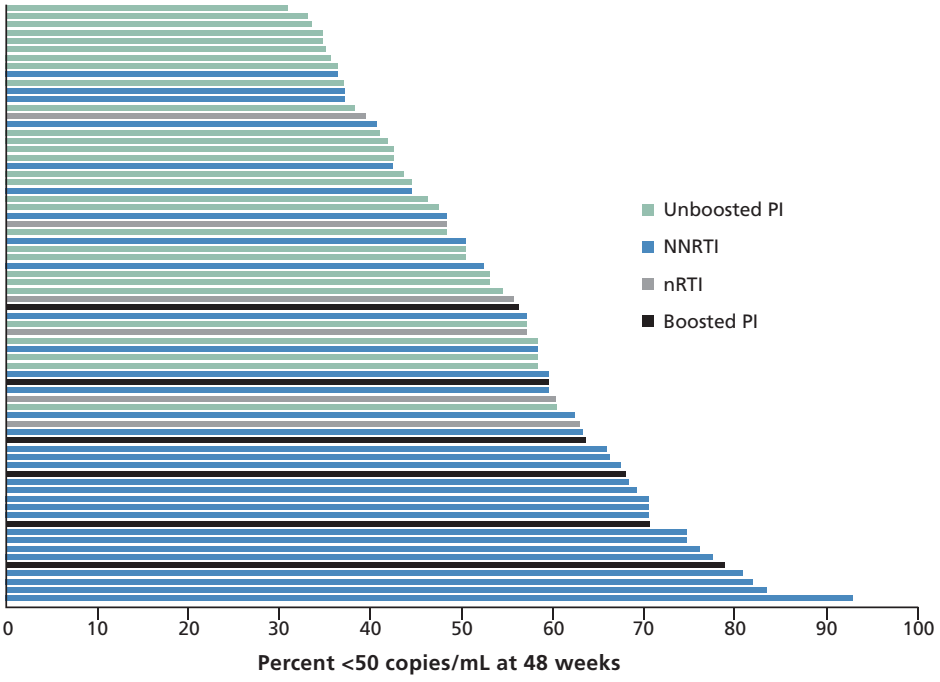

Figure **1.** Percent of patients with plasma HIV RNA levels below 50 copies/mL at 48 weeks with antiretroviral regimens containing indicated components. Unboosted indicates without ritonavir; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; nRTI, nucleoside analogue reverse transcriptase inhibitor; boosted, with low-dose ritonavir added. Adapted from Bartlett et al, *AIDS*, 2006.

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Benefits of Earlier Treatment Initiation in Cohort Studies

With longer follow-up and larger sample sizes, cohort studies have begun to yield a consistent picture of benefits from earlier initiation of antiretroviral therapy. Data from the Antiretroviral Therapy Cohort Collaborative, which involved 10,855 patients (excluding injection drug users) and more than 61,000 person-years of follow-up, showed reduced risk for AIDS or death among patients initiating treatment at CD4+ counts of 351 to 500 cells/μL compared with those starting at lower counts, with the benefit becoming more pronounced over time (Figure 3). The hazard ratio (HR) for AIDS was 3.68 (95% confidence interval [CI], 3.01-4.51) for patients starting treatment at CD4+ counts below 200 cells/μL versus counts of 201 to 350 cells/μL and 1.52 (95% CI, 1.10-2.10) for patients with counts below 350 cells/μL versus 351 to 500 cells/μL. Risk for AIDS or death was significantly increased in patients beginning treatment at counts below 200 cells/μL versus 201 to 350 cells/μL (HR, 2.93; 95% CI, 2.41-3.57) and nonsignificantly increased for those starting at counts less than 350 cells/μL versus 351 to 500 cells/μL (HR, 1.26; 95% CI, 0.94-1.68) (May et al, *AIDS*, 2007).

Similarly, data from 4421 patients in the HIV Outpatient Study (HOPS) cohort show incremental reductions in incidence of both opportunistic infections and mortality with treatment initiated at various CD4+ counts including 200 to 349 cells/μL, 350 to 499 cells/μL, and greater than or equal to 500 cells/μL (Figure 3). Major mutations were 50% less likely to occur in patients starting treatment at counts above 350 cells/μL versus at counts below 200 cells/μL, despite greater treatment exposure among the former, and more nRTI toxicity (anemia, neuropathy, renal insufficiency) occurred with initiation of antiretroviral therapy at lower CD4+ counts (Lichtenstein et al, CROI, 2006). Data on 280 patients with virologic suppression for up to 6 years in the Johns Hopkins HIV cohort show that CD4+ counts returned to near-normal levels only in patients with pretreatment counts above 350 cells/μL (Figure 3). The rate of progression to AIDS or death was statistically significantly higher over time in patients with pretreatment counts below 200 and from 201 to 350 cells/μL versus in those with counts above 350 cells/μL. Overall, AIDS developed in 1.5% of patients starting at counts above 350 cells/μL, in 12% of those starting at 201 to 350 cells/μL, and in 13% of those starting below 200 cells/μL (Moore and Keruly, *Clin Infect Dis*, 2007).

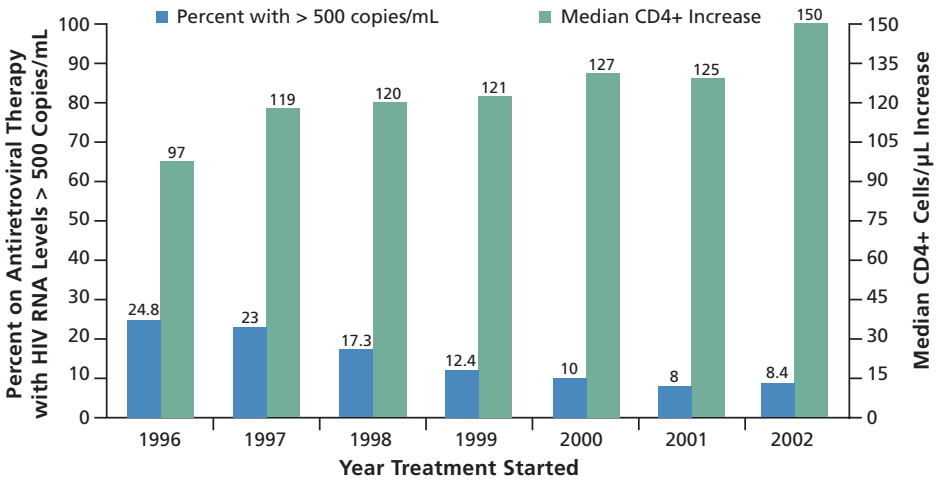

Figure **2.** Rates of virologic failure and median CD4+ cell count increases during the first year of antiretroviral therapy by year of starting treatment in 5 clinic cohorts. Adapted from Lampe et al, *Arch Intern Med*, 2006.

Decreased Transmission Risk

Suppressive therapy begun earlier might reduce HIV transmission. The ability to reduce transmission risk via suppressive therapy has been demonstrated in the setting of perinatal transmission. Considerable evidence from observational studies indicates that viral load is strongly correlated with transmission risk; for example, a study among HIV-discordant couples in Rakai, Uganda, showed that transmission risk was exceedingly low when the infected partner had a plasma HIV RNA level below 1700 copies/mL, with risk incrementally increasing with levels of 1700 to 12,500 copies/mL, 12,500 to 38,500 copies/mL, and above 35,000 copies/mL (with the presence of genital ulcer disease markedly increasing risk in each of these categories) (Gray et al, *Lancet,* 2001).

An ongoing multinational trial is examining whether immediate early therapy in infected individuals in discordant couples reduces transmission risk compared with therapy started according to current guidelines.

Preservation of R5-tropic Virus

Virus with R5-coreceptor tropism is associated with less rapid disease progression than virus with X4-coreceptor tropism or dual/mixed-tropic virus, and R5-tropic virus predominates in earlier infection. Although the precise mechanisms of the switch in tropism are unclear, the switch may be related to nadir CD4+ cell count, and earlier antiretroviral treatment might prevent or delay the switch. Screening in the MERIT study showed that among 1428 antiretroviral therapy–naive patients, 85% had R5-tropic virus, 0.3% had X4-tropic virus, and 14.7% had dual/mixed-tropic virus, whereas among 2560 antiretroviral therapy–experienced patients screening for the MOTIVATE 1 and 2 studies, the respective proportions were 56%, 2.6%, and 41.4% (Coakley et al, International Workshop Targeting HIV Entry, 2006).

A recent example of the effect of tropism is provided by data from 294 antiretroviral therapy–naive patients with baseline CD4+ counts above 450 cells/μL and plasma HIV RNA levels

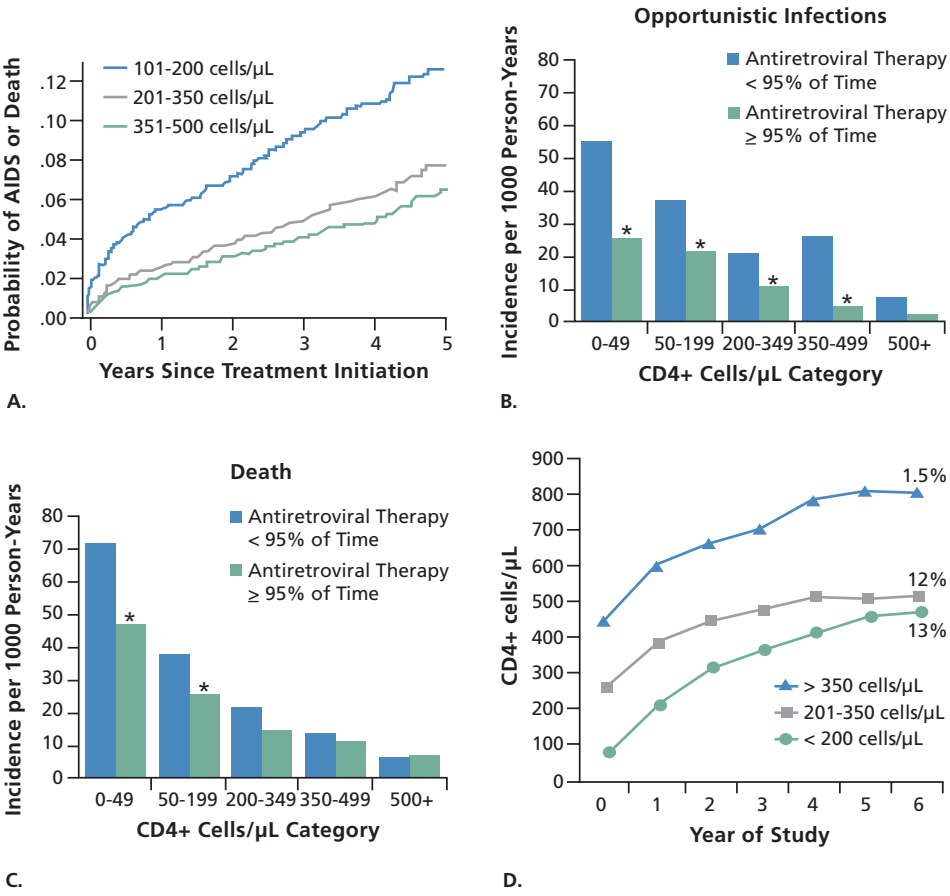

Figure **3.** A: Cumulative probability of AIDS or death by initial CD4+ cell count from the Antiretroviral Therapy Cohort Collaboration. Adapted from May et al, *AIDS*, 2007. Incidence of opportunistic infections (B) and death (C) according to initial CD4+ count (and percent of time on antiretroviral treatment) in the HIV Outpatient Study (HOPS) cohort. Asterisks indicate data for which the difference based on percent of antiretroviral use is statistically significant at $P < .05$. Adapted from Lichtenstein, CROI, 2006. D: CD4+ count increase according to initial CD4+ count in patients with viral suppression on antiretroviral therapy in the Johns Hopkins HIV cohort. Percents are percent of patients in each group who developed AIDS; $P < .05$ for the top curve data compared with the bottom curve data. Adapted from Moore and Keruly, *Clin Infect Dis*, 2007.

above 1000 copies/mL in the Community Program for Clinical Research on AIDS (CPCRA) 060 study. Of these, 262 patients (89%) had R5-tropic virus, and 32 (11%) had dual/mixed-tropic virus. The relative risk of progression, defined as CD4+ count less than 350 cells/μL, initiation of antiretroviral therapy, or death, was 2.11 (95% CI, 1.25-3.57; $P = .005$) for dual/mixed- versus R5-tropic virus; the significant effect of tropism in predicting progression was independent of viral load and CD4+ cell count (Goetz et al, IAC, 2007). In addition to potentially slowing progression by preventing the tropism switch, earlier initiation of antiretroviral treatment might also thus preserve the utility of maraviroc or other CCR5-antagonist antiretroviral drugs.

Cost-effectiveness

Published data support the notion that early initiation of antiretroviral therapy is cost-effective. Markov modeling using the Johns Hopkins Moore Clinic HIV database showed that beginning treatment at CD4+ counts greater than 350 cells/μL versus at counts of 200 to 350 cells/μL resulted in an incremental cost per quality-adjusted life-year (QALY) gained of $31,226, which is well within the limits of current standards of cost-effectiveness, representing greater cost-effectiveness than such widely accepted interventions as coronary bypass, hemodialysis, screening mammograms, and mandatory seat belt laws (Mauskopf et al, *JAIDS*, 2005).

Prevention of Specific Complications of HIV Infection

Some complications of HIV infection are more closely related to low CD4+ count than others. Thus, use of a CD4+ count of 200 cells/μL as a threshold for treatment is effective in preventing such complications as *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia, toxoplasmosis, cryptosporidiosis, and *Mycobacterium avium* complex. However, other complications, including neurocognitive impairment, non-Hodgkin's lymphoma, peripheral neuropathy, human papilloma virus-associated dysplasia/cancer, Kaposi's sarcoma, and HIV-associated nephropathy, are less dependent on CD4+ count. These conditions can be observed at high CD4+ cell counts, frequently in the setting of persistent high viral load, and earlier initiation of treatment might thus reduce risk for these complications.

Prevention of Non-opportunistic Complications

Earlier treatment might also prevent non-opportunistic complications associated with HIV-related immunosuppression. Numerous recent studies have shown that non-opportunistic conditions, including various bacterial infections, liver disease, kidney disease, and non-AIDS-defining malignancies, occur at higher and CD4+ count–dependent rates in individuals with HIV infection. In the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study of more than 23,000 patients with HIV infection, 1248 patients (5.4%) died between 2000 and 2004, of whom 82% were on antiretroviral therapy. Figure 4 shows that both HIV-associated and non–HIV-associated mortality were related to CD4+ cell count in these patients (Weber et al, CROI, 2005).

Similarly, data on 1397 patients starting antiretroviral therapy in the

Flexible Initial Retroviral Suppressive Therapies (FIRST) study showed that the incidence of non-opportunistic diseases declined with higher CD4+ cell count (Figure 4), with the most recent CD4+ count being an independent predictor of risk for non-opportunistic disease. At CD4+ counts above 200 cells/μL, non-opportunistic disease events accounted for more morbidity and mortality than did opportunistic disease (Baker et al, CROI, 2007).

The Strategies for Management of Antiretroviral Therapy (SMART) trial randomized patients on antiretroviral therapy to continue treatment or to stop when the CD4+ count was above 350 cells/μL and resume treatment when the count dropped to 250 cells/μL. The trial showed that interrupting therapy was associated with a statistically significantly increased risk of opportunistic infection or death (HR, 2.6), opportunistic infection (HR, 3.6), or non-opportunistic infection death (HR, 1.8) (SMART Study Group et al, *N Engl J Med,* 2006). Analysis of cardiovascular outcomes in the trial showed that interrupting treatment was associated with an increased risk of the composite of clinical myocardial infarction (MI), silent MI, coronary disease requiring invasive procedure, or cardiovascular death (relative hazard [RH], 1.57; P = .05); the foregoing plus peripheral vascular disease, heart failure, or coronary disease requiring medication (RH, 1.49; P = .03); and the foregoing plus unobserved death from unknown cause (RH, 1.58; P = .009). These findings occurred in the context of a significantly higher ratio of total cholesterol to high-density lipoprotein cholesterol in the treatment-interruption group (Phillips et al, CROI, 2007).

A subset analysis in SMART among patients who were either antiretroviral therapy–naive or not receiving antiretroviral therapy at randomization to immediate (ie, continuous) treatment (n = 249, 131 antiretroviral therapy–naive) or deferred (ie, interrupted) treatment (n = 228, 118 antiretroviral therapy–naive) showed that deferred treatment was associated with a 5-fold increased risk of the composite of opportunistic infection, opportunistic infection or death, or serious non-AIDS events (HR, 5.08; P = .001) (Figure 4) (Emery, IAC, 2007). In the Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE) study, non-AIDS-related deaths accounted for more than 50% of 597 deaths in 9858 patients with a median follow-up period of 8 years from seroconversion; current and nadir CD4+ count and time with CD4+ count below 350 cells/μL were associated with both AIDS deaths and non-AIDS deaths such as infections, liver disease, or malignancy (Marin et al, IAC, 2007).

Potential Immunologic Benefits

Naive and memory CD4+ cells reside in gut-associated lymphoid tissue. Studies of the pathogenesis of acute HIV infection indicate that gut-associated CD4+ cells decline dramatically in early infection, and the hypothesis is that microbial translocation and immune stimulation in the gut drive the continuing loss of CD4+ cells. Earlier (asymptomatic) treatment with antiretroviral therapy is associated with significantly greater increases in the central memory CD4+ cell populations of Peyer's patches than is late (symptomatic) treatment (Estes et al, CROI, 2007). Thus, earlier treatment may lead to improved immune reconstitution. It is unclear, however, at what point early treatment would need to begin to derive clinical benefit in this process and what the precise clinical consequences of such intervention might be.

Special Considerations: Treatment Above 350 CD4+ Cells/μL

In contrast to previous versions of the DHHS guidelines, which included cat-

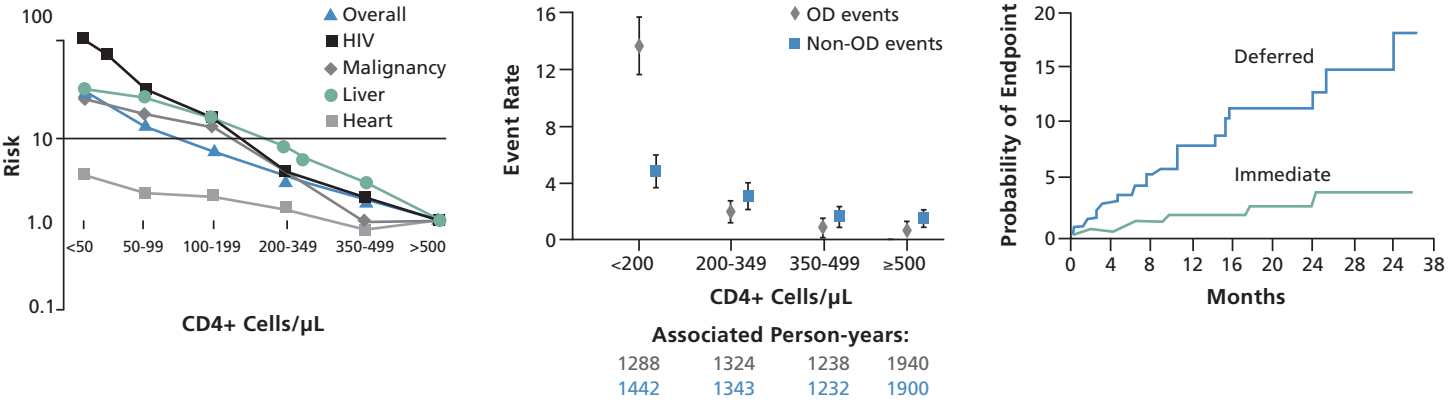

Figure **4.** Left: Relative risk of HIV-related mortality (HIV) and non-HIV-related mortality (malignancy, liver, heart) by CD4+ count <500 versus >500 cells/μL in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. Adapted from Weber et al, CROI, 2005. Center: Rates (events per 100 person-years of observation) of opportunistic disease (OD) and non-OD events by CD4+ count in the Flexible Initial Retroviral Suppressive Therapies (FIRST) study. Adapted from Baker et al, CROI, 2007. Right: Risk for reaching a composite endpoint of opportunistic infection, opportunistic infection or death, or serious non-AIDS event among patients with deferred versus immediate antiretroviral therapy in a subset study in the Strategies for Management of Antiretroviral Therapy (SMART) trial (hazzard ratio, 5.08; 95% CI, 1.91-13.5; P = .001). Adapted from Emery, IAC, 2007.

egories of patients who should not be treated, the current guidelines point out that antiretroviral therapy is indicated or could be considered in some patients whose count does not fall below the 350 cell/μL threshold. The current guidelines (US DHHS, http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf) recommend initiation of antiretroviral therapy at any CD4+ cell count in patients with HIV/HBV coinfection who need treatment for HBV. It is easier to treat both infections simultaneously (using dual-therapy against HBV, tenofovir plus either emtricitabine or lamivudine plus an NNRTI or boosted PI) than it is to attempt to treat either virus alone with drugs that are active against only 1 of the 2 viruses.

The only effective treatment for HIV-associated nephropathy (HIVAN) is antiretroviral therapy. For that reason, the DHHS guidelines also recommend initiation of antiretroviral therapy regardless of CD4+ cell count in patients in whom HIVAN is diagnosed.

Pregnant women should also receive antiretroviral therapy regardless of CD4 + cell count to prevent mother-to-child transmission. Therapy can be stopped after delivery, although in light of the findings of the SMART study, some experts would consider continuing therapy in a woman who was doing well on a suppressive regimen.

Other factors that might prompt consideration of earlier therapy might include rate of CD4+ decline, a high baseline viral load, older age, or concerns about prevention of HIV transmission, as for patients with seronegative partners or patients engaging in ongoing high-risk activity.

Progression of hepatitis C virus (HCV) disease is associated with CD4+ count in coinfected persons, so there is some support for earlier treatment of HIV infection in such patients. This remains controversial, however, given the lack of clinical data and the concern over the potential hepatotoxicity of some antiretroviral drugs. Nevertheless, early antiretroviral therapy could be considered for highly motivated HIV patients who need treatment for HCV disease as well.

Caveats and Concerns

Much of the data supporting earlier initiation of antiretroviral treatment comes from observational studies. One obvious problem with regard to interpreting data is that patients enrolled in such studies who start treatment with advanced disease may do poorly for reasons unrelated to CD4+ cell count (eg, disenfranchisement, illicit drug use, mental illness, homelessness). By the same token, those beginning treatment early are more likely to be highly motivated patients who adhere to therapy. It is unclear whether we will ever have data from a randomized, controlled trial of this issue. A large trial is currently being planned. However, prior attempts to enroll patients in such trials have failed, in part because of the reluctance on the part of both clinicians and patients to leave such an important decision to randomization. The available observational data, while not definitive, provide compelling support for earlier therapy. A large, randomized trial would also be expensive and time-consuming, and it is unclear whether the questions asked or the CD4+ count thresholds examined in such a trial would still be considered relevant by the time the results became available.

A sobering consideration in this discussion is that for much of the HIV-infected population, a recommendation to start antiretroviral treatment at a CD4+ count of 350 cells/μL means little in terms of actual practice. Figure 5 shows CD4+ count at the start of treatment in various worldwide locales for 2003 through 2005, indicating that treatment in many settings is routinely begun at more advanced stages of disease. Frequently, US practitioners first encounter patients when they seek treatment for an acute opportunistic infection, at which point their CD4+ count may be less than 100 cells/μL rather than above 350 cells/μL. Indeed, the starting CD4+ count at first visit in the United States is below that of many developed nations, indicating the true state of HIV health care in this country. It is hoped that implementation of the new CDC recommendations for routine HIV testing will result in earlier diagnosis of HIV infection, allowing more infected individuals to benefit from earlier therapy.

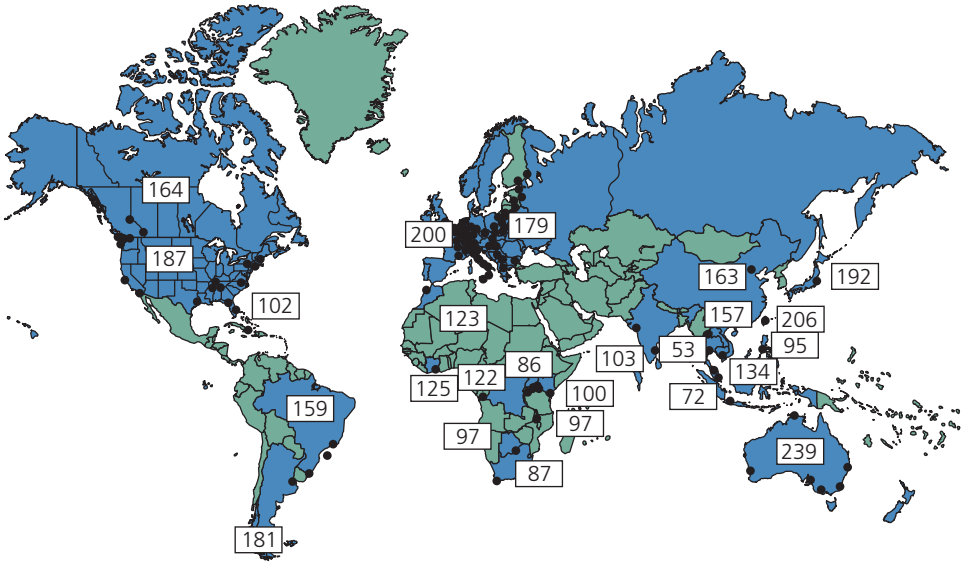

Figure **5.** CD4+ counts (cells/μL) at initiation of antiretroviral therapy in 2003 to 2005. Since 2000, CD4+ count at initiation of treatment has increased in sub-Saharan Africa from 50 to 100 cells/μL, has remained stable in developed countries at approximately 150 to 200 cells/μL, and is lower in the United States than in many other resource-rich countries. Adapted from Egger, CROI, 2007.

Initiating Antiretroviral Therapy in the Setting of Acute Opportunistic Infections

Antiretroviral therapy should be started immediately in patients with conditions for which it is the best or only therapy, such as progressive multifocal leukoencephalopathy, HIV-associated dementia, HIV-associated nephropathy, Kaposi's sarcoma, cryptosporidiosis, or microsporidiosis, and in patients with conditions for which a higher CD4+ cell count improves prognosis, such as primary central nervous system lymphoma or non-Hodgkin's lymphoma. There is also evidence that early initiation of antiretroviral therapy may improve outcome in patients with *Pneumocystis jiroveci* pneumonia (Zolopa et al, CROI, 2008). The data are less clear for other opportunistic infections. For some, such as tuberculosis, *Mycobacterium avium* complex, and cryptococcal meningitis, concerns about the risk of delayed antiretroviral therapy must be balanced against the risk of the immune reconstitution inflammatory syndrome when antiretroviral therapy and treatment of the opportunistic infection are initiated simultaneously. Simultaneous initiation of antiretroviral therapy and therapy for tuberculosis can also lead to overlapping drug toxicity and important drug interactions between rifamycins and antiretroviral agents.

Bottom Line: When to Start

Treatment should be started in any patient with a CD4+ count below 350 cells/µL, any patient with HIV and HBV coinfection requiring treatment for HBV infection, pregnant patients, and patients with HIVAN and other conditions that require antiretroviral therapy, as noted above. Treatment might also be considered at CD4+ counts above 350 cells/µL in selected patients with rapid CD4+ count declines, patients with high viral loads, infected patients with HIV-seronegative partners, and infected patients engaging in high-risk behaviors.

There is clearly a possibility that future guidelines will recommend even earlier treatment. Given the recent improvements in the risk:benefit ratio of antiretroviral therapy, a case could be made for initiating antiretroviral therapy at any CD4+ count in a motivated patient who wants to be treated and has evidence of HIV progression. This approach is not currently the standard of care, however.

Treatment can be deferred in patients with some acute opportunistic infections, as noted above; long-term nonprogressors or those with high CD4+ count and low viral load who might fit into this category after further follow-up; patients who are not ready or motivated to start treatment or not likely to be adherent; and patients with extensive transmitted resistance and few treatment options who are not in immediate need of antiretroviral therapy.

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