The decision about when to start antiretroviral treatment is among the most vexing puzzles in the field of HIV management.

HIV begins killing CD4 T-cells—key players in the body’s immune response—from the time of initial infection, yet many HIV positive people go for years without experiencing clinical symptoms. Antiretroviral drugs effectively suppress viral replication and enable CD4 cell recovery, but also can lead to side effects that are at best bothersome and at worst debilitating or even fatal.

While the optimal time to begin treatment for many diseases is as soon as possible after infection, in the case of HIV the decision involves balancing the benefits of preventing immune system decline—as well as other harmful effects of HIV infection that are only beginning to be understood—against the inconvenience, expense, and health risks associated with antiretroviral therapy.

This calculation has never been static, changing with the development of better medications, advances in management of drug-related toxicities, and improved understanding of HIV and its effects on the body.

In late 2007, U.S. and European antiretroviral treatment guidelines were updated to recommend earlier therapy, beginning when a person’s CD4 cell count falls below 350 cells/mm³. Yet a growing body of evidence suggests that starting treatment even earlier may lead to better outcomes.

Ultimately, the goal of HIV treatment is not just to lower viral load and raise CD4 cell counts, but to improve quality of life and extend survival.

This article presents an overview of shifts in expert opinion about when to start antiretroviral therapy, as well as recent data on the benefits and possible drawbacks of earlier treatment.

**SHIFTING VIEWS OF ANTI-HIV THERAPY**

There are many factors to consider when deciding when to begin treatment for HIV, including disease symptoms, overall health, readiness to start and stick to therapy, and individual risk factors that affect the likelihood of disease progression and drug-related complications.

Clinicians learned early in the HIV/AIDS epidemic that the risk of opportunistic illnesses increased as an individual’s CD4 cell count dropped, with the incidence of various infections and malignancies rising sharply as the level fell below 200, 100, or 50 cells/mm³. In the 1990s, researchers demonstrated that plasma HIV RNA level, or viral load—a sign of ongoing viral replication—was also a strong predictor of disease progression.

Antiretroviral drugs were developed to halt HIV replication and in-
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fection of new cells, thereby preventing immune function from falling into the “danger zone” below 200 cells/mm³, or enabling CD4 cell recovery if this had already occurred. Both CD4 cell count and viral load have been widely adopted as key indicators of when to start antiretroviral therapy and how well treatment is working.

HIT EARLY, HIT HARD

The introduction of the first protease inhibitors in the mid-1990s allowed construction of highly active antiretroviral therapy (HAART) regimens combining drugs from multiple classes that target different steps of the HIV lifecycle. As HAART began to dramatically reduce the risk of disease progression and death, some researchers advocated a “hit early, hit hard” approach in the hope that starting treatment early might limit viral load, minimize immune system damage, and possibly even eradicate the virus.

The first version of the U.S. Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, published in April 1998, recommended initiation of antiretroviral therapy for asymptomatic individuals when the CD4 count fell below 500 cells/mm³ or viral load rose above 20,000 copies/mL; above 500 cells/mm³, patients could be either observed or offered therapy.

DRAWBACKS OF HAART BECOME CLEAR

Some experts, including many European clinicians, were skeptical about the value of early antiretroviral therapy, noting that HAART had only recently been introduced and there was no evidence from long-term studies to show that starting treatment with a high CD4 count provided any additional benefit in terms of delayed disease progression or prolonged survival to balance the risks of earlier therapy.

In the late 1990s, this view appeared to be vindicated. At that time, antiretroviral regimens were difficult to take—often requiring handfuls of pills—which encouraged “treatment fatigue” and pessimism about the prospect of long-term medication adherence.

Furthermore, it soon became evident that antiretroviral therapy could cause unexpected and worrisome side effects, such as body shape changes, mitochondrial toxicity, and metabolic abnormalities associated with increased risk of cardiovascular disease. Such toxicities led many patients who had already started therapy to interrupt treatment, and made others reluctant to start until absolutely necessary. At the same time, emerging data indicated that existing antiretroviral drugs were unlikely to completely eliminate HIV from the body, given the tenacity of latent virus in “reservoir” sites, such as the gut, brain, and lymph nodes. This implied that treatment would probably have to continue for many years—if not for a lifetime—and therefore had to be tolerable over the long term.

In addition, growing concern about the evolution of drug-resistant viral strains and the slow pace of new drug development underlined the importance of preserving future treatment options by not “using up” available therapies too quickly.

DEFERRED THERAPY GAINS GROUND

The turn of the century saw a shift toward delayed treatment, aiming to start antiretroviral therapy before immune dysfunction approached the danger zone for AIDS-related illnesses, but not too much sooner. There was also growing interest in various strategies for reducing the cumulative time spent on intensive HAART, including structured treatment interruption, class-sparing regimens, and maintenance therapy with fewer drugs.

On the basis of studies showing that progression to AIDS-defining illnesses was infrequent among people with 350–500 cells/mm³, as well as increasing evidence that with more potent regimens, even individuals who started therapy with a low CD4 cell nadir (lowest-ever level) could achieve good viral suppression and significant immune recovery, the DHHS issued revised guidelines in February 2001, recommending that asymptomatic individuals start treatment when the CD4 count fell below 350 cells/mm³ or viral load rose above 55,000 copies/mL.

Yet the panel acknowledged uncertainty about this change; among the risks of deferred therapy, they wrote, was “the theoretical possibility that some damage to the immune system that might otherwise be salvaged by earlier therapy is irreversible.” They also noted that the change could sacrifice some of the public health benefit of early treatment in reducing HIV transmission (see sidebar, page 19).

The more conservative approach held sway for several years. In the October 2004 revision of the guidelines, the DHHS panel reaffirmed the desirability of starting therapy before the CD4 cell count fell below 200 cells/mm³, recommending that individuals within the 200–350 cells/mm³ range be offered treatment. They added, however, that “most experienced clinicians defer therapy” for asymptomatic patients with more than 350 cells/mm³ and HIV RNA above 100,000 copies/mL, while people with the same CD4 count and a lower viral load should not start treatment. Yet there was never a consensus about the new threshold, and some experts felt the pendulum had swung too far in the direction of delayed treatment.

THE PENDULUM SWINGS AGAIN

The past few years have witnessed new evidence suggesting that earlier treatment may indeed lead to better outcomes, including subtle and difficult-to-measure benefits beyond reduced risk of progression to AIDS or death.
When to Start Antiretroviral Treatment

PUBLIC HEALTH BENEFITS OF EARLY TREATMENT

Soon after HIV infection, people typically have a high viral load in their blood plasma and semen or cervical-vaginal fluid, which raises the likelihood of transmitting the virus through sex, needle sharing, or during pregnancy, delivery, or breast-feeding. By lowering viral load—ideally to an undetectable level—antiretroviral therapy reduces the risk of passing on HIV.

Using antiretroviral drugs to reduce a pregnant woman’s viral load dramatically lowers the risk of perinatal HIV transmission, and the same may hold true for other routes of transmission. Julio Montaner and colleagues used mathematical models to estimate that if all people with HIV in low- and middle-income countries were to start antiretroviral therapy regardless of CD4 cell count, the rate of new infections could decline by as much as 70%. They estimated that in Canada, HIV incidence could decline by two-thirds if everyone started at the 350 cells/mm³ threshold.

Universal antiretroviral therapy remains controversial, however, due to concerns about cost, allocation of scarce drugs, development of drug resistance, and the risk of side effects among people who do not yet need treatment for their own health.

While the danger of classic AIDS-defining opportunistic infections and malignancies remains low for people with a CD4 count below 350 cells/mm³, it has become increasingly apparent that the risk of several other conditions not traditionally considered to be HIV- or AIDS-related (such as cardiovascular disease and certain non-AIDS-defining cancers) begins to rise as immune function declines, well before it falls below 200 cells/mm³.

Another line of evidence indicates that people who start antiretroviral therapy with the least immune suppression may be able to achieve higher CD4 counts, potentially matching those of HIV-negative individuals. In addition, potent modern antiretroviral regimens (especially those containing boosted protease inhibitors) are less likely to allow drug resistance to emerge, and the approval of new drug classes has lessened concern about running out of drugs that might be needed later.

Equally important, modern regimens are easier to take than older combinations, thanks to such advances as low-dose ritonavir (Norvir) boosting, once-daily regimens, and coformulations that combine two or more drugs in a single pill. Some of the most toxic agents—including full-dose ritonavir and the “d-drugs” d4T (stavudine; Zerit) and ddi (didanosine; Videx)—have fallen out of favor, and clinicians have learned to better manage antiretroviral side effects.

In October 2007, the European AIDS Clinical Society issued updated guidelines advising that asymptomatic HIV positive individuals, regardless of viral load, should start antiretroviral therapy when their CD4 count falls below 350 cells/mm³. The DHHS panel followed suit, with revised guidelines released in December 2007, as did the British HIV Association and the Southern African HIV Clinicians Society.

The optimal time to begin therapy in asymptomatic people with a CD4 cell count above 350 cells/mm³ remains “not well defined,” according to the DHHS panel. “The decision about whether or not to start treatment in these patients should take into account the potential benefits and risks associated with therapy, comorbidities, and patient readiness and willingness to adhere to long-term treatment.”

Yet a growing number of HIV positive individuals and their health care providers, persuaded by data from recent studies, are now considering treatment at CD4 counts within the 350–500 cells/mm³ range and even higher.

TREATMENT DURING PRIMARY INFECTION

Primary or acute HIV infection refers to the period when the virus first establishes itself in the body. The primary phase is generally considered to be the first six (or sometimes 12) months after exposure. Alternatively, some experts define it as the period—typically three to six months—before seroconversion, the point at which the body produces detectable antibodies against the virus; during this “window period,” a standard antibody test may produce negative or indeterminate results.

Viral load testing (also called nucleic acid amplification testing, or NAAT) can be used to diagnose HIV infection but is not FDA-approved for this purpose, and the test’s expense and the difficulty of interpreting results limit its use. (“Pooled PCR” testing, which applies both the viral load test and standard antibody test to a combined blood sample from multiple individuals, offers a less expensive alternative and, if widely adopted, could help to detect cases earlier than traditional testing approaches.)

Primary HIV infection is often asymptomatic and is therefore frequently missed by newly infected individuals and their health care providers. About half of people with primary infection do experience acute antiretroviral syndrome, characterized by such
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symptoms as fever, fatigue, rash, and swollen lymph nodes, but because these are often mistaken for the flu or another illness, many cases of primary HIV infection go undiagnosed.

**IMPACT ON VIRAL LOAD, CD4 COUNT, AND IMMUNE FUNCTION**

Some researchers have hypothesized that starting antiretroviral therapy around the time of initial infection may improve the immune system’s ability to fight HIV, limiting the spread of the virus throughout the body and reducing the rate of disease progression.

Indeed, most individuals who start therapy during early infection achieve an undetectable viral load. With modern HAART, however, most people who start treatment during chronic infection can also achieve full viral suppression, so this is not necessarily a good rationale for very early therapy. More compelling is the prospect that treatment during primary infection might reduce viral load and help maintain immune function over the long term.

Soon after infection, HIV RNA usually rises to a high level—indicative of rapid viral replication—before falling back to a relatively stable level known as the viral “set-point.” Some studies have suggested that starting antiretroviral therapy during primary infection can lower this set-point. A small Dutch study, for example, found that people who began treatment within six months after seroconversion and then interrupted therapy had a significantly lower post-treatment HIV RNA level than untreated individuals.

But several other recent studies have shown that while people who started treatment prior to or soon after seroconversion experienced dramatic initial declines in HIV RNA, treated and untreated patients had similar viral loads after stopping therapy.

Treatment during primary infection may have a more beneficial effect on long-term immune function, though here, too, data are mixed. Researchers with the CASCADE Collaboration found that individuals who received a three-month course of HAART during primary infection experienced significantly slower CD4 cell decline during the three years following seroconversion. Other investigators, however, have shown that this advantage does not appear to last long after treatment is discontinued.

**HIV ERADICATION**

Some experts have suggested that very early antiretroviral therapy might “cure” HIV, or completely eradicate the virus from the body. One hypothesis held that treatment during primary infection might be able to kill off the virus before drug-resistance mutations emerge and before the virus has established itself in reservoir sites throughout the body.

In the late 1990s, David Ho and colleagues used mathematical models to estimate that fully suppressive early antiretroviral therapy might eliminate HIV from the body. But while immediate post-exposure prophylaxis has been used extensively to prevent chronic infection in HIV-exposed health care workers (see sidebar below), HIV eradication in seropositive individuals has yet to be achieved with currently available drugs.

Complete HIV eradication would require eliminating the virus from sequestered sites, such as the gut, brain, and genital tract, that are difficult for antiretroviral drugs to reach. In addition, latent HIV can persist in long-lived resting immune cells, untouched by drugs that are only effective against actively replicating virus. Persistence of even a few latently infected T-cells could allow a resurgence of viral replication if these cells later become activated. Various methods of “flushing out” HIV from resting T-cells have not succeeded in eliminating the virus; therapeutic vaccines and structured treatment interruption have also proven ineffective for this purpose.

**PRIMARY INFECTION TREATMENT GUIDELINES**

Guidelines for the treatment of acute or primary HIV infection have evolved along with those for chronic infection. The June 1998 version of the DHHS guidelines recommended that anti-

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**POST-EXPOSURE PROPHYLAXIS**

Post-exposure prophylaxis (PEP) refers to antiretroviral therapy started immediately—with 48 to 72 hours—after HIV exposure to prevent the virus from taking hold in the body. PEP typically consists of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) taken for four weeks, with the addition of a protease inhibitor in particularly high-risk cases.

Studies of health care workers who have accidentally been exposed to HIV though needle-sticks or other occupational injuries have shown that one month of PEP significantly reduces the risk of developing chronic infection. PEP may also be used for high-risk sexual exposures—for example due to sexual assault or condom failure—or exposures through shared drug injection equipment.

For more information, see the Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis (www.aidsinfo.nih.gov/contentfiles/HealthCareOccupExpoGL.pdf).
retroviral treatment “should be offered to all patients with the acute HIV syndrome, those within six months of seroconversion, and all patients with symptoms ascribed to HIV infection.”

In 2001, the drawbacks of antiretroviral therapy having become more apparent, the guidelines were updated to acknowledge that the risk-benefit trade-off of very early treatment remained uncertain. Nevertheless, the DHHS panel wrote, “most authorities endorse treatment of acute HIV infection based on the theoretical rationale, limited but supportive clinical trial data, and the experience of HIV clinicians.”

The October 2004 revision was more equivocal, stating that “treatment of acute HIV infection should be considered optional at this time.” Despite the recent shift in favor of earlier treatment for chronic HIV infection, this recommendation remains in effect with regard to primary infection.

**WHY STOP AT 350 CELLS/MM³?**

The rationale for the 350 cells/mm³ threshold is that while numerous studies have shown a clear advantage to starting treatment in the 200–350 cells/mm³ range rather than below 200 cells/mm³, there seemed to be little additional virological, immunological, or clinical benefit—at least over the short term—to starting at higher levels.

In the CASCADE cohort, for example, people who began therapy with a CD4 count of 200–350 cells/mm³ or with more than 350 cells/mm³ were equally likely to achieve a gain of at least 100 CD4 cells/mm³ compared with those who started with 50–199 cells/mm³.

In the large ART Cohort Collaboration study of more than 20,000 participants in North America and Europe followed for up to five years, the risk of progression to AIDS or death was significantly lower for individuals who began treatment within the 200–350 cells/mm³ range compared with those who started after falling to the 200 cells/mm³ threshold, regardless of baseline viral load.

But the best time to initiate treatment within the 200–350 cells/mm³ range has never been defined. In the current U.S. guidelines, the DHHS panel acknowledges that “no randomized trial definitively addresses the optimal time to initiate antiretroviral therapy in chronically infected patients with CD4 T-cell counts >200 cells/mm³.”

The guidelines do note, however, that the risk of several non-AIDS-related conditions, including cardiovascular disease, liver and kidney disease, and certain non-AIDS-defining cancers, is greater than the risk of AIDS in people with a CD4 count above 200 cells/mm³, and that “the risk for these events increases progressively” as the CD4 level declines from 350 to 200 cells/mm³.

**WHEN TO START ANTIRETROVIRAL TREATMENT**

There is no question that combination antiretroviral therapy should begin before the CD4 count falls below 200 cells/mm³. Below this level, individuals are at significantly greater risk for opportunistic illnesses, such as Pneumocystis pneumonia. As immune function declines further, people become prone to additional infections, including toxoplasmosis below 100 cells/mm³, and Mycobacterium avium complex and cytomegalovirus below 50 cells/mm³. But even HIV positive people with CD4 counts of 200–350 cells/mm³ or higher remain at increased risk for opportunistic conditions (for example, tuberculosis) compared with HIV negative individuals.

Individuals with serious clinical symptoms of immune deficiency or a history of AIDS-defining illnesses should receive prompt antiretroviral treatment regardless of CD4 cell count. Among asymptomatic individuals, starting combination antiretroviral therapy after the CD4 count falls below 200 cells/mm³ dramatically decreases the risk of disease progression and death. But those who start treatment within the 200–350 cells/mm³ range achieve significantly better outcomes.

Among CASCADE participants, for example, those who started within this range were more likely to achieve a CD4 cell gain of at least 100 cells/mm³ than those who started with a lower level. In the French APROCO cohort, nearly twice as many patients who started treatment with at least 200 cells/mm³ and maintained viral suppression over five years eventually attained a CD4 count above 500 cells/mm³ compared with those who had more severe immune suppression.

Studies have also demonstrated a survival advantage associated with starting treatment within the 200–350 cells/mm³ range as opposed to later. A Canadian analysis from the late 1990s, for example, showed that people who started therapy with more than 200 cells/mm³ were three times less likely to die than those who started with 50–199 cells/mm³.

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attributable to starting therapy with a CD4 count above 350 cells/mm³ is worth the risks. But, as Robert Schooley of the University of California at San Diego explained in a recent interview with TheBody.com, cross-sectional snapshots of cohorts and studies with short follow-up periods do not tell the whole story.

It is to be expected that people who have a higher CD4 count when they enter a study will take longer to reach various clinical endpoints, but this can be misleading. “Making a decision early on in a cohort [study] that the people who are least likely to have events are fine,” said Schooley, “is like watching somebody jump out of a ten-story building and, as they go by the fifth floor, say[ing] they’re fine...so far.”

But once individuals who started treatment with a higher CD4 count are followed for longer periods, he continued, “you begin to see a signal that people who started earlier are doing better.” And this signal appears to be getting stronger.

**SMARTER TO START SOONER?**

Some of the most intriguing findings about HIV-related complications during the HAART era have come from studies looking at structured treatment interruption. Concern about toxicities associated with antiretroviral drugs—in particular, long-term mitochondrial and metabolic complications such as body shape changes and elevated blood lipid levels—has led many patients over the years to embark on “drug holidays,” prompting researchers to design clinical trials looking at the potential risks and benefits of intermittent therapy.

The largest of these trials, known as SMART (Strategies for Management of Antiretroviral Therapy), included nearly 5,500 participants in more than 30 countries. Everyone started the study with a CD4 cell count above 350 cells/mm³ (median about 600 cells/mm³), most were treatment-experienced, and about 70% had a viral load below 400 copies/mL; many, however, had previously had a low nadir CD4 count (median 250 cells/mm³).

Participants were randomly assigned to receive either continuous antiretroviral therapy (dubbed the “viral suppression” arm, since the goal was to keep viral load as low as possible), or else to defer or interrupt therapy when their CD4 cell count was above 350 cells/mm³ and start or resume when it fell below 250 cells/mm³ (dubbed the “drug conservation” arm, under the assumption that spending less time on therapy would save more drug options for later).

SMART was halted in January 2006 after an interim analysis showed inferior outcomes in the treatment interruption arm. On average, over the course of follow-up, participants in the drug conservation arm had a CD4 cell count about 200 cells/mm³ lower than those in the viral suppression group. As expected, the risk of opportunistic illness or death due to any cause was higher in the drug conservation arm compared with the viral suppression arm, though the rate was low overall (4.4% versus 1.7%, respectively) and most deaths were due to non-opportunistic causes.

But participants in the drug conservation arm also had a significantly higher rate of serious cardiovascular, liver, and kidney disease (65 versus 39 total events). This took many experts by surprise, since all three conditions have been attributed to antiretroviral toxicity, and a major rationale for treatment interruption was to reduce drug-related side effects. Did these findings, then, suggest that the observed non-AIDS complications were attributable to something other than antiretroviral drugs?

A subgroup analysis, published in the April 15, 2008, *Journal of Infectious Diseases*, looked at the minority of SMART participants who were not on HAART at the start of the study (249 treatment-naïve; 228 previously treated but off therapy for at least six months). Participants in the drug conservation arm deferred treatment until their CD4 count fell below 250 cells/mm³, while those in the viral suppression arm started therapy upon study entry, when their CD4 count was still above 350 cells/mm³.

Individuals in the deferred therapy group were more likely to experience opportunistic disease, non-AIDS illness (cardiovascular, liver, and kidney disease plus non-AIDS-defining cancers), or death than those who started immediately (21 versus six total events). The investigators concluded that earlier therapy “may reduce both opportunistic disease and serious non-AIDS events.”

According to another SMART analysis in the same issue, study participants in the drug conservation arm still had a significantly higher rate of opportunistic disease or death even during periods in which their CD4 count was above 350 cells/mm³, which the investigators attributed to ongoing uncontrolled HIV replication.

“Because deaths from causes other than opportunistic disease dominate among patients receiving antiretroviral therapy,” they wrote, “the SMART study finding, along with recent data from observational studies, support consideration of initiating antiretroviral therapy before even moderate levels of immunodeficiency develop.”

In yet another analysis from the study, presented at the Conference on Retroviruses and Opportunistic Infections this past February in Boston, investigators looked at a variety of biomarkers associated with inflammation, blood coagulation, and endothelial (blood vessel) dysfunction. They found that SMART participants who died during the trial had higher levels of interleukin-6 (IL-6) and D-dimer. Both markers increased as viral load rose after treatment interruption in the drug conservation arm, while remaining stable in the viral suppression arm. The investigators concluded that the association between these
Summersaults and biomarkers and a higher rate of death due to any cause “suggests that HIV infection results in activation of coagulation and inflammatory pathways that may impact multiple organs.”

Data from another CD4-guided structured treatment interruption trial called STACCATO, which included a very different study population from Thailand, also revealed significant changes in biomarkers associated with endothelial dysfunction following treatment interruption, some of which were not reversed after therapy resumed.

Several ongoing observational studies, including the large D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) cohort, have shown that people with HIV are at higher risk for non-opportunistic conditions, such as cardiovascular disease, accelerated liver disease progression due to hepatitis B or C, and non-AIDS-defining cancers. This occurs even at CD4 counts well above the traditional 200 cells/mm³ danger zone, calling into question the validity of common assumptions about what is an “AIDS-related” condition.

It is often difficult to tease out the relative contributions of antiretroviral drug toxicities, the effects of chronic HIV infection itself, and the normal aging process as HIV positive people live longer. But the new data add to the evidence that continued viral replication—and perhaps especially the bursts of resurgent replication that occur during treatment interruption—has detrimental effects beyond the increased risk of opportunistic illness due to CD4 cell depletion. This, in turn, suggests that keeping HIV suppressed even at the early stages of infection, before serious immune dysfunction occurs, may have previously unrecognized benefits.

**BENEFITS OF STARTING ABOVE 350 CELLS/MM³**

Even as U.S. and European experts have subtly raised the recommended threshold for initiating antiretroviral therapy—from somewhere within the 200–350 cells/mm³ range to just under 350 cells/mm³—evidence continues to accumulate supporting even earlier therapy.

Several recent studies have suggested that starting treatment sooner, above 350 cells/mm³ or even 500 cells/mm³, may lead to reduced progression to AIDS, a lower risk of non-AIDS-defining diseases, longer survival, fewer side effects, less drug resistance, and more complete immune restoration.

**DISEASE PROGRESSION AND DEATH**

Earlier antiretroviral therapy has been linked to a reduced risk of both opportunistic illnesses and conditions not traditionally defined as AIDS-related. Recent data from the large EuroSIDA cohort, for example, showed that people on treatment were less likely to develop AIDS-related illnesses at all CD4 cell counts, including those above 350 cells/mm³.

In the ART Cohort, after about three years of follow-up, patients who started treatment with 350–500 cells/mm³ were less likely to progress to AIDS or death than those who started with 200–350 cells/mm³, who in turn were less likely to progress than those starting with fewer than 200 cells/mm³.

In an analysis of more than 2,000 treatment-naive participants who started HAART in the Spanish PISCIS study, patients who waited to start therapy until their CD4 count fell below 200 cells/mm³ were at higher risk of progression to AIDS or death, as expected. But those who started in the 200–350 cells/mm³ range still did not fare as well as those who started above 350 cells/mm³. Based on these findings, the investigators suggested that “the best time to start HAART is before the CD4 count falls to lower than 350 cells/mm³.”

In the Dutch ATHENA cohort, participants who had a CD4 count of 200–350 cells/mm³ at the time of HIV diagnosis were about 50% more likely to progress to AIDS or death than those with 350–500 cells/mm³ or more than 500 cells/mm³. Furthermore, the risk of disease progression was higher after 2000, leading researchers to suggest that this change might be attributable to that year’s lowering of the threshold for HAART initiation in the Netherlands’ treatment guidelines from the 350–500 cells/mm³ range to the 200–350 cells/mm³ range.

Studies have also looked at starting treatment above 500 cells/mm³—that is, around the lower limit of the normal range for HIV negative people. An analysis of more than 17,600 participants in the UK Collaborative HIV Cohort (CHIC) found that those who started therapy with a CD4 cell count above 650 cells/mm³ were about five times less likely to progress to AIDS or death than those with 200–350 cells/mm³. But the earliest starters were also at lower risk than those with 350–500 cells/mm³, and even half as likely to progress as those with 500–650 cells/mm³, indicating that the benefits of earlier therapy continue to accrue even at near-normal CD4 counts. The researchers calculated that beginning treatment above 500 cells/mm³ would mean starting about two and a half years sooner.

Earlier therapy also appears to lower the risk of non-AIDS-defining major organ diseases and cancers. In the Johns Hopkins HIV cohort, HAART use was associated with a reduced risk of non-AIDS conditions—including cardiovascular, liver, kidney, and lung disease, non-opportunistic cancers, and neuropsychological problems—at all CD4 levels. Notably, while the rate dropped by nearly 50% for patients with a CD4 count below 200 cells/mm³, it still fell by 30% for those with more than 350 cells/mm³.

At the February Retrovirus conference, Rebecca Lodwick and colleagues presented some of the first data from the Study Group on Death Rates at High CD4 Counts in Antiretroviral-Naive Patients, a collaboration looking
at outcomes in people from several industrialized countries who started HAART early.

The researchers analyzed 46,400 study participants, with the data roughly evenly divided between individuals with CD4 counts of 350–500, 500–700, and above 700 cells/mm³. During follow-up, there were 487 total deaths, 16% due to AIDS and 48% due to non-AIDS-related causes (the rest were unknown). Even at these high CD4 levels, the overall risk of death rose with lower CD4 counts and higher viral loads. And a small number of patients died of AIDS-related causes despite well-preserved immune function.

A team of French researchers recently reported that while the overall mortality rate remains higher among HIV positive people on HAART compared with HIV negative individuals, those who were able to maintain a CD4 cell count above 500 cells/mm³ for six years had a risk of death similar to that of the general population.

Finally, as reported in the April 23, 2008, issue of AIDS, researchers with the large FIRST (Flexible Initial Retrovirus Suppressive Therapies) study, following up on the SMART findings, looked at the risk of non-AIDS-related cardiovascular, liver, and kidney disease and non-AIDS-defining cancers in 1,397 people on HAART. Over five years of follow-up, 227 patients experienced an AIDS-related illness and 80 developed a non-AIDS disease. The rate of AIDS-related illness rose sharply as immune function declined, from 0.7% to 2.0% to 13.8% as the pretreatment CD4 count fell from above 350 to 200–350 to below 200 cells/mm³. The rate of non-AIDS disease followed a similar—though less dramatic—pattern, rising from 0.7% to 1.7% to 2.1%, respectively.

"If the potential reduction in non-AIDS risk as well as AIDS risk could be realized through earlier initiation of antiretroviral therapy," the investigators concluded, "the public health benefit would be substantial."

**IMMUNE RECOVERY**

In addition to reducing the risk of clinical illness, earlier antiretroviral therapy also appears to enable more complete immune recovery toward the normal level of 500–1,500 cells/mm³ seen in HIV negative individuals.

Back in 2000, Johns Hopkins researchers found that people who started treatment with a CD4 count above 350 cells/mm³ were more likely to achieve a sustained immunological response. The same team recently reported that while most patients who started therapy initially achieved significant gains, CD4 counts then reached a plateau, so that those who began treatment with a higher count were more likely to achieve a normal level than those who started later.

After six years of follow-up with continued viral suppression, individuals with a baseline CD4 cell level above 350 cells/mm³ attained a median level of 829 cells/mm³, compared with 508 cells/mm³ for those who started in the 200–350 cells/mm³ range and 493 cells/mm³ for those who started with fewer than 200 cells/mm³. Most study participants (85%) who started with more than 350 cells/mm³ eventually achieved a count above 500 cells/mm³, compared with 66% who started with 200–350 cells/mm³ and 42% who started below 200 cells/mm³; 46%, 21%, and 12%, respectively, ultimately exceeded 750 cells/mm³.

Similarly, researchers with the ACTG 384 study found that about three years after starting combination therapy, patients at all pretreatment CD4 levels experienced similar absolute cell gains. But while individuals who started treatment above 350 cells/mm³ usually achieved near-normal levels of both naive and memory CD4 cell subsets, as well as a naive-to-memory and CD4-to-CD8 cell ratios, those who started with lower levels never managed to catch up.

In the Dutch ATHENA cohort, participants who initiated therapy at lower CD4 cell counts tended to achieve larger absolute increases, but those who started at higher levels were still more likely to ultimately attain a normal level. After seven years on HAART, only 20% of patients who started with fewer than 50 cells/mm³ eventually reached 800 cells/mm³, compared with 26% who started with 50–200 cells/mm³, 46% who started with 200–350 cells/mm³, 73% who started with 350–500 cells/mm³, and 87% who started with more than 500 cells/mm³.

In the FIRST study, too, people who started therapy with at least 350 cells/mm³ attained an average CD4 count of 666 cells/mm³ after about three years, while those who started with 200–350 cells/mm³ reached 487 cells/mm³ and those who started below 200 cells/mm³ only reached 335 cells/mm³.

Finally, a study by researchers from the University of California at Davis found that early therapy may help prevent CD4 cell depletion in the gut, which may not be fully restored by later treatment.

**INDIVIDUAL FACTORS FAVORING EARLIER THERAPY**

While 350 cells/mm³ stands as the recommended threshold for starting antiretroviral therapy, there are several individual factors that weigh in favor of considering earlier treatment.

Perhaps most important, anyone with a past history of an AIDS-defining illness or current symptoms of immune deficiency should begin treatment promptly regardless of CD4 cell count.

**VIRAL LOAD**

Recent years have seen decreasing emphasis on viral load as an indicator of when to start treatment, and the current DHHS guidelines no longer include a specific HIV RNA threshold for initiating therapy; it remains, however, a key measure for identifying treatment failure.

Studies have clearly shown that continued high viral load—especially above 100,000 copies/mL—is associat-
ed with poorer outcomes. However, with modern antiretroviral regimens, treatment-naive people with even a high baseline HIV RNA level usually can achieve full viral suppression once they start therapy. Furthermore, individuals starting HAART with high and low viral loads have similar outcomes as long as they maintain good adherence. While a low viral load is certainly preferable to a high one, even low-level ongoing HIV replication appears to have harmful effects. Occasional small, transient viral load increases (“blips”) do not appear to be detrimental, though multiple blips may be a sign of impending treatment failure.

**AGE AND SEX**

Some experts feel that individuals who may experience slower immune recovery after starting HAART should consider therapy before reaching the 350 cells/mm³ threshold. Several studies indicate that older patients (over age 40 or 50 years) do not regain CD4 cells as quickly as younger people and may end up with a smaller total gain. This may be attributable to atrophy of the thymus, the organ where new T-cells mature after they are produced in the bone marrow.

The prospect of slower CD4 cell recovery suggests that it may be especially important for older individuals to start antiretroviral therapy before immune suppression progresses too far. Furthermore, older people, regardless of HIV status, are more prone to conditions such as cardiovascular disease, high blood pressure, and diabetes that can complicate—and be complicated by—chronic viral infection and drug therapy. The current DHHS guidelines, however, do not give different thresholds for starting treatment based on age. Early therapy appears beneficial for babies as well as adults. In the CHER (Children with HIV Early Antiretroviral Therapy) study, 377 South Africa infants infected with HIV via mother-to-child transmission were randomized to receive immediate antiretroviral therapy within six to twelve weeks after birth or else delayed therapy when they started to show signs of disease progression, as is the standard of care throughout much of the world. The study was halted after an interim analysis at 32 weeks showed that infants who received immediate treatment, even if they showed no evidence of illness or immune damage, were four times less likely to die than those who deferred treatment (4% vs 16%, respectively).

As with age, the DHHS treatment guidelines do not make different recommendations according to sex. Several studies have shown that women tend to have a higher CD4 cell count and lower viral load than men during the early stage of HIV infection, and may experience disease progression at a higher CD4 cell level.

Earlier in the epidemic, some experts argued that HIV positive women should perhaps start treatment at a higher CD4 cell count than men. But later data from the WHIS cohort and other studies showed that women and men respond equally well to therapy, and pretreatment sex differences in CD4 cell count and viral load do not matter as long as people achieve viral suppression after starting therapy. U.S. guidelines have never recommended different cut-offs for initiation of therapy in women and men, and there is no evidence that this has put women at a disadvantage.

According to the new U.S. guidelines, all HIV positive pregnant women should be treated with combination HAART—rather than monotherapy with drugs such as AZT (zidovudine, Retrovir) or nevirapine (Viramune)—to prevent perinatal transmission, regardless of CD4 cell count. There remains some debate, however, about whether women with a high CD4 count should discontinue or stay on therapy after delivery.

**COEXISTING CONDITIONS**

The current treatment guidelines recommend combination antiretroviral therapy for HIV/HBV coinfected individuals who need treatment for chronic hepatitis B. Several agents used to treat HBV are also active against HIV, including 3TC (Epivir), emtricitabine (Emtriva), tenofovir (Viread; also combined with emtricitabine in the Truvada pill), and—as recently demonstrated—entecavir (Baraclude).

If such agents are used as monotherapy to treat HBV, they may promote the emergence of drug-resistant HIV. In their December 2007 update, the DHHS panel recommended that if coinfected patients require therapy for either HIV or HBV, they should start on a “fully suppressive antiretroviral regimen” of at least three drugs, including tenofovir plus either 3TC or emtricitabine.

Hepatitis C coinfection raises a different concern. There is considerable evidence that HIV/HCV coinfected individuals tend to experience more rapid liver disease progression than those with HCV alone. Some studies, however, have shown that liver fibrosis may not be more aggressive in coinfected people who maintain high CD4 cell counts.

In addition, several studies have shown that HIV/HCV coinfected patients tend to have slower CD4 cell recovery after starting HAART, though other research has failed to find a difference. In the PISCIS study, HIV/HCV coinfected individuals had a higher risk of progression to AIDS or death than those with HIV alone. For these reasons, most experts recommend that HIV positive people with hepatitis C should receive earlier antiretroviral therapy.

HIV-associated nephropathy (kidney disease), which occurs at a much higher rate among people of African descent, is more likely to develop as HIV disease progresses. The causes of this condition are not fully understood, but continued HIV replication appears to play a role. Antiretroviral therapy has been shown to preserve kidney function and prolong survival.
of nephropathy patients, and the latest DHHS guidelines recommend a full three-drug HAART regimen for all individuals with HIV-associated nephropathy regardless of CD4 count.

HIT EARLY… BUT MAYBE NOT SO HARD

SMART and other studies indicate that there is no truly “latent” stage of HIV infection. While HIV positive people with early disease may seem healthy, without antiretroviral therapy the virus continues to replicate, infecting and killing new CD4 cells. In addition, unsuppressed HIV replication is associated with problems throughout the body—some previously unrecognized and due to biological mechanisms that are not yet fully understood— independent of its impact on CD4 cells.

“One balance, the evidence suggests that HIV may well play a role in several serious non-AIDS defining events,” said Andrew Phillips during a plenary address at the February Retrovirus conference. “It’s possible that starting antiretroviral therapy much earlier could reduce these events.”

While modern antiretroviral therapy produces substantial immune recovery, it is unclear whether bringing the CD4 cell count back up to its former level restores the full repertoire of defenses against pathogens encountered in the past. It therefore makes sense to preserve immune function through early treatment rather than trying to restore it later.

Starting treatment sooner involves added inconvenience, greater expense, the potential for more side effects, and possible health complications related to drug toxicities. Nevertheless, the pendulum appears to be swinging in the direction of earlier treatment.

With improved understanding of antiretroviral therapy and management of toxicities, hitting the virus early—before the immune system sustains extensive damage—may make it possible to hit less hard, using more tolerable drugs with fewer side effects and less arduous dosing schedules.

Today’s combination regimens, started in a timely manner with good continued adherence, could potentially keep HIV suppressed indefinitely, thereby reducing the emergence of resistant virus and the need for multi-drug “salvage” regimens with myriad interactions and additive toxicities. And with the recent approval of new antiretroviral agents in two novel classes (CCR5 antagonists and integrase inhibitors), waiting for better drugs to come along no longer seems like a compelling reason for deferring treatment.

“As HAART evolves over time, newer regimens tend to be simpler and safer,” wrote Evan Wood and Julio Montaner in the June 1, 2007, Journal of Acquired Immune Deficiency Syndromes. “This progressively opens the door for a broader re-evaluation of the ideal time to start therapy, incorporating outcomes other than survival.”

While there is not yet a definitive answer about when to start antiretroviral therapy, there is now enough evidence that HIV positive people and their clinicians should consider earlier treatment, taking into account not only CD4 cell count, but also the many individual factors that can influence the decision. More than early therapy per se, perhaps the most evident trend in HIV management is the move toward more tailored treatment, evaluating such characteristics as patient age, overall health, coexisting conditions, extent of HIV disease progression, and readiness to start treatment. While antiretroviral therapy guidelines are continually updated by experts to reflect the latest scientific research, there is no “one size fits all” approach to HIV care.

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**Selected Sources**


Gras, L. and others. CD4 cell counts of 800 cells/mm³ or greater after 7 years of highly active antiretroviral therapy are feasible in most patients starting with 350 cells/mm³ or greater. Journal of Acquired Immune Deficiency Syndromes 45(2):183–92. June 1, 2007.


