The Case for Earlier Treatment of HIV Infection

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(See the editorial commentary by Cohen and Boyle on pages 1705–8)

Current US guidelines advise that antiretroviral therapy for asymptomatic HIV patients should definitely be started for those who have CD4+ cell counts of >200 cells/µL, but antiretroviral therapy is often not started at CD4+ cell counts much above that level. Guidelines advocating later therapy for HIV infection have been based mainly on sparse and limited cross-sectional data and have been predicated on avoiding drug-related toxicity and viral drug resistance. However, emerging data about factors that contribute to survival and the availability of newer, less toxic drugs are eroding this position. Earlier initiation of antiretroviral therapy—namely, for patients with CD4+ cell counts of >350 cells/µL—may, in fact, be associated with lower mortality, better immune improvement, and less drug-related toxicity. These findings coincide with the introduction of antiretroviral drugs that have become more effective and less difficult to take. Earlier initiation of therapy may also reduce HIV transmission, an important public health consideration, and may be beneficial in terms of overall therapeutic cost-effectiveness. Given these accumulating data, we believe reconsideration of the “when-to-start” question is timely and justified.

Opinions concerning the optimal timing for initiation of highly active antiretroviral therapy for HIV infection have gone through major adjustments since the introduction of protease inhibitor drugs in 1996. At first, after dramatic declines in mortality and morbidity [1–3], there was enthusiasm for providing potent new combination therapy to HIV-infected persons as early in the course of infection as possible. However, it quickly became clear that HIV could not be eradicated because of a long-lived pool of latently infected cells [4–6]. Later initiation of therapy did not appear to preclude immunologic restitution to a CD4+ cell count of >200 cells/µL [7], sufficient for discontinuing antimicrobial prophylaxis for opportunistic infections. There was concern that widespread use of therapy would create an epidemic of infection with multiply drug-resistant strains of HIV [8, 9], and, as efficacy diminished, the duration of sequential regimens became increasingly shorter, as did the options for salvage therapy [10].

Perhaps the most influential factor in the paradigm shift regarding therapy initiation has been drug toxicity. Although the life-saving qualities of antiretroviral therapy were impressive, clinicians recognized new toxicities, especially subtle and dramatic body habitus changes (i.e., lipodystrophy), insulin resistance, and hyperlipidemia [11–12]. These metabolic toxicities were of special concern because pathophysiologic mechanisms were unknown, and potential long-term clinical consequences, such as myocardial infarction [13] and stroke, further diminished enthusiasm for early treatment of HIV disease. In addition, pessimism arose and still exists about the effective or complete treatment of some of these complications of antiretroviral therapy, such as lipodystrophy.

Given these concerns and the growing confidence that antiretroviral therapy is effective even in patients with more advanced disease, clinicians who treat HIV disease are much more cautious about initiating antiretroviral therapy than they were several years ago. The more cautious, “start later” approach has gained greater acceptance, a shift that has been mirrored in a series of recent recommendations for the care of HIV-infected patients in the United States (table 1). Although there is widespread agreement not to delay therapy until it is “too late” if there is acknowledged risk of clinical disease [20–22], and although the guidelines permit starting therapy at any CD4+ cell count >200 cells/µL, the result has been a tendency to start near that threshold. At recent conferences, presenters have advocated starting therapy at CD4+ cell counts of <275 cells/µL [23], and at interactive sessions, 25%–30% of participants indicated that they would not start therapy.
Table 1. Recommendations for when to initiate antiretroviral therapy for asymptomatic HIV-infected US patients.

<table>
<thead>
<tr>
<th>Source of recommendation [reference]</th>
<th>Date of publication</th>
<th>CD4+ lymphocyte count, cells/µL</th>
<th>Plasma HIV RNA concentration, copies/mL</th>
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<tr>
<td>International AIDS Society–USA Panel [18]</td>
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<td>&gt;200</td>
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until a patient with modest viral load (plasma HIV RNA load of 30,000 copies/mL) had CD4+ cell counts of ≤250 cells/µL. Median CD4+ cell counts at the time of therapy initiation for HIV Outpatient Study [1] participants who start therapy while not hospitalized have fallen from 317 to 272 cells/µL between 1997 and 2003 (authors’ unpublished data; $\chi^2$ value for trend, 4.34; $P = .037$), even though several HIV Outpatient Study clinicians are “early treaters.” The situation is mirrored in European [24] and British [25] guidelines that indicate “deferral of therapy is actually a reasonable option for a significant proportion of patients” [24, p. S1]. Some researchers have even concluded that “the current emphasis of therapeutic guidelines on initiating therapy at CD4 cell counts above 200 × 10^6 cells/L should be re-examined” [26, p. 711], sentiments echoed by experts in London and Copenhagen [27].

We are concerned that the therapy-initiation pendulum has swung too far in the direction of later initiation—at a CD4+ cell count near 200 cells/µL—rather than earlier initiation—at a CD4+ cell count of >350/µL. We note a growing body of evidence suggesting that earlier treatment with newer, better, and safer drugs is associated with improved survival, more effective immune-system improvement, less toxicity and drug intolerance, and other clinical and public health benefits.

First, improvement in survival is often considered the “gold standard” of the utility of treatment for HIV infection. To consider this issue, the only practical way of determining whether earlier treatment substantially improves survival is through observation of large cohorts of persons. However, for logistical and ethical reasons, this is not possible: a study of >6500 patients, randomly assigned to receive immediate or deferred therapy, with 10 years of observation, would likely be required [28]. Even the large SMART study [29], which is currently enrolling participants, will not consistently treat patients who have CD4+ cell counts of >350/µL.

It is not well appreciated that recent guidelines on when to initiate therapy have relied on a few short-term, sometimes unpublished cross-sectional analyses of observational cohort and clinical trial data [30–35]. Typically, these analyses just look at survival data for the period after patients in a study start antiretroviral therapy at a particular CD4+ cell count, which does not adjust for “lead-time,” the period when a patient could have taken antiretroviral therapy but did not. Also, these studies almost always measure “soft” end points, such as the development of AIDS. Some studies have tried imputing lead times before observation within a cohort [36], but this is an indirect measurement of true observation time. Data from all such studies are hard to interpret, because they do not use test starting points of observation—that is, a direct head-to-head comparison of persons who do or do not start therapy at specific CD4+ cell counts—and a definitive end point, such as death or undetectable viral load.

To our knowledge, only 2 analyses to date—neither referenced in the latest US [19] or British [25] guidelines—have published data comparing HIV-infected patients who either initiated or deferred therapy from a set start point within a CD4+ cell count stratum of >350 CD4+ cells/µL, and then measured definitive (“hard”) outcomes—that is, mortality rates and rates of attainment of undetectable viral loads. In one of these studies [37], HIV-infected patients who started therapy within the CD4+ cell count stratum of 350–500 cells/µL (mean, 404 cells/µL) had a mortality rate ~60% of the rate for those who delayed taking similar therapy at some point after they had a CD4+ cell count of <350 cells/µL (mean, 258 cells/µL), and they were statistically significantly more likely to achieve an undetectable viral load. This same type of analysis can be applied to the data in the other recent, shorter-term analysis [38], which concluded that, because the difference between those who started therapy at a CD4+ cell count of ≥350 cells/µL and those who delayed or did not start therapy at a lower CD4+ cell count was not statistically significant ($P = .10$, log-rank test), “HAART [should] not be initiated for patients with CD4+ cell counts >350 cells/mm$^3$” [38, p. 812]. However, the relative risk of death—defined as the number of deaths per 1000 patient-years of observation—was only 0.45 for the patients who started therapy at a CD4+ cell count...
of >350 cells/μL, compared with those who were observed from that point but started therapy at lower CD4+ cell counts or not at all. Further, analysis of the data from these 2 studies by usual meta-analytic techniques (i.e., the fixed-effect model) [39, 40] shows the relative risk of death was 0.46 (P = 0.027, Mantel-Haenszel χ² test; 95% CI, 0.24–0.88) for those who started therapy at a CD4+ count of >350 cells/μL, compared with those who started at a lower count.

A more recent analysis [41], an extension of the earlier work summarized above [38], also indicated that the risk of development of a new opportunistic infection or death was significantly lower for patients who started therapy at CD4+ cell counts of 351–500 cells/μL, compared with those who started at counts of 201–350 cells/μL. (However, because the analysis was limited to only those patients who achieved undetectable viral loads, the numbers being compared and the statistical power were both reduced, and this difference was no longer statistically significant.)

Supporting such findings are studies showing that HIV suppression and increases in CD4+ T lymphocyte number and function are much more easily accomplished when treatment is started at a CD4+ count above, rather than below, 350 cells/μL [31, 37, 42, 43] and even at counts of >500 cells/μL [44, 45]. Immunologic and virologic responses are better when treatment is started early [44], and initiation of HAART at early stages of chronic HIV infection seems to allow almost complete normalization of T cell subsets and preservation of T cell functions [45]. Conversely, when treatment is stopped—for example, in “strategic” treatment interruptions—CD4+ cell counts and viral loads usually return to their pretreatment levels [46]. Thus, the decision of when to start therapy could be critical to the long-term preservation of immune function [47].

Given this accumulating evidence, some proponents later therapy initiation are beginning to concede that immediate initiation of therapy for a person with a CD4+ cell count of 350 cells/μL will likely result in a lower risk of AIDS or death than that for deferred initiation of therapy [48]. Nonetheless, they speculate that issues of toxicity and virologic failure may diminish long-term effectiveness.

Thus, second, we think that the issue of toxicity, a frequent reason that clinicians delay therapy, needs reconsideration. The current generation of antiretroviral drugs appears to have better short-term toxicity profiles than do earlier drugs [49]. Further, and perhaps more important, there is a growing appreciation that a low CD4+ cell count is itself a major risk factor for drug-related toxicity [50]. For example, in the HIV Outpatient Study, the factor most strongly associated with the presence of body habitus abnormalities (i.e., lipodystrophy) was the nadir CD4+ cell count: 30.8% of patients with nadir count of <200 cells/μL but only 3.3% of patients with a nadir count of >350 cells/μL developed lipodystrophy. Host factors other than receipt of antiretroviral drugs (advanced age, sex, and race) were also prominently associated with an increased risk of lipodystrophy [51, 52]. Peripheral neuropathy is a frequently diagnosed toxicity associated with the use of some nucleoside reverse-transcriptase inhibitors, but several analyses suggest that this, too, is much more likely to occur among persons with low nadir CD4+ cell counts and that advanced disease predisposes to a higher risk of neuropathy [53–55]. In persons taking newer drugs, such as tenofovir, both lipodystrophy and peripheral neuropathy are also less frequent among those who start therapy at higher CD4+ cell counts than among those who start at lower counts [49]. In patients coinfeeted with HIV and hepatitis C virus, liver fibrosis is more frequent among those who start treatment at low CD4+ cell counts [56]. Loss of bone density also appears more closely related to host risk factors and advanced HIV infection than to the use of antiretroviral agents [57, 58]. Because of these data, we think that delaying therapy until a later stage of HIV disease progression may actually predispose patients to drug-associated toxicities.

Third, although we appreciate concerns about the potential exhaustion of therapeutic options for patients who start therapy earlier, there are now 20 FDA-approved drugs—19 that belong to the 3 usual classes of antiretroviral drugs and 1 approved fusion inhibitor drug—for the treatment of HIV infection. New drugs in the 4 established classes; new classes of agents, such as entry inhibitors and integrase inhibitors; and immune modulators, such as interferons, are being developed and approved for use. Thus, the dramatic mortality reductions that were first observed in 1996 have been durable, without evidence of recrudescence of death rates [8], and the list of novel drugs available for inclusion in “salvage” antiretroviral therapy regimens continues to grow.

The “pill burden” and dosing for most newer antiretroviral therapy regimens, with respect to both the number and type of agents, have dropped markedly in the past few years; less frequent dosing may be especially important for patient adherence [59]. For example, patients seen in the HIV Outpatient Study in 1997 took an average of 13 pills each day for antiretroviral therapy and opportunistic infection prophylaxis [60], but by 2003, a random sample of 165 HIV Outpatient Study patients showed they were taking a mean of 5.6 pills per day, and few patients were taking more than 12 pills per day. There are now options for once- or twice-daily regimens with a daily pill burden of 2 or 3 pills—sometimes coformulated preparations—and many of these antiretroviral medications have greater efficacy and tolerability but less toxicity and likelihood of development of resistance than those available earlier.

Fourth, the cost of initial antiretroviral therapy, including hospitalization, is potently twice as high for patients with late-stage AIDS than for patients with early-stage HIV infection (i.e., patients with
>500 CD4+ cells/µL ($30,261 vs. $15,404) [61]. Also, there is an apparent cost benefit with respect to quality-adjusted life years for patients who start antiretroviral therapy early (at CD4+ cell counts of 350 cells/µL) rather than at some point later in the course of infection [62].

Finally, but not least important, a potential public health benefit of earlier antiretroviral treatment is that it apparently reduces sexual transmission of HIV by reducing HIV viremia and shedding [63] and, possibly, by reducing the transmission fitness of HIV as well [64]. Over time, the population health benefit of earlier treatment, coupled with risk-reduction programs, may be substantial [65, 66]. Although this benefit might arguably be offset by transmission of drug-resistant strains, the occurrence of drug-resistance mutations in the HIV strains infecting antiretroviral therapy–naïve patients in the United States has been low [67], and it is thought that “transmission of resistant strains is, and will remain, a relatively minor public health problem” [68, p. 1016].

In summary, we think that the information currently available and accumulating supports initiation of therapy for asymptomatic HIV-infected patients at CD4+ cell counts of >350 cells/µL—certainly >275 cells/µL—and that we should be receptive to the possibility, as we observe patients treated with newer drugs, that perhaps even earlier initiation of treatment is warranted. Clinicians might consider when they would initiate treatment for themselves if they were HIV infected. Certainly, there are many imponderable considerations that affect when a physician and a patient decide the time is right to start antiretroviral therapy, particularly patient reluctance to start potentially life-long, multidrug therapy. Also, physicians are not always good at assessing the adherence of their patients to prescribed antiretroviral regimens [69]. However, for asymptomatic patients who request it or are likely to be adherent, the decision of when to start antiretroviral therapy must be informed by the best available, if unavoidably imperfect, data.

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