When to Start Antiretroviral Therapy?

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The optimal time to start antiretroviral therapy (ART) for human immunodeficiency virus (HIV)–infected individuals remains uncertain. Although current ART regimens are effective in suppressing viremia and enhancing immune function and are increasingly convenient and well tolerated, ongoing concerns remain about adherence, drug-related toxicities, drug resistance, and cost. Although few clinical trials results are currently available to inform the question of when to start ART, large clinical cohorts clearly have demonstrated the benefits of earlier initiation of ART for reducing both HIV-related and non-HIV–related clinical events. Additional data suggest that the strategy of earlier initiation of ART is cost-effective and efficient. Consequently, many antiretroviral guidelines from around the world now recommend routine initiation of ART when the CD4 cell count decreases to \( \geq 350 \text{ cells/µL} \) or at higher CD4 cell counts for certain subgroups of HIV-infected individuals, such as pregnant and/or breast-feeding women and persons with HIV-related nephropathy or hepatitis virus coinfection. Additional cohort and clinical trials data are needed.

The optimal time to initiate antiretroviral therapy (ART) for HIV infection is unclear. After the development of effective ART in the mid-1990s [1–3], a shift toward earlier initiation of therapy occurred in the late 1990s, largely based on theoretical grounds (“hit early, hit hard”) [4–6]. This was followed by the realization that inconvenience and drug-related toxicity from combination ART challenged patients who often experienced failure of therapy with accompanying drug resistance; this prompted a swing back toward delaying treatment. Most recently, because current ART combinations demonstrate high rates of efficacy with simpler and better-tolerated regimens and because additional drugs and drugs classes are now available, emerging data support a shift back toward earlier initiation of therapy (table 1). This review summarizes recent data that help inform the question of when to start ART.

RATIONAL

The goal of ART is to suppress viral replication, enhance immune function, prevent morbidity and mortality, and ultimately, to prolong healthy survival. There are arguments for early versus late initiation of ART [7]. The rationale for early initiation of therapy is that HIV infection is progressive; current treatment regimens suppress viremia, reduce the risk of the emergence of drug-resistant viral strains, and increase CD4 cell counts and general immune function; current treatment regimens demonstrate durable antiretroviral responses through \( \geq 7 \) years [8]; certain HIV-associated complications may occur, regardless of CD4 cell count (e.g., lymphoma and neurocognitive impairment); and HIV treatment likely reduces HIV transmission in the community. The rationale for delayed therapy is that medications may be inconvenient and have associated adverse effects or toxicities; long-term adverse effects of antiretroviral drugs may be unknown and continue to be reported; risk of progression of HIV infection is low at higher CD4 cell counts; despite reduction of HIV transmission through treatment, an estimated 10% of patients acquire drug-resistant viral strains [9]; and the costs of both the medications and monitoring. Recent data help inform these competing strategies.

COHORT STUDIES

Major cohort studies demonstrate conclusively that mortality is higher for individuals who begin ART when their CD4 cell counts are \(<200 \text{ cells/µL} \), compared with individuals who start ART with higher CD4 cell counts [10]. The ART Cohort Collaboration [11] reported data from 13 North American and European cohorts that comprised 61,798 person-years of follow-up among 20,379 adults who initiated ART between 1995
and 2003. They found that the CD4 cell count at initiation was strongly related to the 5-year risk of developing AIDS or death. Specifically, the risk of death was 1.4 times higher for those who initiated ART with a CD4 cell count of 200–350 cells/μL, compared with those who initiated ART with a CD4 cell count >350 cells/μL (P < .05).

The CASCADE (Concerted Action on Seroconversion to AIDS and Death) collaboration is a collection of 23 cohort studies of HIV-infected adults with well-estimated dates of seroconversion [12]. The collaborators presented predictors of mortality for 9858 patients observed for a median of 8 years after seroconversion. Two-thirds of the participants initiated combination ART during follow-up, and 597 (6%) died. The collaborators found that having a lower recent CD4 cell count, lower nadir CD4 cell count, or a longer duration with a CD4 cell count <350 cells/μL demonstrated clear associations with death due to AIDS, non-AIDS–related infection, liver disease, and non-AIDS–related malignancy.

With the improvement of ART, non-AIDS–defining conditions are causing an increasing proportion of deaths among HIV-infected patients. The Aquitaine cohort observed 4194 HIV-infected persons who received diagnoses of 109 AIDS-defining and 142 non-AIDS–defining cancers during follow-up [13]. The incidence of non-AIDS–defining cancers was independently associated with the duration of time spent with a CD4 cell count <500 cells/μL (rate ratio, 1.11 per year of exposure; 95% CI, 1.01–1.22; P = .02). Lodwick et al. [14] presented mortality data from a combination of cohort studies from Europe and North America comprising nearly 100,000 person-years of follow-up in patients with a recent CD4 cell count of >350 cells/μL; 487 patients died, for an overall death rate of 4.9 per 1000 person-years. The deaths were HIV related for 79 patients (16%), non-HIV related for 235 (48%), and of unknown cause for 173 (36%). They found that even among this group with CD4 cell counts >350/μL, a higher CD4 cell count was independently associated with reduced mortality (rate ratio, 0.95 per 100 cells/μL higher CD4 cell count; 95% CI, 0.90–0.99). This suggests that having CD4 cell counts closer to normal levels is a desired clinical outcome. Other cohort studies suggest that normal levels are achieved more reliably when ART is initiated when the CD4 cell count is >350 cells/μL [15, 16].

A major rationale for deferred ART is the avoidance of drug-induced toxicities. However, investigators from the HIV Outpatient Study [17] used data involving 2165 patients observed for at least 3 years and found that initiation of ART at a CD4 cell count >350 cells/μL was associated with a reduced risk of peripheral neuropathy and anemia, compared with initiation at a CD4 cell count of 200–350 cells/μL. The risk of renal insufficiency was similar in the 2 groups [17].

### CLINICAL TRIALS

Few randomized clinical trials have addressed the question of the optimal CD4 cell count threshold for initiation of ART. The most relevant clinical trial data involving adults are from a post hoc subgroup analysis from the Strategies for Management of Antiretroviral Therapy (SMART) study [18]. This analysis explored subjects who entered the study naive to ART (n = 249) or who had discontinued ART >6 months before the randomization (n = 228). Subjects were randomized either to start ART immediately or to defer ART until the CD4 cell count decreased to <250 cells/μL [19]. In this analysis, the risk of fatal and nonfatal AIDS-defining and serious non-AIDS–defining events was 4 times higher in the deferred ART group, compared with the immediate ART group (95% CI, 1.69–10.39; P = .002), although the absolute numbers of events were only 21 and 6 in the respective groups (figure 1). Generally, the rates of end points were twice as high among subjects who had previously received ART, compared with those who had been ART naive. However, immediate initiation of ART appeared to have the same effect in both groups—the risk of serious events was 75% lower among those randomized to receive ART immediately. Although the SMART subgroup analysis is supportive of earlier initiation of ART, it clearly is not definitive.

Additional analyses of the complete SMART data set found that, among subjects with CD4 cell counts >350 cells/μL, the increased risk of clinical events in the deferred group was explained by higher plasma HIV-1 RNA levels [20]. A fundamental unresolved issue is whether this increased morbidity and mortality will be applicable to those who have never initiated ART. If so, this would strongly support a decision for earlier initiation of ART that is dependent more on having a

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**Table 1. Evolution of US Department of Health and Human Services guidelines for initiation of antiretroviral therapy.**

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<td>&lt;200</td>
<td>Treat</td>
<td>Treat</td>
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<td>200–350</td>
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<td>Offer after discussion with patient</td>
<td>Treat</td>
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<tr>
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<td>Consider if HIV RNA level is &gt;50,000 copies/mL</td>
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- Figure 1. Time to major clinical event among patients who were naive to antiretroviral therapy (ART) or who had discontinued ART for 6 months when they entered the Strategies for Management of Antiretroviral Therapy (SMART) study. Kaplan-Meier time curves for cumulative probability of opportunistic disease, serious non-AIDS events, or death due to any cause are shown. The red line indicates events among participants in the drug conservation (DC) group (i.e., deferring ART), and the blue line indicates events among participants in the viral suppression (VS) group (i.e., immediate ART initiation). Reprinted from the SMART Study Group [19] with permission.

- The Children with HIV Early Antiretroviral Therapy Trial is a phase III study that enrolled 377 infants from South Africa [21]. The infants were HIV infected and 6–12 weeks of age, with a CD4 cell percentage >25%. The subjects were randomized to immediate initiation of ART for 96 weeks, immediate ART for 40 weeks, or deferred therapy until there were signs of clinical or immunological progression. In June 2007, the Data and Safety Monitoring Board for the trial halted enrollment because of increased mortality in the deferred-therapy group. The death rate in the deferred group was 25 deaths per 100 patient-years, compared with 6 deaths per 100 patient-years in the combined immediate therapy groups (hazard ratio, 0.24; 95% CI 0.11–0.52). All subjects were offered ART, and follow-up continues.

ONGOING AND PLANNED CLINICAL TRIALS

The INSIGHT (International Network for Strategic Initiatives in Global HIV Trials) network is planning a large clinical trial that will randomize subjects, on a global basis, who have CD4 cell counts >500 cells/µL to have immediate initiation of ART or deferral of ART until the CD4 cell count is <350 cells/µL [22]. A pilot phase of the study will initially enroll 1200 subjects, with sample size for the remainder of the study to be determined, at the initial Data and Safety Monitoring Board review, on the basis of the event rate. The primary end points will be fatal and nonfatal AIDS-defining events, nonfatal serious non-AIDS–defining events, and fatal non-AIDS events.

Two randomized clinical trials are evaluating the timing of initial ART in developing countries. The HIV Prevention Trials Network (052/ACTG5245 [NCT00074581]) will address the issue of when to initiate ART as a secondary objective. The primary objective of the study is to evaluate whether ART reduces the risk of HIV transmission in 1500 heterosexual couples with discordant HIV status. Eligible couples comprised an HIV-infected partner with a CD4 cell count of 350–550 cells/µL and an HIV-uninfected partner. The HIV-infected partners are randomized to immediate versus deferred therapy until they develop an AIDS-defining illness or a CD4 cell count <250 cells/µL. Although the primary end point is HIV transmission to the HIV-uninfected partner, the study will have a unique opportunity for evaluating the effect of early ART.

Comprehensive International Program of Research on AIDS (HT001 [NCT00120510]) completed enrollment of >800 HIV-infected patients in Port-au-Prince, Haiti, who had CD4 cell counts of 200–350 cells/µL; patients were randomized (1) to have immediate initiation of ART or (2) to have ART deferred until their CD4 cell counts were <200 cells/µL or until development of an AIDS-defining illness. The primary end point is all-cause mortality and will be particularly relevant for resource-limited areas.

COST-EFFECTIVENESS

The Cost-Effectiveness of Preventing AIDS Complications project studied the cost-effectiveness of 3-drug ART by developing a model with data from antiretroviral clinical trials and cohort studies [23]. They found that 3-drug combination therapy increased the projected quality-adjusted life expectancy by 1.4–2.7 years, with cost-effectiveness ratios of $13,000–$23,000 per quality-adjusted year of life (QALY) gained, compared with gains with no therapy. Interestingly, the cost-effectiveness ratio...
decreased as the CD4 cell count at initiation of therapy increased from 50 cells/μL ($26,000 per QALY) to 200 cells/μL ($17,000 per QALY) to 500 cells/μL ($14,000 per QALY). The authors concluded that the cost-effectiveness ratio compared favorably with other common medical interventions and that starting therapy when the patient had higher CD4 cell counts was effective and efficient [23]. The same group applied a similar model to uninsured HIV-infected adults and estimated costs for government payers in Florida, Massachusetts, and New York, with the similar conclusion that initiating ART when the patient’s CD4 cell count reaches 500 cells/μL is cost-effective; they recommended that states consider Medicaid waivers to expand access to early treatment [24]. Another group used a modeling approach to compare starting ART at a CD4 cell count of either >350 cells/μL or 200–350 cells/μL and found a favorable incremental cost-effectiveness ratio in support of earlier initiation of treatment [25].

Researchers have assessed the cost-effectiveness in developing countries. Investigators in Cape Town, South Africa, found that ART was reasonably cost-effective for South African patients and that there were incremental benefits from starting ART at each successively higher CD4 threshold (>350 cells/μL vs. 200–350 cells/μL or <200 cells/μL) [26]. The Cost-Effectiveness of Preventing AIDS Complications group developed models for Cote d’Ivoire [27], India [28], and the eastern Caribbean [29] that yielded similar conclusions.

**CURRENT GUIDELINES**

ART guidelines from around the world recently increased the CD4 cell count threshold for initiating ART (table 2). The US Department of Health and Human Services guidelines updated their recommendations in January 2008 and now recommend ART for all patients with CD4 cell counts <350 cells/μL; they also note that existing data are inadequate to recommend starting ART at higher CD4 cell counts [7]. The International AIDS Society–USA updated their recommendations in August 2008 [30]. The European AIDS Clinical Society updated their guidelines in December 2007 and recommend treatment for all patients with CD4 cell counts <350 cells/μL [31]. They also recommend ART for patients in some groups with CD4 cell counts of 350–500 cells/μL. They recommend deferring therapy, in general, for patients with CD4 cell counts >500 cells/μL. The British HIV Association guidelines also were updated in 2008 and recommend ART for patients with CD4 cell counts ≤350 cells/μL and participation in a “when to start” study for those with CD4 cell counts >350 cells/μL [31].

Guidelines for initiating ART in developing countries also are changing. World Health Organization guidelines, updated in August 2006, recommend treatment for patients with CD4 cell counts <200 cells/μL, consideration of ART for patients with CD4 cell counts of 200–350 cells/μL, and deferral for patients with CD4 cell counts >350 cells/μL [32]. Whereas South African national guidelines, last updated in 2004, recommend ART only for patients with CD4 cell counts <200 cells/μL [33], the Southern African HIV Clinicians’ Society recently updated their recommendation to start ART for patients with CD4 cell counts <350 cells/μL [34].

**SPECIFIC POPULATIONS**

There are certain subgroups of HIV-infected patients for whom earlier initiation of ART should be considered (table 3). These subgroups may be at higher risk of morbidity and mortality as a result of uncontrolled HIV infection or may be at greater risk of transmitting HIV infection. The major ART guidelines have differed in their recommendations for these subgroups of patients.

**Acute opportunistic infection.** ACTG5164 was a randomized, open-label trial comparing early initiation of ART (within 14 days of beginning therapy to treat an acute opportunistic infection) and delayed ART (30 days after beginning therapy to treat an acute opportunistic infection [36]); 282 subjects were randomized. The most common opportunistic infection was *Pneumocystis jirovecii* pneumonia (63%); patients with tuberculosis were excluded. The percentage of subjects with AIDS progression or death was 14% in the early-therapy group versus 24% in the delayed-therapy group (P = .023). There was no difference in toxicity, immune reconstitution inflammatory syndrome, or virological responses 48 weeks after randomi-

<table>
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<tr>
<td>World Health Organization, 2006 [31]</td>
<td>Yes$^3$</td>
<td>Yes</td>
<td>Consider</td>
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* Except for patients who also have tuberculosis.
Chronic HBV infection is common among HIV-infected persons. The nucleoside reverse-transcriptase inhibitors emtricitabine, lamivudine, and tenofovir have activity against HBV; therefore, it is difficult to treat HBV infection optimally without also impacting HIV infection. If treatment of HBV infection is indicated, patients should be treated with a fully suppressive combination ART regimen that includes 2 nucleoside reverse-transcriptase inhibitors with activity against HBV [7, 31].

HCV infection also is a common coinfection among HIV-infected persons. There is compelling evidence that HIV infection accelerates the rate of fibrosis associated with HCV, compared with patients infected with HCV alone [39]. Although there are no clinical trials randomizing HCV-infected subjects to early versus delayed ART, 11 cohort studies have found that ART is associated with a reduced rate of HCV disease progression, and 4 studies have also found a reduced rate of liver-related mortality [39]. Some guidelines recommend earlier initiation of ART for patients with HCV coinfection [31, 32].

**HIV-associated nephropathy.** HIV-associated nephropathy, most commonly seen in patients of African descent, can lead to renal failure in HIV-infected patients. The pathogenesis is not completely understood, but uncontrolled HIV replication is a known risk factor. Recent evidence suggests that the renal function does not generally recover once ART is initiated [40]. Earlier initiation of ART should be considered if the patient has evidence of HIV-associated nephropathy [7].

**Ongoing risk of HIV transmission.** Lower plasma HIV-1 levels are associated with a lower risk of sexual transmission of HIV involving patients not receiving ART [41]. It is likely that control of HIV replication with ART will also reduce the infectiousness of HIV-infected persons [42]. The clear benefit of ART for reducing mother-to-child transmission of HIV [43] provides evidence in support of this claim. Early initiation of ART could be considered for subjects deemed to be at higher risk of transmitting HIV, such as those engaging in high-risk sex with serodiscordant partners. Indeed, some researchers have proposed early initiation of ART for a given population, to reduce the community viral load and the overall risk of sexual transmission of HIV within a sexual network [44].

**Pregnancy and breast-feeding.** ART dramatically reduces the risk of mother-to-child transmission of HIV infection, and major guidelines recommend ART for all pregnant HIV-infected women, regardless of CD4 cell count, in an attempt to achieve an undetectable plasma HIV-1 RNA level at the time of delivery [43]. It is less clear how ART should be managed...
after delivery for women who are receiving ART solely to prevent mother-to-child transmission of HIV. The SMART study suggests that interruption of ART may lead to increased postpartum morbidity and mortality, compared with continuation of ART [18]. Continuation of ART may also reduce transmission through breast-feeding [45], which is a common practice for HIV-infected women in many parts of the world. Taken together, these results suggest that consideration be given to continuing ART for postpartum women, regardless of CD4 cell count at initiation of treatment, unless there is a compelling reason for discontinuing treatment. Randomized studies are planned.

CONCLUSIONS

Despite previous debates about early versus delayed initiation of ART, the current thinking is that ART should be started earlier in the course of HIV infection. Contemporary ART is effective, convenient, and well tolerated, and data from large cohort studies and emerging data from randomized clinical trials suggest that earlier initiation of ART is associated with a reduction in the number of clinical events, both HIV and non-HIV related. Earlier initiation of ART also appears to be cost-effective. Although many current ART treatment guidelines throughout the world now recommend ART for HIV-infected individuals with CD4 cell counts <350 cells/μL, certain subgroups with higher CD4 cell counts may also benefit from ART. As data accumulate, CD4 cell count thresholds for ART initiation may increase further.

Acknowledgments

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