The question of when to start antiretroviral therapy (ART) for infection with HIV has been much discussed, and treatment management guidelines have oscillated from the “hit hard, hit early” philosophy to conservative approaches of deferring treatment in asymptomatic patients until CD4+ cell counts are <200 cells/μL [1, 2], despite their being few data on the subject [3]. In this issue of the Journal, results from a subgroup analysis [4] of a randomized trial, the Strategies for Management of Antiretroviral Therapy (SMART) study, are presented that provide some insight into this question.

Major reasons why, in recent years, guidelines have tended to be more conservative and have recommended deferring treatment until CD4+ cell counts are <200 cells/μL include the following [5]: the low absolute risk of AIDS-defining clinical events at higher CD4+ cell counts; the negative impact of side effects on quality of life as well as the occasional occurrence of life-threatening adverse effects, including ones that have been associated with long-term use of ART (such as myocardial infarction); and the inconvenience of drug regimens, leading to reduced adherence, an increased risk of drug resistance, and limitations on future drug options. Revisiting these issues, Phillips et al. [5] recently concluded that advances in drug development and an improved understanding of the durability and adverse effects of specific drugs have led to renewed interest in the possibility that initiation of ART at CD4+ cell counts >200 cells/μL might be preferable.

The SMART study [6] enrolled HIV-infected subjects with CD4+ cell counts >350 cells/μL (including subjects with prior AIDS events) and randomized participants to a continuous ART strategy versus a CD4+ cell count–guided strategy for interrupting therapy during periods of higher CD4+ cell counts. The study population was predominantly and extensively ART experienced. In this issue, results are presented for a subgroup of SMART participants not receiving ART at the time of enrollment [4]. Specifically, participants who were ART naive (n = 249) or who had not received ART for at least 6 months (n = 228) were included. Per the SMART study design, the subjects in the continuous ART arm were in effect randomized to (re)initiate ART immediately, and those in the CD4+ cell count–guided arm were randomized to defer (re)initiation until their CD4+ cell count fell to <250 cells/μL. Follow-up was for a mean of 18 months. In this subgroup, as in the overall SMART population, subjects who immediately (re)initiated ART experienced fewer grade 4 symptomatic adverse events than did those deferring (re)initiation. In addition, also as in the overall study population, fewer subjects randomized to (re)initiate ART immediately experienced opportunistic disease (OD) events or died (5 vs. 15 participants; P = .02) or experienced major cardiovascular, renal, or hepatic events (the so-called serious non-AIDS events; 2 vs. 12 participants; P = .01). Of importance, this comparison was driven primarily by events among subjects who had previously received ART (for a median of 4 years). The data that more truly address the question of when first to start ART were limited. Of the 249 ART-naive participants, 1 versus 4 participants experienced OD events or died in the immediate versus deferred ART arms, and 1 versus 4 experienced serious non-AIDS events.

That use of ART at higher CD4+ cell counts might reduce the incidence of OD is not surprising: randomized trials conducted in the early 1990s showed a benefit [7], and observational studies have suggested that this is true for regimens in use more recently [8]. What is more important is that this subgroup analysis raises...
the possibility that earlier treatment has a beneficial effect, at least in the short-term, not only with respect to OD but also with respect to other serious morbidities that might be associated with HIV infection, without the effect being counterbalanced by severe toxicity.

It is concluded by the authors of the article that the findings of the subgroup analysis need to be validated in a large, randomized clinical trial. We agree—although, to be specific, such a trial should restrict enrollment to subjects who have no history of ART, because this is the population of real interest for the when-to-start question. Subjects who have previously taken ART, even if they have not done so for several months at the time of enrollment, likely have a distinctly different risk profile for AIDS and possibly other events (as seen in the subgroup analysis and, hence, drive the results of any trial (as also seen in that analysis). Furthermore, there is the potential for differing effects of ART among subjects who have previously received ART versus those who have never received ART—due, for example, to the possibility of the reemergence of archived resistant virus [9–11].

Such trials are under way. For example, one that involves a collaboration between the HIV Prevention Trials Network and the AIDS Clinical Trials Group (HPTN 052/ACTG 5245) highlights another potential benefit of earlier treatment: reducing the risk for transmission. The trial is being undertaken in countries with limited resources, with ~50% of the enrollment expected to come from sub-Saharan Africa. Serodiscordant couples for whom the HIV-positive index subject does not meet World Health Organization guidelines for initiating ART and has a CD4+ cell count between 350 and 550 cells/μL are enrolled. The index subject is randomized to start ART immediately or to defer initiation until either his or her CD4+ cell count falls to <250 cells/μL or he or she experiences an AIDS-defining illness. Although originally designed to evaluate the effects of ART on HIV transmission, by following the HIV-positive index cases for clinical outcomes (over at least 5 years) the study will also provide important data to address the when-to-start question.

Along with many other factors, differences in HIV-related morbidity and comorbidities across different regions of the world mean that there is a need for a randomized trial in countries with more-extensive resources. What is uncertain is whether such a trial is feasible. With current treatment guidelines moving more toward the recommendation that ART be initiated in subjects with CD4+ cell counts <350 cells/μL rather than waiting for counts <200 cells/μL [12], such a trial would need to enroll asymptomatic subjects with a CD4+ cell count >500 cells/μL to provide reasonable separation between the immediate ART and deferred ART strategies. In a recent study, the median time from presenting with a count between 500 and 650 cells/μL to having a count <350 cells/μL was 2.5 years, with ~75% and 90% <350 cells/μL within 5 and 8 years, respectively [13]. Thus, a trial would need to follow all subjects for at least 5 years to quantify just the initial benefits, if any, of immediate ART over deferred ART. Such a duration may also allow the assessment of whether any benefit is transient (as was seen in comparisons of immediate vs. deferred zidovudine monotherapy [7], despite longer-term sustained differences in CD4+ cell count [14, 15]). However, given the potency of many of the currently available ART regimens, very few subjects randomized to an immediate ART strategy would be expected to exhaust treatment options over this time frame. Thus, such a trial could not evaluate the long-term downsides of immediate therapy (and, hence, the benefits of deferred ART) that are due either to toxicity from cumulative drug exposure or to accumulated viral resistance and exhaustion of treatment options leading to an increased risk of HIV-related morbidity. It is likely unrealistic to undertake a randomized trial that could evaluate such very long-term outcomes. It is also unlikely that observational studies will generate answers to such long-term questions without considerable doubt arising with regard to confounding factors. Realistically, such very long-term outcomes will need to be evaluated by the type of computer-simulation models used in cost-effectiveness analysis [16, 17]—although the validity of such long-term models cannot be verified empirically.

The SMART study was important because it showed that the serious morbidity that was considered a priori to be related to ART might, in fact, be beneficially affected by ART, perhaps because such morbidity is a consequence of chronic HIV infection or because some adverse effects of ART might be less frequent when ART is initiated at higher CD4+ cell counts [18]. Because a major argument against the initiation of ART at higher CD4+ cell counts has concerned the risk-benefit ratio for ART when the notion of benefit tended to be focused on AIDS-defining events and mortality, results from the SMART study emphasize the need to look at serious morbidity more broadly in a when-to-start trial, either as a set of coprimary end points or as a composite end point. Whichever, given the cost of ART and associated care, it is unlikely to be adequate to show only that earlier initiation of ART is superior to deferred initiation with respect to one or more such end points; rather, it will be important to establish that any difference is sufficiently large (e.g., greater than a 20% reduction in serious morbidity) and is sustained (rather than transient), to justify the costs. In addition to raising important issues for the informed consent process, this necessarily increases the size of the trial needed—a study population in excess of 10,000 participants might be required. A major hurdle will be finding such a number of participants who, along with their physicians, are willing to be randomized either to commence ART immediately or to defer its use. To succeed, a when-to-start trial will therefore likely need to involve international col-

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laboration and to use a design that facilitates enrollment, perhaps of very small numbers of subjects at numerous locations in many countries, with simple follow-up and high retention.

References