Should the CD4 threshold for starting ART be raised?

Since the development of combination antiretroviral therapy (ART) for HIV in the mid-1990s, changes in recommendations on when to start treatment in high-income countries have been likened to a swinging pendulum.1-3 After the dismal prognosis for patients in the pre-ART era, the initial approach of early aggressive therapy was based on enthusiasm derived from theoretical considerations.4 However, subsequent data from observational studies and short-term clinical trials revealed unexpected long-term metabolic and cardiovascular toxicities, leading to a shift in expert opinion toward a more cautious approach.3 Recommendations to date, however, have largely remained uninformed by data from randomised trials with clinical endpoints.

Current British and American guidelines recommend that, in the absence of an AIDS-defining illness, ART should be started in patients with blood CD4 cell counts in the range 200–350 cells per µL.5,6 With the development of treatment regimens with lower toxicity and increasing evidence that HIV-associated morbidity and mortality develop at CD4 cell counts substantially higher than 200 cells per µL,7 it might be time for the pendulum to swing once more towards earlier treatment.

In The Lancet today, the When To Start Consortium presents an analysis of data from over 45,000 patients from 18 observational HIV cohorts in Europe and North America.7 Frequency of death, or combined AIDS and death, in patients receiving and not receiving ART was used to identify a minimum threshold of 350 cells per µL for starting ART. The validity of this recommendation is greatly strengthened by the large numbers of patients, diversity of cohorts, the ability to compare event frequencies between narrow overlapping strata of CD4 cell counts and, crucially, the adjustment for lead-time bias.

Observational data can be subject to unrecognised confounders, and the analysis did not include non-fatal non-AIDS events or data on quality of life or adherence. At higher CD4 cell counts, differences in non-AIDS morbidity between strata for CD4 cells might be important, as shown in a small subgroup analysis from the Strategies for Management of Antiretroviral Therapy (SMART) study.8 In that study, ART-naive individuals with CD4 cell counts higher than 350 cells per µL were randomly assigned either to receive immediate ART or to defer ART until counts were less than 250 cells per µL. Those who deferred treatment had a far higher rate of major morbidity and all-cause mortality than did those treated immediately (4.9 vs 1.0 events, both per 100 person-years, respectively). These data suggest that, when taking into account serious non-AIDS events, the potential benefit to be derived from earlier initiation of ART might be even greater than that suggested by the When To Start Consortium.

The data presented by the When To Start Consortium support a shift in recommendations towards initiation of ART at a minimum CD4 cell-count threshold of 350 cells per µL.7 However, while acknowledging the strength of this analysis, these observational data are not definitive. Randomised trials are needed in which more varied data are collected. At high CD4 cell counts, differences in absolute risk of AIDS and death between early and deferred ART are small, and uncertainty about the risk to benefit ratio remains. Even when benefits outweigh risks, cost-effectiveness is unclear. Data are needed on serious complications of ART that might negate the benefits, such as cardiovascular, renal, and hepatic disease. Furthermore, the effect on the quality of life should be assessed. A large randomised study assessing such variables, the Strategic Timing of Antiretroviral Treatment (START) study, is due to begin this year.9

The data in the When To Start Consortium study were from cohorts in industrialised countries and cannot be assumed to be directly applicable to patients in all
settings. Mortality rates and the range of morbidity differ between cohorts in industrialised countries and resource-limited settings. Data from South Africa, for example, indicate that unusually high rates of AIDS and death occur in patients with CD4 cell counts in the range 200–350 cells per μL. Early mortality in patients receiving ART in sub-Saharan Africa is also substantially greater than in those treated in high-income countries. Moreover, the range of ART drugs available and cost-effectiveness considerations can be more restrictive in developing countries.

Thus, when considering both high-income and resource-limited settings, the question of when to start ART might have more than one right answer. WHO guidelines for resource-limited settings currently recommend initiation of ART before blood CD4 cell counts fall below 200 cells per μL with an upper threshold of 350 cells per μL. To inform these recommendations, randomised trials should include patients living in resource-limited settings.

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We declare that we have no conflicts of interest.