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# When should antiretroviral therapy be started in HIV-positive persons?

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## Abstract

Recommendations for the initiation of combination antiretroviral therapy in HIV-positive individuals are largely based on data from observational studies. Whilst all guidelines recommend immediate treatment in individuals with a CD4 count of less than 350 cells/mm$^3$, guidelines vary in their recommendations for treatment at higher CD4 counts. Several large cohort studies have published findings that contribute to the debate, although conclusions vary and results from these studies may be subject to bias.

## Introduction and context

In resource-rich settings, treatment guidelines are consistent in recommending the immediate initiation of combination antiretroviral therapy (cART) in all HIV-positive individuals with a CD4 count of less than 350 cells/mm$^3$; in this group, the benefits of cART clearly outweigh its disadvantages. However, there is inconsistency between the guideline committees as to whether asymptomatic individuals with CD4 counts equal to or greater than 350 cells/mm$^3$ should begin cART. For example, whilst the 2009 US Department of Health and Human Services guidelines [1] and the International AIDS Society-USA [2] panel recommend treatment for all patients with a CD4 count of 350-500 cells/mm$^3$, neither the European AIDS Clinical Society [3] nor the British HIV Association [4] recommends treatment at this level unless specific comorbidities are present. This inconsistency largely results from the limited evidence base; as only limited data are available from randomized trials on the benefits or risks of earlier cART [5], guideline committees have based their recommendations on evidence from observational studies and expert clinical opinion.

Until recently, the main arguments for delaying cART related to the toxicities and inconvenience of the drugs, as well as the concern that patients would be unable to maintain the high levels of adherence necessary to ensure sustained virological suppression. Little was felt to be gained from initiating cART in individuals with CD4 counts of greater than 350 cells/mm$^3$ in whom the risk of AIDS and consequent mortality was low. However, antiretroviral drugs are now more potent, have fewer toxicities, and are more forgiving to lapses in adherence. Furthermore, death rates in HIV-positive individuals remain elevated compared to those in the general population [6,7] and it is believed that HIV may play a role in the development of several serious non-AIDS conditions [8-10]. Thus, cART may have a greater positive impact on the health of HIV-positive individuals than anticipated, which may now justify its earlier use. This review briefly summarises the latest evidence on the topic; recent reviews discuss some of the issues in more detail [11,12].

## Recent advances

Many observational studies have compared outcomes among individuals initiating cART at different CD4 counts [13,14]. However, an individual who is not diagnosed with HIV until his/her CD4 count has fallen to a low level could not have received treatment at a higher CD4 count

(as s/he had not been diagnosed) but must have survived long enough to be diagnosed at the lower CD4 count. Failure to take account of this 'lead-time' may result in biased estimates of the benefits of early treatment [15]. Conclusions from early studies that used appropriate methodology to remove the effect of lead-time bias were inconsistent regarding the initiation of cART at a CD4 count of greater than 350 cells/mm$^3$ [16,17]. However, these studies were relatively small, and the methods may not have been optimal.

Investigators from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) study [18] identified individuals who had experienced a CD4 count of either 351-500 cells/mm$^3$ or greater than 500 cells/mm$^3$; these groups were then divided again into those who initiated cART immediately and those who deferred its use. The authors used inverse probability weighting methods to control for biases resulting from informative censoring (which may arise if patients who dropped out of the analysis at any stage had different characteristics to those who did not) and known confounders. Of the 67,527 patients in the study, 8362 had a CD4 count of 351-500 cells/mm$^3$ (2084 initiated cART immediately) and 9155 a CD4 count of greater than 500 cells/mm$^3$ (2220 initiated cART immediately). Death rates were increased by 69% and 94%, respectively, among those who deferred therapy in each group compared to those who started cART immediately. Investigators from the When to Start Consortium [19] considered progression to AIDS and/or death in 24,444 antiretroviral-naive individuals starting cART. Using information from 21,247 patients followed in the pre-cART era, the authors estimated the distribution of lead-times, which was then incorporated into the analysis. Deferred initiation of cART was generally associated with more rapid progression rates than immediate initiation, although the difference was not statistically significant at CD4 counts of greater than 350 cells/mm$^3$. Shepherd *et al.* [20] directly estimated the optimal CD4 count at which to initiate cART. Using a similar method to the NA-ACCORD group, they concluded that the optimal CD4 count depended on whether the ultimate aim of cART was to improve the patient's health (defined by an increase in the CD4 count or reduction in the occurrence of new AIDS events or death), in which case the threshold was between 489 and 554 cells/mm$^3$, or to improve quality-of-life, in which case the threshold was between 337 and 475 cells/mm$^3$. Most recently, Jonsson Funk *et al.* [21] presented data from the CASCADE Collaboration [21] suggesting that whilst the initiation of cART at a CD4 count of 350-500 cells/mm$^3$ may reduce the risk of clinical progression, the low absolute risk of progression meant that 34 patients would need to be treated to prevent one new case of AIDS or death (or 71 patients for death only) over a three-year period.

As an alternative approach, several authors have used computer simulation models to address the issue. Mauskopf *et al.* [22] estimated that initiation of cART at a CD4 count of greater than 350 cells/mm$^3$ would result in longer quality-adjusted survival compared to starting cART at lower CD4 counts. Braithwaite *et al.* [23] demonstrated that treatment at a CD4 count of 500 cells/mm$^3$ resulted in gains in quality-adjusted life-years at all ages, even assuming that patients may not be fully adherent to cART. The validity of results from modelling studies does, however, rely strongly on the assumption that the model accurately describes disease progression.

## Implications for clinical practice

Whilst the accruing evidence would suggest that earlier initiation of cART may be beneficial, one limitation of all observational studies is that of unmeasured confounding. Under most treatment guidelines, few patients initiate cART at high CD4 counts and those who do may differ from those who do not in terms of their likely long-term outcomes, regardless of cART use. It is unlikely that any observational study will be able to fully control for these differences. Even if shown to be beneficial, the full 'costs' (financial or other) of earlier cART must be assessed. At least one randomised trial of earlier versus deferred cART is underway [24] and it would be prudent to wait for the results of this before changing guidelines. Finally, whilst the decision to initiate cART is predominantly based on an individual's CD4 count, other biomarkers [25-27] may also provide information about an individual's risk of clinical events; incorporation of these biomarkers into the decision-making process may further optimise the timing of cART in individual patients.

## Abbreviations

AIDS, acquired immune deficiency syndrome; cART, combination antiretroviral therapy; HIV, human immunodeficiency virus; NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design.

## Competing interests

The author reports that several colleagues are actively involved in the design and management of the Strategic Timing of Antiretroviral Treatment (START) trial.

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