Antiretroviral Therapy
When to Start

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KEYWORDS

• Human immunodeficiency virus • Antiretroviral • Initiation • CD4 • Start • Timing • Therapy

KEY POINTS

- Despite incomplete and in some cases conflicting cohort data regarding the mortality benefit to ART at CD4+ cell counts higher than 500/mm^3, there is evidence to reasonably suggest the existence of harm with untreated HIV, even at high CD4+ cell counts.
- In the absence of evidence of significant harm due to early ART initiation, there are clear reasons to recommend initiation of ART at any CD4 count.

INTRODUCTION

The development of effective antiretroviral therapy (ART) in response to the emerging epidemic of human immunodeficiency virus (HIV) ranks as one of the most remarkable achievements of modern medicine. However, it was not long after the first of these medications became available that the issue of when is the optimal time in the disease course to use these agents was raised: a question that continues to be asked today. The answer, framed in terms of a balance between the potential benefits of therapy and its risks and costs, has evolved along with HIV therapy and our understanding of its benefits and disadvantages.

At lower CD4+ cell counts, there is irrefutable evidence that the benefits of ART outweigh the harms. For individuals with less advanced infection, the balance between the hazards of unchecked viral replication and the possibility of long-term drug toxicities, development of drug resistance, and expense of treatment of many years seemed to favor delaying HIV therapy. As the potency, tolerability, and

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convenience of ART regimens have improved and the deleterious effects of even moderate CD4+ cell depletion have been shown, the calculus of ART initiation has shifted, and the rationale for deferring therapy until a specific CD4+ count threshold has become vulnerable to challenge. However, the evidence supporting the initiation of ART at high CD4+ counts is less robust than that available for those with lower counts, and within this data vacuum, controversy has emerged.

In this article, current expert panels' recommendations on when to start ART are reviewed, and the strengths and weaknesses are discussed of the rationale to treat earlier rather than later in the course of HIV infection.

HIV TREATMENT GUIDELINES

Current recommendations by both major US HIV treatment guideline panels, the Department of Health and Human Services (DHHS) and the International Antiviral Society-USA (IAS-USA), call for the initiation of ART in practically all patients with HIV infection willing and able to take these medications. This position abandons any deferral of treatment until a set CD4+ cell count threshold (a substantial departure from earlier recommendations to hold ART until immunosuppression became evident). The history of the evolution of the guidelines from advocating a cautious application of ART to a near universal approach to HIV therapy is also a history of the evolution of HIV therapeutics and our use of these medications (**Fig. 1**).

The first edition of the DHHS guidelines, published in 1998, recommended ART initiation for asymptomatic individuals with CD4+ counts up to 500 cells/mm^3, underscoring the urgency at the time of what was a dire public health emergency.[1] However, the only therapeutic option available at that time, zidovudine, has low potency and high-level toxicity. With data from the CONCORDE study, a large trial of high-dose zidovudine monotherapy in those with earlier versus more advanced HIV disease, showing no survival or disease progression benefit of this nucleoside,[2] the guidelines downshifted to a more stringent CD4+ count threshold for ART initiation

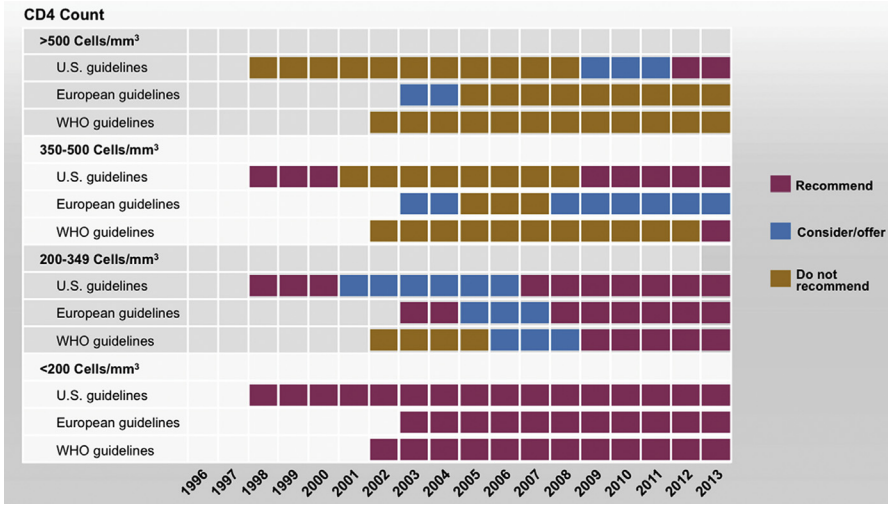

Fig. 1. Evolution of CD4+ count criteria for starting ART in asymptomatic persons with HIV infection, according to different guidelines. (*From* De Cock KM, El-Sadr WM. When to start ART in Africa–an urgent research priority. N Engl J Med 2013;368:887; with permission.)