

Age-Old Questions: When to Start Antiretroviral Therapy and in Whom?

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Two seemingly unrelated themes have emerged in HIV research over recent years. One relates to the increasing evidence that early introduction of antiretroviral therapy (ART) in infected individuals is preferable to delayed therapy, and the second to the interactions between HIV and aging in our population. An article by Edwards et al. in this issue of *Clinical Infectious Diseases* [1] suggests that these themes may be closely related.

When to start ART has been controversial since the 1980s, and recommendations from different guideline committees have fluctuated widely, even within the same groups over time (Figure). The most widely used US guidelines currently recommend treating virtually all HIV-infected persons, regardless of CD4 cell count [2, 3], whereas other guidelines draw rather arbitrary CD4 cell limits for ART initiation (<500 or <350 cells/ μ l) because of the paucity of clinical endpoint data from randomized clinical trials supporting early therapy. Until recently, data to support when to start have come largely from cohort studies that suggest higher death rates are associated with deferred ART [4-6]. Some studies have also utilized non-clinical endpoints to suggest that early ART is preferable to deferred therapy [7, 8]. In addition, one important randomized clinical trial indicated that in a study of discordant couples (one HIV-infected, one not), early ART was associated with a 96% reduction in HIV transmission to the uninfected partner [9]. Thus, early therapy may not only benefit the individual patient, but may have public health advantages as well.

Two recently and preliminarily reported randomized controlled trials have further informed the when to start question. In February 2015, results of the seven-year Temprano trial were presented. In this four-arm factorial design study enrolling 2,056 participants with CD4 cell

counts $>500/\mu\text{l}$ in Côte d'Ivoire, the investigators examined both the benefit of early ART and that of early antituberculosis chemoprophylaxis. Results demonstrated that ART started at CD4 cell counts $>500/\mu\text{l}$ reduced the risk of serious infection and death by 44% compared to ART initiation performed according to current World Health Organization guidelines [10]. In May 2015, the preliminary results of the START trial were announced [11]. Like the TEMPRANO study, the START trial compared initiation of ART in HIV-infected individuals whose CD4 cell counts were $>500/\mu\text{l}$ (early group) with ART initiation when CD4 cell counts declined to $350/\mu\text{l}$ (deferred group). The study enrolled 4,685 participants, and after approximately three years of follow-up, an interim analysis by a Data Safety Monitoring Board found that the risk of the combined clinical outcome, which included AIDS related events, serious non-AIDS events, or death, was reduced by 53% by early compared with deferred treatment (41 vs 86 events). Findings were consistent across geographic regions, and the benefits of early treatment were similar for participants from low-, middle- and high-income countries. Collectively, these two studies offer solid support for starting ART in all HIV-infected individuals as soon as they enter care, irrespective of CD4 cell count. Full publication of both trials is anticipated.

Regarding the aging theme, we also know that the population of HIV-infected individuals is aging. Approximately 30% of HIV-infected persons in the US are now over 50, and this proportion is expected to increase steadily over time; moreover, HIV disease progression appears to be more rapid among older individuals [12], and the reasons for this are likely multifactorial. Older individuals often have co-morbid conditions involving multiple organ systems [13, 14]. In addition, older age may affect susceptibility to, and transmission of, HIV, either physiologically by reducing immunologic or mucosal barriers (e.g., via atrophic vaginitis), or

behaviorally, such as by reduced condom use because of less concern for pregnancy [3]. Finally, HIV itself may affect the biology of aging by mechanisms yet to be determined [15].

The novel findings by Edwards et al. begin to elucidate whether there are different age subgroups within the population of HIV-infected individuals in whom the benefits of early ART initiation are more apparent [1]. In their study, 10-year mortality rates were determined using the parametric g-formula to compare 3,532 US patients in three different age groups (18-34y; 35-45y; 45-65y) who entered care between 1998 and 2013. Overall, projected 10-year mortality increased from 11% when ART was initiated at a CD4 cell count threshold of 500/ μ l to 14% when treatment was initiated at a threshold of 200/ μ l. However, the effect of delaying ART was age-dependent, with the greatest benefit of early ART projected in the oldest age group studied. Although there was little effect of early therapy on the youngest age group studied, the effects of early ART on the oldest age group were profound.

Despite these impressive results, today it is difficult to optimally implement early ART in older patients. Data from 2007 note that the median CD4 count at the first test performed after an HIV diagnosis was 135/ μ l in patients 55-64 years, compared to 313/ μ l for patients 15-24 years [16]. As of 2010, only 37% of persons aged 45-64 years had ever had an HIV test, compared to 57% of persons aged 25-44 years [17]. In addition, linkage to HIV care rates are among the worst for older patients [18]. These markers for delays to care might be attributable to fewer devoted resources because of lower anticipated rates of infection; however, this is not borne out by available data. In a recent Centers for Disease Control and Prevention testing report,

newly identified HIV positivity rates were equal in the age categories of 20-29 years and >50 years (0.5%) and were highest among those 40-49 years (0.7%) [18].

The current report by Edwards et al. must be considered preliminary. This modeling study was based on retrospective and observational data, with many potential confounders. The younger patients were more likely to be male, men who had sex with men (MSM), and Hispanic, whereas the older population was more likely to be injection drug users (IDU) with higher competing morbidities and to have an AIDS diagnosis on entry. In addition, causes of death and co-morbidities were not recorded, and loss to follow-up was high. However, the results are intriguing and do suggest that although the urgency to initiate ART may be less for younger HIV-infected individuals, the need for early ART intervention in older individuals is great. It will be of considerable interest to see whether the age-associated risks of deferring ART are confirmed on closer analysis of the two trials (TEMPRANO and START) mentioned above.

If the findings by Edwards et al. are further confirmed in other cohort or trial-based analyses, what does this mean for policy? In the US, reverting from the current “treatment at any CD4” guidelines is unlikely among any age group. However, the intersection of these new results with current case identification rates and treatment failures in older patients could serve as a critical alarm. If patients over 45 years are to capitalize on the potential benefits of early ART, it is time to redouble national efforts to ensure that early treatment is truly viable. Testing, linkage, ART initiation and retention are key; most importantly, we need to remember that aging -- while putting one at risk for many other things -- does not protect one against infection with HIV.

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Figure Legend

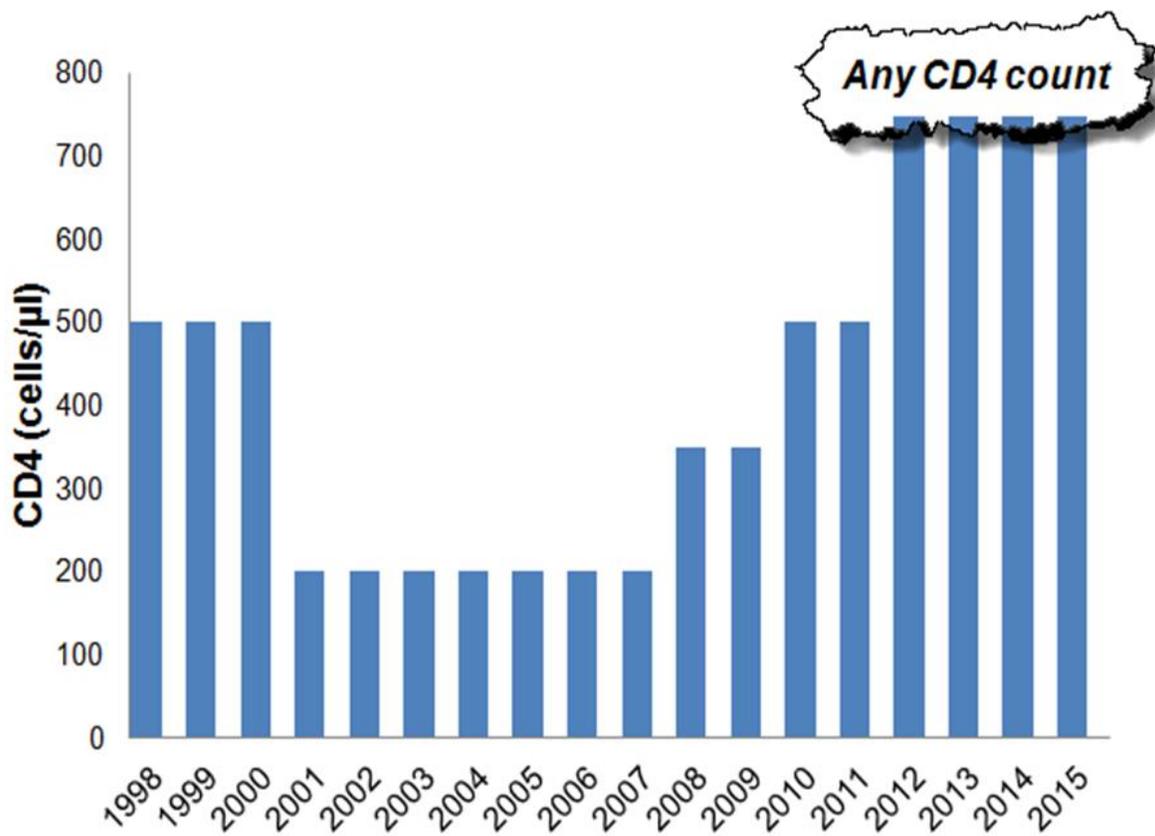
Figure: Evolution of CD4 ART initiation threshold according to the Department of Health and Human Services HIV/AIDS treatment guidelines

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