The death of HIV long-term non-progression?

In the *The Lancet HIV*, Jannie van der Helm and colleagues1 from the CASCADE collaboration present one of the largest and most comprehensive analyses of HIV long-term non-progression (LTNP) reported so far.1 LTNP occurs when an individual is infected with HIV and remains symptom free with a high CD4 count in the absence of antiretroviral therapy for several years. Individuals who can naturally control HIV infection might possess genetic or immunological attributes that could provide important insights for vaccine research efforts.

The definition for LTNP has changed throughout the years as our knowledge of HIV disease progression has increased.2–4 For this analysis, the investigators used a cutoff value of CD4 count of at least 500 cells per μL for 10 years or more, which we believe is appropriate in this case. They analysed 4979 HIV-infected individuals, mainly from Europe, with accurate estimated dates of seroconversion. They report that 10 years after seroconversion, only 283 (6%) could be classified as LTNP. Additionally, over the next 10 years of follow-up, 202 of these individuals progressed to disease. Only seven (0.1% of the original cohort) still qualified as LTNP at 20 years after HIV seroconversion. Of these seven, two subsequently progressed during follow-up. The similarity of the rate of loss of LTNP status in the first and second 10 year periods is striking,1 and these data suggest that determination of LTNP status is mostly a result of the criteria used to classify an individual with LTNP, particularly with respect to the duration of disease-free status.

The researchers also investigated characteristics that are associated with LTNP status, and showed, unsurprisingly, that high HIV viral loads were associated with loss of LTNP status. The association of high viral loads and increased disease progression is well established.5 Since viral load measurements have become more commonplace, most examinations of naturally controlled HIV infection now focus on individuals with undetectable viral loads in the absence of antiretroviral therapy (ie, elite controllers).4 So why then do we care about LTNP when the focus should be more on identifying elite controllers? Some individuals might produce HIV at levels that would predict progression, but remain disease free. These individuals, if they exist in any substantial numbers, would be of great interest to researchers, since one of the driving forces in HIV disease progression is overactivation of the immune system and subsequent killing of bystander cells.2,8 Finding a way to counteract this effect is of crucial importance to understanding HIV pathogenesis.

van der Helm and colleagues’ study is impressive because they have characterised individuals with extended LTNP status. The size of the study emphasises the difficulty in this task, and the research team should be commended for providing such a thorough analysis of the progressive loss of LTNP status over time. Although the investigators conclude that progression-free survival is a rare but real phenomenon, we believe that their data have more likely identified a very small number of individuals at the tail end of the survival curve who, if followed for another decade or two, would eventually progress to disease.

Even if we assume that the seven individuals identified as LTNP after 20 years of follow-up are truly unique, and possess some trait that protects them from progression, their rarity and the length of follow-up needed to properly identify them means that their usefulness in research is limited at best. Additionally, in view of the clear benefits of starting antiretroviral therapy before progression to a CD4 count of less than 500 cells per μL for the prevention of disease and blocking of HIV transmission, we see no reason why individuals should be followed without antiretroviral therapy for the time required to establish LTNP status in the future.9,10 Thus, with the greater focus on viral load to identify elite controllers, and the recommendations of early treatment irrespective of CD4 cell count, we believe that LTNP status is now an outdated and inefficient way to classify individuals who naturally control their HIV infection.

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We declare no competing interests. We thank Thomas C Quinn for reviewing and providing thoughtful suggestions for this commentary. ADR is supported by the Division of Intramural Research (National Institute of Allergy and Infectious
Diseases, National Institutes of Health [NIH]). AART is supported by NIH grant 1K23AI093152-01A1 and the Doris Duke Charitable Foundation Clinician Scientist Development Award (2011036).


