Antiretroviral Therapy in the Elite Controller: Justified or Premature?

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(See the major article by Crowell et al on pages 1692–702.)

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Investigating the immune system of human immunodeficiency virus (HIV) elite controllers, or HIV-infected individuals who maintain undetectable plasma HIV RNA levels without antiretroviral therapy (ART), has led to advances in our understanding of HIV pathogenesis [1] and may be critical to the development of a functional cure for HIV infection [2, 3]. However, although other studies have shown that elite controllers maintain immune control of their viral replication, preventing disease progression in some, these individuals have higher levels of immune activation and chronic inflammation than HIV-infected persons with viral suppression during ART [4–7]. Whether or not elevated markers of inflammation in elite controllers are clinically meaningful is relevant to the question of whether elite controllers should be treated with ART.

Elite controllers have also demonstrated higher levels of atherosclerosis than chronically HIV-1–infected persons receiving ART with undetectable HIV loads and HIV negative controls [5, 8]. The Strategies for Management of Anti-Retroviral Therapy (SMART) trial very clearly highlighted the association between chronic inflammation, observed in suppressed HIV-infected subjects receiving ART, and excess morbidity and mortality; subjects with elevated levels of the inflammatory markers interleukin 6 and D-dimer had higher all-cause mortality [9] and serious non-AIDS events, such as cardiovascular disease (CVD) [10, 11], than similarly suppressed subjects with lower inflammatory markers.

The article by Crowell et al [12] in this issue of the Journal presents a unique analysis of a large cohort of HIV-infected patients, including a fair number of elite controllers (n = 149). To evaluate whether clinical outcomes differed between elite controllers (all not receiving ART) and patients with HIV infection controlled with ART, the authors retrospectively evaluated a multisite cohort and compared hospitalization rates from 2005 to 2011. The major finding was an increased hospitalization rate for elite controllers compared with HIV RNA–suppressed patients receiving ART; surprisingly, hospitalization rates were also higher in elite controller than in subjects with detectable viremia. Differences in hospitalization rates for the elite controllers were largely due to more hospitalizations for cardiovascular and psychiatric disease.

On the surface, these findings seem to provide compelling clinical evidence for ART treatment in elite controller despite chronic viral control and high CD4 cell count, and raise questions as to whether immune viral control will be an adequate end point for functional cure strategies (ie, the ability to stop ART and maintain viral suppression after an immune-based intervention). However, potential study limitations, particularly unmeasured confounders (of common known contributors to CVD) and the interpretation of complex cohort analytic techniques, limit our ability to fully interpret these results and may still leave unanswered the clinical question of the need to treat this rare group of HIV immune controllers.

As is possible in cohort analyses, when subjects are by definition not randomized to comparison groups, baseline characteristics differed significantly between elite controller and other subjects in the study, including HIV-infected persons controlled with ART and subjects with low and high HIV loads. The elite controller cohort was significantly more likely to be female (P < .001) and black (P < .001) and had higher CD4 T-cell counts (P < .001). Using multivariable models, which adjusted for sex, race and other factors, Crowell et al [12] found that elite controllers still had almost 2-fold higher incidence rate ratio for hospitalizations than subjects with controlled viral replication during ART.
The largest number of hospital admissions for elite controllers were attributed to cardiovascular events: chest pain, coronary artery disease, and heart failure accounted for 31.1% of admissions for elite controllers, compared with 13.5% overall. Unfortunately, there was no evaluation of common CVD confounders, such as body mass index, Framingham risk score, total cholesterol or fasting glucose level, or even a history of hypertension, diabetes, and concurrent use of statin medications. Crowell et al [12] did perform a focused chart review on available elite controllers (n = 134) and 555 matched medical controllers, which revealed that a significant higher proportion of elite controllers had a history of ever smoking (82% vs 68%; P = .001), but they commented that this difference alone was unlikely to explain the tripling in cardiovascular hospitalizations observed in that group. However, smoking and other cardiovascular risk factors are key confounders for CVD, and the results of this study cannot be definitively interpreted without accounting for these factors.

Previous evaluation of cardiovascular risk factors among women of different races and ethnicities showed that minority women (black and Mexican American) with lower socioeconomic status have significantly higher prevalence of smoking, physical inactivity, higher body mass index, and non–high-density lipoprotein cholesterol levels [13, 14]. Given the association between race and ethnicity and risk factors for CVD, future studies evaluating the clinical outcome of elite controllers who are not receiving ART would greatly benefit from including CVD risk factors in their analysis or, at a minimum, comparing the prevalence of these factors between groups at baseline.

Crowell et al [12] used sophisticated statistical methods to account for complex issues in cohort analyses, such as subjects who change from one risk group to another during the course of cohort follow-up (ie, medical control to high viremia) and those who have >1 hospitalization event. The extent to which these methods, “generalized estimating equations, clustered on person, with unstructured working correlation, robust variance estimators, and an offset for person-time,” can actually deal with these perplexing analytic problems is difficult to assess, particularly for the practicing clinician. Furthermore, the authors note that elite controllers in care may represent a different population than elite controllers not in care, potentially biasing their population toward elite controllers with concurrent non-HIV associated medical conditions and subsequent higher rates of hospitalization.

Interestingly, psychiatric admission rates were higher in elite controller than in the medical control group, a finding that may support a higher rate of comorbid conditions in the elite controller population (including substance abuse). Alternatively, it is possible that elite controllers have higher rates of low-level viral replication and inflammation at anatomic reservoir sites such as the central nervous system, with subsequent development of HIV-associated neurocognitive disorders. Current work does not support this, but further investigation into rates of such disorders in elite controllers and the effect of ART may provide more support for starting ART in this population [15].

Finally, the cohort selection criteria requiring immune control (CD4 cell count, >350 cells/mm³) for inclusion of persons of comparable years of follow-up in the analysis may bias the assessment of clinical events in subjects not in the elite controller group. Prior studies, including SMART, clearly show that CD4 cell counts drop during periods of CD4 cell counts <350 cells/mm³, the time with low CD4 cell count would not be included in the analysis, nor would hospitalization events during such periods, whereas follow-up periods for the same patients when their CD4 cell counts were >350 cells/mm³ would be included. Because elite controllers have much higher baseline CD4 cell counts [17], they are less likely to have unobserved time when hospitalizations could occur, whereas the other 3 groups might be more likely to have periods of low CD4 cell counts and censored hospitalizations.

Previous studies of elite controllers treated with ART have demonstrated improvements in laboratory parameters such as decreased replication-competent HIV induced from CD4 cells (using quantitative coculture) [18], decreased immune activation [19], and increased total CD4 cell count (but less robust increases than in concomitantly treated viremic patients) [20]. The study by Crowell et al [12] is important because it goes beyond evaluation of surrogate markers and demonstrates that clinical outcomes (hospitalizations) differ between elite controllers and HIV-infected persons controlled with ART, providing further support for the treatment of elite controllers. Methodological issues and missing confounding factors, which may have contributed to the observed increase in hospitalizations among elite controllers, remain important limitations of this study and encourage continued evaluation into the clinical impact of ART on this rare population.

What advice should be provided to clinicians regarding the merits of initiating ART when faced with the rare elite controller in the clinic setting, assuming there are no other compelling reasons to start therapy? Although the current study provides a nudge in the direction favoring therapy, the level of evidence still resides firmly in the category of “expert opinion.” The most cogent decision would be to refer the patient for study until we have better data to formulate stronger recommendations.

Notes

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References