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Antiretroviral Therapy in the Elite Controller, Justified or Premature?

Maile Y. Karris and Richard H. Haubrich

Department of Internal Medicine, University of California San Diego, San Diego, CA, USA

Corresponding Author: Maile Y. Karris, Department of Medicine, 200 W. Arbor Drive MC #8208, San Diego, CA 92103-8208, Phone: (619)543-6146, Fax: (619) 298-0177, m1young@ucsd.edu

Investigating the immune system of HIV elite controllers (EC), or HIV-infected individuals who maintain an undetectable plasma HIV RNA without antiretroviral therapy, has led to advances in our understanding of HIV pathogenesis[1] and may be critical to the development of a functional HIV cure [2, 3]. However, even though previous studies have shown that ECs maintain immune control of their viral replication and, in some, prevent disease progression, these individuals have higher levels of immune activation and chronic inflammation than HIV- infected people with viral suppression on antiretroviral therapy (ART) [4-7]. Whether or not elevated markers of inflammation in ECs are clinically meaningful is relevant to the question of whether ECs should be treated with ART. ECs have also demonstrated higher levels of atherosclerosis compared with chronic HIV-1 infected persons on ART with undetectable HIV viral 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 on ART, and excess morbidity and mortality; subjects with elevated inflammatory markers IL-6 and D-dimer had higher all cause mortality [9] and serious non-AIDS events such as cardiovascular disease[10, 11] than similar suppressed subjects with lower inflammatory markers.

The article by Crowell et al in this issue of *the Journal of Infectious Diseases* 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 ECs (all not on ART) and patients with HIV controlled on ART, the authors retrospectively evaluated a multi-site cohort and compared hospitalization rates from 2005-2011. The major finding was an increased hospitalization rate for elite controllers compared to HIV RNA suppressed patients on ART; surprisingly, hospitalization rates were also higher in EC than in subjects with detectable viremia. Differences in hospitalization rates for the EC were largely due to larger number of hospitalizations for cardiovascular (CV) and psychiatric disease. On the surface, these findings seem to provide compelling clinical evidence for ART treatment in EC despite chronic viral control and high CD4 cell count, and raise questions as to whether immune

viral control will be an adequate endpoint for functional cure strategies (i.e., 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 CV disease) and the interpretation of complex cohort analytic techniques, limit our ability to fully interpret these results and perhaps still leave unanswered the clinical question of the necessity to treat this rare group of HIV immune controllers.

As is possible in cohort analyses, where subjects are by definition not randomized to comparison groups, baseline characteristics of EC significantly differed from other subjects in the study, including HIV infected persons controlled with ART and subjects with low and high HIV viral loads. The EC cohort was significantly more likely to be female ($p<0.001$) and Black ($P<0.001$), and had higher CD4 T cells counts ($P<0.001$). Using multivariable models, which adjusted for gender, race and other factors, the authors found that ECs still had almost two-fold higher hospitalization incidence rate ratio than subjects with controlled viral replication on ART.

The largest number of hospital admissions for ECs were attributed to cardiovascular events: chest pain, coronary artery disease and heart failure accounted for 31.1% of admissions for EC compared to 13.5 % overall. Unfortunately, there was no evaluation of common cardiovascular disease (CVD) confounders such as body mass index (BMI), Framingham risk score, total cholesterol, fasting glucose, or even a history of hypertension, diabetes and concurrent use of statin medications. The authors did perform a focused chart review on available elite controllers (134) and 555 matched medical controllers, that revealed a significant higher proportion of ECs had a history of ever smoking (82% compared to 68%, $p = 0.001$), but commented that they believed 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 can not be definitively interpreted without accounting for these factors. Previous evaluation of cardiovascular risk factors among women of different races and ethnicities report that minority women (Black and Mexican American) with lower socioeconomic status have significantly higher prevalence of

smoking, physical inactivity, higher BMI and non-HDL cholesterol[12, 13]. Given the association between race and ethnicity and risk factors for CVD, future studies evaluating the clinical outcome of ECs who are not receiving ART would greatly benefit from including CVD risk factors in their analysis or, at a minimum, evaluating the prevalence of these factors between groups at baseline.

The authors 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 (i.e., medical control to high viremia) and subjects who have more than one 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. Further, the authors note that evaluation of ECs in care may represent a different population than ECs not in care, potentially biasing their population towards ECs with concurrent non-HIV medical conditions and subsequent higher rates of hospitalization. Interestingly, psychiatric admission rates were higher in EC than in the medical control group, a finding that may support a higher rate of comorbidities in the EC population (including substance abuse). Alternatively, it is possible that ECs have higher rates of low-level viral replication and inflammation at anatomic reservoir sites such as the central nervous system, and subsequently develop HIV associated neurocognitive disorders (HAND). Current work does not support this, but further investigation into rates of HAND in ECs and the effect of ART may provide further support in favor of starting ART in this population [14]. Finally, the cohort selection criteria requiring immune control (CD4 > 350 cells/mm3) for inclusion of person-years of follow-up in the analysis may bias the assessment of clinical events in subjects not in the EC group. Prior studies including SMART clearly show that CD4 cell counts drop during periods of viremia. If viremic (or non viremic) subjects have periods of CD4 < 350 cells/mm3, the time with low CD4 cell count would not be included in the analysis, nor would hospitalization events during this period of low CD4 cell count, while periods of follow up for the same patients, when their CD4 was above 350 cells/mm3, would be included. Since EC have much higher baseline CD4 cell counts, they are less

likely to have unobserved time where hospitalizations could occur, whereas the other three groups might be more likely to have periods of low CD4 cell count and censored hospitalizations.

Previous studies of ECs treated with ART have demonstrated improvements in laboratory parameters such as decreased replication competent HIV induced from CD4 cells (using quantitative co-culture) [15], decreased immune activation[16] and increased total CD4 cell count (but less robust CD4 cell increases compare to concomitantly treated viremic patients) [17]. The study by Crowell et al is important because it goes beyond evaluation of surrogate markers and demonstrates that clinical outcomes (hospitalizations) differ in ECs compared to HIV infected persons controlled on ART, providing further support in favor of treatment of ECs. Methodological issues and missing confounding factors, that may have contributed to the observed increase in hospitalizations among ECs, remain important limitations of this study and encourage continued evaluation into the clinical impact of ART on this rare population. Thus, when faced with the rare elite controller in clinic, what advice should be provided to clinicians regarding the merits of initiating antiretroviral therapy, assuming there are no other compelling reasons to start therapy? Although the study by Crowell 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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Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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