Clinical Infectious Diseases

EDITORIAL COMMENTARY

Very Early ART and Persistent Inflammation in Treated HIV

Peter W. Hunt[1]

[1]Department of Medicine, University of California–San Francisco

(See the Major Article by Sereti et al on pages 124–31.)

Keywords. immune activation; HIV; antiretroviral therapy; acute HIV infection; inflammation.

There is unequivocal evidence that earlier antiretroviral therapy (ART) initiation, even among those with CD4+ T-cell counts >500 cells/mm^3, reduces morbidity in human immunodeficiency virus (HIV)–infected individuals. The Strategic Timing of Antiretroviral Therapy (START) and Temprano trials both demonstrated an approximately 50% reduced risk of AIDS or non-AIDS events in HIV-infected individuals randomized to immediate ART initiation compared to delayed ART initiation [1, 2]. These unambiguous results prompted changes to international treatment guidelines, which now recommend initiating ART in all HIV-infected individuals regardless of CD4+ T-cell count. Nevertheless, there was also a suggestion from both of these trials that immediate ART initiation failed to completely restore normal health. For example, there was a 1% risk of AIDS at 5 years even in the immediate ART arm of START and a 5%–8% incidence of serious morbidity and mortality (largely from tuberculosis) at 30 months in the Temprano trial, even among those who initiated ART at a high CD4+ T-cell count. These rates of infectious complications and cancer are much higher than are observed in the general population in these settings. Thus, while very early ART initiation clearly improves health, it may not completely restore normal health.

The study by Sereti et al in this issue of *Clinical Infectious Diseases* offers important new insights into why very early ART initiation improves but fails to normalize health in HIV-infected individuals [3]. It is now well appreciated that immune activation and inflammation persist at abnormally high levels in many HIV-infected individuals despite suppressive ART, particularly when ART initiation is delayed to more advanced disease stages. This persistent inflammatory state has been linked to an increased risk of subsequent morbidity and mortality in several studies and has emerged as an important target for interventions in the modern treatment era [4]. What has been less clear is whether very early ART initiation could prevent this persistent inflammatory state. In their study, Sereti et al characterized longitudinal changes in immune activation among HIV-infected Thai individuals who initiated ART extremely early, that is, within the first 2–3 weeks of their infection. They found that many markers of immune activation and inflammation were already abnormally elevated in these acutely HIV-infected participants relative to a cohort of at-risk but HIV-uninfected controls. Furthermore, most markers declined during suppressive antiretroviral therapy to levels that were significantly lower than observed in a cohort of HIV-infected Thai individuals who initiated ART during chronic HIV infection and at much lower CD4+ T-cell counts. This provided strong evidence that there is likely to be a cost of delaying antiretroviral therapy on the persistent inflammatory state once ART-mediated viral suppression is established and may at least partially explain why early ART initiation in the START and Temprano trials decreased morbidity. On the other hand, many markers of immune activation and inflammation remained abnormally elevated in the individuals with very early ART initiation, even after 2 years of ART-mediated viral suppression compared to at-risk but HIV-uninfected controls. Abnormal immune activation persisted even among the subgroup of individuals who initiated ART before HIV-specific antibodies were even detectable by fourth generation assays (typically <14 days of infection). This important observation might provide a reason why the risk of infectious and neoplastic complications remained abnormally high in the immediate ART groups in the START and Temprano trials relative to the general population.

While it certainly appears from the study by Sereti et al that many markers of immune activation fail to normalize even when ART is initiated during the earliest stages of acute HIV infection, there are several caveats that need to be considered. First, it is possible that the HIV-uninfected

Received 9 October 2016; editorial decision 12 October 2016; accepted 17 October 2016; published online October 25, 2016.

Correspondence: P. W. Hunt, 1001 Potrero Avenue, SFGH Bldg 3, 6th Floor, Room 645, San Francisco, CA 94110 (Peter.hunt@ucsf.edu.)

Clinical Infectious Diseases® 2017;64(2):132–3

DOI: 10.1093/cid/ciw697

control group had fewer coinfections and other exposures (ie, smoking, alcohol, and substance abuse) that contribute to systemic immune activation than the acutely HIV-infected group, even though they were sampled from an at-risk population of individuals who volunteered for HIV vaccine studies. Thus, confounding by coinfections and other exposures may have contributed to the apparently abnormal persistent inflammatory state in the acutely treated HIV-infected individuals in this study. Second, the acutely HIV-infected individuals in this study were all treated with efavirenz-based regimens. Recent clinical trials suggest that efavirenz-based ART results in greater levels of immune activation (particularly as assessed by soluble CD14) than integrase inhibitor–based ART and other comparator regimens [5, 6]. So it remains to be seen whether abnormal immune activation would persist if acutely HIV-infected individuals were treated with modern efavirenz-sparing regimens.

The study by Sereti et al is also interesting for the biomarkers that did not decline with very early ART initiation. Plasma levels of intestinal fatty acid binding protein (I-FABP), a marker of intestinal epithelial cell turnover and/or death that has been shown to predict increased mortality in treated HIV infection [7], actually increased within the first few weeks of ART in their study and remained abnormally high compared to the HIV-uninfected control group even after 2 years of viral suppression. The fact that efavirenz was used by all participants is again notable as efavirenz-based ART resulted in a greater increase in plasma I-FABP levels than lopinavir/ritonavir-based ART in a recent randomized, controlled trial [8]. It remains unclear whether this reflects a direct effect of efavirenz on the gut epithelium. It also remains unclear whether the early ART-mediated increases in I-FABP in this study reflect increased gut barrier dysfunction (and pathogenic microbial translocation) or simply restoration of normal gut epithelial cell proliferation (coincident with a decline in microbial translocation). These questions will need to be addressed in future studies.

Lastly, the study by Sereti et al raises important questions about the relationship between persistent inflammation and morbidity and mortality in treated HIV infection. Notwithstanding the caveats listed above, their study likely suggests that early ART initiation can attenuate but not fully abrogate the persistent inflammatory state. If this were the case, one might have expected immediate ART initiation in the START and Temprano trials to decrease but not completely abrogate the risk of several morbidities that have previously been linked to the inflammatory state in treated HIV infection, including cardiovascular, pulmonary, and neurocognitive disease. On the contrary, immediate ART failed to improve surrogate markers of these morbidities in START. One possibility is that the participants in START and Temprano were too young to have a significant enough risk for these morbidities to measure a benefit of earlier ART. Another possibility is that these morbidities require much longer term exposure to the HIV-associated inflammatory state to observe. Alternatively, as we have recently argued [4], the determinants of the persistent inflammatory state in individuals who initiated ART at more advanced disease stages may be more diverse and have a broader anatomic distribution (eg, HIV reservoirs not just in T cells but also tissue-based myeloid cells, cytomegalovirus in vascular tissue, and uncontained microbial translocation) than those that persist in individuals who are treated early (ie, HIV reservoirs primarily confined to inductive lymphoid tissues). A more limited anatomic distribution of the root drivers of the inflammatory state in those treated early might result in a narrower spectrum of diseases, particularly those most directly affected by adaptive immune defects. Addressing these hypotheses in future studies may well provide important insights into the pathogenesis of morbidity and mortality in treated HIV infection.

Note

Financial support. The author has received institutional grant funding through the National Institutes of Health (R01AI110271).

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