



Commentary

The Benefits of Early Antiretroviral Therapy for HIV Infection: How Early is Early Enough?



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ARTICLE INFO

Available online 5 August 2016

Keywords:

HIV
Acute
Reservoir
Early treatment
Viral set-point
Cell-associated HIV DNA

The case of the “Berlin Patient” is well-known. In 2007, an HIV-infected adult with leukemia underwent allogeneic hematopoietic stem cell transplant and was cured of his cancer (Hutter et al., 2009). As the donor was homozygous for the CCR5Δ32 deletion (which makes CD4⁺ T cells difficult to infect with HIV), the repopulated immune system lacked any detectable HIV and the patient has been apparently cured. Two subsequent allogeneic transplants performed under potent ART (which protected the donor cells from de novo infection) resulted in a dramatic reduction in the frequency of cells harboring replication-competent HIV (generally referred to as the HIV “reservoir”) (Henrich et al., 2014). This was not enough to cure these two patients, however, as both individuals experienced a delayed but robust rebound in viremia after stopping therapy. A true cure will likely require complete eradication of the entire reservoir of HIV. This is a formidable challenge.

Fortunately, a complete “sterilizing” cure may not be needed. Some people are able to control replication-competent HIV in the absence of therapy (“elite controllers”) or after stopping therapy (“post-treatment controllers”). Extensive research over the past two decades has shown this degree of control requires both a powerful HIV-specific immune response and a low HIV reservoir size. The former may be achieved with vaccines and other immunotherapies. The latter may be achieved with “shock and kill” strategies and/or starting ART very early, before the reservoir is fully established.

Early initiation of ART decreases the size of the HIV reservoir (Cheret et al., 2015; Jain et al., 2013) and has clear benefits on preventing AIDS

and non-AIDS-related morbidity, but it is yet unclear how early is early enough to dramatically alter the establishment of the HIV reservoir. To better define the impact of ART on the reservoir, Ananworanich and colleagues constructed two prospective cohorts of high-risk HIV-uninfected adults in Thailand. In this edition of *eBioMedicine*, they describe the outcomes in those who were diagnosed early and not treated (RV217, $n = 17$) and those who were diagnosed early and treated almost immediately (RV254, $n = 71$) (Ananworanich et al., 2016).

In the untreated state, the level of viremia (plasma HIV RNA levels) reaches a well-characterized and highly informative “set-point” about two months after the start of the infection (Robb et al., 2016). As now described by Ananworanich and colleagues, the frequency of cells harboring HIV DNA (an estimate of the reservoir size) closely follows these same kinetics. The estimated reservoir size rises rapidly during the first few weeks of the infection. At about the time HIV RNA becomes detectable, the reservoir size begins to increase dramatically, with an apparent 100-fold increase over the next two weeks, peaking approximately four weeks after HIV was acquired. Since effective ART blunts HIV spread, achieving a durable and sustained reduction in the reservoir size will require that ART be initiated during this critical phase. Indeed, as shown in the current study, early ART resulted in an approximate 300-fold reduction in the reservoir size, as compared to what would likely have happened had therapy not been started.

As acknowledged by the authors, the current study has a few limitations. The exact duration of infection for many of the participants was not known. Also, the reservoir measurement used was at best imprecise. Most of the measured HIV DNA carries lethal mutations and/or deletions and hence may not be clinically relevant. These measures are assumed to be a surrogate for the size of the true reservoir (defined as virus that can replicate) but this may not be true (Eriksson et al., 2013). Finally, although the frequency of cells harboring HIV DNA in the cohort achieved a stable level after several weeks, it remains unknown as to whether a true “set-point” is achieved. Careful analyses of individual trajectories will be required to determine if a set-point occurs as has been shown for other markers, including HIV RNA (Mellors et al., 1997) and perhaps T cell activation (Deeks et al., 2004).

It remains to be defined as to whether the very early HIV DNA “set-point” may contribute to persistent long-term consequences, such as continued altered CD4/CD8 ratios, chronic inflammation, tissue fibrosis, and clinical outcomes. Though Ananworanich and colleagues did not evaluate tissue-based viral measures where most of the latent HIV

DOI of original article: <http://dx.doi.org/10.1016/j.ebiomed.2016.07.024>.

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E-mail address: Steven.Deeks@ucsf.edu (S.G. Deeks).<http://dx.doi.org/10.1016/j.ebiomed.2016.08.009>2352-3964/© 2016 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

reservoir resides nor the frequency of replication-competent (potentially infectious) virus, levels of total HIV DNA in blood immediately prior to treatment interruption have been shown to predict time to viral rebound in ART-suppressed patients (Williams et al., 2014). Therefore, their findings may have practical implications on the estimated probability of achieving long-term remission off ART in those who are diagnosed and treated during acute HIV infection.

These findings also highlight the importance of several ambitious strategies, such as the “Getting to Zero” campaign being pursued in San Francisco, which aims to rapidly identify HIV-infected individuals – even prior to symptoms (i.e., peak viremia and viral set-point). Results from this study suggest that such aggressive strategies might have meaningful impact in markedly altering the size of the HIV reservoir if acute infection is diagnosed and treated aggressively.

Conflicts of interest

The authors do not have a commercial or other association that might pose a conflict of interest.

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