Universal Antiretroviral Therapy for HIV Infection?

Jens D. Lundgren¹ and Robin Wood²

¹Department of Infectious Diseases, Rigshospitalet/Copenhagen University Hospital, Denmark; and ²Desmond Tutu HIV Centre, Institute of Infectious Diseases and Molecular Medicine (UCT), Faculty of Health Sciences, University of Cape Town, South Africa

(See the HIV/AIDS Invited Article by Gallant et al on pages 884–7.)

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Human immunodeficiency virus (HIV) still infects more people per year than existing health systems are able to initiate and maintain on antiretroviral therapy. Therefore, the development of effective HIV population prevention strategies remains a high priority. There is no immediate promise for an effective HIV vaccine, risk behavior change has been difficult to implement, and biomedical prevention measures lack effectiveness due to inconsistent use. In contrast, antiretroviral therapy (ART) can benefit the infected individual and under clinical trial conditions has been shown to reduce transmission [1]. The use of ART as both treatment and prevention is now a well-established concept, which has been widely welcomed as the “missing link” that will curb HIV incidence [2].

However, a disconnect exists between the individual and transmission benefits of ART. Persons with advanced HIV disease (reflected by having a CD4+ lymphocyte count <250 cells/µL), have clear benefit, documented by several randomized controlled trials (reviewed in [3]). Conversely, the target populations for transmission benefit are those with high CD4 counts, in whom observational studies have shown inconsistent or no clinical benefit (reviewed in [4]). Additional biological plausibility for early treatment has been the observation that untreated HIV infection activates host inflammatory processes associated with organ disease and cancers and that ART partly (but not completely) reverts immune activation. However, no specific anti-inflammatory intervention has been demonstrated to reduce the risk of these adverse outcomes, and changes in inflammatory biomarker levels have not been validated surrogates for clinical benefits of ART. Therefore, whether inflammation is causally involved in the pathogenesis of these events or merely an epiphenomena to the underlying pathology remains to be identified in HIV as it does in the general population.

The uncertainties relating to net benefit of early ART are reflected in disparities between treatment guidelines. Guidelines based on consensus “expert opinion” recommend that all HIV-positive persons, as a matter of principle, should be started on ART [5, 6], and those based on available direct evidence [7–9] (including the 2010 World Health Organization guidelines) are more conservative. Unfortunately, consensus among experts can be prescient or subsequently shown to be incorrect. For example, 10 years ago, expert opinion was that ART could be used intermittently, but the SMART (Strategies for Management of Antiretroviral Therapy) trial demonstrated definitively that this view was wrong [10].

Gallant et al, in this issue of Clinical Infectious Diseases [11], highlight reasons why the recommendations of the US guidelines are not necessarily generalizable to other settings. They highlight a fundamental ethical obligation of clinicians to benefit patients while not causing harm. They note that although the individual benefits of early ART remain undefined in resource-limited settings, the risks associated with early ART may be higher. Cost constraints in resource-limited settings limit the available ART repertoire, resulting in frequent use of older, cheaper drugs with poor adverse event profiles. In a setting where only stavudine-based ART regimens are available, for example, starting ART at a high CD4 count of 650 cells/µL would less likely maintain health than deferring to a more conservative threshold of 250–350 cells/µL. Lack of laboratory monitoring may also potentially increase risk by delayed recognition of toxicity. Tenofovir, which is included in most currently recommended ART regimens, may adversely affect kidney and bone physiology [12, 13]. Emerging reports of more severe renal diseases in settings without access to laboratory monitoring raise
concern [14]. Infrequent viral load monitoring and reliance on CD4 cell counts results in suboptimal use of available ART with unnecessary regimen switches and delay of appropriate switches with resultant risk for development of viral resistance [15]. ART programs in resource-limited settings universally rely on cheap nonnucleoside reverse transcriptase inhibitor–based first-line regimens with relatively low barriers to resistance, which are particularly vulnerable to resistance development.

Furthermore, Gallant et al [11] stress a moral imperative to treat those with advanced life-threatening disease before asymptomatic patients with early HIV infection. Inevitably, where resources are most constrained and there is a large unmet burden, the treatment of the sickest will and should take precedence over treatment solely for prevention.

In the current global economic downturn, there is a need in resource-limited settings to reduce dependence on external donor support, and limited national budgets must also compete for opportunities to improve nutrition, housing, water, and tuberculosis and malaria control. To use limited resources effectively, we urgently need direct evidence to guide use of ART in early HIV infection. Several large randomized trials are under way [16], and more are called for [17]. We need assurance that the benefit-risk ratio from using ART is favorable in the patients starting on ART. However, it is still uncertain in resource-rich countries whether this basic criterion is fulfilled for use of ART in early HIV. The chance of HIV disease progression is low in early HIV and the risk of organ disease and cancer virtually negligible in younger persons (ie, those aged <35–40 years), the predominant portion of the population with early HIV infection. Even contemporary antiretroviral drugs may cause adverse drug reactions, some of which are severe [12–14, 18–20]. In relation to this, observational studies used to argue for early use of ART [11, 21] did not document the existence of such reactions as the endpoint focused on in these studies is all-cause mortality; such studies are hence not useful to clarify potential harm from use of ART. Hence, in all regions of the world (but probably more so in resource-limited settings), it is possible that use of ART in early HIV provides net harm to the person treated. We will know in the next 3–4 years whether this possibility truly exists.

Whereas the longer-term vision that extensive use of ART will effectively curb the global HIV epidemic is very enticing, a limited focus on biomedical interventions may be too simplistic an approach. Behavioral changes resulting in more unsafe sex will likely offset the potential prevention benefits of ART, as exemplified in recent ecological analyses of European populations of men who have sex with men [22]. Health system research on how to improve early entry and retention in care is also necessary as these components of care are challenging from both a logistical as well as from an economic perspective.

In summary, it is important to separate treating for clinical benefit and treatment for prevention. Whereas the latter is based on solid evidence, it is uncertain whether use of ART in early HIV is linked with net benefit to the person treated. The strategic use of ART needs to be based on solid direct evidence. If evidence is only based on expert opinion, it is prudent to be skeptical to implement it everywhere in the world.

Note

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References


13. Ryom L, Mocroft A, Kirk O, et al. on behalf of the D:A:D Study Group. Exposure to antiretrovirals (ARVs) and risk of


