Under the Spell of the Red Queen

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(ASee the HIV/AIDS Major Article by Lesko et al on pages 1027–37 and the HIV/AIDS Major Article by Mocroft et al on pages 1038–47.)

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A systematic review and meta-regression of temporal trends in adult CD4+ cell counts at presentation to human immunodeficiency virus (HIV) care in high-income countries, by Lesko et al in this issue of Clinical Infectious Diseases, brings home a sobering message: Those counts have only risen minimally between 1992 and 2011, that is, from 307 cells/µL to 336 cells/µL (1.5 cells/µL/year). Moreover, during this time span there was negligible change in the proportion of subjects presenting with advanced HIV disease (CD4+ count <200 cells/µL or AIDS) or late (CD4+ count <350 cells/µL or AIDS).

The study had the limitation of having to rely on quite diverse studies and data, and the results differ somewhat from an earlier study from the United States and Canada, covering the years 1997–2007, in which the estimated adjusted mean CD4+ cell count at initial presentation for HIV care increased at a rate of 6 cells/µL/year [1]. However, the level of precision of CD4+ cell count estimates over time is not all that important: the fact of the matter remains that, even in recent years, many people with HIV infection in high-income countries present late for care and may start treatment even later [1–3]. In 2011, in the Netherlands the median CD4+ count at HIV diagnosis was 390 cells/µL, 300 cells/µL at the start of antiretroviral therapy (ART), and 43% of those presenting for care did so with a CD4+ count <350 cells/µL or an AIDS-defining event [4]. In 2012, the US Centers for Disease Control and Prevention reported that 41% of Americans who first received a diagnosis of HIV infection between 2006 and 2009 had no history of HIV testing [5].

The finding that so little has changed with regard to time of presentation to HIV care in a period that saw dramatic improvements in HIV treatment and monitoring options is astonishing. The study period spans the years of sequential monotherapy (1994 and earlier), dual therapy (1994–1995), and highly active antiretroviral therapy (HAART; 1996 and onward) and the introduction of HIV type 1 RNA monitoring (1995 and onward). Moreover, during the HAART years a major shift from complex and toxic regimens to simple, once-daily, well-tolerated, and less toxic first-line regimens occurred [6]. One would expect these respective developments to have had a major influence on earlier uptake of ART. Yet, we are reminded of what the Red Queen said to Alice: “Now, here, you see, it takes all the running you can do, to keep in the same place” [7].

The standstill is all the more astonishing as there can be little doubt that early treatment with current antiretroviral drugs, generally speaking, is of enormous benefit to the individual. Let us briefly recapitulate those benefits: (1) Increased survival: When ART is started early enough and the CD4+ count is kept above 500 cells/µL, life expectancy appears to be similar to that of non-HIV-infected individuals [8, 9]. The results from another article in this issue of Clinical Infectious Diseases, by Mocroft et al from the COHERE Collaboration, indicate that the incidence of AIDS-defining illnesses (ADIs), in particular malignant ADIs, is higher in individuals with a CD4+ count of 500–749 cells/µL compared to those with higher CD4+ cell numbers. (2) It reduces tuberculosis incidence: This may not be of overriding importance in high-income countries, but is in countries with high tuberculosis incidence [10–12]. (3) It reduces the occurrence of immune reconstitution syndrome: This is an important cause of ART-related morbidity and mortality, in particular in resource-poor settings [13]. (4) It may lead to a functional cure in some patients who are treated during primary or acute HIV infection [14, 15]. An ongoing study being conducted in Thailand shows that very early...
treatment in the acute phase of infection restricts the seeding of an HIV reservoir in long-lived central memory CD4+ T cells [16]. Obviously these individual benefits are also beneficial for society, but some other consequences of early ART are more explicitly societal than individual in nature: (1) It is a highly effective tool to prevent transmission of HIV to others [12, 17, 18]. This is now having an impact at the population level in both high-income and resource-poor settings [19, 20]. (2) It allows health systems to task-shift, something that is essential if we are serious about a further scale-up of ART in resource-poor countries. Most countries that are hardest hit by the HIV epidemic also have critical shortages of qualified healthcare workers [21]. The need for task-shifting will become even greater with the World Health Organization (WHO) guidelines moving from a recommendation to initiate treatment at a CD4+ count of <350 cells/µL [22] to a CD4+ count of <500 cells/µL, which adds another 3 million people who “need” ART [23].

The obvious benefits of early therapy for both individuals and society have led to recommendations in the latest US treatment guidelines to offer ART to all HIV-infected adults and adolescents regardless of CD4+ cell count [24, 25]. And, as we saw above, WHO guidelines, which are of great relevance to low- and middle-income countries, are also shifting toward earlier initiation of ART.

Lesko et al refrain from making any specific recommendations, except for stating that “new and innovative strategies are imperative to identify persons earlier in the course of their infection and link them properly with medical care.” The Red Queen gives us at least a hint of what we should do: “If you want to get somewhere else, you must run at least twice as fast as that!” [7]. We definitely need to run faster, and we need to do it at various fronts, that is, across the whole spectrum of engagement in care [2]. The greatest risk of excess mortality in HIV-infected men who have sex with men in high-income countries appears to be due to delays in HIV diagnosis [26]. We also know from studies in several high-income countries that most new HIV infections are transmitted by persons who are unaware of their HIV status [27, 28]; thus, from a societal perspective, first and foremost we need to increase HIV testing to increase the number of people who do know their HIV status. In high-income countries, without generalized epidemics, we need to direct our efforts primarily at those populations most at risk for HIV infection, and repeatedly test those found to be HIV negative [29]. In those found to be infected, we need to spell out clearly, and again and again, the risk of onward transmission of HIV. The individual benefit should come first: People should not feel any pressure to start treatment for society’s sake. Those who decide that in their particular situation initiation of treatment is the right decision should get all the support that is necessary to keep them linked to care and adherent to the therapy. In this regard, there is a lot to learn from the classic paper by Paul Farmer and colleagues describing an effective community-based approach to HIV care in rural Haiti [30]. We should also realize that attempts to tell us that we need more data to determine what is the optimal timing of ART initiation are misguided and detract us from a job that is difficult enough without this detraction.

Particular attention should be given to “catch” as many people as possible in the acute phase of HIV infection, given the chance of a functional cure [14–16], and given their relatively large contribution to sustaining the HIV epidemic [31, 32].

In conclusion, we need to run at least twice as fast as we are currently doing, know our classics, act upon them and upon new opportunities, and keep our eye on the target at all times.

**Note**

Potential conflicts of interest. Author certifies no potential conflicts of interest.


