Plus ça change... Antiretroviral Therapy, HIV Prevention, and the HIV Treatment Cascade

Kevin M. De Cock

KEMR Headquarters, US Centers for Disease Control and Prevention, Nairobi, Kenya

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Global commitments by 2015 include the Millennium Development Goals, elimination of pediatric human immunodeficiency virus (HIV) infection, and having 15 million persons on antiretroviral therapy (ART); in this context, the major question facing the global AIDS response is how best to use ART for individual health as well as the public health. Recognition of the HIV prevention benefit of ART has stimulated calls for earlier and more widespread ART globally, with the 96% efficacy in reducing sexual transmission demonstrated in the landmark HIV Prevention Trials Network (HPTN) 052 [1] study often quoted. Earlier in 2013, the World Health Organization (WHO) issued consolidated ART guidelines that recommend initiation of ART at a CD4 count of ≤500 cells/µL [2], and many expect global guidelines to eventually recommend ART for all persons living with HIV, irrespective of the absence of data from randomized clinical trials [3].

There is more to HIV treatment than guidelines, however, and in the current issue of Clinical Infectious Diseases, McNairy and El-Sadr [4] usefully discuss the health-systems challenges inherent to the “HIV treatment cascade.” This term refers to the sequential steps that take individuals from HIV diagnosis through enrollment into care, timely initiation of ART, adherence to treatment, and viral suppression. An intact cascade is essential if the benefits of ART are not to be squandered and more HIV-infected persons are to be safely placed on therapy.

The HIV treatment cascade is not a new concept but uses earlier modeling applied to tuberculosis and sexually transmitted infections, referred to, respectively, as the Piot and Piot-Fransen models [5, 6]. For these conditions, the multiple steps required for medical success are at risk from constant leakage. Dropout can occur at numerous points so that the final number of beneficial outcomes may be small compared to the number of people entering the cascade. Such observations apply to medical care more broadly and explain the relatively poor impact from interventions for many chronic diseases such as hypertension when analyzed at the population level. In comparison, once-only interventions with sustained benefit such as male circumcision for HIV prevention can have larger population-level impact despite imperfect efficacy.

The central role that ART plays in today's HIV prevention response has roots early in the pandemic. Analytic epidemiologic studies showed that viral load was associated with risk of transmission for all transmission modes. Zidovudine monotherapy reduced transmission from the infected partner in discordant couples in the late 1980s [7], as well as from mothers to infants in the landmark AIDS Clinical Trials Group (ACTG) 076 study [8]. Public health officials raised the possibility of ART and viral load suppression playing a role in reducing HIV transmission at a population level more than a decade ago [9]. The enormous interest today in HIV treatment as prevention and the impetus to implement it result from different but allied forces: the early observations cited above; mathematical modeling showing that ART implemented on a wide scale could substantially reduce and potentially control generalized HIV epidemics [10]; programmatic experience confirming reduced HIV transmission at a population level with ART scale-up [11, 12]; the results of the HPTN 052 study [1]; and the general belief that earlier treatment would be beneficial for individual health. The single most important indicator that HIV treatment and public health programs should be concerned about today is viral load, which is key to both transmission and disease progression. Monitoring and evaluation efforts strive to capture indicators that describe how well viral load is being suppressed across the population.
either through depictions of the cascade or summary estimates such as community viral load [13]. No single measure currently conveys all the information needed, and agreement on key indicators of ART scale-up and its impact is required.

The revised WHO ART recommendations [2] provide a useful prevention stimulus but leave us in uncomfortable clinical terrain because they are based on expert opinion rather than data from randomized clinical trials, and because of the operational challenges that remain. A CD4 cell threshold of 500 cells/µL means more people are eligible than ineligible for ART, and the dominant clinical decision then derived from initial CD4 screening is who should not take the drugs. Operationally, and following a “public health approach,” it might be simpler to treat everyone infected with HIV, as is being recommended for pregnant women under “Option B+,” which calls for immediate and lifelong ART for all HIV-infected pregnant women. The motivation in Malawi for adopting Option B+ was to allow decentralization of service provision in a context of limited laboratory facilities. A pivotal decision for management of all HIV-infected persons now is whether pragmatism and select clinical opinions should outweigh requirement for the highest-quality evidence from a randomized controlled trial of immediate ART for all [3].

The cascade as discussed provides useful but incomplete insight. With only summary statistics reported, it is unclear to what extent there may be double counting. It is assumed that persons entering HIV care programs are counted only once but they may enter care, drop out, and then reenter at a later date—and they may do this multiple times. The outcome of persons who default is unknown without further investigations. What would be desirable is cohort analysis of all individuals entering care with standardized reporting of outcomes. This has been long-standing practice in tuberculosis control where the program assumes accountability for every individual, ascribing standardized outcomes (cure, failure, loss to follow-up, transfer out, death) to every person treated. Analogous outcomes can be defined for HIV treatment—with viral suppression or lack of it replacing tuberculosis cure or failure. Without cohort analysis, some summary statistics such as numbers of people on ART may be questionable, and without measurement of standard outcomes we cannot assess the quality of care being delivered.

Cohort analysis for HIV care would require increased investment in electronic medical records, as paper-based systems rapidly become overwhelmed with the volume of data generated through chronic disease management, and individuals would require some form of unique identifier. These are all important components of health-systems strengthening but raise broader requirements for civil registration and vital statistics, essential for health-systems management and planning but of relevance also to other areas of public health and other sectors. It is extraordinary that in the second decade of the 21st century it is still possible for someone to be born, live, and exit this world with no official record of his or her existence, a denial of human dignity that rivals the deplorable stigma and discrimination that many diseases still engender.

Two other subjects related to the cascade that merit attention are HIV testing and mortality surveillance. Throughout the world, substantial numbers of people living with HIV remain undiagnosed, waiting for immunodeficiency-related disease or death to declare their underlying serostatus. In the United States, approximately 18% of the nation’s HIV-infected population is undiagnosed; in Europe it is higher. In Kenya’s recent AIDS Indicator Survey, 53% of HIV-infected persons were unaware of (or incorrectly reported) their positive infection status [14]. The cascade cannot capture HIV-infected people who have not entered care, HIV care cannot be provided without an HIV diagnosis, and the benefits of ART cannot be fully realized without universal knowledge of HIV serostatus among persons living with HIV [15]. The cascade offers insight only into the world of the diagnosed, not the universe of the HIV infected. William Farr famously said that the death rate is a fact and everything else is inference. The ultimate success of HIV prevention and treatment programs will be no deaths from AIDS. Addressing the question of how much death still occurs from HIV in settings where mortality surveillance is weak but ART access has improved will be an important indicator of the quality of HIV prevention and treatment as well as the meaningfulness of the HIV treatment cascade.

Notes

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