

Perspective

Modelling the Strategic Use of Antiretroviral Therapy for the Treatment and Prevention of HIV

Nathan Ford*, Gottfried Hirschall

HIV/AIDS Department, World Health Organization, Geneva, Switzerland

The impact of increased access to antiretroviral therapy (ART) has principally been measured in lives saved, and justifiably so: over the last decade the scale-up of ART has averted over 4 million deaths in low- and middle-income countries [1]. Almost 10 million people in these countries are currently receiving ART, and widespread access to treatment has transformed HIV from a life-threatening infection to a chronic disease. Less than 20 years ago, patients presenting at clinics in Africa with an AIDS-defining illness would on average have just 9 months to live [2]. Today, people living with HIV in Africa can, with timely and continuous access to effective ART, have a relatively normal life expectancy [3,4].

Yet the benefits of ART extend beyond saving lives, and increasingly attention is being given to the potential for ART to prevent new HIV infections. The specific contribution of ART to reducing HIV infection through mother-to-child transmission of HIV is well described—over 800,000 children have avoided infection over the last decade [1]—but the extent to which ART prevents sexual transmission has until recently been less clear. Data from several observational studies have suggested decreased acquisition of HIV among sexual partners of people on ART [5,6], an association convincingly confirmed by the results of the HPTN 052 trial demonstrating significantly reduced rates of sexual transmission with early ART initiation [7]. At the population level, increased access to ART has been associated with reductions in sexual transmission in ecological studies [8], but the overall proportion of new infections that have been averted by ART is not known. In the absence of such data, mathematical modelling has made an essential contribution.

The Perspective section is for experts to discuss the clinical practice or public health implications of a published study that is freely available online.

Linked Research Article

This Perspective discusses the following new study published in *PLOS Medicine*:

Hontelez JAC, Lurie MN, Bärnighausen T, Bakker R, Baltussen R, et al. (2013) Elimination of HIV in South Africa through Expanded Access to Antiretroviral Therapy: A Model Comparison Study. *PLoS Med* 10(10): e1001534. doi:10.1371/journal.pmed.1001534

Using 9 structurally different models, Jan Hontelez and colleagues investigate timeframes for HIV elimination in South Africa using a universal test and treat strategy.

Models have been used to predict the potential impact of widespread ART on HIV transmission for over two decades [9], but the potential preventive impact of widespread ART access captured international attention only recently, with the landmark publication of what has become known as the “Granich” model in 2009 [10]. Assuming high rates of treatment uptake, coverage, and adherence this model put forward the notion that universal HIV testing and treatment, combined with other interventions, could reduce transmission to low levels such that epidemic would eventually decrease towards elimination. Subsequent models

have all pointed in the same direction of reduced incidence with expanded ART access, albeit with varying assumptions and timeframes [11].

In this issue of *PLOS Medicine* Jan Hontelez and colleagues systematically assessed the universal test and treat intervention suggested by Granich and colleagues by running nine different models with increasing degrees of complexity and realism—including sexual networks, HIV stages with different degrees of infectiousness, and updated treatment effectiveness assumptions—to explore how different scientific approaches to modelling would influence the results [12]. Encouragingly, all models were found to predict that HIV would eventually be eliminated through universal HIV testing and treatment, although timeframes for reaching the elimination phase ranged from 7 to 39 years depending on assumptions about demography, sexual behavior, transmission and natural history, coverage of other prevention interventions (male medical circumcision and condom use), and sexually transmitted infection (STI) co-factors [12]. Of particular note, while previous models have suggested reduced incidence even if treatment is started at a lower CD4 threshold of 350 cells/mm³ [11], this is the first study to predict that the elimination phase will eventually be reached at this threshold, albeit within a longer time horizon and provided very high treatment coverage is attained.

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* E-mail: fordn@who.int

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The notion that ART could help curb the HIV epidemic has fundamentally reframed the global HIV response over the past 5 years. For donors, the clinical and public health benefits provided by expanded ART access make a clear case that ART is a good investment [13], while for care providers the possibility that ART could help control or even eliminate the HIV epidemic has provided a renewed impetus to further expand coverage [14].

The latest ART guidelines released by the World Health Organization (WHO) in June 2013 recognize the multiple benefits of ART for both treatment and prevention of HIV, and provide a number of recommendations for expanded eligibility [15]. ART initiation is recommended at CD4 <500 cells/mm³ (with priority given to those with a CD4 <350 cells/mm³) and three new recommendations are made to provide immediate ART initiation based on clinical benefits and programmatic and prevention considerations: pregnant women, people in serodiscordant couples, and children under 5 years of age. Similar to previous guidelines, people co-infected with tuberculosis and hepatitis B infection are also eligible for immediate ART after diagnosis. In order to develop these guidelines WHO commissioned a series of modelling studies done by the HIV Modelling Consortium, which showed that expanding the criterion for ART eligibility to CD4 cell count ≤500 cells/mm³ was highly cost-effective in low- and middle-income settings, in particular if expanded eligibility was coupled with a large increase in HIV testing and linkage to care [16].

With the preventive benefit of ART firmly established in evidence and policy, what could be the future contribution of modelling to treatment scale-up? Rather than continuing to model the magnitude

and speed of the preventive impact of ART, modelling efforts could be redirected towards helping programmes make choices about which interventions need to be prioritized in order to achieve the levels of enrolment and retention in care required to achieve optimal prevention benefit. There are three key areas where modelling could help, and encouragingly early work has already started in some of these areas.

First, modelling can help define actions to improve access and retention in care. A positive consequence of the recent focus on universal HIV testing and treatment has been to direct attention on the cascade of care. While much of the modelling work to date has focused on refining the horizons for achieving HIV elimination through ART provision, individuals involved in programme implementation have expressed concern about the feasibility of achieving the high rates of ART uptake, coverage, retention, and adherence upon which these models are based [14]. Recent systematic reviews have highlighted substantial patient attrition at every step from HIV testing to ART initiation to long term retention on treatment [17,18]. A number of interventions have recently shown promising results in increasing uptake in HIV testing [19], speeding up eligibility assessments for ART [20], and reducing attrition on ART [21]. Modelling work has already been done to help provide a more nuanced understanding of the dynamics of the treatment cascade [22]. Drawing on data from trials underway to assess the impact of ART initiation on HIV transmission [23], future modelling work could assist decision making about where and how to intervene along the treatment cascade to maximize the treatment and prevention benefits of ART.

Second, modelling can help inform country decisions about who should be

treated early in priority for maximum prevention benefit. Implementation of the new WHO recommendations for early ART initiation will require countries to make strategic choices around how best to use ART for treatment and prevention according to resource constraints, epidemic dynamics, and societal factors. WHO's guidelines include a chapter on decision making for programme managers that outlines how modelling can help support costing and planning [15]. Modelling studies have already assessed the preventive impact of immediate ART initiation among pregnant women and serodiscordant couples [24], and key populations [25,26]. This work will continue to be critical to informing country choices in the strategic use of ART.

Finally, ongoing research will provide further data on the clinical and public health benefits of ART, and future guidelines will likely lead to a continued policy evolution towards earlier initiation. Modelling will make a key contribution to informing future WHO guidance and country decisions about how best to strategically provide ART as a broader package of interventions to save lives, reduce illness, and prevent new infections.

The case for ART impact on HIV transmission is proven. The priority now is to translate this concept into benefits for patients and communities by identifying and implementing approaches that work to maximize early HIV testing and ART uptake and long-term retention in care.

Author Contributions

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