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Modeling Scenarios for the End of AIDS

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At the end of 2012, 3 decades after the human immunodeficiency virus (HIV) was first identified, neither a cure nor a fully preventive vaccine was available. Despite multiple efforts, the epidemic remains an exceptional public health challenge. At the end of 2012, it was estimated that, globally, 35 million people were living with HIV, 2.3 million had become newly infected, and 1.6 million had died from AIDS-related causes. Despite substantial prevention efforts and increases in the number of individuals on highly active antiretroviral therapy (HAART), the epidemic burden continues to be high. Here, we provide a brief overview of the epidemiology of HIV transmission, the work that has been done to date regarding HIV modeling in different settings around the world, and how to finance the response to the HIV epidemic. In addition, we suggest discussion topics on how to move forward with the prevention agenda and highlight the role of treatment as prevention (TasP) in curbing the epidemic.

Keywords. HIV epidemic; mathematical models; prevention; treatment as prevention; TasP.

EVOLUTION OF MODELING IN THE CONTEXT OF TasP

Mathematical models that predict the course of the HIV epidemic have evolved tremendously [1–5]. Most improvements in these models have been the result of clinical trials and cohort and ecological studies that have shown the efficacy and effectiveness of highly active antiretroviral therapy (HAART) in suppressing viral load in blood and sexual fluids and in decreasing morbidity and mortality [6–9]. Thus, mathematical models now incorporate HIV viral load as the main driver of HIV transmission. These models led the scientific community to ask the question, "What will happen to the HIV epidemic if we start treating more people [10–13]?" Montaner and colleagues formally introduced the concept of using HIV treatment to prevent transmission in 2006 [13].

In the context of treatment as prevention (TasP), mathematical models have combined complex individually based knowledge of the clinical and epidemiological aspects of HIV disease in order to inform us about how HIV spreads and to predict and understand the long-term population-level impact of this epidemic. As a result, these models are now useful when making predictions and when comparing the effect of different and complex interventions with different outcomes. More recent models have focused on comparing the effects of different strategies within the TasP framework in order to determine which combinations of interventions will yield the most significant results in terms of reducing the spread of the HIV epidemic [3, 12, 14, 15].

One of the biggest challenges for policymakers and other stakeholders in public health is assessment of the impact of TasP based on the results of mathematical models. These models vary greatly based on the following: type (eg, deterministic vs stochastic); overall assumptions for behavioral parameters and impact on HIV transmission (eg, type of sexual or drug use mixing, size and duration of partnerships, effect of harm-reduction initiatives); different stages of infectiousness (eg, models based on viral load or on CD4 thresholds, models that differentiate stages in the HIV natural history, models that focus on the role of primary infection in HIV transmission); assumption for a reduction in HIV transmission due to HAART (eg, based on the

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efficacy of clinical trials or on the link between viral load and transmission probabilities); transmission probabilities (eg, type of contact, effect of male circumcision); assumption for HAART initiation criteria (eg, immediate vs based on CD4 cell count criteria); and assumptions for retention in care (eg, models that allowed loss to follow-up vs those that did not). Eaton and colleagues elegantly highlighted these issues by comparing 12 independent models that assessed the impact of TasP in South Africa [2]. They showed that although all models indicated that TasP had a positive impact on the reduction of HIV transmission, the models varied considerably regarding their structure and parametric assumptions. Consequently, the predicted impact on the reduction of HIV incidence varied from 35% to 54% in the short term and from 32% to 74% in the long term. Based on results from that study and similar ones in the literature, caution should be exercised when comparing results across models and when making policy recommendations since the parametric assumptions behind these models dictate the models' projections and their effects on the overall HIV epidemic.

We also stress that model scenarios should be realistic and should consider barriers to the success of TasP. These barriers include gaps in antiretroviral coverage, fragmented health systems, acceptability issues (among patients, providers, and decision-makers), community preparedness to adopt the strategy, financial costs, structural components, and human rights. Therefore, for these models to be relevant in informing decision-making, it is important that researchers in diverse fields collaborate to ensure that the results that originate from these models are relevant. In addition, since estimates from these models are very sensitive to their hypotheses and parameters, assumptions need to be sound and, whenever possible, based on empirical data in order for the model results to be valid.

In view of competing interventions that range from TasP strategies to behavioral modification and biomedical interventions, it is important that models consider how to optimize the combination of preventive strategies and, in turn, maximize their effectiveness in curbing growth of the HIV epidemic.

MOVING THE TasP AGENDA FORWARD

Based on the overwhelming effect of TasP, it became apparent that we need to move from "does it work" to "how do we expand" this strategy. Unfortunately, HAART has been expanded around the world too slowly and it is not keeping pace with the growth of the epidemic. In 2013, the World Health Organization (WHO) published treatment guidelines that recommend that HIV-positive individuals in serodiscordant relationships and those coinfected with tuberculosis and hepatitis B virus be offered HAART regardless of CD4 cell count in order to prevent HIV transmission [16]. Note that these same recommendations were put forth in the treatment guidelines from the International AIDS Society–USA and the US Department of Health and Human Services in 2010 [7, 17]. It is important to emphasize that different mathematical models showed not only how crucial it is to engage more people into treatment but that we need to do it more quickly in order to achieve the full benefit of this strategy. Timely or early initiation of treatment is associated with clinical and societal benefits [6].

Although the WHO moved in the right direction, its new guidelines need to be more prescriptive and not rely on a country's ability to implement these guidelines. To date, most countries are still debating whether to adjust the HAART eligibility criterion based on CD4 cell count from 350 to 500 cells/mm^3. Meanwhile, as people wait for treatment, they are still at risk of irreversible immunologic damage, premature mortality, acquisition of AIDS-defining illness and tuberculosis, and, ultimately, transmission of their infection [18]. Politics and political unwillingness are creating obstacles to the optimal implementation of strategies to control the HIV epidemic. Consequently, public health officials need to mobilize and move the TasP agenda forward and show that it is possible to control the epidemic. Because these restrictive treatment guidelines are highly reliant on the CD4 cell count criterion, in many countries with concentrated epidemics, it is difficult to reach minority populations at high risk of acquiring HIV. When we find these individuals, it is important that they be tested and engaged into treatment immediately. In most cases, these individuals are not offered treatment because they do not meet the HAART initiation criterion based on CD4 cell count. Therefore, countries need to adopt broader guidelines more quickly in order to reach these individuals and many others who are not receiving care. Sadly, the price of medication in these countries plays a key role in slowing treatment expansion since several countries (mostly middle-income) are subjected to trade agreements or belong to economic blocks that have very rigid patent protection laws, little space for price reduction negotiations, and several restrictions on access to low-cost generics.

Despite the extraordinary preventive effect of TasP, there is still skepticism regarding its potential to generate behavioral disinhibition and drug resistance. Some studies have suggested that the preventive impact of TasP can potentially be offset by an increase in HIV risk behavior, often due to a reduced perceived risk of transmitting or acquiring HIV [19]. However, different cohorts of injection drug users have not consistently shown changes in risk behavior since the widespread use of HAART [20]. The other main concern regarding use of TasP relates to the emergence of drug resistance [21], which is closely associated with treatment failure due to poor adherence [7, 17, 22]. Consequently, it is important to stress that the success of TasP will depend on an individual's ability to adhere to his or her daily regimens.

ECONOMICS OF TasP

The year 2008 was marked by the beginning of a global economic downturn and, as a result, there has been a major need to do more with limited resources in order to meet the needs of those affected by HIV. More than 5 years since the economic crisis, we continue to struggle to meet the care and treatment needs of millions of people living with HIV. In addition, uncertainties remain regarding the global response to the HIV epidemic, particularly with respect to the feasibility and sustainability of different preventive strategies, especially TasP.

In the clinical setting, TasP has been shown, beyond a doubt, to be cost effective in the prevention of morbidity and mortality. At the public health level, different studies, especially mathematical models, have shown that TasP is not only cost effective but it is also cost saving, especially if aggressively implemented [3,5,15]. These studies led to modeling that used the Investment Framework in 2011 in which the mathematical model compared different prevention interventions for halting HIV transmission [15]. The main goal of the Investment Framework was to model different strategies for HIV prevention, treatment, and care in order to determine which combination of interventions would be the most effective and cost saving in averting new HIV infections (all ages) and premature mortality. The model estimated the yearly cost of achieving universal access to HIV prevention, treatment, care, and support by 2015 to be $22 billion. In addition, implementation of the Investment Framework would avert 12.2 million new HIV infections and 7.4 million deaths from AIDS between 2011 and 2020 when compared with continuation of current approaches and it would result in 29.4 million life-years gained during the same period [15].

More recently, the paradigm regarding the effect of TasP has shifted from thinking of this strategy as "if we treat more people, it will cost more and we will see a prevention benefit" to it will be cost saving and it will benefit society at large, since individuals on treatment will have improved quality of life and be able to return to the workforce and provide for their families. In addition, children in households of HIV-infected adults will be raised by their parents and they will have a chance to go to school with their counterparts from non–HIV-infected households [23,24]. Thus, it is time to move from cost-effectiveness analysis to cost-benefit analysis, since the latter includes benefits that may reflect the economic gains that are possible when individuals are engaged early in antiretroviral treatment. This type of economic modeling is termed "third-generation economic modeling," and the focus is not only on how many dollars and lives we are saving by preventing new infections but also on societal and household benefits via employment gains due to higher labor productivity. In addition to employment gains, children of adults who are on HAART have a higher rate of school enrollment than the children of those off treatment. However, prior to treatment initiation at low CD4 counts, individuals and their households often experience a period of economic decline [23]. The scale-up of TasP would represent a departure from the current strategy of initiating treatment after an individual experiences CD4 decline as well as economic decline. As such, an important economic benefit of TasP approaches could be the prevention of an economic decline among HIV-infected individuals and their households. Therefore, Ministries of Finance and Ministries of Health should be aware of these secondary benefits when making decisions on expanding access to antiretroviral treatment.

IMPLEMENTATION ISSUES

The HIV epidemic has had a significant negative impact on the living standards of many individuals, households, and communities. When the concept of "HIV/AIDS exceptionalism" was introduced, we observed a significant global response to curb the impact of the epidemic. This concept originated from the idea that in order to decrease the impact of the HIV epidemic, a response that is above and beyond "normal" health interventions would be needed. However, since HIV treatment has become highly effective in preventing morbidity, mortality, and HIV transmission, the exceptionalism of HIV/AIDS today is that it is not receiving the attention it once did. Although we were able to dramatically improve the global response to the epidemic, a disproportionate number of individuals are still being infected with HIV. Unfortunately, services and programs for those affected by HIV are tremendously disconnected and highly inefficient in engaging individuals into care and treatment. To this end, strategies should consider task shifting, integration of HIV care with other clinical services, targeting the role of physicians to that of supervising and dealing with complex cases in order to minimize costs, and implementing efficient and effective retention methods.

We should focus on each step in the cascade of care in order to maximize the effectiveness of TasP in reducing the number of new infections [25]. Each step is subject to significant attrition, with the aggregate loss from the cascade easily reaching more than 50% [25]. Thus, to diminish disease burden and HIV transmission, a combined effort of different players in the healthcare system who can develop a comprehensive strategy and identify gaps in the delivery of care to these individuals will be needed. Modeling can help us to compare different strategies that we can use to find the combination of interventions that will be cost effective and have the biggest effect on diminishing the burden of HIV/AIDS. Starting with testing, it should be given voluntarily and offered routinely in healthcare settings. It is important that the community be involved since different demonstration projects have shown that testing coverage can be

increased from very low levels to almost 90% coverage in a very short period and it can be done relatively inexpensively (approximately $10 per person tested) [26]. Next, we need to maximize referral, care initiation, and retention among symptomatic and asymptomatic individuals. Currently, projects are underway to examine interventions such as testing and initiating treatment immediately, to maximize retention into treatment among individuals with high CD4 cell counts, and to identify and address barriers to treatment retention. The third step is to measure the effect of TasP on HIV incidence. In this step, we need to analyze data from research studies and predictions from modeling in order to determine whether viral load suppression is indeed associated with HIV incidence decline. Data should be gathered from community trials and national surveillance systems [27].

In addition, behavioral economics and psychology can help us tackle key issues in the implementation of TasP; these issues should be addressed in mathematical models that assess the cost effectiveness or cost benefit of different interventions. One of the most successful interventions in this field is the role of financial and nonfinancial incentives in motivating patients to adhere to treatment [28]. Incentives are commonly used in developed countries to reduce rates of obesity and smoking in the general population, and these studies are becoming prominent in developing countries. For HIV, provision of incentives might be an effective strategy for increasing testing, maximizing treatment adherence, and achieving viral suppression and retention into care. In addition, incentives can be used to keep individuals enrolled in risk-reduction initiatives that will increase adherence and treatment retention. However, it is too early to ascertain patients' motivation to continue modifying their behavior and to keep them in care once the incentives are stopped, and concerns regarding these incentive-based programs remain.

In conclusion, we continue to face the individual and societal burdens of HIV, and an unacceptable number of individuals are being infected and dying prematurely. In the past 5 years, the research community embraced the notion of using TasP to not only decrease mortality and morbidity but also to decrease HIV transmission. Because HAART has prolonged the lives of many individuals, the health, social, and economic costs to treat this population are likely to continue to increase. If the operational research field does not advance quickly, we will continue to fail these individuals and to incur high costs within healthcare systems that already struggle to cope with the current demand.

Notes

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References

1. Anderson RM, May RM. Epidemiological parameters of HIV transmission. Nature **1988**; 333:514–9.
2. Eaton JW, Johnson LF, Salomon JA, et al. HIV treatment as prevention: systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. PLoS Med **2012**; 9:e1001245.
3. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet **2009**; 373:48–57.
4. Blower SM, Gershengorn HB, Grant RM. A tale of two futures: HIV and antiretroviral therapy in San Francisco. Science **2000**; 287:650–4.
5. Lima VD, Johnston K, Hogg RS, et al. Expanded access to highly active antiretroviral therapy: a potentially powerful strategy to curb the growth of the HIV epidemic. J Infect Dis **2008**; 198:59–67.
6. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med **2011**; 365:493–505.
7. Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. JAMA **2012**; 308:387–402.
8. Kirk GD, Galai N, Astemborski J, et al. Decline in community viral load is strongly associated with declining HIV incidence among IDUs, Abstract 484. In: 18th Conference on Retroviruses and Opportunistic Infections, Boston, MA, **2011**.
9. McCormick AW, Walensky RP, Lipsitch M, et al. The effect of antiretroviral therapy on secondary transmission of HIV among men who have sex with men. Clin Infect Dis **2007**; 44:1115–22.
10. Auvert B, Males S, Puren A, Taljaard D, Caraël M, Williams B. Can highly active antiretroviral therapy reduce the spread of HIV? A study in a township of South Africa. J Acquir Immune Defic Syndr **2004**; 36:613–21.
11. Garnett GP, Becker S, Bertozzi S. Treatment as prevention: translating efficacy trial results to population effectiveness. Curr Opin HIV AIDS **2012**; 7:157–63.
12. Williams BG, Lima V, Gouws E. Modelling the impact of antiretroviral therapy on the epidemic of HIV. Curr HIV Res **2011**; 9:367–82.
13. Montaner JS, Hogg R, Wood E, et al. The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic. Lancet **2006**; 368:531–6.
14. HIV Modelling Consortium Treatment as Prevention Editorial Writing Group. HIV treatment as prevention: models, data, and questions—towards evidence-based decision-making. PLoS Med **2012**; 9:e1001259.
15. Schwartländer B, Stover J, Hallett T, et al. Towards an improved investment approach for an effective response to HIV/AIDS. Lancet **2011**; 377:2031–41.
16. World Health Organization. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection—Recommendations for a Public Health Approach. Geneva, Switzerland, **2013**. Available at: http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf. Accessed 20 November 2013.

17. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. 10 January 2011; Available at: www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 10 April 2014.
18. Egger M. Outcomes of ART in resource-limited and industrialized countries [Abstract 62]. In: 14th Conference on Retroviruses and Opportunistic Infections, Los Angeles, CA, **2007**.
19. Craib KJ, Weber AC, Cornelisse PG, et al. Comparison of sexual behaviors, unprotected sex, and substance use between two independent cohorts of gay and bisexual men. AIDS **2000**; 14:303–11.
20. Marshall BD, Wood E. Putting risk compensation to rest: reframing the relationship between risk behavior and antiretroviral therapy among injection drug users. AIDS **2012**; 26:2405–7.
21. Blower S, Bodine E, Kahn J, McFarland W. The antiretroviral rollout and drug-resistant HIV in Africa: insights from empirical data and theoretical models. AIDS **2005**; 19:1–14.
22. Lima VD, Harrigan PR, Sénécal M, et al. Epidemiology of antiretroviral multiclass resistance. Am J Epidemiol **2010**; 172:460–8.
23. Thirumurthy H, Chamie G, Jain V, et al. Improved employment and education outcomes in households of HIV-infected adults with high CD4 cell counts: evidence from a community health campaign in Uganda. AIDS **2013**; 27:627–34.
24. Thirumurthy H, Jafri A, Srinivas G, et al. Two-year impacts on employment and income among adults receiving antiretroviral therapy in Tamil Nadu, India: a cohort study. AIDS **2011**; 25:239–46.
25. Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. Clin Infect Dis **2011**; 52:793–800.
26. Kahn JG, Harris B, Mermin JH, et al. Cost of community integrated prevention campaign for malaria, HIV, and diarrhea in rural Kenya. BMC Health Serv Res **2011**; 11:346.
27. Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART) Study. Available at: http://clinicaltrials.gov/ct2/show/NCT01900977. Accessed 20 November 2013.
28. Volpp KG, Loewenstein G, Troxel AB, et al. A test of financial incentives to improve warfarin adherence. BMC Health Serv Res **2008**; 8:272.