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Review

The impact of HIV treatment as prevention in the presence of other prevention strategies: Lessons learned from a review of mathematical models set in resource-rich countries

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ABSTRACT

Objective. We aimed to assess the potential prevention benefits of HIV treatment as prevention (TasP) in resource-rich countries and examine the potential interactions between TasP and other prevention strategies by reviewing mathematical models of TasP.

Method. Multiple databases were searched for mathematical models published in the previous 5 years (from July 2007 to July 2012). The nine models located were set in Canada, Australia and the United States.

Results. These models' predictions suggested that the impact of expanding treatment rates on expected new infections could range widely, from no decrease to a decrease of 76%, depending on the time horizon, assumptions and the form of TasP modeled. Increased testing, reducing sexually transmitted infections and reducing risky practices were also predicted to be important strategies for decreasing expected new infections. Sensitivity analysis suggests that current uncertainties such as the effectiveness of highly active antiretroviral therapy outside of heterosexual transmission, less than ideal adherence, and risk compensation, could impact on the success of TasP at the population level.

Conclusion. The results from large scale pilots and community randomized controlled trials will be useful in demonstrating how well this prevention approach works in real world settings, and in identifying the factors that are needed to support its effectiveness.

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Introduction

Combination HIV prevention is defined as the strategic use of biomedical, behavioral, and structural interventions that are evidence-informed, community-owned and designed to meet the needs of particular individuals and communities (UNAIDS, 2007). The key to selecting the right combination of prevention strategies is to “know your epidemic” in order to “know your response” (UNAIDS, 2007).

HIV treatment as prevention (TasP) is a prevention approach that some countries or jurisdictions have used, or are considering, as part of a combination prevention program. TasP is an approach that involves expanding the use of highly active antiretroviral therapy (HAART) among those with HIV, with the goal of reducing HIV transmissions through the suppression of viral load. TasP has gained much attention

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following the 2011 results of a clinical trial (HPTN 052), which examined the use of HAART for the prevention of HIV transmission, found a 96% reduction in the risk of transmission among serodiscordant couples who were predominantly heterosexual (Cohen et al., 2011). These compelling results led some to declare TasP to be a "serious game changer", which, in combination with other interventions, could lead to the end of the AIDS epidemic (Anonymous, 2011; Cohen, 2011).

While the results of HPTN 052 were unequivocal in demonstrating the efficacy of TasP, its effectiveness at the population level is less clear. In particular, it is unclear whether TasP would have an additive or synergistic effect (i.e., when combined, programs produce a total effect that is greater than the sum of individual programs), or whether it would displace or undermine existing effective prevention strategies. It is important to consider how adding such a novel biomedical approach to existing prevention strategies (e.g., promotion of condoms, testing, and treatment of STIs) could contribute to any future decreases in HIV infections.

Pilot studies and community-level randomized controlled trials are needed to confirm that TasP be effective. The decision to initiate a pilot study is often based on the opinions of experts, including the mathematical scenarios, and guided by a precautionary principle (i.e., when there is a threat of harm, preventive measures should be implemented even where there is scientific uncertainty in the cause and effect relationship).

A number of community-level randomized controlled trials are currently underway to examine the effectiveness of TasP at the population level in combination with other prevention approaches. For example, in the US, a community-level test, link to care, plus treat strategy (TLC+) is being evaluated, and includes the use of a combination of behavioral and biological interventions. In sub-Saharan Africa, the Population Effects of Anti-Retroviral Therapy (PopART) is examining the impact of universal testing and treatment as part of a comprehensive combination prevention package and Médecins Sans Frontières is conducting a community-based TasP pilot project using a combination prevention approach, which includes the offer of medical male circumcision (Granich et al., 2011). However, the results of these studies examining TasP as part of a combination approach are two to three years away.

In the meantime, a number of mathematical models have been developed to describe the potential benefits of implementing TasP on a large scale. Mathematical modeling is a useful aid in public health decision making. When timely action is required, even in the absence of high quality evidence, it is relatively easy for mathematical models to produce a number of scenarios that are internally consistent and include stated assumptions and mathematical linkages. For example, conducting an epidemiological study to assess different forms and combinations of interventions would be time consuming, complex and costly, whereas, mathematical modeling can be a more flexible and accessible approach to examining the effects of different combinations of interventions (Garnett et al., 2011; Hankins and De Zalduondo, 2010).

As the decision making process transitions from precautionary decisions towards recommendations of best practices, studies that meet a higher standard of scientific rigor are required to develop these recommendations. Mathematical models can continue to play a role by exploring options for the validation of model outputs, identifying data elements that could reduce the uncertainty identified in a full sensitivity analysis and eventually identifying the conditions needed for success that would assist jurisdictions in determining whether an intervention is appropriate for their setting.

One of the earlier TasP models was published by Granich et al. 2009. This model predicted that, in South Africa, if almost all individuals were tested for HIV annually and if every HIV-positive individual started treatment immediately, HIV would enter an elimination phase (i.e., a reduction in incidence to less than one case per 1000 people per year) within 5 years. Like the Granich model, to-date, many models of TasP have been set in resource-limited countries, often using similar assumptions. Several of these TasP models have been criticized for the use of overly optimistic assumptions, including: high rates of uptake and adherence to treatment; high levels of treatment effectiveness in reducing transmission; underestimating the role of primary HIV infections; and not including the effect of potential increases in drug resistance or risk compensation (Epstein, 2009; Jaffe et al., 2009; Jürgens et al., 2009; Wagner and Blower, 2009; Wilson, 2009). Such models, set in resource-limited countries, may be less applicable to resource-rich countries given the differences in the type of epidemic, the health care systems, access to health care resources, the primary modes of transmission, levels of stigma and discrimination associated with HIV, and access to existing prevention strategies.

The aim of this study was to examine the predictions of TasP models set in resource-rich countries to determine what could be learned about the potential additive, synergistic or other effects that expanding treatment could have on existing prevention strategies, such as: the promotion of condom use; increasing testing; and decreasing the prevalence of other STIs. We outlined the key parameters and assumptions used in these models to aid in the interpretation of the models' predictions, and examined the status of these mathematical modeling studies vis-à-vis the public health decision making process.

Methods

A literature search of Scopus, Medline, Embase and the Global Health database was conducted using the following keywords: (HIV OR AIDS OR immunodeficiency) AND ("test and treat" OR "treatment as prevention") AND (model* OR simulation OR forecast* OR predict* OR mathematical). The search was restricted to English and French language papers, published in the previous five years (from July 2007 till July 2012). Citation searching and reference list checking were also conducted to ensure a complete capture of relevant articles. Given the concerns regarding the discrepancy between conference abstracts and subsequent full-length journal articles (Falagas and Rosmarakis, 2006; Toma et al., 2006), conference abstracts were not included in this review.

Models that examined the impact of scaling up treatment for the purposes of reducing transmission, in a resource-rich country context, were selected for this review. Resource-rich countries were defined as countries with high-income economies, as identified by the World Bank classification (The World Bank, 2011). The outcome of interest was the number or proportion of HIV infections averted as a result of expanded antiretroviral treatment alone, or in combination with related prevention outcomes. Models that attempted to explain past HIV/AIDS trends were excluded.

The models were described by abstracting the following information: details of the TasP intervention modeled; population; time horizon; setting; and projected outcomes. The modeling of other, potentially complementary, prevention strategies were noted, as were the findings related to the inclusion of these prevention strategies in the models. Model parameters and assumptions were examined, with a focus on the assumptions made regarding: the engagement and retention in care (including adherence); HAART effectiveness; the role of primary HIV infection in transmission; drug resistance; and impact of the intervention on risk behaviors.

Results

Fifty-nine articles were located in the literature search. From this search, five were selected for inclusion. Of the 54 that were excluded: 43 were not mathematical models (24 were reviews; 15 were comments or editorials; 2 were randomized clinical trials; 1 was a cost analysis; and 1 was a lab based-study). Another 11 articles were mathematical models, but were excluded because they were set in resource-limited or hypothetical settings (n = 7); they did not include the intervention or outcome of interest (n = 3); or because they sought to explain historical trends (n = 1).

A further four articles were located through citation searching and reference list checking for a total of nine articles. Of the nine models, three were based in Canada (Johnston et al., 2010; Lima et al., 2008, 2010), three in Australia (Heymer and Wilson, 2011; Hoare et al., 2008; Wilson et al., 2009), and three in the United States (U.S.)