Published: June 2011

Evaluating the cost-effectiveness of pre-exposure prophylaxis (PrEP) and its impact on HIV-1 transmission in South Africa

Carel Pretorius - Associate, Futures Institute, Glastonbury, Connecticut, United States of America

The annual international AIDS conference, held last year in Vienna (1), invariably asks new questions and poses new challenges to mathematical modellers. The conference offers clinicians an opportunity to present their latest findings as to whether a particular new preventative technology–a broad term, encompassing 'tools' such as PrEP, topical PrEP or microbicides and future vaccines–prevents new infections. Progress is typically incremental but any news that prevention technology is moving in the right direction is always keenly awaited. Mathematical models often respond to prevention news, adjusting existing models or developing new ones to answer new questions.

Positive developments in preventative technology

One of last year's positive messages came from the Centre for the AIDS Programme of Research in South Africa (CAPRISA 004) trial (2), the first to establish the efficacy of microbicide gel, after many years of setbacks in microbicide efficacy trials (3).

It showed that TDF-based microbicide gel is 39% effective in preventing HIV transmission in women. The level of protection was more than 54% for women who used the gel regularly. The CAPRISA results were the first to establish the efficacy of microbicide gel, after many years of setbacks in microbicide efficacy trials.

Confirmation of the efficacy of oral PrEP, another promising application of antiretroviral therapy to limit the spread of HIV at population level, had to wait until later in the year (4). PrEP proposes the use of antiretroviral therapy by individuals who anticipate exposure to HIV infection, including commercial sex workers (CSW), men who have sex with men (MSM), and partners of individuals who are exposed to risk of infection (e.g. partners of sex work clients and injecting drug users (IDU)) (5). PrEP trials are currently focusing on the oral use of a combination of tenofovir disoproxyl fumarate (TDF) and emtricitabine (FTC). PrEP could be a timely female-controlled strategy for women at high risk (5,6).

The much anticipated Preexposure Prophylaxis Initiative (abbreviated to "iPrEx"), announced in November 2010, shows that oral PrEP (in the form of TDF/FTC) reduces risk of infection by 44% among HIV-negative high-risk MSM. Oral and topical PrEP are not the silver bullets we had hoped they would be, but two new tools that could be added to our prevention arsenal if further trials clear their way. With the CAPRISA and iPrEx efficacy results in hand policy makers are now proactively focusing on implementation and are turning to mathematical modelers to estimate the potential impact of various PrEP strategies.

At the Vienna AIDS conference economists announced the findings of their cost-effectiveness assessments, charting the way to more cost-effective prevention. The HIV prevention world is not immune to financial pressure and is suffering the effects of the 2008 global financial crisis. Funding for prevention is levelling off and in some countries decreasing. Doing-more-with-less messages were rephrased as doing-more-with-much-less for the foreseeable future (1), with a greater emphasis on cost-effective intervention strategies and efficiency of service delivery.

Health economists also need modellers. Supposing that PrEP trials demonstrate efficacy in preventing new infections in general settings, will PrEP be a cost-effective part of a comprehensive prevention package? What return can we expect from this new investment in controlling generalized HIV epidemics? Which prioritising strategies (e.g. young women, CSW, partners of their clients, MSM, and so on) will give the best return on this investment?

Mathematical models have been used to study the potential impact of PrEP at the national level. One study looked at the potential impact of PrEP on the HIV epidemic in Zambia (7) and another studied the potential impact in Botswana, the Nyanza Province in Kenya and India (6). Their findings point to a substantial reduction in the number of new infections (as many as 2.7 to 3.2 million estimated in (7)) should PrEP be deployed as a control strategy in sub-Saharan Africa. Both papers mention that expanding ART programs could limit the impact of PrEP. However, the subtleties of this dependence are still largely unexplored.

Potential impact of PrEP in different scenario's

The focus of this paper is to evaluate PrEP alongside ART and condom-use interventions in South Africa, informed by national HIV and demographical surveys (8). The age-structured model we developed

pays close attention to the distribution of relative infection risks between age categories. It includes dynamical effects usually not explicitly modelled, such as age-dependent condom use and partner choice. Despite some the limitations of the model (8,9), such as the lack of risk structure which does not depend on age and the failure to account for possible drug resistance (5,10), the model offers a relatively simple approach to studying the impact of PrEP in the context of national and generalized HIV epidemics. The inclusion of an age variable offers a direct way of studying age-structured prioritising strategies (Figure 1). In South Africa, for example, the highest risk category would be 25–35-year-old women (Figure 10 (9)). Should PrEP be prioritised to this age category?

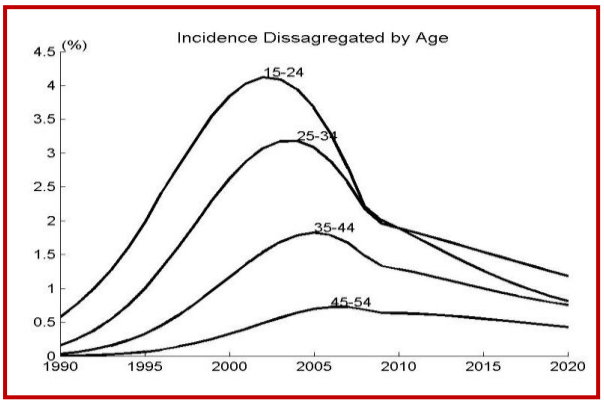

Figure 1. HIV incidence disaggregated by age. Compare with Figure 10 (9).

The model helps us isolate the potential impact of PrEP in an environment of expanding ART programs. Which age groups should be targeted for maximal impact? How could risk compensation (condom substitution in the case of South Africa) negate the benefits of a PrEP program? How would the impact of PrEP be influenced by an uncertainty in base-line incidence (12) and an expanding ART program, including a possible expansion toward universal access to testing and treatment (UTT) (11)?

Our modelling results show that non-targeted PrEP coverage would have to be impractically high to have an effect on incidence reduction comparable to the effect of UTT. In order to approach disease eradication, almost all those susceptible to infection must be protected by PrEP. Prioritising PrEP to 15–35 year-old women would achieve a 10%–25% reduction in new infections by 2025 in this age group. The results come from a model that is optimistic in its assumptions: no condom substitution and 90% PrEP efficacy. While condom substitution can be limited through counselling, it is unlikely that PrEP efficacy will be so high, even for high-adherers. Nevertheless, the best case scenario, together with less optimistic scenarios indicates that properly managed and targeted PrEP interventions can achieve a non-negligible reduction in incidence.

Our analysis shows a smaller impact of condom substitution among targeted PrEP users than was reported in the study conducted in Botswana, Kenya and India (6). A possible explanation could be the relationship between condom use and age. In South Africa condom use is relatively high among 15–30-year-old women (Fig. 5 (9)), but it decreases exponentially with age. Risk compensation by 25–35-year-old women using PrEP could lead to a further decrease in condom use over the period 2014–2025, but our model suggest that this on its own will not necessarily result in an overall increase in incidence.

We studied various scenarios of targeted PrEP as ART coverage gradually expands. Our results show that ART will outcompete PrEP in averting new infection and drastically reduce the cost-effectiveness of PrEP should its coverage reach three times 2010 levels. Both the relative cost-effectiveness of PrEP and its impact on incidence would be considerably reduced should UTT be introduced in South Africa shortly after the initiation of a PrEP strategy. The national ART program of South Africa is currently on a scaling-up trajectory where more than 65% of HIV+ cases may receive ART by 2025. Although this expansion is nothing near what can be described as UTT, it would also obscure the benefits of PrEP.

PrEP could serve as a useful stop-gap control solution until ART coverage is scaled up towards providing this level of ART coverage, after which the epidemic may be substantially controlled in South Africa. However, although ART does reduce infectiousness (11) its efficacy as a prevention tool has not been clearly established outside of controlled settings and UTT trials are far behind microbicide and PrEP trials. Further, the optimistic impact projections of UTT fail to take into account the various development challenges facing South Africa to implementing effective and sustainable ART programs. The ‘stop-gap-period’ of cost-effective PrEP may turn out to be long.

Goals Express tool: studying PrEP in sub-saharan Africa

We have to remind ourselves that PrEP and ART are only two of several interventions that can be scaled up for cost-effective HIV prevention in South Africa. In response to the Vienna conference warning that HIV prevention funding is stagnating we must determine the most cost-effective package of interventions to deal with a generalized HIV epidemic. A new free web-based tool, Goals Express developed by Futures Institute (http://policytools.futuresinstitute.org/goals.html), allows users to study the potential impact of PrEP in 19 sub-Saharan African countries, as it interacts and ‘competes’ with 16 other interventions to avert new infections.

An interesting picture emerges when using Goals Express to study different PrEP programs targeted beyond high-risk groups, which are generally small (a few percent of the total adult population). PrEP will have relatively high impact (10-20% reduction in the overall number of new infections) at 60% coverage, but will be one of the most expensive prevention strategies. Its cost per infection averted is close to that of expanding ART programs. It will be interesting to see how the 'ART for treatment vs. prevention' debate shapes up keeping in mind that ART has a greater impact on infections averted and that ART is both a treatment and a prevention strategy.

This is an abbreviated version of the article published by Carel Pretorius, John Stover, Lori Bollinger, Nicolas Bacaër and Brian Williams in PLoS ONE in November 2010 (8).

Carel Pretorius, Associate, Futures Institute, Glastonbury, Connecticut, United States of America. Interests: Developing strategic planning tools for HIV and TB epidemics. *CPretorius@futuresinstitute.org*

References:

1. WHO, UNAIDS, UNICEF. Rights Here: Rights Now. Technical report, XVII International AIDS conference Viena. 2010. http://www.iasociety.org/Web/WebContent/File/AIDS2010_Impact_Report.pdf Accessed May 27, 2011.
2. Karim A, Karim S, Frolich J, et al. Effectiveness and safety of Tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010;329: 1168–1174.
3. Verguet S. Microbicides: the end of the beginning, not the beginning of the end. SACEMA Quarterly, Issue November 2010. http://www.sacemaquarterly.com/hiv-prevention/microbicides-the-end-of-the-beginning-not-the-beginning-of-the-end.html Accessed March 6, 2011.
4. Grant R. Antiretroviral agents used by HIV-uninfected persons for prevention: pre- and post-exposure prophylaxis. Clin Infect Dis. 2010;50 Suppl 3:S96–101.
5. Grant R, Lama J, Anderson P, et al. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. N Engl J Med. 2010;363(27):2587-2599.
6. Vissers D, Voeten H, Nagelkerke N, Habbema J, de Vlas S. The impact of pre-exposure prophylaxis (PrEP) on HIV epidemics in Africa and India: a simulation study. PLoS One. 2008;3(5):e2077.
7. Abbas U, Anderson R, Mellors J. Potential impact of antiretroviral chemoprophylaxis on HIV-1 transmission in resource-limited settings. PLoS One. 2007;2(9):e875.
8. Pretorius C, Stover J, Bollinger L, Bacaer N, Williams B. Evaluating the cost-effectiveness of pre-exposure prophylaxis (PrEP) and its impact on HIV-1 transmission in South Africa. PLoS One. 2010; 5(11): e13646.
9. Bacaer N, Pretorius C, Auvert B. An age-structured model for the potential impact of generalized access to antiretrovirals on the South African HIV epidemic. Bull Math Biol. 2010;72(8):2180-2198.
10. Wagnera B, Kahn J, Blower S. Should we try to eliminate HIV epidemics by using a 'Test and Treat' strategy? AIDS. 2010;24(5): 775–776.
11. Granich R, Gilks C, Dye C, De Cock K, Williams B. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet. 2009;373(9657): 48–57.
12. Rehle T, Hallett T, Shisana O, et al. A decline in new HIV infections in South Africa: estimating HIV incidence from three national HIV surveys in 2002, 2005 and 2008. PLoS One. 2010;5(6): e11094.