The potential effects of changing HIV treatment policy on tuberculosis outcomes in South Africa: results from three tuberculosis-HIV transmission models

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

Tuberculosis (TB) continues to be one of the most important public health challenges facing South Africa. Approximately 1% of the country's population develops active TB each year, an alarming indicator which has risen sharply over the last 20 years in response to an increase in the number of individuals with advanced HIV disease (1).

The South African National TB Control Program implemented Directly Observed Treatment, Short-course (DOTS) during this period. Despite diagnosing and successfully treating a high proportion of active cases, TB incidence continues to rise (1).

Expanding ART coverage to healthier HIV patients is widely regarded as a potential strategy for addressing the rampant TB epidemic in high HIV-TB burden settings. These expectations are fuelled by a number of clinical and mathematical modelling studies. The effectiveness of ART to fight TB has most recently been confirmed by a meta-analysis which showed that ART reduces the rate at which HIV positive individuals progress to active TB disease, even for individuals with CD4 cell counts more than 350 cells/ml (2).

Estimating the population-level impact of ART expansion on TB disease has proven challenging. One extreme of potential impact is provided by Williams et al. who estimate that immediate ART initiation of all individuals diagnosed with HIV could eventually reduce HIV-associated TB incidence by over 98% by 2050 (3). Currie et al. (4), on the other hand, find the provision of ART to have minor long-term impacts compared to improvements that could be achieved through strengthening conventional TB interventions.

We set out to estimate the potential effects of changing HIV treatment policy on TB outcomes in South Africa, comparing the results of three independent TB models. This project was part of a broader effort to shed light on the consequences of HIV policy changes (5), through model comparison and consensus building, a process pioneered in the

HIV modelling field by the HIV Modelling Consortium (6).

Approaches to antiretroviral therapy expansion

The South African ART program currently sets ART eligibility for HIV patients at CD4 cell counts less than 350 cells/ml, with active TB, with WHO HIV-stage 3 or 4, or belonging to a vulnerable group such as pregnant women. Expanding the ART program in South Africa was modelled as proceeding in two dimensions: relaxing the CD4 eligibility criterion and improving access for those already eligible. ART access was depicted as 'status quo', where current access patterns continue (approximately 75% for eligible adults and children at December 31, 2013) and 'expanded 'access' where HIV testing, linkage and retention in pre-ART care would be improved such that 80% of HIV positive adults initiate treatment soon after becoming eligible. Three ART eligibility criteria were considered within each of the two ART access scenarios: eligibility for HIV-positive adults with CD4 cell count less than 350 cells/ml eligibility (referred to as 'CD4 < 350'), for those with CD4 cell count less than 500 cells/ml (referred to as: 'CD4 < 500'), and immediate eligibility for all HIV-positive adults (referred to as 'universal access').

Mathematical models

Three independent mathematical models, called the "Menzies", "PopART" and "Goals" model were used to estimate the impact of ART expansion on the South African TB epidemic. The three models belong to different model classes: Menzies being compartmental (deterministic), PopART individual-based (stochastic) and Goals being a multivariate regression model. The models are described in detail in the original paper on which this article is based (7).

In each model CD4 cell count mediates the risk of developing active TB, and as such can itself be viewed as a risk factor for various aspects of TB disease. CD4 cell count decline is halted for patients receiving ART, effecting dramatic reductions on

HIV-related mortality and TB-associated HIV mortality. ART further reduces HIV infectiousness, which reduces HIV incidence at population level. None of the models incorporate the influence that immune reconstitution syndrome may have on TB disease (8,9).

All three models base demography projections for South Africa on estimates from the UN Population Division. The TB models were calibrated to WHO Stop TB Department time-series estimates of TB incidence, TB prevalence (1) and related indicators. Each model projects results for the period 2013-2033. HIV sub-models were calibrated to UNAIDS HIV burden and treatment estimates.

Impact on TB incidence and mortality

Compared with ART eligibility continuing at CD4 <350 cells/ml, universal eligibility is projected to reduce cumulative TB incidence by 7, 17, and 30% over 20 years. The number of person-years of ART required to avert one TB case, range from 10 to 13 for universal eligibility, and the same pattern is apparent for TB-related mortality.

The models project that expanding ART access to 80% coverage would produce an 8–14% reduction in TB incidence and 12–21% reduction in TB-related mortality over the period 2014–2033 if the current CD4 <350 eligibility criteria were to be continued. If ART initiation criteria were expanded to universal eligibility, then expanding ART access to 80% coverage is projected to produce an additional 10–23% reduction in cumulative TB incidence and 13–36% reduction in cumulative TB-related mortality over the period 2014–2033. The combined impact of CD4-based eligibility and ART coverage expansion is estimated to be a reduction in incidence, relative to current policy, of 28–37% over 2014–2033. All three models show a stabilization of impact indicators resulting from even the most aggressive ART expansion scenario.

The potential impact of expanding ART on TB mortality mirrors the impact on TB incidence. The maximal impact occurs under universal eligibility, namely a 10–26% reduction in cumulative TB-related deaths over 2014-2033. For ART coverage expansion under universal eligibility the mortality impact range is 13–36%. The combined impact of CD4-based eligibility and ART coverage expansion is estimated to be a reduction in TB mortality, relative to current policy, by 36–44% over 2014–2033.

Implications for TB control in South Africa

Our results project a significant impact on TB incidence and mortality from ART expansion in the period 2014–2033. New TB cases would be 6–30% lower if ART eligibility were expanded to include all HIV-positive adults immediately, relative to continuing eligibility at CD4<350. Expanding access to 80% coverage under universal ART eligibility could reduce the total number of new TB cases further by 10-23%. The combined impact of universal eligibility and expanded ART coverage is projected to produce a 28–37% reduction in new TB cases over 2014–2033 compared with current policies. A similar impact is projected for TB mortality.

The range of results produced by the three models are a consequence of several factors, including variation in TB model structure and parameterization. The models also differ with respect to their HIV sub-structure, in particular with respect to the relative distribution of HIV across CD4 strata and consequently how the proposed ART policy changes will impact ART enrolment.

Despite these differences in projected impact estimates (and the possibility that none of the three model prediction's may ultimately become reality), we have concluded that there will likely be a limited impact of ART expansion on TB disease, as shown by the stabilization of impact indicators resulting from even the most aggressive ART expansion scenario. For this reason, expansions of ART programs in South Africa alone are unlikely to achieve long-term TB control goals. Such a goal will require improvements in TB case detection and treatment too. Projections for TB treatments were not the focus of the paper, however we estimate that reductions in need for TB treatment due to TB cases averted will be small relative to the increases in ART volume associated with ART expansion. We conclude that ART expansion in South Africa can serve as platform but not as solution to TB control, and that a significant increase in treatment volume is required for ultimate TB control in South Africa.

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

References:

1. WHO. WHO Global TB Database. [http://www.who.int/tb/country/data/download/en/index.html] , Accessed April 4, 2013.
2. Suthar AB, Lawn SD, del Amo J, Getahun H, Dye C, Sculier D, et al. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. PLOS Med. 2012; 9:e1001270.
3. Williams BG, Granich R, De Cock KM, Glaziou P, Sharma A, Dye C. Antiretroviral therapy for tuberculosis control in nine African countries. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107:19485–9.
4. Currie CSM, Williams BG, Cheng RCH, Dye C. Tuberculosis epidemics driven by HIV: is prevention better than cure? AIDS. 2003; 17:2501–8.
5. Eaton J. et a.l How should HIV programmes respond to evidence for the benefits of earlier treatment initiation? A combined analysis of twelve mathematical models. [http://apps.who.int/iris/bitstream/10665/93524/1/WHO _HIV_2013.56_eng.pdf] Accessed August 24, 2014.
6. HIV Modeling Consortium. http://www.hivmodelling.org/
7. Pretorius C, Menzies NA, Chindelevitch L, et al. The potential effects of changing HIV treatment policy on tuberculosis outcomes in South Africa: results from three tuberculosis-HIV transmission models. AIDS. 2014;28 Suppl 1:S25-34.
8. Haddow LJ, Moosa M-YS, Mosam A, Moodley P, Parboosing R, Easterbrook PJ. Incidence, clinical spectrum, risk factors and impact of HIV-associated immune reconstitution inflammatory syndrome in South Africa. PLoS ONE. 2012; 7:e40623.
9. Meintjes G, Lawn SD, Scano F, Maartens G, French MA, Worodria W, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. Lancet Infect Dis. 2008; 8:516–23.