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

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Objective(s): Many countries are considering expanding HIV treatment following recent findings emphasizing the effects of antiretroviral therapy (ART) on reducing HIV transmission in addition to already established survival benefits. Given the close interaction of tuberculosis (TB) and HIV epidemics, ART expansion could have important ramifications for TB burden. Previous studies suggest a wide range of possible TB impacts following ART expansion. We used three independently developed TB-HIV models to estimate the TB-related impact of expanding ART in South Africa.

Design: We considered two dimensions of ART expansion – improving coverage of pre-ART and ART services, and expanding CD4-based ART eligibility criteria (from CD4 <350 to CD4 <500 or all HIV-positive).

Methods: Three independent mathematical models were calibrated to the same data pertaining to the South African HIV–TB epidemic, and used to assess standardized ART policy changes. Key TB impact indictors were projected from 2014 to 2033.

Results: Compared with current eligibility and coverage, cumulative TB incidence was projected to decline by 6–30% over the period 2014-2033 if ART eligibility were expanded to all HIV positive individuals, and by 28–37% if effective ART coverage were additionally increased to 80%. Overall, expanding ART was estimated to avert one TB case for each 10–13 additional person-years of ART. All models showed that TB incidence and mortality reductions would grow over time, but would stabilize towards the end of the projection period.

Conclusion: ART expansion could substantially reduce TB incidence and mortality in South Africa and could provide a platform for collaborative HIV-TB programs to effectively halt HIV-associated TB.

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Introduction

The annual number of new tuberculosis (TB) cases in South Africa has increased five-fold between 1990 and 2011, with approximately 350 000 TB cases identified and reported to the WHO during each of the years 2009–2011. Incidence of active TB is estimated at 500 000 cases annually, approximately 1% of the total South African population [1]. The rise in incidence over the last 20 years is attributed to the rapid increase in the number of individuals with advanced HIV disease, and TB has been identified as the leading cause of HIV-related mortality in South Africa [2].

The South African National TB Control Program was launched in 1996 to address the growing TB epidemic [3]. The DOTS strategy implemented by the national program aims to detect a high proportion of active TB cases and providing uninterrupted treatment through direct supervision. Not all of these objectives have been achieved. TB is diagnosed through passive case finding. Treatment is mostly limited to highly symptomatic disease among self-presenting patients, and is often interrupted [4,5]. Despite improvements in case detection and cure rates in recent years, the estimated incidence of TB continues to rise [1].

The potential impact of ART on TB disease has been the subject of a number of clinical and mathematical-modeling studies. A recent meta-analysis has confirmed the effectiveness of ART in reducing the rate at which individuals progress to active disease, even for individuals with CD4 cell counts more than 350 cells/μl [14]. With low CD4 cell count a recognized risk factor for TB progression [6–8] and mortality [9–11], and ART's proven ability to stop immune system decline in typical patients, model-based analyses indicate a potential for dramatic decrease in the number of incident TB cases when ART eligibility is expanded to include asymptomatic HIV cases [12,13]. Although the incidence rate of TB may be lower following ART initiation, long-term observational data from South Africa show that TB reactivation rates in ART cohorts are still two to four times those observed among HIV negative individuals [15]. Also, it is still unclear how the effects of ART on the incidence rate of TB observed in trial settings will translate into changes in lifetime TB risk for clients in routine ART programs, given increased survival in ART cohorts [16].

Since inception in 2004, the South African National ART Program has grown to be the largest in the world, with over 1.7 million HIV patients reported to be receiving ART in South Africa by the end of 2011 [17]. The program has introduced ART eligibility criteria consistent with WHO recommendations [18,19], but has not yet achieved high ART coverage. Many provinces and local authorities face challenges introducing early diagnosis and strengthening the linkage between diagnosis and treatment. Despite these challenges, recent policy debate has focused on potential expansions of the ART program, motivated by the potential of ART to reduce HIV transmission [20,21], and recently released WHO ARV guidelines that recommend expanding ART initiation criteria to include all adults with a CD4 cell count less than 500 cells/μl [22].

A number of prior studies have estimated the implications of ART expansion for TB outcomes in sub-Saharan Africa [12,13,23–25]. Although all studies project declines in TB incidence as ART is expanded, the magnitude of these changes varies substantially between studies – at one extreme Williams *et al.* [13] estimate that immediate ART initiation of all individuals diagnosed with HIV could eventually reduce HIV-associated TB incidence by over 98% by 2050, while at the other extreme Currie *et al.* [24] find the provision of ART to have minor impacts compared to improvements in conventional TB intervention such as better TB case detection over a 20-year period. The extent to which these different conclusions are due to differences in context, intervention, or the mathematical models used to project epidemic outcomes is unclear. Given the limited resources available for disease control, a better understanding of ART's effect on TB epidemiology would be valuable.

In this study, we use three independent TB models, which form part of a broader study into the potential cost and impact of expanding ART eligibility criteria [26], to investigate potential TB outcomes attributable to ART expansion in South Africa over the period 2014–2033. These three models differ in structure but were calibrated to the same data and used to project the consequences of policy options for ART expansion currently being considered by decision-makers.

Methods

Approaches to antiretroviral therapy expansion

The South African ART program follows current WHO eligibility guidelines [27], that is, ART eligibility for all HIV patients with CD4 cell counts less than 350 cells/μl, with active TB, with WHO HIV-stage 3 or 4, or belonging to a vulnerable group such as pregnant women. In addition, the 2012–2016 National Strategic Plan for HIV, South Africa, proposes the strengthening of pre-ART care aspects of the program, by linking patients not yet eligible for ART to routine care and monitoring [28].

Models assumed that HIV-positive individuals are diagnosed and identified for care based on the level of HIV testing in the community. Those found to be HIV

positive and ART-eligible are initiated on ART, and those not yet eligible are provided with pre-ART care until they become ART-eligible. Models allowed for imperfect retention at each stage of this cascade. No independent prevention effects were assumed to result from HIV testing. Further details regarding the model-specific implementation of expanded access to HIV care and ART initiation can be found the Appendix, Chapters 1–3, http://links.lww.com/QAD/A418.

We investigated two different dimensions of ART expansion – changing CD4-based ART eligibility criteria to permit earlier ART initiation, and improved access amongst those eligible for ART under particular eligibility criteria. Two scenarios were created to capture different ART access assumptions. Under a 'status quo' scenario, we assumed current patterns of access to and uptake of HIV testing and care services would continue in the future. Under a 'expanded access' scenario we assumed that 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/μl eligibility (referred to as 'CD4 < 350'), for those with CD4 cell count less than 500 cells/μl (referred to as 'CD4 < 500'), and immediate eligibility for all HIV-positive adults (referred to as 'CD4 < 500').

Mathematical models

Two TB transmission models and one regression model were used to estimate the impact of competing ART expansion approaches on the South African TB epidemic. The two transmission models – the Menzies and PopART models – directly simulate key epidemiological processes (Appendix, Chapters 1 and 2, http://links.lww.com/QAD/A418). Infection with *Mycobacterium tuberculosis* (MTB) results in primary TB disease or latent MTB infection. Individuals with latent infection can develop active TB through progression and can be re-infected. Active TB is characterized as pulmonary smear negative or smear positive. Diagnostic processes, treatment initiation and outcomes are modeled explicitly. Recovery to latent infection is modeled as the result of treatment or self-cure.

The most important differences between the two transmission models stem from the way in which they represent the population and its demographical structure, natural history processes, and how HIV positive clients are linked to care. Key functionalities are described below and summarized in Table 1, and further details may be found in the Technical Appendices, http://links.lww.com/QAD/A418.

The Menzies model (hereafter 'Menzies') is a detailed HIV–TB co-infection model designed to analyze health outcomes and associated economic consequences of alternative TB interventions, which necessitates much detail with respect to diagnostics, treatment and the development/propagation of TB drug resistance [29].

The PopART model (hereafter 'PopART') is an individual-based model, which allows the tracking of individual epidemic history, including a history of TB episodes. A key motivation for such detail is that it allows investigation of different mixing patterns and contact patterns. It was designed to interpret household-centered TB interventions in the ZAMSTAR trial [30].

The Goals model (hereafter 'Goals') is a fundamentally different type of model. It is a regression model that does not attempt to simulate TB infection, recovery or other processes explicitly (Appendix, Chapter 3, http://links.lww.com/QAD/A418). Instead, it uses a functional relationship, which relates output from the Spectrum HIV model [31], used to prepare HIV incidence and prevalence estimates for the UNAIDS Global report on HIV/AIDS, to the incidence of active TB. The functional relationship relates the seven CD4 categories of Spectrum to risk for TB disease. Latent MTB infection is not modeled, and the relationship establishes a direct route from prevalent TB to incident cases. Its main purpose is to aid interpretation of TB-associated HIV mortality estimates.

Effects of CD4 cell count decline and antiretroviral therapy initiation

In Menzies three CD4 strata are distinguished: CD4 <200 cells/μl, CD4 200–350 cells/μl and CD4>350 cells/μl. In PopART CD4 is modeled as a continuous variable that declines linearly from 750 to 0 cells/μl. Goals uses seven CD4 strata: CD4 < 50 cells/μl, 50–99, 100–199, 200–249, 250–349, 350–499 and > 500 cells/μl. In all three models low CD4 cell count increases risks of HIV-related mortality.

In all three models, 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. Low CD4 cell count is a risk factor for the progression of latent to active TB disease in all three models, which is handled explicitly in Menzies and PopART (in Goals, this progression is immediate). In Menzies, reduced CD4 is additionally associated with higher risks for primary TB upon initial infection, higher rates of breakdown from latency to active disease, lower probability of self-cure in those with active disease, the protective effect that prior TB episodes have on TB infection, and lower probability of smear-positivity among those with active disease. In PopART, HIV-status affects these same processes without stratification by CD4 status (except all progression rates to TB, which increase as CD4 cell count decreases).

In all three models, CD4 cell count decline is halted for patients receiving ART, effecting dramatic reductions on

Table 1. Comparing three tuberculosis models in term of model structure and risk factors for tuberculosis disease.

	Menzies	PopART	Goals
Model type	Compartmental, deterministic	Individual based, stochastic	Multivariate-regression
Calibration	Bayesian with sampling-importance resampling	Quasi-Bayesian with adaptive importance sampling	Least-squares optimization
Demographic structure	Single sex and single age category (15+)	Sex and age (15+) are effectively continuously tracked at individual level. However, sex and age are not modeled as risk factors for TB	Single sex and single age (15+) category
HIV structure	HIV-, HIV+ not on ART with CD4 <200, CD4 200–350 and CD4>350. ART linked to CD4 at ART initiation	HIV-, HIV+ not on ART with CD4 drop from 1000 to 750 on seroconversion followed by continuous linear decline to 0 cells/μl	HIV-, HIV+ not on ART with CD4 < 50, 50–99, 100–199, 200–249, 250–349, 350–499 and CD4 > 500. ART linked to CD4 at initiation. ART duration is explicitly tracked
TB structure	Susceptible, latent or active TB	Susceptible, latent or active TB	N/A
Development of active TB	Primary progressive disease, re-activation of latent infection or re-infection	Primary progressive disease, re-activation of latent infection or re-infection	Primary progressive disease (no latency)
Episode recovery	TB treatment and self-cure	TB treatment and self-cure	N/A
TB diagnostics	Explicit detailed algorithm for TB diagnostics	Simplistic case-detection	Simplistic case-detection
TB treatment	Approximates treatment provided within National TB Control Program (DOTS) or through non-DOTS providers	Approximates DOTS	Approximates DOTS
TB risk-factors	TB infection history, TB treatment history, HIV status, CD4 decline, ART status	TB infection history, TB treatment history, HIV status, CD4 decline, ART status	HIV status and CD4 decline. ART status

ART, antiretroviral therapy; TB, tuberculosis.

HIV-related mortality and TB-associated HIV mortality. ART further reduces HIV infectiousness [20,21], which reduces HIV incidence at population level. None of the models incorporate the influence that immune reconstitution syndrome may have on TB disease [32,33]. For each model, Table S2 presents rate ratios of developing active TB, and of TB-associated mortality, as a function of HIV status, CD4 cell count, and receipt of ART.

Model calibration

All three models base historical demography and future population projections for South Africa on estimates from the UN Population Division. Models were calibrated to WHO Stop TB Department time-series estimates of TB incidence, TB prevalence [1] and related indicators. Calibration of each model to these indicators is shown in Figures S2-S4. Model inputs related to TB treatment program coverage and performance were based on routine monitoring data reported by WHO Stop TB Department [1]. Due to known misclassification in vital registration records [34–36], reported estimates for disease-specific mortality [37] are likely biased and were not used for calibration. Mortality projections reported by the models should be interpreted with caution.

Model projections

Alternative CD4-eligibility criteria and health access strategies were simulated for a 20-year period, from 2014 through 2033. Improvements in access to care (i.e. expanded testing and linkage to care) were implemented progressively over 2 years from the beginning of 2014. Changes in eligibility were assumed to be introduced immediately at the beginning of 2014.

Outcome measures

We compare alternative ART eligibility and access strategies by estimating TB incidence and TB-related mortality relative to a continuation of 'status-quo' patterns of access to care and continuation of eligibility for those with CD4 <350. As the various ART expansion options differ in scale (absolute number of patients added to treatment cohorts), the number of additional ART patient-years per TB case averted and per TB-related death averted are also reported.

Results

Results are presented as a comparison of the separate and combined impact of the two ART expansion approaches. We first examine the impact of CD4-eligibility expansion.

Impact on tuberculosis incidence and treatment

Table 2 compares the impact of different CD4-eligbility criteria on TB outcomes, assuming continuation of current ART access patterns. Menzies's CD4 structure does not allow results to be estimated for CD4 < 500 cells/μl, and these rows are left blank. The percentage of new TB cases

Table 2. Impact of alternative CD4-eligibility criteria on tuberculosis outcomes over the period 2014-2033, with current antiretroviral therapy access patterns.

	Reduction in cumulative TB disease incidence	PY ART/TB disease cases averted	Reduction in cumulative TB-related mortality	PY ART/TB-related death averted
Expansion of ART eligibility from CD4 <350 to CD4 <500, with current levels of ART access				
Menzies	–	–	–	–
PopART	8.2%	7.6	8.7%	20.7
Goals	2.3%	11.1	3.4%	29.9
Expansion of ART eligibility from CD4 <500 to all HIV-positive individuals, with current levels of ART access				
Menzies	–	–	–	–
PopART	9.6%	12.3	11.6%	29.3
Goals	4.3%	13.1	6.3%	35.4
Expansion of ART eligibility from CD4 <350 to all HIV-positive individuals, with current levels of ART access				
Menzies	29.9%	13.2	26.3%	43.7
PopART	17.1%	10.0	19.4%	25.5
Goals	6.5%	12.4	9.5%	33.4

ART, antiretroviral therapy; TB, tuberculosis.

averted differs considerably across models. Compared with CD4 <350 cells/μl, universal eligibility is projected to reduce cumulative TB incidence by 7, 17, and 30% over 20 years. These differences are partially due to different assumptions about the rate at which individuals would be initiated on ART following a change in eligibility guidelines. Estimates for the number of person-years of ART required to avert one TB case are much closer, ranging from 10 to 13 for universal eligibility, and the same pattern is apparent for TB-related mortality.

Although TB incidence is lower for individuals with higher CD4 cell counts, universal eligibility still produces significant reductions in TB incidence and mortality, and the magnitude of these reduction grow with time. This results in increasing efficiency of CD4-elibility expansion for preventing new TB cases, as shown in Fig. 1 (top panel). In all models these efficiency gains stabilize over time towards the end of the 20-year projection.

The model results can be used to predict the changes in TB treatment volume that would result from ART expansion. Results from all three models suggest 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. Between 14 and 19 person-years of ART are required to avert one course of TB treatment, based on 10–13 person-years of ART per TB case averted and under the assumption that 70% of incident TB cases are linked to treatment (based on South Africa's current case detection ratio [1]).

Table 3 shows the impact of improving ART access to 80% coverage from current levels, for different CD4-based ART eligibility criteria. 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 continued. If ART initiation criteria were expanded to universal eligibility, 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 2014–2033.

The combined impact of CD4-based eligibility and ART coverage expansion on TB incidence is demonstrated in Fig. 2. The solid line shows the baseline scenario of continuation of status quo access and CD4 <350 eligibility, the dotted line indicates eligibility for all HIV-positive adults assuming continuation of status quo access, and the dashed line shows the combination of immediate eligibility and expanded access. Across all three models, cumulative TB incidence is estimated to be reduced by 28–37% over 2014–2033 in a scenario with expanded ART coverage and eligibility criteria, as compared to incidence under a continuation of current policy. These comparisons corroborate the findings reported in Tables 2 and 3. The model results for ART patients suggest declining incidence for this group following ART expansion, consistent with an improvement in the average immune health of the ART cohort as the average CD4 count of those initiating treatment rises.

The models differ in their attribution of TB impact to CD4 eligibility expansion or ART coverage expansion. Menzies projects significant gains from CD4 expansion, with substantially less impact from subsequent coverage expansion compared to PopART and Goals. PopART and Goals suggest greater impact would result from improving ART coverage rather than CD4 eligibility expansion. These differences appear related to different model assumptions about how ART volume would change following changes in eligibility or access policies, not differences in how the models attribute the relative benefits of providing ART to persons at different CD4 cell counts. This is demonstrated by the greater consistency between models in the person-years of ART required to avert TB incidence and mortality.

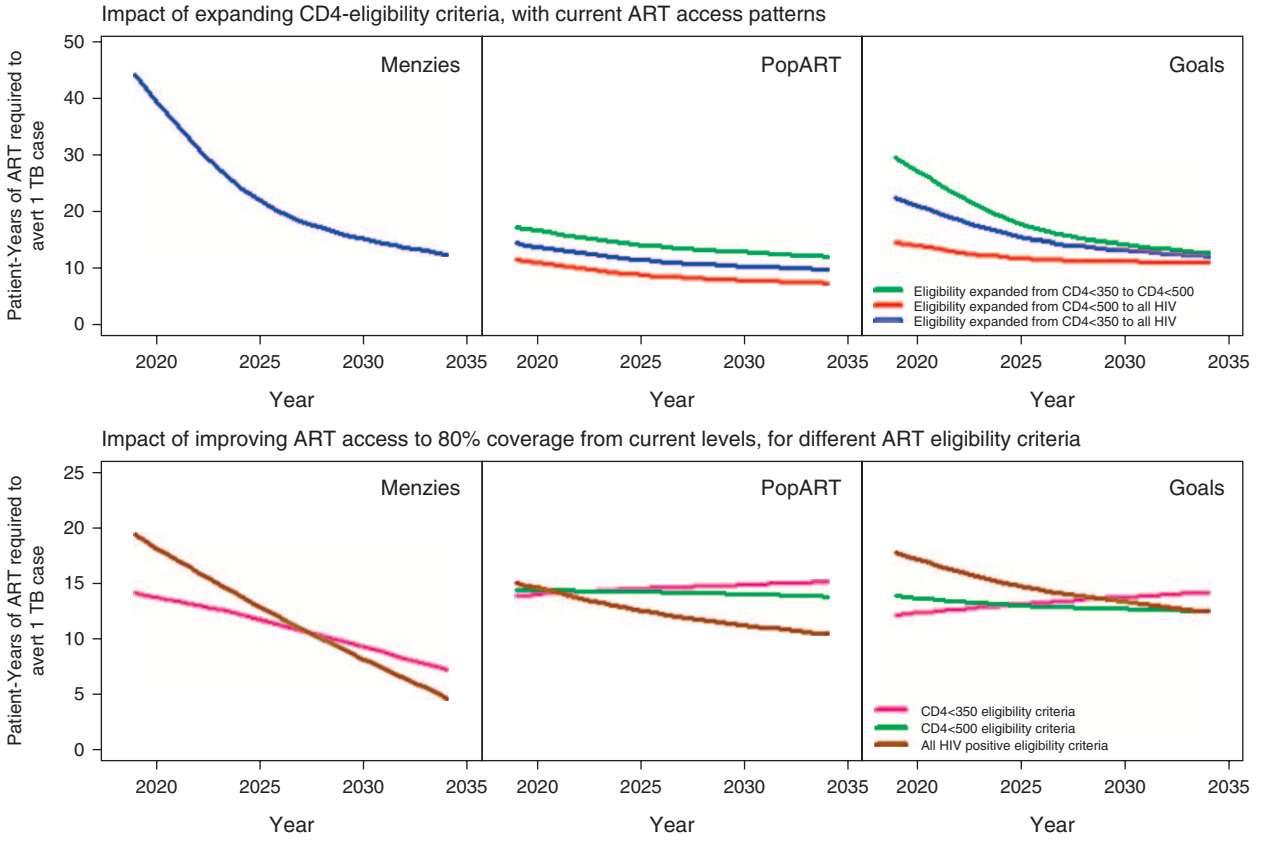

Fig. 1. Number of additional patient-years of antiretroviral therapy (ART) required to avert one tuberculosis (TB) case as a function of time since policy introduction, for expansions in ART eligibility.

Impact on tuberculosis mortality

The potential impact of expanding ART on TB mortality (Fig. 3) mirrors the impact on TB incidence. In terms of CD4-based eligibility expansion, results show a range for the maximal impact, under universal eligibility, of 10–26% reduction in cumulative TB-related deaths over 2014–2033 (Table 2). For effective ART coverage expansion under universal eligibility the range is 13–36% (Table 3). Across all three models, cumulative TB mortality is estimated to be reduced by 36–44% over 2014–2033 in a scenario with expanded ART coverage and eligibility criteria, as compared to mortality under a continuation of current policy. Estimates of the number of person-years of ART required to avert one TB-related death range from 25 to 44 and from 11 to 32 for these two scenarios, respectively. As with the incidence estimates, the results suggest declining TB mortality for ART patients following ART expansion, as a large cohort of

Table 3. Impact of improved antiretroviral therapy access on tuberculosis outcomes over the period 2014-2033, with different antiretroviral therapy eligibility criteria, for expansions in antiretroviral therapy eligibility.

	Reduction in cumulative TB disease incidence	PY ART/TB disease cases averted	Reduction in cumulative TB-related mortality	PY ART/TB-related death averted
Expansion of ART access to 80% coverage, with current CD4 <350 eligibility criteria				
Menzies	8.2%	7.8	12.1%	15.5
PopART	14.1%	15.1	19.2%	31.8
Goals	12.8%	14.1	20.9%	34.1
Expansion of ART access to 80% coverage, with CD4 <500 eligibility criteria				
Menzies	–	–	–	–
PopART	19.3%	13.9	25.8%	29.9
Goals	18.6%	12.6	29.2%	32.0
Expansion of ART access to 80% coverage, with all HIV positive eligible for ART				
Menzies	9.6%	5.6	13.3%	11.3
PopART	23.3%	10.7	30.9%	23.7
Goals	22.9%	12.7	36.3%	32.8

ART, antiretroviral therapy; TB, tuberculosis.

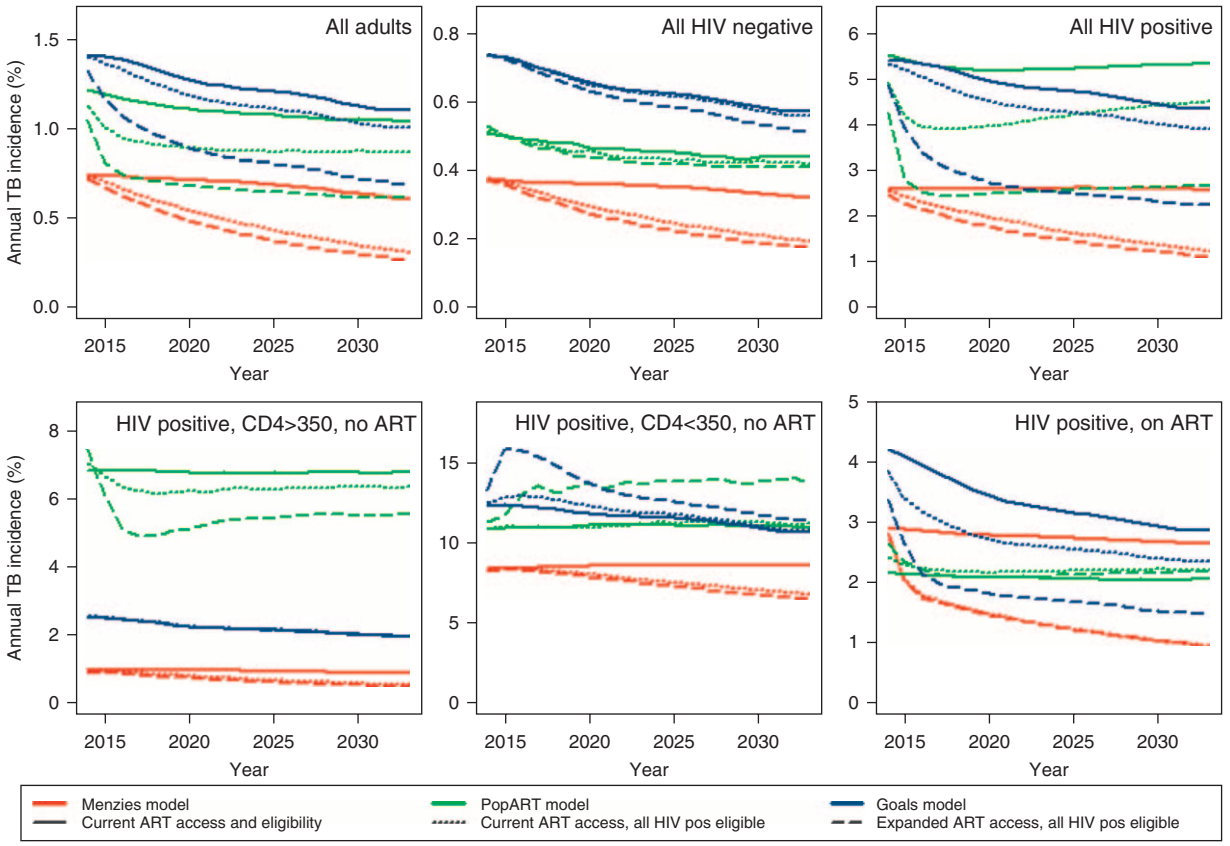

Fig. 2. Impact of different antiretroviral therapy (ART) expansion strategies on tuberculosis (TB) incidence, by risk group.

relatively healthy individuals (compared with past cohorts) is initiated on ART. As individuals with active TB and low CD4 cell count have a very high mortality rate, efforts to expand access to individuals with CD4 <350 will likely be more-effective at averting TB-related mortality, and this is reflected in the model results, all three models estimate a lower number of person-years of ART required to avert one TB treatment episode when access is expanded compared with when eligibility is expanded (Tables 1 and 2, Fig. 1, top and bottom panel).

Discussion

The South African National ART Program, already the largest in the world, may expand in the near future, following new WHO recommendations that ART eligibility be extended to all HIV-positive adults with CD4 cell count below 500 cells/μl [22]. At the same time, the national ART program will move to implement a vision set out within the South African National Strategic Plan for HIV, 2012–2016, to improve the pre-ART program through improved testing and linkage to care.

We studied two broad approaches to expanding the South African National ART Program: expanding CD4-based eligibility, and expanding effective ART coverage through strengthening the links between the HIV testing, pre-ART and ART programs. Our results project significant impact on TB incidence and mortality from ART expansion in the period 2014–2033, even without further improvement to the TB program or to integration between HIV and TB control activities. We estimate that the total number of new TB cases over 2014–2033 would be 6–30% lower if ART eligibility were expanded to include all HIV-positive adults immediately, relative to continuing eligibility for CD4 <350. Expanding access to 80% coverage under this universal 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, given the high case-fatality ratio typically observed among HIV-positive active TB cases in the absence of prompt treatment. Results show, assuming no improvement in TB treatment outcomes, that total TB-related mortality would be 10–26% lower over 2014–2033 if ART eligibility were expanded to all HIV-positive individuals, relative to current patterns of care. Effective coverage expansion under this CD4-eligibility scenario could

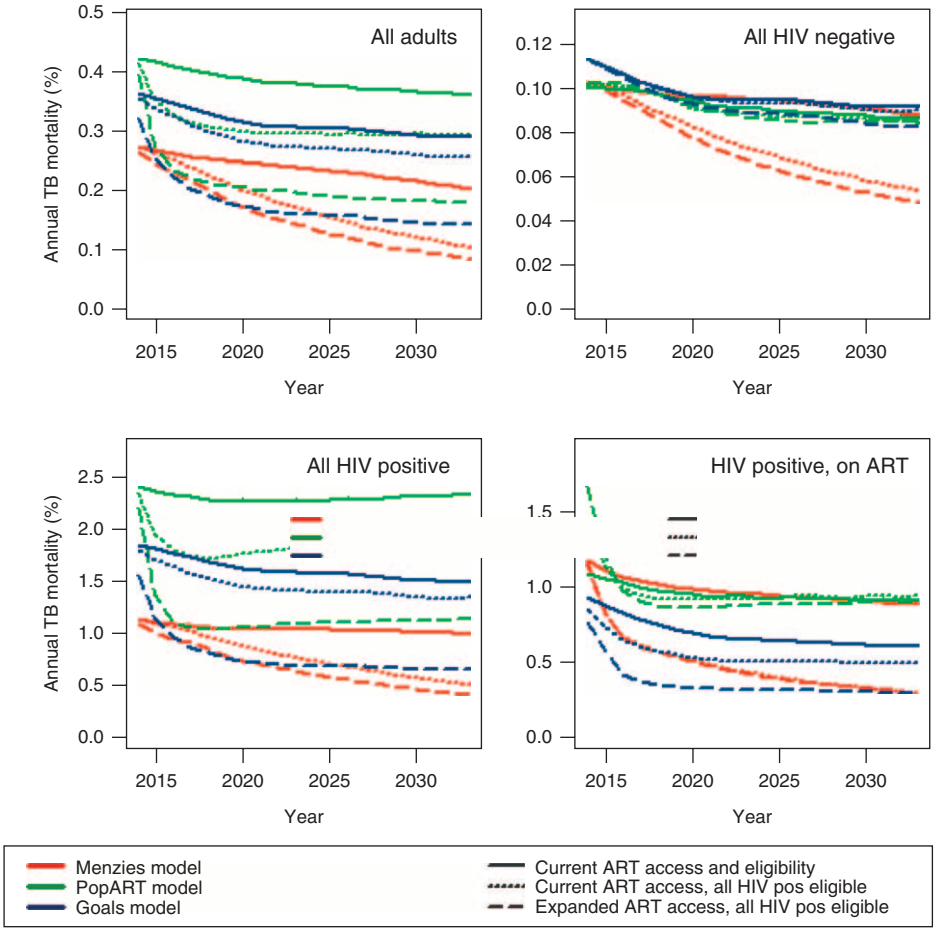

Fig. 3. Impact of different antiretroviral therapy (ART) expansion strategies on tuberculosis (TB) mortality, by risk group.

further reduce total TB-related mortality by 13–36%. The combined impact of universal eligibility and expanded ART coverage is projected to produce a 36–44% reduction in total TB-related deaths over 2014–2033, compared with current policies.

The ranges in these impact estimates reflect uncertainty across models in the relative impact of CD4-eligibility expansion vs. expansion of effective coverage. Much of the difference between the models in this regard can be attributed to structure and parameterization. For example, Goals lacks an explicit transmission structure, through which secondary impacts of averted infections would feed back to further reductions in TB incidence. Menzies shows a significant reduction in HIV-negative TB incidence, and thus assumes a stronger impact on onward transmission. The models also differ with respect to the relative distribution of HIV across CD4 strata, ART coverage within each strata, and the responsiveness of HIV positive individuals to expanded access and eligibility policies. It is not yet clear how major policy changes will impact ART enrollment, and this uncertainty explains a large part of the difference in results between models, and also explains why there is greatest agreement with respect to the number of person-years of ART required to avert new TB cases and TB-related mortality.

The results of these analyses suggest a limit to the 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 alone are unlikely to achieve long-term TB control goals, which will require improvements in TB case detection and treatment. ART expansion can play at least two roles to enable improvement in the TB program. TB treatment resources saved can be redirected towards strengthening key parts of the national TB program, such as TB diagnostics and treatment quality. Effective ART expansion, enabled by improved HIV testing and linkage to care, could also serve as a platform to strengthen monitoring and linkage to care of patients at high risk for developing active TB. In tandem, a program of ART expansion with a collaborative HIV-TB component could substantially decrease not only burden of HIV but also the role HIV has played in exacerbating the TB epidemic over the last two decades.

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Conflicts of interest

None to declare.

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