The potential impact of enhanced diagnostic techniques for tuberculosis driven by HIV: a mathematical model

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Objective: To explore the potential impact of enhanced tuberculosis (TB) diagnostic techniques as a TB control strategy in an adult population with high HIV prevalence.

Design: A compartmental difference-equation model of TB/HIV was developed using parameter estimates from the literature.

Methods: The impact of five TB control interventions (rapid molecular testing, mycobacterial culture, community-wide and HIV-targeted active case finding, and highly active antiretroviral therapy) on TB incidence, prevalence, and mortality was modeled in a steady-state population with an HIV prevalence of 17% and annual TB incidence of 409 per 100 000. Sensitivity analyses assessed the influence of each model parameter on the interventions' mortality impact.

Results: Enhanced diagnostic techniques (rapid molecular testing or culture) are each projected to reduce TB prevalence and mortality by 20% or more, an impact similar to that of active case-finding in 33% of the general community and greater than the effect achievable by case-finding or antiretroviral treatment efforts in HIV-positive patients alone. The projected impact of enhanced diagnostics on TB incidence ($< 10\%$ reduction) is smaller. The impact of TB diagnostics is sensitive to the quality of existing diagnostic standards and the level of access to diagnostic services, but is robust across a wide range of population parameters including HIV and TB incidence.

Conclusions: Enhanced TB diagnostic techniques may have substantial impact on TB morbidity and mortality in HIV-endemic regions. As TB rates continue to increase in these areas, enhanced diagnostic techniques merit further consideration as TB control strategies.

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Introduction

Human immunodeficiency virus (HIV) has changed the global profile of tuberculosis (TB). HIV infection dramatically increases the risk of developing active TB in individuals with latent TB infection and increases the probability of primary TB following new infection [1]. In 2003 an estimated 8.8 million new cases of TB were detected, with incidence increasing most rapidly in countries with high HIV prevalence [2]. The World Health Organization's Directly Observed Therapy, Short Course (DOTS) strategy is failing to reduce TB incidence in HIV-endemic areas [3], fueling interest in supplementing this strategy with additional interventions [4],

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including treatment of HIV-infected individuals with highly active antiretroviral therapy (HAART) [5], treatment of latent TB infection (LTBI) with isoniazid [6], and active TB case finding [7]. Relatively neglected in this discussion, however, are the effect of HIV infection on TB diagnosis, and the ability of improved diagnostic techniques to reduce TB rates in areas of high HIV prevalence.

Improved rates of TB diagnosis may contribute substantially to TB control efforts in areas with endemic HIV. In a recent model of HIV-driven TB, improved detection compared favorably against increased cure rates, LTBI treatment, and HAART; a 1% increase in TB case detection was projected to avert nearly 5000 TB deaths in a country the size of Kenya over 10 years [8]. However, HIV negatively impacts the two most widely used tools for TB diagnosis: sputum smear microscopy and chest X-ray. HIV-positive patients with active TB are more likely to have negative sputum smears [9–11] and atypical chest X-rays [12] than their HIV-negative counterparts. Furthermore, whereas a positive sputum smear is a marker for more severe disease in HIV-negative patients, case-fatality rates in TB/HIV co-infection are high even for smear-negative patients [13]. Fifty percent of HIV-positive, smear-negative TB patients may die within 8 months after their initial TB diagnosis [14,15]. Thus, HIV worsens outcomes in those patients whose TB diagnosis is most challenging to confirm. Improved diagnostic techniques (i.e., techniques other than sputum smear and chest X-ray) are therefore likely to have considerable impact on TB rates in areas with high HIV prevalence, and the ability to implement enhanced diagnostics centrally within an existing healthcare structure is probably cost-effective, in comparison with other TB control strategies [16,17]. Such improved techniques are used in developed countries because of their superior speed and/or sensitivity [17]. However, the potential impact of implementing additional or improved diagnostic techniques on TB control efforts in resource-limited settings has not been widely studied.

Existing prospects for improving laboratory-based diagnosis of TB fall largely into two categories: (1) rapid techniques to increase the sensitivity of the initial diagnostic step (e.g., molecular tests such as nucleic acid amplification tests), and (2) sensitive techniques to detect TB in patients who are persistently smear-negative (e.g., mycobacterial culture). To date, these techniques have found limited utility in developing countries due to lack of sensitivity and specificity [18,19], cost [20], demands for technical expertise [21], and length of time required for diagnosis [22]. However, adaptations of these tools are being developed that may address the current limitations of each [23,24]. Thus, it is important to evaluate the potential impact of implementing these improved diagnostic techniques for TB, particularly in the context of the HIV pandemic.

Here, we present a mathematical model to study the potential impact of improved diagnosis on TB incidence, prevalence, and mortality in a setting of high HIV prevalence. We sought to explore the potential impact of the two above-mentioned general categories of TB diagnostic tests, using rapid molecular testing and mycobacterial culture as prototypical examples that have been implemented in certain resource-limited settings and for which efforts are ongoing to improve both technical feasibility and cost-effectiveness in those settings [18,25]. The potential impact of these diagnostic modalities was compared to that of active TB case finding (community-wide and HIV-targeted) and HAART.

Methods

A compartmental difference-equation model [26] with a time step of 7.3 days (0.02 years) was constructed to describe a mature TB/HIV epidemic in a population of adults aged 15–49 years. This model utilized a hypothetical population of 100 000 adults with a stable HIV incidence of 3.5 per 100 person-years and an annual risk of TB infection of 2.0%. Figure 1 describes the basic structure of the model; a more detailed description of parameters and equations used is found in the Appendix.

The study population is divided into six sub-models based on HIV status (HIV-negative, HIV-positive without acquired immunodeficiency syndrome [AIDS], or HIV-positive with AIDS) and access to clinical services for TB diagnosis and treatment (present or absent). Thus, the model assumes that a proportion of individuals, upon developing active TB, would seek care (after a specified delay) in facilities capable of providing TB diagnostic and treatment services, while the remainder either would not seek care or would seek care in facilities (e.g., traditional

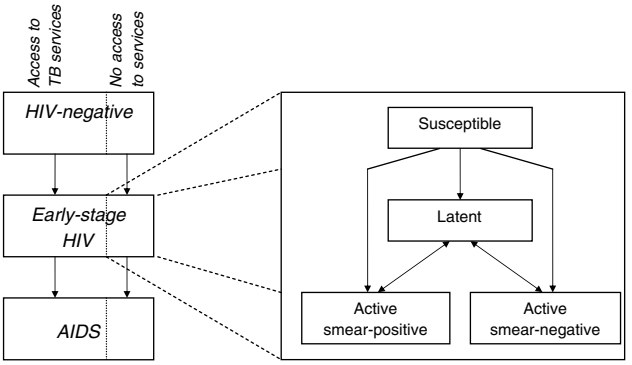

Fig. 1. Compartmental model of HIV-driven tuberculosis (TB). This model comprises 24 total compartments in three strata of HIV status, two strata of access to clinical services, and four strata of TB infection status. The full model equations are described in the Appendix.

healers) without capabilities for TB diagnosis. Access to HIV treatment (i.e. HAART) is modeled separately from access to services for TB diagnosis and treatment. To distinguish TB patients with early versus advanced immunosuppression, HIV-positive patients with active TB are modeled as AIDS-free until fulfilling at least one other criterion for AIDS (e.g., another opportunistic infection or a CD4 cell count < 200 cells/μl).

Within each of the six sub-models, individuals are further sub-divided as having no TB infection (susceptible), latent TB infection, or active TB disease, which can be smear-positive or smear-negative. Effective treatment is modeled as a return to the latently infected state; treatment failures and missed diagnoses are assumed to remain infectious until death or reaching 50 years of age. Although spontaneous cure of active TB is not permitted in the baseline model, sensitivity analysis (described below) was used to assess the potential impact of spontaneous cure. Table 1 describes the other assumptions used to build the model.

The model simulates two forms of diagnostic improvement: rapid molecular testing and culture for *Mycobacterium tuberculosis* ('TB culture'). The existing standard of care was assumed to have a sensitivity of 80% for smear-positive and 25% for smear-negative TB, with a mean diagnostic delay of 90 days between onset of infectiousness and initiation of treatment [43,44]. Rapid molecular testing and culture were modeled as increases in diagnostic sensitivity to 98% for smear-positive, and 50% (molecular testing) or 85% (culture) for smear-negative patients. These values are similar to those published in the literature for existing molecular tests and culture methods [45–47]. Furthermore, culture results on patients not diagnosed by sputum smear were assumed to require an additional 30 days for processing, and 20% of patients were assumed to be lost to follow-up during this time.

The modeled impact of improved diagnosis on TB incidence, prevalence, and mortality was compared to that of two additional interventions: active case finding and highly active antiretroviral therapy (HAART). The basic model assumed that 73% of symptomatic patients had access to TB diagnostic services, in order to give a detection rate of 50% for all TB cases [2]. Active case finding was modeled by increasing the proportion of patients with access to diagnostic services to 82% community-wide (33% coverage of patients without

Table 1. Assumptions for model of HIV-driven tuberculosis (TB) epidemic.

Parameter	Value	Source
TB control		
Proportion of TB patients accessing clinics	0.73	[2]
Treatment success rate if diagnosed with TB	0.82	[2]
TB dynamics		
Relative infectiousness of smear-negative cases	0.22	[27]
Proportion of incident TB that is smear-positive		
HIV-negative or early-stage HIV	0.45	[2]
AIDS	0.35	[22,28,29]
Proportion of TB infections causing primary progression		
HIV-negative or early-stage HIV	0.07	[30]
AIDS	0.56	[31,32]
Proportion of re-infections capable of progression		
HIV-negative or early-stage HIV	0.28	[33]
AIDS	0.75	[8]
Annual rate of endogenous reactivation (%)		
HIV-negative	0.1	[34–36]
AIDS	7.9	[37]
Relative reactivation rate, AIDS versus early HIV	5.1	[38]
Annual rate of TB infection (%)	2.0	Population description
Mortality rates		
Non-TB mortality rate, per 100 person-years		
HIV-negative	0.9	[39]
Early-stage HIV	5.6	[40]
AIDS	35.2	[41]
Annual TB mortality rate (%)		
HIV-negative (smear-positive)	35.0	[8,28,42]
HIV-negative (smear-negative)	10.0	[8,28,42]
Mean duration of TB disease, months		
Early-stage HIV	8.0	None available
AIDS	6.0	[42]
HIV dynamics		
HIV incidence, per 100 person-years	3.5	Population description
Mean time from HIV infection to AIDS (years)	6.9	[40]

prior access) or 91% in HIV-positive patients only (67% coverage). HAART was modeled by preventing progression from early-stage HIV to AIDS in 50% of patients. All models were run to equilibrium, to simulate continued use of each control strategy and to avoid making further assumptions about the time frame of implementation. At equilibrium, mean duration of active TB disease was calculated as point prevalence divided by incidence.

Sensitivity analyses were performed on the characteristics of the diagnostic interventions as well as the underlying assumptions used to generate the model. The sensitivity and additional delay for the existing diagnostic standard, rapid molecular test, and TB culture were independently varied over a reasonable range, and the resulting impact on TB mortality was reported. To test underlying model assumptions, each value in Table 1 was sequentially multiplied and divided by a factor of two or, for proportions with values greater than 0.20, varied by $\pm$ 0.20. If such variation did not result in a change of $\pm$ 5.0% in the percentage of deaths averted by any intervention, the model was reported to be robust to that parameter. The diagnostic test sensitivity parameters were varied over ranges that were intentionally somewhat wider than those indicated in the literature. This was done to better represent the full range of diagnostic test sensitivities that might be found upon test implementation in resource-limited non-research settings, since most of the published studies were performed in developed country research settings. The impact of sensitivity analysis on TB incidence and prevalence was qualitatively similar to the effect on TB mortality in all cases (data not shown); thus, mortality alone was reported.

Results

The hypothetical study population of 100 000 individuals had a TB point prevalence of 288, with 406 new TB cases and 221 deaths due to TB per year (Table 2). The two modeled improvements to TB diagnosis (rapid molecular testing and culture), when implemented for sufficient time to achieve steady-state TB dynamics, reduced TB prevalence and mortality by 19.3–25.7%, while reducing TB incidence by 9.3–9.6%. The mean duration of active TB disease, as estimated by dividing point prevalence by incidence, was 8.5 months under the existing diagnostic standard, 7.2 months with the rapid molecular test, and 6.9 months with TB culture.

Active case-finding (ACF) efforts to effectively extend TB services to one-third of the general population had a similar effect on TB prevalence (28.8%) and mortality (20.1%) as did enhanced diagnosis, but community-wide ACF had a moderately stronger impact on TB incidence (15.0% reduction). By contrast, the HIV-targeted interventions of ACF (67% coverage) or HAART (50% coverage) generated substantially smaller reductions in TB prevalence and mortality (6.1–11.9%) and mildly smaller reductions in incidence (5.0–7.8%) than did the diagnostic interventions. The mean duration of active TB disease was 7.1 months with community-wide ACF, 8.1 months with HIV-based ACF, and 8.6 months with HAART.

This model requires steady-state conditions and makes no assumptions about the speed of intervention implementation; thus, valid estimates of the time required to achieve the modeled reductions in TB rates cannot be obtained. However, under the assumption of complete, immediate uptake of enhanced diagnostic techniques, and ignoring model errors due to non-steady-state conditions, $>$ 35% of the total decrease in TB incidence, $>$ 55% of the total decrease in TB prevalence, and $>$ 65% of the total decrease in TB mortality were achieved within 1 year after implementation of either rapid molecular testing or TB culture. Under similar assumptions, the times required to achieve 90% of the total reductions in TB rates (Table 2) were comparable for enhanced diagnostics and either community-wide or HIV-based ACF (16–23 years for prevalence and mortality, 31–32 years for incidence), but were substantially shorter for HAART (1–4 years).

Sensitivity analysis of diagnostic parameters (Fig. 2) revealed a strong inverse relationship between the impact of improved diagnostic techniques and the sensitivity of the standard of care to detect smear-negative TB. Specifically, compared to the case where 95% of

Table 2. Impact of modeled interventions on hypothetical tuberculosis (TB) epidemic.

	TB incidence		TB prevalence		TB mortality	
Intervention	Cases per 100 000	Reduction (%)	Annual cases per 100 000	Reduction (%)	Deaths per 100 000	Reduction (%)
1. Standard of care	406	–	288	–	221	–
2. Rapid molecular testing	371	9.3%	223	22.8%	178	19.3%
3. TB culture	370	9.6%	214	25.7%	172	22.2%
4. Community-based active case finding	348	15.0%	205	28.8%	177	20.1%
5. HIV-based active case finding	389	5.0%	261	9.6%	195	11.9%
6. Highly active antiretroviral therapy	377	7.8%	271	6.1%	205	7.4%

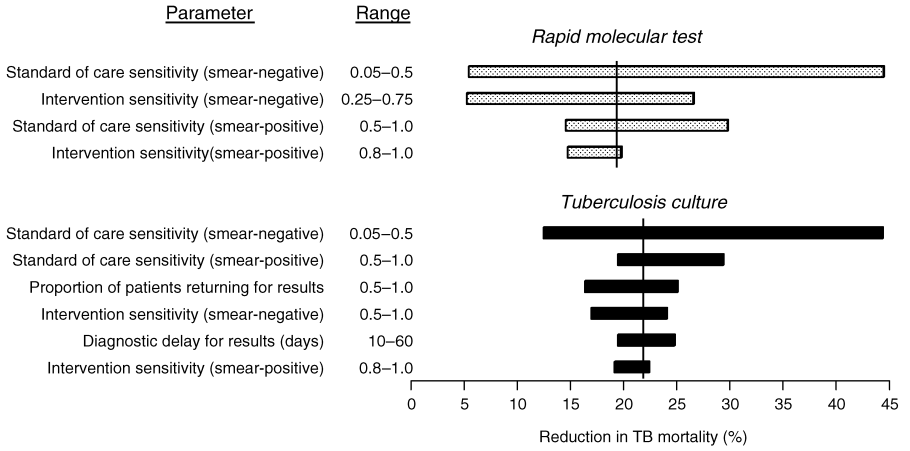

Fig. 2. Sensitivity analysis of diagnostic parameters. Horizontal bars show the range of tuberculosis (TB) mortality reductions achieved under each intervention while varying the given parameter across the stated range of values. Vertical lines depict the mortality reduction achieved assuming diagnostic sensitivity (smear-positive TB/ smear-negative TB) of 0.8/0.25 for the standard of care; 0.98/0.50 for rapid molecular testing; and 0.98/0.85 for TB culture. TB culture was also assumed to incur a diagnostic delay of 30 days and losses to follow-up of 20% beyond those associated with the standard of care or rapid testing (see Methods).

smear-negative cases were missed by standard diagnostic techniques, rapid molecular diagnosis and culture both averted 44% of TB mortality. When the diagnostic standard was modeled as having 50% sensitivity to detect smear-negative TB, the impact of rapid molecular testing and TB culture on TB mortality rates fell to 5.4 and 12.4%, respectively. The impact of rapid molecular testing fell to similar levels if the sensitivity of the rapid test in smear-negatives was lowered to that of the existing standard (25%). Under no other reasonable parameter values did either diagnostic intervention fail to avert at least 14.5% of all TB deaths.

Sensitivity analysis of model variables (Fig. 3) showed the impact of community-based active case finding to be sensitive to four parameters: the proportion of TB patients accessing clinics; proportion of primary TB progression in HIV-negative individuals; TB-related mortality rate in smear-positive, HIV-negative patients; and relative infectiousness of smear-negative TB. The impact of HAART was sensitive to the relative rates of endogenous reactivation and non-TB mortality in early-stage HIV and AIDS, at times generating paradoxical increases in TB mortality. The impact of enhanced diagnosis, however, was sensitive only to the proportion of TB patients accessing clinic services and the relative infectiousness of smear-negative TB. When these parameters were simultaneously set to maximally unfavorable levels for diagnostics (50% of patients with access to diagnostic services and no infectiousness in smear-negatives), rapid molecular testing and TB culture continued to avert 8–9% of TB mortality, outperforming HAART. The relative value of diagnostic techniques and case finding as strategies to prevent TB mortality

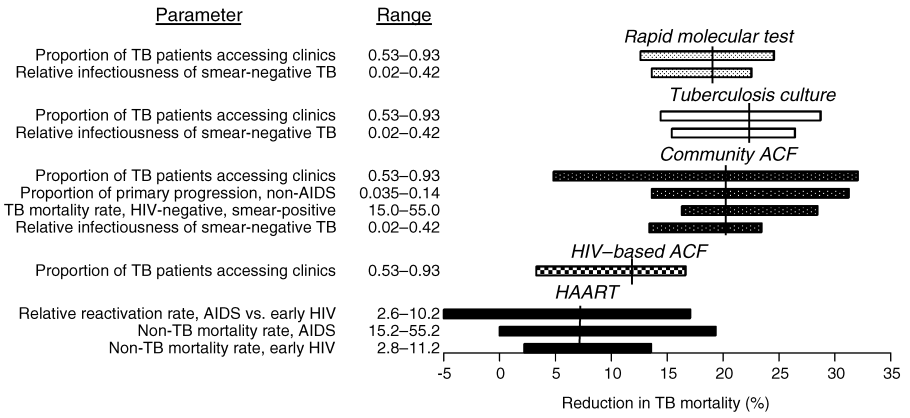

Fig. 3. Sensitivity analysis of model assumptions. Horizontal bars show the range of tuberculosis (TB) mortality reductions achieved under each intervention while varying the given parameter across the stated range of values. Vertical lines depict the mortality reduction achieved in the baseline model, with assumptions given in Table 1. Parameters are not shown if sensitivity analysis failed to change the estimated percentage reduction in TB mortality by more than ± 5.0%. ACF, active case finding for tuberculosis; HAART, highly active antiretroviral therapy.

depended heavily on the proportion of TB patients accessing diagnostic services in the absence of ACF. Enhanced diagnostics prevented 25–29% of TB deaths, versus 5% for community ACF, when 93% of patients had existing access to clinic services, but community ACF prevented 2.2 to 2.5 times as many deaths as enhanced diagnostics (32 versus 12–15%) when levels of access were reduced to 53%. The impact of enhanced diagnosis on TB mortality was robust to a spontaneous TB cure rate of over 50% per year, and to 10-fold variation in the rate of endogenous reactivation, among HIV-negatives.

Discussion

This compartmental model of a tuberculosis epidemic in the context of endemic HIV suggests that improved diagnostic techniques may have substantial impact on TB control efforts. To date, most models of HIV-driven tuberculosis have focused on interventions such as active case finding, antiretroviral therapy, prevention, and DOTS, without exploring the role of diagnostic techniques. The present model suggests that implementation of a rapid molecular test or culture-based system for TB diagnosis could avert 20% or more of all TB deaths, an impact equivalent to that of successfully extending existing diagnostic techniques to 33% of the general community who otherwise would not seek care for symptoms of TB. To have such impact, enhanced TB diagnostics must be implemented in a population with reasonable access to health care, in the absence of existing sophisticated diagnostic techniques, particularly for smear-negative patients. In such a population, enhanced diagnostics should cause substantial reductions in TB mortality across a reasonable range of both diagnostic accuracy and population parameters such as HIV incidence and annual risk of TB infection.

This model also offers insight as to the mechanism whereby enhanced diagnostics contribute to TB control, particularly in the context of HIV. Specifically, as demonstrated by their relative impact on incidence and mortality, diagnostic techniques function primarily to facilitate treatment of diseased individuals; they have less impact on secondary transmission (as captured by incidence rates). Thus, in comparison with other interventions such as community-wide active case finding, enhanced diagnostic techniques are less likely to relieve burdens on those portions of the health-care system charged with diagnosing new cases. However, from the patient perspective, diagnostics have substantial impact; not only is mortality reduced, but the duration of illness is likewise shortened. In a steady-state population, point prevalence is proportional to the number of person-years spent living with TB; thus, enhanced diagnostic techniques may reduce approximately 20% of all TB morbidity (e.g., reduced quality of life) in addition to mortality.

The results from sensitivity analyses are sensible; enhanced diagnostics will have maximum impact when a large proportion of the patient population has access to those diagnostics, and existing diagnostic techniques are substandard. Of particular interest is the contribution of smear-negative patients to ongoing TB transmission. As demonstrated by their sensitivity to the relative infectiousness of smear-negatives and the ability of the existing diagnostic standard to accurately diagnose smear-negative TB, enhanced diagnostics exert a substantial portion of their effect by facilitating treatment of smear-negative cases. When existing diagnostic practices are poor, smear-negative cases will represent an increasing proportion of total TB prevalence with higher relative infectiousness, as some of these patients would be diagnosed as smear-positive given superior smear techniques (e.g., lighter workload [48] or fluorescence microscopy [49]). In the present model, 76% of prevalent TB cases are smear-negative at baseline; these patients are thus responsible for over 40% of all transmission events despite being only one-fifth as infectious as smear-positive individuals. This model suggests that diagnosis of smear-negative TB – whether by enhanced diagnostic techniques or other methods – may be an overlooked priority for TB control efforts in HIV-endemic regions.

This model has a number of limitations. It represents a vast oversimplification of actual TB dynamics, ignoring, for example, treatment failures and relapses as well as the dependence of TB rates on level of immunosuppression [38,50,51] and demographic variables such as gender and poverty [52]. The model also fails to consider extra-pulmonary (or otherwise entirely non-infectious) TB, and it excludes both children and the elderly from the analysis. However, the purpose of this model is not to provide precise estimates of the impact of enhanced TB diagnostics in a given patient population, but rather to explore the mechanism whereby diagnostic techniques might contribute to TB control efforts, and to give a general description of the magnitude of their expected effect. In this regard, the model provides at least four reassuring outputs. First, as expected, enhanced diagnosis, which generally leads directly to treatment of existing cases, has a stronger impact on TB prevalence and mortality than on incidence, reflecting shortened disease duration. Second, the estimates of effect from other interventions are similar to published values from more sophisticated models, including a 10% reduction in TB incidence by HAART at 50% coverage [53] and a 17% reduction in TB mortality by active case finding using ongoing symptomatic screening [39]. Third, the estimates of the impact of enhanced diagnostics are not particularly sensitive to most model parameters. Fourth, the modeled population has realistic TB dynamics for a population of adults aged 15–49 years living in a region with mild TB transmission but endemic HIV (e.g., annual TB incidence of 409 per 100 000, prevalence of 288 per 100 000, and latent TB prevalence of 42%) [2]. Thus, although the

model is an oversimplification, it may generate a sufficiently realistic population to explore general TB dynamics without depending on precise parameter estimates that may not generalize across populations.

In addition to its simplifying assumptions, this model is also limited in the results provided. By only examining populations at steady state, it fails to accurately describe the length of time required to achieve the modeled reductions in incidence and mortality after implementation of a new diagnostic test. Although the fact that these interventions achieve substantial impact within 1 year is reassuring, this model makes the unrealistic assumption that such diagnostic techniques would become immediately available to the entire population at a single time. On the other hand, the model also ignores the possibility that efforts to diagnose TB in patients with respiratory symptoms might be more aggressive if superior diagnostics become available; thus, the model may underestimate both the speed and extent of the impact of enhanced diagnostics. With respect to the other modeled interventions, ACF is implicitly assumed to extend diagnostic services to incident TB cases but not to prevalent cases at the time of implementation. As a result, the model probably overestimates the time required for ACF efforts to achieve equilibrium rates, but it should accurately describe the impact of ACF at steady-state. Ultimately, since many of the equations used rely on a steady-state assumption, this model, like most similar infectious disease models, is valid only at equilibrium; greater attention should be paid to the mathematical structure of infectious disease models that aim to project the impact of specific interventions over time.

Finally, this model cannot address a number of issues (e.g., cost-effectiveness and technical requirements) relevant to the implementation of enhanced diagnostic techniques in the field. Thus, although this model suggests that enhanced diagnostics may have substantial impact on TB prevalence and mortality at steady state, additional research is required to investigate the implementation of such techniques.

In conclusion, a compartmental model of a tuberculosis epidemic in the context of endemic HIV suggests that enhanced diagnostic techniques (rapid molecular testing or culture) might reduce TB prevalence and mortality by 20% or more, an impact similar to that achieved from ACF with coverage of 33% in the general community and greater than the effect achievable by case-finding or antiretroviral treatment efforts in HIV-positive patients alone. By contrast, the impact of enhanced diagnostics on TB incidence is likely to be smaller, with $< 10\%$ of new cases averted. The modeled impact depends strongly on the quality of existing diagnostic services and the population's existing level of access to diagnostic services, but is robust across a wide range of population parameters including HIV and TB incidence. As TB rates continue to increase in HIV-endemic regions, improved diagnostic techniques merit further consideration as TB control strategies.

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Appendix: model parameters and equations

Part I: model parameters

The model assumptions listed in Table 1 of the manuscript text were used to generate parameters for input into the model, as described in the table below.

Parameter	Description	Calculation/justification
Time		
ts	Time step	Set at 0.02 years (7.3 days)
TB transmission		
λ_0	Annual risk of TB infection, per smear-positive active case	Calibrated to provide an overall annual risk of TB infection (ARTI) of 2.0%/year at equilibrium
i^-	Relative infectiousness of smear-negative cases	Table 1, manuscript text
lat	Prevalence of latent TB in 15-year-old recruits	Given an ARTI of 2.0%, calculated as $1-(0.98)^{15}$
fp_{neg}, fp_{hiv}, fp_{aids}	Fraction of incident TB that is smear-positive	Table 1, manuscript text
TB progression		
pp_{neg}, pp_{hiv}, pp_{aids}	Proportion of TB infections causing immediate ('primary') progression to active TB	Table 1, manuscript text
lr_{neg}, lr_{hiv}, lr_{aids}	Proportion of TB reinfections (in individuals with latent TB) capable of primary progression	Table 1, manuscript text
er_{neg}, er_{hiv}, er_{aids}	Endogenous reactivation rate, per year	Table 1, manuscript text
cure	Rate of spontaneous cure in HIV-negative patients from active to latent TB	Used only for sensitivity analysis
HIV transmission and progression		
hivinc	Annual risk of HIV infection (HIV incidence)	Provides an equilibrium HIV prevalence of 16.8%
hivprog	Mean rate of progression from HIV to AIDS	Inverse of mean time from HIV infection to AIDS
TB diagnosis and treatment		
acc	Fraction of TB patients presenting to clinics	Calibrated to provide 50% global detection rate
tx	Success of treatment, once TB is diagnosed	Table 1, manuscript text
dx	Rate of TB detection after symptoms develop	Inverse of mean time, symptom onset to diagnosis
sn^+	Sensitivity of diagnosis, smear-positive	80% (standard), 98% (molecular test or culture)
sn^-	Sensitivity of diagnosis, smear-negative	20% (standard), 50% (molecular), 85% (culture)
lfu	Proportion of detected patients lost to follow-up before treatment (while awaiting culture results)	Set to zero in the baseline model (see Part II below)
Mortality and aging		
μ_{neg}, μ_{hiv}, μ_{aids}	Rate of death or population exit, no active TB	Mortality rate (Table 1) + (1/35) [age 50 − age 15]
μ_{neg}^{tb+}, $\mu_{neg}^{tb-}\mu_{hiv}^{tb}$, μ_{aids}^{tb}	Rate of death or population exit, active TB, stratified by smear status among HIV-negatives	Mortality rate (Table 1) + (1/35) [age 50 − age 15]

Part II: interventions

Antiretroviral therapy was modeled by multiplying the rate of HIV progression to AIDS, *hivprog*, by 0.5. At equilibrium, this action is equivalent to preventing progression in 50% of all HIV-positive patients. All other interventions were modeled as changes to the model parameters dealing with TB diagnosis and treatment, as given below.

Intervention	Parameter values (See Part I of the Appendix for definitions)					
	acc	*tx*	*dx*	sn^+	sn^-	*lfu*
Diagnostic standard	0.734	0.82	4.0	0.80	0.25	0
Rapid molecular test	0.734	0.82	4.0	0.98	0.50	0
TB culture	0.734	0.82	3.0[a]	0.98	0.85	0.2
Community-wide active case finding	0.823[b]	0.82	4.0	0.80	0.25	0
HIV-targeted active case finding	0.911[c]	0.82	4.0	0.80	0.25	0

[a]The detection rate remained at 4.0 for those patients who were detected by sputum smear. For simplicity, the equations describing this effect, as well as those that reduce sensitivity by a factor of $(1 - lfu)$, are omitted from Part III of the Appendix.
[b]Calculated as $0.734 + [(1 - 0.734)/3]$.
[c]Calculated as $0.734 + [2 * (1 - 0.734)/3]$. Applied to HIV-positive TB patients only; the proportion of HIV-negative TB patients accessing diagnostic services remained at 0.734.

Part III: model equations

The following equations give the rate of change in the number of individuals $N(t)$ in each model compartment at time t, with parameters defined as in Part I. The rate of change in a difference-equation model is defined as defined as $[N(t + ts) - N(t)]/ts$, where *ts* is the time step. The first set of equations defines intermediate parameters used to simplify the expressions in the subsequent equations. TB incidence, prevalence, and mortality (after subtraction of the

'aging' rate from the mortality parameter) were evaluated under each intervention described in Part II, using the following equations and allowing the model to achieve equilibrium, defined as a 60-year time course. No compartment changed in size by more than one person between years 40 and 60 in the absence of intervention, and no TB incidence, prevalence, or mortality rate changed by more than 3 per 100 000 under any intervention during this 20-year time frame. The size of the population was modeled as constant, with the number of new 15-year-old recruits (all HIV-negative and without active TB) balancing the number of individuals either dying or reaching the age of 50.

Intermediate Parameters

A. Total number of smear-positive cases at time t, $TSP(t)$, calculated as the sum of smear-positive patients with ['detectable', or $DSP(t)$] or without ['undetectable', $USP(t)$] access to TB diagnostic services

$$TSP(t) = DSP_{\text{neg}}(t) + DSP_{\text{hiv}}(t) + DSP_{\text{aids}}(t) + USP_{\text{neg}}(t) + USP_{\text{hiv}}(t) + USP_{\text{aids}}(t)$$

B. Total number of smear-negative cases at time t, $TSN(t)$, including smear-negative patients with ['detectable', or $DSN(t)$] or without ['undetectable', $USN(t)$] access to TB diagnostic services

$$TSN(t) = DSN_{\text{neg}}(t) + DSN_{\text{hiv}}(t) + DSN_{\text{aids}}(t) + USN_{\text{neg}}(t) + USN_{\text{hiv}}(t) + USN_{\text{aids}}(t)$$

C. The force of infection (annual rate of TB infection) at time t, $\lambda(t)$

$$\lambda(t) = \lambda_0\{TSP(t) + i^{-}[TSN(t)]\}$$

D. Total mortality plus aging at time t, $M(t)$, calculated as the sum of deaths plus aging events in all susceptible [$S(t)$], latently-infected [$L(t)$], and actively-infected patients

$$\begin{aligned} M(t) = {} & \mu_{\text{neg}}[S_{\text{neg}}(t) + L_{\text{neg}}(t)] + \mu_{\text{hiv}}[S_{\text{hiv}}(t) \\ & + L_{\text{hiv}}(t)] + \mu_{\text{aids}}[S_{\text{aids}}(t) + L_{\text{aids}}(t)] \\ & + \mu_{\text{neg}}^{\text{tb}+}[DSP_{\text{neg}}(t) + USP_{\text{neg}}(t)] \\ & + \mu_{\text{neg}}^{\text{tb}-}[DSN_{\text{neg}}(t) + USN_{\text{neg}}(t)] \\ & + \mu_{\text{hiv}}^{\text{tb}}[DSP_{\text{hiv}}(t) + USP_{\text{hiv}}(t) + DSN_{\text{hiv}}(t) \\ & + USN_{\text{hiv}}(t)] + \mu_{\text{aids}}^{\text{tb}}[DSP_{\text{aids}}(t) + USP_{\text{aids}}(t) \\ & + DSN_{\text{aids}}(t) + USN_{\text{aids}}(t)] \end{aligned}$$

Rates of change in compartment populations

1. Individuals who are HIV-negative and never previously infected with TB

$$\Delta S_{\text{neg}}(t)/ts = (1 - lat)M(t) - \{\lambda(t) + hivinc + \mu_{\text{neg}}\}S_{\text{neg}}(t)$$

2. Individuals who are HIV-negative and latently infected with TB

$$\begin{aligned} \Delta L_{\text{neg}}(t)/ts = {} & lat \times M(t) + \{dx \times tx \times [(sn^{+} \times DSP_{\text{neg}}(t)) \\ & + (sn^{-} \times DSN_{\text{neg}}(t))]\} \\ & + cure \times [DSP_{\text{neg}}(t) + USP_{\text{neg}}(t) \\ & + DSN_{\text{neg}}(t) + USN_{\text{neg}}(t)] \\ & + \{\lambda(t) \times (1 - pp_{\text{neg}})\}S_{\text{neg}}(t) \\ & - \{er_{\text{neg}} + hivinc + \mu_{\text{neg}} \\ & + [lr_{\text{neg}} \times pp_{\text{neg}} \times \lambda(t)\,]\}L_{\text{neg}}(t) \end{aligned}$$

3. Individuals who are HIV-negative, actively infected with smear-positive TB, and have access to diagnostic services

$$\begin{aligned} \Delta DSP_{\text{neg}}(t)/ts = {} & \{fp_{\text{neg}} \times acc \times pp_{\text{neg}} \times \lambda(t)\}S_{\text{neg}}(t) \\ & + \{fp_{\text{neg}} \times acc \times [er_{\text{neg}} \\ & + (lr_{\text{neg}} \times pp_{\text{neg}} \times \lambda(t))]\}L_{\text{neg}}(t) \\ & - \{hivinc + \mu_{\text{neg}}^{\text{tb}+} + cure \\ & + [sn^{+} \times tx \times dx]\}DSP_{\text{neg}}(t) \end{aligned}$$

4. Individuals who are HIV-negative, actively infected with smear-positive TB, and lack access to diagnostic services

$$\begin{aligned} & \Delta USP_{\text{neg}}(t)/ts \\ & = \{fp_{\text{neg}} \times (1 - acc) \times pp_{\text{neg}} \times \lambda(t)\}S_{\text{neg}}(t) \\ & \quad + \{fp_{\text{neg}} \times (1 - acc) \times [er_{\text{neg}} \\ & \quad + (lr_{\text{neg}} \times pp_{\text{neg}} \times \lambda(t))]\}L_{\text{neg}}(t) \\ & \quad - \{hivinc + \mu_{\text{neg}}^{\text{tb}+} + cure\}USP_{\text{neg}}(t) \end{aligned}$$

5. Individuals who are HIV-negative, actively infected with smear-negative TB, and have access to diagnostic services

$$\begin{aligned} & \Delta DSN_{\text{neg}}(t)/ts \\ & = \{(1 - fp_{\text{neg}}) \times acc \times pp_{\text{neg}} \times \lambda(t)\}S_{\text{neg}}(t) \\ & \quad + \{(1 - fp_{\text{neg}}) \times acc \times [er_{\text{neg}} + (lr_{\text{neg}} \times pp_{\text{neg}} \\ & \quad \times \lambda(t))]\} \times L_{\text{neg}}(t) - \{hivinc + \mu_{\text{neg}}^{\text{tb}-} + cure \\ & \quad + [sn^{-} \times tx \times dx]\}DSN_{\text{neg}}(t) \end{aligned}$$

6. Individuals who are HIV-negative, actively infected with smear-negative TB, and lack access to diagnostic services

$$\begin{aligned} \Delta USN_{\text{neg}}(t)/ts = {} & \{(1 - fp_{\text{neg}}) \times (1 - acc) \times pp_{\text{neg}} \\ & \times \lambda(t)\}S_{\text{neg}}(t) + \{(1 - fp_{\text{neg}}) \\ & \times (1 - acc) \times [er_{\text{neg}} + (lr_{\text{neg}} \\ & \times pp_{\text{neg}} \times \lambda(t))]\}L_{\text{neg}}(t) \\ & - \{hivinc + \mu_{\text{neg}}^{\text{tb}-} + cure\} \\ & \times USN_{\text{neg}}(t) \end{aligned}$$

7. Individuals who have early-stage HIV and were never previously infected with TB

$$\Delta S_{\text{hiv}}(t)/ts = hivinc \times S_{\text{neg}}(t) - \{\lambda(t) + hivprog + \mu_{\text{hiv}}\}S_{\text{hiv}}(t)$$

8. Individuals who have early-stage HIV and latent TB infection

$$\Delta L_{\text{hiv}}(t)/ts = hivinc \times L_{\text{neg}}(t) + \{dx \times tx \times [(sn^{+} \times DSP_{\text{hiv}}(t)) + (sn^{-} \times DSN_{\text{hiv}}(t))]\} + \{\lambda(t) \times (1 - pp_{\text{hiv}})\}S_{\text{hiv}}(t) - \{er_{\text{hiv}} + hivprog + \mu_{\text{hiv}} + [lr_{\text{hiv}} \times pp_{\text{hiv}} \times \lambda(t)]\}L_{\text{hiv}}(t)$$

9. Individuals who have early-stage HIV and smear-positive active TB, and who have access to diagnostic services

$$\Delta DSP_{\text{hiv}}(t)/ts = hivinc \times DSP_{\text{neg}}(t) + \{fp_{\text{hiv}} \times acc \times pp_{\text{hiv}} \times \lambda(t)\} \times S_{\text{hiv}}(t) + \{fp_{\text{hiv}} \times acc \times [er_{\text{hiv}} + (lr_{\text{hiv}} \times pp_{\text{hiv}} \times \lambda(t))]\} \times L_{\text{hiv}}(t) - \{hivprog + \mu_{\text{hiv}}^{\text{tb}} + [sn^{+} \times tx \times dx]\}DSP_{\text{hiv}}(t)$$

10. Individuals who have early-stage HIV and smear-positive active TB, and who lack access to diagnostic services

$$\Delta USP_{\text{hiv}}(t)/ts = hivinc \times USP_{\text{neg}}(t) + \{fp_{\text{hiv}} \times (1 - acc) \times pp_{\text{hiv}} \times \lambda(t)\}S_{\text{hiv}}(t) + \{fp_{\text{hiv}} \times (1 - acc) \times [er_{\text{hiv}} + (lr_{\text{hiv}} \times pp_{\text{hiv}} \times \lambda(t))]\}L_{\text{hiv}}(t) - \{hivprog + \mu_{\text{hiv}}^{\text{tb}}\}USP_{\text{hiv}}(t)$$

11. Individuals who have early-stage HIV and smear-negative active TB, and who have access to diagnostic services

$$\Delta DSN_{\text{hiv}}(t)/ts = hivinc \times DSN_{\text{neg}}(t) + \{(1 - fp_{\text{hiv}}) \times acc \times pp_{\text{hiv}} \times \lambda(t)\}S_{\text{hiv}}(t) + \{(1 - fp_{\text{hiv}}) \times acc \times [er_{\text{hiv}} + (lr_{\text{hiv}} \times pp_{\text{hiv}} \times \lambda(t))]\} \times L_{\text{hiv}}(t) - \{hivprog + \mu_{\text{hiv}}^{\text{tb}} + [sn^{-} \times tx \times dx]\}DSN_{\text{hiv}}(t)$$

12. Individuals who have early-stage HIV and smear-negative active TB, and who lack access to diagnostic services

$$\Delta USN_{\text{hiv}}(t)/ts = hivinc \times USN_{\text{neg}}(t) + \{(1 - fp_{\text{hiv}}) \times (1 - acc) \times pp_{\text{hiv}} \times \lambda(t)\}S_{\text{hiv}}(t) + \{(1 - fp_{\text{hiv}}) \times (1 - acc) \times [er_{\text{hiv}} + (lr_{\text{hiv}} \times pp_{\text{hiv}} \times \lambda(t))]\}L_{\text{hiv}}(t) - \{hivprog + \mu_{\text{hiv}}^{\text{tb}}\}USN_{\text{hiv}}(t)$$

13. Individuals who have AIDS and were never previously infected with TB

$$\Delta S_{\text{aids}}(t)/ts = hivprog \times S_{\text{hiv}}(t) - \{\lambda(t) + \mu_{\text{aids}}\}S_{\text{aids}}(t)$$

14. Individuals who have AIDS and latent TB infection

$$\Delta L_{\text{aids}}(t)/ts = hivprog \times L_{\text{hiv}}(t) + \{dx \times tx \times [(sn^{+} \times DSP_{\text{aids}}(t)) + (sn^{-} \times DSN_{\text{aids}}(t))]\} + \{\lambda(t) \times (1 - pp_{\text{aids}})\}S_{\text{aids}}(t) - \{er_{\text{aids}} + \mu_{\text{aids}} + [lr_{\text{aids}} \times pp_{\text{aids}} \times \lambda(t)]\}L_{\text{aids}}(t)$$

15. Individuals who have AIDS and smear-positive active TB, and who have access to diagnostic services

$$\Delta DSP_{\text{aids}}(t)/ts = hivprog \times DSP_{\text{hiv}}(t) + \{fp_{\text{aids}} \times acc \times pp_{\text{aids}} \times \lambda(t)\}S_{\text{aids}}(t) + \{fp_{\text{aids}} \times acc \times [er_{\text{aids}} + (lr_{\text{aids}} \times pp_{\text{aids}} \times \lambda(t))]\}L_{\text{aids}}(t) - \{\mu_{\text{aids}}^{\text{tb}} + [sn^{+} \times tx \times dx]\}DSP_{\text{aids}}(t)$$

16. Individuals who have AIDS and smear-positive active TB, and who lack access to diagnostic services

$$\Delta USP_{\text{aids}}(t)/ts = hivprog \times USP_{\text{hiv}}(t) + \{fp_{\text{aids}} \times (1 - acc) \times pp_{\text{aids}} \times \lambda(t)\}S_{\text{aids}}(t) + \{fp_{aids} \times (1 - acc) \times [er_{aids} + (lr_{aids} \times pp_{aids} \times \lambda(t))]\}L_{\text{aids}}(t) - \{\mu_{\text{aids}}^{\text{tb}}\}USP_{\text{aids}}(t)$$

17. Individuals who have AIDS and smear-negative active TB, and who have access to diagnostic services

$$\begin{aligned}\Delta DSN_{\text{aids}}(t)/ts = {} & hivprog \times DSN_{\text{aids}}(t) \\ & + \{(1 - fp_{\text{aids}}) \times acc \times pp_{\text{aids}} \\ & \times \lambda(t)\} S_{\text{aids}}(t) + \{(1 - fp_{\text{aids}}) \\ & \times acc \times [er_{\text{aids}} + (lr_{\text{aids}} \times pp_{\text{aids}} \\ & \times \lambda(t))]\} L_{\text{aids}}(t) - \{\mu^{\text{tb}}_{\text{aids}} \\ & + [sn^{-} \times tx \times dx]\} DSN_{\text{aids}}(t)\end{aligned}$$

18. Individuals who have AIDS and smear-negative active TB, and who lack access to diagnostic services

$$\begin{aligned}\Delta USN_{\text{aids}}(t)/ts = {} & hivprog \times USN_{\text{aids}}(t) \\ & + \{(1 - fp_{\text{aids}}) \times (1 - acc) \\ & \times pp_{\text{aids}} \times \lambda(t)\} S_{\text{aids}}(t) \\ & + \{(1 - fp_{\text{aids}}) \times (1 - acc) \\ & \times [er_{\text{aids}} + (lr_{\text{aids}} \times pp_{\text{aids}} \times \lambda(t))]\} \\ & \times L_{\text{aids}}(t) - \{\mu^{\text{tb}}_{\text{aids}}\} USN_{\text{aids}}(t)\end{aligned}$$