Impact of HIV on novel therapies for tuberculosis control

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Objective and design: The increased risk for tuberculosis in HIV-infected people has fueled a worldwide resurgence of tuberculosis. A major hindrance to controlling tuberculosis is the long treatment duration, leading to default, jeopardizing cure, and generating drug resistance. We investigated how tuberculosis is impacted by reducing treatment duration alone or combined with enhanced case detection and/or cure under different HIV prevalence levels.

Methods: Our model includes HIV stages I–IV and was calibrated to long-term tuberculosis and HIV data from Kenya. Benefits were assessed in terms of absolute and relative reductions in new tuberculosis cases and deaths.

Results: Compared with present-day strategies, at 3–20% HIV prevalence we attain a 6–20% decrease in incidence and mortality in 25 years when reducing treatment duration alone; benefits exceed 300% when combined with increased detection and cure. Benefits vary substantially according to HIV status and prevalence. Challenges arise because in absolute terms the number of infected people and deaths increases dramatically with increasing HIV prevalence, and because the relative efficacy of tuberculosis control policies displays a nonlinear pattern whereby they become less effective on a per capita basis at HIV prevalence levels greater than 15%. Benefits of reducing treatment duration may even be reversed at extreme HIV prevalence levels. Benefits of increasing cure versus detection increase as HIV prevalence increases.

Conclusion: Reducing tuberculosis treatment duration, alone or in combination with other control strategies, can provide enormous benefits at high HIV prevalence. Tuberculosis control policies need to account for HIV levels because the efficacy of different interventions varies substantially with HIV prevalence.

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Introduction

During the first half of the twentieth century, tuberculosis (TB) rates fell in industrialized countries as living conditions improved; in 1944, cure rates improved dramatically with the development of effective TB chemotherapy following the discovery of streptomycin [1]. Subsequent drug discovery led to the current combination therapies. The HIV epidemic and the associated TB risk have, however, led to a resurgence of TB in countries with high HIV prevalence [2,3]. Immunocompromised persons are more likely to become infected with *Mycobacterium tuberculosis*, progress to active disease if already infected, relapse if cured, and die of TB if not adequately treated [4]. Sub-Saharan Africa has the highest HIV infection rates, especially eastern and southern Africa [5,6]. In some countries of the former Soviet Union, TB notification rates increased rapidly because of the decline in public health services following the Soviet Union's end, but this trend has been reversed [7]. Both TB and HIV still threaten marginalized people such as drug users, homeless, immigrants, and prisoners [8–11]. Effective TB control falls under the auspices of the Millennium Development Goals; in 2005, the World Health Organization (WHO) declared the TB epidemic in Africa a regional emergency. The UN General Assembly Special Session on AIDS (2006) and the G8 summit (2006) advocated for intensifying TB and HIV collaborative activities [12,13].

The first supragovernmental global program specifically targeted at TB was not officially implemented until the mid-1990s by WHO, under the name of Directly Observed Treatment, Short-course (DOTS). The cornerstone of DOTS is individual monitoring of chemotherapy administered to patients with active pulmonary TB. DOTS has achieved considerable success in many countries (Peru and China), but not in all, especially where HIV prevalence is high [2,14–16].

In the present study, we are concerned with TB control in countries with generalized HIV epidemics [16–19] and, in particular, with the development of shorter drug regimens [20–23]. The medications used today were developed over 40 years ago [1] and, although success rates can be high when taken as prescribed, treatment regimens for persons with active TB last for 6–8 months, can cause serious side effects and can have negative interactions with HIV drugs [24]. Long treatment duration generates problems at both the clinical and public health levels because of the need to ensure high compliance levels for a long time to minimize treatment default, guarantee high cure rates, and avoid drug resistance [25,26]. The latter is a significant problem as shown by the recent outbreak of extensively drug-resistant TB in South Africa [27,28]. There is considerable interest in the development of shorter drug regimens, both for the individual's benefit and to free scarce resources for other uses [20,26,29–31].

In this analysis, we evaluated the potential health impact of shortening treatment duration, alone or in combination with other advances in TB detection and treatment, compared with present-day control programs. We developed a detailed mathematical and computational framework, elaborating the TB treatment model of [30] to include four HIV stages [32]. We calibrated our model to TB and HIV data from Kenya (M.S. Sánchez, J. Lloyd-Smith, B.G. Williams, *et al.*, in preparation), a sub-Saharan African country with a high HIV and TB prevalence and a strong disease surveillance program. We investigated the impact of various TB interventions as a function of HIV prevalence, which is important because HIV prevalence varies greatly geographically and among different populations [17]. The benefits provided by each intervention were assessed using both absolute and relative measures, posed, respectively, in terms of total numbers of TB cases and deaths averted or proportional reductions. We considered the following scenarios reflecting enhancements over the status quo:

(1) reduced treatment duration (several drugs that could eliminate TB more quickly than current drugs are in advanced development stages),
(2) reduced treatment duration combined with increased case detection (previous studies support the importance of case detection for DOTS success),
(3) reduced treatment duration combined with increased cure rates (in order to evaluate the relative importance of increasing cure versus detection rates in relation to HIV prevalence), and
(4) combined implementation of all three enhancements, that is, shorter treatment duration, increased detection, and increased cure [18,20,26,30,33–35].

Methods

Our compartmental TB model includes 42 TB infection and treatment categories; flows among these categories reflect the most important processes determining TB incidence, prevalence, and mortality. We included five HIV clinically recognized categories (uninfected and WHO stages I–IV [32]) and calibrated our model using TB and HIV data from Kenya spanning 1980–2004 [5,7]. The most recent official HIV trends reported for Kenya [36] show prevalence peaking at 10% in 1997 and dropping to 7% in 2005. As discussed in another study (M.S. Sánchez, J. Lloyd-Smith, B.G. Williams, *et al.*, in preparation), given the adequate fit of the model to Kenyan TB-HIV data up to 1997, the analyses we present here used the parameter set with the best fit to this time period. The supporting document provides a detailed

explanation of the TB–HIV category structure, model formulation, and parameter values used.

HIV prevalence levels

To generalize our findings to other HIV-affected settings, we evaluated the benefits obtained by implementing the alternative TB control measures described below under five different HIV prevalence levels, that is, 3, 7, 15, 20, and 35%. We introduced the alternative scenarios in 2006 and projected the data forward for 25 years, until 2030 (Fig. S2). During this period, we assumed HIV prevalence remained approximately constant for the five different levels considered. For each HIV setting, HIV trends prior to 2006 were scaled to those reported in another study [36]. As such, the HIV epidemic with a 35% prevalence in 2006 peaked at approximately 51% in 1997–1998. We investigated TB dynamics at such an elevated HIV prevalence because similar levels have been reported in certain populations [5].

Scenario analyses

In order to determine the most effective TB control policies in different HIV settings, we compared how HIV impacts TB trends under programs that emphasize alternative control measures in addition to reduced treatment duration [30]. The scenarios considered are discussed below.

Baseline scenario: The first scenario followed present-day Kenyan conditions, with treatment under DOTS lasting 6 months and that under non-DOTS programs lasting 8 months. Default rates in the second and the third month were assumed to be, respectively, three and two times more than the default rates in the first month. Patients in the fourth to sixth month of DOTS and those in the fourth to eighth month for non-DOTS defaulted at the same rate as those in the first month. This pattern follows observed default rates [29,37,38].

Alternative scenarios:

(1) Reduced treatment duration. We reduced treatment duration to 2 months in both DOTS and non-DOTS regimens and for smear-positive and smear-negative TB cases. We assumed there was a corresponding reduction in the rate at which patients stopped treatment before completing their regimen, such that default rates in the second month were equal to those in the first month. In this scenario, the probability of cure at the end of 2 months was assumed to be equal to the probability of cure at the end of treatment (6 or 8 months) in the status quo.
(2) Reduced treatment duration and increased detection rate. We reran scenario 1 but doubled the case detection rate across all HIV categories.
(3) Reduced treatment duration and increased cure rate. We reran scenario 1 but now directed into the completely cured category 80% of patients who were previously susceptible to relapse (i.e., transiently recovered) upon completion of both DOTS and non-DOTS treatment across all five HIV categories.
(4) Reduced treatment duration, increased detection rate, and increased cure rate. We reran scenario 1 with both scenario 2 and 3 modifications (i.e., interventions in all three scenarios combined).

Benefits

Benefits were measured as 'new TB cases' and 'TB deaths' avoided under each alternative scenario (1–4) as compared with the baseline. We considered both the absolute number of cases avoided:

$$\text{TBcases\_avoided} = \text{New\_TBcases\_baseline} - \text{New\_TBcases\_alternative},$$

and the relative benefits:

$$\text{TBcases\_avoided} = \frac{\text{New\_TBcases\_baseline}}{\text{New\_TBcases\_alternative}}.$$

Under this definition, a relative benefit of three corresponds to a three-fold decrease in new TB cases under the alternative as compared with the baseline scenario. The same reasoning was applied to obtain absolute and relative benefits in terms of TB deaths avoided.

Results

In our simulations of present-day TB control conditions, TB incidence and mortality rates decrease throughout the period examined, assuming an HIV prevalence of 7% in the period 2006–2030 (Fig. 1). Shortening treatment duration from 6 to 2 months could additionally reduce TB incidence and deaths by approximately 15–20%, respectively, over the next 25 years. Reducing treatment duration and increasing detection or cure rates provide further benefits, and, if all three interventions were implemented together, it should be possible to reduce incidence and deaths by 80% during the projection period. Under our model formulation, treatment programs were shortened instantaneously from 6 to 2 months. This generated an initial adjustment period due to the momentarily greater influx of persons completing treatment and the corresponding short-term rise in the number of people eligible to relapse. We observed a temporary increase in TB incidence under those scenarios that did not include an increase in cure rate (i.e., scenarios 1 and 2; Fig. 1a). The brief increase displayed by TB mortality under all scenarios was very small in magnitude (Fig. 1b).

Figures 2–5 show that HIV prevalence had a strong influence on the efficacy of TB control programs, which varied between HIV-uninfected and HIV-infected persons. In these plots, HIV prevalence peaked in 1997

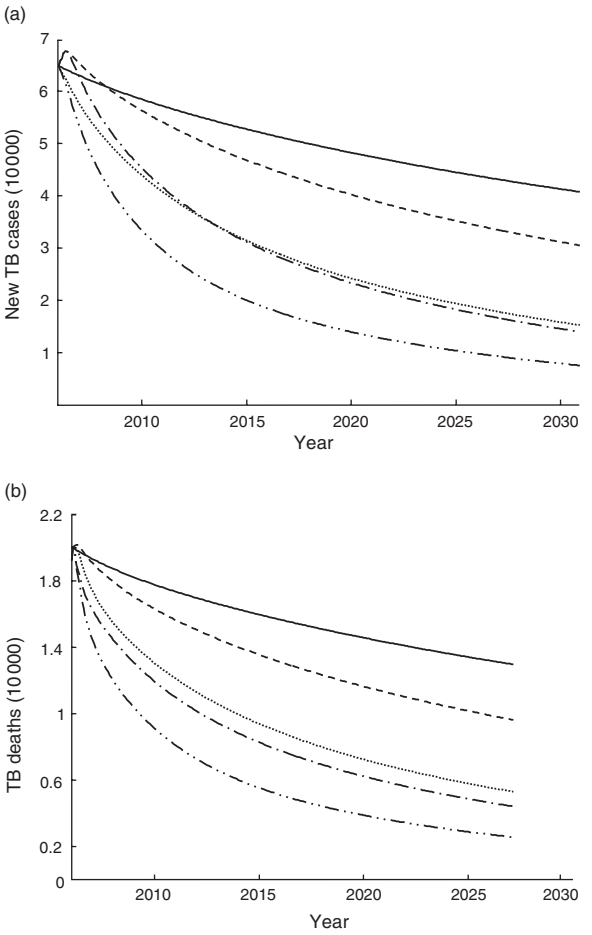

Fig. 1. Projected trends in absolute number of annual (a) new TB cases and (b) deaths during a 25-year period for several scenarios using parameter values fitted to Kenyan tuberculosis (TB) and HIV data up to 1997. Compared with current TB control programs (solid line), all four alternative TB control programs offer substantial reductions in both TB incidence and mortality. (——) Baseline; (- - -) reduced duration; (– · –) reduced duration and increased detection; (· · · ·) reduced duration and increased cure; (– · · – · · –) reduced duration, increased detection, and increased cure.

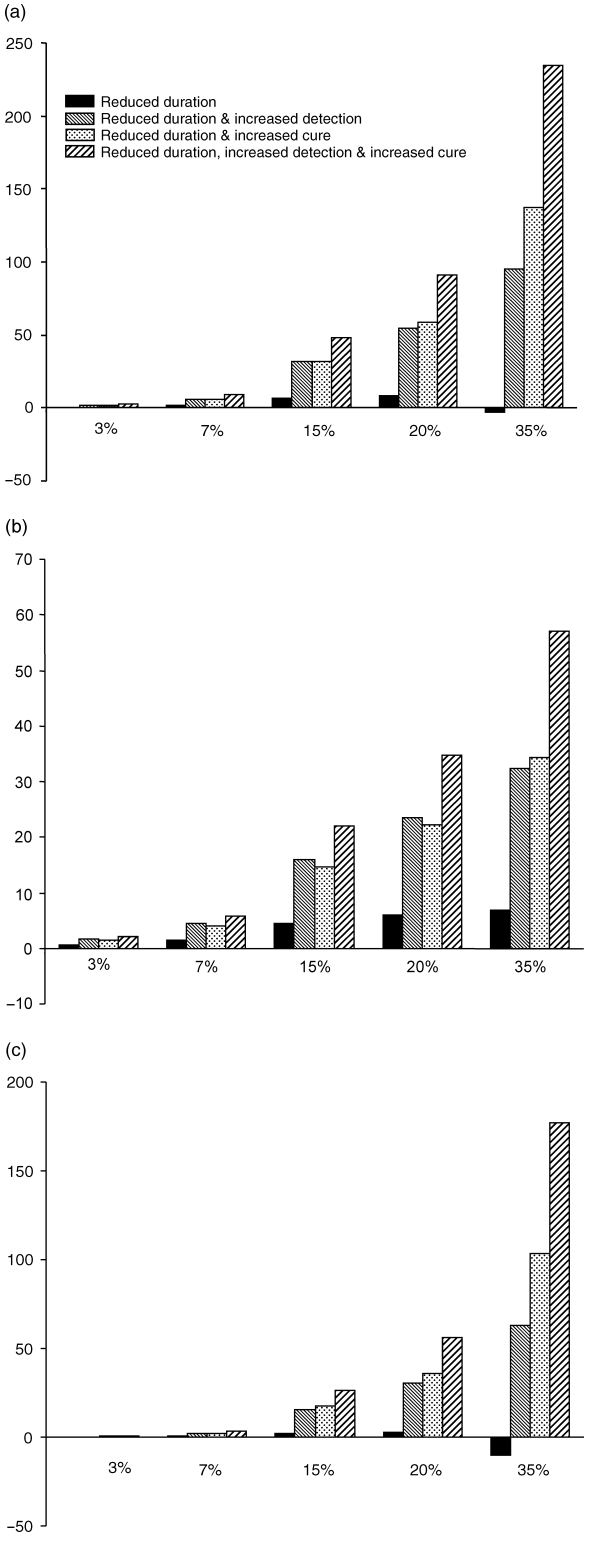

Fig. 2. Projected absolute number of new tuberculosis (TB) cases avoided from 2006 to 2030 under different control scenarios compared with current TB control programs. As HIV prevalence increases (*x*- axis), the TB burden increases and more effective TB control measures provide greater benefits in terms of millions of new TB cases avoided (y-axis) in the whole population (a) and in the HIV-negative

and approached a lower steady state in 2005 (Fig. S2), with trends scaled to those reported in another study [36]. We observed qualitatively similar results in response to the different TB control strategies considered under different calibration schemes, that is, calibrating to previously reported HIV numbers in Kenya depicting a monotonically increasing HIV epidemic that reached 14% prevalence in 2003 [33], and using the same parameter values obtained in our calibration as that used in another study (M.S. Sánchez, J. Lloyd-Smith, B.G. Williams, *et al.*, in preparation) (Table S2) but assuming HIV prevalence increased monotonically until a 7% HIV prevalence was reached. The numerical values plotted in Figs. 2–5 are presented in Table S4. We further discuss

our observations on the benefits derived from increasing detection and/or cure without reducing treatment duration in the supporting document.

Absolute benefits

When measured in terms of total numbers of cases and deaths averted, the benefits obtained by all four alternative TB control options rose considerably with increasing HIV prevalence. The only exception occurred at the extreme HIV prevalence of 35% when only reducing treatment duration, in which the number of new cases slightly increased. This result was evident when considering the whole population (Fig. 2a), but was due to an increase in only the HIV-infected subpopulation (Fig. 2c). A reduction in treatment duration always decreased the number of TB cases in the HIV-uninfected subpopulation (Fig. 2b). The absolute number of deaths avoided increased with HIV prevalence for all control scenarios (Fig. 3).

Relative benefits

Relative benefits, measured as the proportional reductions in numbers of TB cases and deaths, exhibited markedly different patterns from those of the absolute benefits. In the scenario in which only treatment time is reduced, relative reductions in incidence and mortality decreased slightly as HIV prevalence increased (Figs 4a and 5a). As for the absolute benefits, this effect culminated at the 35% HIV prevalence, with a slightly greater number of cases in the whole population (Fig. 4a) and in the people infected with HIV (Fig. 4c). For the people not infected with HIV, reducing treatment duration always provided a net increase in TB cases and deaths avoided (Figs 4b and 5b). The reduction in treatment duration combined with increased detection and/or cure provided a different pattern regarding the relative reductions in cases and deaths: benefits initially increased until an HIV prevalence of approximately 15%, after which they gradually decreased, both for the whole population and when partitioning the population into HIV uninfected and infected (Figs 4 and 5). On a relative scale, the improved TB control strategies provided greater benefits in terms of deaths avoided than in cases avoided.

Fig. 2. (*Continued*).
(b) and HIV-positive (c) subpopulations. The only exception is at extremely high HIV prevalence levels (35%), in which the reduction in treatment time scenario generates a greater number of new cases among HIV-positive persons. Absolute benefits are much larger in the HIV-positive population – note the different scales of the *y* axes. The legend applies to all panels in the figure. (▬) Reduced duration; (▨) reduced duration and increased detection; (▩) reduced duration and increased cure; (▨) reduced duration, increased detection, and increased cure.

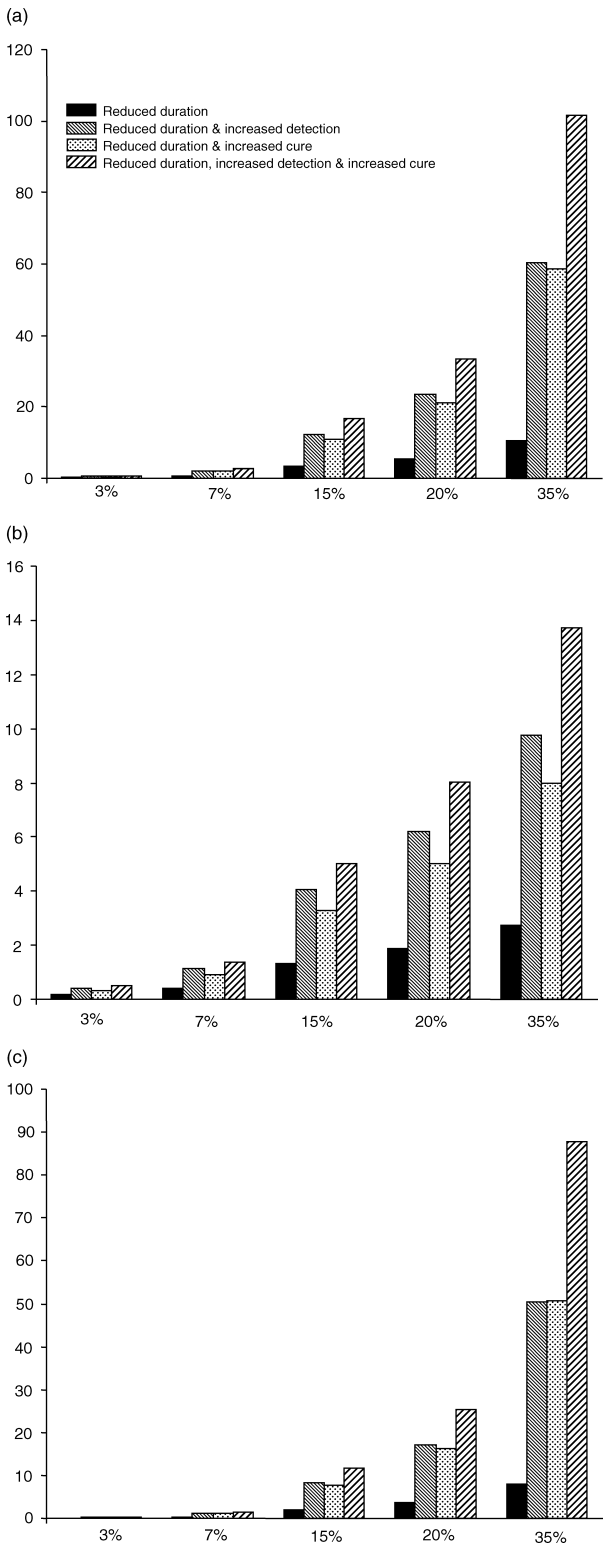

Fig. 3. Projected absolute number of tuberculosis (TB) deaths avoided from 2006 to 2030 under different control scenarios compared with current TB control programs. As HIV prevalence increases (*x*- axis), the TB burden increases and more effective TB control measures provide greater benefits in terms of millions of TB deaths avoided (y-axis) in the whole population

Comparing benefits of the alternative scenarios according to HIV status

In terms of absolute cases and deaths avoided, benefits were proportionally greater among the people infected with HIV than among those not infected with HIV for the same HIV prevalence. This pattern was most noticeable at higher HIV prevalence levels (Figs 2 and 3). Again, the only exception arose for the 35% HIV prevalence, because the model predicted a greater number of HIV-infected persons would become infected with TB when only reduced treatment duration is implemented (Fig. 2c). In contrast, the relative benefits for all alternative TB control programs considered were consistently smaller for people infected with HIV than those not infected with HIV at the same HIV prevalence (Figs 4 and 5).

Comparing the benefits of increasing detection in comparison with cure

When comparing the benefits obtained from combining reduced treatment duration with either increased detection or cure, results varied depending on HIV prevalence and on whether we considered the people not infected with HIV together with, or separately from, those infected with HIV. The qualitative impact of HIV on TB control already became evident when investigating avoided cases under the different scenarios in the whole population Figs 2a and 4a: for an HIV prevalence less than 15%, increasing detection provided slightly greater benefits, but for higher HIV levels, increasing cure became progressively more effective. Detection always avoided a greater number of deaths when considering the whole population, but the relative gains were minimal at 35% HIV prevalence (Figs 3a and 5a).

Additional insight was gained when comparing benefits obtained from increased detection in comparison with increased cure according to HIV status. In the whole population, improved cure rate out-performed improved detection in terms of reducing TB incidence for HIV prevalences of 15% or higher. In the HIV-uninfected people, this shift was observed only at 35% HIV prevalence (Figs 2b and 4b), whereas among the HIV infected people, it held at all HIV levels (Figs 2c and 4c). A greater number of deaths were avoided by decreasing treatment duration combined with increased detection, as compared with increased cure, for all HIV levels in the HIV-uninfected people (Figs 3b and 5b) and HIV-

Fig. 3. (*Continued*).
(a) and in HIV-negative (b) and HIV-positive (c) subpopulations. Absolute benefits are much larger in the HIV-positive population – note the different scales of the *y* axes. The legend applies to all panels in the figure. (▬) Reduced duration; (▨) reduced duration and increased detection; (▩) reduced duration and increased cure; (▨) reduced duration, increased detection, and increased cure.

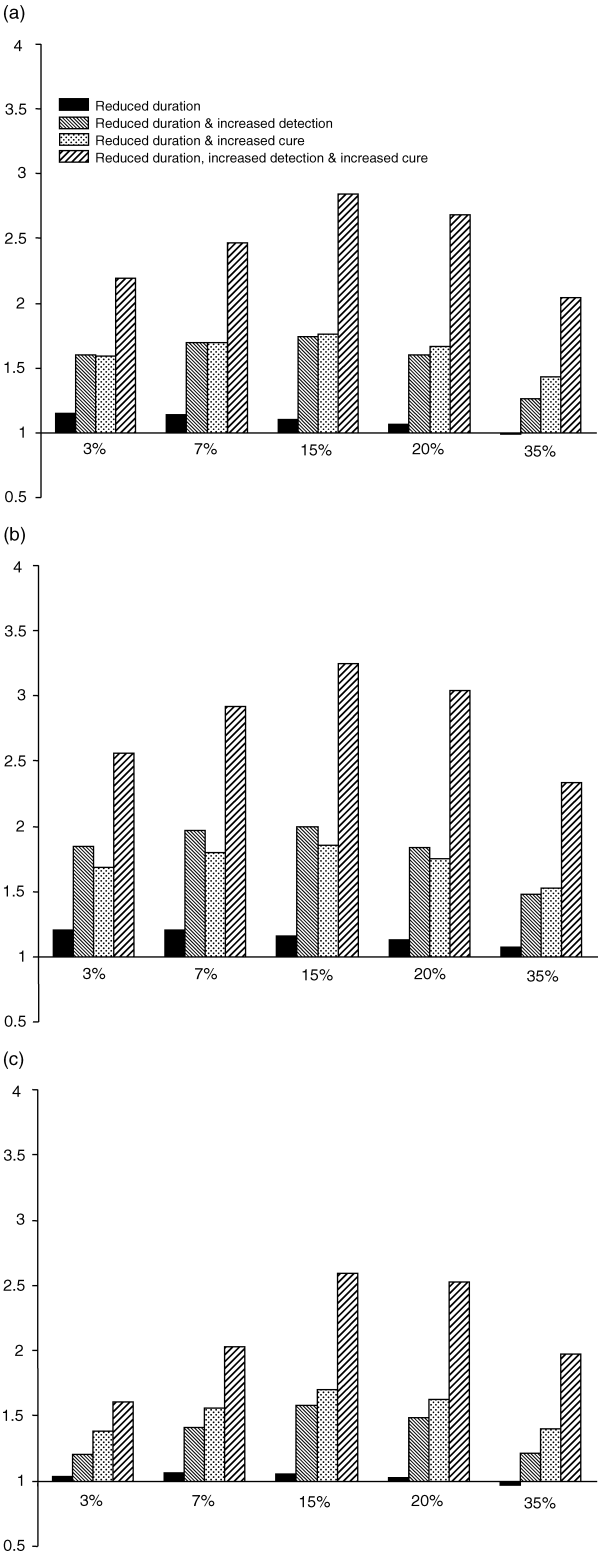

Fig. 4. Projected relative number of new tuberculosis (TB) cases avoided from 2006 to 2030 under different control scenarios compared to current TB control programs. We evaluated benefits in the whole population (a) and the HIV-negative (b) and HIV-positive (c) subpopulations. The relative benefits for the shorter treatment time scenario decrease as HIV prevalence increases.

infected people for HIV prevalences less than 35% (Figs 3c and 5c). At the extreme HIV prevalence of 35%, the deaths avoided in the HIV-infected people by the two TB control policies, although comparable, begin to favor an increased cure rate.

Discussion

Our investigation into the impact of HIV on TB control shows that, as expected, the number of new TB cases and deaths increases substantially as HIV prevalence increases. More effective measures, therefore, have the potential to provide correspondingly greater absolute benefits at higher HIV levels [2,3,30,33]. The relative benefits of improved TB control, however, either become progressively smaller as HIV prevalence increases when only implementing reduced treatment duration, or increase with rising HIV prevalence up to 15%, then decrease at higher prevalence levels for the three remaining scenarios (reduced treatment time combined with increased detection, increased cure, or all concurrently). We do stress that, because of the great uncertainties regarding TB–HIV codynamics [4,14, 39,40], we focused our analysis on understanding interactions and potential qualitative outcomes rather than obtaining precise numerical predictions. In particular, we consider cure rates close to those officially reported for Kenya (supporting document [7]); substantially lower population-level cure rates may influence the response of the TB epidemic to the interventions considered, highlighting the critical need for thorough data collection and evaluation on appropriate managerial scales.

TB control measures are less effective among the HIV-infected TB patients. Although in absolute terms benefits are proportionally greater among the HIV-infected patients for a given HIV prevalence (a pattern most noticeable at higher levels, with the exception of decreasing treatment duration at 35% HIV prevalence), relative benefits are always smaller. We therefore observed substantially different epidemiological responses to TB control in the HIV-uninfected and HIV-infected patients, even when assuming the two groups mixed randomly (and hence TB transmission was not biased by contact patterns).

Fig. 4. (*Continued*).
For the other three scenarios, increasing HIV prevalence has a nonlinear impact, with relative benefits increasing until an HIV prevalence of 15% and decreasing thereafter. The relative benefits are smaller in the HIV-positive persons compared with the HIV negative. The legend applies to all panels in the figure. (▬) Reduced duration; (▨) reduced duration and increased detection; (▩) reduced duration and increased cure; (▨) reduced duration, increased detection, and increased cure.

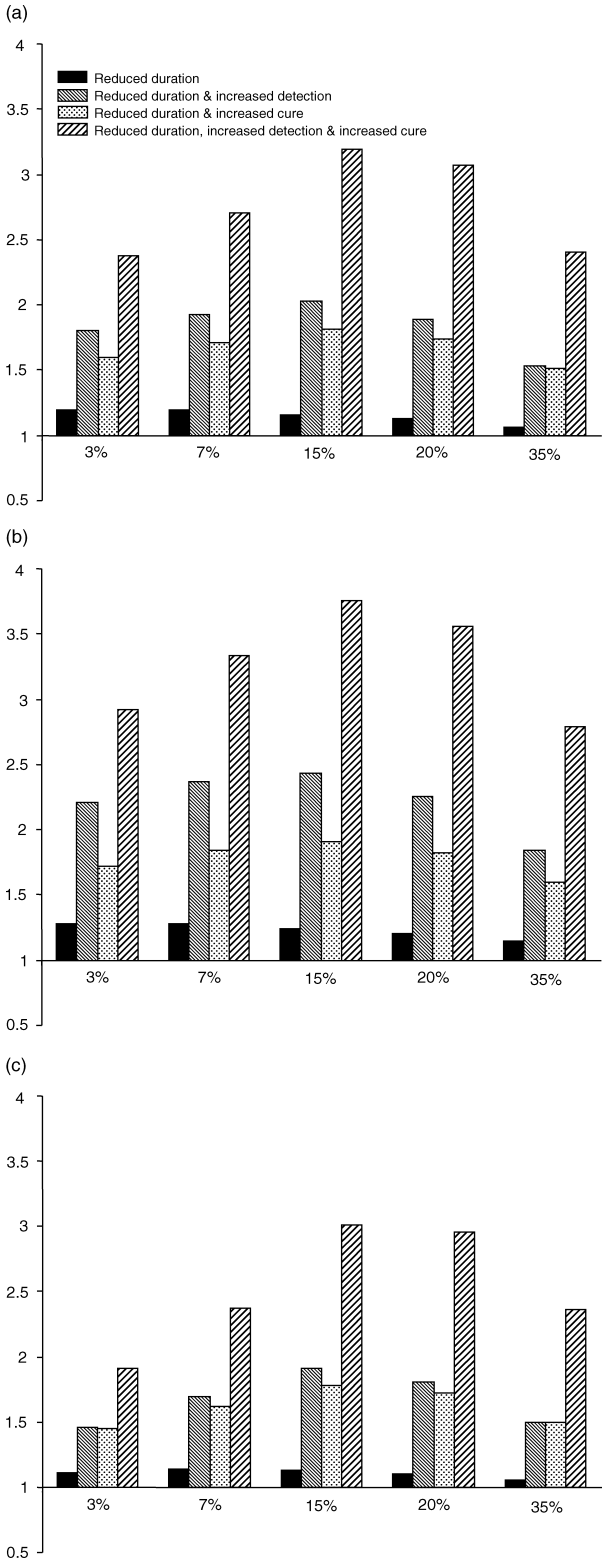

Fig. 5. Projected relative number of tuberculosis (TB) deaths avoided from 2006 to 2030 under different control scenarios compared with current TB control programs. We evaluated benefits in the whole population (a) and HIV-negative (b) and HIV-positive (c) subpopulations. The relative benefits for the shorter treatment time scenario decrease as HIV prevalence increases.

Extremely high HIV prevalence appears to reverse the positive epidemiological impact of reducing TB treatment duration: the absolute number of new TB cases and deaths always decreases when changing from a 6-month to a 2-month regimen, except at 35% HIV prevalence when the number of new TB cases increases over the 25-year period considered. This pattern occurs in the HIV-infected patients but not in the HIV-uninfected patients. Moreover, because of the overwhelming proportion of HIV-infected patients, it translates into an increased number of new cases when considering the whole population. This outcome is due to immunocompromised persons being very susceptible to TB infection, reinfection, progression, and relapse following treatment completion. In effect, extended TB treatment can act as a prophylactic and transmission blocker for this population, such that in our model there is an epidemiological benefit to longer treatment duration when HIV prevalence reaches these levels. In this regard, TB relapse rates in TB–HIV-coinfected patients may be reduced when TB treatment is extended beyond the routinely recommended treatment duration with current drugs [41]. In any case, we need to bear in mind that our evaluation does not account for the potentially toxic effects of extended chemotherapy, negative interactions with HIV treatments, or the additional burden on public health systems of longer TB treatment regimes [26].

Considering benefits both in absolute and relative terms provides complementary information regarding the potential impact of different TB interventions. Considering first the benefits among HIV-uninfected patients, we find that absolute benefits rise with increasing HIV prevalence, because of the greater TB burden present in the population at higher HIV levels; in contrast, relative benefits rise as HIV prevalence increases to 15% but then decline at higher HIV prevalence levels because of diminishing per capita efficiency of TB control measures. Comparisons of absolute and relative benefits in the HIV-infected patients yield further insights: the absolute number of cases avoided when increasing cure versus detection is substantially greater at higher HIV levels among the HIV-infected patients; conversely, increasing cure provides similar relative benefits in terms of cases avoided in comparison to increasing detection at all HIV levels. Therefore, although knowledge of absolute measures is essential, relative numbers can provide further critical insights into relevance to cost-effective analyses [35], particularly when differences in absolute terms are small.

The magnitude of the impact of HIV on TB control will vary across geographic areas and social groups, but will be greatest in settings of high HIV prevalence, including countries (sub-Saharan Africa [2]), regions or communities within countries (Carletonville South African gold mining community in South Africa [42,43]), and high-risk groups (the homeless, incarcerated, and drug users in industrialized nations [8,10,11], military personnel [44]). Our study further indicates that if HIV treatment is effective in making the treated HIV-infected patients behave epidemiologically as if they were not infected with HIV, then such treatment can provide valuable secondary benefits in TB control both on an absolute and on a per capita basis. However, if the mortality of treated HIV-infected persons is reduced by antiretrovirals (ARVs) but their susceptibility to disease remains higher than that of the HIV-uninfected persons, the overall TB burden in the population will likely increase [4,6,45–48]. Further detailed investigations are required to fully evaluate the public health impact of shortening TB treatment duration, in particular regarding the rollout of antiretroviral drugs, and the generation and spread of multidrug-resistant and extensively drug-resistant tuberculosis [6,49–52]. Moreover, results also indicate greater benefits may be obtained by interventions targeted at communities according to their TB and HIV risk [11,53–56]. For instance, we observed that the benefits of increasing detection versus cure varied according to HIV levels, depending on how HIV interacts with the intervention. As the proportion of HIV-infected persons increased, increasing cure gradually became more beneficial compared with increasing detection; this pattern was most apparent in the HIV-infected fraction. A targeted approach may be particularly fruitful for those groups with extremely high HIV prevalence compared with the general population, as evidenced by the exceptional results obtained at the 35% HIV prevalence level.

Fig. 5. (*Continued*).
For the other three scenarios, increasing HIV prevalence has a nonlinear impact, with relative benefits increasing until an HIV prevalence of 15% and decreasing thereafter. The relative benefits are smaller in the HIV-positive persons compared with the HIV negative. The legend applies to all panels in the figure. (▬) Reduced duration; (▧) reduced duration and increased detection; (▩) reduced duration and increased cure; (▨) reduced duration, increased detection, and increased cure.

Conclusion

Our study shows how reducing treatment duration, alone or in combination with other TB control strategies, can provide enormous benefits at high HIV prevalence, although both absolute and relative benefits vary substantially according to the proportion of the population that is HIV infected. Challenges arise not only because in absolute terms the total amount of infected people and deaths increases dramatically with increasing HIV prevalence [2,3,30,33] but also because the relative efficacy of TB control measures display a nonlinear

pattern whereby they become less effective on a per capita basis at HIV prevalences higher than 15%. Therefore, a qualitative shift in TB dynamics occurs as HIV levels increase – the population's response to TB control becomes more in consonance with the response of the HIV-infected fraction ([57] and references therein) up to the point where the benefits of reducing treatment duration may even be reversed at extreme HIV levels. Moreover, the benefits of increasing detection versus cure decrease as HIV prevalence increases. Our results indicate that TB control policies need to consider HIV levels because the efficacy of different interventions varies substantially with HIV prevalence [58,59].

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