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Modeling the joint epidemics of TB and HIV in a South African township

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Abstract We present a simple mathematical model with six compartments for the interaction between HIV and TB epidemics. Using data from a township near Cape Town, South Africa, where the prevalence of HIV is above 20% and where the TB notification rate is close to 2,000 per 100,000 per year, we estimate some of the model parameters and study how various control measures might change the course of these epidemics. Condom promotion, increased TB detection and TB preventive therapy have a clear positive effect. The impact of antiretroviral therapy on the incidence of HIV is unclear and depends on the extent to which it reduces sexual transmission. However, our analysis suggests that it will greatly reduce the TB notification rate.

Keywords HIV · TB · Epidemic model · Bifurcation diagram

Mathematics Subject Classification (2000) 34C60 · 92D30

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1 Introduction

In South Africa, 5.5 million people are infected with the human immunodeficiency virus (HIV), that is 12% of the country's total population [66, p. 455]. Approximately 270,000 cases of active tuberculosis (TB) are notified each year [76, p. 137]. Among adult cases of active TB, nearly 60% are HIV_+ because coinfection with HIV and *Mycobacterium tuberculosis* (MTB) increases greatly the probability of progressing from latent to active TB.

Detailed studies of these epidemics in a township near Cape Town have been published recently [35,75]. Estimates of the TB notification rate (based on the yearly number of TB notifications, on two population censes conducted in 1996 and in 2004, and assuming a linear population increase in between) and of the prevalence of HIV (estimated using data from an antenatal clinic) are shown in Table 1.

For the year 2005, 259 TB cases were reported among adults (age $\geq$ 15) [75]; 66% of those who were tested for HIV were HIV_+. The adult population was then estimated to be 10,400 and the total population 13,000. So the TB notification rate in the whole population was over $259/13,000 \simeq 1,992$ per 100,000 per year. Moreover, in a sample population of 762 adults, 12 had undiagnosed TB (3 HIV_- and 9 HIV_+). Around 23% (174/762) of the sample population was HIV_+. More than 80% of smear-positive TB cases receiving treatment were cured.

There have been many studies in the medical literature focusing on particular aspects of the joint HIV–TB epidemics in this and other similar townships near Cape Town [3,34,35,37–40,75]. In the present paper, we build a mathematical model to integrate the data on TB and HIV in order to develop a better understanding of the epidemic. We keep the model as simple as possible consistent with the available data and we do not stratify the model by age. The main focus is on the impact of various control measures. Given the extremely high levels of both HIV and TB in this setting, it is essential to know what are the most effective control measures. Of particular importance is the fact that a substantial project is being planned to control HIV and TB in this township. The model may help the planning and design of the intervention. Furthermore, the model and its predictions may provide a framework for evaluating the success or failure of the intervention.

Section 2 reviews mathematical models that have previously been developed to investigate joint epidemics of HIV and TB. Section 3 introduces the model we use, which we have tried to keep as simple as possible. Section 4 analyzes some mathematical properties of the model. Section 5 reviews parameter values in the medical literature. Section 6 estimates several parameters using the data from the South African

Table 1 TB notifications per 100,000 per year and HIV prevalence (%)

Year	1996	1997	1998	1999	2000	2001	2002	2003	2004
TB	580	653	913	897	982	1,410	1,366	1,472	1,468
HIV	6.3	8.9	11.6	14.2	16.5	18.4	19.9	21.1	21.9

Data from [35, Table 1]

township. Section 7 contains bifurcation diagrams showing qualitatively and quantitatively how the steady states of the model change for different sets of parameter values. This approach is needed since some parameters are known only approximately. Section 8 investigates how various control measures might affect the HIV and TB epidemics with a focus on transient dynamics, since the convergence to a steady state takes many decades. The main question is about the impact of antiretroviral therapy (ART) on the TB notification rate, the answer to which is not obvious. Indeed, coinfected people on ART have a risk of developing TB reduced by 80%, but their life expectancy is also greatly increased. As their risk of developing TB is still several times higher than for HIV_- people, this may increase TB transmission. Our numerical results suggest the contrary: ART could decrease considerably the TB notification rate even as it increases the prevalence of HIV. This conclusion should be considered with caution as there are uncertainties not only in parameter values but also in model formulation.

2 Review of HIV–TB epidemic models

Table 2 reviews HIV–TB epidemic models. The models have been of essentially two different types: either computer simulation studies focusing on transient behavior of realistic but complex models, or "mathematical" studies of simpler but less realistic models focusing on steady states and their stability. These models have considered the situation in sub-Saharan Africa, the USA, Russia, India, or in Brazilian prisons. Some models tried to present a global view by considering all of the five WHO-regions. Other models did not focus on any specific area. The compartments combined a certain number of HIV-states (call it i) and a possibly different number of TB-states (call it j). In such a case, one would expect the model to contain $i \times j$ compartments. Some models have aggregated several compartments while others have added more compartments to take into account specific interventions. This is why the number of compartments is written as $i \times j \pm k$ in Table 2. Some models took the form of a system of ordinary differential equations (ODEs). Most others used discrete-time difference equations. Finally, we mention the ongoing work of Lungu [43]. Several other models have considered generically two diseases infecting a single population, but either they did not include a separate compartment for coinfected people [47], or they did not include a latent state [5], an important feature of TB.

All these models contain many unknown parameters but rely on little data. For example, it seems that [14,15,32,57,70] were the only ones to fit their parameters by using real time series of both HIV prevalence (AIDS cases in [70]) and TB notifications. For the South African township under study, we have two extra pieces of information: the percentage of HIV_+ people among TB notifications and the prevalence of TB at one time point. These two extra constraints should make our parameter estimations more robust. Moreover, the township is certainly more homogeneous than whole countries (the USA in [70], Kenya in [14,15], Zimbabwe in [32]) and less exceptional than a female prison [57]. Besides, we have focused our attention on one of the simplest models we could reasonably think of, with a minimum number of compartments and parameters but even so, our model contains 22 parameters. This should also make our estimates more robust.

Table 2 Review of HIV–TB models

Year	References	Type of model, area studied, model structure and summary
1992	[4]	Static model for sub-Saharan Africa with $2 \times 2 - 2 = 2$ compartments. Affine relationship between TB incidence and HIV prevalence
	[59]	Simulation over 20 years for sub-Saharan Africa (details in [60]). Impact of assumed HIV prevalence increase on TB incidence
1993	[31]	Simulation over 10 years for Uganda with $2 \times 4 = 8$ compartments. TB chemoprophylaxis more efficient than treatment
	[44]	Mathematical analysis of 16 ODEs. Numerical study of the stability of steady states
1994	[60]	Simulation over 20 years for sub-Saharan Africa and Canada structured by age and time since HIV or MTB infection. Impact of assumed HIV prevalence increase on TB incidence
1996	[8]	Simulation over 10 years for the USA with $3 \times 5 - 2 = 13$ compartments, 3 age groups and drug-resistant TB. Combining TB prevention and treatment necessary to reach current goals
1997	[70]	Simulation over 25 years for the USA with 30 ODEs including homosexuals, drug users and immigration. More data on HIV status of TB cases needed
1998	[21]	Simulation over 22 years for the whole World with age structure. Model details no longer on journal website. Impact of WHO TB-strategy on number of deaths
	[51]	Simulation over 32 years for the whole World with $2 \times 19 = 38$ ODEs. Estimation of the size of the TB problem
2000	[17]	Simulation over 30 years for the USA structured by age, sex, ethnicity and location. 14 compartments in TB sub-model
2001	[55]	Stochastic simulation over 2 years for the USA with $5 \times 6 = 30$ compartments. Size of TB outbreaks are very sensitive to TB treatment rate
2002	[56]	Mathematical analysis for Brazil of $3 \times 3 - 1 = 8$ ODEs. Bifurcation diagram of steady states. TB transmission occurs in prisons
2003	[14]	Simulation over 20 years for Kenya, Uganda and South Africa with $3 \times 6 = 18$ compartments. Improving TB detection and treatment more efficient than other interventions
	[57]	Mathematical analysis for Brazil of $3 \times 3 - 2 = 7$ ODEs. Stability of steady states
	[58]	Mathematical analysis of 3 ODES and of a stochastic spatial model for South East Asia. HIV maybe unable to invade populations with high TB burden
2004	[29]	Simulation over 20 years for Uganda of $2 \times 5 + 1 = 11$ ODEs with constant HIV prevalence and BCG vaccination. TB chemoprophylaxis for HIV_+ has a small impact on total TB burden
2005	[1]	Simulation over 20 years for Russia with $3 \times 18 = 54$ compartments. Impact of cure rates for drug-resistant TB on number of deaths
	[72]	Simulation over 40 years for India. Model details not shown. ART necessary to reach Millennium Development Goals for TB
	[15]	Simulation over 20 years for Kenya with $2 \times 6 = 12$ compartments. Improving TB detection and treatment more cost-effective than ART
	[52]	Mathematical analysis of 4 ODEs. Stability of steady states

Table 2 continued

Year	References	Type of model, area studied, model structure and summary.
2006	[10]	Simulation over 30 years for sub-Saharan Africa of $2 \times 22 + 1 = 45$ ODEs. TB chemoprophylaxis speeds up the emergence of drug resistant TB
	[20]	Simulation until steady state for sub-Saharan Africa with $3 \times 8 = 24$ compartments. Impact of better TB diagnostic techniques compared with other interventions
	[32]	Stochastic simulation over 70 years for Zimbabwe with $3 \times 6 = 18$ compartments. 10,000 people in households. Work in progress
2007	[2]	Simulation over 10 years for Russia with $3 \times 18 = 54$ compartments as in [1]. High ART coverage necessary with drug-resistant TB
2008	[63]	Mathematical analysis of $4 \times 4 - 1 = 15$ ODEs with reinfection. Stability of steady states. Backward bifurcation for TB

3 The model

The compartmental structure of our model combines two states for HIV (HIV_- and HIV_+) with three states for TB (susceptible, latent TB and active TB as in [46,48, 64]). The notations for the resulting six compartments are shown in Table 3. The subscript 1 always refers to HIV_- people and the subscript 2 to HIV_+ people. People in compartments E_1, E_2, I_1 and I_2 are those infected with MTB.

The parameters of the model are shown in Table 4. The physiological parameters are more or less the same for people throughout the world or at least for people living in sub-Saharan Africa: the death rates μ_1 and μ_2, the TB parameters $p_1, p_2, q_1, q_2, a_1, a_2, m_1$ and m_2. On the contrary, the "social" parameters depend on the area under study, in particular on population density and living conditions (the transmission rates k_1 and k_2), access to TB clinics (the detection rates γ_1 and γ_2), quality of treatment (ε_1 and ε_2), sexual habits and local cofactors for the transmission of HIV such as other sexually transmitted diseases and male circumcision (d), speed at which information on HIV diffuses (λ) or epidemic history (t_0). Estimates for most physiological parameters can be found in the medical literature. All "social" parameters have to be estimated from local data.

Table 3 The six compartments of the model and some notations

S_1	Number of HIV_- people who are not infected with MTB
S_2	Number of HIV_+ people who are not infected with MTB
E_1	Number of HIV_- people with latent TB
E_2	Number of HIV_+ people with latent TB
I_1	Number of HIV_- people with active TB
I_2	Number of HIV_+ people with active TB
P	Total population: $P = S_1 + E_1 + I_1 + S_2 + E_2 + I_2$
H	HIV prevalence: $H = (S_2 + E_2 + I_2)/P$

Table 4 The 22 parameters of the model and some extra notations (subscript 1 for HIV$_-$ people, subscript 2 for HIV$_+$ people)

B	Birth rate
μ_1, μ_2	Death rate of people who do not have active TB
k_1, k_2	Maximum transmission rate of MTB
p_1, p_2	Proportion of new infections with fast progression to TB
q_1, q_2	Proportion of reinfections with fast progression to TB
a_1, a_2	Progression rate from latent TB to active TB
β_1, β_2	Recovery rate from active TB without treatment
γ_1, γ_2	Detection rate of active TB cases
$\varepsilon_1, \varepsilon_2$	Probability of successful treatment for detected active TB cases
m_1, m_2	Death rate for active TB cases
d	Maximum transmission rate of HIV
λ	Parameter representing behavior change
t_0	Time of introduction of HIV
p_1', p_2'	Proportion with slow progression to TB: $p_1' = 1 - p_1$, $p_2' = 1 - p_2$
b_1, b_2	Recovery rate from TB: $b_1 = \beta_1 + \gamma_1\,\varepsilon_1$, $b_2 = \beta_2 + \gamma_2\,\varepsilon_2$
$f(H)$	Reduced transmission rate of HIV: $f(H) = d\,e^{-\lambda H}$

The equations of our model are

$$\frac{dS_1}{dt} = B - S_1\,(k_1\,I_1 + k_2\,I_2)/P - \mu_1\,S_1 - f(H)\,H\,S_1\,, \tag{1}$$

$$\frac{dE_1}{dt} = (p_1'\,S_1 - q_1\,E_1)(k_1\,I_1 + k_2\,I_2)/P - (a_1 + \mu_1)\,E_1 + b_1\,I_1 - f(H)\,H\,E_1\,, \tag{2}$$

$$\frac{dI_1}{dt} = (p_1\,S_1 + q_1\,E_1)(k_1\,I_1 + k_2\,I_2)/P - (b_1 + m_1)\,I_1 + a_1\,E_1 - f(H)\,H\,I_1\,, \tag{3}$$

for HIV$_-$ people and

$$\frac{dS_2}{dt} = -S_2\,(k_1\,I_1 + k_2\,I_2)/P - \mu_2\,S_2 + f(H)\,H\,S_1\,, \tag{4}$$

$$\frac{dE_2}{dt} = (p_2'\,S_2 - q_2\,E_2)(k_1\,I_1 + k_2\,I_2)/P - (a_2 + \mu_2)\,E_2 + b_2\,I_2 + f(H)\,H\,E_1\,, \tag{5}$$

$$\frac{dI_2}{dt} = (p_2\,S_2 + q_2\,E_2)(k_1\,I_1 + k_2\,I_2)/P - (b_2 + m_2)I_2 + a_2\,E_2 + f(H)\,H\,I_1\,, \tag{6}$$

for HIV$_+$ people. The flows between the different compartments are shown in Fig. 1.

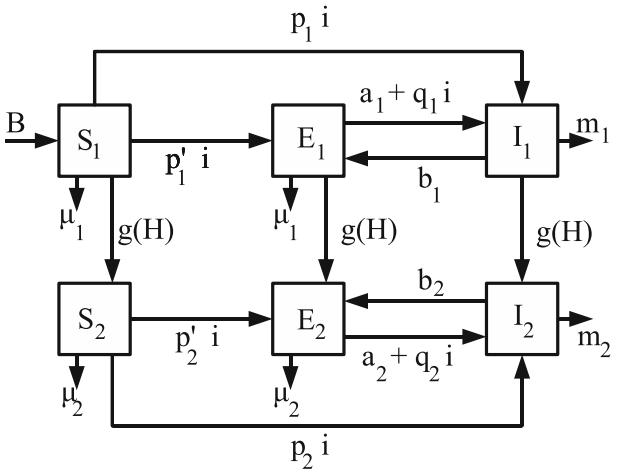

Fig. 1 Flows between the compartments of the model. Here, $i = (k_1 I_1 + k_2 I_2)/P$ and $g(H) = f(H)\,H$

Table 5 Correspondence between some medical vocabulary and the model

TB notification rate	$(\gamma_1 I_1 + \gamma_2 I_2)/P$
MTB infection rate	$(k_1 I_1 + k_2 I_2)/P$
"total" TB incidence rate	$T = a_1 E_1 + a_2 E_2$ $+ (p_1 S_1 + p_2 S_2 + q_1 E_1 + q_2 E_2)(k_1 I_1 + k_2 I_2)/P$
TB incidence rate	T/P
MTB prevalence	$(E_1 + I_1 + E_2 + I_2)/P$
TB prevalence	$(I_1 + I_2)/P$
"Styblo's ratio"	1,000×(TB incidence rate)/(MTB infection rate)
Endogenous reactivation (%)	$(a_1 E_1 + a_2 E_2)/T$
Exogenous reinfection (%)	$(q_1 E_1 + q_2 E_2)(k_1 I_1 + k_2 I_2)/T/P$
Primary disease (%)	$(p_1 S_1 + p_2 S_2)\,(k_1 I_1 + k_2 I_2)/T/P$

Table 5 shows the correspondence we will use between some medical vocabulary and our model. The TB notification rate is the rate at which people in compartments I_1 and I_2 are detected (only a fraction ε_1 or ε_2 of these really move back to the latent compartments E_1 and E_2). The TB incidence rate is the rate at which people enter the compartments I_1 and I_2 divided by the total population usually given "per 100,000 population per year". The MTB infection rate (the continuous-time analogue of the annual risk of infection) is the rate at which people in compartments S_1 (resp. S_2) move to compartments E_1 or I_1 (resp. E_2 or I_2). MTB prevalence is the proportion of the total population in compartments E_1, I_1, E_2 or I_2. TB prevalence is the proportion of the total population in compartments I_1 or I_2. It includes active TB cases, i.e., either undiagnosed TB cases or TB cases that have been detected but that are unsuccessfully treated. We use the expression "Styblo's ratio" to refer to the ratio between TB incidence rate (any form of TB) and MTB infection rate (1,000×). In the literature, the ratio is generally restricted to smear-positive TB notifications (usually about half of all

TB notifications) and the corresponding value has often been assumed to be constant and equal to 50 for HIV$_-$ populations. In other words, an infection rate of 1% per year corresponds to an incidence rate of 50 smear-positive cases per 100,000 per year, or about 100 cases (smear positive and smear-negative) per 100,000 per year. This hypothesis is usually called "Styblo's rule" [6]. However, as we will see in Table 7, Styblo's ratio can no longer be assumed to be the same in areas with a high prevalence of HIV. This remark raises some doubts concerning the method used by Schulzer et al. [59]. Endogenous reactivation is the contribution to the TB incidence coming from compartments E_1 or E_2 at a constant rate a_1 or a_2, exogenous reinfection is the contribution coming from compartments E_1 or E_2 at a rate depending on the number of active TB cases I_1 and I_2. Primary disease is the contribution coming directly from compartments S_1 and S_2 after infection.

A number of key points should be borne in mind:

- At time t_0, we assume that one HIV$_+$ person is introduced in an HIV-free steady population where TB is endemic. We chose this first HIV case to be in state S_2. The formulas for S_1, E_1 and I_1 at the endemic TB steady state will be given in Sect. 4.1.
- Age and sex are not taken into account. In particular, the model cannot distinguish different routes of transmission of HIV, such as sexual transmission and mother-to-child transmission. We did not distinguish pulmonary from extra-pulmonary TB, smear-positive (infectious) TB from smear-negative (non-infectious) TB in order to reduce the number of compartments to a minimum.
- Drug-resistant TB is still very limited in the South African township under study. The efficiency of BCG vaccination is also unclear. We have not included these aspects in our model.
- In Eq. (1), the birth rate is assumed to be a constant independent of the number of people who die of HIV and/or TB. Therefore, our model considers the evolution of cohorts with a fixed size at birth. This is not unreasonable if we use only data on the prevalence of HIV, i.e., the percentage of the population with HIV (not the total number of HIV-infected people), and on the TB notification rate per 100,000 population per year (not the total number of TB notifications during 1 year). If we assumed that deaths are replaced by new "immigrants", we would have to specify their TB and HIV status, something for which it is difficult to get any information. If on the other hand we assumed that births are proportional to the population, then a steady state analysis would become impossible. The demography of the township is in fact quite complex. The population has grown considerably over the past decade. The age pyramid is skewed with more young adults and few children and old people. There are also population inflows and outflows.
- In Eqs. (1) and (4), we chose the "standard form" for TB infection and reinfection as in [24,63,64], and not the "mass action" form used e.g. in [26,46,48]. With a constant birth rate, the total population decreases as the HIV epidemic develops. If we used the "mass action" form for TB transmission, the transmission rate would also decrease and this would artificially slow down the TB epidemic.
- In Eqs. (1)–(3), we also chose the "standard form" for the transmission of HIV as e.g. in [63]. This is the form most commonly used for sexually transmitted

diseases. Following [73] and unlike [63], we assumed however, that the transmission rate is an exponentially decreasing function of HIV prevalence to reflect behavioral changes as HIV awareness develops in the HIV$_-$ population. Reference [73, Suppl.] showed that this special function gives a good fit to HIV infection rate data from another survey in South Africa. It is essential to keep HIV prevalence at realistic levels in a model with no heterogeneity in sexual behavior.

- All other terms are linear. In reality, the rate of progression to active TB is a function of the time since infection, the rate being high during the first 1 or 2 years and relatively low for the rest of one's life [68]. Of course, it is possible to put this into equations [25]. But to keep the number of parameters in the model as small as possible, we have assumed as in [26,46,48,54,64] that a certain fraction of new MTB infections develops active TB immediately, the rest entering a latent state with a constant rate of progression to active TB. Similarly, a certain fraction of reinfections is assumed to lead immediately to active TB as in [24,26,46,48,64]. The other reinfections are "lost" as these people are already latently infected.
- Notice how the equations model people that are unsuccessfully treated for TB. They are counted in the TB notification rate $\gamma_1 I_1 + \gamma_2 I_2$, and induce lower recovery rates $b_1 = \beta_1 + \gamma_1 \varepsilon_1$ and $b_2 = \beta_2 + \gamma_2 \varepsilon_2$ among active TB cases. But they are not counted in a separate compartment.

4 Mathematical analysis

The disease-free steady state with no TB and no HIV is given by $S_1^0 = B/\mu_1$ and $E_1 = I_1 = S_2 = E_2 = I_2 = 0$.

4.1 TB only

Background. The model with TB but no HIV consists only of three compartments (S_1, E_1, I_1) satisfying Eqs. (1)–(3) with $I_2 = 0$, $H = 0$, and $P = S_1 + E_1 + I_1$:

$$\frac{dS_1}{dt} = B - k_1 S_1 I_1/P - \mu_1 S_1 \,, \tag{7}$$

$$\frac{dE_1}{dt} = (p_1' S_1 - q_1 E_1) k_1 I_1/P - (a_1 + \mu_1) E_1 + b_1 I_1 \,, \tag{8}$$

$$\frac{dI_1}{dt} = (p_1 S_1 + q_1 E_1) k_1 I_1/P - (b_1 + m_1) I_1 + a_1 E_1 \,. \tag{9}$$

These equations are up to notations the same as those considered by Singer and Kirschner in [64, Sect. 3]. Building on one side on the earlier work by Feng et al. [24] on a model with four compartments (one more compartment for recovered people) including reinfection but no primary progression (see also the review in [9, Sect. 4.5]) and on the other side on the remarks made by Lipsitch and Murray [42] on the model in [24], reference [64] aimed to show that for a model including all three routes to TB (primary progression, reactivation, and reinfection), a backward bifurcation occurred if the reinfection parameter q_1 was high enough (as noticed in [24]), but too high to be

realistic (as noticed in [42]). In our opinion, there are two weak points in the analysis presented in [64, Sect. 3]. The first point is that, following the idea used in [42], realistic parameters have to satisfy the inequality $q_1 \le p_1$, as latent TB tends to protect against fast progression to active TB in case of reinfection [68]. This inequality did not appear in [64]. The second weak point is that the threshold given in [64, Eq. (7)] is estimated using Latin hypercube sampling of a set of parameter values. With such a method, the conclusion reached is probable but not sure, and can depend on the choice of the set of parameter values. We will show below that the backward bifurcation occurs when q_1 is above a threshold q_1^* which is always bigger than p_1. This proves that the backward bifurcation does not occur for realistic parameter values. Finally, [64] did not show the details of their analysis of the steady states, emphasizing only the conclusions. For our study, we need the formula for the endemic steady state with TB only, as it serves as the initial condition for the full model with both TB and HIV.

One should also mention here the work of Moghadas et al. [46,48] on a model similar to Eqs. (7)–(9) but with "mass action" instead of "standard" incidence. Their model also assumes implicitly that people who have recovered from TB are protected for the rest of their life (they do not return to the latent state), a somewhat unrealistic hypothesis. Formally, this corresponds to the case $b_1 = 0$ in our model. Despite the remarks made by Lipsitch and Murray [42], reference [48] claimed that this backward bifurcation could occur for realistic parameter values. Notice, however, that the parameter values used in [48] for k_1, p_1, and the product $k_1 q_1$ do not satisfy the inequality $q_1 \le p_1$, so they seem to be unrealistic.

Recently, as a part of their analysis of an HIV–TB model, Sharomi et al. [63] studied an extension of the TB-model with four compartments and reinfection introduced by Feng et al. [24]. Again, much emphasis was put on backward bifurcation, which was shown to occur if the ratio q_1/p_1 was above a certain threshold. But this threshold may be bigger than 1 (it is hard to say if this is always so as the formulas for models with four compartments are very complicated). And indeed, the authors chose the unrealistic ratio $q_1/p_1 = 3$ (called η_r in [63]) to illustrate their results.

Analysis. Linearizing system (7)–(9) near the disease-free steady state, we obtain

$$\frac{dE_1}{dt} \simeq k_1 p_1' I_1 - (a_1 + \mu_1)\, E_1 + b_1 I_1\,, \quad \frac{dI_1}{dt} \simeq k_1 p_1 I_1 - (b_1 + m_1)\, I_1 + a_1 E_1\,.$$

So the basic reproduction number R_0^{TB} for TB, as defined in [18], is the spectral radius of the matrix

$$\begin{pmatrix} 0 & k_1 p_1' \\ 0 & k_1 p_1 \end{pmatrix} \begin{pmatrix} a_1 + \mu_1 & -b_1 \\ -a_1 & b_1 + m_1 \end{pmatrix}^{-1},$$

which can easily be computed:

$$R_0^{\mathrm{TB}} = \frac{k_1 (a_1 + p_1\, \mu_1)}{a_1 m_1 + m_1 \mu_1 + \mu_1 b_1}\,. \tag{10}$$

Because this formula does not depend on the reinfection parameter q_1, it is the same as [49, Eq. (10)]. When $b_1 = 0$ and $p_1 = 0$, it is the same as the formula given in [24, Sect. 1]. A slightly more intuitive way of deriving (10) consists in writing that R_0^{TB} is the expected number of secondary infectious cases produced by one infectious index case in an otherwise disease free population. This index case transmits MTB to k_1 people per unit of time and stays infectious on average $1/(b_1 + m_1)$ units of time. Moreover, each new infected person will be immediately infectious with a probability p_1 and infectious only after reactivation with a probability $(1 - p_1)\, a_1/(a_1 + \mu_1)$. Finally, the index case can become infectious again after recovering (possibly several times), with a probability which is the product of $b_1/(b_1 + \mu_1)$ and of $a_1/(a_1 + \mu_1)$. One can check that the formula

$$R_0^{\mathrm{TB}} = \frac{k_1}{b_1 + m_1}\left[p_1 + (1 - p_1)\,\frac{a_1}{a_1 + \mu_1}\right]\sum_{n=0}^{\infty}\left(\frac{b_1}{b_1 + m_1} \times \frac{a_1}{a_1 + \mu_1}\right)^n \tag{11}$$

gives indeed the same result as (10). Since the probability $a_1/(a_1 + \mu_1)$ of developing active TB by reactivation is small, a good approximation for R_0^{TB} would be obtained by replacing the infinite sum in (11) by its first term, which is equal to 1.

Let us look for an endemic TB steady state of the form $(S_1^*, E_1^*, I_1^*, 0, 0, 0)$ of system (1)–(6) with $S_1^* > 0$, $E_1^* > 0$, and $I_1^* > 0$, i.e., a nontrivial steady state (S_1^*, E_1^*, I_1^*) of system (7)–(9). For convenience, let us introduce the following notations:

$$P^* = S_1^* + E_1^* + I_1^*, \quad s_1^* = S_1^*/P^*, \quad e_1^* = E_1^*/P^*, \quad i_1^* = I_1^*/P^*. \tag{12}$$

After some tedious computations, one can show starting from Eqs. (7)–(9) that the fraction of active TB cases i_1^* has to be a positive root of the quadratic equation

$$\begin{aligned}\left(i_1^*\right)^2 + \left[\frac{a_1 + b_1 + (1 - p_1)\, m_1 + p_1\mu_1}{q_1 k_1} + \frac{m_1}{k_1} - 1\right] i_1^* \\ + \frac{a_1 m_1 + m_1\mu_1 + \mu_1 b_1}{q_1 k_1^2}\,(1 - R_0^{\mathrm{TB}}) = 0.\end{aligned} \tag{13}$$

Moreover, we have

$$e_1^* = i_1^*\,\frac{k_1 - m_1 - k_1 i_1^*}{\mu_1 + k_1 i_1^*}, \quad S_1^* = \frac{B}{k_1 i_1^* + \mu_1}, \tag{14}$$

from which we can compute

$$s_1^* = 1 - e_1^* - i_1^*, \quad P^* = S_1^*/s_1^*, \quad E_1^* = e_1^* P^*, \quad I_1^* = i_1^* P^*. \tag{15}$$

Quadratic equations similar to Eq. (13) were found in [24, Eq. (A.1)] and [46, Eq. (5.3)]. Set

$$k_1^* = \frac{a_1 m_1 + m_1 \mu_1 + \mu_1 b_1}{a_1 + p_1 \mu_1} . \tag{16}$$

and

$$q_1^* = \frac{a_1 + b_1 + (1 - p_1) m_1 + p_1 \mu_1}{b_1 + (1 - p_1) m_1} \times \frac{a_1 + p_1 \mu_1}{\mu_1} . \tag{17}$$

Because of (10), we have $R_0^{\mathrm{TB}} = k_1 / k_1^*$. So $R_0^{\mathrm{TB}} < 1$ when $k_1 < k_1^*$, and $R_0^{\mathrm{TB}} > 1$ when $k_1 > k_1^*$. Let us study the steady states of Eqs. (7)–(9) in the parameter space (k_1, q_1). In the appendix, we show that:

- for $q_1 < q_1^*$, system (7)–(9) has no endemic steady state when $0 < k_1 < k_1^*$, and one endemic steady state when $k_1 > k_1^*$ ("transcritical bifurcation" as k_1 increases from 0 to $+\infty$);
- for $q_1 > q_1^*$, there exists another threshold $\widehat{k}_1(q_1) < k_1^*$, depending on q_1, such that system (7)–(9) has no endemic steady state when $0 < k_1 < \widehat{k}_1(q_1)$, two endemic steady states when $\widehat{k}_1(q_1) < k_1 < k_1^*$, and one endemic steady state when $k_1 > k_1^*$ ("backward bifurcation").

Notice that the first fraction in (17) is bigger than 1 and that the second fraction is bigger than p_1. So q_1^* is always bigger than p_1. But realistic values for q_1 are necessarily less than p_1, as already mentioned. This shows that the parameter region with a backward bifurcation is a mathematical curiosity that does not occur in practice, confirming the remarks in [42] and the conclusion suggested by [64]. Notice that formula (17) for q_1^* could have been obtained in [64] if the expression (16) for k_1^* had been inserted in the condition [64, Eq. (7)].

4.2 HIV only

When there is no TB, system (1)–(6) reduces to

$$\frac{dS_1}{dt} = B - \mu_1 S_1 - f(H) H S_1 , \quad \frac{dS_2}{dt} = -\mu_2 S_2 + f(H) H S_1 \tag{18}$$

with $H = S_2/(S_1 + S_2)$. Similar epidemic models with a contact rate depending nonlinearly on the number of infected people have been studied for example in [30, 69]. A more complicated model for HIV transmission with a contact rate depending nonlinearly on the prevalence was used in [73]. First, let us linearize the second equation in (18) near the disease-free steady state $S_1 = S_1^0$ and $S_2 = 0$:

$$\frac{dS_2}{dt} \simeq -\mu_2 S_2 + f(0) S_2 .$$

Hence, the basic reproduction number for HIV is given by

$$R_0^{\mathrm{HIV}} = f(0)/\mu_2\,.$$

It is easily shown using (18) that any endemic steady state with HIV but no TB has to be given by

$$\widehat{S}_1 = \frac{B\,(1-\widehat{H})}{\mu_1(1-\widehat{H})+\mu_2\,\widehat{H}}, \quad \widehat{S}_2 = \frac{B\,\widehat{H}}{\mu_1\,(1-\widehat{H})+\mu_2\,\widehat{H}},$$

where $\widehat{H}$ is the steady state prevalence of HIV, $\widehat{S}_2/(\widehat{S}_1+\widehat{S}_2)$, and is the solution of the equation

$$(1-\widehat{H})\,f(\widehat{H}) = \mu_2 \tag{19}$$

in the interval (0, 1). Notice that the left side of (19) is a decreasing function of $\widehat{H}$, taking the value $f(0) = d$ when $\widehat{H} = 0$ and the value 0 when $\widehat{H} = 1$. So Eq. (19) has no solution in (0, 1) if $R_0^{\mathrm{HIV}} < 1$ and exactly one solution in (0,1) if $R_0^{\mathrm{HIV}} > 1$.

4.3 HIV and TB

The endemic TB steady state can be invaded by HIV. Linearizing system (4)–(6) near this steady state and using the notations introduced in (12), we obtain

$$\begin{aligned}
\frac{dS_2}{dt} &\simeq -k_1 S_2\, i_1^* - \mu_2\, S_2 + f(0)\, s_1^*\,(S_2+E_2+I_2)\,,\\
\frac{dE_2}{dt} &\simeq k_1\,(p_2'\,S_2 - q_2\,E_2)\,i_1^* - (a_2+\mu_2)\,E_2 + b_2\,I_2 + f(0)\,e_1^*\,(S_2+E_2+I_2)\,,\\
\frac{dI_2}{dt} &\simeq k_1\,(p_2\,S_2 + q_2\,E_2)\,i_1^* - (b_2+m_2)\,I_2 + a_2\,E_2 + f(0)\,i_1^*\,(S_2+E_2+I_2)\,.
\end{aligned}$$

So the basic reproduction number r_0^{HIV} for HIV when introduced in a population at the TB endemic steady state (notice that r_0^{HIV} is different from R_0^{HIV}) is the spectral radius of the matrix

$$f(0)\begin{pmatrix} s_1^* & s_1^* & s_1^* \\ e_1^* & e_1^* & e_1^* \\ i_1^* & i_1^* & i_1^* \end{pmatrix}\begin{pmatrix} k_1 i_1^* + \mu_2 & 0 & 0 \\ -k_1 p_2'\, i_1^* & k_1 q_2\, i_1^* + a_2 + \mu_2 & -b_2 \\ -k_1 p_2\, i_1^* & -k_1 q_2\, i_1^* - a_2 & b_2 + m_2 \end{pmatrix}^{-1}. \tag{20}$$

Notice that this matrix is of rank 1 so the spectral radius is equal to the trace. Hence, one gets

$$r_0^{\mathrm{HIV}} = f(0)\,(s_1^*\,\tau_{S_2} + e_1^*\,\tau_{E_2} + i_1^*\,\tau_{I_2})\,,$$

where τ_{S_2}, τ_{E_2} and τ_{I_2} are complex expressions with a simple interpretation. For example, τ_{S_2} is the life expectation of a person from the moment he/she enters state S_2 (in the linearized model). In particular, τ_{S_2}, τ_{E_2} and τ_{I_2} are all strictly less than $1/\mu_2$ if $m_2 > \mu_2$ (as should be). So

$$r_0^{\mathrm{HIV}} < R_0^{\mathrm{HIV}}.$$

Not surprisingly, the expected number of secondary HIV-cases produced by an "average" HIV_+ person in a population with endemic TB is less then in a population with no TB since active TB may shorten the life of such a person.

Similarly, the endemic steady state with HIV can be invaded by TB. Linearizing Eqs. (2)–(3)–(5)–(6) near $(\widehat{S}_1, 0, 0, \widehat{S}_2, 0, 0)$ and setting

$$\widehat{P} = \widehat{S}_1 + \widehat{S}_2\,, \quad \widehat{s}_1 = \widehat{S}_1/\widehat{P} = 1 - \widehat{H}\,, \quad \widehat{s}_2 = \widehat{S}_2/\widehat{P} = \widehat{H}\,,$$

we obtain

$$\begin{aligned}
\frac{dE_1}{dt} &\simeq p_1'\widehat{s}_1(k_1 I_1 + k_2 I_2) - (a_1 + \mu_1)\, E_1 + b_1\, I_1 - f(\widehat{H})\, \widehat{H}\, E_1\,,\\
\frac{dI_1}{dt} &\simeq p_1\widehat{s}_1(k_1 I_1 + k_2 I_2) - (b_1 + m_1)\, I_1 + a_1\, E_1 - f(\widehat{H})\, \widehat{H}\, I_1\,,\\
\frac{dE_2}{dt} &\simeq p_2'\widehat{s}_2\,(k_1 I_1 + k_2 I_2) - (a_2 + \mu_2)\, E_2 + b_2\, I_2 + f(\widehat{H})\, \widehat{H}\, E_1\,,\\
\frac{dI_2}{dt} &\simeq p_2\widehat{s}_2\,(k_1 I_1 + k_2 I_2) - (b_2 + m_2) I_2 + a_2\, E_2 + f(\widehat{H})\, \widehat{H}\, I_1\,.
\end{aligned}$$

So the basic reproduction number r_0^{TB} for TB when introduced in a population at the HIV endemic steady state is the spectral radius of the matrix $M\,N^{-1}$, where

$$M = \begin{pmatrix}
0 & p_1' k_1 \widehat{s_1} & 0 & p_1' k_2\, \widehat{s_1} \\
0 & p_1 k_1 \widehat{s_1} & 0 & p_1 k_2\, \widehat{s_1} \\
0 & p_2' \, k_1 \widehat{s_2} & 0 & p_2' k_2\, \widehat{s_2} \\
0 & p_2 \, k_1 \widehat{s_2} & 0 & p_2 \, k_2\, \widehat{s_2}
\end{pmatrix} \tag{21}$$

and

$$N = \begin{pmatrix}
a_1 + \mu_1 + f(\widehat{H})\, \widehat{H} & -b_1 & 0 & 0 \\
-a_1 & b_1 + m_1 + f(\widehat{H})\, \widehat{H} & 0 & 0 \\
-f(\widehat{H})\, \widehat{H} & 0 & a_2 + \mu_2 & -b_2 \\
0 & -f(\widehat{H})\, \widehat{H} & -a_2 & b_2 + m_2
\end{pmatrix}.$$

Whether r_0^{TB} is bigger or smaller than R_0^{TB} seems to depend on the numerical values chosen for the parameters.

Assuming realistically that $q_1 \leq p_1$ (so that there is no backward bifurcation for the model with TB but no HIV), this linear stability analysis suggests the following conjecture:

- when $R_0^{\mathrm{HIV}} < 1$ and $R_0^{\mathrm{TB}} < 1$, the disease-free steady state is a global attractor of system (1)–(6);
- when $R_0^{\mathrm{HIV}} > 1$ and $r_0^{\mathrm{TB}} < 1$, the HIV-endemic steady state is a global attractor;
- when $R_0^{\mathrm{TB}} > 1$ and $r_0^{\mathrm{HIV}} < 1$, the TB-endemic steady state is a global attractor;
- in all other cases, there is an endemic steady state with both HIV and TB, which has to be computed numerically, and which is a global attractor.

Since $R_0^{\mathrm{HIV}} > r_0^{\mathrm{HIV}}$, the fourth case contains in fact only two subcases:

- $R_0^{\mathrm{HIV}} > 1$, $r_0^{\mathrm{TB}} > 1$, $R_0^{\mathrm{TB}} > 1$ and $r_0^{\mathrm{HIV}} > 1$. Both the HIV-endemic and the TB-endemic steady states exist but they are saddle points.
- $R_0^{\mathrm{HIV}} > 1$, $r_0^{\mathrm{TB}} > 1$, and $R_0^{\mathrm{TB}} < 1$. The HIV-endemic steady state exists but it is a saddle point. There is no TB-endemic steady state.

5 Parameter values fixed after reviewing the medical literature

5.1 Demographic parameters

Natural mortality was taken to be $\mu_1 = 0.02$ per year as e.g. in [10], corresponding to a life expectancy equal to $1/\mu_1 = 50$ years. This is a little pessimistic even for an area where people live in severe poverty, such as the South African township we are considering. The mortality was assumed to be 0.0064 per year in [31], 0.0081 per year in [29], and 0.0167 per year in [56]. Notice that the mortalities in [29,31] correspond to life expectancies which are much too high.

The birth rate B was chosen to attain a total population for the disease-free steady state ($S_1 = B/\mu_1$) of 10,000, the approximate size of the township [35]. This yields $B = 200$ per year.

5.2 HIV parameters for people not infected with MTB

Mortality for HIV_+ people was taken to be $\mu_2 = 0.1$ per year as is usually done (see e.g. [10]) to get an average survival time of 10 years. This mortality was 0.13 per year in [31] and in [29] (citing a study from Uganda [53]). Schulzer et al. [59] assumed a fixed survival time of 10 years.

5.3 TB parameters for HIV_- people

Parameters p_1 and a_1 modeling the progression to active TB. As already mentioned, the rate of progression to active TB is a decreasing function of the time since infection. Using data from the Netherlands for the period 1951–1970, Sutherland et al. [65] estimated that men have a 5% annual risk of developing primary TB disease during 5 years following the first MTB infection and a 0.025% annual risk of reactivation

after 5 years. For women, the numbers were 6 and 0.002%. Vynnycky and Fine [68] did a similar study using data from England and Wales for the period 1953–1988. For individuals over 20 years old, they estimated that the cumulative risk during the first 5 years was about 14%, with a risk of approximately 8% during the first year, 3% during the second, 1% during the third year. The risk of later reactivation was estimated to be 0.03% per year. For individuals aged 0–10 and 15, the cumulative risks for the first 5 years were 4 and 9% and the risks of reactivation close to 0 and 0.015% per year, respectively. Notice that the cumulative risk during the first 5 years in [65] is about 25%, considerably higher than the 14% from [68]. Our model does not include the time since infection as a variable but assumes instead that a certain fraction of new infections will develop TB immediately while the rest will enter a latent stage where the rate of progression to active TB is constant. Following the more recent estimates of Vynnycky and Fine [68], we will assume that $p_1 = 11\%$ (the estimated cumulative risk for the first 2 years) and $a_1 = 0.03\%$ per year.

Given the natural mortality μ_1 previously chosen, these parameter values correspond to a probability $a_1/(a_1 + \mu_1) \simeq 1.5\%$ of progressing from latent to active TB and to a total probability $p_1 + a_1/(a_1 + \mu_1) \simeq 12.5\%$ of developing active TB after MTB infection. Notice that it is not sure if parameter estimates of TB progression from a study of British people are relevant for black Africans living in very different conditions. More data is needed on this issue.

As a comparison, the percentage of HIV$_-$ people that progress rapidly to active TB in previous mathematical models was assumed to be 5% in [59] (within 1 year; no reference), 5% in [70] (after a short latent period of about 1 year; no reference), 5% in [29] (immediate progression; no reference), 5% per year in [56] (constant risk; no reference), 7% in [20] (immediate progression; citing [67]), 14% in [10] (after a short latent period of about 1 year; citing [65] and other references), 14% in [32] (within 5 years; citing [65,68] and other references). The rate of reactivation was assumed to be 0.01% per year in [10] (citing [68] and other references), 0.074% per year in [29], 0.1% per year in [20], and 0.1% per year in [32] (after 5 years of infection, also citing [68]). Both [59] and [70] used more complex models taking into account the time since infection. Notice the disagreement concerning parameter values.

Infection versus reinfection: q_1/p_1. Sutherland et al. [65] estimated that a previous MTB infection reduced the risk of disease after reinfection by 63% for HIV$_-$ males and by 81% for HIV$_-$ females. Vynnycky and Fine [68] found a reduction of risk by 16% among HIV$_-$ adolescents and by 41% among HIV$_-$ adults. In their model, Cohen et al. [10] assumed a reduction of risk of 65% for HIV$_-$ people (citing [65,68]). Dowdy et al. [20] assumed a reduction by 72% for HIV$_-$ people and people with early stage HIV (citing [65]). The two previous studies seem to follow the results of [65] rather than the more recent results of [68]. Here, we prefer using an average of the values found in [68]. We assume that $q_1/p_1 = 0.7$, corresponding to a 30% risk reduction for HIV$_-$ people.

Mortality m_1 and natural recovery rate β_1. Data on TB mortality without treatment goes back to the era when no effective treatment was available, that is at the beginning of the twentieth century. The case fatality ratio $[m_1/(m_1+\beta_1)]$ was then approximately

50%. This is the estimate mentioned in the review [50]. Another review [13, Table 1] estimated that the mean duration of disease for untreated HIV$_-$ TB cases $[1/(m_1+\beta_1)]$ was approximately 2 years. These two estimates for $1/(m_1+\beta_1)$ and $m_1/(m_1+\beta_1)$ correspond to $m_1 = 0.25$ per year and $\beta_1 = 0.25$ per year. These are the values that we shall use for our model. Another model assumed 35% deaths after 1 year [31, p. 407]. In those models that considered different mortalities for infectious and non-infectious untreated TB cases, the mortalities were 0.3 and 0.2 per year, respectively [10], or 35 and 10% after 1 year [20]. The rate at which untreated HIV$_-$ TB cases could return to the latent state $[\beta_1]$ was assumed to be 0.2 per year in [10]. All these values are not too far from the ones we have chosen.

5.4 Parameters involving both HIV and TB

The infectiousness ratio k_2/k_1. HIV$_+$ TB cases are on average less infectious than HIV$_-$ TB cases as extrapulmonary TB occurs more often among HIV$_+$ people. Previous models have often split the compartments for active TB cases (whether HIV$_-$ or HIV$_+$) in two, with one sub-compartment for infectious TB and one sub-compartment for non-infectious TB. The percentages of HIV$_-$ and HIV$_+$ TB cases that are infectious were 50 and 40% in [59], 57 and 50% in [29], 45 and 30% in [10]. In the present model, we do not distinguish those TB cases that are infectious from those that are not infectious. Instead, we use an average infectiousness k_1 for all HIV$_-$ TB cases and an average infectiousness k_2 for all HIV$_+$ TB cases. Given the structure of our model, the difference in infectiousness can be taken into account by choosing an appropriate value for the ratio k_2/k_1. Following the numerical values from [10], we assume that $k_2/k_1 = 30/45 = 2/3$.

Progression rate a_2 to active TB for HIV$_+$ people. As for HIV$_-$ people, the rate of progression from latent to active TB depends on the time since infection but also on the stage of HIV infection. However, our model does not distinguish HIV stages, so we will focus only on estimates that are averages over all stages. For HIV$_+$ injecting drug users in the USA, Selwyn et al. [61,62] found an average rate of progression between 0.079 and 0.097 per year. In Cape Town, Badri et al. [3] found an average TB incidence (including reactivation, fast progression, and reinfection) of 0.097 per year. But the incidence of TB was as high as 0.24 per year among HIV$_+$ people in WHO stage 3 or 4 [3]. Following [61,62], we assume for the reactivation rate of our model that $a_2 = 0.08$ per year, an estimate which seems also compatible with the data from [3]. Heymann [31] also used the estimate from [61,62] in his model. Other studies used 0.0074 per year [29] (assuming a ten-fold increase compared to HIV$_-$ people), 0.05 per year [56], or 0.17 per year [10] (no reference). Schulzer et al. [59] used a more complicated model distinguishing whether MTB infection occurred before or after HIV infection. Notice again the disagreement concerning parameter values.

Infection versus reinfection: q_2/p_2. Data concerning reinfection in HIV$_+$ people is scarce. In the outbreak of TB studied by Di Perri et al. [19], none of four individuals that already had a positive tuberculin skin test developed TB. Cohen et al. [10] assumed a

reduction of risk of 25% for HIV_+ people [10, Suppl., Table 2] (no reference). Dowdy et al. [20] assumed a reduction by 25% for people with AIDS (citing [14]). Here, we will assume as in [10] that $q_2/p_2 = 0.75$. But more data is needed to confirm this hypothesis. Recall that for HIV_- people, we assumed that $q_1/p_1 = 0.7$.

Mortality m_2 and natural recovery rate β_2. The mortality of HIV_+ TB cases [m_2] was assumed to be 0.325 per year in [29] (citing [23]) and 1.0 per year in [10] (citing [53]) for both infectious and non-infectious TB. The rate at which untreated HIV_+ TB cases could return to the latent state [β_2] was 0.1 per year in [10]. For our model, we will again use the data from [13, Table 1]: the mean duration of disease for untreated HIV_+ TB cases [$1/(m_2 + \beta_2)$] was given as 0.5 year. In the same reference, the associated case fatality ratio [$m_2/(m_2+\beta_2)$] was 81% for infectious TB (35% of cases) and 76% for non-infectious TB (65% of cases): we use the weighted average, which is close to 80%. These two estimations for $1/(m_2 + \beta_2)$ and $m_2/(m_2 + \beta_2)$ correspond to $m_2 = 1.6$ per year and $\beta_2 = 0.4$ per year.

6 Estimation of the other parameters from the South African data

Proportions ε_1 and ε_2 of successful treatments. The proportion of successful treatments is approximately 80% [75]. We take this value for ε_1 and ε_2.

Detection rates γ_1 and γ_2. [75] reported 259 TB notifications among adults (age $\geq$ 15) in 2005; 66% of those who were tested for HIV were HIV_+. The adult population in that year was estimated to be 10,400. Moreover, in a sample population of 762 adults, 12 had undiagnosed TB (3 HIV_- and 9 HIV_+). So we expect the following equations to hold:

$$\gamma_1 I_1^{\text{adult}} \simeq 34\% \times 259, \quad I_1^{\text{adult}} \simeq 10,400 \times 3/762\,, \tag{22}$$

$$\gamma_2 I_2^{\text{adult}} \simeq 66\% \times 259\,, \quad I_2^{\text{adult}} \simeq 10,400 \times 9/762\,. \tag{23}$$

This gives the estimates $\gamma_1 \simeq 2.2$ per year and $\gamma_2 \simeq 1.4$ per year. But notice that since the ratios 3/762 and 9/762 are small, the uncertainty is large: the 95% binomial confidence interval for the ratios 3/762 and 9/762 are (0.08%, 1.15%) and (0.54%, 2.23%), respectively. Using Eqs. (22)–(23), the corresponding interval for γ_1 is (0.74, 10.6) per year, and the one for γ_2 is (0.74, 3.0) per year. Corbett et al. [12] suggest that γ_2 may be larger than γ_1. For our model, we chose the lower bound of the confidence interval for γ_1 ($\gamma_1 = 0.74$ per year) and the upper bound of the confidence interval for γ_2 ($\gamma_2 = 3.0$ per year). One motivation was that recent unpublished data shows that the MTB infection rate in the past few years has not increased so much. In our simulations, we found that this was only possible with values of γ_2 that are several times higher than γ_1. Indeed, the great increase in TB notifications has to be compensated by a shorter infectious period to keep the MTB infection rate at a relatively low level.

With these choices, we obtain $b_1 = \beta_1 + \gamma_1\varepsilon_1 \simeq 0.84$ per year and $b_2 = \beta_2 + \gamma_2\varepsilon_2 \simeq 2.8$ per year. For comparison, the values used for the whole of Uganda in [29] for b_1

and b_2 were both equal to 0.3 per year, but case detection is probably not as good as in the South African township under study here.

We notice also that the probabilities for TB to be detected are given by

$$\frac{\gamma_1}{m_1+\beta_1+\gamma_1} \simeq 60\%, \quad \frac{\gamma_2}{m_2+\beta_2+\gamma_2} \simeq 60\% .$$

Despite the high death rate m_2, the detection probability for HIV_+ TB cases is the same as for HIV_- because of the high value of γ_2 used here. Recall that the target set by the World Health Organization for case detection is 70%. The average durations of disease are

$$\frac{1}{b_1+m_1} \simeq 0.92 \text{ year}, \quad \frac{1}{b_2+m_2} \simeq 0.23 \text{ year} .$$

As a comparison, Corbett et al. [12] estimated the duration of (smear-positive) disease before diagnosis to be 1.15 and 0.17 year for HIV_- and HIV_+ South African gold miners, respectively.

MTB transmission rate k_1. The average TB notification rate in the decade before 1995 in South Africa, i.e. before the rise of HIV prevalence, was about 200 per 100,000 per year (see [74] and [76, p. 184]). This is also a reasonable estimate for the township under study given the data from Table 1. In our model, the TB notification rate when there is no HIV is $\gamma_1 i_1^*$. Using Eq. (13) for i_1^*, it is possible to estimate the only unknown parameter left: k_1. We take $k_1 = 11.4$ per year, which corresponds to a TB notification rate of 203 per 100,000 per year. In the review [50], each HIV_- person with undiagnosed and untreated smear-positive TB was believed to cause 10 to 14 infections per year. If smear-positive cases make half of all cases, an "average" HIV_- TB case would cause 5–7 infections per year. This range is consistent with our estimate $k_1 = 11.4$ per year for the maximum infection rate in a completely susceptible population and with our estimate of nearly 1 year for the average duration of disease $1/(b_1+m_1)$. If for example $x = 60\%$ of the population is already infected with MTB, one active TB case infects about $x\,k_1/(b_1+m_1)$ susceptible people.

HIV parameters d, λ and t_0. Summing the three equations (1)–(3) for HIV_- people and the three equations (4)–(6) for HIV_+ people, setting $X_1 = S_1 + E_1 + I_1$ and $X_2 = S_2 + E_2 + I_2$, and noticing that the prevalence of HIV is $H = X_2/(X_1+X_2)$, we obtain the system

$$\frac{dX_1}{dt} = B - \mu_1 X_1 - f(H)\, H\, X_1 + (\mu_1 - m_1)\, I_1 , \tag{24}$$

$$\frac{dX_2}{dt} = -\mu_2 X_2 + f(H)\, H\, X_1 + (\mu_2 - m_2)\, I_2 . \tag{25}$$

To get a first estimation of d, λ and t_0, we neglect the terms involving I_1 and I_2 (active TB cases form a very small proportion of the population). The resulting system involves only X_1 and X_2, and it is formally the same as system (18) for HIV without TB. Taking

$X_1(t_0) = B/\mu_1$ and $X_2(t_0) = 1$, a good fit to HIV prevalence data from Table 1 is obtained with the parameters $d = 0.7$/year, $\lambda = 5.9$, and the year $t_0 = 1984$ for the beginning of the HIV epidemic. Three parameters are necessary and usually sufficient to fit any set of increasing numbers resembling the logistic curve, as is the case here. Recall that d, λ and t_0 cannot be taken from studies of other areas.

The parameter p_2 for fast progression to TB among HIV$_+$ people. In 1989, Di Perri et al. [19] studied an outbreak of TB among HIV$_+$ people: after the index case, eight people developed TB rapidly and six had a newly positive tuberculin skin test, suggesting that $8/14 \simeq 57\%$ of newly infected HIV$_+$ people develop primary TB disease. In 1992, Daley et al. [16] studied a similar outbreak and found a proportion equal to $11/15 \simeq 73\%$. But it is possible that only large outbreaks are studied, and that outbreaks with less cases of primary TB disease either are not noticed or are not a good subject for publication. A similar bias would occur if we based our estimate for the probability of fast progression to TB among HIV$_-$ people on reports of TB outbreaks such as the one investigated in [33], during which 14 out of 41 newly infected people (34%) developed primary disease. As a result, we prefer to let p_2 vary in order to fit the data concerning the TB notification rate from Table 4. For this purpose, we simulated system (1)–(6) starting from the initial condition

$$S_1(t_0) = S_1^*, \quad E_1(t_0) = E_1^*, \quad I_1(t_0) = I_1^*, \quad S_2(t_0) = 1, \quad E_2(t_0) = 0, \quad I_2(t_0) = 0.$$

Notice at this point that all the parameters in Table 1 have already been fixed except p_2. A relatively good fit was obtained with $p_2 = 30\%$ (plain line in Fig. 2a), i.e., nearly 3 times the value p_1 for HIV$_-$ people. Notice that this value for p_2 is still lower than the ones obtained by studying TB outbreaks among HIV$_+$ people [16,19]. Given the mortality μ_2 previously chosen for HIV$_+$ people, the estimates for a_2 and p_2 correspond to a probability $a_2/(a_2+\mu_2) \simeq 44\%$ of progressing slowly from latent to active TB and to a probability $p_2 + a_2/(a_2 + \mu_2) \simeq 74\%$ of developing active TB after infection by MTB. As a comparison, the percentage of HIV$_+$ people that progress rapidly (either immediately or within 1 year) to active TB after infection by MTB was assumed to be 20% in [29] (no reference), 42% in [59] (no reference), 67% in [10] (citing [16]), and 100% in [70]. In models with a separate compartment for AIDS such as [20], the percentage was assumed to be 7% for early stage HIV (the same as for HIV$_-$ people) and 56% at the AIDS stage (citing [16,19]).

All the parameter values have now been fixed and are summarized in Table 6.

The percentage of HIV$_+$ TB notifications. The dashed line in Fig. 2a shows the contribution of HIV$_+$ people to the TB notification rate, as given by the simulation of the full model (1)–(6) with the parameters from Table 6. The curve passes close to the only data point we have (66% HIV$_+$ among TB notifications in 2005 [75]). This suggests that our parameter estimates are not unreasonable.

Checking the hypothesis used to estimate the HIV parameters d, λ and t_0. One can check if neglecting the terms involving I_1 and I_2 in (24)–(25) was reasonable. Figure 2b shows indeed that the simulation of the full model (1)–(6) with the parameters from

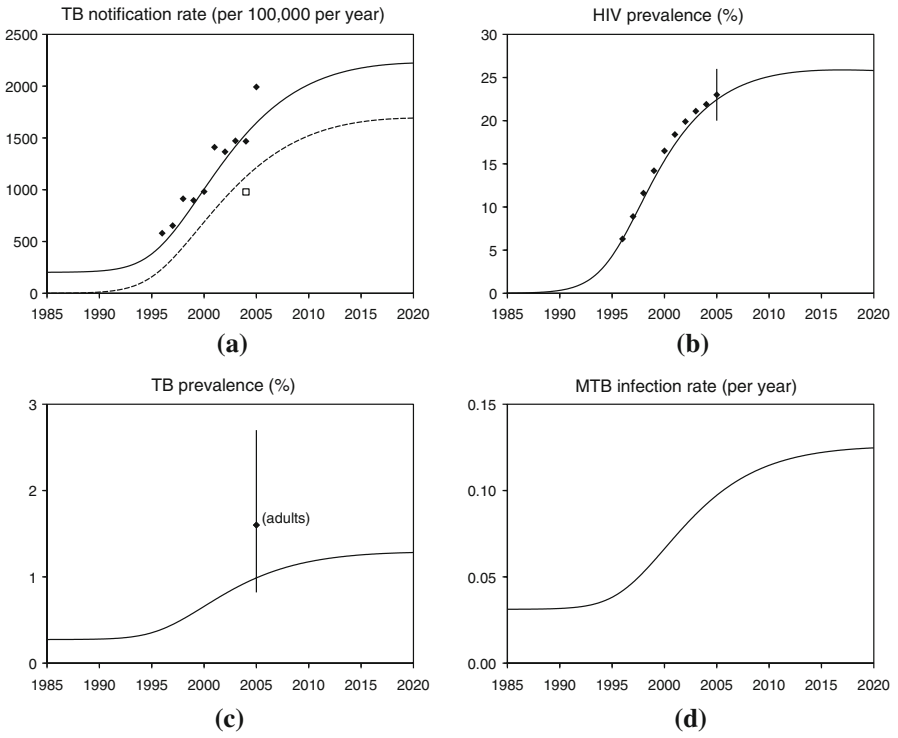

Fig. 2 **a** Data and simulation curve for the TB notification rate. The *dashed curve* shows the contribution of HIV_+ people (only one data point). **b** Data and simulation curve for HIV prevalence. **c** Simulation curve for the prevalence of active TB. The data point with 95% binomial CI corresponds to the prevalence of undiagnosed TB among adults, which is higher than for the whole population. **d** MTB infection rate

Table 6 Numerical values for the parameters of the model

	HIV_-			HIV_+		
Mortality	μ_1	0.02/year	[10]	μ_2	0.1/year	[10]
TB mortality	m_1	0.25/year	[13]	m_2	1.6/year	[13]
MTB infections	k_1	11.4/year	Fit	k_2	$k_1 \times 2/3$	[10]
Fast route	p_1	11%	[68]	p_2	30%	Fit
Slow route	a_1	0.0003/year	[68]	a_2	0.08/year	[3,61,62]
Reinfection	q_1	0.7 p_1	[68]	q_2	0.75 p_2	[10]
Recovery	β_1	0.25/year	[13]	β_2	0.4/year	[13]
Detection	γ_1	0.74/year	[12,75]	γ_2	3.0/year	[12,75]
Treatment	ε_1	80%	[75]	ε_2	80%	[75]
Births	B	200/year	[35]			
Contact rate	d	0.7/year	Fit			
Prevention	λ	5.9	Fit			
Initial year	t_0	1984	Fit			

Table 6 still gives a reasonably good fit to the HIV data. Notice that the data point with a 95% binomial confidence interval in Fig. 2b corresponds to the 23% HIV prevalence (174/762) in the sample population taken in the year 2005 [75].

Other curves. Figure 2c shows the prevalence of undiagnosed TB computed by simulating the full model (1)–(6) with the parameters from Table 6. The data point with a 95% binomial confidence interval corresponds to the prevalence of undiagnosed TB among adults (12/762), which should be higher than for the whole population. Hence, Fig. 2c also suggests that our parameter estimates are not unreasonable. Finally, we also show the MTB infection rate (Fig. 2d), for which data has been collected recently but has not yet been published. Recall, however, that our choice for the TB detection rates γ_1 and γ_2 was influenced by the knowledge that MTB infection rate had not risen as steeply as the TB notification rate.

7 Sensitivity of steady states with respect to changes in parameter values

All the parameter having been fixed or estimated (Table 6), we look at the numerical results following from the mathematical formulas of Sect. 4 for the steady states. First, the disease-free steady state with no HIV and no TB is $S_1^0 = 10,000$. We also obtain

$$R_0^{\mathrm{TB}} \simeq 1.3\,, \quad R_0^{\mathrm{HIV}} \simeq 7.0\,, \quad r_0^{\mathrm{TB}} \simeq 1.7\,, \quad r_0^{\mathrm{HIV}} \simeq 5.8.$$

The estimate $R_0^{\mathrm{TB}} \simeq 1.3$ is close to the range 0.6–1.2 mentioned in the review [50]. Using national HIV prevalence data from antenatal clinics, Williams et al. [71,73] found a similar result for R_0^{HIV}, namely 6.4 ± 1.6. Notice also that $r_0^{\mathrm{TB}} > R_0^{\mathrm{TB}}$: an "average" person newly infected with MTB will produce more secondary cases if introduced in a TB-free population where HIV is endemic than if introduced in a completely disease-free population. This is mainly because this "average" person is likely to be HIV_+, so its probability of progressing to active TB and of infecting other people is high (this depends on the numerical values of several parameters, including a_2, but not on the structure of the model). Finally, r_0^{HIV} is less than R_0^{HIV} as explained in Sect. 4.3. In some sense, TB slows down the HIV epidemic.

In the following subsections, we study the sensitivity of the different steady states with respect to the most important parameters of the model, namely those that enter in the nonlinear terms of system (1)–(6): the TB transmission rates k_1 and k_2, the reinfection parameters q_1 and q_2, and the parameters d and λ for HIV.

7.1 A global look at steady states in the (k_1, d) parameter space

Figure 3 shows a bifurcation diagram of the steady states in the (k_1, d) parameter space using the numerical values from Table 6 except of course for k_1 and d and assuming that the ratio k_2/k_1 is fixed. The black dot near the 2,000 per 100,000 per year level curve for the TB notification rate corresponds to the values of k_1 and d in Table 6. The boundaries between the four domains of the bifurcation diagram ("disease-free", "HIV", "TB", and "HIV + TB") are obtained by the solving the four

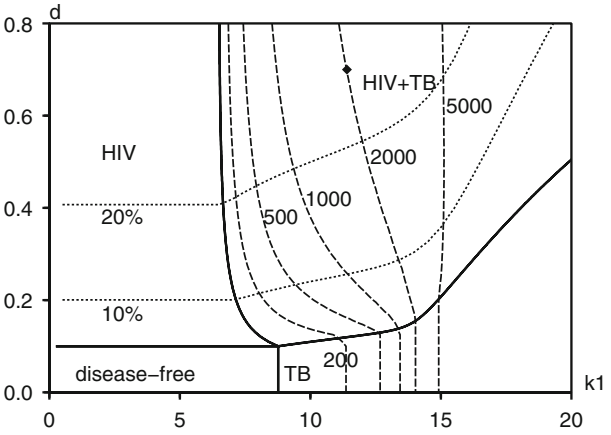

Fig. 3 Bifurcation diagram in the (k_1, d) phase plane and level curves of the steady state TB notification rate (*dashed lines*, 500 stands for 500 per 100,000 per year) and of the steady state prevalence of HIV (*dotted lines*)

equations $R_0^{\mathrm{HIV}} = 1$, $r_0^{\mathrm{HIV}} = 1$, $R_0^{\mathrm{TB}} = 1$ and $r_0^{\mathrm{TB}} = 1$ with respect to k_1 and d. Since R_0^{HIV} does not depend on k_1 and R_0^{TB} does not depend on d, the line $R_0^{\mathrm{HIV}} = 1$ is horizontal and the line $R_0^{\mathrm{TB}} = 1$ is vertical. The line $r_0^{\mathrm{HIV}} = 1$ separates "TB" from "HIV+TB". The line $r_0^{\mathrm{TB}} = 1$ separates "HIV" from "HIV+TB".

Notice in Fig. 3 how the level curves for the TB notification rate are distorted as they cross the line $r_0^{\mathrm{HIV}} = 1$ from the area labeled "TB" to the area labeled "HIV+TB". Notification rates near the "reinfection threshold" mentioned in Sect. 4.1 (for example the 1,000 and 2,000 level curves), which seemed totally unrealistic in the absence of HIV, occur now for smaller values of the transmission rate k_1 if HIV prevalence is high enough. With $k_1 = 11.4$ per year as in Table 6, the steady state TB notification rate increases from 200 to 2,000 per 100,000 per year as HIV prevalence increases from 0 to about 25%.

7.2 The steady state with TB but no HIV

The steady state with TB but no HIV is shown in the left part of Table 7. This is the steady state used as the initial condition in the simulations for the complete model with both HIV and TB. Notice that "Styblo's ratio" (for both smear-positive and smear-negative cases) is about 100, the value commonly admitted for HIV$_-$ populations. Figure 4 shows how the TB steady state changes if we let k_1 and q_1 vary. The level curves of the steady state TB notification rate are also drawn. The black dot on the 200 per 100,000 per year level curve corresponds to the numerical values of k_1 and q_1 in Table 6. A similar "hand-drawn" picture without the level curves appears in [24, Fig. 3]. Some level curves cross each other in the zone of Fig. 4 with two positive solutions. They are the projections on the plane of level curves on a three-dimensional surface with a fold.

Table 7 Characteristics of the endemic steady state with TB only (Sect. 4.1) and with TB and HIV (Sect. 4.3)

	TB only	TB and HIV
Total population	9,695	4,161
Susceptible (HIV−) S_1	3,904	1,112
Latent TB (HIV−) E_1	5,764	2,029
Active TB (HIV−) I_1	27	30
Susceptible (HIV+) S_2	0	208
Latent TB (HIV+) E_2	0	762
Active TB (HIV+) I_2	0	20
HIV prevalence	0	24%
TB notification rate/100,000 per year	203	2,005
HIV_+ TB notifications	0	74%
MTB prevalence	60%	68%
TB prevalence	0.27%	1.2%
MTB infection rate/year	3.1%	12%
TB incidence rate/100,000 per year	299	2,945
"Styblo's ratio"	96	222
Reactivation (among TB cases)	6%	50%
Reinfection (among TB cases)	48%	32%
Primary progression (among TB cases)	46%	18%

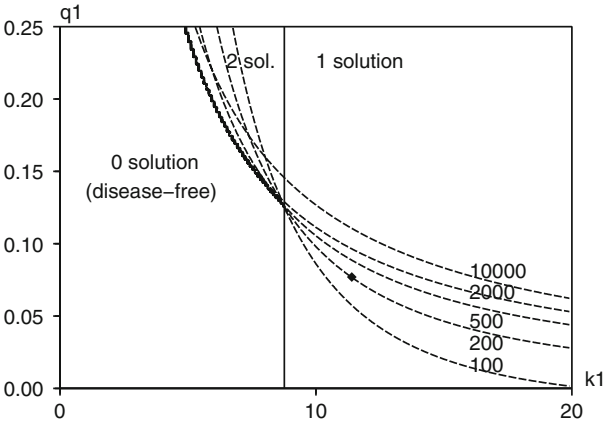

Fig. 4 TB only. Number of positive steady solutions of (7)–(9) in the parameter space (k_1, q_1). There is only one such solution to the *right of the vertical line* and either 0 or 2 to the left. The level curves of the steady state TB notification rate (per 100,000 per year) are also shown (*dashed lines*). Some level curves cross each other in the area with two solutions

Numerically, the threshold above which two positive steady states can exist is $q_1^* \simeq 12.5\%$, while we have chosen $q_1 = 7.7\%$. The other threshold separating the area where there are either 0 or 2 positive solutions from the area where there is 1 solution is $k_1^* \simeq 8.8$ per year, while our estimate is $k_1 = 11.4$ per year. The level curves in Fig. 4 show that the steady state TB notification rate is sensitive to variations

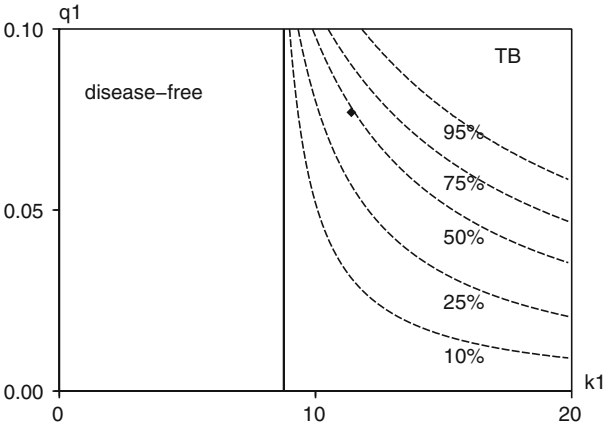

Fig. 5 TB only. Level curves of the percentage of new TB cases due to reinfection in the parameter space (k_1, q_1)

in q_1. This means that our estimation in Sect. 6 of the parameter k_1 (q_1 being fixed) should be considered with caution.

As noticed in [26,64] for a slightly different model, the dependence of the TB notification rate with respect to q_1 is even greater above a certain "reinfection threshold" (see the remarks at the end of the appendix and [7,27] for a dispute over this terminology). Notice for example how close the 2,000- and 10,000-level curves in Fig. 4 are. However, notification rates close to 2,000 per 100,000 per year as in the township under study here (with HIV) are already among the highest ever reported in a community. So it seems unlikely that TB parameter values for a community without HIV can be above the "reinfection threshold" as suggested in [26,64].

The percentage of new TB cases due to reinfection is shown as a function of k_1 and q_1 in Fig. 5. Notice that the vertical scale is not the same as in Fig. 4. A black dot indicates the numerical values for k_1 and q_1 from Table 6 that correspond to 45% of reinfection among new TB cases.

7.3 The steady state with HIV but no TB

In our model, the steady state with HIV but no TB is given by $\widehat{S}_1 \simeq 3{,}450$, $\widehat{S}_2 \simeq 1{,}310$, and $\widehat{H} \simeq 28\%$. The total equilibrium population with HIV is less than half of the disease-free steady state S_1^0, because we consider cohorts of B births per year and not the real total population with its inflows and outflows. The sensitivity of the steady state prevalence of HIV with respect to variations in λ and d are shown in Fig. 6. The black dot in the top right corner corresponds to the numerical values for λ and d from Table 6.

7.4 The steady state with both HIV and TB

The endemic steady state with both HIV and TB can be computed numerically. Its characteristics are shown in the right part of Table 7, and are those that would have

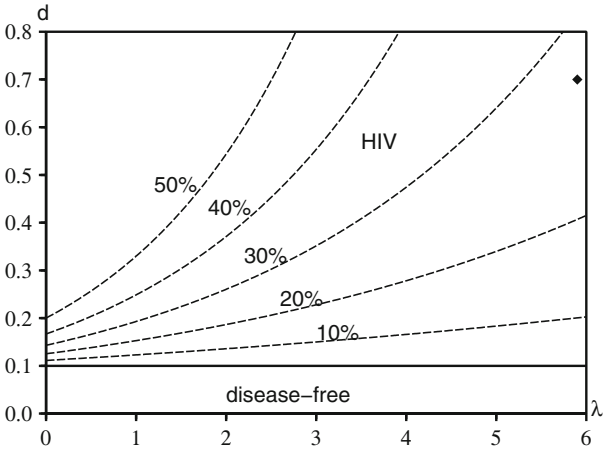

Fig. 6 HIV only. Bifurcation diagram in (λ, d) parameter space and level curves of the steady state HIV prevalence

been obtained if the simulations in Fig. 2 had been continued until reaching a steady state. Compared to the endemic steady state with TB only (left part of Table 7), the TB notification rate and the TB incidence have been multiplied by 10, the TB prevalence and the MTB infection rate by 4. The prevalence of MTB has only slightly increased. Reactivation has become the most important way of progression to active TB. The sensitivity of the steady state with both HIV and TB with respect to variations in k_1 or d was already shown in Fig. 3.

The question of whether the HIV-associated TB epidemic leads to an increased risk of MTB infection in the population (and in particular among HIV$_-$ people) has been a subject of discussion in the medical literature [22,38,74]. Egwaga et al. [22] found that the risk of infection had decreased between 1983 and 2003 in Tanzania among children aged 6–14 years despite the increase of HIV-associated TB incidence in the population. Similarly, Corbett et al. [11] did not find any increase in TB incidence among HIV$_-$ South African gold miners. On the contrary, Lawn and Wood [38] noticed that in the South African township under study here, the TB notification rate among HIV$_-$ adolescents had dramatically increased in recent years, so the risk of infection must have also increased. This is also what happens in our model: the MTB infection rate is multiplied by 4 as HIV prevalence increases from 0 to a steady state at 24%.

8 Control measures

8.1 Increasing condom use

Notice from (20)–(21) that r_0^{HIV} is proportional to $f(0) = d$ (the maximum transmission rate of HIV) and that r_0^{TB} is proportional to k_1 (the maximum transmission rate of TB), the ratio k_2/k_1 being fixed. So if d is divided by at least r_0^{HIV} (the other parameters being kept constant), the new r_0^{HIV} will be less than 1 and HIV will disappear

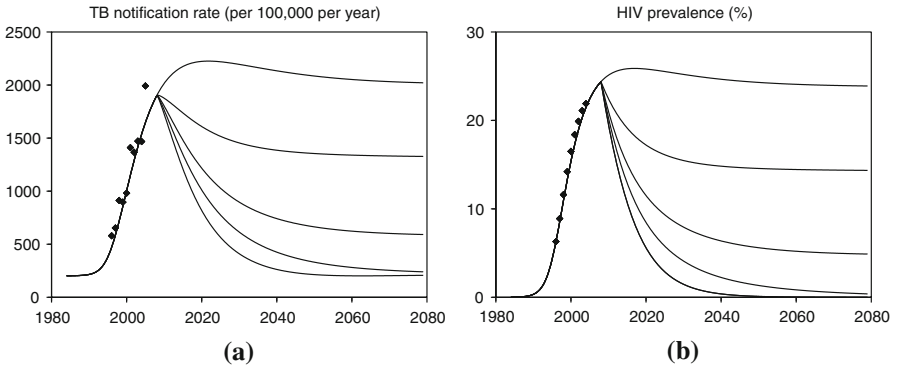

Fig. 7 Assuming that a sudden increase in condom use occurs in the year 2008 (the maximum transmission rate d becomes d'). The different curves correspond from *top* to *bottom* to $d' = d$, $d' = d/2$, $d' = d/4$, $d' = d/8$ and $d' = 0$. **a** TB notification rate. **b** Prevalence of HIV

in the long run. Similarly, if k_1 is divided by at least r_0^{TB}, the new r_0^{TB} will be less than 1 and TB will disappear in the long run. In Fig. 3, starting from the black dot representing the real situation, one can check that if k_1 is divided by $r_0^{\mathrm{TB}} \simeq 1.7$, we move from the area labeled "HIV+TB" to the area with HIV only. If d is divided by $r_0^{\mathrm{HIV}} \simeq 5.8$, we move from the area "HIV+TB" to the area with TB only. To decrease the parameter k_1, living conditions should be changed. The parameter d decreases if more condoms are used.

Figure 7 shows the impact of a sudden decrease of the HIV transmission rate d, from an initial value d to a new value d', on the prevalence of HIV (Fig. 7b) and also indirectly on the TB notification rate (Fig. 7a). The impact is obviously a monotonic function of d', as one would expect. We can check on these simulations that HIV disappears in the long run only if $d' < d/r_0^{\mathrm{HIV}} \simeq d/5.8$ (that is in the two simulations $d' = d/8$ and $d' = 0$ but not when $d' = d$, $d' = d/2$ or $d' = d/4$). If so, the TB notification rate returns finally to its level of the beginning of the 1980s, before HIV was introduced. The asymptotic TB notification rate and prevalence of HIV can also be read directly by looking at the level curves in Fig. 3, but the speed at which these steady states are reached can only be seen in Fig. 7.

In the absence of intervention (Fig. 7, $d' = d$), notice in the simulation that the peak for the prevalence of HIV occurs at about the same time as the peak for the TB notification rate. This does not seem incompatible with the data from Kenya [15, Fig. 1], which suggested a delay of several years between the rise of HIV and the rise of TB. One reason for such a delay may be that active TB tends to appear with a higher frequency in late stages of HIV infection. Notice, however, that the data from the South African township does not show any clear delay. Our model with just two compartments for HIV (HIV_- and HIV_+) could fit reasonably well the data for both TB and HIV although it does not include any delay. The background environments in the Kenyan study and in the South African township are probably quite different since for similar levels of HIV prevalence, the TB notification rate in Kenya is only one third of what it is in the South African township.

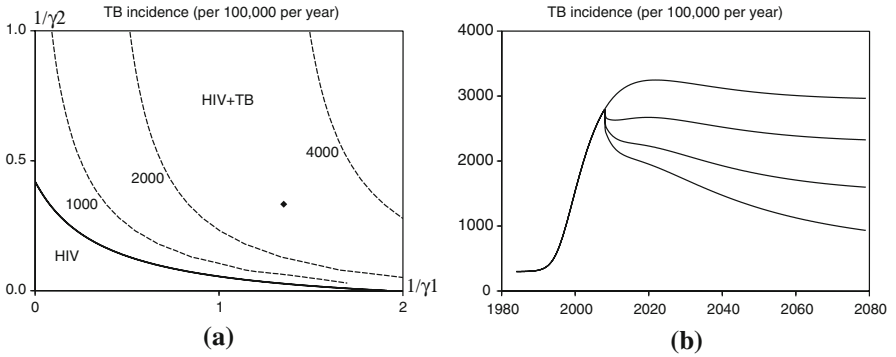

Fig. 8 Increasing the TB detection rate: **a** bifurcation diagram in the phase plane $(1/\gamma_1, 1/\gamma_2)$ and level curves of the TB incidence rate. **b** TB incidence rate as a function of time, assuming that a sudden increase in the TB detection rate for HIV_+ people occurs in the year 2008. The parameter γ_2 is replaced from top to bottom by γ_2, $2\gamma_2$, $4\gamma_2$ or $8\gamma_2$

Finally, one should mention that large scale prevention campaigns promoting condom use on television started at the end of the year 2006 in South Africa. In principle, one might be able to get data concerning the number of condoms purchased by the population of the township and check if behaviors have changed.

8.2 Increasing TB detection

Now we consider the possibility of increasing the TB detection rates γ_1 and γ_2 and increasing the probabilities ε_1 and ε_2 of successful treatment. For the township, this could be achieved by actively searching for TB cases instead of waiting for them to come to the TB clinic. Notice that the four parameters above enter the system of differential equations (1)–(6) only through the combination $b_1 = \beta_1 + \gamma_1 \varepsilon_1$ and $b_2 = \beta_2 + \gamma_2 \varepsilon_2$. However, we have to be a little careful because γ_1 and γ_2 enter in the expression of the TB notification rate (through $\gamma_1 I_1 + \gamma_2 I_2$). If γ_1 or γ_2 increase, the steady state TB notification rate may increase and will start decreasing only if γ_1 or γ_2 are high enough. It is therefore not suitable to use the TB notification rate as a measure of the severity of the situation when the detection rate changes. Instead, we will use the TB incidence rate.

Figure 8a shows the bifurcation diagram and the level curves of the steady state TB incidence rate in the parameter space $(1/\gamma_1, 1/\gamma_2)$, using the numerical values from Table 6 for the other parameters. Since γ_1 and γ_2 do not enter in the formula for R_0^{HIV}, the HIV-endemic steady state is always there. The question is: when can it be invaded by TB? This is given by the equation $r_0^{\text{TB}} = 1$, an implicit equation for γ_1 and γ_2 shown by the thick black line separating "HIV" from "HIV+TB" in the bottom left corner of Fig. 8a. The values for γ_1 and γ_2 in Table 6 correspond to the black dot shown in the figure.

Figure 8b shows the impact of a sudden increase in the TB detection rate γ_2 for HIV_+ people. This has almost no impact on the curve for the prevalence of HIV so we

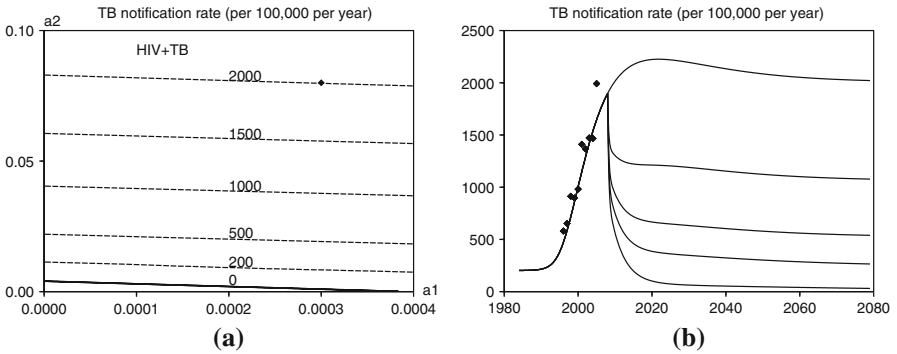

Fig. 9 Isoniazid preventive therapy for HIV_+ people (decreasing a_2): **a** bifurcation diagram in the phase plane (a_1, a_2) and level curves of the steady state TB notification rate. **b** TB notification rate as a function of time. Assumption: starting in 2008, a_2 is replaced from *top* to *bottom* by a_2, $a_2/2$, $a_2/4$, $a_2/8$ or 0

do not show it. Of course, the TB incidence decreases monotonically as the detection rate increases.

8.3 Isoniazid preventive therapy

This control measure reduces the parameter a_1 if used for HIV_- people and the parameter a_2 if used for HIV_+ people. These parameters do not enter in the formula for R_0^{HIV}, so HIV is always present and the question is whether TB can be stopped in the presence of HIV: the threshold is given by $r_0^{TB} = 1$ (the corresponding curve appears in the bottom of Fig. 9a as the level set 0). The level curves of the TB notification rate in the diagram (a_1, a_2) are almost horizontal (Fig. 9a). So preventive therapy used for HIV_+ people (reducing a_2) has a much greater impact on the TB notification rate than if used for HIV_- people (reducing a_1). The values for a_1 and a_2 in Table 6 correspond to the black dot in Fig. 9a close to the 2,000 per 100,000 per year level curve.

Figure 9b shows the impact of a sudden decrease of the progression rate a_2 for HIV_+ people due to isoniazid preventive therapy. Since this has almost no impact on the curve for the prevalence of HIV, we do not show it. The steady state TB notification rate decreases monotonically as a_2 decreases.

8.4 ART

We consider now the possible impact of antiretroviral treatment (ART), more precisely, of highly active antiretroviral treatment (HAART). ART reduces viral load and therefore also the transmission parameter d for HIV. But ART also increases the life expectancy of HIV_+ people by decreasing μ_2 and m_2 (of course not below the natural mortality μ_1), a fact which increases the number of people living with HIV and enhances further transmission of HIV. These two effects are antagonistic, so the impact on HIV at the population level is not obvious and depends very much on how much each of the three parameters involved changes with ART. Besides, ART reduces the

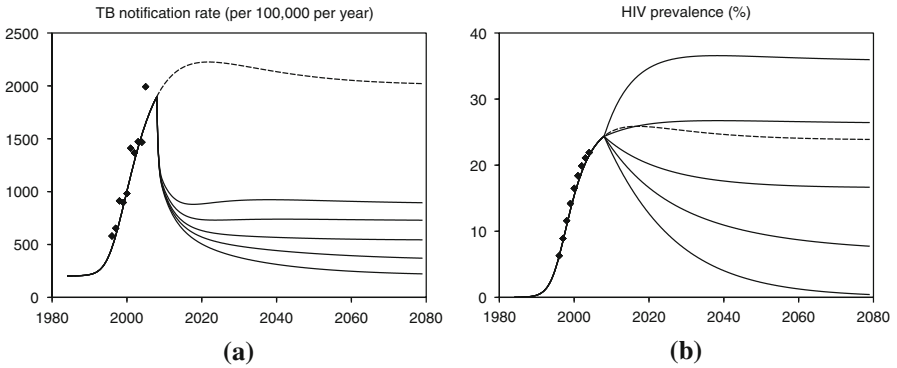

Fig. 10 ART. *a* TB notification rate as a function of time. *b* HIV prevalence as a function of time. Assumption: 100% of HIV_+ people are put on ART starting in 2008. The parameter μ_2 is replaced by $\mu_2/2$, the parameter m_2 by $m_2/2$, the parameter a_2 by $a_2/5$, while the parameter d is replaced either by d, $d/2$, $d/4$, $d/8$, or 0 (from *top* to *bottom*). The *dashed line* shows the case without intervention

average rate a_2 at which coinfected people develop active TB, though not to the same level a_1 as HIV_- MTB-infected people [3,34,36,39], and even if "immune reconstitution disease" may on the contrary increase a_2 during the first few months of ART treatment [41]. Again, the effect of ART on TB is not clear because HIV_+ people under ART live longer. Quantitatively, ART was shown in studies in South Africa [3,36] and Brazil [45] to reduce a_2 by 80% , i.e., to divide a_2 by 5. With $a_2 = 0.08$ per year without ART, this gives $a_2 = 0.016$ per year under ART. This is still 50 times higher than the parameter $a_1 = 0.0003$ per year for HIV_- people. Another report [37] mentioned a risk 5 to 10 times higher after 3 years of ART compared to HIV_- people. We assume furthermore that:

- μ_2 is divided by 2 under ART, giving $\mu_2 = 0.05$ per year instead of 0.1 per year, still higher than the natural mortality $\mu_1 = 0.02$ per year; the new life expectancy for HIV_+ people under ART is 20 years;
- m_2 is divided by 2 under ART (the new m_2 is 0.8 per year, compared to $m_1 = 0.25$ per year).

We determined what would happen under various assumptions for the HIV transmission parameter d (Fig. 10), assuming that 100% of HIV_+ people are put immediately on ART starting in 2008, independently of their CD4 cell count (a variable which is not included in our model anyway). This hypothesis is of course quite optimistic and would require the entire adult population of the township to be tested for HIV. Notice also that in practice and in more realistic models, some factors may favour a delayed initiation of ART [40]. With our choice of parameter values, we find a decrease for the TB notification rate even in the extreme case where ART would have no influence on the parameter d (Fig. 10a, top plain curve), a case which would lead to an increase in HIV prevalence (Fig. 10b, top plain curve). The cases where $d' = d/2$ and $d' = d/4$ are probably more realistic, since we expect HIV transmission to decrease if everybody knows his/her HIV status. In such cases (and assuming that the other parameters values have been correctly chosen), HIV prevalence would decrease for

$d' = d/4$ but not for $d' = d/2$ (Fig. 10b, second and third plain curves from the top). So the future of HIV prevalence under ART is uncertain. But with a progression rate a_2 reduced by 80% and a life expectancy $1/\mu_2$ multiplied by 2, it seems that ART would dramatically decrease the TB notification rate even though the new reactivation rate for HIV_+ people would still be several times higher than the one for HIV_- people.

ART has become increasingly available in the township since 2006. But it is still too early to understand what its impact on both the HIV and TB epidemics has really been.

9 Conclusion

This work is a first attempt to model the simultaneous HIV and TB epidemics in a township near Cape Town, South Africa, for which a considerable amount of data is available. The main difficulty is due to the large number of parameters in the model, which makes estimations and mathematical analysis a little difficult. Keeping this number as small as possible, we have been able to provide a fairly complete picture of the model with HIV or TB only.

Backward bifurcation for our model with TB only was shown to be impossible under realistic parameter values because MTB infection provides a certain degree of protection against a fast progression to active TB after reinfection ($q_1 \leq p_1$). To our knowledge, no TB model has ever been shown to exhibit backward bifurcation under realistic parameter values despite all the emphasis put on this possibility in the more mathematically oriented articles on TB [24,48,63]. On this point, we agree with Lipsitch and Murray [42] and with Singer and Kirschner [64].

For the full model (1)–(6) with both HIV and TB, we analyzed the linear stability of the endemic steady states with either TB or HIV. We conjectured that there was still no backward bifurcation for (1)–(6) when $q_1 \leq p_1$. Verifying this point can be considered as an open mathematical problem. We used numerical methods to draw bifurcation diagrams with level curves for HIV prevalence and TB notification rate. The most interesting diagram is Fig. 3. It shows how for a fixed value of the TB transmission rate k_1, the steady state TB notification rate can increase from 200 to 2,000 per 100,000 per year as HIV prevalence increases from 0 to around 25%.

Gomes et al. [26–28] have emphasized the role of a "reinfection threshold" in TB models without HIV. In [26, Fig. 3] or [28, Fig. 2], the "reinfection threshold" occurred when approximately 1% of the population had active TB. In the South African township, $12/762 \simeq 1.6\%$ of a sample population was found to have undiagnosed active TB in 2005. This could suggest that there are indeed populations above the "reinfection threshold". However, one can wonder if populations with endemic TB but with low HIV prevalence can really reach 1% prevalence of active TB. In other words, one can wonder if such populations are not systematically below the "reinfection threshold", and if the "reinfection threshold" can still be used to explain problems in TB epidemiology such as the inefficiency of BCG vaccination [26]. Even in populations with high HIV prevalence, the "reinfection threshold" does not seem to play such an important role. Table 7 suggests that the percentage of reinfection with HIV and TB is less than with TB only.

Among the control measures studied, most have an obvious positive impact in controlling the HIV or TB epidemics: this is the case for condom use, increased TB detection and preventive treatment. The situation for ART is more complicated. However, although the future for the prevalence of HIV is uncertain, it seems that a generalized access to ART would lead to a significant decrease of the TB notification rate. Indeed, ART has been shown both in South Africa and in Brazil to reduce the progression rate from latent to active TB by about 80%, i.e., to divide it by a factor 5. If HIV_+ people under ART live approximately 2 times longer than the average 10-year survival time of HIV_+ people with no access to ART, then one could expect the TB incidence to be multiplied by $0.4 = 2/5$, i.e. to be reduced by 60%. This simple argument may be wrong if ART increases the prevalence of HIV and indirectly the incidence of TB. Our numerical results suggest that this is not so. Even in the worst scenario we considered where HIV prevalence increased as a result of ART (top plain curve in Fig. 10b), the TB notification rate decreased considerably (top plain curve in Fig. 10a).

It is difficult to guess if the observations drawn from this model with parameters adapted to this particular South African township are still valid for less crowded areas with high HIV prevalence. One could try to use the same model and adapt the parameters to data from such areas. Unfortunately, reliable data on both HIV and TB is still rare. For example, HIV prevalence in Zimbabwe has probably not been estimated as regularly as [32, Fig. 5] might suggest (J. Hargrove, personal communication).

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Appendix

Let us call i_1^+ and i_1^- the two (possibly complex) roots of Eq. (13), which for convenience we rewrite as

$$\left(i_1^*\right)^2 + c_1\, i_1^* + c_0 = 0\,. \tag{26}$$

We are only interested in positive roots, which are the ones with a biological meaning. The existence of positive roots depends in particular on the signs of c_1 and c_0. We need to distinguish several cases:

- The case $k_1 > k_1^*$. Since $c_0 < 0$, it follows that $i_1^+ \times i_1^- < 0$. This case occurs only if $i_1^+ > 0$ and $i_1^- < 0$. So there is only one positive solution of (13).
- The case where $0 < k_1 < k_1^*$ and $0 < k_1 < \widetilde{k}_1(q_1)$, the new parameter $\widetilde{k}_1(q_1)$ being defined by

$$\widetilde{k}_1(q_1) = \frac{a_1 + b_1 + (1-p_1)\,m_1 + p_1\mu_1}{q_1} + m_1\,. \tag{27}$$

In this case we have $c_1 > 0$, so $i_1^+ + i_1^- < 0$. But $i_1^+ \times i_1^- > 0$, so this case occurs only if i_1^+ and i_1^- are both negative or if i_1^+ and i_1^- are complex conjugates with a negative real part. So there is no positive solution of (13). Notice that $\widetilde{k}_1(q_1) < k_1^*$ only when $q_1 > q_1^*$, the definition (17) of q_1^* having been precisely chosen for this purpose.

- The case where $0 < k_1 < k_1^*$ and $k_1 > \widetilde{k}_1(q_1)$ (which implies that $q_1 > q_1^*$). Let Δ be the discriminant of (13). Let us emphasize its dependence on k_1 by writing $\Delta(k_1)$ while we keep q_1 fixed. From (13), we see that $\Delta(k_1)$ is a quadratic polynomial with respect to $1/k_1$, so the equation $\Delta(k_1) = 0$ has at most two roots in the half-line $k_1 > 0$. Since $\Delta(k_1) = c_1^2 - 4\,c_0$, since $c_1 = 0$ when $k_1 = \widetilde{k}_1(q_1)$ and $c_0 = 0$ when $k_1 = k_1^*$, it follows that $\Delta(\widetilde{k}_1(q_1)) < 0$ and $\Delta(k_1^*) > 0$. So the equation $\Delta(k_1) = 0$ has at least one root in the interval $(\widetilde{k}_1(q_1), k_1^*)$, and it cannot have two roots since the function $k_1 \mapsto \Delta(k_1)$ has to change sign an odd number of times in this interval. Call $\widehat{k}_1(q_1)$ the unique root. Then $\Delta(k_1) < 0$ for $\widetilde{k}_1(q_1) < k_1 < \widehat{k}_1(q_1)$: in this case, Eq. (13) has no real solution. For $\widehat{k}_1(q_1) < k_1 < k_1^*$, we have $\Delta(k_1) > 0$, $c_0 = i_1^+ \times i_1^- > 0$, and $c_1 = -(i_1^+ + i_1^-) < 0$: in this case, Eq. (13) has two positive solutions.

We still have to check that if (13) has a positive root i_1^*, then all the components of the triplet (S_1^*, E_1^*, I_1^*) given by (14)–(15) are positive. For this purpose, it is enough to show that $s_1^* > 0$ and $e_1^* > 0$. But adding (8) and (9), we find that $s_1^* = (\mu_1 e_1^* + m_1 i_1^*)/(k_1 i_1^*)$. So it is enough to show just that $e_1^* > 0$, i.e., $i_1^* < 1 - m_1/k_1$. Notice first from (27) that if (13) has a positive root i_1^*, then $k_1 > m_1$ necessarily holds. Let us call $\chi(i_1)$ the quadratic polynomial on the left of (13), so that $\chi(i_1^*) = 0$. Simple computations show that

$$\chi(1 - m_1/k_1) = \frac{[b_1 + (1-p_1)\,m_1]\,(k_1 - m_1 + \mu_1)}{q_1 k_1^2} > 0\,,$$
$$\chi'(1 - m_1/k_1) = 1 - \frac{m_1}{k_1} + \frac{a_1 + b_1 + (1-p_1)m_1 + p_1\mu_1}{q_1 k_1} > 0\,,$$

which imply that $i_1^* < 1 - m_1/k_1$. Q.E.D.

Finally, let us add a short comment on the notion of "reinfection threshold" [7,26,27] for our model in the case $k_1 > k_1^*$ (which is equivalent to $R_0^{\mathrm{TB}} > 1$ and also to $c_0 < 0$). The unique positive solution of (26) is

$$i_1^* = \left[-c_1 + \sqrt{c_1^2 - 4\,c_0}\right]/2\,.$$

Consider the special case where $4|c_0|/c_1^2$ is small. This case turns out to be satisfied numerically in the whole area $k_1 > k_1^*$ of Fig. 4 except in a very narrow strip around the curve $c_1 = 0$, whose equation can be rewritten as

$$q_1 = Q_1(k_1) = \frac{a_1 + b_1 + (1-p_1)m_1 + p_1\mu_1}{k_1 - m_1}\,.$$

Then one can show that

$$i_1^* \simeq \begin{cases} -c_0/c_1 & \text{if } c_1 > 0\,, \\ -c_1 & \text{if } c_1 < 0\,. \end{cases}$$

The approximation for $c_1 > 0$ corresponds to neglecting the quadratic term in Eq. (26), while the approximation for $c_1 < 0$ corresponds to neglecting the constant term. Notice that because $4|c_0|/c_1^2$ was assumed to be small, the expression $-c_0/c_1$ is much smaller than $-c_1$. So the prevalence of TB is high when $q_1 > Q_1(k_1)$ and much smaller when $q_1 < Q_1(k_1)$. But as pointed out in [7,27] for a slightly different model, the "reinfection threshold" we have just obtained is not very well defined from a mathematical point of view (a similar situation happens e.g. when defining the width of "boundary layers" in physics).

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