Supplementary material

Model description

Demography

We used an individual-based model, written in Netlogo 6.0.1[1]. A constant population size of *pop_size* individuals was simulated, with each simulated individual being replaced at death by a new individual with the same HIV status. A lifespan of *max_age* years was simulated, with no mortality during that time other than mortality due to tuberculosis. The population was homogeneous across different age groups, with a paediatric population not being explicitly simulated.

Disease states

Figure S1 shows the simulated tuberculosis natural history in the model, and transitions between stages. Simulated individuals could be uninfected with *Mycobacterium tuberculosis* (*Mtb*), have a latent infection, have smear-negative disease, have smear-positive disease, or be receiving tuberculosis treatment.

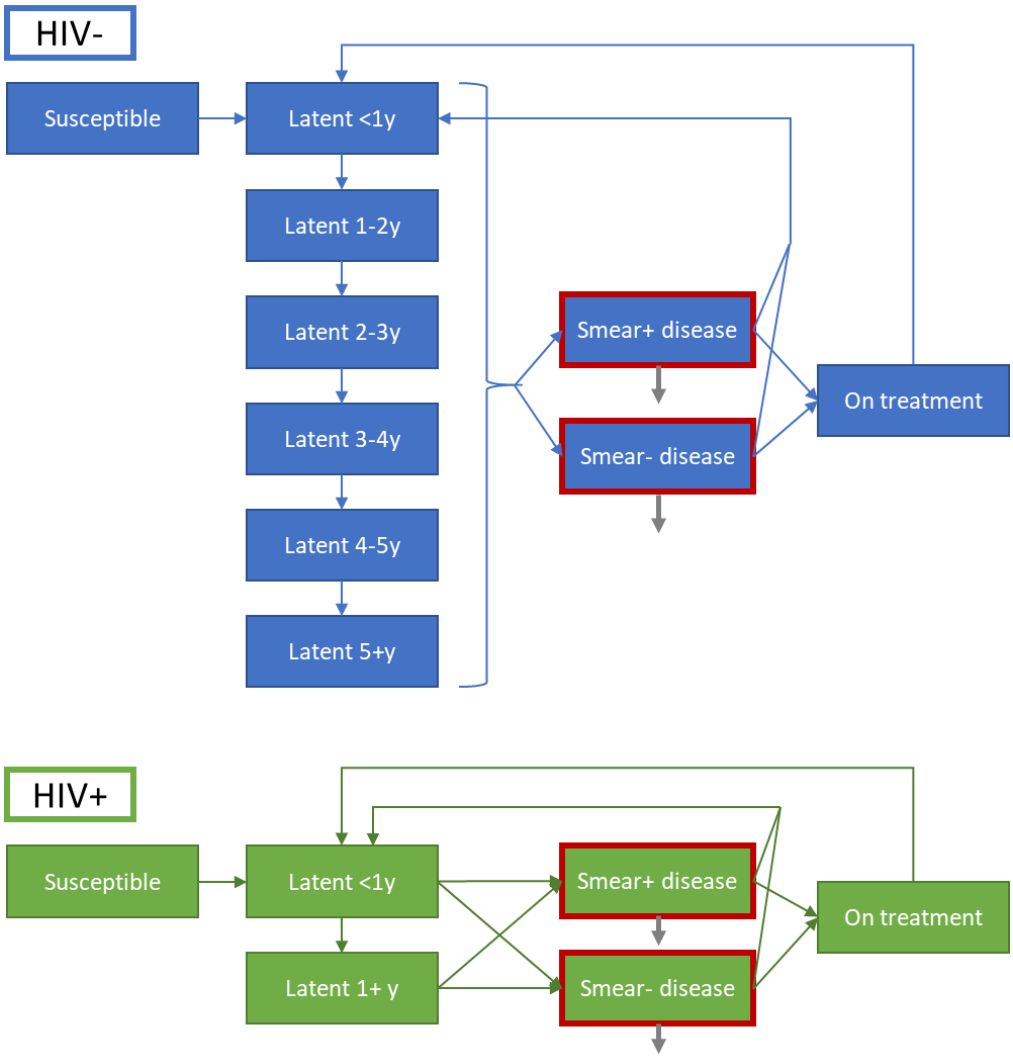

Figure S1. Simulated tuberculosis natural history. Blue and green boxes show the natural history for HIV-negative and HIV-positive individuals respectively. Grey arrows indicate tuberculosis mortality. Boxes with red outlines indicate stages where contact in clinics is increased if $RR_{TB} > 1$. Green boxes indicate stages where contact in clinics is increased if $RR_{HIV} > 1$.

Disease progression

The rate of developing disease in the model depended on an individual's time since infection (or self-cure or treatment end), and their HIV status. For HIV-negative individuals, the rate was highest in the first year following infection (*develop_tb_y1_rate_HIV0),* and decreased each subsequent year (*develop_tb_y2_rate_HIV0, develop_tb_y3_rate_HIV0*, *develop_tb_y4_rate_HIV0*,

develop_tb_y5_rate_HIV0), before having a constant value at six or more years following infection (*develop_tb_reactivation_rate_HIV0*). In HIV-positive people the risk of developing disease following infection was highest in the first year (*1 - (1 - develop_tb_reactivation_rate_HIV1) ^ increased_develop_tb_y1_rate_HIV1*), and the same in all subsequent years (*develop_tb_reactivation_rate_HIV1*).

A constant rate of starting tuberculosis treatment was simulated, and the rate varied by HIV status (*treatment_rate_HIV0* and *treatment_rate_HIV1* in HIV-negative and HIV-positive people respectively). Treatment lasted six months in the model, and no treatment interruptions, treatment failure, or tuberculosis mortality during treatment were simulated. Upon finishing treatment, individuals restarted the latent stage. Self-cure in the smear-negative and smear-positive stages was also simulated, with individuals who self-cured restarting the first latent stage. Rates of self-cure in HIV-negative and HIV-positive people were *self_cure_rate_HIV0* and *self_cure_rate_HIV1* respectively. A constant rate of tuberculosis mortality was simulated for individuals with untreated disease, equal to *TB_mortality_rate_HIV0_smear1*, *TB_mortality_rate_HIV0_smear0*, *TB_mortality_rate_HIV1_smear1*, and *TB_mortality_rate_HIV1_smear0* in HIV-negative people with smear-positive disease, HIV-negative people with smear-negative disease, HIV-positive people with smear-positive disease, and HIV-positive people with smear-negative disease respectively.

HIV

HIV was included in the model as a binary variable, with simulated individuals either being HIV-positive or HIV-negative. CD4 categories and ART were not explicitly simulated. HIV status was determined at birth, and fixed for life. Individuals were assigned to be HIV-positive with probability *proportion_HIV1*. Compared to simulated HIV-negative individuals, simulated HIV-positive individuals had higher rates of progression to disease following infection, lower rates of self-cure, higher tuberculosis mortality rates, and lower protection against reinfection. Rates of starting TB

treatment and the probability of developing smear-positive disease (as opposed to smear-negative disease) were also allowed to differ between HIV-positive and HIV-negative individuals.

Contact/Transmission

Overall, 1% of contact time in the model occurs in clinics (*contact_proportion_clinics*), with the other 99% occurring in a homogenous 'other locations', representing all other settings. Random mixing was assumed between people in clinics and in other locations. Each simulated individual had the same contact rate. The ratio of clinic contact in HIV-positive individuals compared to HIV-negative individuals, and in people with tuberculosis compared to people without tuberculosis, could be varied, while keeping the overall proportion of contact that occurred in clinics and the contact rate of each simulated individual constant.

Smear-negative disease was assumed to be less infectious than smear-positive disease, by a factor of *reduced_transmission_smear0*. Existing infection provided partial protection against reinfection in the model, by a factor of *reinfection_relative_risk_HIV0* for HIV-negative individuals, and *reinfection_relative_risk_HIV1* for HIV-positive individuals.

Transmission was simulated using a monthly time-step. The number of people HIV-positive and HIV-negative people to be infected or reinfected each month, *I*, in clinics or in other locations, was calculated as:

$$I_{fhc} = binomial(N_{hf}, 1 - \sum_{HS}(1 - p_c b_S a_{fh} v_{cht} v_{cHT})^{N_{HS}})$$

Where *f* = *Mtb* infection status (susceptible or latent), *h* = HIV status (1 = positive, 0 = negative), c = contact location (1 = clinics or 0 = other locations), s = smear status (smear-positive or smear-negative), t = tuberculosis status (1 = has tuberculosis, 0 = no tuberculosis). Lower-case subscripts indicate characteristics of the potential infectees, and upper-case subscripts indicate characteristics of the potential infectors.

N_{HS} indicates the number of people in the model with the corresponding HIV status and *Mtb* infection or TB smear status. P_c is the overall proportion of contact that occurs in that location (c*ontact_proportion_clinics* in clinics, and 1 - c*ontact_proportion_clinics* in other locations). b_S is the transmission rate, adjusted according to the smear status of the potential infector (*baseline_transmission_rate* if smear-positive, *baseline_transmission_rate * reduced_transmission_smear0* if smear-negative). a_{fh} is the relative probability of (re)infection, according to the *Mtb* infection status and HIV status of the potential infectee (1 if *Mtb* uninfected, *reinfection_relative_risk_HIV0* if *Mtb* infected and HIV-negative, *reinfection_relative_risk_HIV1* if *Mtb* infected and HIV-positive).

v_{cht} and v_{cHT} are factors that adjust the proportion of contact that occurs in clinics/other locations, given an individual's HIV status, and whether or not they have tuberculosis. They are calculated as follows:

1. In the low clinic-based transmission and low combined RR scenarios:

   $v_{100} = (n_{00} + n_{01}RR_{TB} + n_{10}RR_{HIV} + n_{11} * max(RR_{HIV}, RR_{TB}))^{-1}$

   In the high clinic-based transmission and high combined RR scenarios:

   $v_{100} = (n_{00} + n_{01}RR_{TB} + n_{10}RR_{HIV} + n_{11} * (RR_{HIV} + RR_{TB} - 1))^{-1}$

   In all other scenarios:

   $v_{100} = (n_{00} + n_{01}RR_{TB} + n_{10}RR_{HIV} + n_{11} * max(RR_{HIV}, RR_{TB}) + 0.5 * min(RR_{HIV}, RR_{TB}) - 0.5)^{-1}$

2. $v_{101} = n_{00}RR_{TB}$

   $v_{110} = n_{00}RR_{HIV}$

3. In the low clinic-based transmission and low combined RR scenarios:

   $v_{111} = max(v_{101}, v_{110})$

   In the high clinic-based transmission and high combined RR scenarios:

   $v_{111} = v_{110} + v_{101} - v_{100}$

   In all other scenarios:

$v_{111} = max(v_{101}, v_{110}) + 0.5 * min(v_{101}, v_{110}) - 0.5 * v_{100}$

4. $v_{0ht} = (1 - v_{1ht}c_1)/(1 - c_1)$

Where n_{ht} is the proportion of all simulated individuals with HIV status *h* and TB status *t*.

Individuals to be infected each month are selected at random from simulated individuals with the corresponding *Mtb* infection and HIV status.

Model initialisation

To initialise the model, *pop_size* people are created, with their ages drawn from a uniform distribution between 0 and *max_age*. They are infected with HIV with probability *proportion_HIV1*. Simulated individuals given smear-positive disease with probability *seed_prop*. The remaining individuals are given the status susceptible. The model was run for 50 years to allow equilibrium to be reached, before any results were outputted.

Scheduling

The model is implemented as a continuous time model, with the exception of *Mtb* transmission, which is simulated with a monthly time step. This hybrid scheduling structure was chosen as it minimises model run times.

Calibration

The model was fitted to estimates of overall tuberculosis incidence in South Africa and the proportion of incident tuberculosis that occurred in HIV-positive people in 2017[2] 'by hand', by varying the transmission probability and the rate of developing tuberculosis in HIV-positive people. The model was fitted to the data using the parameter combination with $RR_{HIV} = 5.25$ and $RR_{TB} = 3$, which preliminary runs suggested had values of the fitting outputs close to the median values of

those outputs across all scenarios. The same values for all parameters other than RR_{HIV} and RR_{TB} were then used for each of the parameter combinations.

Univariate sensitivity analyses

Three main univariate sensitivity analyses were conducted, where the three factors that were varied together in the low and high clinic-based transmission were varied individually, and the model was recalibrated:

1. The proportion of incident tuberculosis that was in HIV-positive people was changed from 60% in the main scenarios to 55% and 64% in the 'low HIV TB' and 'high HIV TB' scenarios respectively (proportions equal to the best estimate and low and high bounds from WHO estimates[2]).
2. The proportion of HIV-positive and HIV-negative people with tuberculosis who had smear-positive disease was changed from 35% and 45% respectively in the main scenario, to 30% and 50%, and to 40% and 40%, in the 'low smear-positive in HIV-positive' and 'high smear-positive in HIV-positive' scenarios respectively[3].
3. The rate ratio of clinic visiting in people with both HIV and TB relative to people with neither HIV nor TB (RR_{HIV_TB}) was assumed to be equal to $max(RR_{HIV}, RR_{TB})$ and $RR_{HIV} + RR_{TB} - 1$ in the 'low combined RR' and 'high combined RR' scenarios respectively.

Four additional one-way sensitivity analyses were conducted where variables were varied by ±20%. The variables varied were:

1. The self-cure rate was increased for HIV-positive people and decreased for HIV-negative people, and vice versa.
2. The TB mortality rates (smear positive and smear negative) were increased for HIV-positive people and decreased for HIV-negative people, and vice versa.
3. The increased rate of developing TB in the first year following infection (compared to subsequent years) in HIV-positive people

4. The degree of protection against reinfection was increased for HIV-positive people and decreased for HIV-negative people, and vice versa.

Model input parameters

Table S1. Model input parameters

Name	Description	Range	Source
pop_size	Simulated population size	100000	NA
max_age	Maximum age in years	60	NA
seed_prop	Proportion of people initially seeded with smear-positive TB	0.005	NA
treatment_rate_HIV0	Rate at which HIV-negative people with TB start treatment/year	0.682	Calculated to fit estimated TB treatment coverage in HIV-negative people for South Africa in 2017[2]
treatment_rate_HIV1	Rate at which HIV-positive people with TB start treatment/year	0.806	Calculated to fit estimated TB treatment coverage in HIV-positive people for South Africa in 2017[2]
self_cure_rate_HIV0	Rate at which HIV-negative people with TB self-cure/year	0.2	Menzies *et al* (2012)[4]

self_cure_rate_HIV1	Rate at which HIV-positive people with TB self-cure/year	0.1	Menzies *et al* (2012)[4]
TB_mortality_rate_HIV0_smear1	TB Mortality rate for HIV-negative people with smear-positive TB/year	0.3	Houben *et al* (2016)[5]
TB_mortality_rate_HIV0_smear0	TB Mortality rate for HIV-negative people with smear-negative TB/year	0.21	Houben *et al* (2016)[5]
TB_mortality_rate_HIV1_smear1	TB Mortality rate for HIV-positive people with smear-positive TB/year	0.6	Houben *et al* (2016)[5]
TB_mortality_rate_HIV1_smear0	TB Mortality rate for HIV-positive people with smear-negative TB/year	0.42	Houben *et al* (2016)[5]
proportion_HIV1	Proportion of simulated people who are HIV-positive	0.127	Estimated HIV prevalence in South Africa in 2017[6, 7]
develop_tb_y1_rate_HIV-negative	Rate of developing TB in HIV-negative people in 1st year following infection/year	$8.66*10^{-2}$	Kasaie *et al* (2014)[8]
develop_tb_y2_rate_HIV-negative	Rate of developing TB in HIV-negative people in 2nd year following infection/year	$3.55*10^{-2}$	Kasaie *et al* (2014)[8]

develop_tb_y3_rate_HIV-negative	Rate of developing TB in HIV-negative people in 3rd year following infection/year	$1.12*10^{-2}$	Kasaie *et al* (2014)[8]
develop_tb_y4_rate_HIV-negative	Rate of developing TB in HIV-negative people in 4th year following infection/year	$7.40*10^{-3}$	Kasaie *et al* (2014)[8]
develop_tb_y5_rate_HIV-negative	Rate of developing TB in HIV-negative people in 5th year following infection/year	$2.40*10^{-3}$	Kasaie *et al* (2014)[8]
develop_tb_reactivation_rate_HIV-negative	Rate of developing TB in HIV-negative people 6+ years following infection/year	$5.00*10^{-3}$	Kasaie *et al* (2014)[8]
develop_tb_reactivation_rate_HIV-positive	Rate of developing TB in HIV-positive people 1+ years following infection/year	$>=3.55*10^{-2}$	Varied to fit data. See calibration section
increased_develop_tb_y1_rate_HIV-positive	Increased rate of developing TB in first year following infection compared to subsequent years, for HIV-positive	5.14	Dowdy and Chaisson (2009)[9]
baseline_transmission_rate	Baseline transmission rate between an infectious (smear-positive) person and a susceptible individual/month	0-1	Varied to fit data. See calibration section

reinfection_relative_risk_HIV0	Reduced risk of reinfection compared to primary infection, in HIV-negative	0.25	Dowdy and Chaisson (2009)[9]
reinfection_relative_risk_HIV1	Reduced risk of reinfection compared to primary infection, in HIV-positive	0.72	Dowdy and Chaisson (2009)[9]
contact_proportion_clinic	Proportion of all contact that occurs in clinics	0.01	Arbitrary
RR_{HIV}	Increased rate of clinic visiting in HIV-positive people compared to HIV-negative people	1-10	Varied in parameter combinations
RR_{TB}	Increased rate of clinic visiting in people with tuberculosis compared to people without tuberculosis	1-5	Varied in parameter combinations
reduced_transmission_smear0	Reduced transmission probability from people with smear-negative disease, compared to people with smear-positive disease	0.22	Menzies *et al* (2012)[4]
prop_smear1_HIV0	Proportion of HIV-negative people who develop smear-positive disease	0.4-0.5. Varied in scenarios	Corbett *et al* (2010) and Corbett *et al* (2003)[3, 10]

prop_smear1_HIV1	Proportion of HIV-positive people who develop smear-positive disease	0.3-0.4. Varied in scenarios	Corbett *et al* (2010) and Corbett *et al* (2003)[3, 10]
RR_{HIV_TB}	Rate ratio of clinic visiting in people with both HIV and TB relative to people with neither HIV nor TB	See sections 'Scenarios' and 'Univariate sensitivity analyses'	

Fitted input parameter values

Table S2 fitted input parameter values

Parameter	**Scenario**								
	Best	**Low clinic-based transmission**	**High clinic-based transmission**	**Low HIV TB**	**High HIV TB**	**Low smear-positive in HIV-positive**	**High smear-positive in HIV-positive**	**Low combined RR**	**High combined RR**
baseline_transmission_rate	1.28E-05	1.45E-05	1.12E-05	1.45E-05	1.12E-05	1.28E-05	1.28E-05	1.28E-05	1.28E-05
develop_tb_reactivation_rate_HIV1	0.0715	0.056	0.0897	0.056	0.0897	0.0715	0.0715	0.0715	0.0715
prop_smear1_HIV0	0.45	0.5	0.4	0.45	0.45	0.5	0.4	0.45	0.45
prop_smear1_HIV1	0.35	0.3	0.4	0.35	0.35	0.3	0.4	0.35	0.35
RR_{HIV_TB}	$max(RR_{HIV}, RR_{TB}) + 0.5*min(RR_{HIV}, RR_{TB}) - 0.5$	$max(RR_{HIV}, RR_{TB})$	$RR_{HIV} + RR_{TB} - 1$	$max(RR_{HIV}, RR_{TB}) + 0.5*min(RR_{HIV}, RR_{TB}) - 0.5$	$max(RR_{HIV}, RR_{TB}) + 0.5*min(RR_{HIV}, RR_{TB}) - 0.5$	$max(RR_{HIV}, RR_{TB}) + 0.5*min(RR_{HIV}, RR_{TB}) - 0.5$	$max(RR_{HIV}, RR_{TB}) + 0.5*min(RR_{HIV}, RR_{TB}) - 0.5$	$max(RR_{HIV}, RR_{TB})$	$RR_{HIV} + RR_{TB} - 1$

Results

Univariate sensitivity analyses – fit to data

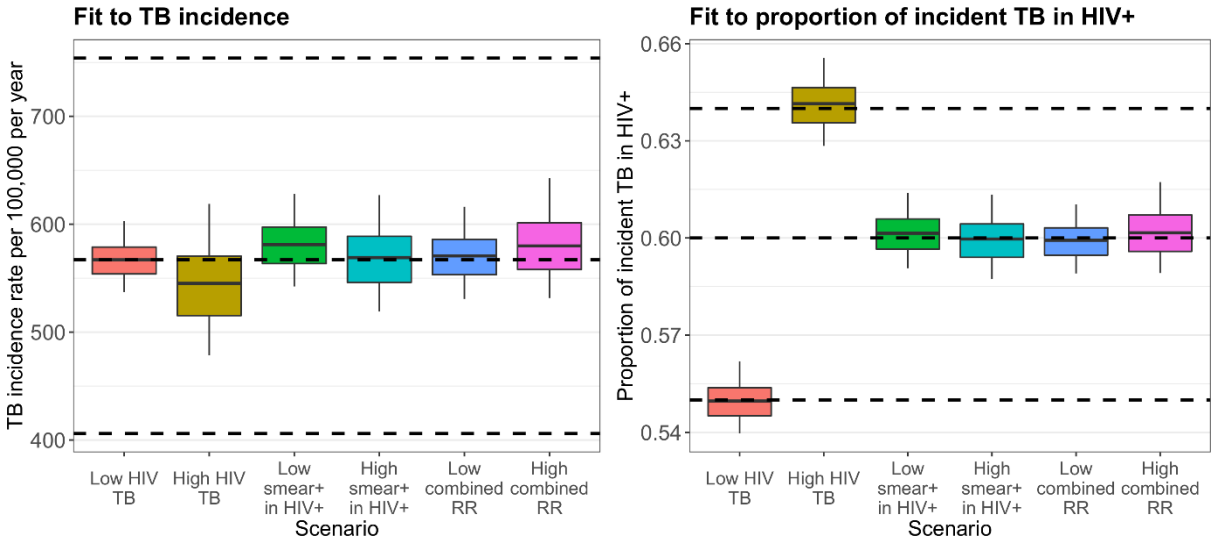

Figure S2. Model fit to a) TB incidence and b) the proportion of incident TB in HIV-positive people, in the low HIV TB, high HIV TB, low smear-positive in HIV-positive, high smear-positive in HIV-positive, low combined RR, and high combined RR scenarios. Box hinges indicate the upper, middle and lower quartiles of the values in each parameter set, and whiskers extend to the upper and lower ranges of the values. The horizontal dashed lines show the best estimate and lower and upper ranges of the empirical data.

Proportion of contact in clinics

Figure S3, S4, and S5 show the proportion of contact time that occurs in clinics overall, for HIV-positive and HIV-negative people, and people with and without TB, in the best estimate, low clinic-based transmission, and high clinic-based transmission scenarios. Contact patterns in the low HIV TB, high HIV TB, low smear-positive in HIV-positive, and high smear-positive in HIV-positive scenarios vary little from those in the best estimate scenario, those in the low combined scenario vary little from those in the low clinic-based transmission scenario, and in those in the high combined scenario vary little from those in high low clinic-based transmission scenario. They are therefore not shown.

In all scenarios and parameter combinations, 1% of contact occurred in clinics overall. As the prevalence of tuberculosis was low, the proportion of contact that occurred in clinics for people without tuberculosis varied little from 1%.

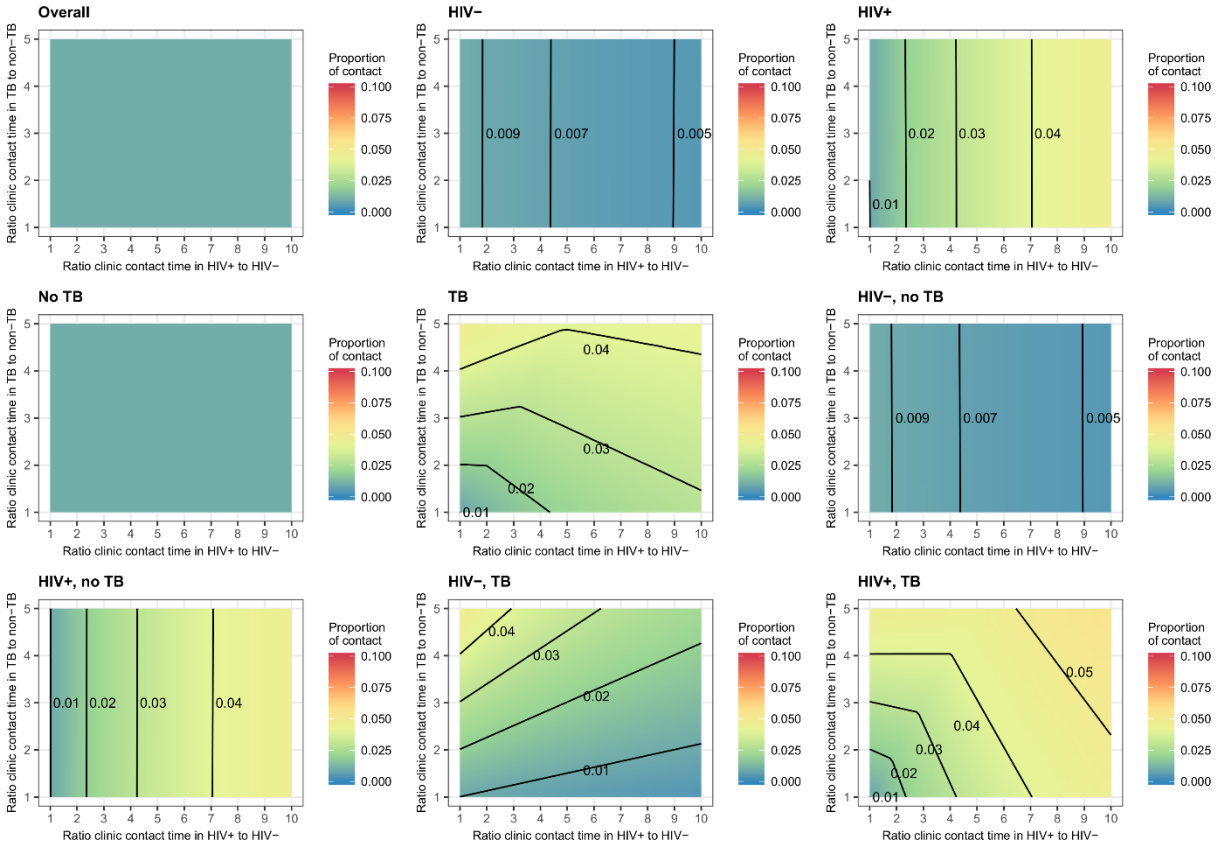

Figure S3 Proportion of contact that occurs in clinics in the best estimate scenario, overall, in HIV-negative individuals, in HIV-positive individuals, in individuals without TB, in individuals with TB, in HIV-negative individuals without TB, in HIV-positive individuals without TB, in HIV-negative individuals with TB, and in HIV-positive individuals with TB.

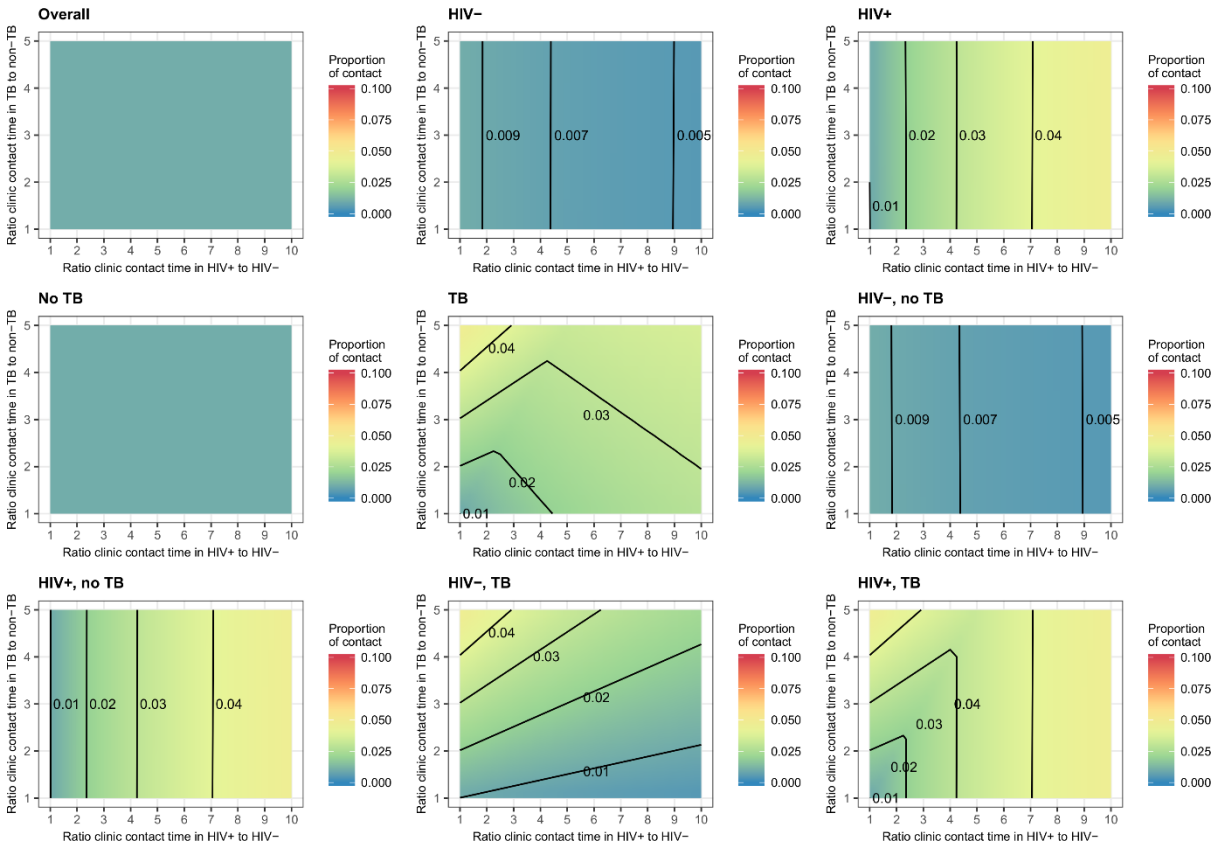

Figure S4 Proportion of contact that occurs in clinics in the low clinic-based transmission scenario, overall, in HIV-negative individuals, in HIV-positive individuals, in individuals without TB, in individuals with TB, in HIV-negative individuals without TB, in HIV-positive individuals without TB, in HIV-negative individuals with TB, and in HIV-positive individuals with TB.

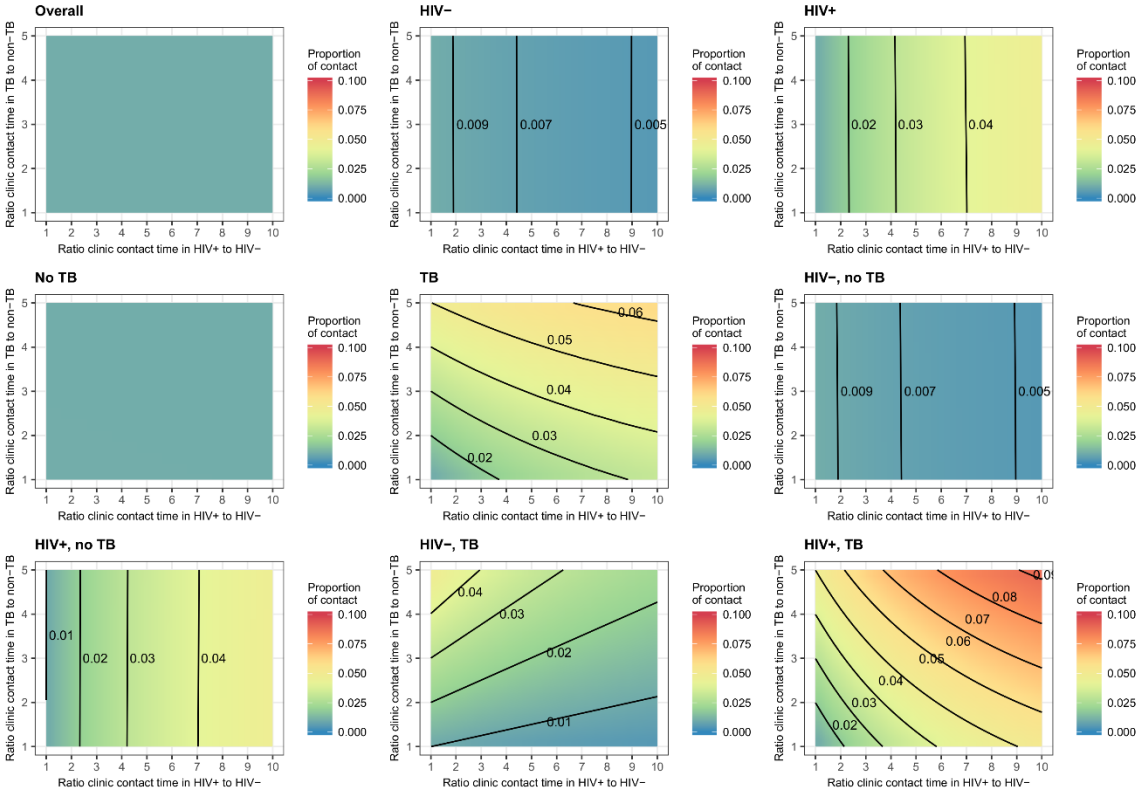

Figure S5 Proportion of contact that occurs in clinics in the high clinic-based transmission scenario, overall, in HIV-negative individuals, in HIV-positive individuals, in individuals without TB, in individuals with TB, in HIV-negative individuals without TB, in HIV-positive individuals without TB, in HIV-negative individuals with TB, and in HIV-positive individuals with TB.

Univariate sensitivity analyses – proportion of transmission in clinics

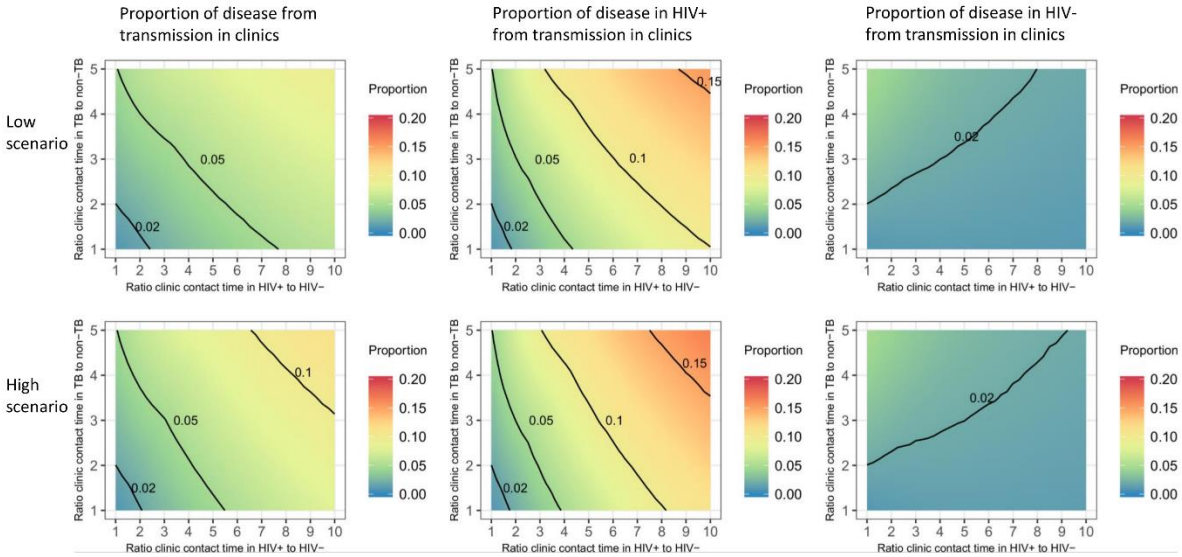

Figure S6. Proportion of disease resulting from transmission in clinics overall (1st column), in HIV-positive people (2nd column) and in HIV-negative people (3rd column) in the low HIV TB (1st row) and high HIV TB (2nd row) scenarios.

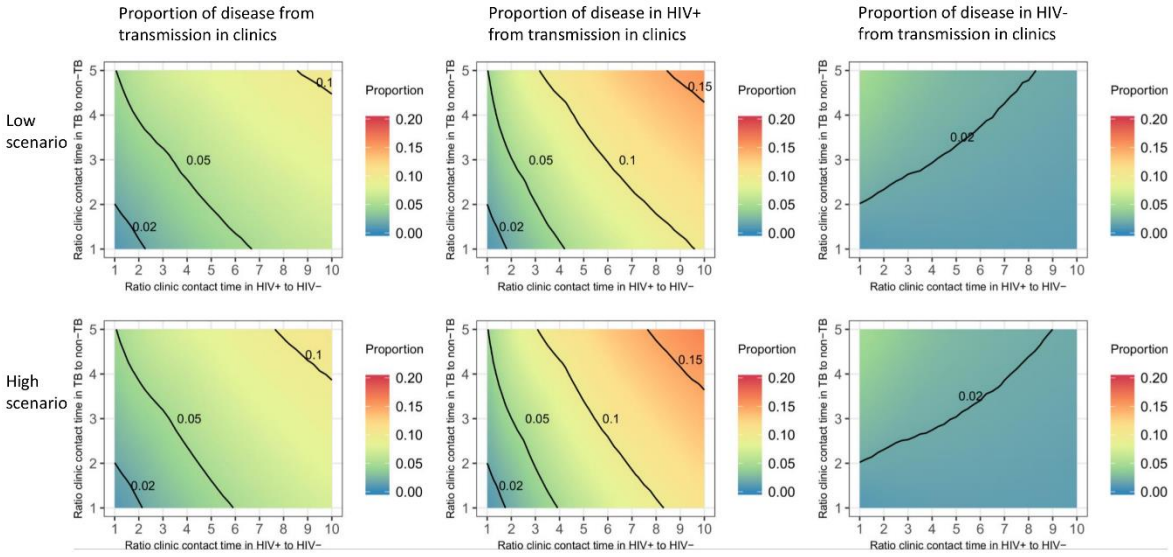

Figure S7. Proportion of disease resulting from transmission in clinics overall (1st column), in HIV-positive people (2nd column) and in HIV-negative people (3rd column) in the low smear-positive in HIV-positive (1st row) and high smear-positive in HIV-positive (2nd row) scenarios.

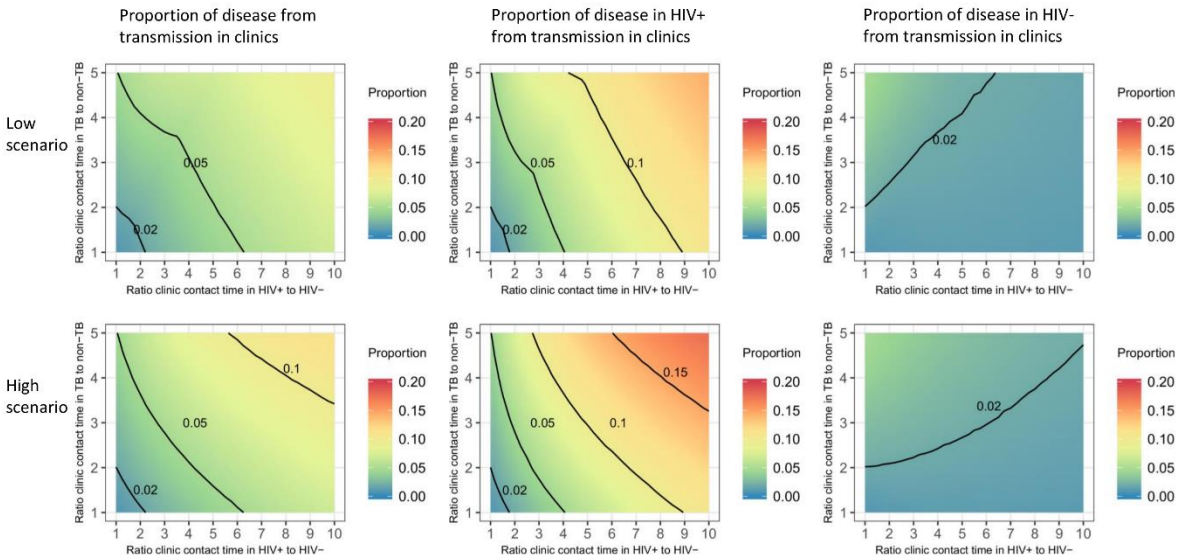

Figure S8. Proportion of disease resulting from transmission in clinics overall (1st column), in HIV-positive people (2nd column) and in HIV-negative people (3rd column) in the low combined RR (1st row) and high combined RR (2nd row) scenarios

Varying the self-cure rates, the TB mortality rates, the increased rate of developing disease in the first year following infection (compared to subsequent years) in HIV-positive people, and the degree of protection against reinfection by ±20% had little effect on the proportion of disease that results in clinics (Table S3).

Table S3. Proportion of disease resulting from transmission in clinics in the one-way sensitivity analyses

		Proportion of disease resulting from transmission in clinics		Proportion of disease in HIV-positive people resulting from transmission in clinics		Proportion of disease in HIV-negative people resulting from transmission in clinics	
		RR_{HIV} =5, RR_{TB} =2	RR_{HIV} =10, RR_{TB} =5	RR_{HIV} =5, RR_{TB} =2	RR_{HIV} =10, RR_{TB} =5	RR_{HIV} =5, RR_{TB} =2	RR_{HIV} =10, RR_{TB} =5
Self-cure rates	self_cure_rate_HIVneg_annual=0.24 self_cure_rate_HIVpos_annual=0.08	5.3%	10.8%	7.8%	16.5%	1.6%	1.8%
	self_cure_rate_HIVneg_annual=0.16 self_cure_rate_HIVpos_annual=0.12	5.2%	10.7%	7.6%	16.2%	1.6%	1.8%
TB mortality rates	TB_mortality_rate_smearneg_HIVneg_annual=0.168 TB_mortality_rate_smearpos_HIVneg_annual=0.24 TB_mortality_rate_smearneg_HIVpos_annual=0.504 TB_mortality_rate_smearpos_HIVpos_annual=0.72	4.9%	10.1%	7.3%	15.7%	1.5%	1.7%
	TB_mortality_rate_smearneg_HIVneg_annual=0.252 TB_mortality_rate_smearpos_HIVneg_annual=0.36 TB_mortality_rate_smearneg_HIVpos_annual=0.336 TB_mortality_rate_smearpos_HIVpos_annual=0.48	5.6%	11.3%	8.0%	16.9%	1.7%	1.9%
Increased rate of developing TB in first year following infection in HIV-positive people	increased_develop_tb_y1_rate_HIVpos=4.11	5.0%	10.3%	7.6%	16.1%	1.6%	1.8%
	increased_develop_tb_y1_rate_HIVpos=6.17	5.4%	11.1%	7.8%	16.5%	1.6%	1.9%
Protection against reinfection	reinfection_relative_risk_HIV0=0.2 reinfection_relative_risk_HIV1=0.86	5.3%	10.9%	7.8%	16.4%	1.6%	1.9%
	reinfection_relative_risk_HIV0=0.3 reinfection_relative_risk_HIV1=0.58	5.2%	10.6%	7.7%	16.3%	1.6%	1.8%

References

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