Antiretroviral therapy for tuberculosis control in nine African countries

Brian G. Williams, Reuben Granich, Kevin M. De Cock, Philippe Glaziou, Abhishek Sharma, and Christopher Dye

South African Centre for Epidemiological Modelling and Analysis, Stellenbosch 7600, South Africa; World Health Organization, 1211 Geneva, Switzerland; and Department of Public Health, University of Oxford, Oxford OX3 7LF, United Kingdom

HIV has increased the incidence of tuberculosis (TB) by up to sevenfold in African countries, but antiretroviral therapy (ART) reduces the incidence of AIDS-related TB. We use a mathematical model to investigate the short-term and long-term impacts of ART on the incidence of TB, assuming that people are tested for HIV once a year, and start ART at a fixed time after HIV seroconversion or at a fixed CD4+ cell count. We fit the model to trends in HIV prevalence and TB incidence in nine countries in sub-Saharan Africa. If HIV-positive people start ART within 5 y of seroconversion, the incidence of AIDS-related TB in 2015 will be reduced by 48% (range: 37–55%). Long-term reductions depend sensitively on the delay to starting ART. If treatment is started 2, 1 y after HIV seroconversion, or as soon as people test positive, the incidence in 2050 will be reduced by 66% (range: 57–80%), 95% (range: 93–96%), 97.7% (range: 96.9–98.2%) and 98.4% (range: 97.8–98.9%), respectively. In the countries considered here, early ART could avert 0.71 ± 0.36 [95% confidence interval (CI)] million of 3.4 million cases of TB between 2010 and 2015 and 5.8 ± 2.9 (95% CI) million of 15 million cases between 2015 and 2050. As more countries provide ART at higher CD4+ cell counts, the impact on TB should be investigated to test the predictions of this model.

In southern and East Africa, the epidemic of HIV has increased national tuberculosis (TB) case notification rates by up to sevenfold and up to 85% of sputum smear-positive TB cases are HIV-positive (1). However, mathematical modeling suggests that it may be possible to contain heterosexual transmission of HIV within 10 y with widespread and frequent HIV testing and access to antiretroviral therapy (ART) (2) provided that HIV-positive individuals start ART as soon as they are found to be HIV-positive (3). A less ambitious strategy in which all HIV-positive people start ART at a CD4+ cell count of 350 cells/µL would reduce but not eliminate HIV transmission (3). Here, we consider the impact on HIV and TB of testing everyone once a year, on average, and starting HIV-positive people on ART at different times after infection or at different CD4+ cell count thresholds. Because increasing numbers of people are encouraged to take an HIV test (4), it is important to decide when they should start treatment.

To reduce the lifetime risk for TB in HIV-positive individuals by more than twofold, we have previously shown that they should start combination ART at a CD4+ cell count above 500 cells/µL with coverage and adherence, taken together, exceeding 85% (5). Acceptable data on time trends in HIV prevalence (6) and TB notification rates (1) are now available for nine countries in sub-Saharan Africa: Gabon and Ghana in West Africa; Tanzania in East Africa; and Botswana, Lesotho, Malawi, South Africa, Swaziland, and Zambia in southern Africa. Here, we extend the earlier study to investigate the impact over time of frequent testing and the provision of ART on the number of TB cases between now and 2050.

We fit mathematical models to trend data for HIV prevalence and TB notification rates (details provided in Methods) to determine epidemiological parameters. We use data from published studies to estimate the impact that ART will have on the incidence of TB in HIV-positive people. We make predictions of the future time course of HIV and TB under a range of scenarios depending on the time between HIV seroconversion and the start of ART or on the CD4+ cell count at which people start ART. We assume that intervention starts in 2010 and reaches full coverage in 2015 (details provided in Methods).

Results

Trends in HIV infection and TB incidence as well as model fits with projections up to 2050 are given in Fig. 1 for three of the nine countries and in SI Appendix, Fig. S5 for the remaining six countries. For countries such as Ghana and Botswana, where the HIV-prevalence peaked relatively early, there has subsequently been a small but significant drop in HIV-prevalence that we attribute partly to AIDS-related mortality and partly to behavior change. For countries such as South Africa, where the prevalence of HIV has only recently leveled off, we assume that this will be followed by a similar small drop in prevalence. These projections provide the baseline against which we estimate the impact of ART on TB.

A key feature of TB-HIV epidemiology is that the epidemic of HIV drives up the incidence of TB in HIV-positive but not HIV-negative people, as seen in Fig. 1. This is because the increase in the incidence of TB in HIV-positive people is balanced to some extent by the decrease in the duration of TB disease in HIV-positive people (7) (SI Appendix, section 4).

Here, we consider two key incidence rate ratios: IRR_{HIV}, the incidence of TB in HIV-positive adults divided by the incidence of TB in HIV-negative people, and IRR_{HIV}^{ART}, the incidence of TB in HIV-positive people who are on ART divided by the incidence of TB in HIV-positive people who are not on ART. IRR_{HIV}^{ART} determines the increase in TB incidence when people are infected with HIV; IRR_{HIV}^{ART} determines the reduction in TB incidence when people who are already infected with HIV start ART. Both depend on the CD4+ cell counts of the infected person.

IRR_{HIV} varies among countries (Fig. 1). In Ghana, the prevalence of HIV in adults aged 15–49 y peaked at 2.5% in 1998, the TB notification at the start of the HIV epidemic was 38 per 100,000 per year, and the IRR_{HIV}^{ART} was 7.2. In Botswana, the peak prevalence of HIV was 10-fold higher, reaching 27% in 2002; the TB notification rate at the start of the HIV epidemic was also higher at 220 per 100,000 per year, but the IRR_{HIV}^{ART} was only 2.9. In South Africa, the peak prevalence of HIV was 17%, about two-thirds of that in Botswana: the TB notification rate at the start of the epidemic was 200 per 100,000 per year, but the IRR_{HIV}^{ART} was 5.0.
As the epidemic of HIV progresses and more of those infected with HIV have low CD4+ cell counts, the $IRR_{TB}$ increases from 2.9 in Botswana and 7.2 in Ghana at the start of the epidemic to 5.2 in Botswana and 19 in Ghana 2050 (Fig. 1 and SI Appendix, Fig. S5).

We first consider the impact of ART on TB for different treatment delays (Fig. 2) setting $IRR_{TB}^{ART} = 0.39$ (Methods). In 2015, the incidence of HIV-related TB will be reduced by 48% (range: 37–55%) if people start ART when they have been HIV-positive for 5 y or more and by 63% (range: 72–52%) if they start ART when they have been HIV-positive for 2 y or more (Fig. 2A). The reduction is greater if treatment is started earlier, but most of the benefit is obtained if treatment is started less than 5 y after infection with HIV. The reduction in the incidence of HIV-related TB is slightly greater in countries in which the infection rate ratio is higher (Fig. 2A). More substantial reductions can be achieved if the program is maintained until 2050 (Fig. 2B). If treatment is started 5, 2, or 1 y after HIV seroconversion, or as soon as people test positive, the incidence in 2050 will be reduced by 66% (range: 57–80%), 95% (range: 93–96%), 97.7% (range: 96.9–98.2%), and 98.4% (range: 97.8–98.9%), respectively. The reduction in the incidence of HIV-related TB is again greater when the $IRR_{TB}^{HIV}$ is higher (Fig. 2B), but the most important factor is the time since infection at which ART is started.

Because we do not generally know when people were infected with HIV, CD4+ cell counts are used as a measure of immune suppression in HIV-positive people in spite of the substantial variation in counts among and within populations (8). Table 1 shows the mean CD4+ cell count in HIV-negative people.
Table 1. Mean CD4+ cell count in HIV-negative people immediately after the acute phase and 1, 2, and 5 y after infection with HIV, as estimated from the model for the nine countries under consideration

<table>
<thead>
<tr>
<th>Country</th>
<th>Negative</th>
<th>Acute</th>
<th>1 y</th>
<th>2 y</th>
<th>5 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botswana</td>
<td>666</td>
<td>499</td>
<td>450</td>
<td>400</td>
<td>250</td>
</tr>
<tr>
<td>Gabon</td>
<td>1,262</td>
<td>947</td>
<td>852</td>
<td>757</td>
<td>473</td>
</tr>
<tr>
<td>Ghana</td>
<td>1,147</td>
<td>860</td>
<td>774</td>
<td>688</td>
<td>430</td>
</tr>
<tr>
<td>Lesotho</td>
<td>729</td>
<td>546</td>
<td>492</td>
<td>437</td>
<td>273</td>
</tr>
<tr>
<td>Malawi</td>
<td>972</td>
<td>729</td>
<td>656</td>
<td>583</td>
<td>365</td>
</tr>
<tr>
<td>Tanzania</td>
<td>1,200</td>
<td>900</td>
<td>810</td>
<td>720</td>
<td>450</td>
</tr>
<tr>
<td>South Africa</td>
<td>973</td>
<td>730</td>
<td>657</td>
<td>584</td>
<td>365</td>
</tr>
<tr>
<td>Swaziland</td>
<td>946</td>
<td>710</td>
<td>639</td>
<td>568</td>
<td>355</td>
</tr>
<tr>
<td>Zambia</td>
<td>1,184</td>
<td>888</td>
<td>799</td>
<td>710</td>
<td>444</td>
</tr>
</tbody>
</table>

immediately after the acute phase and 1, 2, and 5 y after infection as estimated from the model. If the target is to start within 1 y of infection, people in Botswana should start ART when their CD4+ cell count reaches 450 cells/μL. In Gabon, conversely, they should start treatment when their CD4+ cell count reaches 852 cells/μL. The impact of ART on the dynamics of TB in Botswana, Ghana, and South Africa is shown in Fig. 3, and it is shown for all nine countries in SI Appendix, Fig. S9, assuming that people are tested once a year, on average, and start ART if their CD4+ cell count is less than 200, 350, or 500 CD4+ cells/μL, or as soon as they are found to be HIV-positive. If people start treatment early, HIV-related TB falls by about one-half once full coverage is achieved in 2015 (Fig. 3 and SI Appendix, Fig. S9) but then falls more slowly to 2050 as those who are on ART age and die.

For the nine countries considered here, a policy of annual testing and immediate ART would avert 0.71 [95% confidence interval (CI): ±0.36] million of a total of 3.4 million cases of TB, a reduction of 21% between 2010 and 2015, and a further 5.8 (95% CL: ±2.9) million of a total of 15 million cases of TB, a reduction of 40%, between 2015 and 2050 (country data are presented in SI Appendix, section 9).

Using this model, the lifetime risk for TB infection for HIV-negative people is 4% (range: 2–9%), assuming that they are at risk for an average of 40 y; and in HIV-positive people, the lifetime risk is 13% (range: 6–20%), assuming that they are at risk for 10 y.

The main source of uncertainty in the impact of ART on TB disease incidence (Fig. 2) arises from the uncertainty in IRRTART, the TB incidence rate ratio comparing those on ART with those not on ART. Although none of the estimates (9–19) differ significantly from the mean value of 0.39 used here (SI Appendix, Fig. S2 and SI Appendix, Table S3), the individual estimates all have large associated errors and this introduces an approximately twofold uncertainty in the estimates of the reduction in TB in HIV-positive people. Additional uncertainty arises from estimates of the TB disease duration in different stages of HIV infection and from fitting the model to the TB trend data; the uncertainty in the estimates of the reduction in TB in HIV-positive people introduced by the former is ±14%, and that introduced by the latter is ±5% (95% uncertainty ranges, averaged over countries). However, errors in IRRTART and in the disease duration will increase or decrease the estimated proportional impact of ART on TB by about the same amount, such that the estimates in Fig. 2 will all be increased or decreased but the ordering and relative magnitude of the impact of starting at different times after infection with HIV will remain the same. The error bars in Fig. 2 show the systematic uncertainty in the overall estimates.

Discussion

Frequent annual testing with immediate ART could reduce the incidence of HIV-related TB in the nine countries under consideration by 48% (range: 37–55%) by 2015 and by 98.4% (range: 97.8–98.9%) by 2050, averting 5.8 million, or 32%, of the expected 15 million cases of TB between now and 2050. The reduction in 2015 does not depend strongly on the time between infection with HIV and the start of ART provided that this is not more than about 5 y, but to achieve the full impact in 2050...
requires the immediate start of HIV treatment. Testing people less often than once a year will increase the time between infection and the start of treatment.

The sensitivity of frequent testing and treatment to the CD4+ cell count at the start of treatment varies among countries in sub-Saharan Africa (Table 1). In Botswana, the mean CD4+ cell count among HIV-negative people is 666 cells/μL (20), it will have fallen to about 499 cells/μL by the end of the acute phase of HIV infection, and the difference between starting immediately and starting at a CD4+ cell count of 500 cells/μL is marginal. In South Africa, conversely, the mean CD4+ cell count among HIV-negative people in South Africa is 973 cells/μL (8), such that the CD4+ cell count is about 730 cells/μL by the end of the acute phase and only reaches 500 cells/μL after 3 y.

It is not clear why IRHIV varies among countries. In concentrated epidemics, HIV and TB may be clustered in the same relatively small groups, including people who inject drugs, drink alcohol to excess, and are homeless or otherwise marginalized. In this case, the population prevalence of HIV will underestimate the prevalence of HIV among those at risk for TB, leading to an apparently high IRHIV. In generalized epidemics, this is less likely to be the case, but it may still be groups of people, including migrant workers, for example, among whom the two infections are clustered. An alternative explanation is that the variability in CD4+ cell counts among and within populations (8) affects the risk for developing TB, and hence the IRHIV.

In this analysis, we use TB notification rates as a surrogate for incidence. If the case detection rate is constant and is less than 100%, the notification rates will underestimate the incidence but always by the same proportion and this will not affect the analysis. If the case detection rate changes over time, it will affect the interpretation of trends. However, in the countries that are affected the worst, HIV has led to an increase of up to 700% in the notification rates, whereas case detection rates in these countries are unlikely to have changed by more than about 25%; thus, this is unlikely to affect the overall conclusions.

The duration of TB disease in HIV-positive as compared with HIV-negative people is not known precisely, but the results are relatively insensitive to the precise value of the ratio as shown in SI Appendix, section 11 and SI Appendix, Fig. S10.

Our best estimate of the relative risk for TB in people on and off ART is 0.39. However, it is likely that the risk for TB continues to fall for up to 5 y after the start of ART (21), such that the present model may underestimate the impact of ART on TB. We have not included the impact of isoniazid preventive therapy (IPT) on the risk for developing TB in HIV-positive people, which may give a further reduction of about 50% (15, 22). Because HIV-related TB has relatively little impact on the risk for TB in HIV-negative people, a good TB control program should be able to reduce the incidence of TB in HIV-negative people, even in the presence of a severe epidemic of HIV.

Frequent testing and early treatment raise important challenges, including ensuring confidentiality and preventing stigma and discrimination. However, in 42 countries across 176 sites between 2003 and 2005, the mean CD4+ cell count at which people started ART was 137 ± 100 cells/μL (range: 53–239 cells/μL), and in South Africa, it was 87 cells/μL* which is well below the current guidelines; hence, current practice is unlikely to have a significant impact on HIV transmission or TB incidence. The decision as to when to start treatment could be simplified if treatment were started immediately on diagnosis irrespective of CD4+ cell counts. There is increasing evidence from observational studies that starting ART at CD4+ cell counts above 500 cells/μL improves the prognosis for individual patients (23–26) and also reduces the risk for TB disease (27). The World Health Organization has increased the CD4+ cell count threshold for starting treatment from 200 to 350 cells/μL and has recommended immediate ART for people with HIV and active TB and for HIV-positive pregnant women (28). Our model suggests that when implemented, this will significantly reduce the incidence of both HIV and TB.

Frequent testing and immediate treatment may bring about an initial rapid reduction in TB notification rates, but the decline will slow once most HIV-positive people are on ART. Delaying treatment will reduce the long-term impact on TB but will have less effect on the short-term impact. The use of IPT could further reduce the incidence of TB in those on treatment. If frequent testing and immediate treatment can effectively eliminate HIV in the long run, they will inevitably eliminate HIV-related TB, and this result is robust to the precise parameter values used in this analysis. If, as our model suggests, current levels of coverage and provision of ART are having a significant impact on TB, it should be possible to measure the impact not only in research sites but in routinely collected national data. This would help to inform the development of international public health policy in regard to the control of TB and HIV.

Our paper on the impact of early treatment on HIV transmission generated considerable interest (3), and a recent modeling study has shown that the impact of early treatment on HIV may be greater than or less than we predicted, depending on the particular epidemiological context (29). Field trials are needed to test the feasibility and effectiveness of early treatment both as a form of HIV prevention and as a way of controlling HIV-related TB. More detailed models of both TB and HIV epidemiology, including age, sex, and sexual and social mixing patterns, will make it possible to explore more nuanced ways of intervening by focusing initially on high-risk groups for both TB and HIV. Such models could also be used to explore potential synergies between ART and other TB control methods. The focus here is on ways to reduce the incidence of HIV-related TB. Better ways of preventing HIV, including male circumcision, vaginal microbiotics, and more effective behavior change programs, may be implemented in the coming years and will further reduce HIV, and therefore HIV-related TB. It is to be hoped that the development of previously undescribed tools for the diagnosis and treatment of TB will greatly increase the impact of DOTS programs on TB among HIV-negative people with a corresponding benefit to HIV-positive people. TB-HIV collaborative activities, including giving IPT to HIV-positive people, improved TB infection control, and intensified case finding and cross-referral of patients between TB and HIV programs also need to be strengthened (6). Nonetheless, we suggest that frequent HIV testing and immediate ART in generalized HIV epidemic settings could rapidly reduce and eventually eliminate HIV-associated TB.

Methods

We consider scenarios in which ART is started at different times after infection so that the impact on the HIV epidemic and the TB epidemic varies. The model is given schematically and described in detail in SI Appendix, section 1 and SI Appendix, Fig. S1. We fit time trends in HIV prevalence (6) to a compartmental model with four stages of infection, as described previously (3). The output of this HIV model drives the TB model, which we fit to time trends in TB notification rates (1). People in any of the stages in the HIV model, with or without ART, can develop TB disease and recover from, or be treated for, TB disease. In the TB model, we consider only people who are susceptible to TB disease and people who have TB disease. We do not consider latent infection or distinguish between the breakdown of latent infection and reinfection, because trend data for latent infection are not available. The risk for developing TB (without ART) depends on the population prevalence of TB and on the particular HIV state (SI Appendix, section 2). The model is used to explore the impact on TB of different levels of...
implementation of ART (3). We assume that people are tested randomly once a year, on average. We consider scenarios in which HIV-positive people start ART either they have been infected for more than a given number of years or if their CD4+ cell count is below a given threshold.

The HIV model in SI Appendix, section 1 and SI Appendix, Fig. 5 gives the proportion of people in each of four stages of infection, with or without ART. Assuming that a person’s CD4+ cell count drops by 25 ± 16% (95% confidence interval (CI)) 0 during the acute phase and then declines linearly to death when it reaches zero (8), we calculate the mean CD4+ cell count in each of the four stages of infection. Based on available data (5, 21, 27), we estimate that the incidence of TB increases by 36 ± 12% for each decrease of 100 CD4+ cells/μL and use this to calculate the incidence of TB in each stage of infection.

HIV-positive people are more likely than HIV-negative people to develop TB but have a shorter TB disease duration and are less infectious for TB (7, 30–32). The prevalence of TB disease, and hence transmission, is therefore a balance between the increase in TB incidence and the decrease in TB disease duration, allowing for the decrease in TB infectiousness. To incorporate this into our model, we let the TB disease duration vary as the incidence of TB disease raised to the power of −δ so that when δ = 0, the TB disease duration is the same for all stages of HIV and when δ = 1, the increase in TB incidence is exactly balanced by the decrease in TB disease duration and the prevalence of TB disease is unchanged (SI Appendix, section 3). The estimated TB disease duration in HIV-positive as compared with HIV-negative people, averaged over all stages of HIV infection, is 0.31 (95% CI: 0.18–0.53) (7, 30–32). Fitting the TB model to trend data for South Africa and setting δ = 0.60 (95% CI: 0.20–0.86) matches the estimated average disease duration.

The incidence rate for TB among people on and off ART, IRAT+, has been measured in several studies (9–19), giving an average value of 0.39 ± 0.06 ranging from 0.2 to 0.75 (SI Appendix, section 4). We assume that the duration of TB and setting δ = 0.60 to the decrease in incidence as it does for people not on ART (SI Appendix, section 4).

Trend data are available for HIV prevalence in adults aged 15–49 y and for TB notification rates in the whole population in 18 countries in sub-Saharan Africa (1, 6). The quality of trend data collected in public health facilities is variable, and we exercised judgment in deciding which datasets are acceptable for use in this analysis. In several countries, the data show large fluctuations over time that are inconsistent with the known epidemiology of TB, and this led us to exclude seven datasets. In Côte d’Ivoire and Zimbabwe, the prevalence of HIV has been falling rapidly for several years and early treatment will add little to current trends if they continue. In those countries for which the prevalence of HIV has peaked, this has been followed by a small decline in TB incidence, the relation of the decline is the same across all the countries included in the analysis, we allowed the decline to vary and then found the value that gave the best fit over all countries (full dataset provided in SI Appendix, section 5).

We let the coverage of HIV testing increase logistically from 5% in 2008 to 95% in 2015 and consider strategies in which people are tested once a year, on average, and start ART if they have been infected for more than 1, 2, or 5 y; if their CD4+ cell counts are less than 200, 350, or 500 cells/μL or if they start as soon as they test positive for HIV.

To check the validity of the model, we first compare the estimates of IRAH, the TB incidence in HIV-positive compared with HIV-negative people, with direct estimates for six countries; the estimates are not significantly different (SI Appendix, section 7). Second, we estimate the mean CD4+ cell count at the onset of TB disease. For the nine countries under consideration, the value is 230 ± 55 cells/μL. An earlier review of seven published estimates (5) gave a mean value of 202 ± 67 cells/μL. Because CD4+ cell counts are likely to fall after the onset of TB disease, the agreement between the estimates is acceptable (SI Appendix, section 8).

Finally, we estimate the mean CD4+ cell counts in HIV-negative people in each country to determine the relationship between CD4+ cell counts and the incidence of TB. The incidence of TB increases by 0.30 ± 0.16 per a decline of 100 cells/μL in CD4+ cell counts, which is not significantly different from the value of 0.36 ± 0.12 per 100 cells/μL, the measured value for HIV-positive people (SI Appendix, section 8). The impact of ART on HIV and TB for all nine countries and for different CD4+ cell counts at the start of treatment is given in SI Appendix, Figs. 5A and 5B. The cumulative number of TB cases averted by country is given in SI Appendix, Table S6, details of the uncertainty analysis are given in SI Appendix, section 11, and differences among countries in the response of TB to HIV and ART are given in SI Appendix, section 12.
Anti-retroviral therapy for tuberculosis control in nine African countries

Supporting Information

Brian G. Williams, Reuben Granich, Kevin De Cock, Philippe Glaziou, Abhishek Sharma, Christopher Dye
e-mail: BrianGerardWilliams@gmail.com

1. Model structure

The model for HIV and TB with and without ART is illustrated schematically in Figure S1.

![Figure S1](image)

**Figure S1.** Schematic representation of the HIV-TB model. $H_0$: uninfected with TB or HIV. $H_1$ to $H_4$: four stages of HIV infection. $A_1$ to $A_4$ four stages of HIV infection for people on ART. For each of these nine states there is a corresponding state in which people are also infected with TB labelled $T_i$ (HIV-negative, or HIV-positive not on ART) and $U_i$ (HIV-positive on ART). People move from left to right across the model as people progress through the different stages of HIV; they move down and up as they start and fail ART; they move backwards and forwards to the TB disease state and the TB free state. $D$ indicates people who die of AIDS. Details of the parameters are given in the text.

The dark green ($H_0$) and dark blue ($H_1$ to $H_4$) boxes in Figure S1 describe the HIV model without ART or TB and the corresponding equations are:

\[
\frac{dH_0(t)}{dt} = bN(t - T) - \lambda(P, t)P(t)H_0(t) - \mu H_0(t)
\]

\[
\frac{dH_1(t)}{dt} = \lambda(P, t)P(t)H_1(t) - (\rho + \mu)H_1(t)
\]

\[
\frac{dH_i(t)}{dt} = \rho H_{i-1}(t) - (\rho + \mu)H_i(t) \quad i = 2 \text{ to } 4
\]

where

\[
\lambda(P, t) = \lambda(P)\eta(t)
\]

\[
\lambda(P) = \lambda_0 \, e^{-aP(t)}
\]
In Equations 1 to 8 $H_0(t)$ is the number of susceptible adults in the population, $N(t)$ is the total number of adults, $H_i(t)$ is the number of adults in stages $i = 1$ to 4 of HIV infection, and $P(t)$ is the adult prevalence of HIV. The rate of progression, $\rho$, is the same from each stage to the next. $b$ is the annual birth rate; $\bar{t}$ is set to 15 years and gives the delay between birth and reaching adulthood since we only include adults in the HIV model; $\mu$ is the background mortality rate; $\rho$ determines the rate of progression from each stage of HIV-infection to the next and from the last stage to death; $\lambda(P)$ allows the transmission to decline at a rate $a$ as the prevalence increases so that the peak prevalence of HIV can be adjusted to fit the data; $\eta(t)$ determines the reduction in transmission arising from changes in behaviour over time, $\eta_\infty$ is the asymptotic value of the reduction in transmission due to changes in behaviour, $t_0$ determines the timing of the changes which happen at a rate $\gamma$.

The HIV-progression parameter $\rho = 0.30/\text{year}$ is chosen to fit a $\Gamma$-distribution, with four stages, to a Weibull distribution with a mean of 11 years (1). $\lambda_0$, $a$, $\eta_\infty$, $t_0$ and $\gamma$ are varied to fit the trend data for HIV-prevalence for each country. The initial rate of increase in prevalence and incidence is determined mainly by $\lambda_0$, the peak prevalence mainly by $a$, the timing of the reduction, if any, in transmission due to changes in behaviour by $t_0$, the magnitude of the reduction by $\eta_\infty$ and the rate at which the reduction occurs by $\gamma$. The HIV-trend data are taken from UNAIDS (2) who fitted their epidemiological projection package to the data from each country. Since the UNAIDS model is similar to the model used here we obtain, as expected, a good fit to their data. We use our model in order to determine the number of people in each stage of infection as the epidemic matures.

**HIV model with ART but not TB**

The red boxes ($A_1$ to $A_4$) in Figure S1 allow HIV positive people to start ART and we include four stages, $A_i(t)$, for those on ART each corresponding to one of the four stages, $H_i(t)$, of infection in those not on ART. As in our earlier publication (3) people start ART at a rate $\tau$ and fail ART at a rate $\phi$. Equations 2 and 3 then become

\[
\frac{dH_i(t)}{dt} = R_i(t) - \tau_i H_i(t) + \phi A_i(t) \tag{9}
\]

where $R_i(t)$ is the right-hand-side of Equation 2 for $i = 1$ or Equation 3 for $i = 2$ to 4, and we introduce the following equations for those on ART

\[
\frac{dA_i(t)}{dt} = \tau_i H_i(t) - (\phi + \mu) A_i(t) + \sigma \left( A_{i-1}(t) - A_i(t) \right) \tag{10}
\]

for $i = 1$ to 4. Assuming that the life-expectancy of HIV-positive people on ART is double the life-expectancy of HIV-positive people not on ART (4) we set $\sigma = \rho/2$. 

\[
\eta(t) = \eta_\infty + (1-\eta_\infty) \frac{e^{-\gamma(t-t_0)}}{1 + e^{-\gamma(t-t_0)}} \tag{6}
\]

\[
H(t) = \sum_{i=1}^{4} H_i(t) \tag{7}
\]

\[
P(t) = \frac{H(t)}{N} \tag{8}
\]
To allow for the effect that those people on ART have on transmission we modify Equation 8 which becomes

\[ P(t) = \frac{H(t) + \varepsilon A(t)}{N(t)} \]

so that, following our earlier notation (3), \( \varepsilon \) allows for the reduction in infectivity of those on ART. Few studies have been carried out to measure transmission either comparing people on and off ART or as a function of viral load. As in our previous study we set \( \varepsilon = 0.01 \). The sensitivity analysis in that study showed that increasing \( \varepsilon \) to 0.04 would lead to a steady state reduction in HIV incidence of 92% rather than 96%. (For details of the data and the sensitivity analysis see the Supporting On-line Information in (3) also available from the first author on request.) Measuring transmission as a function of viral load is difficult, especially at very low viral load. Although it is generally agreed that ART reduces HIV transmission there is still no consensus on the precise extent of the reduction. Field trials, including the HIV Prevention Trials Network (HPTN) study 052, are underway to assess the impact of ART on transmission in discordant couples. These results will help to assess the impact of test-and-treat on HIV. It will also be important to ensure that risk compensation, among people on ART, does not significantly reduce the impact of ART on HIV-transmission.

Model with HIV, ART and TB

The light green (\( T_0 \)), light blue (\( T_1 \) to \( T_4 \)) and pink (\( U_1 \) to \( U_4 \)) boxes in Figure S1 allow people to develop TB from the corresponding states without TB. We are concerned with the impact of HIV on TB, beginning with TB in an endemic steady-state and assuming that without HIV TB would remain in a steady state for the duration of the simulations. In previous publications (5-7) we used a full transmission model for TB with the TB model repeated for each stage of the HIV epidemic in order to compare the effectiveness and the cost-effectiveness for TB control of various interventions targeted either at TB or HIV. Here we are not concerned with the impact of other interventions to control TB and this allows us to simplify the model and focus on the interaction between TB and HIV. We consider two states of TB for each stage of HIV; those with TB disease and those without. We limit ourselves to this parsimonious model for three main reasons. Firstly, trend data on the proportion of people who have latent TB or the proportion of cases that arise from reactivation or exogenous transmission are not available. Secondly, studies of the impact of HIV on TB and of the impact of ART on TB in those with HIV only report the impact on all cases of TB disease and do not distinguish between the impact on break-down from latent infection and on the risk of acquiring a new infection. Finally, the model provides a good fit the trend data from all those countries in sub-Saharan Africa for which good data are available. Considering only the development of, and recovery from, TB the corresponding equations are (Figure S1):

\[ \frac{dH_i(t)}{dt} = -\beta_i Q(t)H_i(t) + \delta_i T_i(t) \]
\[
\frac{dI_i(t)}{dt} = \beta_i Q(t)H_i(t) - \delta_i T_i(t) \\
\frac{dA_i(t)}{dt} = -\gamma_i Q(t)A_i(t) + \xi_i U_i(t) \\
\frac{dU_i(t)}{dt} = \gamma_i Q(t)A_i(t) - \xi_i U_i(t)
\]

where

\[Q(t) = \sum_{i=0}^{4} \frac{T_i(t) + U_i(t)}{N(t)}\]

is the prevalence of tuberculosis. In Equations 10 to 16, \(i = 0\) to 4 and, by definition, \(U_0(t) = 0\) for all \(t\). \(\beta_i\) and \(\gamma_i\) are the transmission parameters for people not on ART and on ART, respectively, in state \(i\) and these increase as \(i\) increases as described below (Section 2); \(\delta_i\) and \(\xi_i\) are the rates at which people with active TB recover or are successfully treated among those not on ART and on ART, respectively, so that \(D_i = 1/\delta_i\) and \(E_i = 1/\xi_i\) are the corresponding durations of disease as discussed below (SI Sections 3 and 4).

**The full model**

Combining the models for HIV progression, ART provision and the development of TB, the full set of 18 equations (Equations 17 to 26 allowing for the repeat values of the subscript \(i\)) and the five supplementary equations (Equations 27 to 31) describing the model in Figure S1 is as follows:

\[
\frac{dH_0(t)}{dt} = bN(t - \tau) - (\lambda(P,t)P(t) + \beta_0 Q(t) + \mu)H_0(t) + \delta_0 T_0(t) \\
\frac{dH_i(t)}{dt} = \lambda(P,t)P(t)H_i(t) - (\beta_i Q(t) + \rho + \tau_1 + \mu)H_i(t) + \delta_i T_i(t) + \phi A_i(t) \\
\frac{dH_i(t)}{dt} = \rho H_{i-1}(t) - (\beta_i Q(t) + \rho + \tau_1 + \mu)H_i(t) + \delta_i T_i(t) + \phi A_i(t) \\
\frac{dT_0(t)}{dt} = \beta_0 Q(t)H_0(t) - (\lambda(P,t)P(t) + \delta_0 + \mu)T_0(t) \\
\frac{dT_i(t)}{dt} = \lambda(P,t)P(t)T_i(t) + \beta_i Q(t)H_i(t) + \phi U_i(t) - (\delta_i + \tau_1 + \rho + \mu)T_i(t) \\
\frac{dT_i(t)}{dt} = \rho T_{i-1}(t) + \beta_i Q(t)H_i(t) + \phi U_i(t) - (\delta_i + \tau_1 + \rho + \mu)T_i(t) \\
\frac{dA_0(t)}{dt} = \gamma_0 Q(t) - (\rho + \tau_1 + \phi + \mu)A_0(t) + \xi_0 U_0(t) \\
\frac{dA_i(t)}{dt} = \gamma_i Q(t)A_i(t) + \tau_1 F_i(t) - (\delta_i + \tau_1 + X + \mu)A_i(t) \\
\frac{dA_i(t)}{dt} = \tau_i H_i(t) - (\gamma_i Q(t) + \phi + \mu)A_i(t) + \xi_i U_i(t) + \sigma A_{i-1}(t) \\
\frac{dA_i(t)}{dt} = \tau_i H_i(t) - (\gamma_i Q(t) + \phi + \mu)A_i(t) + \xi_i U_i(t) + \sigma A_{i-1}(t) \\
\frac{dA_i(t)}{dt} = \tau_i H_i(t) - (\gamma_i Q(t) + \phi + \mu)A_i(t) + \xi_i U_i(t) + \sigma A_{i-1}(t)
\]
In these equations the different states of people in the population are defined in Table S1.

Table S1. The states in the model. \( i = 1 \) to 4 represents the four stages of progression for people infected with HIV.

<table>
<thead>
<tr>
<th>Label</th>
<th>HIV</th>
<th>TB</th>
<th>ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>( H_0 )</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>( H_i )</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>( T_0 )</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>( T_i )</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>( A_i )</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>( U_i )</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

In Equations 17 to 31 the parameters represent the processes and quantities as described in Table S2.

**Implementing the model**

For each country we first fit the HIV model (Equations 1 to 8) to the data for the time trend in the prevalence of HIV. This enables us to determine the proportion of people in each stage of HIV-infection and we let the HIV epidemic drive the TB epidemic.

We initialize the TB model to a steady state for TB without HIV by setting the disease duration \( \delta_0 \) to one year, setting the initial incidence of TB, calculating the initial prevalence of TB and then varying the transmission parameter \( \beta_0 \) to fit the initial steady state prevalence of TB. We then introduce the HIV epidemic, as determined by the HIV model, and let this drive
the TB epidemic. The dependence of the various parameters on the stage of the HIV-infection is discussed below in Sections 2 to 4.

**Model parameters**

The HIV parameters are calculated by fitting the trend data for each country to the epidemics of HIV. We are concerned to explore the likely impact of HIV and ART on TB so that there are four key parameters that determine the time trends of the TB epidemics, two global and two local. The first global parameter, $\delta$, determines the disease duration ratio (Equation 36), the second, $IRR_{ART}^{TB}$, is the incidence rate ratio for TB in those who are or are not receiving ART (Equation 37). For each country we fit the data by varying $I_0(0)$, the incidence of TB before the start of the HIV epidemic, and the CD4$^+$ cell count in HIV negative people, $C_0$ (Equation 32). To fit the trends in TB we therefore have two global parameters, which we apply across all countries, and two local parameters for each country.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>$b$</td>
<td>Birth rate</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Background mortality</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>Force of infection</td>
</tr>
<tr>
<td>$\rho$</td>
<td>Rate of HIV progression not on ART</td>
</tr>
<tr>
<td>$\tau_i$</td>
<td>Rate at which people start ART</td>
</tr>
<tr>
<td>$\beta_i$</td>
<td>Rate at which people not on ART develop TB</td>
</tr>
<tr>
<td>$\delta_i$</td>
<td>Rate at which people not on ART recover from TB</td>
</tr>
<tr>
<td>$\phi$</td>
<td>Rate at which people fail ART</td>
</tr>
<tr>
<td>$\gamma_i$</td>
<td>Rate at which people on ART develop TB</td>
</tr>
<tr>
<td>$\xi_i$</td>
<td>Rate at which people on ART recover from TB</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Rate of HIV progression on ART</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Rate at which transmission declines with prevalence</td>
</tr>
<tr>
<td>$\eta$</td>
<td>Reduction in transmission with time if behaviour changes</td>
</tr>
<tr>
<td>$P$</td>
<td>Prevalence of HIV</td>
</tr>
<tr>
<td>$Q$</td>
<td>Prevalence of TB</td>
</tr>
</tbody>
</table>

Two important points should be noted in relation to the parameter estimation. First the fitted trends depend only on the disease duration ratio, and not separately on the disease duration for HIV-positive and negative people. If we change the disease duration by multiplying the disease duration in each class of people by, say $\alpha$, and refit the data, then the incidence of TB in each class is multiplied by $\alpha$. In fitting the TB incidence from the model to
the data, the prevalence of TB in each class is reduced by $\alpha$ and the fitted incidence remains the same. Consequently, the results do not depend on the initial assumption made about the disease duration in HIV-negative people. Second, the results do not depend on the value assumed for the rate of increase of TB incidence with CD4$^+$ cell count; rather this parameter only allows us to make an estimate of the CD4$^+$ cell count in HIV-negative people. The reason for this is clear from Equation 32: adjusting $C_0$ to get the best fit to the data is equivalent to keeping $C_0$ fixed and adjusting $\alpha$.

2. TB incidence without ART
In three studies the incidence of TB increased as the CD4$^+$ cell count decreased at a rate $\alpha$ equal to 0.29 $\pm$ 0.20 (8), 0.37 $\pm$ 0.20, (9) and 0.42 $\pm$ 0.17 (10, 11) for each decline of 100 CD4$^+$ cells/µL. These estimates do not differ significantly and the weighted average is $\alpha = 0.36 \pm 0.12$. In the first two studies (8, 9) ART was not available and infected people were progressing to lower CD4$^+$ cell counts; in the third study (10, 11) people were on ART and CD4$^+$ cell counts were measured as they progressed to higher CD4$^+$ cell counts. Letting $I_0$ be the incidence of TB in HIV-negative people whose mean CD4$^+$ cell counts is $C_0$ and $I_i$ be the incidence of TB in people whose CD4$^+$ cell counts is $C_i$ we have

$$I_i = I_0 e^{\alpha(C_0-C_i)} = IR_{\text{HIV}}^{\text{TB}} I_0$$

where $IR_{\text{HIV}}^{\text{TB}}$ is the incidence rate ratio for a person in HIV stage $i$ as compared to an HIV-negative person. We can reparameterize Equation 32 as follows. CD4$^+$ cell counts drop by about 25% immediately after seroconversion and then decline linearly through four stages of infection to death (12) so that

$$C_i = (C_0 - \Delta) - \epsilon t_i$$

where $\Delta$ is the initial drop in CD4$^+$ cell counts immediately after the acute phase of infection and $t_i$ is the mean time since infection for a person in stage $i$. Then Equation 32 may be written

$$I(t) = I_0 R e^{\alpha t}$$

where

$$R = e^{\alpha \Delta}$$

is the increase in the incidence of infection during the acute phase. The average value of the mean CD4$^+$ cell count in 18 studies of HIV-negative people in Africa (12-14) was 879/µL (range: 626 to 1244/µL). With $\alpha = 0.36/100$ cells/µL and $\Delta = 0.25 \times 879$ (12, 15-18), Equation 35 suggests that the incidence in TB at the end of the acute phase will be 2.2 (1.3–3.7) times the incidence in HIV negative people in agreement with previous estimates (9, 19).

3. Disease duration
To determine the impact of AIDS-related TB on transmission we need to know how the duration of TB disease changes as the HIV infection progresses. Since TB disease progresses more rapidly in HIV-positive people than in HIV-negative people, the disease duration ratio $D_i/D_0$ must be less than 1. If $D_i = D_0$ the disease duration ratio is exactly 1 and the disease
duration is independent of HIV infection; if \( D_t \propto 1/I_t \) the decline in disease duration exactly balances the increase in incidence and the prevalence of TB disease is unchanged. We therefore seek a simple functional form to parameterize the relationship between the disease duration and the incidence of infection so that we can vary the relationship between the disease duration and the incidence of infection between these two extremes. To do this we let the duration of TB infectiousness, in each stage, be

\[
\frac{D_i}{D_0} = \left( \frac{I_i}{I_0} \right)^{-d}
\]

With \( d = 0 \) the disease duration is independent of the progression of HIV infection and \( D_i = D_0 \) in all stages; with \( d = 1 \) the duration is inversely proportional to the incidence of infection and the increase in TB among HIV-positive people has no impact on transmission.

The disease duration ratio in HIV-positive and HIV-negative people is difficult to measure directly and where it has been measured it has been averaged over all stages of infection. An early estimate of the disease duration ratio was 0.25 ± 0.14 (20). An estimate of the disease duration ratio for sputum smear-positive (SS+) TB in South African gold miners, averaged over all stages of infection, gave a value of 0.13 (0.02–0.75) (21) and an estimate in the Western Cape gave a value of 1.34 (0.41–6.56) (22). The weighted geometrical mean of these various estimates is 0.31 (0.18–0.53) and fitting the model presented here to the data for South Africa gives \( d = 0.60 \) (0.20–0.86).

Because \( d \) determines the impact that the HIV-epidemic has on TB in HIV-negative people, the incidence rate ratio, \( IRR_{\text{HIV}}^{\text{TB}} \), the ratio of the incidence of TB in HIV-positive and HIV-negative people, depends on the value of \( d \). For five countries in sub-Saharan Africa independent estimates of \( IRR_{\text{HIV}}^{\text{TB}} \) have been made using data from cross-sectional surveys of the prevalence of HIV in TB patients and the prevalence in adults. In Section 7 we show that \( IRR_{\text{HIV}}^{\text{TB}} \) calculated from this model is not significantly different from the values calculated from survey data where independent estimates are available. An uncertainty analysis (Section 11) shows that the impact of ART on TB in the presence of HIV is insensitive to the precise value of \( d \).

**Impact of HIV on transmission**

HIV increases the risk of TB and reduces the duration of disease but the way in which these balance out at a population level is not entirely intuitive and we illustrate it with reference to the data for South Africa. In South Africa, at a steady state, HIV-positive people are at 12.4 times greater risk of TB than HIV-negative people, averaged over all CD4+ cell counts. With \( \delta = 0.6 \) (Equation 18) the disease duration is reduced by a factor of \( 12.4^{0.6} = 4.5 \) so that each HIV-positive person transmits 12.4/4.5 = 2.7 times as much TB as each HIV negative person. Since, in South Africa at the peak of the epidemic 16% of adults are HIV positive, overall transmission increases by a factor of 0.16×2.7 + 0.84 = 1.27. The risk of TB in HIV-negative people is therefore increased by 27% as a result of the epidemic of HIV. However, the proportion of people in the population who are HIV-negative has fallen to 84% of what it was.
so that the number of cases of TB in people who are HIV negative only increases by a factor of \(1.27 \times 0.84 = 1.07\) or 7%.

Figure S2. Estimates of the incidence rate ratio for TB among people on ART and not on ART. Details of studies in Table S3. Heavy red line weighted geometric mean; 95% confidence limits on the mean (light red lines) and of the population distribution (green lines).

4. Impact of ART on TB

Having parameterized the TB model without ART we need to determine the extent to which ART reduces the incidence of TB in HIV-positive people. The impact of ART on TB incidence has been measured either by comparing the incidence soon after the start of ART with the incidence up to five years later or by comparing the incidence among people on ART matched to people not on ART. The data are shown in Figure S2 and in Table S3. In these studies the mean incidence rate ratio for TB among people on and off ART, \(IRR_{\text{ART}}^{TB}\), is 0.39 (0.32 to 0.46) and should not be confused with \(IRR_{\text{HIV}}^{TB}\), the incident rate ratio for TB among people who are HIV-positive and HIV-negative. We then have

\[
A_i = IRR_{\text{ART}}^{TB} I_i
\]

and we assume that the duration of infection bears the same relationship to \(I_0\) as it does for people not on ART so that

\[
\frac{E_i}{D_0} = \left(\frac{A_i}{I_0}\right)^{-\delta}
\]

where \(E_i\) is the duration of TB infectiousness for a person on ART in stage \(i\).
Table S3. Reduction in the incidence of TB for people on ART and the approximate duration of follow up. ‘Mean’ gives the geometric weighted mean. Lower and upper are 95% confidence limits.

<table>
<thead>
<tr>
<th>Number</th>
<th>Mean</th>
<th>Lower</th>
<th>Upper</th>
<th>Follow-up (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.48</td>
<td>0.36</td>
<td>0.64</td>
<td>0.7</td>
</tr>
<tr>
<td>2</td>
<td>0.36</td>
<td>0.26</td>
<td>0.50</td>
<td>0.7</td>
</tr>
<tr>
<td>3</td>
<td>0.36</td>
<td>0.25</td>
<td>0.51</td>
<td>1.5</td>
</tr>
<tr>
<td>4</td>
<td>0.49</td>
<td>0.25</td>
<td>0.96</td>
<td>3.8</td>
</tr>
<tr>
<td>5</td>
<td>0.60</td>
<td>0.39</td>
<td>0.89</td>
<td>1.0</td>
</tr>
<tr>
<td>6</td>
<td>0.36</td>
<td>0.15</td>
<td>0.79</td>
<td>2.0</td>
</tr>
<tr>
<td>7</td>
<td>0.25</td>
<td>0.06</td>
<td>0.70</td>
<td>3.0</td>
</tr>
<tr>
<td>8</td>
<td>0.48</td>
<td>0.39</td>
<td>0.59</td>
<td>2.0</td>
</tr>
<tr>
<td>9</td>
<td>0.08</td>
<td>0.01</td>
<td>0.88</td>
<td>0.9</td>
</tr>
<tr>
<td>10</td>
<td>0.19</td>
<td>0.03</td>
<td>1.09</td>
<td>1.5</td>
</tr>
<tr>
<td>11</td>
<td>0.26</td>
<td>0.16</td>
<td>0.40</td>
<td>3.8</td>
</tr>
<tr>
<td>12</td>
<td>0.20</td>
<td>0.10</td>
<td>0.50</td>
<td>2.5</td>
</tr>
<tr>
<td>13</td>
<td>0.29</td>
<td>0.18</td>
<td>0.48</td>
<td>4.0</td>
</tr>
<tr>
<td>14</td>
<td>0.20</td>
<td>0.10</td>
<td>0.60</td>
<td>3.0</td>
</tr>
</tbody>
</table>

| Mean | 0.39 | 0.33 | 0.46 |

1. Low income countries (23); 2. High income countries (23); 3. South Africa (24); 4. Europe (25); 5. Europe and North America (26); 6. Europe and North America (26); 7. Europe and North America (26); 8. Brazil (27); 9. Italy (28); 10. Brazil (29); 11. Spain (30); 12. United States (31); 13. Europe (32); 14. Brazil (33)

5. Complete data set

Before fitting the data we adjusted the HIV data for Ghana, Malawi and Lesotho. In Ghana (Figure S3A) the initial rate of increase is almost double the rate in the other countries, the turn over at the peak is very fast, and the decline is rapid. The implied effect of the behaviour change is to reduce transmission by 70% in less than three months (Figure S3A). Furthermore, the fit to the TB data is not good (Figure S3B). We therefore assumed that the initial increase was half as fast as the reported rate of increase and used the data shown in Figure S5 rather then the data as shown in Figure S3. This gives a more convincing estimate of the trend in incidence and a much better fit to the TB data.
Similar problems arise with the data for Malawi (Figure S4). The initial rise is very fast, although not as fast as in Ghana, the decline in incidence arising from behaviour change is also fast and the fit to the TB data is not good. Furthermore, the prevalence of HIV in Malawian men working on the gold-mines in South Africa in 1987 was 4% (34). The value implied by the UNAIDS data, 0.36%, is therefore too low by a factor of about 10. Here we set the value in 1987 to 4.8% bearing in mind that the prevalence in women is generally about 30% to 40% higher than in men. We omit the data points corresponding to the initial rise and this gave the results shown in Figure S5.

Lesotho is similar to Malawi. The data as given suggest a doubling time of the HIV prevalence in Lesotho of 2.8 months which is four times faster than in any other country in the region. We therefore allow the initial rise in prevalence to take place more slowly, assuming that the rapid rise was a reflection of better monitoring, to give an initial doubling time of about one year as shown in Figure S5.

The TB data for Mali, Mozambique, Namibia, Niger and Nigeria are not inconsistent with the model fits but they are highly variable, in ways that are not biologically plausible, and are excluded from further analysis. The data for Angola are also inconsistent. The incidence rate ratio implied by the fit to the TB data reaches 130 in 2008 which is four times greater than in Gabon, the next highest rate ratio among the sites that are included for further analysis. Furthermore, an incidence rate ratio of 100 would imply that the prevalence of HIV in TB patients would be 67% which is unlikely given the prevalence of HIV. Having made these adjustments we fit the available trend data to the model as described in the text.
Figure S5. Eleven countries (the nine under consideration plus Côte d’Ivoire and Zimbabwe) for which reliable and consistent data on trends in HIV prevalence and TB notifications are available. Left: HIV prevalence (red), incidence (blue), mortality (black), data (red dots). Centre: TB notification rates (red dots), and fitted estimate (red line). Notification rate in HIV-negative people (blue line). Right: incidence rate ratio for the prevalence of HIV in TB patients compared to the prevalence in adults.

In some countries the prevalence of HIV has peaked and has now fallen slightly; in others it has only just reached a peak. For countries in which the prevalence of HIV is decreasing we allow for a logistic reduction in transmission arising from changes in behaviour (35). In all but two countries we constrain the magnitude, but not the timing, of the reduction to have the same value, which we determine by fitting the model to the available HIV trend-data. In Côte d’Ivoire and Zimbabwe the data suggest that the reduction is significantly greater than elsewhere and the prevalence in these two countries continues to fall rapidly. Since HIV appears to be declining rapidly, for reasons that are not understood, early treatment with ART will have little additional effect on transmission, although it may well benefit individual people. We exclude these two countries from further analysis but note that, especially in Zimbabwe, our model gives a good fit to the observed decline in TB incidence. Knowing the reasons for the HIV declines in Côte d’Ivoire and Zimbabwe could provide

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valuable lessons for the control of HIV in other countries in Africa. Figure S5 gives the results for the nine countries which are included in this analysis as well as Côte d’Ivoire and Zimbabwe.

6. Parameter values for the country fits

The fitted values of the parameters for the different countries are given in Table S4. For the HIV-epidemics $\lambda_0$ determines the initial rate of increase in the prevalence and $a$ determines the peak prevalence (see Equation 28). ‘Timing’, the time at which the prevalence reaches half of its peak value, is varied by changing the prevalence of HIV in 1980 and allows for the fact that the epidemic in Zambia started much earlier than the epidemic in South Africa, for example.

Table S4. The country specific parameters used to fit the data. Three parameters are varied to fit the HIV-epidemic in each country: $\lambda_0$ the initial force of infection (Equation 28); $a$ the rate at which the risk of HIV-infection declines as prevalence increases (Equation 28); and ‘Timing’ the year in which the prevalence of HIV reaches half its maximum value. Two parameters are varied to fit the TB epidemic in each country: The initial CD4 cell count and the initial incidence of TB ($I_0$). From these two parameters we can calculate the relative risk of infection in each stage of infection, $\beta_i$, $i = 1$ to 4 as described in the text.

<table>
<thead>
<tr>
<th>Country</th>
<th>$\lambda_0$/yr</th>
<th>$a$</th>
<th>Timing</th>
<th>Initial CD4/μL</th>
<th>$I_0$/100k</th>
<th>$\beta_1$</th>
<th>$\beta_2$</th>
<th>$\beta_3$</th>
<th>$\beta_4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botswana</td>
<td>0.80</td>
<td>6.7</td>
<td>1994</td>
<td>666</td>
<td>228</td>
<td>2.33</td>
<td>3.70</td>
<td>5.88</td>
<td>9.33</td>
</tr>
<tr>
<td>Gabon</td>
<td>0.37</td>
<td>14.7</td>
<td>1996</td>
<td>1262</td>
<td>80</td>
<td>4.98</td>
<td>11.96</td>
<td>28.70</td>
<td>68.91</td>
</tr>
<tr>
<td>Ghana</td>
<td>0.70</td>
<td>81.2</td>
<td>1989</td>
<td>1147</td>
<td>38</td>
<td>4.30</td>
<td>9.52</td>
<td>21.09</td>
<td>46.73</td>
</tr>
<tr>
<td>Lesotho</td>
<td>1.00</td>
<td>7.9</td>
<td>1994</td>
<td>729</td>
<td>212</td>
<td>2.53</td>
<td>4.19</td>
<td>6.94</td>
<td>11.51</td>
</tr>
<tr>
<td>Malawi</td>
<td>0.48</td>
<td>9.6</td>
<td>1989</td>
<td>972</td>
<td>71</td>
<td>3.44</td>
<td>6.76</td>
<td>13.28</td>
<td>26.06</td>
</tr>
<tr>
<td>South Africa</td>
<td>0.77</td>
<td>12.5</td>
<td>1997</td>
<td>973</td>
<td>189</td>
<td>3.45</td>
<td>6.77</td>
<td>13.29</td>
<td>26.10</td>
</tr>
<tr>
<td>Swaziland</td>
<td>0.95</td>
<td>6.7</td>
<td>1996</td>
<td>946</td>
<td>148</td>
<td>3.33</td>
<td>6.43</td>
<td>12.39</td>
<td>23.89</td>
</tr>
<tr>
<td>Tanzania</td>
<td>0.75</td>
<td>25.4</td>
<td>1989</td>
<td>1200</td>
<td>55</td>
<td>4.60</td>
<td>10.58</td>
<td>24.33</td>
<td>55.93</td>
</tr>
<tr>
<td>Zambia</td>
<td>1.00</td>
<td>11.8</td>
<td>1987</td>
<td>1184</td>
<td>78</td>
<td>4.51</td>
<td>10.24</td>
<td>23.29</td>
<td>52.94</td>
</tr>
</tbody>
</table>

To fit the TB epidemics we vary two parameters for each country, the initial value of the CD4$^+$ cell count and the initial incidence of TB. To estimate the transmission parameter $\beta_0$ (Figure S1 and Equation 17) we assume that the TB disease duration for HIV-negative people is 1 year so that the initial prevalence (before the epidemic of HIV starts) is equal to the initial incidence and $\beta_0 = 1$. The rate at which the incidence of TB increases as the CD4$^+$ cell count decreases then depends on the initial CD4$^+$ cell count and the initial incidence through Equation 32. To estimate the parameters $\beta_i$, $i = 1$ to 4 (Figure S1 and Equations 18 to 22) we then calculate the relative incidence of TB in each stage of HIV-infection so that
\[ \beta_i = \beta_0 \frac{I_i}{I_0} \]

One could vary all five parameters \( \beta_i, i = 0 \text{ to } 4, \) but the advantage of the approach taken here is that it reduces the number of parameters required to fit the TB data for each country from five to two and at the same time allows us to use the fits to estimate the CD4+ cell count in HIV-negative people and then to compare these estimates with observed values to check for consistency (see Table S5).

7. Comparing estimates of the IRR

In some countries the prevalence of HIV in TB patients and in adults has been measured in cross-sectional surveys. Since the odds ratio for HIV in TB patients and in adults gives the \( IRR_{\text{HIV}} \) for TB in HIV positive and HIV negative people (36) we can compare the \( IRR_{\text{HIV}} \) obtained here with the \( IRR_{\text{HIV}} \) estimated from survey data (Figure S6). The two estimates do not differ significantly but the estimates made using survey data are uncertain and a true difference between estimated and observed values is difficult to detect.

![Figure S6. The IRR calculated using survey data plotted against the value calculated using this model with \( \delta = 0.60 \). The diagonal line is the line of equality.](image)

8. CD4 cell counts and TB incidence in HIV-negative people

The model allows us to estimate the CD4+ cell count and the incidence of TB in HIV-negative people (Figure S7). The slope of the regression line is 0.30 ± 0.16 per 100 cells/μL which is not significantly different from the value of 0.36 ± 0.06 per 100 cells/μL, the value assumed for HIV-positive people.

Measurements of the CD4+ cell count in HIV-negative people are only available for four of the nine countries considered here: Botswana, Tanzania, South Africa and Zambia (12, 13). The results are given in Table S5. The estimates made using this model are within about 30% of the values measured directly in surveys. The estimate for South Africa is significantly less than the measured value and the estimates for Tanzania and Zambia are significantly greater than the published values. However, in other countries in Africa where more than one
survey has been carried out the mean CD4⁺ cell counts differ by up to 101/μL in Ethiopia, 259/μL in Guinea Bissau, 28/μL in Nigeria, 110/μL in Tanzania and 136/μL in Uganda. The average difference between the estimates made here and the published estimates is 235/μL and the differences may be due to differences in the populations sampled.

Table S5. CD4⁺ cell counts/μL in HIV negative people from published surveys and as estimated in this study.

<table>
<thead>
<tr>
<th>Country</th>
<th>CD4 survey ± SE</th>
<th>CD4 this study ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botswana</td>
<td>626 ± 26</td>
<td>666 ± 40</td>
</tr>
<tr>
<td>South Africa</td>
<td>1179 ± 36</td>
<td>964 ± 35</td>
</tr>
<tr>
<td>Tanzania</td>
<td>911 ± 38</td>
<td>1201 ± 28</td>
</tr>
<tr>
<td>Zambia</td>
<td>840 ± 60</td>
<td>1189 ± 26</td>
</tr>
</tbody>
</table>

9. Impact of regular testing for HIV on ART and TB

For the nine countries under consideration Figure S8 shows the impact on HIV of starting ART when if the CD4⁺ cell count is less than 200, 350 or 500/μL or starting immediately while Figure S9 shows the corresponding impact on TB.
Figure S8. HIV in nine countries for which consistent data on trends in HIV prevalence and TB notifications are available. The four columns correspond to people starting ART when their CD4 cell count is below 200, 350 or 500/µL or if they start immediately, irrespective of CD4+ cell count. HIV prevalence not on ART (red), data (red dots) and on ART (pink); HIV incidence (blue); AIDS related mortality not on ART (black) and on ART (grey).
Figure S9. TB in nine countries for which consistent data on trends in HIV prevalence and TB notifications are available. The four columns correspond to people starting ART when their CD4 cell count is below 200, 350 or 500/μL or if they start immediately, irrespective of CD4+ cell count. TB incidence from HIV-negative people (dark blue); including HIV-positive people, not on ART (pink) or HIV-positive people on ART (light blue); total (red); data (red dots).
10. TB cases averted by country

We estimate the number of TB cases that arise between 2010 and 2015, and between 2015 and 2050 if there is no expansion of ART or with regular testing and immediate treatment (Table S6). Among the nine countries included in the final analysis, regular testing with immediate treatment reduces the number of TB cases from 3.4 million to 2.7 million between 2010 and 2015 and from 15 million to 9 million between 2015 and 2050.

Table S6. The current population of the nine countries included in this study, the cumulative number of TB cases between 2009 and 2015 and between 2015 and 2050 with no expansion of ART, and with regular testing and immediate treatment and the reduction from one to the other. All numbers in millions.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Botswana</td>
<td>1.882</td>
<td>0.070</td>
<td>0.262</td>
<td>0.060</td>
<td>0.209</td>
<td>0.009</td>
<td>0.053</td>
</tr>
<tr>
<td>Gabon</td>
<td>1.331</td>
<td>0.021</td>
<td>0.089</td>
<td>0.020</td>
<td>0.068</td>
<td>0.001</td>
<td>0.021</td>
</tr>
<tr>
<td>Ghana</td>
<td>23.478</td>
<td>0.088</td>
<td>0.485</td>
<td>0.086</td>
<td>0.443</td>
<td>0.003</td>
<td>0.042</td>
</tr>
<tr>
<td>Lesotho</td>
<td>2.008</td>
<td>0.076</td>
<td>0.294</td>
<td>0.066</td>
<td>0.226</td>
<td>0.010</td>
<td>0.068</td>
</tr>
<tr>
<td>Malawi</td>
<td>13.925</td>
<td>0.182</td>
<td>0.740</td>
<td>0.165</td>
<td>0.564</td>
<td>0.017</td>
<td>0.176</td>
</tr>
<tr>
<td>Tanzania</td>
<td>40.454</td>
<td>0.408</td>
<td>1.906</td>
<td>0.379</td>
<td>1.495</td>
<td>0.029</td>
<td>0.411</td>
</tr>
<tr>
<td>South Africa</td>
<td>48.577</td>
<td>2.173</td>
<td>9.282</td>
<td>1.578</td>
<td>4.708</td>
<td>0.595</td>
<td>4.575</td>
</tr>
<tr>
<td>Swaziland</td>
<td>1.141</td>
<td>0.057</td>
<td>0.191</td>
<td>0.049</td>
<td>0.131</td>
<td>0.008</td>
<td>0.059</td>
</tr>
<tr>
<td>Zambia</td>
<td>11.922</td>
<td>0.339</td>
<td>1.366</td>
<td>0.306</td>
<td>0.962</td>
<td>0.034</td>
<td>0.404</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>144.718</strong></td>
<td><strong>3.415</strong></td>
<td><strong>14.616</strong></td>
<td><strong>2.709</strong></td>
<td><strong>8.806</strong></td>
<td><strong>0.706</strong></td>
<td><strong>5.810</strong></td>
</tr>
</tbody>
</table>

11. Uncertainty analysis

The statistical uncertainty in the predicted impact of ART on TB, given the epidemic of HIV and the structure of the TB model, arises from a) the uncertainty in fitting the two country specific parameters: $I_0$ that determines the steady state incidence of TB before the epidemic of HIV starts and $C_0$ that determines, indirectly, the extent to which HIV increases the risk of TB disease (Equation 32); and b) the uncertainty in the two global parameters $\delta$ (Equation 36) which defines the ratio of the duration of TB disease in HIV-positive and HIV-negative people and hence the extent to which HIV increases the prevalence of TB disease; and $IRR_{ART}^{TB}$ (Equation 37) which determines the extent to which ART reduces the incidence of TB disease.

We first varied the two country specific parameters, $I_0$ and $C_0$, to determine the 95% confidence limits in parameter space consistent with the observed trend data. We then used this uncertainty to determine the variation in the predicted reduction in TB incidence in 2015 and 2050. The average value of this uncertainty across countries had 95% uncertainty ranges of ±5%. As shown below, this is much less than introduced by the other two sources of uncertainty.

The two global parameters introduce a greater degree of uncertainty. The first is $d$ (Equation 36) which determines the extent to which the epidemic of TB in HIV positive...
people changes the overall prevalence of TB disease and hence overall transmission. The uncertainty introduced through imprecision in our estimate of $d$ is limited by the constraint that the model must fit the TB trend data. Consider, for example, the impact of test and treat in South Africa allowing $d$ to range from 0 to 1 around the estimate value of 0.60. For example, setting $d = 0$ increases the duration of infection among HIV positive people and hence increases the incidence of TB. However, to fit the trend data, we have to reduce the rate at which the incidence of TB increases as the infection progresses and this reduces the incidence in both HIV-positive and HIV-negative people as shown in Figure S10.

When $d = 0$ the epidemic of TB in HIV-positive people increases overall transmission and increases the number of cases of TB in HIV negative people (Figure S10A, left); when $d = 1$ the epidemic of TB in HIV-positive people does not affect the overall transmission and the number of cases of TB in HIV negative people falls simply because the number of people who are HIV-negative falls (Figure S10C, right). When $d = 0.60$ the incidence rate in HIV negative people increases slightly but the number of HIV-negative people falls slightly and the overall contribution to the incidence of TB disease from HIV-negative people remains roughly constant (Figure S10B, centre).

![Figure S10. The TB epidemic in South Africa. A to C without ART; E to G with testing and immediate ART. A and D: $\delta = 0$; B and E: $\delta = 0.60$; C and F; $\delta = 1.0$.](image)

When we consider the impact of ART on TB we see that in 2015 the impact is greater when $d = 0$ than it is when $d = 1$. The reason for this is that when $d = 0$ HIV has a greater impact on transmission and putting people on ART leads to a greater reduction while the reverse is true when $d = 1$. The impact in 2050, on the other hand, is determined mainly by the extent to which HIV is reduced, rather than the relative risk of TB among people on and off ART, and the outcome is then less sensitive to the value of $d$. Allowing $d$ to range from 0.20 to 0.86, as suggested in 3, introduces an uncertainty of 14% in the reduction in the reduction of HIV-related TB, average over the nine countries.
The most important source of statistical uncertainty is in the estimate of $IRR_{ART}^{TB}$ (Equation 37) since this determines the extent to which ART reduces the risk of TB disease. Our best estimate of $IRR_{ART}^{TB}$ is 0.39 but, among different populations, this could vary from 0.20 to 0.75. In the former case the incidence of TB in HIV positive people would be halved, in the latter case it would be doubled so that this introduces a two fold uncertainty in the impact of ART on HIV-positive TB incidence. Better estimates of $IRR_{ART}^{TB}$ are needed if we are to make more precise estimates of the impact of ART on the incidence of TB. In particular, long term follow up studies carried out as a function of CD4$^+$ cell counts at the start of treatment are needed as it likely that the impact of ART on the incidence of TB disease increases over up to five years as the immune system is reconstituted.

Errors in either $\delta$ (Equation 36) or $IRR_{ART}^{TB}$ (Equation 37) will increase or decrease the estimated proportional impact of ART on TB by about the same amount so that the estimates of the reduction will be all be increased or decreased but the ordering and relative magnitude of the impact of starting at different times after infection with HIV will remain the same. The error bars in Figure 2 in the main text reflect the systematic uncertainty in the overall estimates arising from uncertainty in $\delta$ and $IRR_{ART}^{TB}$.

12. Differences among countries in the response of TB to HIV and ART

In different countries the impact of HIV and of ART on TB is different because of differences in the incidence rate ratio. The $IRR_{HIV}^{TB}$ in Botswana is relatively small (Main text, Figure 1), the impact of HIV is correspondingly small and the impact of HIV is more easily reversed. This is supported by a recent study of CD4$^+$ cell counts in HIV-negative adults in Botswana (13) which showed that the mean value was 626 ± 26/μL so that immediately after the acute phase the mean count will be about 470/μL and more than half of those infected with HIV will be below 500/μL immediately after the acute phase. Starting ART in Botswana when a person’s CD4$^+$ cell count is above 500/μL effectively means starting very soon after HIV-seroconversion.

The $IRR_{HIV}^{TB}$ in South Africa is significantly greater than in Botswana and starting ART at a CD4$^+$ cell count of 500/μL or less has a significantly greater impact than starting at lower CD4$^+$ cell counts but the full impact is only seen if treatment is started immediately, irrespective of the CD4$^+$ cell count. Because the $IRR_{HIV}^{TB}$ for TB in HIV-positive and HIV-negative people is more than twice as great as in Botswana the impact of HIV is correspondingly greater and harder to reverse. A study in South Africa found a mean CD4$^+$ cell count in HIV-negative people of 1179 ± 36/μL so that the mean count after the acute phase is likely to be about 884/μL and fewer people will then have a CD4$^+$ cell count below 500/μL.

In Ghana, as in South Africa, ART should be started as soon as people test positive for HIV if the aim is to eliminate HIV-related TB although there is relatively little TB or HIV in Ghana so the benefits are correspondingly small.
Figure S11 shows plots of $IRR_{TB}$, TB notifications in 1980, and the peak prevalence of HIV in adults. The estimated $IRR_{TB}$ is highest when TB notifications, before the epidemic of HIV starts, are lowest but also when the size of the subsequent HIV epidemic is smallest. However, the TB notification rate, before the epidemic of HIV, is also correlated with the size of the HIV epidemic ($\rho = 0.84; p = 0.0024$) so that we cannot distinguish, on statistical grounds alone, if it is the initial TB notification rate, the size of the subsequent HIV epidemic, or some combination of the two, that determines the $IRR_{TB}$.

The relationship between the size of the HIV epidemic and the TB notification rate before the epidemic started is of particular interest and the reason for this could be biological or socio-economic. If the early TB notification rate determines the $IRR_{TB}$, then the biological hypothesis is that where the initial CD4+ cell counts are low people are at high risk of TB, before becoming infected with HIV, but since the CD4+ cell count cannot fall much further the risk of TB does not increase by very much and the $IRR_{TB}$ is low. Conversely, where initial CD4 cell counts are high their initial risk is low but since they can fall by a large amount their final risk is high and the $IRR_{TB}$ is high. If this is the case, the risk of TB in HIV-negative people should vary by a factor of more than 6 between those in the bottom quartile of CD4+ cell counts and those in the top quartile since the inter-quartile range of CD4+ cell counts in South Africa is 496 cell/μL (12).

If the subsequent size of the HIV epidemic determines the $IRR_{TB}$, the socio-economic hypothesis is that, where HIV rates are low, HIV is likely to be concentrated in small sub-populations of marginalized people who are also at high risk of TB. The high levels of circular migration which are almost certainly responsible for the historically high levels of TB in southern Africa (Botswana, Lesotho, Swaziland and South Africa) may also be the reason for the recent high levels of HIV in southern Africa (37-39). In this case the prevalence of HIV among those at risk of TB is much higher than the national estimate where the national prevalence of HIV is low. This is supported by the observation that a similar relationship holds between the $IRR_{TB}$ and the size of the HIV epidemic down to much lower levels of HIV in concentrated epidemics, of the order of 0.1% (36).
References


