

Antiretroviral therapy for tuberculosis control in nine African countries

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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, on average, and start ART at a fixed time after HIV seroconversion or at a fixed CD4⁺ cell count. We fit the model to trend data on 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 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. 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.

Africa | HIV | test-and-treat

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/ μ L 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/ μ L 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 pub-

lished 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}^{TB} , the incidence of TB in HIV-positive adults divided by the incidence of TB in HIV-negative people, and IRR_{ART}^{TB} , 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}^{TB} determines the increase in TB incidence when people are infected with HIV; IRR_{ART}^{TB} 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}^{TB} 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}^{TB} 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}^{TB} 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}^{TB} was 5.0.

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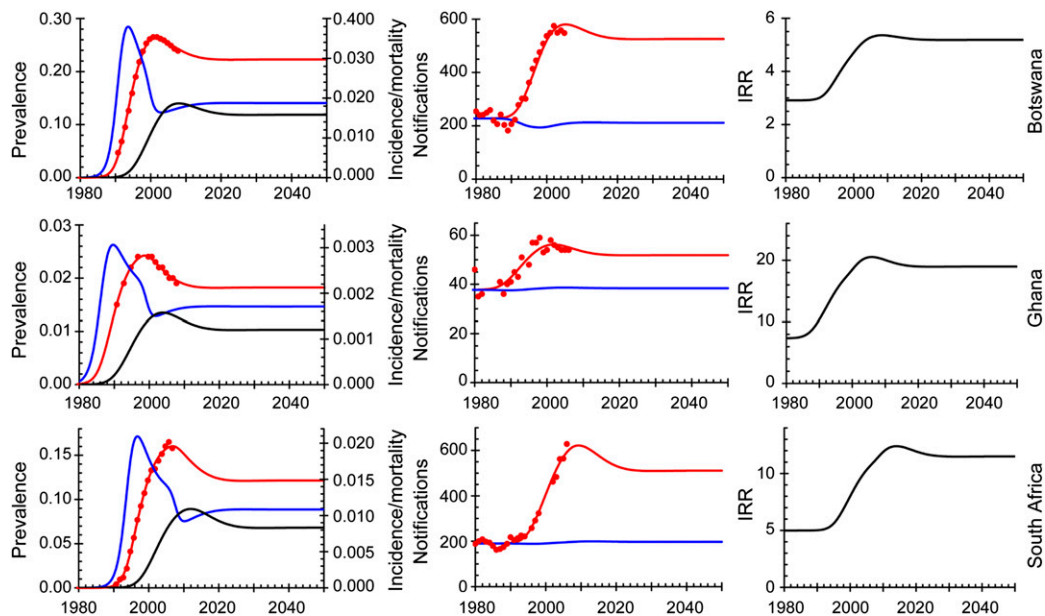


Fig. 1. (Left) HIV prevalence (red line), annual incidence (blue), annual mortality (black), and prevalence in adults aged 15–49 y (red dots) (6). (Center) TB notification rates per 100,000 population per year (red dots) (1), fitted estimate (red line), and notifications in HIV-negative people (blue line). (Right) IRR_{HIV}^{TB} , TB incidence rate ratio in HIV-positive compared with HIV-negative people. Note the different vertical scales.

As the epidemic of HIV progresses and more of those infected with HIV have low $CD4^+$ cell counts, the IRR_{HIV}^{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 $IRR_{ART}^{TB} = 0.39$ (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 incident

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_{HIV}^{TB} 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

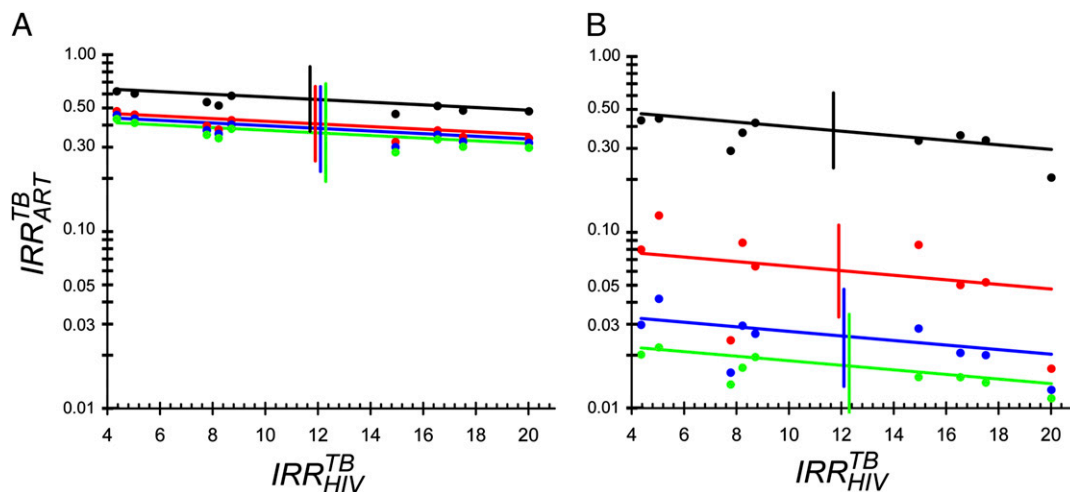


Fig. 2. IRR_{ART}^{TB} , the TB incidence rate ratio for HIV-positive people on ART compared with those not on ART in 2015 (A) and 2050 (B) plotted against IRR_{HIV}^{TB} , the TB incidence rate ratio for HIV-positive adults compared with HIV-negative people. People start ART if they have been infected for more than 5 y (black), 2 y (red), 1 y (blue), or immediately (green). The dots indicate countries (left to right): Botswana, Lesotho, South Africa, Swaziland, Malawi, Ghana, Zambia, Gabon, and Tanzania. The lines are exponential trend lines fitted to the data. Error bars show the systematic uncertainty in the overall estimates.

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

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

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/ μ L. In Gabon, conversely, they should start treatment when their CD4⁺ cell count reaches 852 cells/ μ L.

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/ μ L, 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. Because of the variation in the mean CD4⁺ cell counts among and within countries, it is difficult to establish a summary conclusion concerning the impact on TB incidence of starting ART at different CD4⁺ cell counts. If ART is started at a CD4⁺ cell count of 500 cells/ μ L, the reduction in HIV-related TB in 2015 is about the same in Botswana as in South Africa; however, in 2050, it leads to elimination in Botswana but not in South Africa.

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 IRR_{ART}^{TB} , 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 $\pm 14\%$, and that introduced by the latter is $\pm 5\%$ (95% uncertainty ranges, averaged over countries). However, errors in IRR_{ART}^{TB} 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

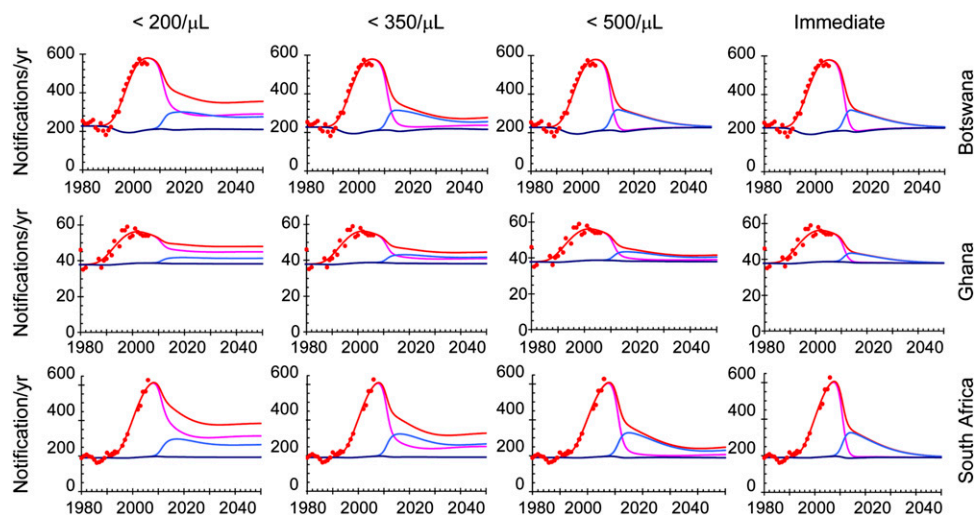


Fig. 3. Impact of ART on the TB notification rate per 100,000 population per year. In all cases, we assume that people are tested once a year, on average. The columns (left to right) show the impact of starting ART when the CD4⁺ cell count is 200, 350, or 500 cells/ μ L or starting immediately irrespective of CD4 cell count. The rows (top to bottom) show the model estimates for Botswana, Ghana, and South Africa. Dark blue lines indicate HIV-negative people, pink lines indicate HIV-positive people not on ART, light blue lines indicate HIV-positive people on ART, red lines indicate total, and red dots indicate data (6).

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 IRR_{HIV}^{TB} 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 IRR_{HIV}^{TB} . In generalized epidemics, this is less likely to be the case, but there 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 IRR_{HIV}^{TB} .

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 microbicides, 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

*Egger M (2007) 14th Conference on Retroviruses and Opportunistic Infections, February 25–28, 2007, Los Angeles, CA, abstr. 62. Available at www.retroconference.org/abstract-search/.

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 if 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. S1* 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 $25 \pm 16\%$ [95% confidence interval (CI)] (8) 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 $36 \pm 12\%$ 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 $-\delta$ so that when $\delta = 0$, the TB disease duration is the same for all stages of HIV and when $\delta = 1$, 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 $\delta = 0.60$ (95% CI: 0.20–0.86) matches the estimated average disease duration.

The incidence rate ratio for TB among people on and off ART, $IRR_{\text{ART}}^{\text{TB}}$, has been measured in several studies (9–19), giving an average value of 0.39 but ranging from 0.2 to 0.75 (*SI Appendix, section 4*). We assume that the duration of TB disease bears the same relationship to the 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. Assuming that 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 $IRR_{\text{HIV}}^{\text{TB}}$, 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. S8 and S9*. 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*.

- World Health Organization (2009) *Global Tuberculosis Control: Surveillance, Planning, Financing* (World Health Organization, Geneva).
- Dieffenbach CW, Fauci AS (2009) Universal voluntary testing and treatment for prevention of HIV transmission. *JAMA* 301:2380–2382.
- Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG (2009) Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: A mathematical model. *Lancet* 373:48–57.
- De Cock KM, Marum E, Mbori-Ngacha D (2003) A serostatus-based approach to HIV/AIDS prevention and care in Africa. *Lancet* 362:1847–1849.
- Williams BG, Dye C (2003) Antiretroviral drugs for tuberculosis control in the era of HIV/AIDS. *Science* 301:1535–1537.
- UNAIDS (2008) *Report on the Global AIDS Epidemic* (United Nations Joint Programme on AIDS, Geneva).
- Corbett EL, et al. (2004) Human immunodeficiency virus and the prevalence of undiagnosed tuberculosis in African gold miners. *Am J Respir Crit Care Med* 170:673–679.
- Williams BG, et al. (2006) HIV infection, antiretroviral therapy, and CD4+ cell count distributions in African populations. *J Infect Dis* 194:1450–1458.
- Brinkhof MW, Egger M, Boule A (2007) Tuberculosis after initiation of antiretroviral therapy in low-income and high-income countries. *Clin Infect Dis* 45:1518–1521.
- Moore RD, Keruly JC (2007) CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. *Clin Infect Dis* 44:441–446.
- Podlekareva D, et al. (2006) Factors associated with the development of opportunistic infections in HIV-1 infected adults with high CD4+ cell counts: A EuroSIDA study. *J Infect Dis* 194:633–641.
- The Antiretroviral Therapy (ART) Cohort Collaboration (2006) HIV treatment response and prognosis in Europe and North America in the first decade of highly active antiretroviral therapy: A collaborative analysis. *Lancet* 368:451–458.
- Girardi E, et al. (2004) Tuberculosis in HIV-infected persons in the context of wide availability of highly active antiretroviral therapy. *Eur Respir J* 24:11–17.
- Santoro-Lopes G, de Pinho AM, Harrison LH, Schechter M (2002) Reduced risk of tuberculosis among Brazilian patients with advanced human immunodeficiency virus infection treated with highly active antiretroviral therapy. *Clin Infect Dis* 34:543–546.
- Golub JE, et al. (2007) The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. *AIDS* 21:1441–1448.
- Miranda A, et al. (2007) Impact of antiretroviral therapy on the incidence of tuberculosis: The Brazilian experience, 1995–2001. *PLoS ONE* 2:e826.
- Jones JL, Hanson DL, Dworkin MS, De Cock KM (2000) HIV-associated tuberculosis in the era of highly active antiretroviral therapy. *Int J Tuberc Lung Dis* 4:1026–1031.
- Kirk OLE, et al. (2000) Infections with *Mycobacterium tuberculosis* and *Mycobacterium avium* among HIV-infected patients after the introduction of highly active antiretroviral therapy. *Am J Respir Crit Care Med* 162:865–872.
- Moreno S, et al. (2008) Incidence and risk factors for tuberculosis in HIV-positive subjects by HAART status. *Int J Tuberc Lung Dis* 12:1393–1400.
- Bussmann H, et al. (2004) Low CD4+ T-lymphocyte values in human immunodeficiency virus-negative adults in Botswana. *Clin Diagn Lab Immunol* 11:930–935.
- Lawn SD, et al. (2009) Changing mortality risk associated with CD4 cell response to antiretroviral therapy in South Africa. *AIDS* 23:335–342.
- Golub JE, et al. (2009) Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: A prospective cohort. *AIDS* 23:631–636.
- Kitahata MM, et al. (2009) Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med* 360:1815–1826.
- Marin B, et al. (2009) Non-AIDS-defining deaths and immunodeficiency in the era of combination antiretroviral therapy. *AIDS* 23:1743–1753.
- Sterne JA, et al. (2009) Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: A collaborative analysis of 18 HIV cohort studies. *Lancet* 373:1352–1363.
- Hargrove JW, Humphrey JH (2010) Mortality among HIV-positive postpartum women with high CD4 cell counts in Zimbabwe. *AIDS* 24:F11–F14.
- Lawn SD, Myer L, Edwards D, Bekker L-G (2009) Short- and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa. *AIDS* 23:1717–1725.
- World Health Organization (2009) *Antiretroviral Therapy for HIV Infection in Adults and Adolescents* (World Health Organization, Geneva).
- Dodd PJ, Garnett GP, Hallett TB (2010) Examining the promise of HIV elimination by 'test and treat' in hyperendemic settings. *AIDS* 24:729–735.
- Corbett EL, et al. (2003) The growing burden of tuberculosis: Global trends and interactions with the HIV epidemic. *Arch Intern Med* 163:1009–1021.
- Wood R, et al. (2007) Undiagnosed tuberculosis in a community with high HIV prevalence: Implications for tuberculosis control. *Am J Respir Crit Care Med* 175:87–93.
- Williams B, Maher D (2007) Tuberculosis fuelled by HIV: Putting out the flames. *Am J Respir Crit Care Med* 175:6–8.