HIV MODELING

Modeling the Dynamic Relationship Between HIV and the Risk of Drug-Resistant Tuberculosis

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The emergence of highly drug-resistant tuberculosis (TB) and interactions between TB and HIV epidemics pose serious challenges for TB control. Previous researchers have presented several hypotheses for why HIV-coinfected TB patients may suffer an increased risk of drug-resistant TB (DRTB) compared to other TB patients. Although some studies have found a positive association between an individual's HIV status and his or her subsequent risk of multidrug-resistant TB (MDRTB), the observed individual-level relationship between HIV and DRTB varies substantially among settings. Here, we develop a modeling framework to explore the effect of HIV on the dynamics of DRTB. The model captures the acquisition of resistance to important classes of TB drugs, imposes fitness costs associated with resistance-conferring mutations, and allows for subsequent restoration of fitness because of compensatory mutations. Despite uncertainty in several key parameters, we demonstrate epidemic behavior that is robust over a range of assumptions. Whereas HIV facilitates the emergence of MDRTB within a community over several decades, HIV-seropositive individuals presenting with TB may, counterintuitively, be at lower risk of drug-resistant TB at early stages of the co-epidemic. This situation arises because many individuals with incident HIV infection will already harbor latent *Mycobacterium tuberculosis* infection acquired at an earlier time when drug resistance was less prevalent. We find that the rise of HIV can increase the prevalence of MDRTB within populations even as it lowers the average fitness of circulating MDRTB strains compared to similar populations unaffected by HIV. Preferential social mixing among individuals with similar HIV status and lower average CD4 counts among HIV-seropositive individuals further increase the expected burden of MDRTB. This model suggests that the individual-level association between HIV and drug-resistant forms of TB is dynamic, and therefore, cross-sectional studies that do not report a positive individual-level association will not provide assurance that HIV does not exacerbate the burden of resistant TB in the community.

INTRODUCTION

There were 8.8 million new cases of tuberculosis (TB) in 2010, with nearly 1.5 million TB-associated deaths despite the availability of antibiotic therapy (*1*). Two factors that contribute to the continued morbidity and mortality of TB are its association with the HIV epidemic (*2*, *3*) and the appearance of drug-resistant TB (DRTB) (*4*, *5*). On one hand, HIV infection increases the probability of developing active TB disease after infection as a result of immunosuppression (*6*), and HIV epidemics have led to marked rises in the incidence of TB (*7*–*9*). On the other hand, drug-resistant *Mycobacterium tuberculosis* (*M. Tb*), which cannot be treated by standard therapies, poses problems not only for the treatment of affected individuals but also for the control of TB in populations (*10*).

HIV and DRTB constitute two distinct obstacles for TB control; however, when combined, their synergistic effect is marked: In an outbreak of extensively drug-resistant TB (XDRTB) occurring among HIV-infected individuals in KwaZulu-Natal, South Africa, 52 of 53 patients affected died, with a median time of death after detection of 16 days (*11*). The collision of these two epidemics has raised international concern about epidemics of essentially untreatable forms of TB (*12*).

Simple inference alone cannot explain the effect of HIV on *M. Tb* drug resistance, and whether HIV is selectively beneficial for the development of DRTB is still not clear (*13*). On a community level, HIV is expected to increase both the prevalence of DRTB and the total *M. Tb* burden in the population (*14*), despite lower levels (*15*, *16*) and shorter duration (*17*) of infectiousness of HIV-coinfected individuals. In 2002, Dye *et al.* presented five hypotheses that might explain an association between HIV infection and an increased risk of DRTB (*18*). They suggested that (i) immunocompromised hosts may be at more risk of disease from low-fitness drug-resistant *M. Tb* strains; (ii) newly circulating DRTB will appear earlier among the HIV-infected than the HIV-uninfected because HIV patients are at the highest risk for progression after infection; (iii) HIV and DRTB may be jointly distributed because patients may have shared risk factors for the two infections, such as injection drug use, incarceration, and hospitalization; (iv) HIV-infected TB patients may have larger mycobacterial burdens and therefore be more likely to harbor DR mutations; and (v) HIV-infected patients may have reduced drug absorption or more limited therapeutic options and thus have a higher risk of suboptimal TB treatment.

There are a limited number of studies that have tested the individual-level association of HIV infection and DRTB emergence; an unbiased estimate can be obtained only when HIV and TB drug resistance are tested among all TB patients or in settings where population-representative DRTB surveys with obligatory testing on HIV have been used. The World Health Organization (WHO) has reported (*5*) (Fig. 1A) a positive association between HIV infection and multidrug-resistant TB (MDRTB) in some European and North American countries, consistent

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with Dye *et al.*'s hypotheses. However, a recent literature review of earlier surveys from sub-Saharan African countries (*19*) (Fig. 1B) does not support this association. Instead, it suggests that in the countries where HIV was rapidly emerging in areas with relatively low levels of anti-TB drug resistance, the nature of the individual-level association may be different. Conversely, a new study from Swaziland (*20*) performed in 2009 to 2010 shows a strong individual-level association between MDRTB and HIV.

Mathematical models have been increasingly used to understand the behavior of epidemics. In the case of the interacting epidemics of HIV and TB, which occur in settings where data are limited, models can play a key role in explaining complex patterns. Here, we describe a model that is designed to explore the dynamic individual-level relationship between HIV and drug-resistant forms of TB as epidemics progress in communities where the burdens of both HIV and TB are high. The model builds on our understanding of how drug-resistant *M. Tb* is selected within hosts during ineffective treatment and is subsequently spread within the population. We address diversity both in terms of drug resistance profiles and fitness costs of different *M. Tb* strains and in terms of the HIV status of the host. Our results have implications for the design and interpretation of surveillance studies and suggest that the cross-sectional studies of the individual-level association between MDRTB and HIV may not be a useful marker of the propensity of HIV to increase the burden of DRTB.

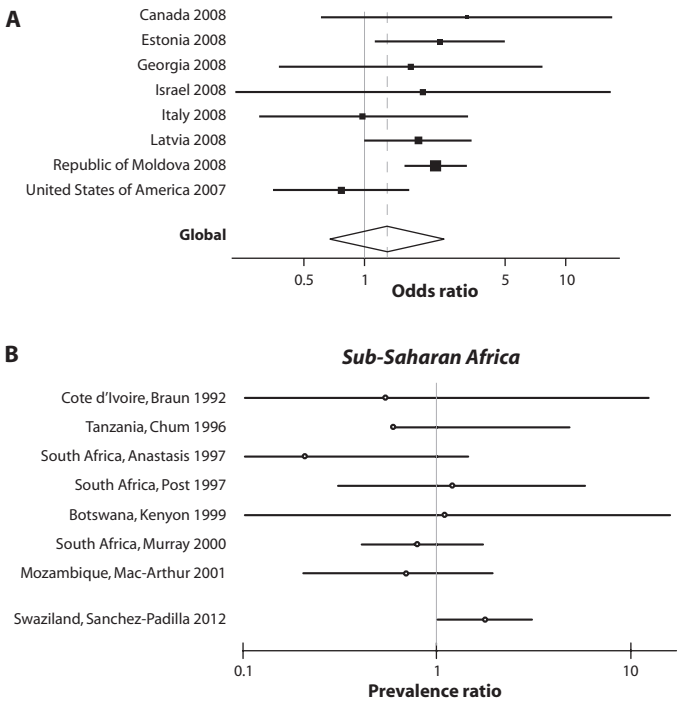

Fig. 1. Reported individual-level associations between HIV and MDRTB. (**A**) Forest plot depicting the association between cases of HIV infection and MDRTB and corresponding 95% confidence intervals in countries reporting at least one MDRTB case among patients with HIV-positive and HIV-negative status in population-representative TB drug resistance surveys/surveillance. The plot is adopted from the WHO 2010 report (*5*), with permission from WHO. (**B**) Figure adapted with permission from Suchindran *et al.* (*19*). Forest plot of MDRTB prevalence ratios (PRs) by HIV status and corresponding 95% confidence intervals from studies in sub-Saharan Africa regions (see references therein for studies included). The result of the latest study of Sanchez-Padilla *et al.* (*20*) is added.

RESULTS

Model

We developed a differential equation model of the TB-HIV co-epidemics that classified hosts by infection/disease status (Fig. 2A) and mycobacteria by level of drug resistance and reproductive fitness (Fig. 2B)—the ability of an infecting mycobacterium to cause TB disease within that host and be successfully transmitted to others. A simplified overview of the model is presented in Materials and Methods; the complete model description with the full set of equations and parameters (table S1) as well as details of the multivariable sensitivity analysis (*21*) are provided in the Supplementary Materials.

We chose Swaziland as a motivating example of a setting with a severe HIV epidemic and growing levels of DRTB, and we fit the model to trends in estimated TB incidence and HIV prevalence (Fig. 3A), assuming that case-finding and treatment success followed reported by WHO (*22*) patterns (inset of the figure). The model generated reasonable fits to the current estimated frequencies (*20*) of MDRTB among new (7.7%) and retreatment (34%) cases. The model also reproduced (without fitting) the fraction of incident TB cases that are coinfected with HIV: 78% from the model compared with 82% from Swaziland (*20*).

We used a prevalence ratio (PR) as the measure of association between DRTB and HIV. The PR was calculated as the ratio of the proportion of TB cases that were drug-resistant among HIV-seropositive individuals to the proportion of TB cases that were drug-resistant among HIV-seronegative individuals. Accordingly, when PR > 1, there is a positive association between HIV and DRTB among individuals with TB, and when PR < 1, there is a negative association. To assess the effect of HIV on the community burden of DRTB, we also performed comparative simulations under the counterfactual scenario where HIV did not enter the population.

Impact of HIV on the total incidence of TB and DRTB

Figure 3B displays the simulated trends of TB incidence in two (otherwise identical) populations: one with a co-occurring HIV epidemic (solid lines) and the other free of HIV (dotted lines). As expected, the introduction of HIV caused a reversal of secular declines in overall TB incidence (*23*) and an increase of the absolute incidence of drug-resistant forms of TB (compare solid and dotted curves for DR, MDR, and XDR). The return to sustained reductions in TB incidence overall, and drug-resistant forms of TB in particular, which occurred after the peak of HIV incidence, was dependent on continued high rates of TB case finding and treatment success and assumptions of lower reproductive fitness of drug-resistant strains compared with drug-sensitive strains. In fig. S5, we offer additional results that show that the central findings presented here are unchanged when TB and DRTB rise over the course of the simulations, which may realistically occur if treatment programs are not sustained and extended to cover drug-resistant disease, or if fitness costs associated with resistance can be completely compensated for by the mycobacteria.

Association between DRTB and HIV

Figure 4 shows that the individual-level association between HIV and DRTB (PR, right panels) may change markedly over time. During

the period of early emergence and exponential rise of HIV, we observed that the risk of resistance among TB patients was lower among those with HIV infection than it was among those without HIV infection. The model projected this early negative association between HIV and DRTB for all classes of drug resistance, but was most marked for the most common (and least severe) forms. As the HIV epidemic matured, this pattern was reversed and we saw that a positive association between HIV and DRTB emerges; moreover, also in contrast to the early period, during this later stage, the positive association between HIV and DRTB increased for more extreme forms of resistance. Consistent with the review cited above (*19*), we found that the association between DRTB and HIV was substantially more pronounced for DRTB among cases without previous treatment than those with previous treatment (Fig. 4C, right panel). The relative contributions of transmission of resistant strains and acquisition of resistance during treatment (Fig. 4C, left panel) are expected to change during the epidemic, with acquired resistance dominating early and transmitted resistance increasing in importance over time. This transition is expedited by a substantial improvement in quality of TB treatment programs focused on effective delivery of first-line drug regimens between 2000 and 2010 (see inset of Fig. 3A), which reduced the probability of resistance acquired during treatment.

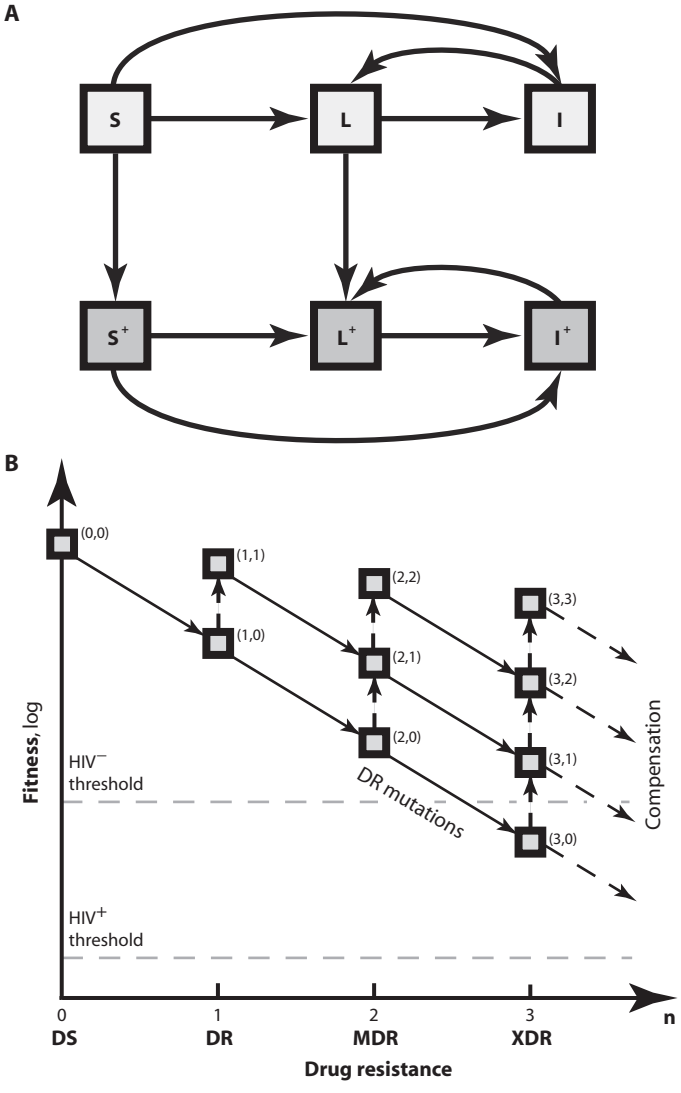

Fig. 2. Simplified model structure. (**A**) Schematic overview of the mathematical model of TB/HIV dynamics. The natural history of TB is represented by compartments for susceptible (S), latently infected (L), and infectious individuals (I). HIV-seropositive individuals are designated by the superscript +. Details of flow between compartments and model equations are provided in the Supplementary Materials. (**B**) Fitness mapping of mycobacterial strains modeled by the number of drug resistances ($n = 0$ for DS strain; 1 for single DR; 2 for MDR; 3 for XDR; etc.) and by the number of compensatory events ($0 \le k \le n$, one compensatory mutation per each resistance). The pair of numbers (n,k) defines each type of mycobacteria modeled. The y axis shows the relative fitness of each strains compared to wild type on the log scale (according to Eq. 4). Assumed fitness thresholds for HIV$^-$ and HIV$^+$ individuals are shown by the thin dashed black lines for reference.

Effect of HIV on average strain fitness

Although the average relative reproductive fitness of resistant strains increased over time because the most reproductively fit strains preferentially cause disease and are transmitted (*24*), the presence of HIV within the population allowed for strains of lower reproductive fitness to succeed, and thus the average fitness of resistant strains was reduced

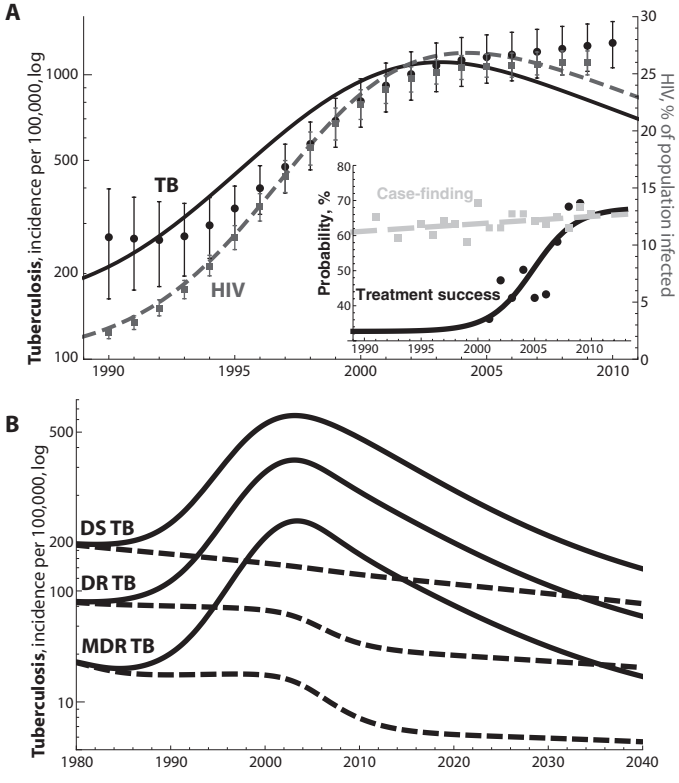

Fig. 3. Simulated epidemics. (**A**) Total TB incidence and HIV prevalence (black solid and gray dashed lines) in comparison with the data for adults (age 15+) from Swaziland (*22*) (black dots and gray squares with corresponding 95% confidence intervals, respectively). The inset shows the data and approximations used for case finding (gray) and treatment success (black) (see also fig. S2 in the Supplementary Materials). (**B**) Modeled trends of the incidence of drug-sensitive, drug-resistant, and multidrug-resistant (MDR) in populations with epidemic HIV (solid lines) and without HIV (thick dashed lines).

(compare solid to dotted lines in Fig. 5A). When we compared HIV-seronegative hosts in populations affected by HIV with individuals in populations free of HIV, we found similar average fitness of resistant strains. This suggests that the reduction of DRTB fitness observed at the community level in the presence of HIV was restricted to the immunocompromised hosts. Figure 5B shows that the strains of lowest fitness (solid lines) were predominantly restricted to immunocompromised individuals (reflected by a high positive value of individual-level association, PR > 1), whereas strains of higher fitness (dashed lines) also spread into the immunocompetent population.

Sensitivity of the results to uncertain parameter values

To examine the influence of model parameters on behavior, we conducted a multivariable sensitivity analysis by Latin hypercube sampling (*21*) (Fig. 6; see also figs. S3 and S4 in the Supplementary Materials for details and sensitivity/uncertainty analysis results). We found that although the HIV (Fig. 6B) and TB (Fig. 6C) epidemic trajectories were modified by changes in parameter values, the key qualitative finding in the trend MDRTB PR was quite robust. In particular, the PR trajectories on Fig. 6A fell within a narrow range and demonstrate a stable monotonic growth of the individual-level association between MDRTB and HIV that crosses from negative to positive over time. In the Supplementary Materials (see fig. S3A), we showed that variation over assumed ranges of each parameter resulted in less than 10% change in the value of the time derivative of PR, further demonstrating that this trend is not sensitive to uncertainty in our input parameter values.

In the examples below, we examined the impact of several parameters related to Dye *et al.*'s proposed mechanisms (*18*) on the association between HIV and DRTB and the projected trajectory of DRTB within communities (Fig. 7).

Differences in the vulnerability of immunocompromised individuals to be infected by low-fitness strains. Although there is some support for the claim that specific strains of relatively low-fitness, highly drug-resistant TB appear to be able to cause disease only among those with impaired immune systems (*25*, *26*), the actual value of this "fitness threshold" is not known. Furthermore, because the distribution of severity of immunosuppression changes with HIV epidemic phase and availability of antiretroviral therapy (*27*), we explored the effect of altering the fitness threshold for HIV seropositives on the proportion of all TB that is MDR (Fig. 7A). As we increased the fitness threshold for HIV-coinfected patients from the original value (increasing this threshold means that less fit strains were not capable of infecting immunocompromised hosts), the expected frequency of MDRTB in this vulnerable subpopulation (left panel), as well as the association between MDRTB and HIV (right panel), was reduced. These results demonstrated that the relative fitness threshold of immunocompromised individuals has an influence on the individual-level association between HIV and DRTB and anticipated burden of DRTB.

Mixing patterns. For the baseline results, we assumed that respiratory contacts (that is, contacts sufficient for transmission of *M. Tb*) were equally likely to occur among any members of the population. This assumption would be violated if there is preferential association between individuals of similar HIV status because of social preference or because individuals with HIV infection are more likely to contact each other within hospitals or other institutional settings. Figure 7B showed that as the likelihood of having respiratory contact with those of similar HIV status rises, there were short-term increases in the individual-level association for MDR among HIV-infected TB patients (right panel), but this effect waned over time.

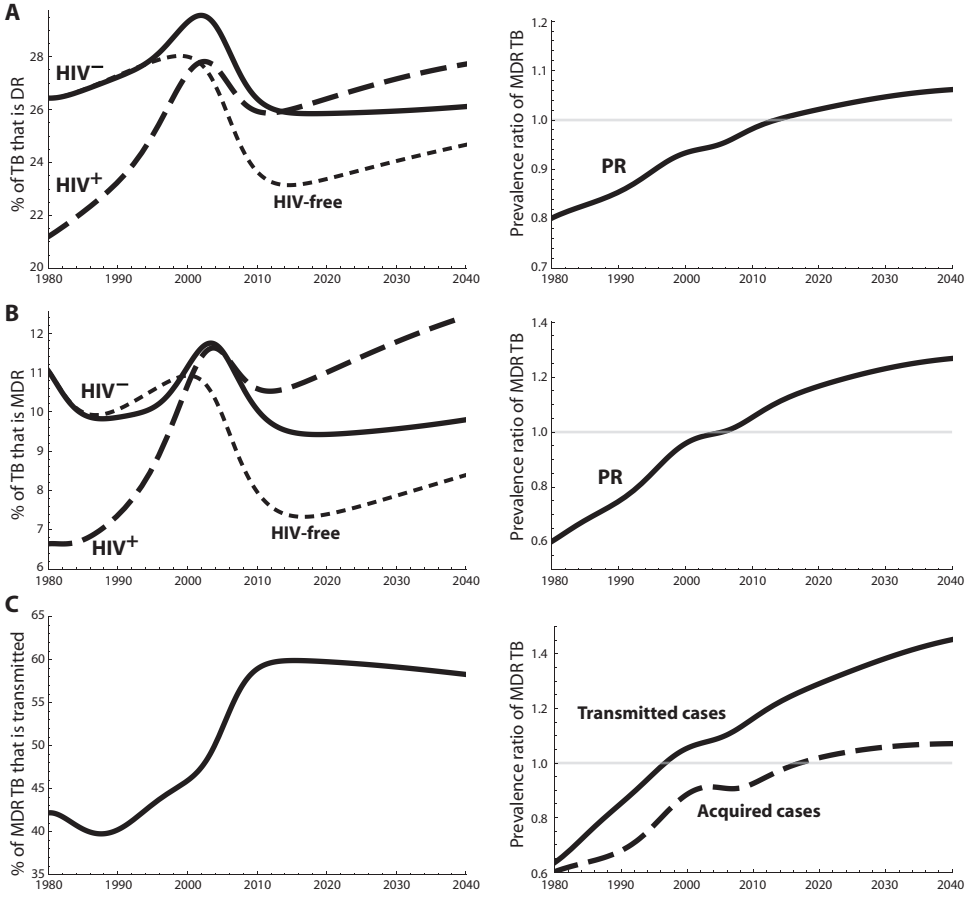

Fig. 4. Trends in the individual-level association between HIV and DRTB. (**A** and **B**) The projected trends in the percentage of TB incidence (left panels) that is with (A) DR strains and (B) MDR strains. For (A) and (B), trends for HIV^+ and HIV^- individuals within populations with epidemic HIV are represented by dashed lines and solid lines, respectively. The trend for individuals in populations unaffected by HIV is shown with a thin dashed line. The right panels show the PRs of drug resistance between HIV-seropositive and HIV-seronegative hosts (PR) in the population with epidemic HIV. A value PR = 1, representing the absence of association between drug resistance of *M. Tb* and HIV, is shown as thin gray line. (**C**) Fraction of total MDRTB that is due to transmission (left panel). The right panel shows the PR for transmitted (solid line) and acquired (dashed line) MDRTB.

Differences in case finding. The natural history and clinical presentation of TB disease differ between patients with and without HIV coinfection and also as a function of severity of HIV-associated immunosuppression (*28*). In some settings, individuals with HIV may be more likely than those without HIV to be diagnosed rapidly after the onset of TB infectiousness (*29*), whereas in other settings this might not be true (*16*). To examine the sensitivity of the model to possible differences in access to diagnosis, we varied the rate with which HIV-seropositive individuals with active TB are detected and placed on treatment. Figure 7C shows that differences in TB case finding by HIV status of hosts can substantially modify the expected individual-level association between HIV and DRTB. Higher rates of case finding among those with HIV resulted in greater overall usage of drugs, higher proportions of TB being MDR (left panel), and a more rapid appearance of a positive individual-level association for MDR among HIV-infected TB patients (right panel).

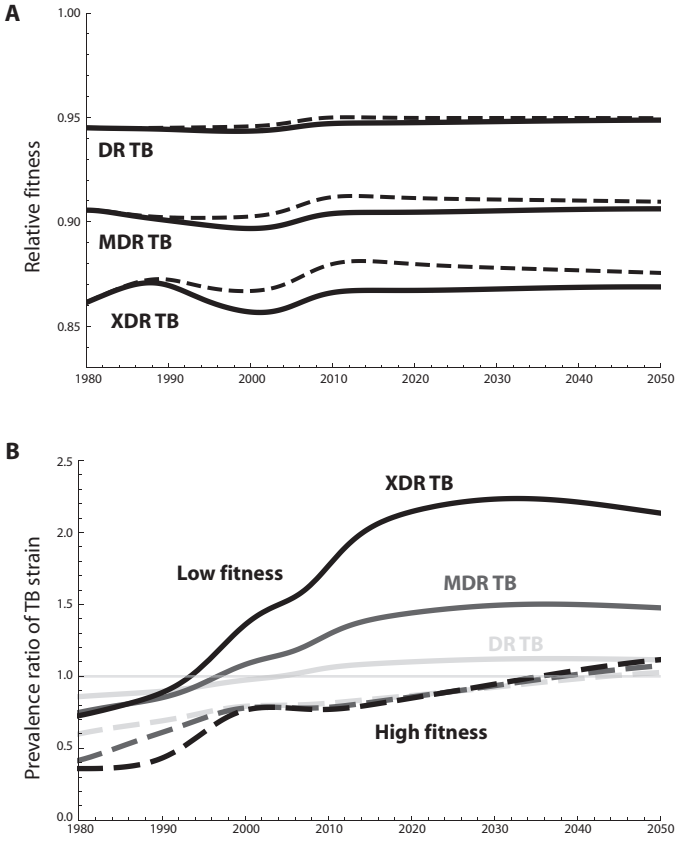

Fig. 5. Trends in the average relative fitness of DRTB and its impact on PR. (**A**) Relative fitness values are compared with the referent drug-sensitive TB. The solid lines represent the fitness trends in populations with both TB and HIV. The dashed lines show the fitness trajectories in an HIV-free population. The maximum possible values for the fitness of each type of resistance (that is, where all resistance mutations are accompanied by compensatory mutations, $k = n$) are 0.99 for DRTB, 0.98 for MDRTB, and 0.97 for XDRTB. Trends in fitness for the resistant strains do not approach these maximal levels over the next several decades in our simulations. (**B**) PR of drug resistance between HIV-seropositive and HIV-seronegative hosts for low-fit ($k = 0$, solid lines) and high-fit ($k = n$, dashed lines) drug-resistant strains. Strains with different number of resistances are represented by shading: light gray, DR ($n = 1$); gray, MDR ($n = 2$); and black, XDR ($n = 3$).

In addition to considering each of these proposed mechanisms alone, we found that when these factors were present in combination, there was a more pronounced positive association between HIV and MDRTB throughout the epidemic (fig. S6).

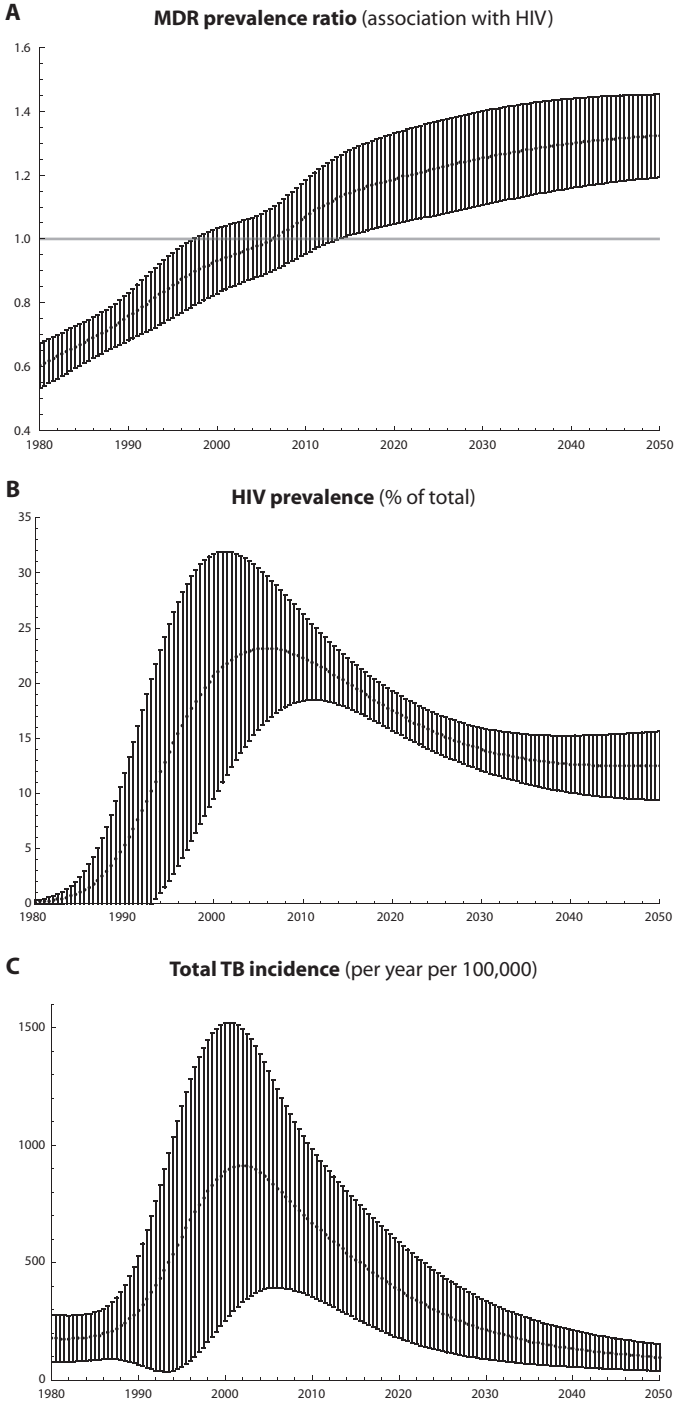

Fig. 6. Multivariable sensitivity analysis. Distribution of 3000 simulation runs with model parameter sets sampled over the ranges listed in table S1. The mean value is shown by the dotted line; the bars indicate 1 SD above and below this mean value. (**A**) Individual-level association (PR) between MDRTB and HIV. (**B**) Prevalence of HIV (%). (**C**) Incidence of all forms of TB (per 100,000).

DISCUSSION

Our model expands existing dynamic models of TB and DRTB to consider the emergence of drug-resistant strains of *M. Tb* in the presence of HIV. Although previous models touch on related questions of emergence of DRTB, including amplification (*30*), coexistence (*31*–*33*), and interactions with HIV (*34*–*38*), we are not aware of other models that have attempted to represent the process of acquisition of multiple drug resistance in *M. Tb*, the effects of resistance-associated fitness deficits (*24*, *39*, *40*), and compensation for these reproductive costs (*41*, *42*). This model allowed us to investigate whether the potential HIV-associated host effects summarized by Dye *et al.* (*18*), which reduce immune integrity, accelerate the natural history of TB, and offer opportunities for strain evolution, can essentially serve as "stepping stones" (*43*) for the appearance and spread of highly drug-resistant forms of TB.

We found that the rise of HIV within populations was likely to result in an increased incidence of DRTB because HIV causes an overall increase in the incidence of all forms of TB. However, we also found that the individual-level association between HIV and DRTB may not be a useful proxy measure to indicate whether HIV is acting to facilitate the emergence of DRTB on the population level. In particular, we found that TB patients with HIV coinfection may actually be less likely to have MDRTB disease than other TB patients without immunocompromise at the time that HIV is first emerging within the population. Although this counterintuitive relationship (HIV increasing the level of DRTB at the population level while being inversely associated with DRTB at the individual level) is only temporary, it reveals the complex interaction between these epidemics with different time scales (see hypothesis 2 below).

We return to Dye's initial hypotheses (*18*) to assess what additional insight is offered by this model.

Dye's hypothesis 1: Immunocompromised hosts may be at more risk of disease from low-fitness drug-resistant *M. Tb* strains. Figure 7A demonstrated that enhanced sensitivity of immunocompromised hosts to low-fitness *M. Tb* strains does act to increase the association between DRTB and HIV. However, we found that even if we assume a similar fitness threshold for HIV-infected and HIV-uninfected hosts, we saw an increasing individual-level relationship between HIV and MDRTB and an increase in DRTB strains overall in the presence of HIV. Furthermore, the impact of a lower fitness threshold was more important for strains with higher levels of resistance (such as XDR), and thus, enhanced vulnerability to low-fitness TB strains provided by HIV may indeed serve as an important "stepping stone" on the way to emergence of highly drug-resistant TB strains that are able to recover fitness costs and eventually spread among immunocompetent persons.

Dye's hypothesis 2: Newly circulating DRTB will appear earlier among the HIV-infected than the uninfected because HIV patients are at the highest risk for progression after infection. Although newly circulating strains of DRTB may first appear among those with HIV coinfection, the individual-level association between HIV and DRTB may actually be negative. When HIV first invades a population, many (if not most) of the individuals with incident HIV infections will harbor latent *M. Tb* infections acquired many years in the past when there was a very low prevalence of DRTB. As a result, these individuals with preexisting latent *M. Tb* infections and incident HIV will be at high risk of progression to drug-sensitive TB. In contrast, HIV-seronegative individuals with incident TB, despite having a similar risk of harboring a latent infection with a drug-sensitive strain as

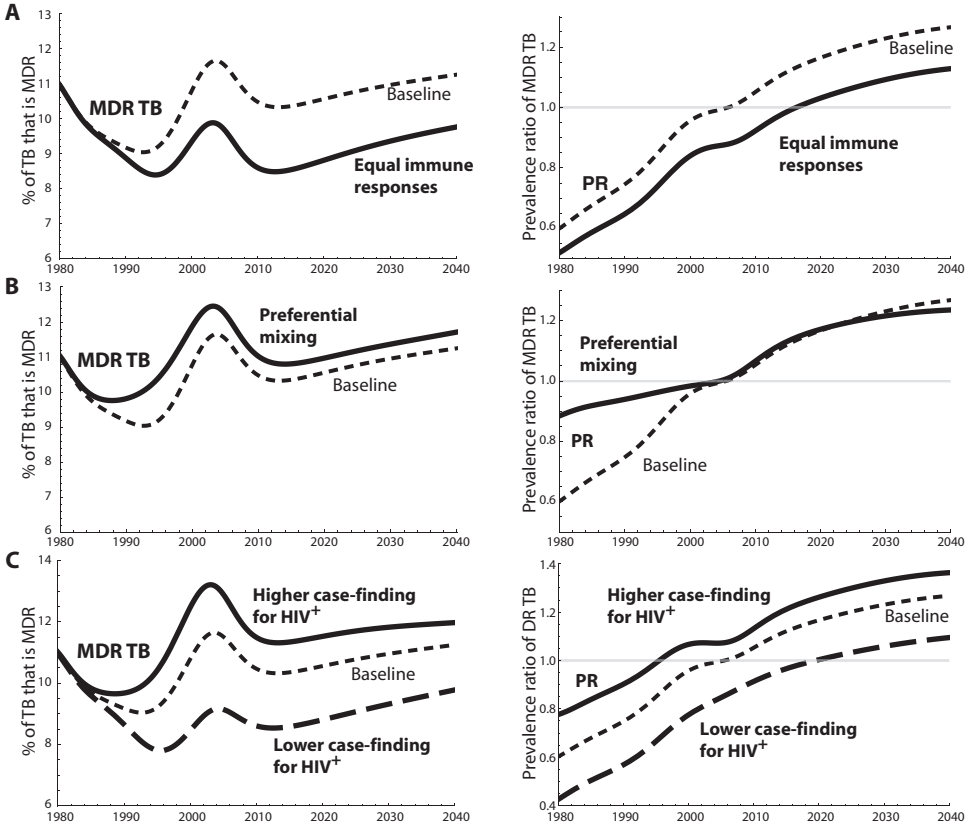

Fig. 7. Effects of altering key model parameters. The left panels indicate the trend in the proportion of TB that is MDR, and the right panels indicate the trend in the individual-level relative risk of MDR among HIV-seropositive and HIV-seronegative hosts with TB. The solid lines represent an increase in the value of each parameter over baseline, the dashed lines represent a decrease in the value, and the thin dashed lines represent a baseline value. (**A**) Variation of the fitness threshold for HIV seropositives compared to hosts without HIV. Solid line, fitness thresholds are equal; thin dashed line, fitness threshold for HIV seropositives is 0.75 of that for HIV seronegatives. (**B**) Variation of mixing patterns. Solid line, assortative mixing such that individuals with the same HIV status are twice as likely to contact each other; thin dashed line, homogeneous mixing (see the Supplementary Materials for additional details). (**C**) Variation of the relative rate of case detection. The probability of case detection before self-cure or death is set to be 50% higher (solid), equal (thin dashed), and 50% lower (dashed) for an HIV-coinfected TB patient than a TB patient without HIV.

those with HIV, are more likely to have TB disease that is due to a recent reinfection event than to reactivation of a previous infection. Our simulation for Swaziland showed that in the early stage of HIV invasion, up to 68% of TB cases among HIV negatives were the result of recent infection or reinfection compared with only 24% among HIV positives. The early inverse association observed between HIV and MDRTB (PR < 1) among new TB patients also supported this conclusion (right panel of Fig. 4C).

Dye's hypothesis 3: HIV and DRTB may be jointly distributed because patients may have shared risk factors for the two infections, such as injection drug use, incarceration, and hospitalization. Preferential mixing of highly susceptible HIV-seropositive individuals promoted the transmission of low-fitness drug-resistant strains and boosted the frequency of MDR (left panel of Fig. 7B). These mixing patterns may act to increase the effective force of TB infection among HIV seropositives, thus accelerating the transmission of all TB, including highly drug-resistant strains, especially within nosocomial settings (*11*, *44*, *45*). However, the longer-term effect of these mixing patterns on the total burden of MDR strains may be less pronounced and is greatly diminished if drug-resistant forms of the disease begin to spread outside settings where highly vulnerable individuals are concentrated. Although it is possible that the concentration of immunocompromised individuals within nosocomial or prison settings can allow for the emergence of novel, low-fitness, highly drug-resistant strains of TB that can subsequently compensate for initial fitness costs and be transmitted among immunocompetent hosts, this model does not allow us to gain quantitative insight into the likelihood of such an event.

Dye's hypotheses 4 and 5: HIV-infected TB patients may have larger mycobacterial burdens and therefore be more likely to harbor DR mutations, and HIV-infected patients may have reduced drug absorption or more limited therapeutic options and thus have a higher risk of suboptimal TB treatment. The differences in clinical presentation of TB disease among those with and without HIV coinfection affect the probabilities of timely disease detection, of treatment after disease, and of outcome after treatment. Although the probability of acquiring resistance, according to Dye's arguments, may be higher for HIV-coinfected TB patients on treatment, the relative probability that an HIV-coinfected individual with TB disease is actually diagnosed with TB and initiated into treatment differs between settings. In our model, inadequate case finding among HIV-coinfected TB patients (Fig. 7C) resulted in less treatment applied, lower levels of drug resistance, and a reduction of the individual-level association between HIV and DRTB.

Our model results are broadly consistent with the small number of studies of the individual-level association between HIV and DRTB: There is no clear association in early studies within sub-Saharan Africa (*46*–*52*) as HIV and DRTB were first appearing, whereas in areas with longer, more severe DRTB epidemics [such as Eastern Europe (*53*–*55*)], there is a more clear positive association between HIV and DRTB. Our results also support previous observations (*19*) of a greater positive individual-level association between MDR and HIV for transmitted than for acquired resistance (Fig. 4C). We believe that this model provides a mechanistic explanation for why the individual-level association between HIV and MDRTB may be negative even as HIV is causing higher absolute levels of DRTB than would have otherwise been expected.

As with all models, we made important simplifying assumptions. We greatly reduced the complexities of the natural histories of both diseases considered in the model. Our model was not age-structured, described only the adult population, and assumed that the level of host immunosuppression was the same for all HIV-positive hosts and is constant over time. We evaluated the sensitivity of the model to some of these simplifications and found, for example, that changes in the level of the fitness threshold (Fig. 7A), which may serve as a marker of average level of HIV-related immunosuppression (which will change with access to antiretroviral therapy), did not affect the central qualitative results that we reported. We also assumed that the probability of acquisition and fitness costs of resistance and compensation were similar across classes of drugs. Although TB drug resistance is generally mediated through chromosomal mutations (although some recent data implicate other mechanisms such as efflux pump activation) (*56*, *57*), the rates of acquisition of DR actually vary by drug, and each resistance-associated genotype may have a unique profile in terms of fitness effects and the probability of compensation (*58*). These parameters are also likely to differ by mycobacterial lineage (*59*–*61*). We also have not accounted for stochastic effects and reserve our main comments to the qualitative behaviors of relatively well-populated model classes (for example, MDR rather than XDR and more resistant strains). We have also assumed in our base case scenario that TB detection and treatment success will continue at high levels in the future and that drug-resistant forms of disease will also be effectively detected and treated such that there will be steady and sustained declines in all TB and more rapid declines in DRTB over the next several decades. This is an optimistic assumption, and these stable improvements are dependent on many uncertain factors (including that drug-resistant strains continue to harbor some fitness costs). Accordingly, these simulations are not meant to serve as predictions of what will happen in the future, and in many areas with poor TB infrastructure, we would expect that control of DRTB epidemics may not be as successful. However, we showed in the Supplementary Materials (fig. S5) that the central findings we reported here about how HIV and the DRTB epidemic interact are robust to the projected long-term trends in these epidemics or assumptions about how effective TB case finding and treatment was over the past several decades.

This model offers new insight into how the spread of HIV in areas with endemic TB can affect the emergence of DRTB. In particular, this model helps to better explain why HIV may be associated with increased individual-level risk of DRTB in some settings but not in others, and how these individual-level relationships can change as these epidemics progress together. Accordingly, longitudinal studies that can evaluate the dynamic nature of this individual-level association will be useful, and single cross-sectional studies should be interpreted with caution. Serial surveys in areas where surveillance systems are less robust, such as sub-Saharan Africa, are likely to be especially informative.

MATERIALS AND METHODS

We used a differential equation model of TB-HIV co-epidemics that classified hosts by infection/disease status (Fig. 2A) and mycobacteria by level of drug resistance and reproductive fitness (Fig. 2B), which is the ability of an infecting mycobacterium to cause TB disease within that host and be successfully transmitted to others. In the main text, we presented a simplified overview of the model; the complete model description with the full set of equations and parameters (table S1) is provided in the Supplementary Materials.

TB transmission component of model

We categorized hosts according to their status of TB into three broad classes: S, susceptible; L, latently infected; and I, infectious (Fig. 2A). Individuals entered the model as susceptible to TB infection (such as birth or immigration) and exited this compartment upon infection or death. A fraction of those infected with *M. Tb* developed TB rapidly (fast progressors), whereas the remainder contained the infection and entered a period of asymptomatic and noninfectious latency. Most (~90%) of immunocompetent (not HIV-infected) latently infected individuals did not reactivate during their lifetimes (*62*). Latently infected individuals could be reinfected upon subsequent exposure to *M. Tb*, and these people experienced an increased risk of developing fast TB, although this risk was less than would occur after a first infection (*63*, *64*). Individuals with active TB suffered an increased mortality rate, but could control the infection and survive if they either received curative treatment or experienced "self-cure" (*65*). TB transmission could occur as a result of contact between an individual with active disease and an individual who was either susceptible or latently infected.

Heterogeneity among hosts: Incorporating HIV coinfection

In addition to TB infection/disease status, we also distinguished individuals by HIV infection status, denoting those infected with HIV by the superscript "+" (Fig. 2A). We simplified the natural history of HIV infection in this model by incorporating HIV as a binary variable (infected/not infected classes). HIV-infected hosts had higher rates of TB progression and mortality (*66*), much higher risk of fast progression to disease after *M. Tb* infection, a reduced ability to resist reinfection, a lower probability of self-cure in the absence of treatment and higher risk of TB-induced death if untreated (*67*–*70*). HIV-infected individuals progressing to active TB disease were more likely to have extrapulmonary or smear-negative forms of disease, making them, on average, less infectious per unit of time than HIV-seronegative hosts with active TB. HIV transmission could occur as a result of contact between an individual with HIV infection and a vulnerable individual not yet infected with HIV; following (*71*), we assumed that only a fraction of the population had behavioral risk factors that put them at risk of HIV infection.

Heterogeneity among *M. tuberculosis*: Incorporating drug resistance

We categorized the circulating strains of mycobacteria by the number of antibiotics to which they were resistant and their reproductive fitness (Fig. 2B). We assumed that the acquisition of resistance to any class of anti-TB drugs reduced treatment efficiency but also imposed a reproductive fitness cost on the mycobacteria (*72*–*75*). These fitness costs could be partially restored over time as a result of accumulation of compensatory mutations (*59*, *76*–*78*). We made the assumption that fitness costs of resistance-conferring mutations and the frequency and restoration effect of compensatory mutation were comparable for each class of anti-TB drug, a simplification that allowed us to markedly reduce the number of model compartments. This assumption permitted us to classify broad categories of resistance (n = 0 for DS strain; 1 for single DR; 2 for MDR; 3 for XDR) and to tally compensatory events ($0 \le k \le n$) without specifying the pattern of resistance/compensations. Accordingly, the set of two numbers (n,k) fully described the resistance level and compensatory state of each mycobacterial strain in the model. The mycobacterial state (n,k) could change as a result of two events: (i) inadequate treatment could result in selection of mycobacteria with additional resistance, which led to an increase in n and a subsequent reduction in fitness in the absence of drug treatment, or (ii) sporadic mutation could occur that compensated for a fraction of the fitness cost associated with resistance, which led to an increase in k.

Interaction of bacteria with heterogeneous fitness with heterogeneous hosts: Incorporating immune response and immunosuppression

For each mycobacterial state (n,k), we assumed a fitness that decreases monotonically with every additional drug resistance mutation (n) and was partially restored by every compensatory mutation (k), as shown on the y axis in Fig. 2B. We assumed that a reduction in fitness led to decreased ability for the strain to cause both rapid progression to TB disease and reactivation from latency.

We represented the strength of the immune response of the host by specifying a fitness threshold that the bacteria had to exceed to overcome the immune response and cause disease. Consistent with previous hypotheses and evidence (*18*, *25*–*26*), we implemented a lower (more permissive) fitness threshold for HIV-infected hosts than for hosts with intact immunity (see Fig. 2B for a graphical depiction of these thresholds and fig. S1 for additional details).

SUPPLEMENTARY MATERIALS

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Model structure
Fig. S1. Fitness costs for the strains.
Fig. S2. Assumed patterns for case finding, treatment success and failure.
Fig. S3. Uncertainty analysis.
Fig. S4. Partial rank correlation coefficients.
Fig. S5. Simulation of pessimistic scenario for MDRTB control.
Fig. S6. Cumulative effect of the mechanisms promoting HIV-MDRTB association.
Table S1. Model parameters.

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Modeling the Dynamic Relationship Between HIV and the Risk of Drug-Resistant Tuberculosis

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Only Time Will Tell

A picture may be worth a thousand words, but a snapshot only gives you part of the story. Comparing snapshots can help, but inconsistencies may remain. Such is the case for the epidemiological interactions of HIV and tuberculosis (TB). Some researchers have suggested that HIV-infected populations are more susceptible to developing drug-resistant TB. However, different studies of HIV-infected individuals with TB have yielded conflicting results. Now, Sergeev *et al*. provide a dynamic look at the relationship between HIV infection and the risk of acquiring drug-resistant TB.

The authors developed a mathematical model to explore the effect of HIV on the dynamics of emerging drug-resistant TB. They found that, whereas HIV infection facilitated the rise in numbers of drug-resistant TB infections within a community over several decades, HIV-infected individuals may actually be at lower relative risk of developing drug-resistant TB at the early stages of the coepidemic. Although counterintuitive, these results may be explained by HIV-stimulated reactivation of latent *M. Tb* infections, acquired at a time when drug-resistant TB was rare. Intriguingly, although HIV infection may increase the prevalence of drug-resistant TB within a population, drug-resistant TB in HIV-seropositive populations may actually be less fit than drug-resistant TB that develops in HIV-seronegative populations—perhaps as a result of less stringent selective pressure. Thus, Sergeev *et al*. suggest that longitudinal studies, not a snapshot, will provide a better picture of the whole evolving story.