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In sub-Saharan Africa, where the emergence of HIV has caused dramatic increases in tuberculosis (TB) case notifications, new strategies for TB control are necessary. Isoniazid preventive therapy (IPT) for HIV–TB coinfected individuals reduces the reactivation of latent *Mycobacterium tuberculosis* infections and is being evaluated as a potential community-wide strategy for improving TB control. We developed a mathematical model of TB/HIV coepidemics to examine the impact of community-wide implementation of IPT for TB–HIV coinfected individuals on the dynamics of drug-sensitive and -resistant TB epidemics. We found that community-wide IPT will reduce the incidence of TB in the short-term but may also speed the emergence of drug-resistant TB. We conclude that community-wide IPT in areas of emerging HIV and drug-resistant TB should be coupled with diagnostic and treatment policies designed to identify and effectively treat the increasing proportion of patients with drug-resistant TB.

mathematical model | AIDS | prophylaxis

Tuberculosis (TB) incidence and mortality in sub-Saharan Africa have reached alarming levels and continue to rise. TB control in this region has been hindered by the emergence of HIV (1); in areas most affected, annual TB case notifications have quadrupled over the past 15 years (2). In August 2005, 46 regional Ministers of Health declared that the TB epidemic is an emergency in Africa.

HIV significantly affects the progression of *Mycobacterium tuberculosis* infection. Whereas *M. tuberculosis* infection in immunocompetent hosts usually results in latent nontransmissible infection, individuals coinfected with HIV/TB are at high risk of progressing from latent infection to active TB. Because of this interaction, most public health authorities have concluded that the World Health Organization's Stop TB Strategy will fail to curb the epidemic in areas where HIV is prevalent. This strategy emphasizes the rapid diagnosis of TB and the reliable availability and administration of antibiotics to those affected. Although this approach has been successful in areas of low HIV prevalence, additional measures are necessary to reduce TB incidence in high HIV-burden regions (3).

To identify such measures, investigators are conducting several large studies of the community impact of preventive therapy to interrupt progression from latent infection to active TB among HIV–TB coinfected individuals. This strategy, called isoniazid (INH) preventive therapy (IPT), uses INH monodrug therapy for coinfected patients. Clinical trials in the 1950s showed that IPT reduced the incidence of active TB in immunocompetent individuals infected with *M. tuberculosis* (4); more recent studies have also demonstrated its efficacy among HIV–TB coinfected individuals (5–7). The World Health Organization currently recommends that HIV/AIDS programs include IPT as part of their package of care for the HIV infected.

Despite evidence that IPT reduces TB incidence among HIV–TB coinfected individuals, it is not clear that community-wide IPT will prove effective at controlling TB in areas with a high burden of HIV. This strategy may be compromised by low adherence over the many months necessary to complete a single course of IPT, a problem that is worsened in HIV–TB coinfected individuals for whom the IPT durations are prolonged. Furthermore, exogenous reinfection may be common in high-incidence areas (8, 9), and recent theoretical work suggests there exists a TB incidence threshold above which reinfection is the predominant type of transmission (10). In areas where reinfection is common, individuals are likely to be reinfected after completion of a single course of IPT, and preventive therapy may fail to control TB at the population level, even if it can reduce the risk of disease among treated individuals.

In many high-TB-, high-HIV-burden areas, a substantial proportion of TB cases are resistant to first-line anti-TB agents (11). INH resistance threatens the success of IPT programs, because individuals infected with drug-resistant strains are unlikely to benefit from this regimen. Although IPT is unlikely to generate drug resistance among individuals infected with INH-sensitive *M. tuberculosis* strains (4), that IPT protects only against progression with INH-sensitive strains suggests these control programs may nevertheless speed the emergence of drug resistance at the population level. Recent evidence for the importance of multiple (serial) and mixed-strain *M. tuberculosis* infections (12–16), coupled with our understanding of the population dynamics of antibiotic resistance (17), indicates that IPT programs may have perverse effects on the epidemic of drug-resistant TB.

Mathematical models serve as important tools to assess the population-level effects of individual-level processes. Policy makers and public health researchers use these models to gain insight into the potential long-term consequences of programmatic decisions. Given the protracted course of TB epidemics (18), the impact of policy decisions made today may not be observed for many decades in the future. To project the long-term effects of IPT programs, we developed a mathematical model to evaluate the effects of various IPT policies targeted to HIV–TB coinfected subpopulations in areas with emerging TB and HIV epidemics. Our primary aim was to describe the effect of such policies on the transmission dynamics of drug-resistant TB in areas in which community-wide IPT may be used as a strategy to control HIV–TB coinfection.

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Abbreviations: TB, tuberculosis; INH, isoniazid; IPT, INH preventive therapy; ARV, antiretroviral drug.

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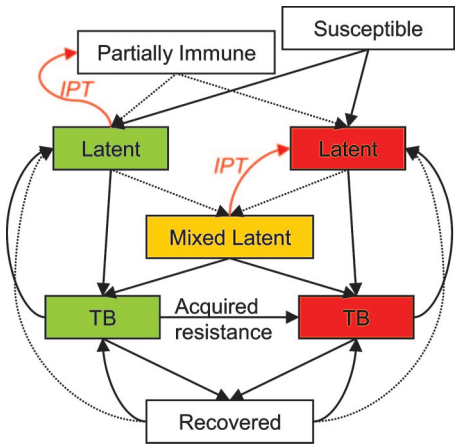

Fig. 1. Condensed model structure. The full model consists of two parallel models (one for HIV-infected and one for HIV-uninfected) that have structures similar to the one depicted here. Individuals move from one submodel to the other when they are infected with HIV. The full model structure can be found in *Supporting Text*. Green compartments represent infection/disease with a drug-sensitive *M. tuberculosis* strain; red compartments represent infection/disease with either a fit or unfit drug-resistant strain; the yellow compartment represents infection with two strains (i.e., drug-sensitive and fit/unfit drug-resistant or unfit and fit drug-resistant). Each of the compartments summarizes a number of distinct infection/disease states. The latent infection compartments include individuals who can progress to TB disease either slowly or rapidly or who can be reinfected with another strain of circulating *M. tuberculosis*. The TB disease compartments include those who have active (infectious) disease and extrapulmonary (noninfectious) disease. Individuals with TB disease may self-cure (contain their infection and return to latency) or, if they have active disease and are detected and treated, they may recover from disease. Those who are treated for drug-sensitive TB may acquire drug resistance. Individuals in all compartments (with the exception of those with TB disease) may be reinfected by circulating strains of *M. tuberculosis* (dotted arrows). IPT works by clearing drug-sensitive organisms from latently infected individuals (red arrows).

Model

Model Overview. To assess the impact of community-wide IPT on the dynamics of drug-resistant TB, we constructed a simple deterministic model of TB transmission based on a structure previously developed for the evaluation of control policies (19–23). The TB infection process was linked to a dynamic model of HIV transmission, and the model thus included interacting subpopulations of HIV-infected and noninfected individuals. We also simulated the emergence of drug-resistant TB and its subsequent spread in the population (see Fig. 1 for condensed model structure); the full model structure (Fig. 4, which is published as supporting information on the PNAS web site) and set of expressions governing state transitions and model input parameters are available as Lists 1 and 2 and *Supporting Text*, which are published as supporting information on the PNAS web site.

Drug-Resistant TB. We assumed that drug-resistant strains were initially generated through inadequate treatment of drug-sensitive TB, and that these strains could subsequently be transmitted to other individuals. We modeled the appearance of drug resistance as follows: among HIV noninfected persons, 5% of those who were treated, but not cured, acquired drug resistance (24). We then explored the sensitivity of these findings to the proportion of treatment failures that acquire drug-resistant *M. tuberculosis* phenotypes by allowing this parameter to vary between 1% and 10%.

Resistance to anti-TB drugs is conferred through chromosomal point mutations, which have different consequences for the reproductive fitness of the *Mycobacterium*; some mutations appear to exert a fitness cost, whereas others have a minimal effect on fitness (25–27). We modeled this heterogeneity by including two drug-resistant phenotypes that differed in fitness. Because some drug-resistant strains appear to be transmitted less readily than drug-sensitive strains (28, 29), we assumed that most newly generated drug-resistant mutants were 30% as fit as drug-sensitive strains, but that 5% of these resistant strains retained full fitness. We also considered scenarios where the most fit strain was only 70% as fit as the sensitive strain. The fitness of each strain determined both the probability of infection given exposure and the probability of progression given concurrent infection with more than one strain.

Here the term drug resistance refers to strains resistant to INH and at least one other first-line antibiotic. We assumed that IPT provides no protection from progression with drug-resistant infection, and that among HIV-uninfected persons, first-line treatments cured 85% of those who did not acquire drug resistance but slightly less than half of those with drug-resistant disease.

Exogenous Reinfection. Previous models demonstrated that exogenous reinfection affects the dynamics of TB epidemics in high-incidence areas (30), and molecular epidemiologic studies confirmed that reinfection and multiple strain infection are common in high-transmission settings (9, 31). We therefore incorporated both serial reinfection and concurrent infection with two strains of *M. tuberculosis*. For individuals simultaneously infected with both drug-resistant and -sensitive strains, the probability of progressing to drug-resistant disease was proportional to the relative fitness of the drug-resistant strain. We assumed that, for individuals infected with both drug-resistant and -sensitive strains, IPT would clear only the sensitive strain.

IPT Strategy. We examined the effects of several different IPT strategies. We varied both the proportion of the eligible population covered and the time at which the policy was implemented relative to the maturity of the TB and HIV epidemics. Because HIV must be diagnosed, latent *M. tuberculosis* infection detected, and active TB disease ruled out before IPT is administered, we assumed that only those individuals who were HIV–TB-coinfected and had slowly progressing latent infections would be identified rapidly enough to receive preventive therapy. The initiation of community-wide IPT programs was triggered when the prevalence of HIV infection exceeded specific population thresholds. We also varied levels of drug resistance at the time of IPT introduction.

Results

Projected Effects of IPT Intervention on TB and TB Drug Resistance. In the first few years after program introduction, community-wide IPT was associated with reductions in the prevalence of both latent infection and active infectious TB; this trend was more marked as coverage increased. Despite these reductions in the overall burden of TB, increasing IPT coverage led to an increasing proportion of TB that was drug-resistant. Because the absolute number of cases was falling, higher proportions of drug resistance still corresponded to lower numbers of drug-resistant TB cases (Table 1).

Over the course of the following several decades, there was a shift in the dynamics of the epidemic as a result of increasing IPT coverage. As more of the circulating strains became resistant to the standard treatment regimens, early IPT-related gains in TB control were reversed (Fig. 2 *a* and *b*). Once drug-resistant strains replaced most of the drug-sensitive strains in the population, IPT had no further effect. Thus, over the long term, each simulation converged to similar levels of TB.

The impact of the IPT strategy was not sensitive to either the timing of the intervention or the prevalence of drug-resistant TB

Table 1. Baseline epidemiologic measures and 5-year impact of IPT

Outcome	Baseline*	Five-year projections under varying IPT coverage			
		0%	33%	66%	99%
TB prevalence per 100,000 people	252	779	675	496	190
Proportion of population with latent infection, %	34.5	37.4	34.1	28.6	19.8
Proportion of TB that is drug-resistant, %	4.0	4.9	5.3	6.4	12.7
Prevalence of drug-resistant TB per 100,000 people	10	38	36	32	24
Proportion of population HIV-infected, %	16.3	33.5	34.4	36.1	39.6
Percent reduction in cumulative HIV deaths (years 0–5) attributable to IPT, %	—	Reference†	3.5	9.6	21.2

*Baseline = year 0 = time IPT was introduced.
†Baseline no. of cumulative HIV deaths (years 0–5) when IPT coverage = 0% (number of deaths to which increased levels of IPT coverage were compared).

at the time IPT was initiated (Figs. 5–7, which are published as supporting information on the PNAS web site). Fig. 2 demonstrates the results of simulations in which IPT was introduced into epidemiologic scenarios which reflect sub-Saharan settings with respect to the burden of HIV, TB, and drug-resistant TB (11, 32).

We also tested the sensitivity of these dynamics to our fitness assumptions by reducing the relative fitness of the fittest drug-resistant strain to 70%. In scenarios where drug-resistant strains would not otherwise be expected to emerge, initiation of an IPT program exerted enough additional selective pressure to tip the balance in favor of the resistant strains despite this fitness deficit (Fig. 2*d*).

Projected Effects of IPT Intervention on HIV. The purpose of IPT is to prevent progression of TB disease in those infected and thus to reduce morbidity and mortality among HIV–TB coinfected individuals. Effective IPT will avert a major cause of death among HIV-infected individuals in high TB burden settings. Our simulations showed reductions in HIV-related deaths during the first few years after initiation of IPT programs (Table 1 and Fig. 2*c*). Because the average lifespan of HIV-infected individuals was extended under IPT, HIV prevalence increased, and HIV-infected individuals had more time to transmit HIV to others. This process led to an increase in later HIV-related deaths as a result of delayed early mortality and increased transmission opportunity (Fig. 2*c*).

To further explore the potential impact of these programs on HIV dynamics, we conducted a set of analyses in which we simulated the introduction of antiretroviral drugs (ARVs) at the same time as IPT programs. We found that, although ARVs immediately reduced HIV-related deaths, they had minimal additional short-term effect on the prevalence of latent and active TB or measures of drug resistance (Table 2, which is published as supporting information on the PNAS web site).

Improving the Performance of Preventive Therapy for Latent TB Infection. We compared the effects of enhancing IPT programs in three ways: (*i*) providing IPT to all HIV-infected individuals without active TB rather than limiting this intervention only to those identified as latently infected; (*ii*) modifying the preventive therapy drug regimen so that both drug-resistant and -sensitive strains were covered; and (*iii*) improving the treatment of drug-resistant disease. In the first case, we found that using IPT as empiric preventive therapy for all HIV-infected individuals without active TB increased the proportion of drug-resistant TB in the short term but did not alter the projected long-term levels of drug-resistant disease (Fig. 8, which is published as supporting information on the PNAS web site). In the second case, preventive regimens that target both drug-resistant and -sensitive strains were effective in delaying the emergence of drug-resistant disease (Fig. 3*b*) but yielded only a modest reduction in the TB burden and HIV-related deaths (Fig. 3 *a* and *c*). When we assumed that the efficacy of treatment for drug-resistant cases

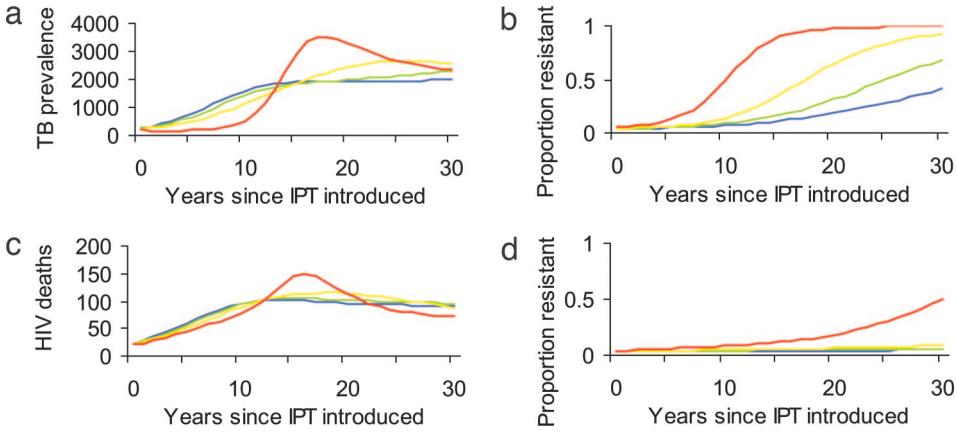

Fig. 2. Effects of IPT. Varying coverage of IPT (blue = 0% coverage, green = 33% coverage, orange = 66% coverage, and red = 99% coverage). (*a*) TB prevalence (per 100,000) by years since IPT was introduced. (*b*) Proportion of TB that is drug-resistant by years since IPT was introduced. (*c*) HIV-associated deaths (per 1,000) by years since IPT was introduced. (*d*) IPT selective pressure. Increasing IPT coverage can cause a "phase change" from the coexistence of drug-sensitive and -resistant strains to dominance of the drug-resistant strains. Here the relative fitness of the most fit drug-resistant strains were assumed to be only 70% of the fitness of the drug-sensitive strains.

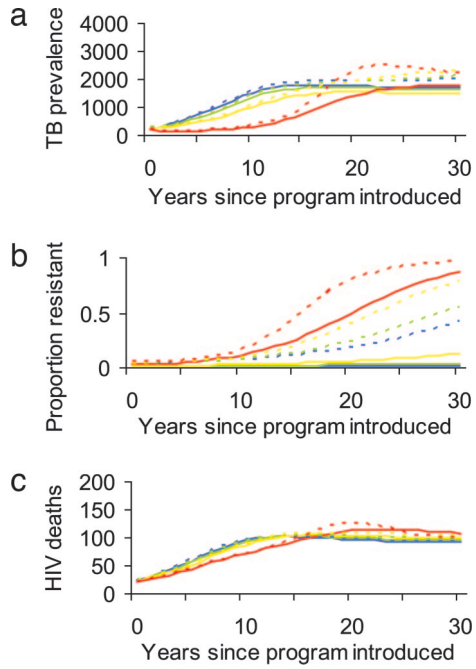

Fig. 3. Adjuncts to improve the performance of preventive therapy for latent TB infection. Comparison of using drugs that treat latent resistant infections (dashed lines) versus improving treatment of resistant TB disease (solid lines) in addition to baseline IPT coverage (blue = 0% coverage, green = 33% coverage, orange = 66% coverage, and red = 99% coverage). (*a*) TB prevalence (per 100,000) by years since the policy was introduced. (*b*) Proportion of TB that is drug-resistant by years since the policy was introduced. (*c*) HIV-associated deaths (per 1,000) by years since the policy was introduced.

was equal to that for sensitive ones, we found this alternative attained the most sustained reduction in TB and prevention of HIV-related deaths, especially when it was coupled with high IPT coverage (Fig. 3 *a* and *c*).

Discussion

Mathematical models have been used to project the effect of treating latent TB infections in populations with (22, 33–37) and without concurrent HIV epidemics (19, 38). We have extended these models to evaluate the potential impact of programs for community-wide IPT on the dynamics of drug-resistant TB.

Our model of emerging coepidemics of TB, drug-resistant TB, and HIV allows qualitative assessment of the short- and longer-term effects of community-wide IPT for HIV–TB coinfected individuals. We found that, in areas where HIV is emerging, use of single-drug preventive therapy reduced the burden of TB in the short term but also had perverse effects on the rapidity at which drug-resistant TB emerged. It has previously been shown that INH monotherapy is unlikely to cause the selection of rare drug-resistant mutants in those who are latently infected with a drug-sensitive TB strain (4); the increase in drug-resistant TB observed here was not the result of acquired resistance generated by IPT. Rather, IPT promoted the emergence of drug resistance in two ways: (*i*) IPT prevented disease among individuals infected with drug-sensitive *M. tuberculosis* strains, thereby decreasing further transmission of these strains. Because infection with one strain provided partial protection against infection with another, there was competition between sensitive and resistant strains, so this effect promoted the spread of resistant strains. (*ii*) IPT cured drug-sensitive latent infections in patients dually infected with sensitive and resistant strains and thus increased the likelihood that reactivation with a resistant strain would occur. Although the pattern of short-term reductions in TB incidence followed by higher longer-term prevalence of drug-resistant disease was a robust effect of community-wide IPT programs, we stress that the timing of these dynamics is inexact and depends upon assumptions for which conclusive data are unavailable, including the TB case finding and treatment rates, the efficacy of TB treatment, the rates of acquired drug resistance, and the distribution of fitness of drug-resistant strains.

By necessity, our model is based on several assumptions about the efficacy of IPT. First, we assumed that IPT is completely effective in preventing disease with a drug-sensitive strain. A metaanalysis of five trials of IPT among tuberculin skin test-positive HIV-infected individuals found that IPT reduced the risk of TB by ≈40% (39). This figure may underestimate the efficacy of IPT against drug-sensitive strains. Because drug susceptibility cannot be ascertained during latency, and reinfection after IPT administration cannot be excluded, the ability of IPT to prevent progression of a drug-sensitive infection may be higher than this estimate. Adherence to lengthy IPT regimens has been shown to be poor; thus even if the efficacy of IPT were 100%, its effectiveness would be substantially less. If nonadherence with IPT does not lead to the selection of drug-resistant strains among those with multiple strain infections, we would expect slower emergence of drug resistance than is projected here. Second, although we assumed that IPT does not prevent disease with a drug-resistant strain, there are no data available on the efficacy of IPT for drug-resistant infections.

In our model, we assumed that individuals infected with multiple strains could progress to active disease with only one strain. Because no technologies yet exist for strain identification during latency, this assumption is not currently testable. Efforts to improve the sensitivity of laboratory testing for mixed infections during active TB disease may help improve our understanding of the natural history of multiple strain infections (40).

Because the primary focus of this study is to gain insight into the impact of these strategies on the TB epidemic, the dynamic model for HIV transmission is greatly simplified. We did not account for sex, age, or sexual behaviors known to be important modifiers of HIV transmission. We also did not model vertical transmission or account for the fact that some social groups may be at increased risk of both HIV and TB. Nevertheless, our model allows for dynamic transmission of HIV and thus permits insight into the potential effects of IPT on the emerging HIV epidemic. We observed that IPT programs may lead to higher short-term HIV prevalence by reducing HIV-associated deaths and increasing transmission opportunities associated with a longer average duration of HIV infection. Similar observations have been made by modelers who have studied the potential impact of chemotherapy or vaccination on HIV epidemics (41–43). The projected increase in HIV prevalence occurred in the absence of measures designed to limit the secondary spread of HIV and should therefore be interpreted with caution. Finally, our finding that ARVs will reduce HIV-related deaths, but have limited short-term effects on TB indices, is consistent with others' projections (44).

The identification of individuals eligible for preventive therapy poses a potential obstacle for the implementation of community-wide IPT programs. For example, in most high-burden HIV/TB areas, the majority of HIV-infected individuals do not know their HIV status, and active TB often precipitates the diagnosis of HIV (45). Obviously, in these instances, the opportunity for primary prevention of TB is missed. Additionally, among those identified as HIV-infected, the diagnosis of latent infection is compromised by the relatively poor performance of tuberculin skin testing. We note that achieving the highest level of IPT coverage that we simulated is unlikely given the dual challenges of identifying eligible persons and assuring adequate

adherence; we therefore point to the 33% and 66% levels as more attainable levels of coverage.

Conclusions

In summary, our results suggest that the systematic use of IPT to prevent progression of latent *M. tuberculosis* infections among those with HIV infection will reduce the local burden of TB disease and infection for several years, but that this early benefit may be followed by a rapid emergence of drug resistance. This effect is most pronounced when the coverage levels of these IPT programs are high, but the qualitative dynamics are relatively insensitive to the prevalence of either HIV or of drug-resistant TB at the time of IPT program initiation.

Should we use IPT for coinfected individuals in areas of emergent HIV and prevalent drug-resistant TB? Our results suggest that programs for preventive therapy for latent *M. tuberculosis* infection may perform best when incorporated into treatment programs that can diagnose and effectively treat the increasing proportion of patients that will present with drug-resistant TB. Recent observational studies demonstrate that treatment regimens for individuals with highly drug-resistant TB can achieve outcomes similar to regimens for individuals with drug-sensitive disease, even in resource-constrained settings (46). Programs that couple IPT with effective treatment of those with drug-resistant TB appear to be better than programs that use alternative drug regimens to attempt to prevent progression from either drug-sensitive or -resistant latent infections. The successful control of TB in high-burden HIV settings may require policies that simultaneously target the risk of progression given infection and the risk of transmission given disease.

Methods

Base Case Scenario. To generate the base case scenarios from which we compare various prophylactic control policies, we introduced a single case of drug-sensitive TB into a homogeneously mixing population (of size 10^6) and allowed the disease to equilibrate in the absence of chemotherapy. Because the transmission parameter for drug-sensitive TB was parameterized as persons^{-1}·time^{-1}, our fitted transmission parameter reflects the choice of population size under study. This parameter was calibrated to generate a scenario typical of a high-TB-burden country before drug availability. We used a time step of 0.1 year and the fourth-order Runge–Kutta integration method. Our base case equilibrates with 67% of the population with latent infection and a prevalence of just over 300 TB cases per 100,000 people. We then introduced anti-TB chemotherapy; we allowed that 50% of infectious cases are detected and treated, and 85% of those treated are cured by drugs.

The presence of antibiotics leads to the appearance of drug-resistant strains of disease. Among those treated for drug-sensitive TB, we used varying rates of acquired resistance to generate drug resistance that reflects currently observed levels (11, 24). Once drug-resistant strains are generated through failed therapy, they may be transmitted to others (primary drug resistance). For the purposes of the baseline analyses, we assume that most mutations that confer drug resistance have fitness costs, but a small minority of drug-resistant strains will have no reduction in fitness. Earlier work has demonstrated how, as the epidemic progresses in the presence of antibiotics, an increasing proportion of new drug-resistant cases will be caused by transmission (rather than acquired during therapy), and the mean relative fitness of the resistant strains will increase (23).

To simulate co-occurring HIV and TB epidemics in high-burden areas, we calibrated the transmission parameter for HIV to generate an equilibrium HIV prevalence of ≈25%. We also altered TB parameter values to reflect the higher rates of progression from latency and reduced infectiousness for HIV–TB coinfected individuals. As with TB dynamics, we assume homogeneous mixing and examine the effects of IPT introduction at different times in these epidemics.

Introducing Prophylactic Regimens for Latent TB Infection in HIV+. In our base case scenario (Fig. 2), we introduce treatment for latent *M. tuberculosis* infection when the prevalence of latency is 35%, the prevalence of infectious TB is ≈250 cases per 100,000, the proportion of TB that is multidrug resistant (MDR) is ≈4%, and the population prevalence of HIV infection is ≈15%. At this time, the proportion of infectious TB that is MDR is slowly increasing, and the prevalence of HIV is increasing much more rapidly, consistent with patterns observed in sub-Saharan Africa (32, 47).

For our main analyses, we assume that IPT is completely effective in preventing disease for those with latent drug-sensitive infections and completely ineffective for those latently infected with the drug-resistant strain. We also assume that those with HIV and rapidly progressing latent *M. tuberculosis* infections will not be detected rapidly enough to receive IPT. Among those simultaneously infected with a drug-sensitive and -resistant strain, IPT eliminates the sensitive strain, but the individual continues to be infected with the resistant strain.

Introducing ARVs. We considered the effect of the concurrent introduction of ARVs with IPT by assuming that these drugs would reduce HIV transmission and render the disease progression of those who had HIV–TB coinfections to be like those who were infected only by *M. tuberculosis*. We considered scenarios in which all eligible HIV-infected individuals would receive ARVs within 10 years of program introduction. The HIV-transmission parameter was allowed to decrease by 50%, and we assumed that all HIV-specific parameters would trend linearly to the values of those for the HIV-uninfected population over 10 years. The short-term impact of such programs is provided in Table 3, which is published as supporting information on the PNAS web site; these results are from IPT and ARV programs introduced into the base case scenario and should be compared with those in Table 1.

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