Re-evaluating the health impact and cost-effectiveness of tuberculosis preventive treatment for modern HIV cohorts on antiretroviral therapy: a modelling analysis using data from Tanzania

Jinyi Zhu, Goodluck Lyatuu, Christopher R Sudfeld, Anna Kiravu, David Sando, Lameck Machumi, John Minde, Fikiri Chisonjela, Ted Cohen, Nicolas A Menzies

Summary

Background Isoniazid preventive therapy (IPT) can prevent tuberculosis among people receiving antiretroviral therapy (ART). HIV programmes are now initiating patients on ART with higher average CD4 cell counts and lower tuberculosis risks under test-and-treat guidelines. We aimed to investigate how this change has affected the health impact and cost-effectiveness of IPT.

Methods We constructed a tuberculosis–HIV microsimulation model parameterised using data from a large HIV treatment programme in Dar es Salaam, Tanzania. We simulated long-term health and cost outcomes for the 211 748 individuals initiating ART between Jan 1, 2014, and Dec 31, 2020, under three scenarios: no IPT access; observed levels of IPT access (75%) and completion (71%); and full (100%) IPT access and completion. We stratified results by ART initiation year and starting CD4 cell count.

Findings Observed levels of IPT access were estimated to have averted 12 800 (95% uncertainty interval 7300 to 21 600) disability-adjusted life-years (DALYs) and saved US$23 000 (–2 268 000 to 1 388 000). Full IPT access would have averted 24 500 (15 100 to 38 300) DALYs and cost $825 000 (–1 594 000 to 4 751 000), equivalent to $23·4 per DALY averted. Lifetime health benefits of IPT were estimated to be greater for more recent ART cohorts, while lifetime costs were stable. In subgroup analyses, a higher CD4 cell count at ART initiation was associated with greater health gains from IPT (15 900 [10 300 to 22 500] DALYs averted by full IPT per 100 000 patients for CD4 count >500 cells per µL at ART initiation, versus 7400 [4500 to 11 600] for CD4 count <100 cells per µL) and lower incremental lifetime costs.

Interpretation IPT remains highly cost-effective or cost-saving for recent ART cohorts. The health impact and cost-effectiveness of IPT are estimated to improve as patients initiate ART earlier in the course of infection.

Funding US National Institutes of Health.

Lancet Glob Health 2022; 10: e1646–54

See **Comment** page e1549

Department of Health Policy, Vanderbilt University School of Medicine, Nashville, TN, USA (J Zhu PhD)**; Center for Health Decision Science** (J Zhu, N A Menzies PhD) **and Department of Global Health and Population** (C R Sudfeld ScD, N A Menzies), **Harvard T.H. Chan School of Public Health, Boston, MA, USA; Management and Development for Health, Dar es Salaam, Tanzania** (G Lyatuu MD, A Kiravu MD, D Sando PhD, L Machumi MD, J Minde MSc, F Chisonjela BSc)**; Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, CT, USA** (Prof T Cohen DPH)

Correspondence to: Dr Jinyi Zhu, Department of Health Policy, Vanderbilt University School of Medicine, Nashville, TN 37203, USA **jinyi.zhu.1@vanderbilt.edu**

Introduction

Tuberculosis is the leading cause of mortality among people living with HIV, and is the proximal cause of over a quarter of all HIV-associated deaths.[1] Isoniazid preventive therapy (IPT) prevents progression from latent infection to tuberculosis disease, and reduces tuberculosis incidence among people with HIV on and off antiretroviral therapy (ART).[2] IPT has been consistently found to be cost-effective,[3] and is recommended by WHO for all adults with HIV. However, IPT coverage remains low globally: coverage among individuals receiving ART in 2019 was 50% in the 62 countries that reported to WHO.[4] Reported IPT coverage in Tanzania, a country with a high burden of tuberculosis and HIV, was only 45% in 2019, although it has seen notable improvements in recent years following improved isoniazid availability and strengthened national IPT guidelines.

Due to test-and-treat guidelines, HIV treatment programmes have seen a shift in the case mix of individuals initiating ART, such that contemporary cohorts are, on average, healthier—with a higher CD4 cell count—than in previous years.[5] Earlier ART initiation improves health outcomes and reduces opportunistic infections,[6] including tuberculosis. Accordingly, early ART initiation can reduce the expected impact of IPT on tuberculosis prevention in recent and future years. A meta-analysis of HIV cohorts found that the proportional reduction in tuberculosis incidence produced by IPT was lower among individuals who initiated ART with higher CD4 cell counts.[7] Similarly, the TEMPRANO trial found that IPT produced a 1·7 percentage point reduction in cumulative incidence of severe illness or death at 30 months among individuals initiating ART early, compared with a 5·3 percentage

Research in context

Evidence before this study

We examined two sources of evidence on the cost-effectiveness of isoniazid preventive therapy (IPT) for preventing tuberculosis among people living with HIV: (1) a systematic review and meta-analysis on this subject conducted by Uppal and colleagues (2021), and (2) a PubMed search to update from the end date of this review (Dec 31, 2020) to Jan 31, 2022, without language restrictions, using the search terms "(tuberculosis) AND (HIV or AIDS) AND (prevent*) AND (economic evaluation or cost-effective*) AND (model* or simulation)". A large number of studies found IPT to be cost-effective for patients with HIV receiving antiretroviral therapy (ART). However, we found no previous study estimating how the cost-effectiveness of IPT has changed for recent cohorts initiating ART with high average CD4 cell counts.

Added value of this study

We evaluated the lifetime health impact and cost-effectiveness of IPT for a large study population initiating ART between 2014 and 2020 in Dar es Salaam, Tanzania. The results of this analysis show that among cohorts initiating ART more recently (eg, 2020 *vs* 2014), IPT resulted in greater health benefits and relatively stable incremental costs, as compared with earlier cohorts. When results were stratified by CD4 cell count at ART initiation, we found that individuals with higher starting CD4 cell counts experienced greater health gains and lower lifetime costs for IPT, as compared with individuals with lower starting CD4 cell counts. We also found that risks of isoniazid resistance (measured as the ratio of additional isoniazid-resistant tuberculosis cases *vs* total tuberculosis cases averted by IPT) were consistently low across calendar years and slightly lower in more recent ART cohorts. With many countries successfully expanding HIV testing and linkage to care under test-and-treat guidelines, the results of this study highlight the health gains foregone by slow IPT scale-up.

Implications of all the available evidence

This study, combined with earlier evidence, shows that expanded IPT is one of the most cost-effective approaches for improving survival and quality-of-life for patients receiving ART, and that the lifetime health benefit and cost-effectiveness of IPT improve as patients initiate ART earlier in the course of HIV disease with higher CD4 cell counts. Since tuberculosis still causes over a quarter of all HIV-associated deaths, the low coverage of IPT within many HIV programmes is a major concern. Ensuring timely initiation and completion of IPT should be prioritised for ART programmes in settings with a high burden of tuberculosis and HIV.

point reduction with delayed ART initiation.[8] However, this difference in IPT impact was not observed on long-term follow-up.[9] Although these studies confirm the incremental benefit of IPT in addition to ART for preventing tuberculosis, they suggest that these benefits might be smaller when individuals initiate ART with higher average CD4 cell counts. Given these changes, it is important to weigh the health benefits against the costs of IPT, to examine whether earlier conclusions about IPT cost-effectiveness still hold in contemporary ART programmes. Moreover, current evidence does not exclude a risk of increased isoniazid resistance from IPT.[10] Given concerns about isoniazid resistance acquired during IPT, it is useful to compare the magnitude of disease prevention benefits against potential drug resistance risks.

See Online for appendix

In this study, we evaluated the expansion of IPT coverage among adult patients on ART in the HIV treatment programme in Dar es Salaam, Tanzania, managed by Management and Development for Health (MDH). Using detailed clinical data on patients initiating ART between 2014 and 2020, we parameterised a mathematical model of tuberculosis–HIV co-infection to estimate lifetime health impact and costs of IPT, including the isoniazid resistance risks. We report how outcomes varied over time and by CD4 cell count at ART initiation, and discuss the implications for expanding IPT access in contemporary ART cohorts in which ART is initiated earlier in the course of HIV disease.

Methods

Study cohort

The Dar es Salaam HIV treatment programme is administered by the Government of Tanzania with support from MDH and funding from the US President's Emergency Plan for AIDS Relief. MDH is a non-governmental organisation that provides technical support on HIV and other health programme implementation in Dar es Salaam and across Tanzania. By 2020, the MDH programme covered 94% of all patients on ART in Dar es Salaam. Since 2017, under the test-and-treat strategy, HIV-positive patients initiate ART immediately after diagnosis, and are evaluated monthly. Demographic and clinical information is recorded at each clinical visit. Additional details on the MDH programme are included in the appendix (p 18). This study was approved by institutional review boards at the Harvard T.H. Chan School of Public Health and Tanzanian National Institute of Medical Research.

We extracted individual-level data on age, sex, and CD4 cell count to create the starting cohort for our analysis. We used observed tuberculosis incidence, tuberculosis-attributed mortality, all-cause mortality, retention in care, and coverage of tuberculosis prevention interventions to parameterise selected inputs.

Simulation model

We developed a stochastic individual-based simulation model of tuberculosis–HIV co-infection. The model was

organised into three dimensions, representing: (1) tuberculosis infection, progression, and treatment; (2) HIV natural history and care; and (3) tuberculosis drug resistance. Figure 1 shows health states and transitions for each dimension. At any point in time, a modelled individual resides in one health state in each dimension, and moves between health states on the basis of predefined monthly probabilities. We simulated individuals from ART initiation until death, to capture the health and economic effects of IPT over a lifetime horizon.

Individuals enter the model on the basis of their tuberculosis status and diagnosis at ART initiation. Individuals in the susceptible state face monthly tuberculosis infection risks, which were assumed to be exogenous and not modelled dynamically. A fraction of incident tuberculosis infections were assumed to be isoniazid-resistant, on the basis of the reported prevalence of isoniazid resistance.[11] Newly infected individuals transition to the latent infection state, in which they face monthly risks of progression to tuberculosis disease. These risks were assumed to decrease with higher CD4 cell count and greater time since tuberculosis infection, on the basis of empirical data[12–14] and published modelling approaches for this key assumption.[15] Previous tuberculosis infection was assumed to confer partial immunity against reinfection.[16] Individuals with tuberculosis disease could be diagnosed and initiated on tuberculosis treatment, and subsequently die during treatment, discontinue the regimen,[17] or complete treatment. Individuals cured through treatment return to the recovered state. Individuals not achieving cure return to the tuberculosis disease state. Monthly mortality risks were assumed to vary by age and sex,[18] as well as tuberculosis and HIV health state.

IPT was assumed to cure tuberculosis infection in a fraction of individuals completing treatment, with this preventive effect applied to both prevalent infections and new tuberculosis exposures during IPT (appendix p 8).[2] Individuals with tuberculosis infection cured by IPT were assumed to have no further risk of progression to tuberculosis, and retained partial immunity against reinfection. Although IPT is provided only after screening to exclude tuberculosis disease, we assumed a fraction of tuberculosis cases would be missed by screening and incorrectly initiated on IPT. For these individuals, we allowed for the potential acquisition of isoniazid resistance during IPT.[19] Isoniazid resistance was assumed to result in lower cure rates for subsequent tuberculosis treatment.[20] In the main analysis, we assumed IPT would have no curative effect for individuals with tuberculosis disease; this assumption was revisited in our secondary analyses.

Modelled individuals were assumed to receive ART until death or loss to follow-up. CD4 cell count was used to track HIV-related immune function, which was assumed to rebound upon ART initiation and decline linearly among those discontinuing ART.[21] The effect of HIV on mortality and tuberculosis natural history parameters was governed by ART status and CD4 cell count.[22,23]

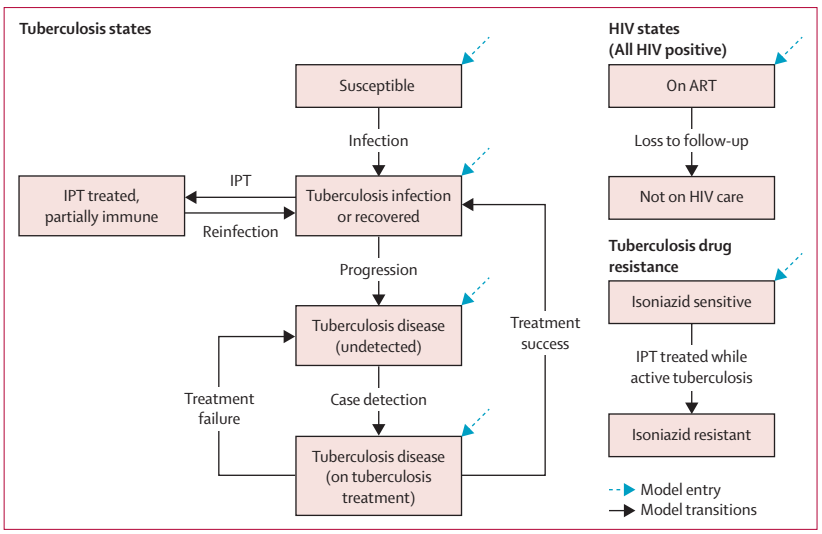

Figure 1: **Model schematic**
Mortality is omitted in the diagram. ART=antiretroviral therapy. IPT=isoniazid preventive therapy.

Model calibration

We calibrated the model to the fraction of tuberculosis cases due to recent infection,[24] and observed trends of tuberculosis cases, tuberculosis-specific deaths, and all-cause deaths in MDH-supported clinics. We used a Bayesian approach for calibration, implemented with incremental mixture importance sampling.[25] Prior distributions were based on published estimates (table 1 and appendix pp 2–8). We assumed weakly informative prior distributions for unknown inputs (eg, tuberculosis force of infection, baseline latent infection prevalence, and undiagnosed tuberculosis disease). Goodness-of-fit was measured using likelihood functions created from the calibration data. We obtained a posterior sample of 10 000 parameter sets, and used this sample for all subsequent analyses (appendix pp 2–10). Appendix p 10 shows model fit to calibration data.

Modelled scenarios

We compared three implementation scenarios for a one-time, 6-month course of isoniazid. First, no IPT: a hypothetical reference scenario in which no IPT is provided. Second, observed IPT: a scenario reproducing empirical trends in IPT initiation and completion in MDH clinics from 2014 to 2020. In this scenario, 75% of individuals initiated IPT, among which 71% completed the full 6-month regimen. The mean time of IPT initiation was 25·3 months (SD 24·8) after ART initiation. Third, full IPT: a hypothetical scenario with all eligible individuals initiating IPT 1 month after ART initiation, and 100% completion.

	Value or assumption	Data source
Cohort characteristics		
Age at ART initiation, years	Mean 36·2 (SD 10·6)	MDH
Sex*	..	MDH
Female	151 611 (71·6%)	..
Male	60 137 (28·4%)	..
CD4 count distribution at ART initiation*	..	MDH
<100 cells per μL	33 033 (15·6%)	..
100–200 cells per μL	32 821 (15·5%)	..
200–350 cells per μL	55 054 (26·0%)	..
350–500 cells per μL	40 656 (19·2%)	..
>500 cells per μL	50 184 (23·7%)	..
Background mortality		
Non-tuberculosis or HIV-related mortality	Age-specific and sex-specific	UN Department of Economic and Social Affairs (2021)[18]
Tuberculosis-related parameters		
Tuberculosis force of infection	Estimated through calibration†	Houben et al (2011)[24]
Progression rate from LTBI to active tuberculosis disease	Function of CD4 cell count and time since ART initiation†	Borgdorff et al (2011);[12] Ferebee et al (1970);[13] Sutherland et al (1976)[14]
Excess mortality rate due to active tuberculosis disease	Estimated through calibration†	MDH
HIV-related parameters		
CD4 cell count trajectory, on ART	Log-linear function of time since ART initiation with an asymptote†	MDH
CD4 cell count trajectory, off ART	Linear decline at 5·08 (3·83–6·75) cells per μL per month	Wolbers et al (2010)[21]
Excess mortality rate due to HIV, on ART	Log-linear function of CD4 cell count†	Anglaret et al (2012)[22]
Excess mortality rate due to HIV, off ART	Log-linear function of CD4 cell count†	Kroeze et al (2018)[23]
Rate of stopping HIV care or LTFU	Weibull function of time since ART initiation†	MDH
Probability of true LTFU among observed LTFU	36% (20–53)	Geng et al (2016)[17]
IPT-related parameters		
IPT efficacy, risk ratio of tuberculosis incidence	0·67 (0·51–0·87)	Akolo et al (2010)[2]
Disability weights		
Active tuberculosis, HIV positive	0·408 (0·274–0·549)	GBD Collaborative Network (2020)[26]
HIV positive, on ART	0·078 (0·052–0·111)	GBD Collaborative Network (2020)[26]
HIV positive, off ART	..	GBD Collaborative Network (2020)[26]
CD4 count <200 cells per μL	0·582 (0·406–0·743)	..
CD4 count ≥200 cells per μL	0·274 (0·184–0·377)	..
Costs‡		
Tuberculosis treatment cost per month	$93·2 (70–131·2)	Siapka et al (2020)[27]
HIV care cost per month	$22·1 (17·0–27·1)	Cerecero-García et al (2019)[28]
IPT cost per month	$0·56 (0·53–0·60)	Stop TB Partnership (2020)[29]

Intervals in parentheses denote 95% uncertainty intervals. ART=antiretroviral therapy. GBD=Global Burden of Disease. IPT=isoniazid preventive therapy. LTBI=latent tuberculosis infection. LTFU=loss to follow-up. MDH=Management and Development for Health. *Denominator for the percentages is 211 748. †Details on the functional form or estimation procedure are documented in the appendix (pp 2–10). ‡Costs parameters presented in 2020 US dollars.

Table 1: **Key model parameters**

Outcomes

Our primary health outcomes were life-years gained and disability-adjusted life-years (DALYs) averted. We also report long-term trends for tuberculosis incidence, tuberculosis-specific mortality, and all-cause mortality. We report total lifetime costs as our primary cost outcome, including costs of HIV care, tuberculosis care, and IPT. We did not include programmatic costs of IPT scale-up apart from direct service delivery. Costs were assessed from the health sector perspective, in 2020 US dollars. We also evaluated the cost-effectiveness of IPT implementation: for any intervention scenario that was not dominated (more costly and less beneficial) nor dominant (less costly and more beneficial), we estimated the incremental cost-effectiveness ratio (ICER), calculated as the incremental cost per DALY averted. Using recent health opportunity costs estimates,[30] we set the cost-effectiveness threshold at 30% of Tanzania per capita gross domestic product (GDP), equivalent to US$323 per DALY averted. Interventions with an ICER below this threshold are considered cost-effective. Future outcomes were discounted annually at 3%. We reported results for the overall study population as well as subgroups stratified by initial CD4 cell count and year of ART initiation.

Sensitivity analyses

We calculated the mean and 95% uncertainty intervals (UIs) for each outcome from the posterior sample of 10 000 parameter sets. In probabilistic sensitivity analyses we compared observed IPT and full IPT, respectively, with no IPT, to estimate their probability of being cost-effective at various cost-effectiveness thresholds.

We also calculated partial rank correlation coefficients (PRCCs) for each parameter. PRCCs quantify the monotonic relationship between individual parameters and a model outcome, controlling for other parameters. We used the net monetary benefit of observed or full IPT versus no IPT, defined as monetised health benefits (cost-effectiveness threshold × DALYs averted) minus incremental costs, as the outcome to estimate PRCCs. Finally, we did a traditional univariate sensitivity analysis, varying each parameter between its 95% UI bounds, holding other parameters constant.

In a secondary analysis, we assumed that some individuals with isoniazid-sensitive tuberculosis disease would be cured if incorrectly initiated on IPT, based on historical data reporting the efficacy of isoniazid monotherapy for treating tuberculosis.[19]

We performed analyses using R (version 4.1.0) and programmed the simulation model using the *Rcpp* package (version 1.0.6).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The study cohort consisted of 211748 adults with HIV initiating ART in MDH-supported clinics from Jan 1, 2014, to Dec 31, 2020. Table 1 summarises key cohort characteristics. Average CD4 counts at ART initiation increased over time (appendix p 2), from 283 cells per µL in 2014, to 400 cells per µL in 2020. From 2014 to 2020, IPT coverage increased from 10% to 81%, while IPT regimen completion increased from 60% to 80%.

IPT implementation was projected to produce both short-term and long-term effects on tuberculosis incidence, isoniazid resistance, tuberculosis mortality, and all-cause mortality (figure 2). Under the scenario of no IPT, we estimated that 36742 (95% UI 32836–41658) cumulative tuberculosis cases would occur over the lifetime of the study cohort. Compared with no IPT, the observed IPT scenario was estimated to avert 15·6% (13·1–18·6) of lifetime tuberculosis cases, while full IPT averted 25·9% (22·8–29·7) of total cases (figure 2A). The estimated average lifetime number of isoniazid-resistant tuberculosis cases under no IPT was 1170 (716–1766). Both observed IPT and full IPT were estimated to produce additional isoniazid-resistant tuberculosis cases (figure 2B), but the number of these cases was small compared with the total number of tuberculosis cases averted by IPT. Under the observed IPT scenario, there were 208 (69–541) total tuberculosis cases averted for every additional isoniazid-resistant tuberculosis case, while for full IPT, the ratio was 102 (50–199). For tuberculosis-specific mortality (figure 2C), observed IPT reduced tuberculosis-attributable deaths by 19·6% (16·4–23·9), and full IPT produced a 36·2% (31·7–41·0) reduction. IPT was projected to improve mean survival, and this effect was greater for the full IPT scenario (figure 2D).

Table 2 reports summary health outcomes. Compared with no IPT, observed IPT produced 17300 (95% UI 10500–27700) life-years gained, and averted 12800 (7300–21600) DALYs. Full IPT produced 32400 (20800–48700) incremental life-years gained and averted 24500 (15100–38300) DALYs.

Increased IPT coverage increased IPT costs, but lowered tuberculosis treatment costs due to reduced tuberculosis incidence, and increased ART costs due to prolonged life expectancy. Table 2 provides a breakdown of costs by scenario. Relative to no IPT, observed IPT was estimated to have an average incremental cost of –$23000 (95% UI –1388000 to 2268000; ie, cost-saving on average), while full IPT had an incremental cost of $825000 (–1594000 to 4751000).

Compared with no IPT, observed IPT produced positive health effects and was cost-saving (95% UI of the ICER: dominant to $96·8 per DALY averted). Relative to no IPT, full IPT produced positive health effects and higher costs, with an ICER of $23·4 per DALY averted (dominant to 121·4). This ICER is below the cost-effectiveness threshold of $323 per DALY averted. At this threshold, both observed and full IPT were preferred to no IPT in 100% of model simulations. Compared with observed IPT, full IPT had an ICER of $57·5 per DALY averted (dominant to 148·4), still below the cost-effectiveness threshold. We found strong evidence that IPT implementation would be cost-effective across a wide range of cost-effectiveness thresholds (appendix p 15). Health gains and cost savings were greater in the alternative model specification, for which we allowed for a curative effect for tuberculosis among individuals with tuberculosis disease incorrectly initiated on IPT (appendix p 16).

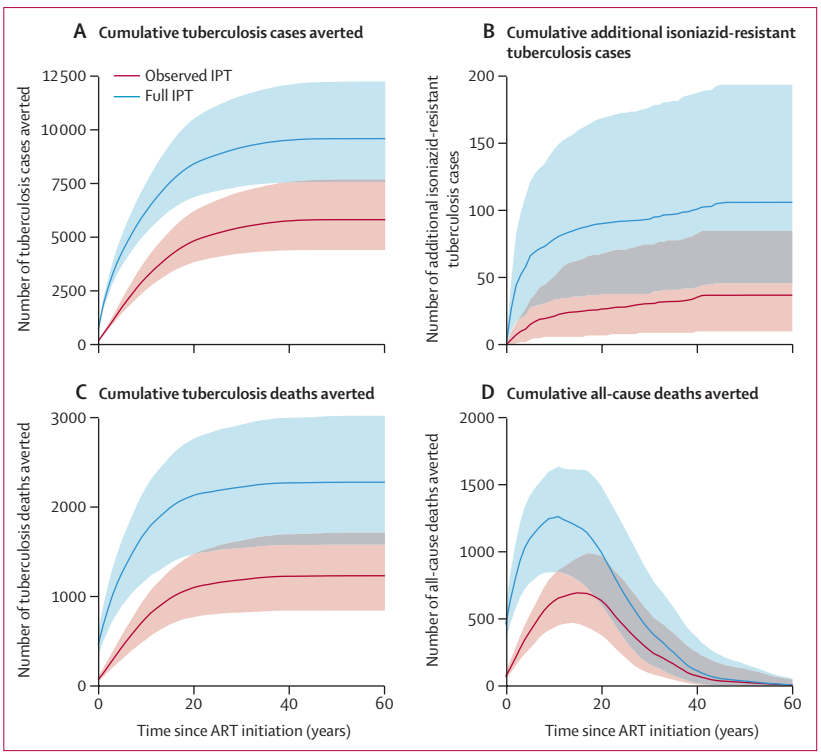

Figure 2: **Comparison of the projected epidemiological effect of IPT implementation scenarios in relation to no IPT**

All panels plot cumulative outcomes, so in panel D, no all-cause death was averted in the long term, but the timing of death was delayed by IPT. Solid lines represent mean estimates; shaded areas represent 95% uncertainty intervals. ART=antiretroviral therapy. IPT=isoniazid preventive therapy.

Sensitivity analyses results are displayed in the appendix (pp 13–14), and show that IPT cost-effectiveness was most sensitive to uncertainty in the costs of tuberculosis treatment and ART, the tuberculosis force of infection, tuberculosis progression rate, and IPT efficacy.

Appendix p 17 shows the cumulative tuberculosis incidence across CD4 cell count strata under the no IPT scenario. Higher CD4 cell count at ART initiation was associated with a higher lifetime tuberculosis incidence. For example, lifetime tuberculosis incidence was 12·5% for a starting CD4 count of more than 500 cells per µL, compared with 9·6% for a CD4 count of less than 100 cells per µL.

Table 3 presents outcomes of observed IPT and full IPT compared with no IPT stratified by starting CD4 cell

	No IPT (reference)	Observed IPT	Full IPT
Undiscounted outcomes			
Life-years, thousands	3671·6 (3104·3 to 4372·1)	3688·9 (3117·8 to 4396·5)	3703·9 (3131·5 to 4415·3)
Incremental life-years, thousands	..	17·3 (10·5 to 27·7)	32·4 (20·8 to 48·7)
DALYs, thousands	8957·8 (8289·6 to 9487·7)	8945·0 (8270·2 to 9479·0)	8933·4 (8254·9 to 9468·4)
DALYs averted, thousands	..	12·8 (7·3 to 21·6)	24·5 (15·1 to 38·3)
Cost of ART, thousands	$628 708 (396 518 to 954 621)	$630 828 (397 203 to 959 213)	$633 096 (398 282 to 962 644)
Incremental cost of ART, thousands	..	$2120 (750 to 4800)	$4388 (1952 to 8809)
Cost of tuberculosis care, thousands	$16 972 (12 866 to 21 921)	$14 412 (11 042 to 18 401)	$12 781 (9805 to 16 245)
Incremental cost of tuberculosis care, thousands	..	–$2560 (–3721 to –1679)	–$4191 (–5893 to –2847)
Cost of IPT, thousands	$0 (0 to 0)	$417 (373 to 464)	$629 (589 to 671)
Incremental cost of IPT, thousands	..	$417 (373 to 464)	$629 (589 to 671)
Total cost, thousands	$645 680 (413 703 to 973 571)	$645 657 (412 576 to 975 942)	$646 506 (412 400 to 977 297)
Incremental total cost, thousands	..	–$23 (–1388 to 2268)	$825 (–1594 to 4751)
Discounted outcomes			
DALYs averted, thousands	..	7·4 (4·5 to 11·5)	15·4 (10·1 to 22·4)
Incremental total cost, thousands	..	–$102 (–870 to 967)	$360 (–1116 to 2370)
ICER (cost per DALY averted)	..	Dominant (dominant to $96·8)	$23·4 (dominant to 121·4)

Intervals in parentheses denote 95% uncertainty intervals. ART=antiretroviral therapy. DALY=disability-adjusted life-year. ICER=incremental cost-effectiveness ratio. IPT=isoniazid preventive therapy.

Table 2: **Projected overall health outcomes, costs, and cost-effectiveness for each IPT scenario (n=211 748)**

count. The life expectancy gains and DALYs averted by IPT were greater for individuals starting ART with a higher CD4 cell count. Incremental costs were also lower for higher CD4 cell count categories, driven by reduced tuberculosis treatment costs. Overall, the cost-effectiveness of IPT was more favourable for individuals initiating ART with less advanced immunosuppression.

When results were stratified by calendar year of ART initiation, we found that the lifetime health benefits and cost-effectiveness of IPT (full IPT scenario) improved for more recent versus earlier ART cohorts. Between 2014 and 2020, incremental survival due to IPT increased by 22·3% (95% UI 11·3–35·1), and DALYs averted increased by 19·1% (8·7–31·8). Incremental lifetime costs were relatively stable over this period (figure 3). The ratio of total tuberculosis cases averted to isoniazid-resistant cases induced by IPT remained stable (120 [54–276] in 2014 *vs* 143 [63–357] in 2020). The trends in these outcomes across calendar years were contributed by temporal changes in starting CD4 cell count distribution (appendix p 2).

Discussion

In this study, we estimated the long-term consequences of IPT for patients in a large urban HIV treatment cohort in Tanzania. We found that the observed scale-up of IPT produced major health benefits and was cost-saving when tuberculosis and HIV treatment costs were factored in. However, full coverage of IPT would approximately double the health gains under the observed IPT scenario, while still being highly cost-effective. Although IPT cannot prevent disease resulting from subsequent tuberculosis infection, the full IPT scenario would avert approximately a quarter of lifetime tuberculosis cases, which is a major health gain. Although the incremental cost of full IPT was relatively uncertain, this uncertainty did not affect the qualitative conclusion that IPT was favourable because its small incremental cost, even at its upper bound, would still yield an ICER below the cost-effectiveness threshold. We also found that IPT cost-effectiveness remained stable or slightly improved over time, with both intervention scenarios being cost-saving or having a very low ICER (highly cost-effective) for each of the annual ART initiation cohorts from 2014 to 2020.

When outcomes were stratified by CD4 count at ART initiation, we found that health impact was greater for individuals with a higher starting CD4 count, even though these individuals experience lower tuberculosis incidence rates. For example, individuals with a starting CD4 count of more than 500 cells per µL were estimated to experience an average survival gain of 2·7 months under the full IPT scenario, compared with 1·1 months for a starting CD4 count of less than 100 cells per µL. This pattern (greater IPT health gains with higher starting CD4 count) was observed across all CD4 cell count strata, for both full IPT and observed IPT scenarios. Two mechanisms contributed to this outcome. Firstly, although higher CD4 cell count is associated with lower annual tuberculosis risks, it is also associated with greater expected survival, thereby increasing the period during which tuberculosis can develop. These two factors have conflicting effects on lifetime tuberculosis risks and, in our analysis, the effect of increased life expectancy

	Undiscounted outcomes						Discounted outcomes		
	Incremental life-years, thousands	DALYs averted, thousands	Incremental cost of ART, thousands	Incremental cost of tuberculosis care, thousands	Incremental cost of IPT, thousands	Incremental total cost, thousands	DALYs averted, thousands	Incremental total cost, thousands	ICER (cost per DALY averted)
CD4 count <100 cells per µL									
Observed IPT *vs* no IPT	3·7 (1·8 to 6·1)	3·0 (1·5 to 5·2)	$672 ($272 to 1337)	–$833 (–$1349 to –522)	$161 ($142 to 181)	$0 (–376 to 472)	1·9 (1·1 to 3·0)	–$35 (–274 to 230)	Dominant (dominant to $98·5)
Full IPT *vs* no IPT	9·0 (5·5 to 13·7)	7·4 (4·5 to 11·6)	$1736 ($882 to 3126)	–$1602 (–$2391 to –1057)	$276 ($257 to 294)	$410 (–406 to 1494)	5·3 (3·4 to 7·6)	$207 (–361 to 878)	$39·3 (dominant to 143·2)
CD4 count 100–200 cells per µL									
Observed IPT *vs* no IPT	4·8 (2·3 to 8·0)	3·8 (1·9 to 6·6)	$784 ($279 to 1614)	–$1031 (–$1570 to –674)	$176 ($156 to 197)	–$71 (–551 to 553)	2·4 (1·3 to 3·7)	–$102 (–385 to 225)	Dominant (dominant to $75·3)
Full IPT *vs* no IPT	10·9 (6·5 to 16·8)	8·8 (5·1 to 14·0)	$1895 ($886 to 3611)	–$1863 (–$2674 to –1256)	$288 ($269 to 307)	$319 (–670 to 1675)	5·9 (3·8 to 8·6)	$94 (–539 to 868)	$15·8 (dominant to 118·8)
CD4 count 200–350 cells per µL									
Observed IPT *vs* no IPT	6·2 (3·3 to 9·8)	4·8 (2·5 to 7·9)	$828 ($299 to 1661)	–$1175 (–$1765 to –771)	$186 ($165 to 208)	–$160 (–661 to 473)	2·9 (1·7 to 4·3)	–$144 (–445 to 205)	Dominant (dominant to $59·9)
Full IPT *vs* no IPT	12·8 (7·7 to 19·1)	10·1 (5·9 to 15·4)	$1874 ($849 to 3516)	–$2071 (–$2921 to –1431)	$295 ($276 to 314)	$98 (–923 to 1460)	6·6 (4·2 to 9·3)	–$59 (–709 to 737)	Dominant (dominant to $91·8)
CD4 count 350–500 cells per µL									
Observed IPT *vs* no IPT	8·4 (4·9 to 13·1)	6·2 (3·5 to 9·8)	$886 ($334 to 1812)	–$1476 (–$2090 to –996)	$204 ($182 to 226)	–$387 (–988 to 393)	3·7 (2·2 to 5·4)	–$251 (–608 to 164)	Dominant (dominant to $35·7)
Full IPT *vs* no IPT	15·7 (9·9 to 23·0)	11·8 (7·3 to 17·6)	$1886 ($845 to 3512)	–$2372 (–$3233 to –1659)	$304 ($284 to 324)	–$183 (–1297 to 1274)	7·5 (5·0 to 10·4)	–$192 (–896 to 630)	Dominant (dominant to $70·5)
CD4 count >500 cells per µL									
Observed IPT *vs* no IPT	13·5 (8·5 to 19·5)	9·4 (5·8 to 13·9)	$972 ($370 to 2,060)	–$1791 (–$2452 to –1238)	$218 ($196 to 241)	–$601 (–1294 to 344)	5·1 (3·3 to 7·2)	–$322 (–711 to 152)	Dominant (dominant to $26·0)
Full IPT *vs* no IPT	22·3 (14·7 to 31·2)	15·9 (10·3 to 22·5)	$1858 ($821 to 3648)	–$2761 (–$3683 to –1963)	$311 ($291 to 332)	–$592 (–1809 to 1051)	9·3 (6·3 to 12·6)	–$372 (–1108 to 506)	Dominant (dominant to $46·9)

Absolute levels of outcomes for each scenario are presented in the appendix (pp 11–12). Intervals in parentheses denote 95% uncertainty intervals. ART=antiretroviral therapy. DALY=disability-adjusted life-year. ICER=incremental cost-effectiveness ratio. IPT=isoniazid preventive therapy.

***Table 3*: Projected incremental health outcomes, costs, and cost-effectiveness per 100 000 individuals for observed IPT and full IPT scenarios, stratified by CD4 cell count at ART initiation**

was greater. Secondly, the greater life expectancy of individuals with higher CD4 cell count means that a greater number of life-years are gained for each tuberculosis death averted.

In addition to larger IPT health gains for individuals with higher starting CD4 cell count, we also estimated greater cost savings for this group. As HIV treatment programmes identify individuals for ART earlier in the course of infection, these results suggest the economic argument for IPT provision is even stronger than it has been in the past. Concerns about the potential selection of drug resistance is one factor cited for slow IPT uptake in HIV treatment programmes, despite evidence of cost-effectiveness. Our study estimated that greater IPT provision would lead to more individuals developing isoniazid-resistant tuberculosis. This is consistent with other modelling studies,[31] despite inconsistent empirical evidence for this effect.[32] However, the additional number of isoniazid-resistant tuberculosis cases was consistently small compared with other health outcomes, with over 100 tuberculosis cases averted for each additional isoniazid-resistant tuberculosis case. Moreover, newer multidrug preventive regimens, although relatively expensive now, provide an alternative with shorter duration, higher completion rates, and lower resistance risks.[33]

This study benefited from the availability of detailed programme data, allowing the analysis to reflect realistic programme functioning and health outcomes (particularly, how outcomes varied over time and by CD4 cell count stratum). However, there are several limitations. Firstly, we did not model changes in tuberculosis transmission resulting from IPT. Reduced tuberculosis incidence would probably reduce tuberculosis transmission by individuals in the ART cohort, either to household members or other ART clinic attendees, thereby amplifying the health benefits of IPT provision. As all scenarios showed IPT to be highly cost-effective, additional health benefits would not change this conclusion. However, the omitted transmission effects also apply to the additional isoniazid-resistant tuberculosis cases. It is unlikely that transmission from the small number of additional isoniazid-resistant tuberculosis cases would change our conclusions, but we did not estimate these effects. Secondly, we assessed cost-effectiveness against a generic standard for cost-effectiveness, based on recently reported estimates of the health opportunity costs of additional spending.[30] Since these estimates are more conservative than earlier

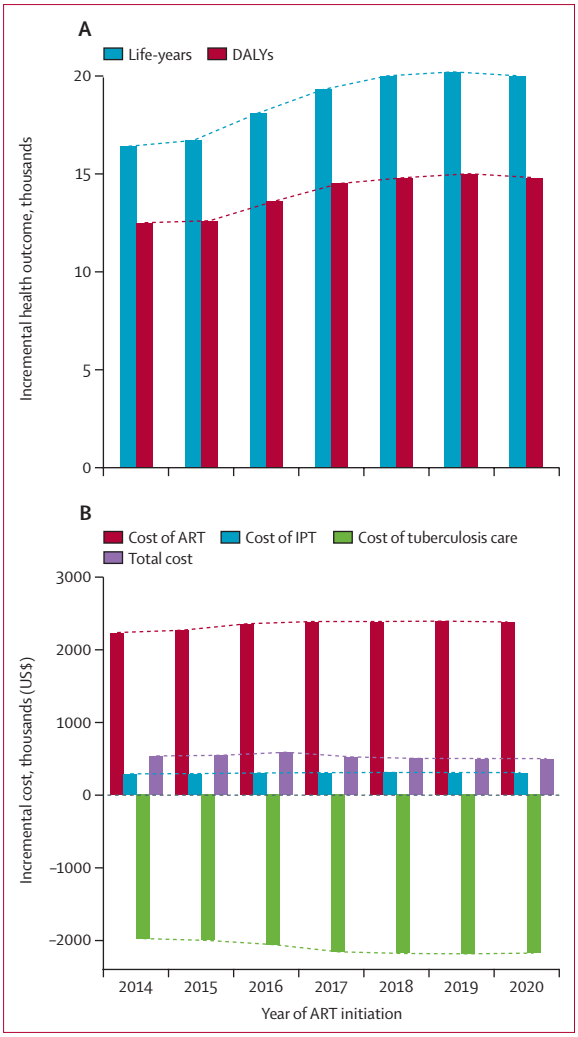

Figure 3: **Projected undiscounted incremental health outcomes (A) and incremental costs (B) for full IPT compared with no IPT per 100 000 individuals by year of ART initiation**

Dashed lines represent the time trends of each outcome. ART=antiretroviral therapy. DALY=disability-adjusted life-year. IPT=isoniazid preventive therapy.

recommendations of one to three times GDP per capita, the cost-effectiveness of IPT would be even more favourable under traditional cost-effectiveness thresholds. Comparison with published cost-effectiveness evidence for other HIV services suggests that IPT is also cost-effective relative to other interventions within the HIV control budget—eg, estimates of ART cost-effectiveness range from $60 to $5500 per DALY averted[34]—but we did not directly consider other uses of funding. Thirdly, we did not have precise input data for several important factors. These include tuberculosis-specific mortality risks differentiated by CD4 cell count for those with tuberculosis disease, rates of acquired resistance and cure among individuals with tuberculosis disease inappropriately receiving IPT, and the effects of IPT among individuals subsequently lost to follow-up, because these individuals are not included in IPT trial data. Not differentiating tuberculosis-specific mortality risks by CD4 cell count, in particular, might overestimate the impact of IPT at averting tuberculosis deaths for higher CD4 cell count groups. Finally, we did not examine the higher-level programmatic investments needed to increase IPT coverage. Given the low ICERs estimated for IPT, it is unlikely that the qualitative conclusions about IPT cost-effectiveness would change once these resources are factored in.

The study results are likely to be generalisable to similar settings with a high burden of tuberculosis and HIV. Epidemiological and programmatic factors that vary across settings—risks of tuberculosis infection, CD4 cell count distributions for cohorts initiating ART, the quality of HIV and tuberculosis care—were all varied in subgroups or sensitivity analyses, and the major results were robust to changes in these inputs. Similarly, although tuberculosis and HIV services costs vary substantially across countries, the unit costs of these services (and cost-effectiveness thresholds) are generally correlated across settings, so the relative magnitude of intervention costs and cost savings will probably be similar. As evidence of this, our cost-effectiveness results for the low CD4 cell count strata are consistent with earlier modelled cost-effectiveness studies from other settings, which examined IPT among cohorts with more advanced HIV disease at ART initiation.[3] However, conclusions might not hold if a particular service component had much higher relative costs in a given setting. Additionally, conclusions might differ for settings with a much greater prevalence of tuberculosis drug resistance, which would affect both IPT effectiveness and the costs and outcomes of tuberculosis disease treatment.

In summary, this study provides evidence of greater health impact and cost-effectiveness of IPT for contemporary HIV cohorts initiating ART at higher CD4 cell counts, despite lower annual tuberculosis risks faced by these individuals. With many countries successfully expanding HIV testing and linkage to care, the results of this study highlight the health gains foregone by slow IPT scale-up. Higher IPT coverage would also reduce tuberculosis transmission, although this issue was not considered in this analysis. Based on these results, expanded IPT is one of the most cost-effective approaches for improving survival and quality-of-life within HIV programmes. Given that tuberculosis still causes over a quarter of all deaths among individuals with HIV, the low coverage of IPT within many HIV programmes is a major concern. Although 100% IPT coverage (the full IPT scenario) might not be feasible for all programmes, several high-burden countries currently report IPT coverage above 90% for new ART patients,[4] demonstrating that high coverage is achievable. While IPT coverage has improved for many countries in recent years, greater efforts—including clear leadership,

stakeholder involvement, accountability mechanisms, and attention to supply chain disruptions—are needed to ensure timely IPT initiation and completion for all patients on ART.

Contributors

JZ, NAM, and CRS conceived the study. GL and TC helped refine the study approach. GL, CRS, AK, DS, LM, JM, and FC collected the MDH cohort data. JZ performed the statistical and modelling analyses. JZ and NAM accessed and verified the data. JZ and NAM developed the first draft of the manuscript and all authors contributed to revisions. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Analytic code and model inputs are available through the following link: https://github.com/jinyizhu/IPTinTZ.

Acknowledgments

This work was supported through grants provided by the US National Institutes of Health to NAM (R01AI146555) and to TC (R01AI147854). GL was supported by the Fogarty International Center of the US National Institutes of Health under award number D43TW009775. The findings and conclusions in this paper are those of the authors and do not represent the views of the funding sources or the authors' affiliated institutions.

References

1 UNAIDS. 2021 Global AIDS update—confronting inequalities—lessons for pandemic responses from 40 years of AIDS. Geneva: UNAIDS, 2021.
2 Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev* 2010; **1:** CD000171.
3 Uppal A, Rahman S, Campbell JR, Oxlade O, Menzies D. Economic and modeling evidence for tuberculosis preventive therapy among people living with HIV: a systematic review and meta-analysis. *PLoS Med* 2021; **18:** e1003712.
4 WHO. Global tuberculosis report 2020. Geneva: World Health Organization, 2020.
5 Anderegg N, Panayidou K, Abo Y, et al. Global trends in CD4 cell count at the start of antiretroviral therapy: collaborative study of treatment programs. *Clin Infect Dis* 2018; **66:** 893–903.
6 Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015; **373:** 795–807.
7 Suthar AB, Lawn SD, del Amo J, et al. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. *PloS Med* 2012; **9:** e1001270.
8 Danel C, Moh R, Gabillard D, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med* 2015; **373:** 808–22.
9 Badje A, Moh R, Gabillard D, et al. Effect of isoniazid preventive therapy on risk of death in west African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial. *Lancet Glob Health* 2017; **5:** e1080–89.
10 Balcells ME, Thomas SL, Godfrey-Faussett P, Grant AD. Isoniazid preventive therapy and risk for resistant tuberculosis. *Emerg Infect Dis* 2006; **12:** 744–51.
11 Chonde TM, Basra D, Mfinanga SGM, et al. National anti-tuberculosis drug resistance study in Tanzania. *Int J Tuberc Lung Dis* 2010; **14:** 967–72.
12 Borgdorff MW, Sebek M, Geskus RB, Kremer K, Kalisvaart N, van Soolingen D. The incubation period distribution of tuberculosis estimated with a molecular epidemiological approach. *Int J Epidemiol* 2011; **40:** 964–70.
13 Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. A general review. *Bibl Tuberc* 1970; **26:** 28–106.
14 Sutherland I. Recent studies in the epidemiology of tuberculosis, based on the risk of being infected with tubercle bacilli. *Adv Tuberc Res* 1976; **19:** 1–63.
15 Menzies NA, Wolf E, Connors D, et al. Progression from latent infection to active disease in dynamic tuberculosis transmission models: a systematic review of the validity of modelling assumptions. *Lancet Infect Dis* 2018; **18:** e228–38.
16 Andrews JR, Noubary F, Walensky RP, Cerda R, Losina E, Horsburgh CR. Risk of progression to active tuberculosis following reinfection with *Mycobacterium tuberculosis*. *Clin Infect Dis* 2012; **54:** 784–91.
17 Geng EH, Odeny TA, Lyamuya R, et al. Retention in care and patient-reported reasons for undocumented transfer or stopping care among HIV-infected patients on antiretroviral therapy in eastern Africa: application of a sampling-based approach. *Clin Infect Dis* 2016; **62:** 935–44.
18 UN Department of Economic and Social Affairs. World population prospects. https://population.un.org/wpp/Download/Standard/Mortality/ (accessed Aug 9, 2021).
19 Tuberculosis Chemotherapy Centre. A concurrent comparison of isoniazid plus PAS with three regimens of isoniazid alone in the domiciliary treatment of pulmonary tuberculosis in South India. *Bull World Health Organ* 1960; **23:** 535–85.
20 Gegia M, Winters N, Benedetti A, van Soolingen D, Menzies D. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. *Lancet Infect Dis* 2017; **17:** 223–34.
21 Wolbers M, Babiker A, Sabin C, et al. Pretreatment CD4 cell slope and progression to AIDS or death in HIV-infected patients initiating antiretroviral therapy—the CASCADE collaboration: a collaboration of 23 cohort studies. *PLoS Med* 2010; **7:** e1000239.
22 Anglaret X, Minga A, Gabillard D, et al. AIDS and non-AIDS morbidity and mortality across the spectrum of CD4 cell counts in HIV-infected adults before starting antiretroviral therapy in Cote d'Ivoire. *Clin Infect Dis* 2012; **54:** 714–23.
23 Kroeze S, Ondoa P, Kityo CM, et al. Suboptimal immune recovery during antiretroviral therapy with sustained HIV suppression in sub-Saharan Africa. *AIDS* 2018; **32:** 1043–51.
24 Houben RMGJ, Crampin AC, Ndhlovu R, et al. Human immunodeficiency virus associated tuberculosis more often due to recent infection than reactivation of latent infection. *Int J Tuberc Lung Dis* 2011; **15:** 24–31.
25 Raftery AE, Bao L. Estimating and projecting trends in HIV/AIDS generalized epidemics using incremental mixture importance sampling. *Biometrics* 2010; **66:** 1162–73.
26 Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) disability weights. Seattle, WA: Institute for Health Metrics and Evaluation (IHME), 2020. https://doi.org/10.6069/1W19-VX76 (accessed Aug 8, 2021).
27 Siapka M, Vassall A, Cunnama L, et al. Cost of tuberculosis treatment in low- and middle-income countries: systematic review and meta-regression. *Int J Tuberc Lung Dis* 2020; **24:** 802–10.
28 Cerecero-García D, Pineda-Antunez C, Alexander L, et al. A meta-analysis approach for estimating average unit costs for ART using pooled facility-level primary data from African countries. *Afr J AIDS Res* 2019; **18:** 297–305.
29 Stop TB Partnership. Global Drug Facility Medicines Catalog. 2021. http://www.stoptb.org/assets/documents/gdf/drugsupply/GDFMedicinesCatalog.pdf (accessed Nov 8, 2021).
30 Ochalek J, Lomas J, Claxton K. Estimating health opportunity costs in low-income and middle-income countries: a novel approach and evidence from cross-country data. *BMJ Glob Health* 2018; **3:** e000964.
31 Kunkel A, Colijn C, Lipsitch M, Cohen T. How could preventive therapy affect the prevalence of drug resistance? Causes and consequences. *Philos Trans R Soc Lond B Biol Sci* 2015; **370:** 20140306.
32 Balcells ME, Thomas SL, Godfrey-Faussett P, Grant AD. Isoniazid preventive therapy and risk for resistant tuberculosis. *Emerg Infect Dis* 2006; **12:** 744–51.
33 Johnson KT, Churchyard GJ, Sohn H, Dowdy DW. Cost-effectiveness of preventive therapy for tuberculosis with isoniazid and rifapentine versus isoniazid alone in high-burden settings. *Clin Infect Dis* 2018; **67:** 1072–78.
34 Center for Evaluation of Value and Risk in Health (CEVR). Global Health Cost-Effectiveness Analysis (GH CEA) Registry. http://ghcearegistry.org/ghcearegistry/ (accessed Jan 27, 2022).