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An evaluation of 6-month versus continuous isoniazid preventive therapy for *M. tuberculosis* in adults living with HIV/AIDS in Malawi

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Abstract

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Background.—To assist the Malawi Ministry of Health to evaluate two competing strategies for scale-up of isoniazid preventive therapy (IPT) among HIV-positive adults receiving ART.

Setting.—Malawi.

Methods.—We used a multi-district, compartmental model of the Malawi TB/HIV epidemic to compare the anticipated health impacts of 6-month versus continuous IPT programs over a 12-year horizon, while respecting a US$10.8 million constraint on drug costs in the first three years.

Results.—The 6-month IPT program could be implemented nationwide while the continuous IPT alternative could be introduced in 14 (out of 27) districts. By the end of year 12, the continuous IPT strategy was predicted to avert more TB cases than the 6-month alternative, although not statistically significantly (2368 additional cases averted; 95%PI, −1459, 5023). The 6-month strategy required fewer person-years of IPT to avert a case of TB or death than the continuous strategy. For both programs, the mean reductions in TB incidence among PLHIV by year 12 were expected to be <10%, and the cumulative numbers of IPT-related hepatotoxicity to exceed the number of all-cause deaths averted in the first three years.

Conclusion.—With the given budgetary constraint, nationwide implementation of 6-month IPT would be more efficient and yield comparable health benefits than implementing continuous IPT program in fewer districts. The anticipated health effects associated with both IPT strategies suggested a combination of different TB intervention strategies would likely be required to yield greater impact on TB control in settings like Malawi, where ART coverage is relatively high.

Keywords

tuberculosis; preventive therapy; PLHIV; Malawi; transmission model; resource allocation

Background

Isoniazid preventive therapy (IPT) is recommended by the WHO for people living with HIV (PLHIV), to reduce the elevated risk of TB these individuals experience[1]. However, there is a lack of consensus on the optimal length of IPT among PLHIV. While previous studies have demonstrated reduced TB incidence with IPT, the duration of protection associated with a 6-month IPT regimen has varied between settings. Randomized controlled trials conducted in Brazil and the Côte d'Ivoire found sustained protective effects after completion of a 6-month IPT in PLHIV[2,3]. In contrast, trials in Botswana and South Africa, settings where the force of TB infection is higher than the Brazil and Côte d'Ivoire trials, found that PLHIV required longer durations of IPT to retain protection from TB[4,5]. For Malawi, when this study was conducted, the National Task Force on TB Preventive Therapy (TPT) recommended IPT consisting of continuous (i.e. lifelong) isoniazid (INH) and pyridoxine, along with continuous cotrimoxazole preventive therapy (CPT), to all PLHIV receiving ART, for whom active TB has been ruled out[6]. While CPT coverage was high for individuals on ART[7], adoption of IPT had been slower.

Hence, when the Global Fund offered US$10.8 million to Malawi to procure isoniazid and pyridoxine in 2017 for the period 2018-2020, policymakers at the Ministry of Health (MOH) Malawi wanted to evaluate the comparative health impacts of distributing isoniazid from this

procurement as (a) 6-month IPT to PLHIV on ART across districts; or (b) continuous IPT to PLHIV on ART across potentially fewer districts. To address this question, we worked with representatives from the MOH Malawi to develop a calibrated transmission dynamic model and decision support framework to compare the health impacts of these two competing IPT allocation strategies.

Methods

Intervention scenarios

We defined one base scenario and two IPT intervention scenarios (Fig. 1). The base scenario represented no IPT intervention, reflecting the status quo in 2017 when IPT access was minimal. The first intervention scenario was defined as allocating 6-month IPT to as many districts as possible, up to the limit of IPT doses available in the three-year budget period of 2018-2020. The alternative was to implement continuous IPT across districts up to the same limit of IPT doses, which was 1,003,423 person-years of IPT, based on the US$10.8 million budgetary limit and the commodity costs of isoniazid (300 mg) and pyridoxine (25 mg) in Malawi. The aim was to allocate the fixed number of IPT doses across districts to maximize the overall health benefit at the national level. As the model projections incorporated uncertainties in the amount of IPT required in each district over time, we assumed the policymakers had a willingness to accept a 10% chance of exceeding the 2018-2020 budget.

Appendix 1 describes how IPT doses were allocated across districts under each intervention scenarios in our model. Briefly, IPT was made available district-by-district, and districts with the highest TB incidence rates in 2018 were prioritized for enrolment. Each district was treated as an indivisible unit (Fig. 1, blue circles), and would only be enrolled if there were enough IPT available for all eligible patients in that district in 2018-2020. We assumed the spending rate within this three-year budget period was flexible. No fixed costs were accounted for in our study; the MOH Malawi planned to allocate the US$10.8 million on procurement of isoniazid and pyridoxine only. The 6-month and continuous IPT strategies were assessed as static intervention policies over a 12-year horizon, assuming funding would be available.

Following the 2015 WHO recommendation on IPT in PLHIV[8], we assumed IPT eligibility would be restricted to adults (≥ 15 years old) living with HIV/AIDS, with an unknown or positive tuberculin skin test (TST) status, had active TB disease ruled out, and currently receiving ART. Additionally, each patient was assumed to receive a single IPT course (6-month or continuous, depending on the intervention scenario) unless they developed active TB and became eligible for another IPT course (secondary IPT) after completing TB treatment. The length of treatment for secondary IPT was the same as primary IPT. There was no limit to the number of courses of secondary IPT a patient could receive.

Modelling approach

We projected the policy outcomes in each of 27 districts in Malawi (excluding Likoma, a very small island district) under each intervention scenario over a 12-year period

(2018-2030) to determine the short- and medium-term impacts of IPT scale-up in Malawi. The model was operationalized as a set of ordinary differential equations, which were numerically integrated by the deSolve package in R version 3.5.1[9].

Model overview on TB and HIV states—We stratified the compartmental model into children (< 15 y.o.) and adult (≥ 15 y.o.) populations. We assumed all children were HIV-negative[10], and could be TB susceptible or latently infected with TB. For adults, HIV-related states included susceptible to HIV infection; undiagnosed HIV infection; diagnosed HIV infection receiving ART but not IPT; diagnosed HIV infection receiving ART and IPT; or diagnosed HIV infection receiving ART post-IPT (top margin in Fig. 1). TB-related states included TB susceptible; latent TB infection; untreated active TB; or active TB undergoing treatment (left margin in Fig. 1). Deaths occurring among active TB cases and those receiving TB treatment were counted towards TB-related deaths in our study.

TB/HIV epidemics were modeled for each district, assuming no population mixing between districts. We estimated the district-specific TB force of infection as a function of the number of individuals with active TB in the model, assuming frequency dependent transmission and a stable population size over the simulation period. The district-level HIV force of infection was incorporated into the model as an exogenous input, based on UNAIDS national HIV incidence estimates for the period 1990-2017[11]. We assumed the HIV incidence rate would continue to decrease after 2017 and would be halved by the end of 2030. Appendices 2–3 present details of model and parameters.

Model overview on IPT implementation—We assumed individuals receiving IPT would experience decreased risks of TB infection, reinfection, and reactivation. We also allowed 35% of latently infected individuals completing IPT and continuing on ART to be ‘cured’ of TB infection (no reactivation risk) and retain partial immunity to future TB infections[12]. We assumed IPT had no protective effect on individuals with active TB.

For every 1000 treatment initiations in our model, we assumed IPT would cause 6 hepatic dysfunction cases, defined as serum aminotransferase levels >5 times the upper limit of normal values (grade 3/4 elevation in ALT/AST levels)[13], and an excess mortality of 0.04 deaths due to INH-related hepatotoxicity[14]. The modeled frequency of hepatotoxicity was dependent on the number of IPT initiators rather than the total person-time spent on IPT in each scenario, as previous findings suggested most INH-associated hepatotoxicity occurs in early phases of the intervention[15].

With input from local healthcare providers, we assumed a catch-up campaign would allow 77.5% (range, 60.0-95.0%) of eligible patients to initiate IPT in targeted districts by the end of first year. We assumed a constant retention rate of 84.25% (beta distribution, 2.5th percentile, 84.09%, 97.5th percentile, 84.41%) by the end of every 6-month of IPT in both strategies[16]. That is, the median treatment duration for patients enrolled in 6-month IPT and continuous IPT was approximately 4 and 28 months, respectively.

Model calibration—A two-stage calibration procedure was used. In the first stage, the model was calibrated using the Nelder-Mead algorithm to national-level data, including the

number of notified TB cases, the number of notified TB cases confirmed to be HIV-infected, the number of patients retained on ART at mid-year, and HIV prevalence from 2008-2017 (TB surveillance data and Spectrum file from MOH Malawi). We also included the expected percentage (30%) of HIV deaths from TB cases among PLHIV as a calibration target [17]. The excess mortality of TB/HIV co-infection, and the TB reactivation rate and the probability of having progressive primary TB for those with undiagnosed HIV, were estimated through this stage of the calibration and input as fixed parameters in the second stage of the calibration.

In the second stage, incremental mixture importance sampling (IMIS)[18] was used to calibrate the model to district-level data on notified TB cases, notified TB cases confirmed to be HIV-infected, the number of patients retained on ART in mid-year, as well as HIV prevalence estimates for 2008-2017 (TB surveillance data and Spectrum file from MOH Malawi). The TB transmission parameters and the scaling factors for HIV incidence rate were estimated and allowed to vary between districts. Prior distributions of these parameters are provided in Appendix 3 Table 2. Comparisons of model outputs and observed data are in Appendix 4.

Model simulation and outcome comparison

We estimated future outcomes for each scenario in all 27 districts separately, and aggregated these district-level outcomes to compare the impact of IPT policy alternatives at the national level. We compared the cumulative number of active TB cases, all-cause deaths and TB-related deaths, and episodes of IPT-induced hepatotoxicity among adults at three and 12 years after program initiation. We also compared the efficiency of the two intervention programs, defined as the ratio of the total amount of IPT dispensed to cumulative TB cases averted, equivalent to the number of person-years of IPT required to avert one TB case, by year three and 12.

Given limited data for IPT-related parameters (Appendix 3 Table 4), uncertainty analysis with Latin hypercube sampling was performed to produce a range of plausible outcome estimates for both IPT programs. Along with the resampled parameter sets from IMIS, 300 simulations were obtained for each policy alternative. Additionally, a one-way sensitivity analysis was conducted for the rate of INH-associated hepatotoxicity.

For each outcome, the point estimate represents the arithmetic mean of the distribution, and the uncertainty intervals represent the 95% projection intervals. All comparisons were conducted at the significance level of 0.05.

Results

Baseline epidemiological characteristics

At the beginning of 2018, model-estimated district-specific TB prevalence ranged from 101 to 674 per 100,000 person-years, and the HIV prevalence ranged from 4.37% to 15.69%. National TB prevalence and incidence were 337 per 100,000 and 246 per 100,000 person-years, respectively. National HIV prevalence and incidence were 8.80% and 0.15% per year. The baseline TB/HIV epidemiological characteristics of each district at the start of IPT programs are shown in Appendix 5 Table 1.

Allocation of IPT intervention programs

In each of our model simulations (n=300), we found that the 6-month IPT program could be implemented nationwide in 2018-2020, while leaving US$7.04 million (out of 10.8 million) unused (Appendix 5 Table 2). In contrast, the continuous IPT program could only be introduced in 14 districts (Appendix 5 Fig. 1B). The uncertainty to the total amount of IPT doses required annually increased with time and with the number of districts where continuous IPT was introduced (Fig. 2A, Appendix 5 Fig. 1C). For the analyses below, we compared the health outcomes between nationwide implementation of 6-month IPT with the implementation of continuous IPT in 14 districts. The list of targeted districts for each alternative can be found in Appendix 5 Table 2.

The consumption of IPT in both intervention scenarios was greatest in the first three years of the intervention programs (Fig. 2B). The sharp increase in the first year was due to the catch-up campaign. The relatively steep decrease in the 6-month IPT curve reflects treatment completion and patient drop-out. The decrease was slower in the continuous IPT scenario and only caused by early treatment terminations. The number of patients starting IPT was minimal after the first couple of years because patients were only allowed one course of IPT treatment, most eligible patients were initiated on IPT early in the projection period, and the number of ART initiators was relatively small over time. The amount of IPT consumed in the 6-month IPT program was significantly less than the continuous program.

Health effects of IPT intervention programs

Compared to the base case scenario, the 6-month IPT program reduced national TB incidence among PLHIV by 5.05% (95% projection interval, PI, 3.19-7.60%) at the end of year three and 7.02% (95% PI, 3.71-11.58%) at the end of year 12 (Fig. 3B). For the continuous IPT program, the estimates were 6.38% (95% PI, 3.97-8.71%) and 9.81% (95%PI, 5.28-13.37%). No rebound in TB prevalence or incidence was predicted for either program (Fig. 3), even after most patients have completed or dropped out from IPT treatment (Fig. 2B). This can be attributed to the effect of IPT on decreasing the TB force of infection in the population, relative to the base case.

The mean reductions in TB-related mortality rate among PLHIV in the 6-month IPT scenario, compared to the base case scenario, was 10.38% (95% PI, 8.28-12.15%) by the end of year three and 12.04% (95% PI, 9.29-15.46%) by the end of year 12, while the continuous IPT scenario attained a 9.33% (95% PI, 7.406.98-10.91%) reduction by the end of year three and a 12.53% (95% PI, 9.40-15.02%) reduction by the end of year 12 (Fig. 4B). The impact on all-cause mortality among PLHIV in either intervention scenario, in comparison to the base case, was < 5% over the simulation period (Fig. 4C).

For the continuous IPT program, an estimated 3,562 patients were expected to experience grade 3/4 hepatotoxicity in the first three years, exceeding the number of all-cause deaths averted. By the end of year 12, the number of hepatotoxicity events accumulated to 4500, but was surpassed by the number of all-cause deaths averted (Fig. 5). The 6-month IPT program displayed similar trends.

Comparison between 6-month and continuous IPT intervention scenarios

The continuous IPT strategy was predicted to avert more TB cases among adults compared to the 6-month strategy, although not statistically significantly: 36 (95% PI, −489, 524) additional cases by the end of year three and 2368 (95% PI, −1459, 5023) additional cases by the end of year 12. The 6-month IPT strategy was predicted to avert more TB-related and all-cause deaths among PLHIV than the continuous strategy by year three; the reverse was observed by year 12, although without statistical significance, either (Fig. 4). The 6-month scenario accumulated more IPT-associated hepatotoxicity than the continuous scenario (Fig. 5).

The 6-month IPT program was more efficient than the continuous scenario in terms of person-years of IPT required to prevent a TB case (Appendix 6 Table 1). The efficiency of IPT programs improved with time regardless of the choice of intervention strategy, because the TB force of infection decreased and the number of IPT initiators was minimal after the first three years (Fig. 1B) while the population continued to benefit from the curative effect of IPT over time.

Discussion

In this study, we used a decision analytic framework, in conjunction with a calibrated, district-level model of the TB/HIV epidemics in Malawi, to compare the health effects of 6-month and continuous IPT programs under budgetary constraints. Our models allowed us to understand the tradeoffs between continuous IPT implemented in selected districts versus 6-month IPT available nationwide.

Under the given budgetary constraints, we found that nationwide implementation of 6-month IPT would yield comparable health benefits to the implementation of continuous IPT in selected districts despite significant under-spending in the 6-month IPT strategy in our model. Additionally, the 6-month strategy was shown to be more efficient than the continuous IPT strategy, in terms of person-years of IPT needed to avert a TB case or TB death. Accordingly, the 6-month regimen may be more appealing under the current epidemiological context in Malawi, especially if leftover funding from IPT implementation can be reallocated to other TB interventions. We also recognize the serious ethical concerns with the continuous IPT strategy which would not be available to individuals in several districts due to anticipated budgetary constraints.

The 6-month strategy was shown to avert more TB-related deaths, but less TB cases, than the continuous strategy by the end of year three. This is because deaths averted among those receiving active TB treatment were included in the number of TB-related deaths averted in our analysis. Since the 6-month program covered more districts, more deaths could be prevented from screening and subsequently treating more people for active TB near the start of the IPT programs.

Regardless of the strategy chosen, the population level impact of IPT was modest in our modeled population in Malawi and the estimated number of patients experiencing grade 3/4 hepatotoxic events was greater than the number of all-cause deaths averted in the first three

years of program implementation. These will likely be major challenges for the scale-up of IPT programs, as most healthcare facilities in Malawi do not currently have the laboratory capacity for routine monitoring of liver function among patients on IPT, which may preclude the opportunity for early detection and timely intervention of serious drug-related adverse events.

Results from the trial-based modelling study done by Pho *et al.*[19] for southern India indicated a 62% decrease in TB incidence among PLHIV from a 6-month IPT at three-year follow-up, whereas the mean reduction in TB incidence among PLHIV in our study was 5%. The underlying assumptions in their model are similar to ours, except we assumed only PLHIV on ART could receive IPT while in their study all PLHIV, with 27% receiving ART at baseline, were considered for IPT. Similarly, several studies demonstrating cost-effectiveness or cost-savings of IPT programs were done in the pre-ART era, when the background mortality was higher[20–22]. It is possible that high ART coverage in PLHIV in our patient population conferred survival and immunological benefits and crowded out some of the potential impacts of IPT in our model, as compared to times and settings with less ART access[23–25].

Furthermore, a more recent trial-based modelling study that examined the impact of delivering 12-month IPT to those receiving ART in a South African setting with a 48%-61% ART coverage predicted a 7.6% reduction in TB incidence among adults over five years[26]. This was similar to our 6-month IPT scenario predictions where the ART coverage ranged from 68%-89%, signifying that in settings with relatively high ART coverages among PLHIV, delivering 6-12 month IPT to those receiving ART will produce only modest changes in TB risk in the overall PLHIV population.

An important feature of this modelling study is that we were able to capture the spatial heterogeneity in HIV and TB burden across districts by incorporating district-level demographic, epidemiological, and health service data. Another strength of this study is that the model incorporated most barriers to IPT program implemenation[27], including imperfect patient adherence, low program uptake, and the potential of clinical error in screening for active TB. Inputs from our colleagues in Malawi on local care patterns and health care capacity were highly valuable, and our findings were used by policymakers at MOH Malawi to inform recommendations.

Our study has some limitations. One is that we did not consider drug resistance in our model. However, as suggested by previous findings from Kunkel *et al.*, the risks of spreading INH resistance may be limited given the declining TB/HIV co-epidemic[28]. Also, we assumed the population size remained constant over time, while Malawi has an annual population growth rate close to 3% in the past decade.[29] This, however, should not have a significant impact on the volume of IPT required because its main driver is the number of people on ART, the projection of which was calibrated to available data. Additionally, we assumed a 50% reduction in HIV incidence by 2030, which may be optimistic. Therefore, we analyzed a pessimistic scenario where the HIV incidence remained constant throughout 2017-2030. Instead of a steady decrease in TB burden across IPT strategies, a rebound in TB

prevalence and incidence was shown for both IPT strategies, but the relative effectiveness of the two strategies remained the same (Appendix 7).

Another limitation is that we assumed about one third of those completing IPT attained partial immunity against TB. If such protection wanes over time, the comparative effect of the 6-month IPT strategy, relative to the continuous alternative, would be worse than estimated. Furthermore, we assumed funding would be available for other costs incurred from IPT programs, including TB screening and patient follow-up. In practice, healthcare capacity is limited and different between districts, so the effectiveness of the two IPT programs could be lower than estimated. These costs could differ between the two strategies as they require different amounts of these additional costs.

It is worth noting that our model incorporated secondary IPT courses, a strength of our study as reactivation and reinfection rates have been shown to be high shortly after TB treatment in high TB burden regions[30]. The WHO also recommends secondary IPT for PLHIV in resource constrained settings[31]. However, to keep our model parsimonious, our model is not equipped to limit the number of secondary IPT courses an individual can receive, which may raise an issue on allocation efficiency.

Lastly, it is common for patients to travel across district or country borders for routine HIV and TB care. We did not capture this health seeking behaviour in our model because the population movement between districts is poorly characterized. This data limitation might affect local notification rates, and complicates district-level estimation of epidemiological outcomes and resource utilization of IPT, particularly in the continuous IPT strategy, where IPT scale-up is not universal.

Overall, our results suggest that under given budgetary constraints, nationwide implementation of 6-month IPT program could produce comparable health benefits as implementation of continuous IPT program in selected districts, and would be a more efficient strategy. However, the high level of adverse events and the modest reduction in TB transmission and mortality associated with both IPT strategies suggests that a combination of different TB intervention strategies will be required to have a transformative impact on TB control in settings like Malawi, where ART and CPT coverages are already relatively high.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. WHO HIV/AIDS and TB Department Three I's Meeting Report. Geneva, Switzerland: World Health Organization (WHO); 2-4 4, 2008 2008.
2. Golub JE, Cohn S, Saraceni V, et al. Long-term protection from isoniazid preventive therapy for tuberculosis in HIV-infected patients in a medium-burden tuberculosis setting: the TB/HIV in Rio (THRio) study. Clin Infect Dis. 2015;60(4):639–645. [PubMed: 25365974]
3. 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(11):e1080–e1089. [PubMed: 29025631]
4. Samandari T, Agizew TB, Nyirenda S, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. Lancet. 2011;377(9777):1588–1598. [PubMed: 21492926]
5. Martinson NA, Barnes GL, Moulton LH, et al. New Regimens to Prevent Tuberculosis in Adults with HIV Infection. New England Journal of Medicine. 2011;365(1):11–20.
6. Malawi Country Operational Plan Strategic Direction Summary. In: U.S. President's Emergency Plan for AIDS Relief (PEPFAR); 2017:48.
7. Harries AD, Zachariah R, Chimzizi R, et al. Operational research in Malawi: making a difference with cotrimoxazole preventive therapy in patients with tuberculosis and HIV. BMC public health. 2011;11:593–593. [PubMed: 21794154]
8. Recommendation on 36 months isoniazid preventive therapy to adults and adolescents living with HIV in resource-constrained and high TB- and HIV prevalence setting: 2015 update. Geneva, Switzerlad: World Health Organization (WHO);2015.
9. R Core Team (2018). R: A language and environment for statistical computing [computer program]. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.
10. Ministry of Health M Malawi Population-Based HIV Impact Assessment (MPHIA) 2015–2016: First Report. 2017.
11. UNAIDS. Malawi New HIV Infections. http://aidsinfo.unaids.org/. Accessed August 29, 2018.
12. Sumner T, Houben RMGJ, Rangaka MX, et al. Post-treatment effect of isoniazid preventive therapy on tuberculosis incidence in HIV-infected individuals on antiretroviral therapy. AIDS. 2016;30(8):1279–1286. [PubMed: 26950316]
13. Steele MA, Burk RF, DesPrez RM. Toxic Hepatitis with Isoniazid and Rifampin: A Meta-analysis. Chest. 1991;99(2):465–471. [PubMed: 1824929]
14. McElroy PD, Ijaz K, Lambert LA, et al. National Survey to Measure Rates of Liver Injury, Hospitalization, and Death Associated with Rifampin and Pyrazinamide for Latent Tuberculosis Infection. Clinical Infectious Diseases. 2005;41(8):1125–1133. [PubMed: 16163632]
15. Metushi I, Uetrecht J, Phillips E. Mechanism of isoniazid-induced hepatotoxicity: then and now. British journal of clinical pharmacology. 2016;81(6):1030–1036. [PubMed: 26773235]
16. Takarinda KC, Choto RC, Harries AD, Mutasa-Apollo T, Chakanyuka-Musanhu C. Routine implementation of isoniazid preventive therapy in HIV-infected patients in seven pilot sites in Zimbabwe. Public Health Action. 2017;7(1):55–60. [PubMed: 28775944]
17. (WHO) WHO. HIV-Associated Tuberculosis. https://www.who.int/tb/areas-of-work/tb-hiv/tbhiv_factsheet.pdf?ua=1. Published 2018. Accessed.
18. Raftery AE, Bao L. Estimating and Projecting Trends in HIV/AIDS Generalized Epidemics Using Incremental Mixture Importance Sampling. Biometrics. 2010;66(4):1162–1173. [PubMed: 20222935]

19. Pho MT, Swaminathan S, Kumarasamy N, et al. The Cost-Effectiveness of Tuberculosis Preventive Therapy for HIV-Infected Individuals in Southern India: A Trial-Based Analysis. PLOS ONE. 2012;7(4):e36001. [PubMed: 22558301]
20. Bell JC, Rose DN, Sacks HS. Tuberculosis preventive therapy for HIV-infected people in sub-Saharan Africa is cost-effective. AIDS. 1999;13(12):1549–1556. [PubMed: 10465080]
21. Masobe P, Lee T, Price M. Isoniazid prophylactic therapy for tuberculosis in HIV-seropositive patients--a least-cost analysis. S Afr Med J. 1995;85(2):75–81. [PubMed: 7597538]
22. Sutton BS, Arias MS, Chheng P, Eang MT, Kimerling ME. The cost of intensified case finding and isoniazid preventive therapy for HIV-infected patients in Battambang, Cambodia. Int J Tuberc Lung Dis. 2009;13(6):713–718. [PubMed: 19460246]
23. Kanyerere H, Harries AD, Tayler-Smith K, et al. The rise and fall of tuberculosis in Malawi: associations with HIV infection and antiretroviral therapy. Trop Med Int Health. 2016;21(1):101–107. [PubMed: 26509352]
24. (PEPFAR) USPsEPfAR. Malawi Country Operational Plan Strategic Direction Summary 2017. 2017.
25. Price AJ, Glynn J, Chihana M, et al. Sustained 10-year gain in adult life expectancy following antiretroviral therapy roll-out in rural Malawi: July 2005 to June 2014. International Journal of Epidemiology. 2017;46(2):479–491. [PubMed: 28338707]
26. Kendall EA, Azman AS, Maartens G, et al. Projected population-wide impact of antiretroviral therapy-linked isoniazid preventive therapy in a high-burden setting. Aids. 2019;33(3):525–536. [PubMed: 30325773]
27. Howard AA, El-Sadr WM. Integration of tuberculosis and HIV services in sub-Saharan Africa: lessons learned. Clin Infect Dis. 2010;50 Suppl 3:S238–244. [PubMed: 20397954]
28. Kunkel A, Crawford FW, Shepherd J, Cohen T. Benefits of continuous isoniazid preventive therapy may outweigh resistance risks in a declining tuberculosis/HIV coepidemic. AIDS. 2016;30(17):2715–2723. [PubMed: 27782966]
29. Population growth (annual %) - Malawi. The World Bank. https://data.worldbank.org/indicator/SP.POP.GROW?locations=MW.
30. Marx FM, Dunbar R, Enarson DA, et al. The Temporal Dynamics of Relapse and Reinfection Tuberculosis After Successful Treatment: A Retrospective Cohort Study. Clinical Infectious Diseases. 2014;58(12):1676–1683. [PubMed: 24647020]
31. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva, Switzerland: World Health Organization (WHO);2011.
32. Kopanoff DE, Snider DE Jr., Caras GJ. Isoniazid-related hepatitis: a U.S. Public Health Service cooperative surveillance study. Am Rev Respir Dis. 1978;117(6):991–1001. [PubMed: 666111]
33. Rudoy R, Stuemky J, Poley J. Isoniazid administration and liver injury. American Journal of Diseases of Children. 1973;125(5):733–736. [PubMed: 4266968]
34. Mosimaneotsile B, Mathoma A, Chengeta B, et al. Isoniazid Tuberculosis Preventive Therapy in HIV-Infected Adults Accessing Antiretroviral Therapy: A Botswana Experience, 2004–2006. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2010;54(1):71–77. [PubMed: 19934764]

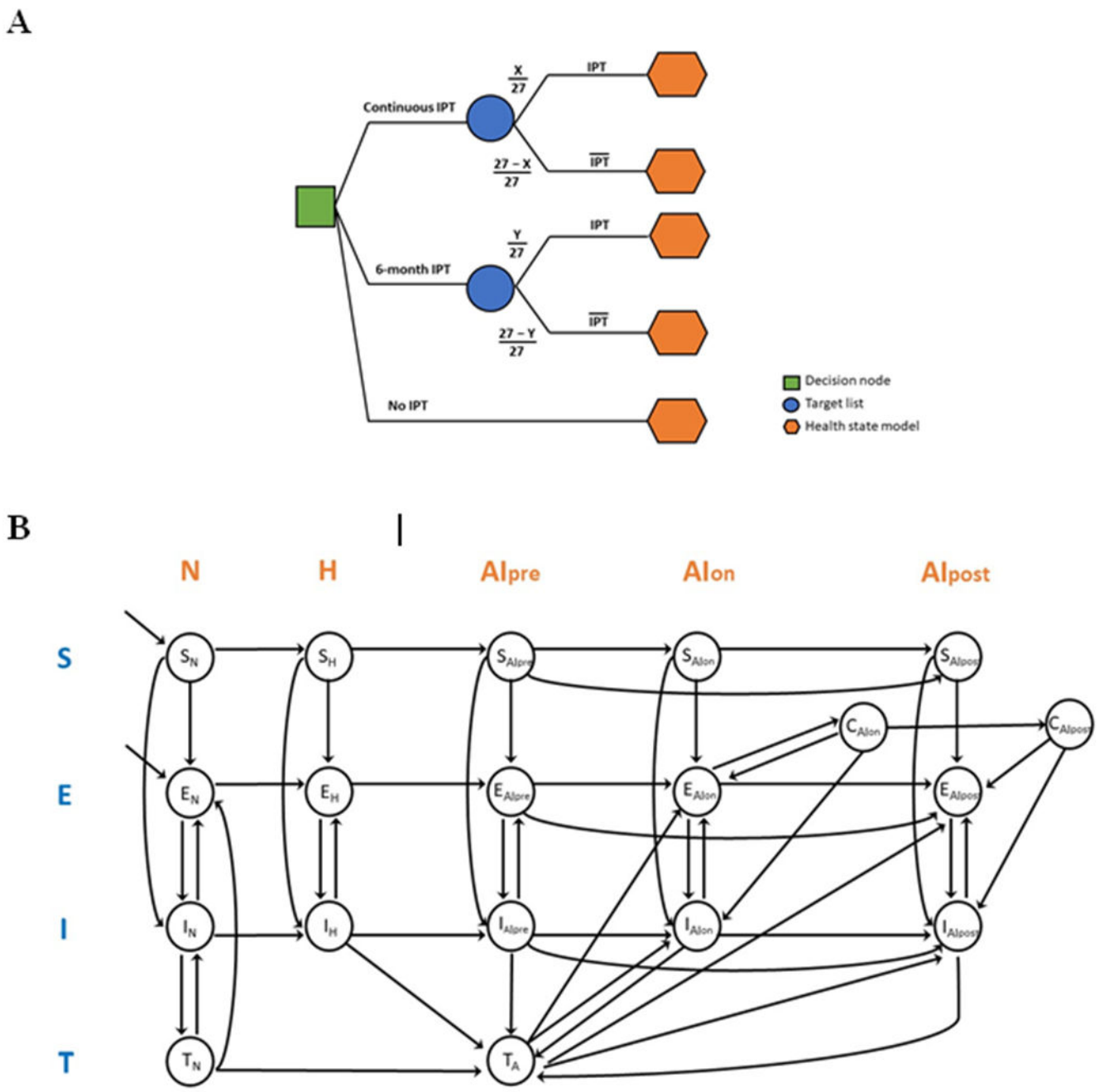

Figure 1. The modelling approach.

A. The decision analytic framework with three IPT policy alternatives. Green square, decision node; blue circles, allocation of IPT intervention programs across 27* indivisible districts, based on the allocated budget and the expected number of IPT doses required in 2018-2020; X, implementing continuous IPT program in X number of districts; Y, implementing 6-month IPT program in Y number of districts; orange hexagons, the HIV/TB compartmental model. *Likoma was excluded from the analysis due to limited TB and HIV service and surveillance data. **B. The HIV/TB compartmental model** captures both the TB and HIV related health states among adults (≥ 15 years old): N, susceptible to HIV,

H, undiagnosed HIV infection; AI_pre, diagnosed HIV infection on ART before having received IPT; AI_on, diagnosed HIV infection on ART and IPT; AI_post, diagnosed HIV infection on ART after having received IPT (top margin). S, susceptible to TB; E, latent TB; I, untreated active TB; T, on treatment for active TB disease; C, cured from latent TB (left margin). Mortality rates are not shown in the figure.

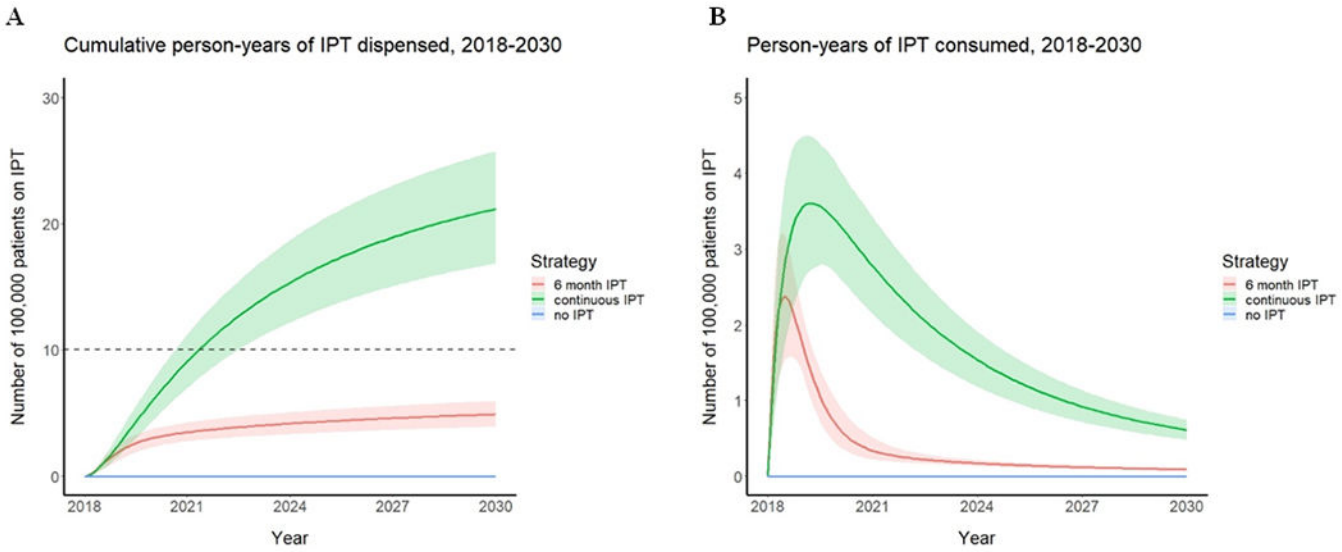

Figure 2. Person-years of IPT delivered under the three IPT policy alternatives.

The 6-month and continuous IPT program were introduced to 28 and 14 districts with the highest TB incidence rates, respectively. The number of districts intervened over the simulation period was fixed in either intervention scenario, reflecting a static intervention policy. **A, cumulative person-years of IPT delivered.** Grey dashed line (- - -), the maximum PY of IPT available in 2018-2020. **B, person-years of IPT delivered.** Solid lines, arithmetic means of the distributions of resampled parameter sets; the ribbons, 95% projection intervals.

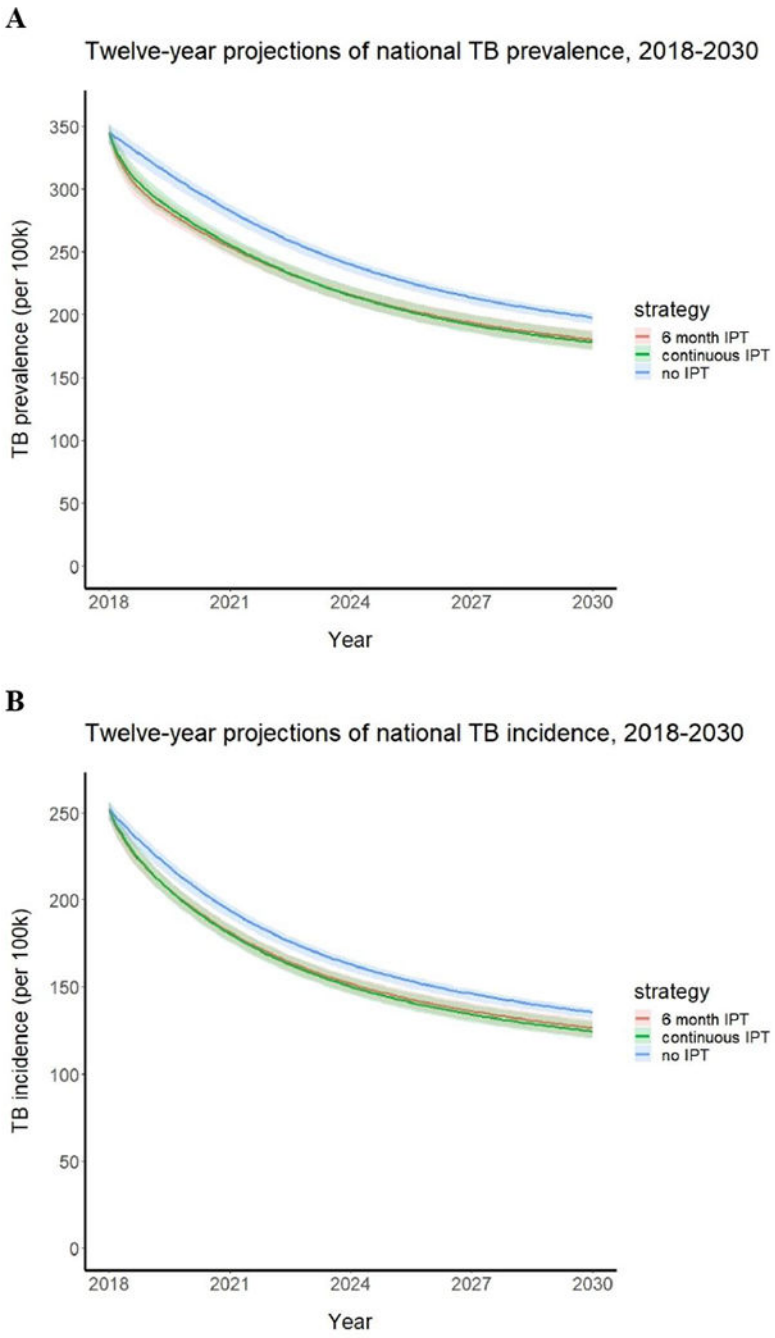

Figure 3. Twelve-year projection of TB burden among adults under the three IPT policy alternatives.

A. National TB prevalence (per 100,000). B. National TB incidence (per 100,000). The 6-month IPT program was introduced nationwide and the continuous IPT program was implemented in 14 districts with the highest estimated TB incidence rates in 2018. The number of districts intervened over the simulation period was fixed in either intervention scenario, reflecting a static intervention policy. Solid lines, arithmetic means of the distributions of resampled parameter sets; the ribbons, 95% projection intervals.

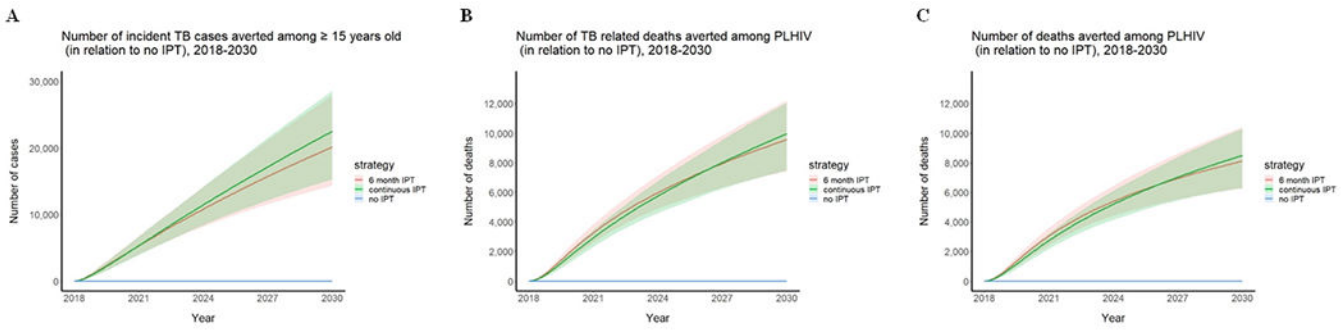

Figure 4. Comparisons of the health impacts of IPT between policy alternatives.

A, cumulative number of TB cases averted among adults, in relation to the base case. **B**, cumulative number of TB-related deaths averted among PLHIV, in relation to the base case. This includes the deaths averted among active TB cases that are being treated. **C**, cumulative number of all-cause deaths averted among PLHIV, in relation to the base case. For A-C: Solid lines, arithmetic means of the distributions of resampled parameter sets; the ribbons, 95% projection intervals.

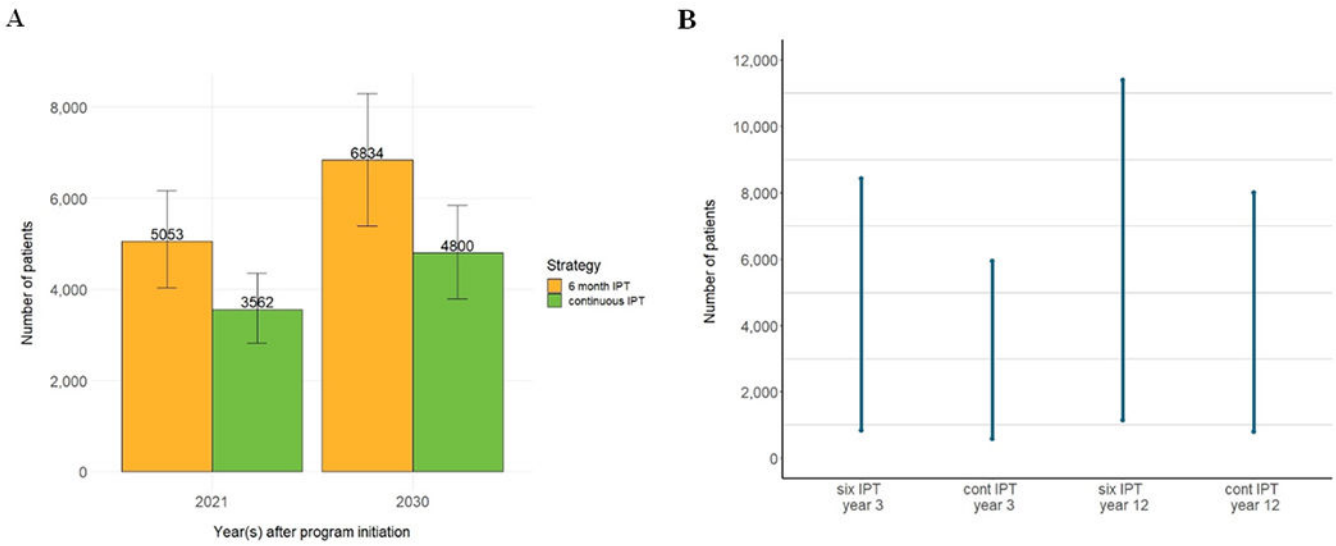

Figure 5. IPT-associated adverse events.

A. Expected cumulative number of patients with grade 3 or 4 INH-associated hepatotoxicity. The expected number of patients who might experience severe hepatoxicity events, assuming the rate of occurrence was 6 per 1000 IPT initiations. The uncertainty bars, 95% projection intervals. **B. One-way sensitivity analysis on the mean number of patients with severe INH-associated hepatotoxicity**, assuming the range of grade 3 or 4 INH-associated hepatotoxicity is 1-10 episodes per 1000 IPT initiations [13,32–34].