**Supporting Information**

**Model Details**

The model was implemented in the R programming language [[1](#_ENREF_1)] and solved using the ode function of the deSolve package [[2](#_ENREF_2)].

Table S1 lists the model variables. To allow us to keep track of the origin of TB cases and the status of the previously cured population several variables are split for “cure” status. Superscript C indicates individuals who were previously cured. Table S2 lists the parameter values. The model equations are shown below.

|  |  |
| --- | --- |
| **Variable** | **Symbol** |
| Individuals cured of latent infection following IPT | C |
| Susceptible (i.e. never infected) individuals | S |
| Latently infected individuals (> 2 years since infection) | L |
| Recently infected individuals (in first or second year) | Ii, i=1,2 |
| Recently reinfected individuals (in first or second year) | Ri, i=1,2 |
| Primary TB disease occurring in first 2 years following infection | TBp |
| Exogenous TB disease occurring in first 2 years following reinfection | TBx |
| Endogenous (reactivation) TB disease | TBn |

**Table S1** – Model variables

|  |  |  |
| --- | --- | --- |
| **Parameter** | **Range** | **Reference** |
| Annual risk of infection, *ARI* | 1-10% (uniform) | Estimated via fitting |
| Proportion of latent infections “cured” by INH, *p* | 0-1 (uniform) | Estimated via fitting |
| Annual risk of TB disease in first year following infection in HIV negative individuals, *dp1* | 8.5% [2,15] (normal) | [[3](#_ENREF_3)] |
| CD4 in HIV negative individuals, *CD4-* | 1179 [1143, 1215] (lognormal) | [[4](#_ENREF_4)] |
| Increase in risk of TB per 100 cells/μL decline in CD4 in PLWH, *α* | 0.36 [0.24,0.48] (normal) | [[5](#_ENREF_5)] |
| Relative risk of TB in second year after infection (independent of HIV status), ν | 0.41 | [[3](#_ENREF_3), [6](#_ENREF_6)]  |
| Relative risk of TB > 2 years post infection (independent of HIV status, γ | 0.13 | [[3](#_ENREF_3), [6](#_ENREF_6)] |
| Relative risk of disease following reinfection (independent of HIV status), *ε* | 0.6 [0.55,0.65] (normal) | [[3](#_ENREF_3)] |
| Ratio of RR for reinfection to reactivation in HIV positives, ω | 3 [1,5] (beta) | [[7](#_ENREF_7)] |

**Table S2 –** Parameter ranges used in model calibration

**Model Equations**

$\frac{dC}{dt}=-λC-δ\left(t\right)C$

$\frac{dS}{dt}=-λS-δ\left(t\right)S$

$\frac{dI\_{1}}{dt}=λS-rI\_{1}-RR\_{px}dp\_{1}I\_{1}-δ\left(t\right)I\_{1}$

$\frac{dI\_{2}}{dt}=rI\_{1}-rI\_{2}-RR\_{px}dp\_{2}I\_{2}-δ\left(t\right)I\_{2}$

$\frac{dR\_{1}}{dt}=λL-rR\_{1}-RR\_{px}dx\_{1}R\_{1}-δ\left(t\right)R\_{1}$

$\frac{dR\_{2}}{dt}=rR\_{1}-rR\_{2}-RR\_{px}dx\_{2}R\_{2}-δ\left(t\right)R\_{2}$

$\frac{dR\_{1}^{c}}{dt}=λ(C+L^{C})-rR\_{1}^{c}-RR\_{px}dx\_{1}R\_{1}-δ\left(t\right)R\_{1}$

$\frac{dR\_{2}^{c}}{dt}=rR\_{1}^{c}-rR\_{2}^{c}-RR\_{px}dx\_{2}R\_{2}-δ\left(t\right)R\_{2}$

$\frac{dL}{dt}=rI\_{2}+rR\_{2}-λL-RR\_{n}dnL-δ\left(t\right)L$

$\frac{dL^{C}}{dt}=rR\_{2}^{C}-λL^{C}-RR\_{n}dnL^{C}-δ\left(t\right)L^{C}$

$\frac{dTB\_{p}}{dt}=RR\_{px}dp\_{1}I\_{1}+RR\_{px}dp\_{2}I\_{2}$

$\frac{dTB\_{x}}{dt}=RR\_{px}dx\_{1}R\_{1}+RR\_{px}dx\_{2}R\_{2}$

$\frac{dTB\_{n}}{dt}=RR\_{n}dnL$

$\frac{dTB\_{x}^{C}}{dt}=RR\_{px}dx\_{1}R\_{1}^{c}+RR\_{px}dx\_{2}R\_{2}^{c}$

$\frac{dTB\_{n}^{C}}{dt}=RR\_{n}dnL^{C}$

Where:

$λ=1-(1-ARI)^{(\frac{1}{52})}$ is the weekly force of infection

$δ(t)$ is the rate at which individuals drop out of each cohort at time t and is based on trial data.

The risk of TB disease in HIV negative individuals in the first year following infection is equal to *dp1.* The risks of disease in subsequent years or following reinfection are:

$dp\_{2}=vdp\_{1}$ (risk of disease in second year following infection)

$dx\_{1}=εdp\_{1}$ (risk of disease in first year following reinfection)

$dx\_{2}=νdx\_{1}$ (risk of disease in second year following reinfection)

$dn=γdp\_{1}$ (risk of disease more than 2 years following (re)infection)

The relative risks of TB in the HIV infected trial population are assumed to depend only on the distribution of CD4 counts observed in the trial. Following Williams et al. [[5](#_ENREF_5)] we assume that the relative risk of TB increases exponentially with decreasing CD4 cell count at a rate α for each decline of 100 cells/μL. The relative risk of TB in a HIV infected person with CD4 count CD4(t) is given by:

$RR\_{HIV}=e^{α(CD4\_{neg}-CD4\left(t\right))}$

where CD4neg is the average CD4 in HIV uninfected individuals

Data also suggest that HIV infection increases the risk of (re)infection disease more than reactivation disease [[7-10](#_ENREF_7)]. This difference is described by the parameter ω. The relative risks of primary or exogenous (reinfection) disease (*px*) and endogenous (reactivation) disease (*n*) in PLWH are then given by:

$$RR\_{px}=RR\_{HIV}\frac{2ω}{(1+ω)}$$

$$RR\_{n}=RR\_{HIV}\frac{2}{(1+ω)}$$

This ensures that *RRpx* is equal to *ωRRn* and that the average risk in PLWH is still equal to *RRHIV*

**Sensitivity analysis**

In the sensitivity analysis we explored the impact of different assumptions about the level of resistance and the effectiveness of IPT against drug resistant strains of TB.

In the primary analysis we assumed drug resistance of 24% based on the occurrence of cases of drug resistant active TB during the trial. We also assumed that IPT was sufficient to suppress infection to the latent state in those recently infected with drug susceptible strains and to cure latent infection in some proportion *p* of individuals with susceptible infections.

In scenario 1 we assumed that drug resistance was 0%. This can be viewed as either an absence of drug resistance in the population or that INH is equally effective in resistant and susceptible strains. In scenario 2 we assumed resistance was 24% based on observed levels of drug resistance in the trial cohort.

In scenario 3 we assumed that drug resistance was 12.5% but that INH was sufficient to suppress recent infections with susceptible and resistant strains of TB.

These scenarios were modelled by varying the initial conditions in the intervention arm to reflect the assumptions about drug resistance and mechanism of action (see table S2).

|  |  |  |
| --- | --- | --- |
| **State** | **Primary analysis, Scenarios 1 and 2** | **Scenario 3** |
| Cured | (1-(1-ARI)a) p (1-δ) | (1-(1-ARI)a) p (1-δ) |
| Never Infected | (1-ARI)a | (1-ARI)a |
| Recently infected | ((1-ARI)(a-i))(1-(1-ARI))δ | 0 |
| Recently reinfected | (1-(1-*ARI*)(a-i))(1-(1-ARI))δ | 0 |
| Latently infected | 1-*C*-*S*-*I*-*R* | 1-*C*-*S*-*I*-*R* |
| Primary TB | 0 | 0 |
| Endogenous TB | 0 | 0 |
| Exogenous TB | 0 | 0 |

**Table S3** – Initial conditions in the placebo arm for the base-case and alternative scenarios. ARI=Annual risk of infection; p=proportion cured following IPT; a=average age of the cohort; δ=proportion of drug resistance in the population.

Table S4 compares the posterior estimates for *p* and the *ARI* under the different scenarios.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Output** | **Resistance=12.5%****(primary analysis)** | **Resistance=0%**  | **Resistance= 24%,**  | **Resistance=12.5%, INH suppresses recent infection with any strain** |
| ARI, % | 4.0% (2.6-5.8) | 4.0 (2.7-5.9) | 4.0 (2.6-5.9). | 4.0 (2.6-5.9) |
| *p*, % | 35.4 (2.4-76.4). | 23.2 (1.0-61.5) | 39.8 (1.9-86.7). | 30.5 (2.1-6.8) |

**Table S4 – Sensitivity analysis.** Posterior estimates for annual risk of infection (ARI) and proportion cured by IPT (*p*) for differentassumptions about drug resistance

**Supplementary figures**

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**Figure S1 – Posterior distributions for the primary analysis (resistance=12.5%)**

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**Figure S2 – Posterior distributions resistance=0%**

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**Figure S3 – Posterior distributions resistance=24%**



**Figure S4 – Source of TB cases in the intervention arm.** Median output from the 200,000 resampled model runs. **“**Primary” refers to disease occurring during the 2 years following first infection. “All recent transmission” includes primary TB and disease due to reinfection (within 2 years) in individuals who were cured and in those who remained latently infected following IPT. “Reactivation (cured)” refers to individuals who were cured, reinfected and developed disease (on average) 2 or more years after reinfection. “Reinfection (not cured)” refers to individuals who were not cured, reinfected and developed exogenous disease within 2 years of reinfection.

**References**

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