Isoniazid Preventive Therapy Added to ART to Prevent TB: An Individual Participant Data Meta-Analysis

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Summary:

Background

Isoniazid preventive therapy (IPT) prevents active TB in people living with HIV (PLHIV), but prior studies found no evidence of benefit in PLHIV with a negative tuberculin skin test (TST) and non-significant impact on mortality. We conducted an individual participant data meta-analysis of randomized controlled trials to estimate the effect of IPT given with ART to prevent TB and death among PLHIV across population subgroups.

Methods

We searched PubMed, Embase, the Cochrane database, and conference abstracts. Eligible studies included trials of HIV-positive adults taking ART randomized to daily IPT versus no IPT. We performed a single-stage individual participant data meta-analysis of the outcomes of incident TB disease and all-cause mortality using stratified Cox-proportional hazards models. Registration: PROSPERO (CRD42019121400).

Findings

We found 838 citations and included 2611 participants from three trials in Cote D'Ivoire, Malawi, and South Africa. IPT with ART was associated with lower risk for TB than ART alone (hazard ratio=0·68, 95% CI 0·49–0·95, p=0·02) and non-significantly lower all-cause mortality (hazard ratio=0·69, 95% CI 0·43–1·10, p=0.12). TB risk differed by baseline CD4 <200 cells/mm^3, but there was no evidence of varying benefit of IPT with ART by sex, baseline CD4, or results of TST or interferon gamma release assays. Elevated alanine aminotransferase occurred in 65/2611 (2.5%) of participants, but data were insufficient to calculate a hazard ratio.

Interpretation

IPT with ART prevents TB across demographic and HIV- and TB-specific subgroups, which supports efforts to further increase use of IPT with ART broadly among PLHIV.

Funding

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Research in Context

Evidence before this study

We searched PubMed, Embase, and the Cochrane Database of Systematic Reviews using combinations of the terms “isoniazid”, “IPT”, “HIV”, “human immunodeficiency virus”, “antiretroviral therapy”, and “ART” for studies up through January 15, 2019. We identified a systematic review of 12 randomized controlled trials of several TB preventive therapy regimens among PLHIV, including IPT, that were published between 1997 and 2007. This review found that IPT reduced the risk of TB, with the benefit driven by the effect in PLHIV with a positive tuberculin skin test (TST), but did not find evidence of an effect on all-cause mortality. None of the trials in this review included PLHIV taking ART. Another systematic review included 10 studies published between 1997 and 2015 found no benefit of IPT in participants with negative or unknown TST, and just two studies included participants taking ART. These reviews did not stratify across subgroups by interferon gamma release assay (IGRA) status.

Added value of this study

Our study uses individual participant data from three randomized controlled trials of IPT given with ART versus ART alone to examine the impact on TB and all-cause mortality according to individual characteristics, such as sex, CD4 T-cell count, TST and IGRA. Additionally, we evaluate the safety of IPT with ART by comparing the proportion of participants experiencing liver injury by treatment groups. We found that IPT with ART was associated with lower risk for TB than ART alone, and a non-significantly lower all-cause mortality. We found no evidence of varying benefit of IPT with ART by sex, baseline CD4, or results of TST or IGRA.

Implications of all the available evidence

These findings support current guidelines to provide IPT to all PLHIV to reduce the risk of developing TB. They align with the recommendation to provide IPT to PLHIV without requiring testing for immune sensitization to TB by TST or IGRA. They suggest that the benefit of IPT among PLHIV taking ART may not vary according to TST or IGRA results.

Introduction and Rationale

Preventing tuberculosis (TB) and TB-associated mortality is critical to extending healthy life for PLHIV and to achieving the Sustainable Development Goal 3.3 to end the epidemics of TB and HIV.[1] Taking isoniazid preventive therapy (IPT) reduces the risk of active TB among PLHIV, but the impact of IPT on all-cause mortality among PLHIV is unclear.[2–4] Antiretroviral therapy (ART) reduces the risk of TB and death.[5–7] As the number of persons accessing ART more than tripled in the past decade, from an estimated 7·7 million in 2010 to 24·5 million in 2019, and IPT access has also improved, ART and IPT are increasingly studied together in clinical trials and taken together in practice.[8–11] Clear characterization of the health benefits and risks of IPT when given with ART is essential to inform health policy by estimating the impact of current, large-scale efforts to make both available to PLHIV.[12,13]

Important questions remain about the benefit of IPT together with ART, particularly across population subgroups. A meta-analysis of ten randomized controlled trials published between 1997 and 2015 found that IPT reduced the risk of active TB disease with a relative risk of 0·65 (95% CI 0·51–0·84) among the pooled study population of PLHIV, though only two of the trials reported results among participants taking ART.[3] Additionally, the subset of participants without evidence of immune sensitization to TB (i.e. negative tuberculin skin test (TST)) had no evidence of benefit, and the data were not disaggregated by both ART and TST subgroups simultaneously. Interferon gamma release assays (IGRAs), which have been adopted into clinical and research settings to screen for immune sensitization to TB, were not considered. Finally, the 2015 meta-analysis found that all-cause mortality was not affected by IPT.[3] Newly published trials prompt the need for an updated and focused synthesis of the data for IPT in the context of ART across populations of PLHIV, and to examine the impact on mortality.[11,14]

We therefore conducted a systematic literature review and individual participant data meta-analysis to estimate the impact of IPT among adult PLHIV taking ART on risk of active TB and death. The meta-analysis of individual participant data permitted analysis according to individual characteristics, such as sex, CD4 T-cell count, and evidence of immune sensitization to TB, as measured by a positive

TST or IGRA. The primary study objectives were to determine the relative risk of (a) incident TB and (b) all-cause mortality among adults living with HIV taking ART with IPT versus without IPT. Pre-specified secondary objectives were to assess for effect modification of the primary objectives by baseline CD4 count or evidence of immune sensitization. A final pre-specified secondary objective was to determine the relative risk of liver injury between PLHIV on ART taking IPT versus no IPT.

Methods

Search strategy and selection criteria

This systematic review and individual patient data meta-analysis followed Cochrane Collaboration guidelines for the review and PRISMA guidelines in reporting the results.[15,16] We registered the study protocol with PROSPERO (CRD42019121400). The University of Washington Institutional Review Board approved the study.

Eligible studies included randomized controlled trials that enrolled adults (age ≥ 15 years) who were HIV-positive and taking ART, including studies that initiated ART on enrolment. Additionally, we required that participants were randomized to receive daily IPT versus no IPT and were followed longitudinally for outcomes of incident tuberculosis and death. For multi-arm trials where data from a subset of arms met inclusion criteria, we requested data from the eligible arms. We excluded observational studies due to potential bias in IPT use. We also excluded studies enrolling only children aged under 15 years and studies for which rifapentine was given in addition to isoniazid.

We searched the following databases without language restriction on January 15, 2019: PubMed, Embase, and Cochrane Clinical Trials Database. We did not limit the start date of the search. Search terms are listed in the Supplementary Material (appendix page 2). Two investigators (JR, A Badje) screened titles and abstracts for eligibility, followed by full-text review by JR and A Badje. The full investigator team determined final study eligibility by consensus. The grey literature search included the previous four years of proceedings from the Conference on Retroviruses and Opportunistic Infections, the International AIDS Society Annual Meeting, and The Union World Conference on Lung Health. One reviewer (AS) screened titles and abstracts for eligibility and presented eligible abstracts for review by

the full investigator team. We completed a risk of bias assessment for the included studies using the Cochrane Risk of Bias Assessment Tool for Randomized Controlled Trials, Version 2.0.[17]

Data management and definitions

We requested de-identified individual patient data from study authors using a standard list of variables. These variables included age, sex, CD4 T-cell count at enrolment, ART and IPT start dates, IPT completion date, result of TST and IGRA, method of TB screening at enrolment, incident TB date, date of elevated alanine aminotransferase, date and cause of death, date of study closure, and date of last known contact (appendix page 4). We aligned variable formatting and mapped them to a common naming structure, which we confirmed with each primary investigator.

We defined the primary outcome of incident TB as bacteriologically confirmed, probable, or possible TB, as defined by the primary studies, which largely aligned in their classification systems (Supplementary Appendix). Death from any cause was a co-primary outcome. Baseline CD4 cells/mm^3 was measured at study enrolment. We defined separate variables for immune sensitization status to TB based on response to TST or IGRA. Liver injury was defined as alanine aminotransferase (ALT) > 2.5 times the upper limit of normal. We censored observation time from patients who were lost to follow-up from the date of their last known study contact.

Data analysis

We analyzed the data from each study together in a single-stage meta-analysis.[18] We estimated the cumulative probability of all-cause mortality using the Kaplan-Meier method implemented with the R package ‘survival’ and plotted with ‘survminer’.[19] We used multivariable Cox proportional hazards regression to compare event rates for each outcome between the exposure groups in an intent-to-treat analysis, stratified by trial. We calculated the subdistribution hazard for incident TB in the presence of the competing risk of mortality using the R package ‘cmprsk’ as a sensitivity analysis.[20,21] We assessed the proportionality assumption by testing the correlation between Schoenfeld residuals and survival time. We assessed heterogeneity using the I^2 statistic. We compared treatment arms using the log-rank test and two-sided p-values with a significance level of $p<0{\cdot}05$.

We evaluated effect modification using likelihood ratio tests of models containing main effects and interaction terms between treatment arm and the variable of interest versus models containing terms only as main effects.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The literature search identified unique citations from the databases and conference abstracts, from which we identified a subset of studies for full-text review and three studies that met eligibility criteria (Fig. 1). The primary reasons for excluding studies at the full-text stage were for interventions other than IPT with ART versus ART alone, study populations that overlapped with the primary publications of the included trials and study designs other than individually-randomized controlled trials. Characteristics of the three included studies are shown in Table 1. Each of the included studies enrolled participants with HIV-1, and the TEMPRANO study also included participants with dual HIV-1 and HIV-2 infections. The risk of bias in the included studies was assessed to be low across the five domains for each outcome in the eligible subsets from the included studies (appendix page 7).

The individual participant data meta-analysis included 2611 participants who contributed a combined 8584.8 person-years of follow-up time to the outcome of incident TB. A subset of 2362 participants contributed 8631.6 person-years of follow-up time to the outcome of all-cause mortality. Participants from the REALITY trial were included in the incident TB analysis but not in the mortality analysis because the intervention package in the REALITY trial included other medications (fluconazole, azithromycin, and albendazole) in addition to IPT, which may have affected the risk of death in this trial but would be unlikely to affect the risk of incident TB. A sensitivity analysis including all trials in the mortality analysis is included in the Supplementary Appendix.

Participants randomized to receive IPT with ART versus ART had similar baseline characteristics (Table 2). Nearly three-quarters of the participants were female. Two of the three studies specified different CD4 cell count criteria for enrolment (Table 1). In the combined study population, nearly one-third of participants had a CD4 cell count <200 cells/mm^3 at enrolment (including all REALITY participants except for one), 42.5% 200-499 cells/mm^3, and 22.3% at least 500 cells per mm^3. Participants in TEMPRANO and REALITY were ART naïve, whereas 72% of participants in the ART-IPT study were established on ART.[10,11,14] Studies differed according to their protocols in the proportion screened for immune sensitization to TB by IGRA and TST, with 998/1329 (75.1%) participants with IGRA results and 944/1329 (71%) participants with TST results in the ART-IPT study; 482/1033 (46.7%) participants with IGRA results and no participants with TST results in TEMPRANO, and no participants with either measure in REALITY. Of persons with results available, 549 of 1480 (37.1%) had a positive IGRA and 392 of 944 (41.5%) had a positive TST (Table 2).

The risk of incident TB was lower in persons randomized to take IPT (HR 0·68, 95% CI 0·49–0·95, p=0·02) (appendix page 9). The risk of all-cause mortality tended to be lower in persons randomized to take IPT, but was not statistically significant (HR 0·69 (95% CI 0·43–1·10, p=0.12)) (appendix page 10). The I^2 statistic for the outcome of incident TB was 0 (95% CI 0%-87·4%). The I^2 statistic for the outcome of all-cause mortality was 0 (95% CI 0%-99·7%).

241 The risk of incident TB and death varied according to known risk factors (appendix page 12). The
242 hazard ratio for incident TB was non-significantly greater among men compared to women. Men had a
243 higher all-cause mortality rate than women. TB incidence was highest in participants with CD4 <200
244 cells/mm^3, corresponding to a hazard ratio of 2·45 (95% CI 1·30–4·63) when compared to persons with
245 CD4 of at least 500 cells/mm^3. TB incidence was nearly equal among participants with positive versus
246 negative TST, but persons with a positive IGRA had a higher incidence of TB than persons with a negative
247 IGRA (HR 1·90, 95% CI 1·23–2·94). Mortality did not differ substantially by TST or IGRA status (appendix
248 page 12).
249 We did not find evidence of substantial differences in the benefit of IPT given with ART in
250 preventing TB disease and death by population subgroups according to sex, baseline CD4 or evidence
251 of immune sensitization to TB (Tables 3-4). The hazard ratio for TB among men taking IPT with ART
252 versus ART alone was 0·53 (95% CI 0·29-0·97), as compared to 0·77 (95% CI 0·52–1·14) among
253 women, with no evidence of interaction between IPT assignment and sex (heterogeneity p=0·32). The
254 hazard ratios for IPT with ART versus ART alone did not show a dose-response relationship with baseline
255 CD4 category. IPT given with ART reduced the risk of incident TB in persons with a negative TST (HR
256 =0·42, 95% CI 0·21–0·84) or IGRA (HR=0·45, 95% CI 0·22–0·89); while the estimated hazard ratios
257 were higher in persons with positive TST and IGRA groups, there was no evidence of effect modification
258 by immune sensitization to TB (heterogeneity p>0·05). Similarly, we did not find evidence of effect
259 modification in the risk of mortality between IPT given with ART and the factors of sex, CD4, and TST or
260 IGRA (heterogeneity p>0·05). The confidence limits for the interaction terms are shown in the appendix
261 (page 17).

Studies differed according to their measurement frequency for ALT, with the result that time-to-event analysis was not possible for this outcome. The proportion of participants who experienced an elevation in ALT at least 2.5 times the upper limit of normal ranged from 0.8% to 3.17% per study arm, except in the enhanced prophylaxis arm of the REALITY study, where 12/124 (9.68%) of participants developed this degree of ALT elevation while taking ART with IPT and other medications, including daily fluconazole (appendix page 13).

In sensitivity analysis, the competing risks approach for the outcome of incident TB yielded the same hazard ratio as the primary analysis (appendix page 14). Including all three trials in a sensitivity analysis for the all-cause mortality outcome also identified a point estimate for mortality that was lower among persons randomized to take IPT, but was not statistically significant (HR 0·79, 95% CI 0.53 – 1.12, p=0.24)(appendix page 17).

Discussion

We found that IPT given with ART reduced the risk of incident TB by nearly one third as compared to ART alone in PLHIV. This benefit of IPT with ART to prevent incident TB was more pronounced than the benefit to prevent death, though PLHIV who received IPT with ART also tended to have a lower risk of death than PLHIV who received ART without IPT. The benefit of IPT with ART to prevent incident TB or death did not differ substantially across population subgroups by sex, baseline CD4, or immune sensitization, with no evidence of effect modification of IPT with ART by any of these factors.

The pooled estimates of risk reduction for TB and death from all causes are largely consistent with prior studies, though they differ in the subgroup analysis by evidence of immune sensitization to TB. The meta-analysis conducted by Ayele, et al identified a relative risk for TB of 0·65 among persons receiving IPT versus not receiving IPT, which is comparable to the point estimate of 0·68 in this study.[3] Similarly, both analyses demonstrated a non-significantly lower risk of death among persons receiving IPT. The results of this study differ in the subgroup analyses, where we found no evidence that benefits of IPT with ART varied by TST or IGRA status. This finding initially was reported by the ART-IPT study and is further supported by the addition of TEMPRANO data for persons tested with IGRA.[10] It differs from the findings

in the reviews by Ayele, et al and Akolo, et al of a benefit of IPT in the subgroup of participants with a positive TST but not those with a negative TST.[2,3] Our study differs from the populations studied in the earlier reviews because we include only participants taking ART. This result highlights limitations of TST or IGRA among persons with immune suppression, and supports current guidelines which do not require screening with TST or IGRA prior to initiating IPT in PLHIV.[22]

We assessed the safety of ART with IPT by evaluating the frequency of grade 2 or higher ALT elevation. These events were generally rare, and we found no evidence of a difference by study group in the ART-IPT and TEMPRANO studies. However, the proportion of participants who experienced hepatotoxicity in the enhanced prophylaxis group of the REALITY trial at the Malawi site was substantially greater than in the group that received ART alone. We hypothesize that this may be due to co-administration of isoniazid with other medications including daily fluconazole, and also note the small sample size of participants included from the REALITY trial. The safety and efficacy of IPT together with ART among pregnant women is an important consideration that was not addressed in this review. The studies in this review excluded women who were pregnant at the time of enrolment; however, women who became pregnant during the study were retained. The TB APPRISE trial raised concern for the risk of adverse events due to IPT initiation during pregnancy.[23] In consultation with the trial investigators, the TB APPRISE trial was not considered eligible for inclusion in the meta-analysis due to the study design of immediate versus deferred IPT, which was similar to the implementation of the REALITY trial outside of Malawi.

This meta-analysis focused on TB preventive therapy with isoniazid, which is the most common regimen given for TB preventive therapy globally.[9] Alternative regimens with a combination of rifapentine and isoniazid given weekly for 12 weeks or given daily for one month have shown non-inferior efficacy for TB prevention and better adherence when compared to nine months of isoniazid.[24–26] We did not combine these studies into our analysis, as these represent different interventions with different adverse event profiles. Additionally, rifapentine with isoniazid is available in few settings in sub-Saharan Africa outside of clinical trials, and the cost of rifapentine has been identified as a barrier to implementation in high-burden settings.[9,27] Similarly, we focused this study on adults and excluded studies or study subsets

of children. A meta-analysis of randomized controlled trials providing IPT to children living with HIV in southern Africa identified a benefit of IPT to prevent active TB among children not receiving ART, but was inconclusive regarding the benefit in children receiving ART.[28]

Our study has several strengths, as well as limitations necessitated by inevitable trade-offs. We included only randomized controlled trials and excluded observational studies, which resulted in a study dataset that was well-balanced for potential confounders, but limited the analysis to three trials. Still, these three trials represent an important diversity of sites within sub-Saharan Africa, which is the geographic region with the highest burden of HIV-TB co-infection.[19] Another limitation is that we were unable to assess the effect of IPT with ART on TB-specific mortality due to a small number of TB deaths and relatively large numbers of deaths from unknown causes. Additionally, the trials differed in the duration of IPT provided, from 12 weeks in the REALITY subset to 6 months in TEMPRANO to 12 months in the ART-IPT study. We were not able to separately test for differences in the duration of therapy on the risk of TB because therapy length was determined by each study protocol. The trials differed in the distributions of CD4 cell counts at enrolment. Despite these differences, we found that the direction and magnitude of the effect size for IPT with ART was similar between the studies. Additionally, the I^2 statistics indicated a low degree of heterogeneity but had a wide confidence interval due to imprecision in this measure in meta-analyses of few studies.[29] Studies differed in the length of follow-up time over which they ascertained incident TB disease and death, with the result that the study population followed after 30 months predominantly includes participants in the TEMPRANO study. We evaluated the impact of this variation, as well as the potential difference in TB ascertainment during the initial study period versus the extended follow up through using a sensitivity analysis that limited TEMPRANO observation time to 30 months. The hazard ratio for TB in this sensitivity analysis aligned well with the full study dataset (appendix page 16). Finally, our statistical method of testing interactions utilized a stratified Cox proportional hazards model fit to the pooled data, which is often applied, though Fisher and colleagues recommended testing interactions using within-trials information alone.[30]

In summary, we found that IPT given with ART reduces the risk of TB among PLHIV across population subgroups, including among participants with a negative TST or IGRA. Participants receiving IPT with

ART had a non-significantly lower risk of death than participants who received ART alone. This analysis updates the data synthesis for IPT efficacy to reflect current paradigm of universal ART eligibility for PLHIV. It affirms the goal committed by the UN high-level meeting on TB to scale-up TB preventive therapy to at least 6 million PLHIV by 2022 to prevent TB disease and death.[12]

Contributors

XA, A Badje, RVB, NF, GM, JMR, MXR, and BW conceived of the study idea and developed the study design. JMR, AB, and AES performed the systematic literature review. A Badje, A Boulle, SE, DG, GM, MXR, ASW, and RJW collected and prepared the primary study data. JMR performed the analysis with guidance from KKT. JMR wrote the first draft of the manuscript. All authors critically revised the manuscript.

Declaration of interests

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Data sharing

De-identified data from the trials included in these analyses may be requested from the primary trial investigators.

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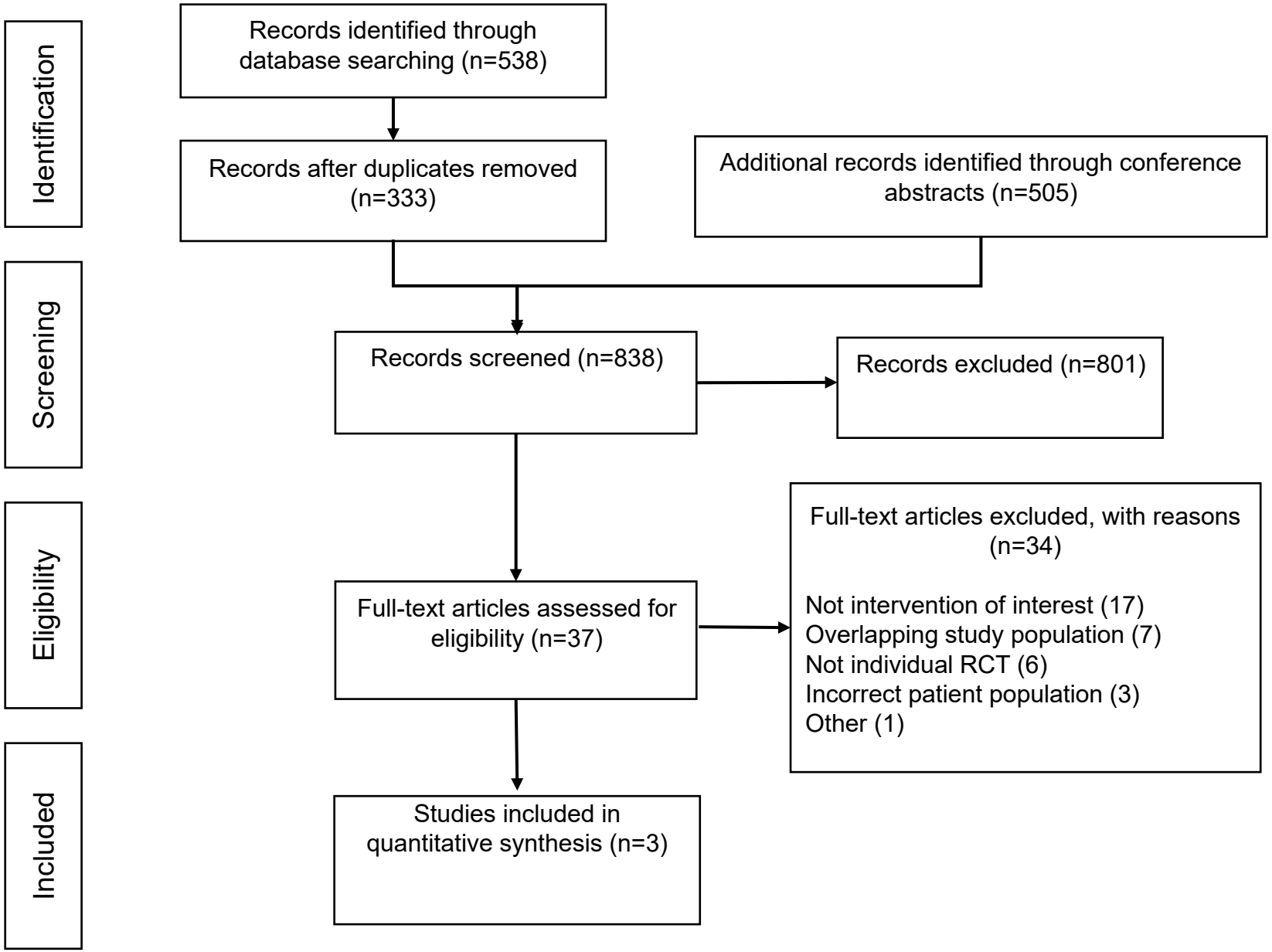

Identification
Screening
Eligibility
Included
Records identified through database searching (n=538)
Records after duplicates removed (n=333)
Additional records identified through conference abstracts (n=505)
Records screened (n=838)
Records excluded (n=801)
Full-text articles assessed for eligibility (n=37)
Full-text articles excluded, with reasons (n=34)
Not intervention of interest (17)
Overlapping study population (7)
Not individual RCT (6)
Incorrect patient population (3)
Other (1)
Studies included in quantitative synthesis (n=3)

Table 1: Characteristics of included studies

	Study Name	Location	Dates	IPT intervention	Enrolment CD4 criteria (cells per mm^3)	Participants randomized to IPT+ART	Participants randomized to ART	Follow-up duration
Rangaka, et al (2014)	ART-IPT	South Africa	2007 - 2011	Daily – 12 months	None	662	667	Median 2.5 years (IQR 2.1-3.1)
Hakim, et al (2017)	REALITY	Malawi¶	2013 - 2017	Daily – 3 months*	<100	124	125	48 weeks
Badje, et al (2017) §	TEMPRANO	Cote D'Ivoire	2008 - 2015	Daily - 6 months	<800	518	515	30 months + extended observation ±

§Data from participants in the early ART arms of the TEMPRANO study, with and without IPT, was included, but data from participants in the deferred ART arms was not included.

±The primary TEMPRANO study follow-up period was 30 months, after which participants entered an extended follow-up period until the last participant completed 30 months of follow-up. The median total duration of follow-up was 4.9 years (IQR 3.3 – 5.8).

¶Only data from adult participants at the Malawi site met eligibility criteria, as substantial numbers of participants in the standard of care arms at the other three trial locations initiated IPT at twelve weeks post randomization, per national guidelines.

*Participants in the IPT + ART arm of the REALITY study also received single dose (400 mg) of albendazole, 5 days of azithromycin (500 mg once daily), and 12 weeks of fluconazole (100 mg once daily) as part of an enhanced prophylaxis package. Participants from the REALITY study were not included in the mortality analysis.

Table 2: Baseline characteristics of all participants (n=2611)

	ART (n=1307)	**IPT + ART (n=1304)**
Age, years	34.7 (IQR 29.6 – 40.3)	34.5 (IQR 29.5 – 41.0)
Sex		
Female	963 (73.6%)	975 (74.8%)
Male	344 (26.3%)	329 (25.2%)
Location		
Cote d'Ivoire	515 (39.4%)	518 (39.7%)
Malawi	125 (9.6%)	124 (9.5%)
South Africa	667 (51.0%)	662 (50.8%)
CD4 at enrollment		
<200	401 (30.7%)	379 (29.1%)
200 - 499	566 (43.3%)	541 (41.5%)
≥500	275 (21.0%)	307 (23.5%)
Unknown	65 (5.0%)	77 (5.9%)
TST		
Positive	202 (15.5%)	190 (14.6%)
Negative	283 (21.7%)	269 (20.6%)
Unknown	822 (62.9%)	845 (64.8%)
IGRA		
Positive	289 (22.1%)	260 (19.9%)
Negative	409 (31.3%)	433 (33.2%)
Indeterminate	47 (3.6%)	42 (3.2%)
Unknown	562 (43.0%)	569 (43.6%)

Data are median (IQR) or n(%). TST = tuberculin skin test. IGRA = interferon gamma release assay.

Table 3. Effect modification analyses for incident TB (n=2611)

	IPT+ ART arm				ART alone arm						
Group	**N**	**Person-Years**	**TB events**	**TB incidence per 100k person-years**	**N**	**Person-Years**	**TB events**	**TB incidence per 100k person-years**	**HR (ART+IPT) vs ART alone**	**95% CI**	**Interaction p**
Sex											0.32
Female	975	3366.0	44	1307.2	963	3240.6	55	1697.2	0.77	0.52 – 1.14	
Male	329	988.4	16	1618.8	344	989.8	31	3131.9	0.53	0.29 – 0.97	
CD4 at enrolment											0.25
<200	379	835.8	24	2871.5	401	855.9	39	4556.6	0.62	0.37 – 1.03	
200 - 499	541	2152.3	27	1254.5	566	2181.0	31	1421.4	0.92	0.55 – 1.55	
≥500	307	1157.5	5	432.0	275	1008.5	11	1090.7	0.37	0.13 – 1.07	
TST											0.14
Positive	190	538.1	12	2230.1	202	582.4	14	2403.8	0.92	0.43 – 1.99	
Negative	269	766.3	11	1435.5	283	770.3	27	3505.1	0.42	0.21 – 0.84	
IGRA											0.23
Positive	260	907.5	20	2203.9	289	987.4	27	2734.5	0.82	0.46 – 1.46	
Negative	433	1702.1	12	705.0	409	1570.4	25	1592.0	0.45	0.22 – 0.89	
Indeterminate	42	143.4	5	3486.8	47	163.8	4	2442.0	1.37	0.37 – 5.08	

TST = tuberculin skin test. IGRA = interferon gamma release assay.

Table 4. Effect modification analyses for all-cause mortality (n=2362)

	IPT+ ART arm				ART alone arm						
	N	**Person-Years**	**Mortality events**	**Mortality per 100k person-years**	**N**	**Person-Years**	**Mortality events**	**Mortality per 100k person-years**	**HR (ART+IPT) vs ART alone**	**95% CI**	**Interaction p**
Sex											0.76
Female	916	3391.7	21	619.2	905	3298.0	29	879.3	0.73	0.41 – 1.28	
Male	264	952.7	9	944.9	277	989.2	15	1516.4	0.62	0.27 – 1.42	
CD4 at enrolment											0.16
<200	255	757.5	4	528.1	277	802.5	12	1495.3	0.39	0.12 – 1.21	
200 - 499	541	2205.5	22	997.5	565	2252.2	23	1021.2	0.98	0.55 – 1.76	
≥500	307	1168.6	3	256.7	275	1039.1	8	769.9	0.33	0.09 – 1.25	
TST											0.83
Positive	190	554.6	4	721.2	202	608.1	5	822.2	0.87	0.23 – 3.23	
Negative	269	781.5	9	1151.6	283	807.0	10	1239.2	1.04	0.41 – 2.62	
IGRA											0.21
Positive	260	947.9	20	2109.9	289	1041.9	27	2591.4	1.45	0.50 – 4.19	
Negative	433	1722.2	12	696.8	409	1618.8	25	1544.4	0.70	0.35 – 1.39	
Indeterminate	42	150.4	5	3324.5	47	169.3	4	2362.7	0.22	0.03 – 1.91	

TST = tuberculin skin test. IGRA = interferon gamma release assay.

Supplementary Material
Isoniazid Preventive Therapy Added to ART to Prevent TB Disease: An Individual Participant Data Meta-Analysis

Table of contents

Supplementary Methods

Literature search strategies

We searched the databases without language restriction on January 15, 2019 using the following strategies.

PubMed search strategy

(Tuberculosis[mesh] OR "Mycobacterium tuberculosis"[Mesh] OR tuberculosis[tiab] OR TB[tiab] OR tuberculin[tiab] OR antitubercul*[tiab]) AND ("Isoniazid"[Mesh] OR isoniazid* OR IPT[tiab] OR “isonicotinic acid hydrazide” OR Isonicotinylhydrazine* OR isonicotinoylhydrazine*) AND (HIV[Mesh] OR "HIV Infections"[Mesh] OR HIV[tiab] OR hiv1[tiab] OR hiv2[tiab] OR "human immunodeficiency virus”[tiab] OR “human immunedeficiency virus”[tiab] OR “human immune deficiency virus”[tiab] OR “human immuno deficiency virus”[tiab] OR ((human immun*[tiab]) AND (“deficiency virus”[tiab])) OR "acquired immunodeficiency"[tiab] OR "acquired immuno deficiency"[tiab] OR “acquired immune deficiency”[tiab] OR “acquired immunedeficiency”[tiab] OR aids[tiab]) AND ("Anti-Retroviral Agents"[Mesh] OR "Antiretroviral Therapy, Highly Active"[Mesh] OR “Antiviral Agents”[MeSH:NoExp] OR "Reverse Transcriptase Inhibitors" [Pharmacological Action] OR "AIDS Vaccines"[Mesh] OR Antiretroviral[tiab] OR antiretrovirus[tiab] OR “anti retroviral”[tiab] OR “anti retrovirus”[tiab] OR ART[tiab] OR HAART[tiab] OR reverse transcriptase*[tiab]) AND ("Randomized Controlled Trials as Topic"[Mesh] OR "Randomized Controlled Trial"[Publication Type] OR “Controlled Clinical Trials as Topic"[Mesh] OR " Controlled Clinical Trial"[Publication Type OR rct[tiab] OR rcts[tiab] OR random*)

Embase search strategy

('tuberculosis'/exp OR 'drug resistant tuberculosis'/exp OR 'Mycobacterium tuberculosis'/exp OR tuberculosis:ti,ab OR tuberculin:ti,ab OR tb:ti,ab OR antitubercul*:ti,ab) AND ('isoniazid'/exp OR isoniazid* OR 'isonicotinylhydrazine'/exp OR ‘isonicotinic acid hydrazide’ OR isonicotinylhydrazine* OR 'isonicotinoylhydrazine'/exp OR isonicotinoylhydrazine*) AND ('human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus'/exp OR ‘human immunodeficiency virus’ OR hiv OR ‘human immunedeficiency virus’ OR ‘human immune deficiency virus’ OR ‘human immuno deficiency virus’ OR aids OR ‘acquired immunodeficiency’ OR ‘acquired immunedeficiency’ OR ‘acquired immuno deficiency’ OR ‘acquired immune deficiency’) AND ('highly active antiretroviral therapy'/exp OR 'antiretrovirus agent'/exp OR 'Human immunodeficiency virus vaccine'/exp OR ‘human immunodeficiency virus vaccine’ OR ‘human immunodeficiency virus vaccines’ OR ‘hiv vaccine’ OR ‘hiv vaccines’ OR ‘aids vaccine’ OR ‘aids vaccines’ OR ‘anti hiv’ OR ‘anti human immunodeficiency’ OR ‘anti human immunedeficiency’ OR ‘anti human immuno deficiency’ OR ‘anti human immune deficiency’ OR ‘anti acquired immunodeficiency’ OR ‘anti acquired immunedeficiency’ OR ‘anti acquired immuno deficiency’ OR ‘anti acquired immune deficiency’ OR art OR haart OR antiretroviral* OR 'anti retroviral' OR ‘anti retrovirals’ OR antiretrovirus OR 'anti retrovirus') AND ('randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/exp OR ‘controlled clinical trial'/exp OR ‘controlled clinical trial (topic)'/exp OR rct:ti,ab OR rcts:ti,ab OR random*)

Cochrane Trials Database search

Title, abstract, keywords: (tuberculosis OR antitubercul* OR TB OR tuberculin)

AND

Title, abstract, keywords: (isoniazid* OR ipt)

AND

Title, abstract, keywords: (hiv OR "human immunodeficiency virus" OR "human immuno deficiency virus" OR "acquired immunodeficiency" OR "acquired immune deficiency" OR "acquired immuno deficiency" OR aids)

AND

Title, abstract, keywords: (antiretrovir* OR "anti retroviral" OR "anti retrovirus" OR haart OR art OR "reverse transcriptase inhibitor" OR "reverse transcriptase inhibitors")

AND

Search All Text: (random* OR RCT)

Conference abstracts

We searched for abstracts from the past four years of the Conference on Retroviruses and Opportunistic Infections (CROI), the annual meeting of the International AIDS Society (IAS), and The Union World Conference on Lung Health.

Variables requested from the trials

Table S1: Variables requested from studies		
Variable Name	**Type**	**Description**
Age	Continuous	Age in years
Gender	Categorical	Male, female, transgender
Treatment site	Categorical	Country location of trial
Enrollment Date	Date	Date
ART start date	Date	Date
Baseline CD4 count	Continuous	CD4 in cells/μL at trial enrollment
IPT assignment	Categorical	6 months, 12 months, or none
IPT start date	Date	Date
IPT completion date	Date	Date
Method of TB screening (enrollment)	Categorical	Participants were screened by TB symptom screen, chest x-ray, sputum smear, or sputum culture prior to initiation of IPT
Evidence of immune sensitization to TB	Categorical	Screening at enrollment is positive, negative, or not performed
Immune sensitization screening method	Categorical	Testing method is TST, IGRA, or not performed
TB disease	Binary	Participant did or did not develop definite or probable TB during observation
TB disease date	Date	Date
History of TB	Categorical	Participant did or did not have history of prior therapy for TB disease.
Hepatitis	Binary	Participant did or did not develop ALT elevation >2.5 times the upper limit of normal
Hepatitis Date	Date	Date
Death	Binary	Participant did or did not die during observation period
TB death	Binary	Participant did or did not die of TB during the observation period
Death date	Date	Date

Study definitions for incident TB

ART-IPT Study - Rangaka, et al.(1) Supplementary material.

Definite TB	Compatible clinical features plus one or both cultures is positive for Mtb
Probable TB	Compatible clinical or radiographic features plus one or both smears is positive for acid-fast bacilli (AFB) or histology positive for AFB or granulomatous disease on any specimen
Possible TB	Compatible clinical features with radiographic features
Not TB	If none of the conditions above are met
Notes: 1. Compatible clinical features include on or more of the symptoms or signs printed on the clinic case report form with or without any of the following: haemoptysis, shortness of breath, pleuritic chest pain, loss of appetite, extreme fatigue or lethargy, pallor or anaemia. 2. Compatible radiological features refers to films taken at the first assessment or during follow-up, up to 8 weeks since first presentation or until culture results are available. 3. Response to antibiotics refers to a clinical and/or radiological response assessed two to eight weeks after the first presentation. 4. The 2007 WHO diagnostic algorithm for extra-pulmonary TB was followed.	

REALITY – Hakim, et al. Protocol version 1.02.(2)

The REALITY trial followed WHO diagnostic criteria for HIV/AIDS Stage 4 and Stage 3 conditions. Final adjudication of endpoints was made by the Endpoint Review Committee, which was blinded to intervention group.

Definitive Diagnosis of Pulmonary TB	Isolation of M. tuberculosis on sputum culture or histology of lung biopsy (with compatible symptoms).
Clinical Diagnosis of Pulmonary TB	Chronic symptoms: (lasting at least 2–3 weeks) cough, haemoptysis, shortness of breath, chest pain, weight loss, fever, night sweats; AND - positive sputum smear OR - negative sputum smear; AND compatible chest radiograph (including but not restricted to upper lobe infiltrates, caritation, pulmonary fibrosist shrinkage. No evidence of extrapulmonary disease.
Definitive Diagnosis of Extrapulmonary TB	M. tuberculosis isolation or compatible histology from appropriate site or radiological evidence of miliary tuberculosis; (diffuse uniformly distributed small miliary shadows or micronodules on chest X-ray).
Clinical Diagnosis of Extrapulmonary TB	Systemic illness (such as fever, night sweats, weakness and weight loss). Other evidence for extrapulmonary or disseminated tuberculosis varies by site: Pleural, pericardia, peritoneal involvement, meningitis, mediastinal or abdominal lymphadenopathy or ostetis. Discrete peripheral lymph node Mycobacterium tuberculosis infection (especially cervical) is considered a less severe form of extrapulmonary tuberculosis.

TEMPRANO - Danel, et al.(3) Supplementary material.

Definitive TB	Clinical manifestations including signs, symptoms, and evolution suggestive of pulmonary and/or extra-pulmonary tuberculosis, AND - Positive culture for Mtb complex of a body fluid or tissue, OR

	- Typical caseous or granulomatous appearance of a histological sample
Probable TB	Clinical manifestations including signs symptoms, and evolution suggestive of pulmonary and/or extra-pulmonary tuberculosis, AND - Smear-positivity for acid-fast bacilli or typical appearance on immunofluorescence in a body fluid or tissue, OR - At least one of the following: (i) chest x-ray, CT scan, or MRI images showing new-onset upper lobe opacities, cavitational lesions, or miliary opacities highly suggestive of tuberculosis; (ii) lymphocytic pleural effusion; (iii) bone x-ray, CT, or MRI images suggestive of bone tuberculosis; (iv) abscessed peripheral lymphadenopathy. AND Significant improvement on anti-tuberculosis treatment
Possible TB	Clinical manifestations including signs, symptoms, and evolution suggestive of pulmonary and/or extra-pulmonary tuberculosis AND No criteria met for any other specific disease AND Significant improvement on anti-tuberculosis treatment

Supplementary Results

Risk of bias assessment

We assessed the risk of bias in each trial for the outcomes of incident TB, TB-specific mortality, all-cause mortality, and hepatotoxicity using the Cochrane Risk of Bias Assessment Tool for Randomized Trials, Version 2.0.(4) For each trial, we reviewed the study publication(s), supplementary materials, published protocol, and additional information provided by trial investigators.(1–3,5)

Table S2 – Risk of bias assessment

	Assessment	Summary Comments
Domain 1: Risk of bias arising from the randomization process		
ART-IPT	Low	No concerns.
REALITY	Low	No concerns.
TEMPRANO	Low	No concerns.
Domain 2: Risk of bias due to deviations from the intended interventions		
ART-IPT	Low	
REALITY	Some concerns	Co-interventions likely to affect TB (e.g. nutrition supplementation, cotrimoxazole) were balanced between the groups. There was sufficient concern for the outcome of all-cause mortality to remove this trial from that analysis. This was based on members of the enhanced prophylaxis group also receiving daily fluconazole and shorter-term azithromycin and albendazole. Additionally, a substantial portion of participants in the standard prophylaxis group at ¾ sites initiated IPT per national guidelines. This led to our decision to only include data from the Malawi site.
TEMPRANO	Low	
Domain 3: Missing outcome data		
ART-IPT	Low/some concerns	Risk of bias was low for outcomes of incident TB and all-cause mortality. Some concerns were noted with outcome of TB-specific mortality due to greater proportion of deaths with unknown cause (16/37) than TB deaths (8/37).
REALITY	Low/some concerns	Low risk of bias assessed for the outcomes of incident TB and all-cause mortality. Some concerns were noted about TB-specific mortality as more than twice as many deaths with unknown cause (88) were recorded as TB deaths (42).

TEMPRANO	Low/some concerns	Incident TB outcome may not have complete ascertainment after 30 months, but does not differ by arm. See sensitivity analysis Figure S2.
Domain 4: Risk of bias in measurement of outcome		
ART-IPT	Low	
REALITY	Low	Unblinded trial, though used standardized criteria for TB outcome assessment and had event validation committee.
TEMPRANO	Low	Unblinded trial, though used standardized criteria for TB outcome assessment and had event validation committee.
Domain 5: Risk of bias in selection of reported result		
ART-IPT	Low	Pre-specified analysis plan.
REALITY	Low	Pre-specified analysis plan.
TEMPRANO	Low	Pre-specified analysis plan.
Overall risk of bias assessment		
ART-IPT	Low	Low risk of bias for outcomes of incident TB, all-cause mortality, and hepatotoxicity. Elected not to pursue outcome of TB-specific mortality.
REALITY	Low	Low risk of bias for incident TB outcome in Malawi site. Use of IPT made other sites in eligible. Use of co-intervention made this trial ineligible for the all-cause mortality outcome.
TEMPRANO	Low	Low risk of bias. Further evaluation of incident TB outcome provided in sensitivity analysis.

Fig S1 – Cumulative hazard of TB by IPT with ART versus ART alone

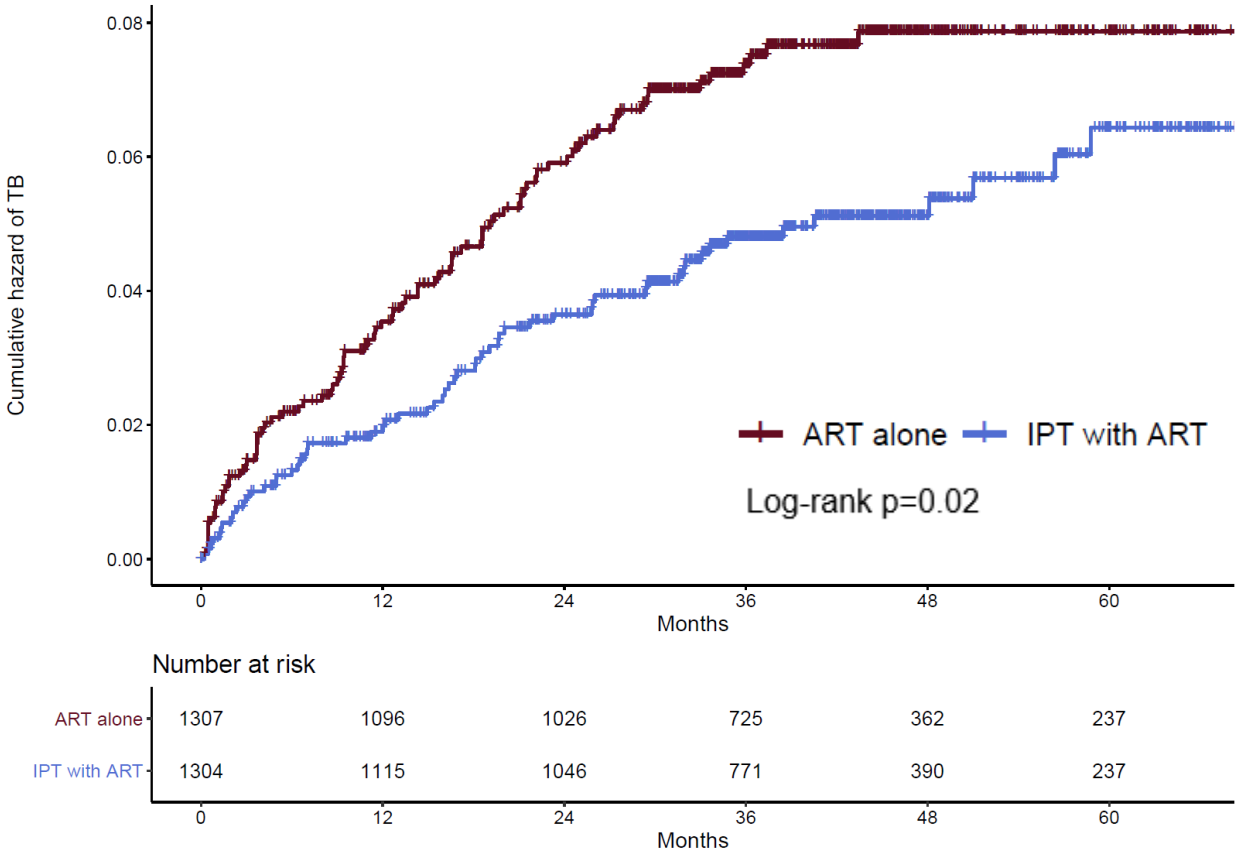
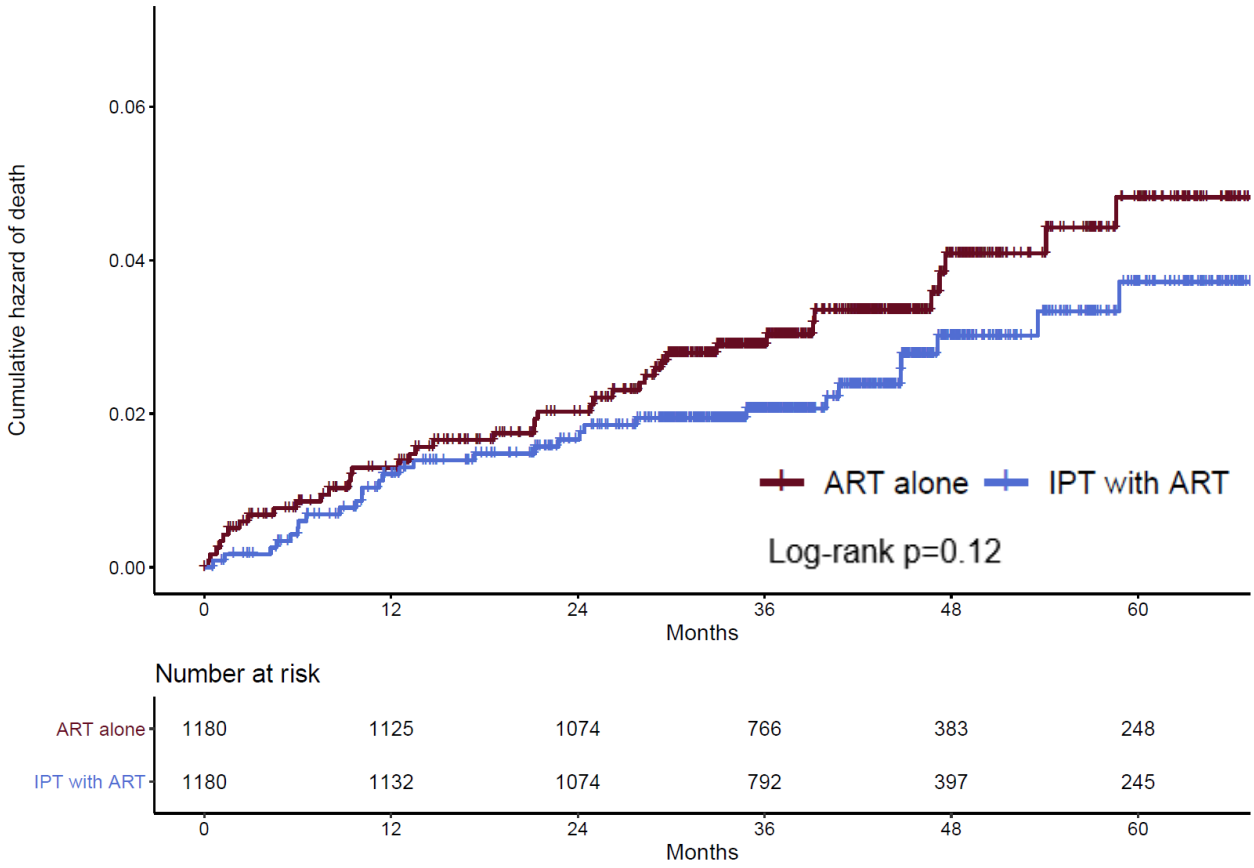


Fig S2 – Cumulative hazard of all-cause mortality by IPT with ART versus ART alone



Two-stage analysis to assess heterogeneity

Though the primary analysis was a single-stage meta-analysis, we performed a two-stage (aggregated) meta-analysis as an interim step to visualize heterogeneity between the study subsets and calculate the I^2 statistic. The hazard ratios for the individual studies for the outcomes of incident TB and all-cause mortality are shown in figures S3 and S4, respectively. Primarily, we assessed heterogeneity by visual inspection of the plots. The I^2 statistic for the outcome of incident TB was 0 (95% CI 0%-87·4%). The I^2 statistic for the outcome of all-cause mortality was 0 (95% CI 0%-99·7%). Interpretation of the I^2 statistic is limited with small numbers of studies.(6)

Figure S3 – Forest plot for included trial subsets for outcome of incident TB

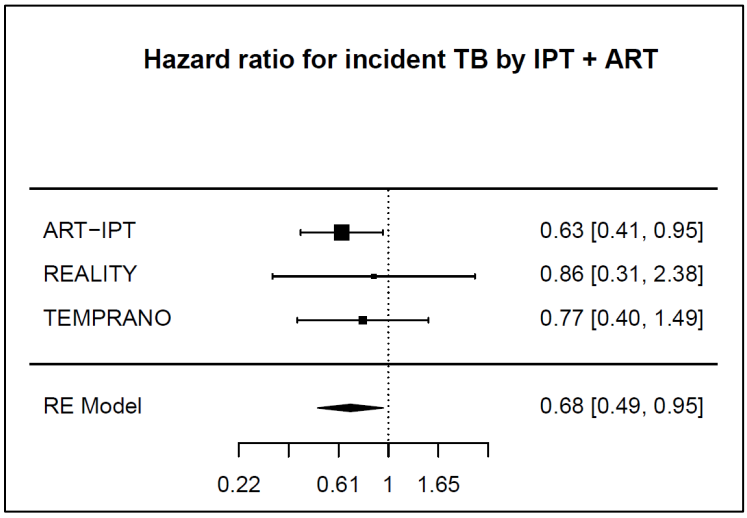


Figure S4 – Forest plot for included trial subsets for outcome of all-cause mortality

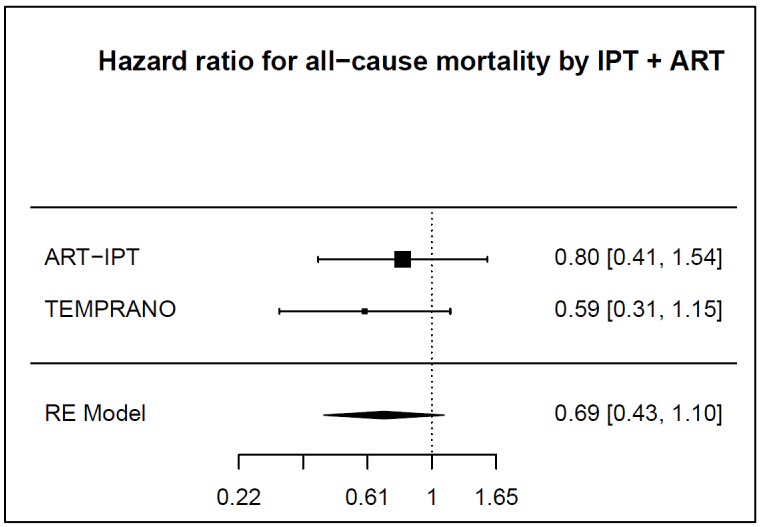


Table S3. Main effects table for incident TB (n=2611)

Group	N	Person-Years	TB events	TB incidence per 100k person-years	HR for TB	95% CI	p
Sex							0.11
Female	1938	6606.6	99	1483.4	Ref	---	
Male	673	1978.1	47	2376.0	1.33	0.93 – 1.90	
CD4 at enrolment							0.01
≥500	582	2166.0	16	738.7	Ref	---	
200 - 499	1107	4333.3	58	1338.5	1.64	0.93 – 2.88	
<200	780	1691.7	63	3724.1	2.45	1.30 – 4.63	
TST							0.82
Negative	552	1536.7	38	2472.8	Ref	---	
Positive	392	1120.4	26	2320.6	0.97	0.59 – 1.60	
IGRA							0.006
Negative	842	3272.5	37	1130.6	Ref	---	
Positive	549	1895.0	47	2480.2	1.90	1.23 – 2.94	
Indeterminate	89	307.2	9	2929.7	2.13	1.02 – 4.43	

TST = tuberculin skin test. IGRA = interferon gamma release assay.

Table S4. Main effects table for mortality (n=2362)

Group	N	Person-Years	Death events	Mortality rate per 100k person-years	HR for death	95% CI	p
Sex							0.05
Female	1821	6689.7	50	747.4	Ref	---	
Male	541	1941.9	24	1235.9	1.65	1.01 – 2.69	
CD4 at enrolment							0.11
≥500	582	2207.8	11	498.2	Ref	---	
200 - 499	1106	4457.7	45	1009.5	1.96	1.00 – 3.82	
<200	532	1560	16	1025.6	1.7	0.71 – 4.1	
TST							0.35
Negative	552	1588.5	19	1196.1	Ref	---	
Positive	392	1162.7	9	774.1	0.69	0.31 – 1.52	
IGRA							0.15
Negative	842	3341	33	987.7	Ref	---	
Positive	549	1989.7	15	753.9	0.69	0.37 – 1.29	
Indeterminate	89	319.7	6	1876.8	1.82	0.75 – 4.38	

TST = tuberculin skin test. IGRA = interferon gamma release assay.

Table S5 – Occurrence of liver injury by study and arm

	IPT + ART arm			ART alone			
	N	**ALT events***	**Proportion**	**N**	**ALT events***	**Proportion**	**p**
ART-IPT	662	21	3.17%	667	13	1.95%	0.17
REALITY Malawi[±]	124	12	9.68%	125	1	0.80%	0.001
TEMPRANO	518	10	1.93%	515	8	1.55%	0.81

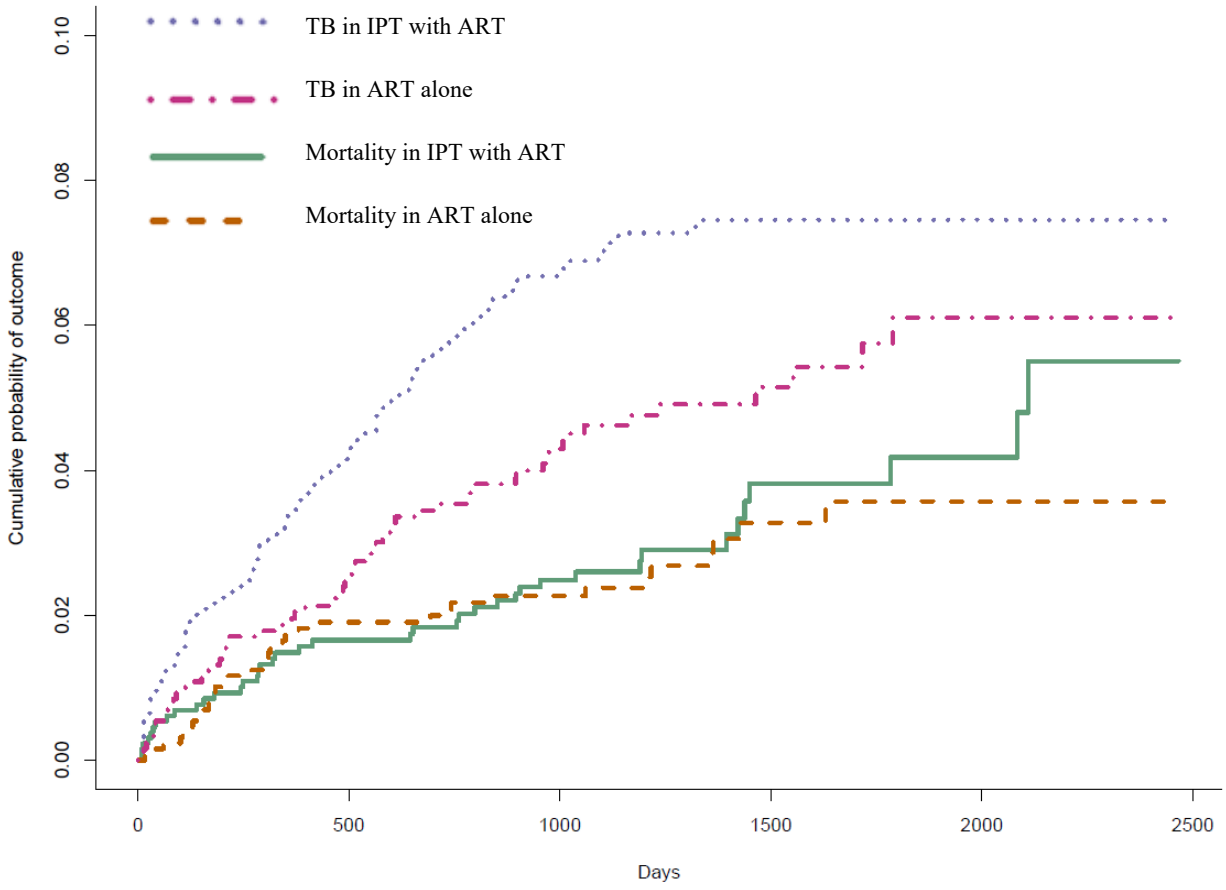
*ALT elevation ≥ 2.5 times the upper limit of normal

[±]Participants in the IPT + ART arm of the REALITY study also received single dose (400 mg) of albendazole, 5 days of azithromycin (500 mg once daily), 12 weeks of fluconazole (100 mg once daily) as part of an enhanced prophylaxis package.

Sensitivity analysis for competing risks survival approach

We completed an alternative survival analysis using a competing risks approach to evaluate the competing event of mortality for participants who died before developing TB on the outcome of incident TB. In our study, 75/2611 participants died before developing TB and could be classified as having a competing event from death. We calculated the cumulative incidence in the competing risks approaching using the R package 'cmprsk' and function 'cuminc'. Participants taking ART with IPT were significantly less likely to develop TB accounting for the competing risk of death (p=0.03, Gray modified chi-square test).

Figure S3 – Cumulative probability of outcomes in competing risks survival analysis



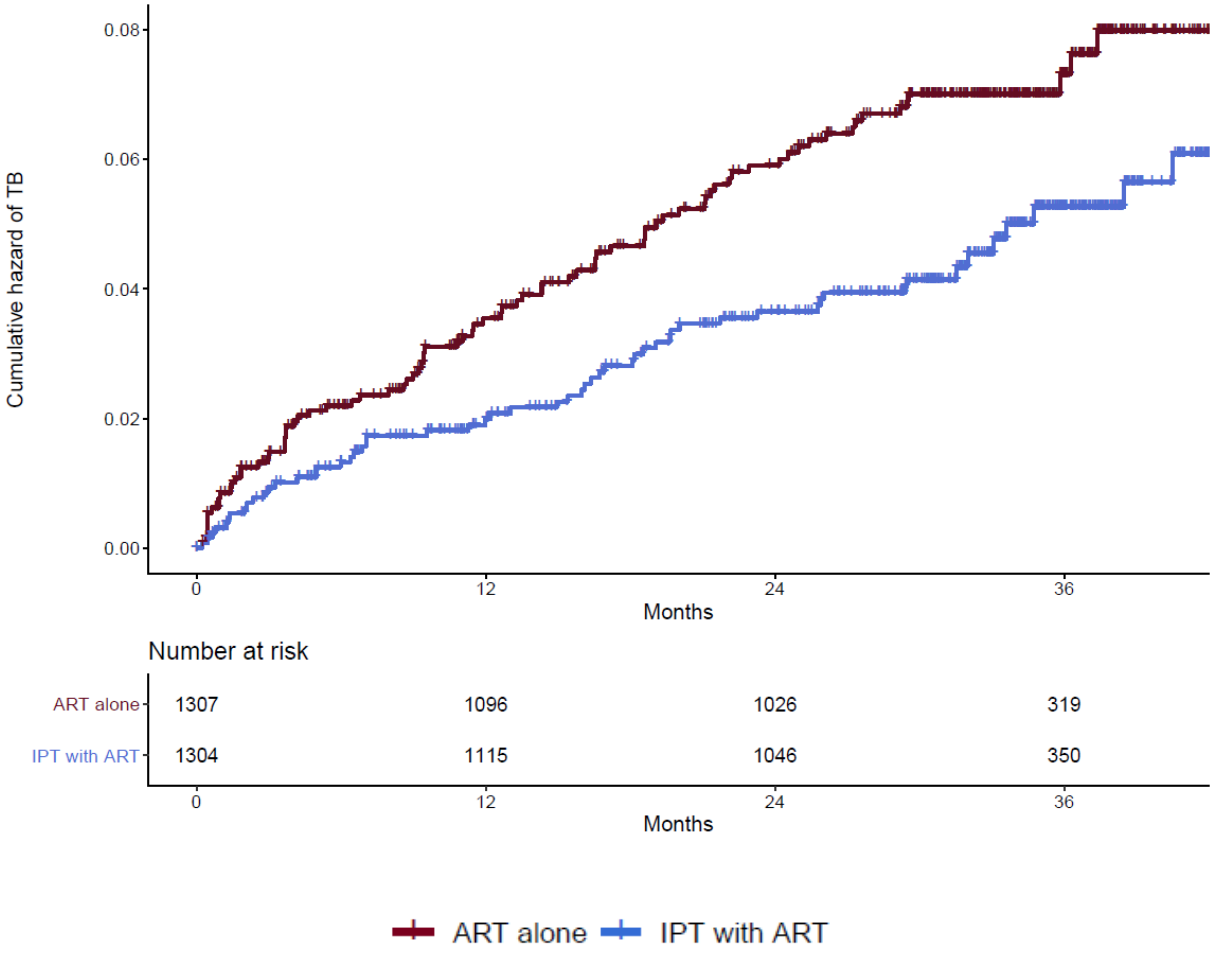
We implemented the Fine-Gray approach of calculating the subdistribution hazard with the function 'crr' in the package "cmprsk".(7,8) This subdistribution hazard for TB among participants taking IPT+ART was 0·684 (95% CI 0·492 – 0·951, p=0·024), which was very close to our approach using the Kaplan-Meier method. Noting the similarity

in estimates, we used the Kaplan-Meier method for the remainder of the analysis to maintain alignment with the methods applied in the primary studies and with the analysis of the mortality outcome.

Sensitivity analysis for duration of TEMPRANO follow-up

The primary study period for TEMPRANO ended after 30 months. Ascertainment of incident TB cases may not have been as complete in the period of extended follow-up as they were during the study period. In this sensitivity analysis, we censored TEMPRANO participants who did not develop TB after 30 months of follow-up. We analyzed these data together with the full datasets from the study by Rangaka et al and REALITY and found that the hazard ratio for IPT+ART was similar to the result reported using the full follow-up period. In this sensitivity analysis, the hazard ratio for TB in participants receiving IPT with ART versus ART along was 0·65 (95% CI 0·46 – 0·91, p=0·01), as compared to HR 0·68 (95% CI 0·49 – 0·95, p=0·02) in the full dataset.

Figure S4 – Cumulative hazard for incident TB with TEMPRANO follow-up limited to 30 months



Three study mortality analysis

The primary mortality analysis included data from the ART-IPT and TEMPRANO trials. We decided not to include data from the REALITY trial in the primary mortality analysis because the intervention package in the REALITY trial included other medications (fluconazole, azithromycin, and albendazole) in addition to IPT, which may have affected the risk of death in this trial but would be unlikely to affect the risk of incident TB. However, we include it here as an exploratory alternative to the primary analysis. In the three study analysis, the risk of all-cause mortality still tended to be lower in persons randomized to take IPT, but was not statistically significant (HR 0·79, 95% CI 0.53 – 1.12, p=0.24).

Relative hazard ratios across population sub-groups

Post-hoc power calculations across sub-groups are not recommended by the CONSORT statement that provides guidance for reporting of randomized trials.(9) However, we appreciate that group sizes may have affected the power of our analysis to detect differences in the benefit of IPT across sub-groups. As an alternative to sub-group power calculations, we present a table below of the 95% confidence limits for the interaction terms (ie the ratio of hazard ratios) for each of the subgroups.

Table S5 – ratio of hazard ratios for benefit of IPT to prevent incident TB across population subgroups

Sub-group	**Ratio of HR**	**95% CI for ratio of HR**
IPT among males (relative to females)	0.69	0.34 – 1.43
IPT among CD4<200 (relative to CD4>500	1.67	0.52 – 5.41
IPT among CD4 200-499 (relative to CD4>500	2.49	0.76 – 8.08
IPT among TST-negative (relative to TST-positive)	0.45	0.16 – 1.29
IPT among IGRA-negative (relative to IGRA-positive)	0.52	0.34 – 0.80
IPT among IGRA-indeterminate (relative to IGRA-positive)	1.10	0.54 – 2.26

For example, the interaction term for TST with IPT using TST-positive individuals as the reference group is 0.45 (0.16 – 1.29) for the outcome of incident TB. This means that we can exclude a hypothesis that TST-positive individuals have a benefit from IPT that is more than 1.3 times the benefit for TST-negative individuals, but that a greater benefit for TST-negative individuals or a small relatively greater benefit (up to 1.29 times) for TST-positive

individuals are potentially consistent with our findings. Similarly, with an estimate of 0.52 (0.34 – 0.80) we can exclude the hypothesis that IGRA-positive individuals had a greater benefit from IPT than IGRA-negative individuals to prevent incident TB.

Tests of the proportional hazards assumption

Figure S5 – Incident TB

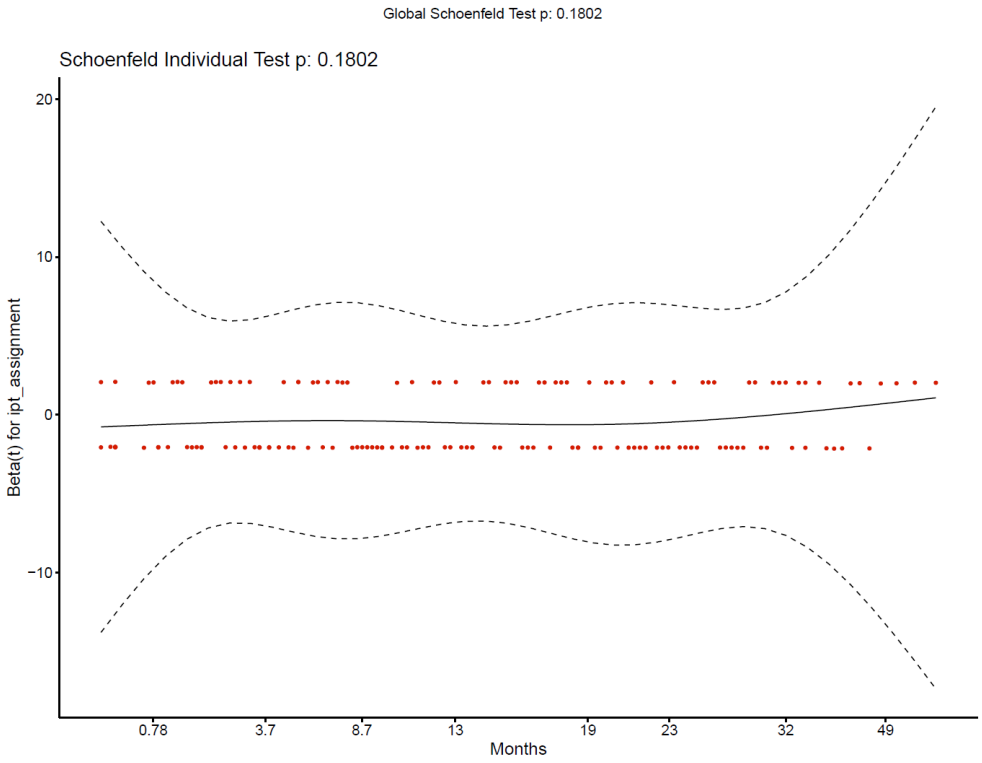
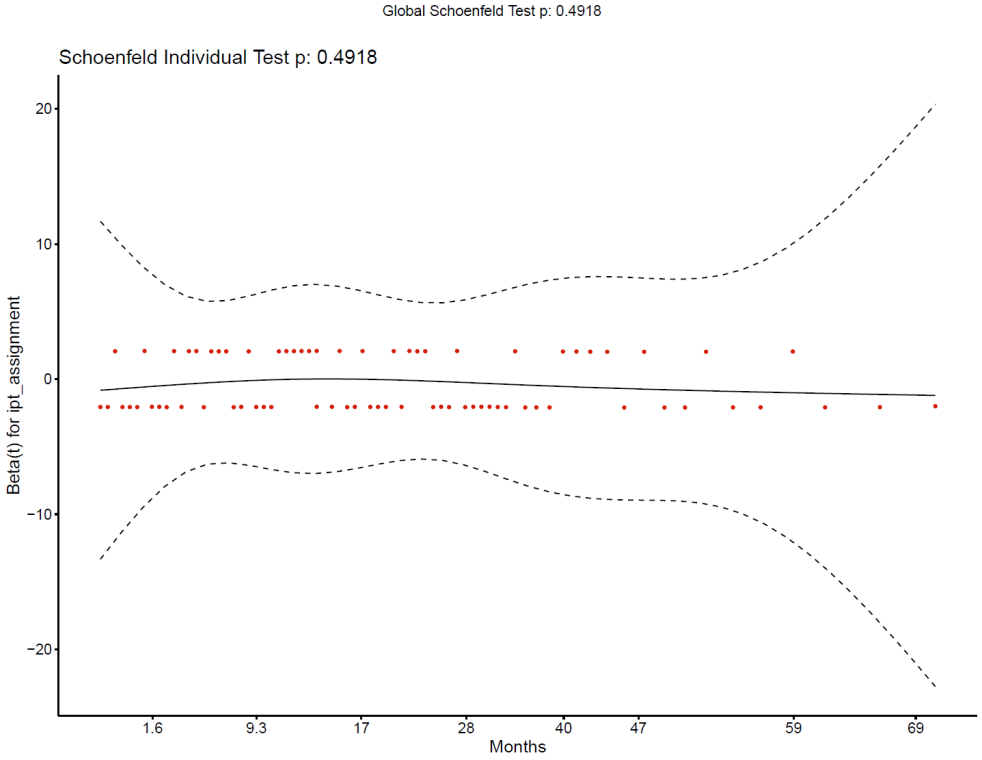


Figure S6 - Death



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