Recommendation on 36 months isoniazid preventive therapy to adults and adolescents living with HIV in resource-constrained and high TB- and HIV-prevalence settings

2015 update

World Health Organization

HIV TB

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This is an update to the 2011 WHO Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings

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Next update of these guidelines: The next update will be done in conjunction with the revision of the 2011 WHO "Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings".

Declaration and management of conflict of interest

All the contributors completed a WHO Declaration of Interest form. All stated declarations of interest were evaluated by three members of the Steering Group (the Legal Department of WHO was consulted when necessary) for the existence of possible financial conflicts of interest which warrant exclusion from membership of the Guidelines Development or Peer Review Groups or from the discussions as part of the guidelines development process. Intellectual conflict of interest was not considered grounds for exclusion from membership of the Guidelines Development Group as broader expertise on Latent TB Infection (LTBI) was the main criteria for selection and representation on the group; the group itself was felt to be large enough to overcome any potential intellectual conflict of interest. During the guidelines development process and the Guideline Development Group meeting, any emergence of intellectual conflict of interest was monitored by the Chairs and the Coordinator of the Secretariat, and any perceived intellectual conflict of interest was discussed with members of the Guidelines Development Group.

The following interests were declared:

WHO Guidelines Development Group:

Ibrahim Abubakar declared that his employer received grants from the National Institutes of Health (£2.7 million for the PREDICT study: Prognostic Evaluation of Interferon Gamma Release Assays (IGRAs) and Skin test in a cohort of 10 000 contacts and migrants) and the UK Department of Health (£900 000 for a randomized controlled trial to assess isoniazid-rifapentine compared to isoniazid-rifampicin on LTBI treatment completion and £490 000 for the Academic, Clinical & Enterprise (ACE) study, and detection of latent TB in emergency departments). He is currently the chair of the UK National Institute for Health and Care Excellence (NICE) guideline development group developing guidelines on TB which includes active and latent TB treatment. NICE pays his employer (University College London) for his time at about £500 a day. He was a member of the European Centre for Disease Prevention and Control (ECDC) guideline development group on IGRAs published in 2011, for which he did not receive any remuneration. He has written extensively on this subject including a recent commentary in The Lancet on LTBI in the UK.

Cynthia Bin-Eng Chee declared that she has attended meetings pertaining to IGRAs sponsored by Qiagen (1st meeting of Asia TB Experts Community, Chiba, Japan 13 May 2012 and the 2nd Meeting of Asia TB Experts Community, Bangkok, Thailand, July 2013) and University of California, San Diego (3rd Global IGRA Symposium, Waikoloa, Hawaii, January 2012) with an estimated overall value of US$ 4500 for travel and accommodation.

Richard Chaisson declared that he received remuneration for consulting on TB drug development from Vertex of US$ 2000 in 2012 one time only and received research grants from the National Institutes of Health, the Centers for Disease Control and Prevention (CDC) and the Gates Foundation of more than US$ 15 million which is ongoing.

Liz Corbett declared that her employer received research grants concerning the public health impact of combined TB prevention from Wellcome Trust grants.

Guy Marks declared that his employer received research grants (related to TB, though not specifically on LTBI) from the National Health and Medical Research Council of Australia.

Richard Menzies declared that he received research support from the Canadian Institutes of Health Research with a total grant related to latent TB infection – approximately C$ 6 million over a six-year period. The main research is a randomized control trial comparing 4 month-RIF to 9-month INH for LTBI (about C$ 1 million each year).

Surender Sharma declared that his employer received a research grant for “impact of HIV infection on latent TB among patients with HIV/TB co-infection” supported by the Department of Biotechnology, Ministry of Science & Technology, Government of India (US$ 133 197.56) for which the project work is over.

Timothy Sterling declared that he received remuneration from Sanofi for a one-day consultancy meeting (and preparation) at the Food and Drug Administration (FDA) to answer questions related to the CDC-sponsored Study 26 of the TB Trials Consortium where he was the protocol chair (US$ 3800 in 2012).

Peer Review Group:

Gavin Churchyard declared that he received research support grants for the following trials at the Aurum Institute: Rifaquin approximately €500 000 expired in 2011; Remox less than €200 000 which is ongoing; Thibela TB, US$ 32 million expired in 2012; evaluation of Expert MTB/RIF US$ 13 million which is ongoing; evaluation of TB/HIV integration US$ 250 000 expired in 2011.

Raquel Duarte declared that she received payments from 2011 to 2014 for lectures on TB screening in patients with immune mediated inflammatory diseases who are candidate for biological therapy from Pfizer, Abbot and Janssen.

Diane Havlir declared that she received support grants from the National Institutes of Health for research on TB.

Christopher Lange declared that he received remuneration from Celltrion Korea for consultation on the risk of TB related to treatment with bio similar TNF antagonists for one time in 2013.

Martina Sester declared that she received non-monetary support from Qiagen (formerly Cellestis) and Oxford Immunotech to perform investigator-initiated research studies, where the kits were in part provided free-of-charge by the two companies. She received travel support from Qiagen for presentation of the data in scientific meetings. She is a co-inventor for a patent application entitled "in vitro process for the quick determination of a patient's status relating to infection with *Mycobacterium tuberculosis*" (international patent number WO2011113953/A1).

Dalene von Delft declared that she received support for giving presentations or speeches at the International Union against TB and Lung Diseases Conferences in 2012 and 2013 from the Treatment Action Group (TAG) and United States Agency for International Development (USAID); support from Janssen Pharmaceuticals to attend the Leadership Summit Critical Path to TB Drug Regimens (CPTR); and, support from the American Society of Tropical Medicine and Hygiene (ASTMH)-AERAS to attend meetings.

Dominik Zenner declared that he is a co-author of one of the underpinning systematic reviews on LTBI treatment and also the head of the TB screening unit in Public Health England and has a professional interest in the subject matter.

All declarations of interest are available on electronic file at the WHO Global Tuberculosis Programme.

Executive summary

Human immunodeficiency virus (HIV) infection is the strongest risk factor for developing tuberculosis (TB) disease in those with latent or new *Mycobacterium tuberculosis* infection. TB is responsible for more than a quarter of deaths in people living with HIV. Isoniazid preventive therapy (IPT) is recognized as a key intervention for the prevention of TB among people living with HIV.

In 2011, the World Health Organization (WHO) issued "Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource constrained settings" and conditionally recommended the use of at least 36 months of IPT (as a proxy for lifelong or continuous treatment) for people living with HIV in high TB-prevalence and transmission settings, based on the results of unpublished studies. It was decided to update the evidence as the studies are now published, and explore whether the findings might require any change in the recommendation of lifelong IPT for people living with HIV.

The main objective of this update is to reassess the recommendation to provide IPT for 36 months to children and adults living with HIV, including pregnant women, those receiving antiretroviral therapy (ART), and those who have successfully completed TB treatment and are living in settings with high TB and HIV prevalence and transmission, based on the requirements of the WHO Guidelines Review Committee. One systematic review of the literature was conducted, restricted to randomized controlled trials, and a meta-analysis of all the different outcomes of interest was performed. The GRADE system was used for quality assessment of the body of evidence for each outcome and for going from evidence to recommendations. The recommendation was developed by a Guidelines Development Group composed of external content experts, national TB programme managers, academicians and representatives of patients groups and civil society, led by the WHO Guideline Steering Group. The External Review Group reviewed the draft of the guidelines and gave further contributions.

Based on this, the following conditional recommendation was made: "In resource-constrained settings with high TB incidence and transmission, adults and adolescents living with HIV, who have an unknown or positive tuberculin skin test (TST) status and among whom active TB disease has been safely ruled out, should receive at least 36 months of IPT. IPT should be given to such individuals regardless of whether or not they are receiving ART. IPT should also be given irrespective of the degree of immunosuppression, history of previous TB treatment, and pregnancy." The quality of evidence was rated as low. The conditionality of the recommendation was primarily due to the fact that implementation of continuous IPT requires considerations of TB epidemiology, health infrastructure, programmatic priorities and patient adherence.

1. Background and process

1.1 Background

Human immunodeficiency virus (HIV) infection is the strongest risk factor for developing TB disease in those with latent or new *Mycobacterium tuberculosis* infection. The risk of developing TB is approximately 30 times greater among people living with HIV than among those with no HIV infection *(1)*. TB is responsible for more than a quarter of deaths in people living with HIV. IPT is recognized as a key intervention for the prevention of TB among people living with HIV.

In 2011, WHO issued the "Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource constrained settings" *(2)*. This guideline strongly recommends providing at least six months of IPT for children and adults living with HIV, including pregnant women, those receiving ART, and those who have successfully completed TB treatment. It also conditionally recommends providing IPT for 36 months (as a proxy for lifelong or continuous treatment) to children and adults living with HIV in settings with high TB prevalence and transmission. The conditionality of the recommendation was based on the weakness of the evidence, which was based on unpublished data, feasibility concerns and potential adverse events. Following the 2011 WHO guidelines and the conditional recommendation on the 36 months of IPT for people living with HIV in high TB prevalence and transmission settings, new studies including randomized controlled trials were published necessitating an update of the recommendation *(3–5)*.

1.2 Scope of the update to the recommendation

The main objective is to reassess the 2011 recommendation to provide IPT for 36 months (as a proxy for lifelong or continuous treatment) to children and adults living with HIV, including pregnant women, those receiving ART, and those who have successfully completed TB treatment and are living in settings with high TB and HIV prevalence and transmission. As the 2011 recommendation on 36 months of IPT was based on unpublished data, it was decided to update the evidence as the studies are now published and explore whether the findings might require any change in the recommendation of lifelong IPT for people living with HIV.

1.3 Target audience for the update

This update is aimed at health-care workers providing care for people living with HIV, policy-makers and health programme managers working in the field of HIV and TB in resource-constrained settings with high TB and HIV prevalence. These guidelines are also intended for governments, nongovernmental organizations, donors and patient support groups who address HIV and TB.

1.4 Process of development of the guidelines

The update to this recommendation was conducted in parallel with the WHO guidelines development process on the management of latent TB infection. The following three groups were established to develop the guidelines in agreement with the WHO Guideline Review Committee's recommended process:

- The WHO Guideline Steering Group with the Global TB Programme, the HIV/AIDS Department, and the Department of Knowledge, Ethics and Research to lead the guideline development process;
- The Guidelines Development Group (hereafter known as the Panel) comprising external content experts, national programme managers, academics and representatives of civil society to provide inputs throughout all the stages of the guideline development process. Panel members were carefully selected to ensure relevant expertise, and geographic and gender balanced representation of both stakeholders and patient groups; and
- The External Review Group comprising individuals with expertise in HIV care, latent TB infection and TB/HIV co-infection to provide inputs and perspectives at selected stages of the guideline development process and to review the final draft of the guidelines.

The WHO Steering Group identified the following key question and developed the scoping document: In people living with HIV/AIDS, does prophylaxis with 36 months (or longer) of IPT versus six months of IPT decrease the likelihood of progression to active TB? The Panel reviewed the document and agreed with the WHO Steering Group regarding the scope of the update.

The table below shows the list of potential outcomes of interest, which were pre-defined for the question and were circulated to all members of the Panel. Each member of the Panel scored the importance of each outcome on a scale of 1 to 9 as follows: 1 to 3 to indicate an outcome considered not important; 4 to 6 to indicate an outcome considered important; 7 to 9 to indicate an outcome considered critical.

Outcomes	Relative importance (average)
Active TB incidence (presumptive, probable, confirmed)	9
Confirmed TB	9
Mortality	9
Progression of HIV disease	8
Adverse events	8
Adherence	7
TB drug resistance	7
Cost–effectiveness	7
Interval to active TB	6
Interval to death	6

The Panel met in person and also conducted meetings electronically. The meetings were co-chaired by a technical expert and a Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodologist. Recommendations were drafted taking into consideration the costs, feasibility, acceptability and values and preferences of the individuals and stakeholders, as well as the benefits/harms profile. Recommendations and their relative strengths were decided by consensus and when consensus could not be reached according to the judgment of the Chairs, open voting was used to arrive at a decision. Consensus was defined either as unanimous or majority agreement. A majority was defined by a proportion of more than 50% of those having the right to vote and expressing their vote. Additional inputs from the Peer Review Group were also obtained and incorporated. For definitions of strength of recommendations and evidence, please refer to the original WHO 2011 guidelines.

2. Recommendation

In resource-constrained settings with high TB incidence and transmission, adults and adolescents living with HIV, who have an unknown or positive tuberculin skin test (TST) status and among whom active TB disease has been safely ruled out, should receive at least 36 months of isoniazid preventive therapy (IPT). IPT should be given to such individuals regardless of whether or not they are receiving ART. IPT should also be given irrespective of the degree of immunosuppression, history of previous TB treatment, and pregnancy.

(Conditional recommendation, low quality of evidence).

Remarks: *People living with HIV in high TB incidence and transmission settings, regardless of their TST status, benefit more from IPT of 36 months or longer, compared to six-month IPT, with greater protective benefit in those with a positive TST. There is a significant additional benefit from longer-term IPT for those receiving ART. TST is encouraged whenever feasible, but it is not a pre-requisite for IPT. If TST is performed, those with a negative TST should not receive 36 months of IPT. Settings with high TB incidence and transmission should be defined by national authorities, taking into consideration the local epidemiology and transmission of both TB and HIV.*

2.1 Summary of the evidence

A systematic review was carried out and a meta-analysis of the three identified randomized controlled trials was performed (Annex 1). The number of events of the pre-specified outcomes was compared in those receiving continuous IPT and those who received a six-month IPT regimen or an equivalent one (isoniazid plus ethambutol). Data on population with "irrespective of TST" status obtained from the meta-analysis was assumed to be equivalent to the population "with unknown TST" status to draw the recommendation.

2.1.1 Incidence of active TB and mortality

In the population with "irrespective of TST" status, the incidence of active TB was significantly lower in the continuous IPT group (41 cases among 1509 individuals, 2.7%) compared to the control group (78 cases among 1659 individuals, 4.7%), (relative risk, RR, 0.62; 95% confidence interval, CI: 0.42–0.89). There was no difference in mortality (RR 0.87; 95% CI: 0.63–1.19) between the two groups.

2.1.2 Adverse events

A meta-analysis of adverse events was not performed due to the heterogeneity in the definition of side effects and reporting among the studies. One of the studies (Annex 1) reported significantly more grade 3 or grade 4 elevations in the aspartate and/or alanine aminotransferase levels in the continuous isoniazid group (RR 3.41; 95% CI: 2.28–5.09) *(5)*. The other two studies reported a non-significant increased risk for grade 3 or 4 adverse events in the continuous IPT group *(3, 4)*. The systematic review we performed identified five additional observational studies describing 36 months of IPT in persons living with HIV. No information on side effects was available in these studies.

2.1.3 Adherence

Adherence was not adequately defined and reported in the studies. Swaminathan et al. did not report information on adherence *(4)*. Samandari et al. found that high adherence to continued isoniazid treatment in participants with a positive tuberculin skin test was associated with the largest decrease in tuberculosis incidence *(3)*. In Martinson's et al study adherence was 83.8% in the 6-month–isoniazid group, compared to 60.4% in patients on 36 months treatment *(5)*.

2.1.4 Effect of TST

When the analysis was restricted to individuals with a positive TST, the protective effect on active TB was stronger (RR 0.51; 95% CI: 0.30–0.86); in those with a negative TST, the difference between the two treatment regimens was not statistically significant (RR 0.73; 95% CI: 0.43–1.26).

A reduction in mortality was also seen among TST-positive individuals (RR 0.50; 95% CI: 0.27–0.91) but not among TST-negative individuals (RR 1.29; 95% CI: 0.77–2.16).

2.1.5 Effect of concomitant use of IPT with ART

Samandari et al. study carried out in Botswana reported data on TB incidence according to the IPT group and duration of ART *(3)*. The results of this study showed additional protective benefit from IPT among people living with HIV receiving 360 days of ART and who were TST positive; in TST-negative persons, IPT had only a marginal beneficial effect in addition to ART.

2.1.6 Drug resistance

All three studies were reviewed to appraise whether 36 months of IPT leads to significant development of drug resistance compared to six months of IPT. Martinson's et al study reported resistance rates in both the continuous IPT and six-month IPT groups. They found one case of isoniazid resistance in 164 individuals (0.6%) receiving 36 months of IPT and 0 (0%) cases in 327 individuals receiving six months of IPT (RR 5.96; 95% CI: 0.24–146) *(5)*. The other two studies reported that the observed proportion of resistant cases among confirmed TB cases was similar to the expected rate *(3,4)*.

2.1.7 Cost–effectiveness of 36 months of IPT

Data on the cost–effectiveness of continuous IPT is limited. In a study from India *(6)* the incremental cost per year of life saved for people living with HIV (27% of whom were on ART), compared to no intervention, was estimated to be US$ 1,140 for six months of IPT and US$ 3120 for 36 months of IPT. In this study 36 months of IPT only provided one additional month of life; an increase from a projected life expectancy of 136.1 months to 137.1 months. Another study from Botswana *(7)* found that, compared to six months of IPT, treating TST-positive persons living with HIV with a 36-month IPT would result in an incremental cost of US$ 1282 per TB case averted and of US$ 1436 per death averted.

2.1.8 Conclusions on the evidence

In summary, these data show that, for people living with HIV in settings with high TB prevalence and transmission, continuous IPT reduced the risk of developing active TB by 38% compared to six-months of IPT. The effect was stronger in those with a positive TST (49% for active TB and 50% for death). In those with a negative TST, neither effect was significant.

Continuous IPT conferred significant additional protection to people living with HIV who are on ART. In the study reported by Samandari *(3)*, the effect appeared to be limited to TST-positive individuals. Additionally, the Panel also considered the results of a recently published study showing a significant benefit of administering 12-month IPT among TST-negative people living with HIV receiving ART in South Africa *(8)*.

There is insufficient evidence to indicate whether or not continuous use of isoniazid increases the risk of isoniazid resistance.

2.2 Balance of benefits and harms

After careful consideration of the benefits/harms balance, the Panel concluded by unanimous consensus that, for people living with HIV in settings of high TB prevalence and transmission, continuous IPT is beneficial and probably outweighs the risk of adverse events. Although not statistically significant, the Panel noted a reduction in TB incidence of 27% among TST-negative persons. The Panel concluded by majority agreement that there is benefit in providing IPT for 36 months or longer to people living with HIV regardless of their TST status in settings

of high TB prevalence and transmission. TST is encouraged whenever feasible and in this case continuous IPT should be limited to people living with HIV with a positive TST. Continuous IPT is recommended regardless of the ART status. The Panel underlined the importance of regular adverse event monitoring and measures to ensure a high level of treatment adherence and completion for people living with HIV who will receive continuous IPT depending on the national and local context.

2.3 Values and preferences of clients and health-care providers

The Panel noted that the current global implementation of six-month IPT for people living with HIV is very low *(1)*, and the provision of continuous IPT as a public health intervention is almost non-existent, even in settings with high TB prevalence and transmission. Concern was also expressed that treatment completion rates and adherence may be lower with longer treatment *(9-11)*. In addition, the Panel recognized that concerns about the development of resistance to isoniazid *(12)* as well as about the possible need for TST before starting continuous IPT *(13)*, are potential barriers to implementation. National TB and HIV programmes should consider the local epidemiology and health infrastructure context to identify and address these potential challenges. It was also noted that individual factors among people living with HIV should be considered prior to starting treatment.

2.4 Resource considerations

The Panel noted that the decision to extend the duration of IPT among people living with HIV to 36 months or longer, should include consideration of the availability and efficient use of resources. In addition the Panel stated the need for national programmes to consider the potential implications for additional human and financial resources necessary to implement continuous IPT compared to a six-month IPT regimen.

2.5 Conclusion

The Panel agreed to retain the conditional strength of the recommendation based on majority agreement. The conditionality of the recommendation was primarily due to the fact that implementation of continuous IPT requires considerations of TB epidemiology, health infrastructure and programmatic priorities.

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Annex 1: "Evidence to decision framework"

Problem:
Progression to active TB in people living with HIV/AIDS

Option:
Continuous IPT (operationalized as isoniazid for 36 months or longer)

Comparison:
Six months IPT

Setting:
High TB prevalence

Perspective:
Public health

Background: HIV is the strongest risk factor for developing TB disease in those with latent or new *Mycobacterium tuberculosis* infection. The risk of developing TB is approximately 30 times greater in people living with HIV than among those who do not have HIV infection. TB is responsible for more than a quarter of deaths in people living with HIV. IPT is a key public health intervention for the prevention of TB among people living with HIV.

In 2011, WHO issued the "Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource constrained settings". The guidelines included a strong recommendation to provide at least six months of IPT for children and adults living with HIV, including pregnant women, those receiving antiretroviral therapy (ART), and those who have successfully completed TB treatment. IPT for 36 months (as a proxy for lifelong or continuous treatment) was conditionally recommended in HIV prevalent settings with a high transmission of TB (as defined by national authorities) among people living with HIV. The guidelines also emphasized that a tuberculin skin test (TST) was not a requirement for initiating IPT in people living with HIV, although in some settings where it is feasible, it can help to identify those who would benefit most from IPT. As the 2011 recommendation on 36 months of IPT was based on two unpublished studies, it was decided to update the evidence as the studies are now published and explore whether the findings might require any change in the recommendation of lifelong IPT for people living with HIV.

Subgroup considerations: We also aimed to determine whether testing for latent TB infection (for example with TST) should be a requirement before starting continuous IPT in people living with HIV. In addition, we looked at the evidence of the effect of concomitant ART on the effect of continuous IPT.

<table>
<tr><th></th><th>CRITERIA</th><th>JUDGEMENTS</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>PROBLEM</td><td>Is the problem a priority?</td><td>No ☐ | Probably No ☐ | Uncertain ☐ | Probably Yes ☐ | Yes ☒ | Varies ☐
Detailed judgements</td><td>Among people living with HIV, TB is the most common cause of morbidity and mortality, and responsible for more than a quarter of deaths globally. Previous studies have shown that IPT for 6-12 months significantly reduces the risk of TB in HIV-infected individuals. However, evidence shows that the protective effect of IPT decreases with time particularly in settings with high TB tranmission. One hypothesis is that IPT of six months duration does not give protection because of continous reinfection.
We aimed to update the evidence on the duration and durability of the effect of IPT among people living with HIV. We aimed to find out whether continuous prophylaxis with isoniazid (operationalized as 36 months or more) decreases the likelihood of progression to active TB compared to IPT for 6–12 months.The critical outcomes of interest considered were the efficacy of IPT in preventing active TB, relapse, reinfection and toxicity.</td><td>The problem is expected to be limited to settings with high M. tuberculosis transmission. Recommendations may therefore only be applicable to these settings.</td></tr>
<tr><td>VALUES</td><td>Is there important uncertainty or variability about how much people value the main outcomes?</td><td>Important uncertainty or variability ☐ | Possibly important uncertainty or variability ☐ | Probably no important uncertainty or variability ☐ | Probably Yes ☐ | No important uncertainty or variability ☒ | No known undesirable outcomes ☐
Detailed judgements</td><td>The relative importance or values of the main outcomes of interest:
<table><tr><th>Outcome</th><th>Relative importance</th><th>Certainty of the evidence</th></tr><tr><td>Active TB</td><td>Critical</td><td>Low</td></tr><tr><td>Confirmed TB</td><td>Critical</td><td>Low</td></tr><tr><td>Death due to TB</td><td>Critical</td><td>Low</td></tr><tr><td>Adverse events</td><td>Critical</td><td>Very low</td></tr></table></td><td>No additional considerations</td></tr>
</table>

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
BENEFITS & HARMS OF THE OPTIONS	**What is the overall certainty of the evidence of effectiveness?**	No included studies ☐ | Very low ☐ | Low ☒ | Moderate ☐ | High ☐ **Detailed judgements**	**Summary of findings: [Comparison]** **Risk population:** 6 months of IPT vs Continuous IPT **Difference (x 1,000) (95% C.I.) / Pooled estimate risk ratio (range) / Certainty of the evidence (GRADE):** Active TB: 78/1659 vs 41/1509; 18 (5–27) less; RR 0.62 (0.42 to 0.89); Low Confirmed TB: 28/671 vs 10/503; 20 less (31 less – 4 more); RR 0.52 (0.25 to 1.09; Low Death: 88/1660 vs 67/1509; 7 less (20 less – 10 more); RR 0.87 (0.63 to 1.19); Low Death due to TB: 8/1333 vs 4/1345; 3 less (5 less – 4 more); RR 0.52 (0.17 to 1.64; Low Adverse events: – vs – ; – ; – ; – ; See additional considerations	**Adverse events** In the BOTUSA trial there were 21 (2.1%) grade 3 or 4 adverse events in 989 controls and 27 (2.7%) grade 3 or 4 adverse events in 1006 participants in the 36-month IPT group (RR 1.26, 95% CI: 0.72-2.22) (Samandari, 2011). In the India trial (Swaminathan et al. 2011) there were 11 cases of adverse drug reactions in both groups. Grade 3 or 4 adverse events were reported in 4 (1.2%) of 344 control subjects and 8 (2.4%) of 339 subjects in the 36-month IPT group (RR 2.03; 95% CI: 0.83–2.30). For the Soweto trial Martinson et al. reported grade 3 or grade 4 elevations in aspartate or alanine aminotransferase levels. They found 31 (9.5%) grade 3 or 4 elevations in 327 control subjects and 53 (32%) in 164 participants in the continuous IPT group (RR 3.41; 95% CI: 2.28–5.09).
	How substantial are the desirable anticipated effects?	Don't know ☐ | Not important ☐ | Somewhat important ☐ | Moderately important ☒ | Very important ☐ | Varies ☐ **Detailed judgements**		
	How substantial are the undesirable anticipated effects?	Don't know ☐ | Very important ☐ | Moderately important ☒ | Somewhat important ☐ | Not important ☐ | Varies ☐ **Detailed judgements**		
	Do the desirable effects outweigh the undesirable effects?	No ☐ | Probably No ☐ | Uncertain ☐ | Probably Yes ☒ | Yes ☐ | Varies ☐ **Detailed judgements**		
RESOURCE USE	**How large are the resource requirements?**	Large costs ☐ | Moderate costs ☒ | Small ☐ | Moderate savings ☐ | Large savings ☐ | Varies ☐ **Detailed judgements**	No evidence on resource requirements collected.	No additional considerations.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	**How large is the incremental cost relative to the net benefit?**	Very large ICER ☐ | Large ICER ☐ | Moderate ICER ☒ | Small ICER ☐ | Savings ☐ | Varies ☐ **Detailed judgements**	In a study from India (Pho et al. 2012) the incremental cost per year of life saved for persons living with HIV (27% on ART), compared to no intervention, was estimated to be US$ 1140 and US$ 3120 for six months and 36 months of IPT, respectively. However, it should be noted that the 36-month IPT model only provided one additional month of life, an increase from a projected life expectancy of 136.1 months to 137.1 months. Another study (Gupta et al. 2013) found that, compared to six months IPT, treating TST-positive persons living with HIV in Botswana with 36 months of IPT would result in an incremental cost of US$ 1282 per TB case averted and US$ 1436 per death averted. A modelling study (Smith et al. 2011) evaluating the different strategies to prevent HIV-associated TB found that the strategy with 90% ART coverage, TB infection control (IC), intensified TB case finding (ICF)/IPT for 36 months, and Gene-Xpert laboratory diagnosis for TB case finding averted the most TB cases at the lowest cost with an incremental cost–effectiveness ratio of US$ 5547 per TB case averted compared with the base case (55% ART coverage and TB screening using cough).	No additional considerations.
EQUITY	**What would be the impact on health inequities?**	Increased ☐ | Probably increased ☐ | Uncertain ☐ | Probably reduced ☒ | Reduced ☐ | Varies ☐ **Detailed judgements**	No evidence collected.	The Guideline Development Group/Panel recommends considering possible impacts on health inequities of IPT for all people living with HIV versus those people living with HIV who are TST positive.
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	No ☐ | Probably No ☐ | Uncertain ☐ | Probably Yes ☒ | Yes ☐ | Varies ☐ **Detailed judgements**	No evidence collected.	The number of programmes providing TB preventive therapy in people living with HIV has been low. The following reasons are often given for not providing (continuous) IPT: low completion rates (adherence may particularly be a problem in prolonged treatment), and the creation of resistance against the drugs used for prophylaxis (key is to exclude active TB before starting IPT). A potential third barrier may be the need to test for latent TB infection if this is a requirement before starting IPT.
FEASIBILITY	**Is the option feasible to implement?**	No ☐ | Probably No ☐ | Uncertain ☐ | Probably Yes ☒ | Yes ☐ | Varies ☐ **Detailed judgements**	No evidence collected.	TB and HIV programmes are increasingly being integrated. Since health-care workers frequently monitor HIV-positive individuals on ART, it may be relatively easy to add the management of IPT. This would involve screening for active TB, monitoring adverse events, and monitoring adherence. HIV-positive individuals not (yet) on ART are also monitored, providing opportunities to offer continuous IPT.

SUMMARY OF JUDGMENTS					
Criteria	Favours 36 months of IPT	Probably favours 36 months of IPT	Choose either 36 months of IPT or six months of IPT	Probably favours six months of IPT	Favours six months of IPT
Balance of effects	☐	☒	☐	☐	☐
Problem	☐	☐	☒	☐	☐
Values	☐	☒	☐	☐	☐
Certainty of the evidence of effects	☐	☒	☐	☐	☐
Resource use	☐	☐	☒	☐	☐
Equity	☐	☒	☐	☐	☐
Acceptability	☐	☐	☐	☐	☐
Feasibility	☐	☐	☐	☒	☐

Type of recommendation	We recommend 36 months of IPT	We suggest 36 months of IPT	We suggest using either 36 months of IPT or six months of IPT	We suggest six months of IPT	We recommend six months of IPT
	☐	☒	☐	☐	☐
Recommendation	**In resource-constrained settings with high TB incidence and transmission adults and adolescents living with HIV, who have an unknown or positive tuberculin skin test (TST) status, and among whom active TB disease has been ruled out, should receive at least 36 months of isoniazid preventive therapy (IPT). IPT should be given to such individuals regardless of whether or not they are receiving ART. IPT should also be given irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy.**				
Subgroup considerations	**TST** Prophylaxis with isoniazid for 36 months or longer reduced TB incidence in people living with HIV by 38% compared to IPT for six months. Though not significant, prolonged IPT also seemed to reduce the incidence of confirmed TB and death due to TB. In those with confirmed latent TB infection (as measured by a TST >5 mm), continuous IPT significantly reduced the risk of active TB (by 49%) and death (by 50%). In those with a negative TST, none of the findings were significant. These findings are consistent with those from a recent systematic review that assessed various treatment options for latent TB infection in HIV-infected individuals (Akolo et al. 2010). They found that in TST-positive individuals any preventive treatment reduced the risk by 62% (RR 0.38; 95% CI: 0.25–0.57). There was no evidence of effect on individuals with a negative TST (RR 0.89; 95% CI: 0.64–1.24). Contradicting these results, a recent study that compared 12 months IPT with placebo in HIV-positive individuals on ART found a significant effect of IPT on the rate of all TB in those who were TST negative (adjusted Hazard Ratio (HR) 0.43; 95% CI: 0.21–0.86), but not in those who were TST positive (adjusted HR 0.86; 95% CI: 0.37–2.0) (Rangaka et al. 2014). The most likely explanation for TST negatives not benefitting as much from IPT is that they are not infected with *M. tuberculosis*. However, Rangaka and co-workers mentioned that many negative TST results in HIV-infected individuals in areas with a high TB prevalence are likely to be false negatives, especially in those with lower CD4-counts. A study in Uganda reported a high negative to positive TST conversion rate of 30.2/100 person-years in the first six months after starting ART (Kirenga et al. 2013). **ART** Only the BOTUSA trial (Samandari, 2011) reported data on TB incidence according to the IPT group and ART duration. The results of this study showed that in TST positives 36 months of IPT provided a 46% further reduction in TB incidence compared to six months of IPT, in those receiving 360 days ART (reduction in TB incidence is 50% with six months IPT and 96% with 36 months IPT, both compared to a group receiving no ART and six months IPT). On the contrary, in TST-negative persons, 36 months of IPT provided only a 4% further reduction in TB incidence on top of the 50% reduction achieved by ART (and six months IPT), (reduction in TB incidence is 50% in those on six months IPT and 54% in those on 36 months IPT, both compared to a group receiving no ART and six months IPT). Evidence from a recently published study showed that HIV-infected individuals concurrently receiving ART significantly benefitted from 12 months IPT compared to placebo, regardless of TST or interferon-gamma release assay (IGRA) status (HR 0.63; 95% CI: 0.41–0.94) (Rangaka et al. 2014). Together this seems to indicate that there is a significant additional benefit from longer-term IPT for people living with HIV and receiving ART in high TB-incidence areas.				

Implementation considerations	The main implementation consideration is knowing in which settings long-term IPT would be of benefit. Implementation of long-term IPT should possibly be restricted to high burden TB settings such as those included in the systematic review (2012 prevalence of TB per 100,000 in India: 230 (155–319), Botswana: 343 (157–600), South Africa: 857 (305–1685). Six months IPT in HIV-positive individuals with a positive TST was shown to be effective in preventing TB up to seven years after cessation of IPT in the medium- burden TB setting of Rio de Janeiro in Brazil (2012 prevalence of TB per 100 000 in Brazil: 59 (25–107). Although this study reported an initial increase in TB risk immediately after cessation of IPT, there was no increase over the seven-year follow-up period (Golub et al. 2014). In moderate TB incidence settings, six months of IPT may be robust and sufficient to prevent TB in HIV-infected individuals.
Monitoring and evaluation considerations	To evaluate whether the revised monitoring and evaluation recommendation for IPT in people living with HIV is applicable to the 36 months of IPT.
Research priorities	**Eligibility criteria** • A new point-of-care test to identify those with active TB, latent TB infection and those not infected with *M. tuberculosis*, with a particular emphasis on new diagnostics for children. • The role of IGRA in people living with HIV who are infected with *M. tuberculosis* with or without active TB, with information about the association between performance of IGRA and immune status. • The use of TST in people living with HIV and receiving ART, with a particular emphasis on the frequency of performing TST to determine immune reconstitution and/or boosting in those who were initially TST negative. **Preventive treatment for TB** • Evaluate benefits and harms of rifamycin-containing regimens for TB preventive therapy in people living with HIV in resource-constrained settings with high HIV and TB prevalence. • Co-formulate a fixed-dose combination of isoniazid and vitamin B6 with co-trimoxazole along with antiretrovirals, and evaluate the efficacy and effectiveness of such fixed-dose combinations. • Evaluate the efficacy and feasibility of long-term IPT in HIV-positive children. • Study the efficacy and adverse events of long-term IPT in people with HIV and hepatitis C virus (HCV) co-infection. • Determine optimal timing for initiation of long-term IPT in relation to initiation of ART. • Determine if there is value in discontinuing lifelong IPT after immune reconstitution. • Undertake modelling studies to estimate the risks and benefits of long-term IPT – key considerations should include the incidence and prevalence of HIV and TB, risk for TB by immune status, impact of ART on prevention of both HIV and TB, added benefit of long-term IPT, optimum duration of IPT, prevalence of isoniazid and rifampicin resistance, immune status and TST status. **Operational research** • Study potential limitations of long-term IPT in populations with a high prevalence of isoniazid-resistant TB. • Determine the risks and benefits of administering isoniazid (in error) to undiagnosed people with active TB. • Ascertain the effectiveness of long-term IPT programmes in resource-limited settings; cost–effectiveness and cost–benefit from the perspective of health systems and patients. • Determine the use of long-term IPT for special populations: benefits/duration for health-care workers living with HIV; frequency of screening; benefits for TST-negative health-care workers; HIV-exposed children. • Determine operationalization of short-term and lifelong IPT with a particular focus on monitoring programmes and individuals (i.e. clinical status and adherence). • Undertake population-based drug-resistance surveillance to determine the impact of long-term IPT programmes on drug-resistant TB in the community, including increases or decreases in mono-isoniazid and mono-rifampicin resistance, and multidrug-resistant TB. • Evaluate the best national programmes or services to lead the implementation of long-term IPT (e.g. HIV, maternal and child health (MCH), TB, all programmes). • Ensure optimal delivery of long-term IPT and other HIV care for special groups including women and children.

Evidence profile

Among those with confirmed, probable or possible TB disease, preventive chemotherapy reduces the overall risk of developing TB by 38% (RR 0.62; CI: 0.42–0.89). For those who were TST positive, the reduction in confirmed, probable or possible TB increased to 49% (RR 0.51; 95% CI: 0.3–0.86). Although not statistically significant, the reduction among TST-negative persons was 27% (RR 0.73; 95% CI: 0.43–1.26).

Author(s): Saskia den Boon
Date: 2014-04-28
Question: Should continuous IPT versus six-month IPT be used for TB prevention in people living with HIV, irrespective of TST?
Settings: South Africa, Botswana, India
Bibliography: Martinson et al. 2011, Samandari et al. 2011, Swaminathan et al. 2012

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous IPT	Six-month IPT	Relative (95% CI)	Absolute		
Active TB (confirmed, probable, possible), (follow-up 30–47 months;1 assessed with culture, smear, signs and symptoms of TB + response to treatment)												
3	Randomized trials	serious[2]	no serious inconsistency	serious[3,4,5]	no serious imprecision	none	41/1509 (2.7%)	78/1659 (4.7%)	RR 0.62 (0.42 to 0.89)	18 fewer per 1000 (from 5 fewer to 27 fewer)	⨁⨁◯◯ LOW	CRITICAL
								2%		8 fewer per 1000 (from 2 fewer to 12 fewer)		
								50%		190 fewer per 1000 (from 55 fewer to 290 fewer)		
Confirmed TB (follow-up 30–47 months; assessed with culture positive for M.tuberculosis												
2	Randomized trials	serious[6]	no serious inconsistency	serious[3,5]	no serious imprecision	none	10/503 (2%)	28/671 (4.2%)	OR 0.52 (0.25 to 1.09)	20 fewer per 1000 (from 31 fewer to 4 more)	⨁⨁◯◯ LOW	CRITICAL
								2%		9 fewer per 1000 (from 15 fewer to 2 more)		
								50%		158 fewer per 1000 (from 300 fewer to 22 more)		
Death (follow-up 30–47 months; assessed with clinical or verbal autopsy, hospital records, or death certificates)												
3	Randomized trials	serious[6]	no serious inconsistency	serious[3,4,5]	no serious imprecision	none	67/1509 (4.4%)	88/1660 (5.3%)	RR 0.87 (0.63 to 1.19)	7 fewer per 1000 (from 20 fewer to 10 more)	⨁⨁◯◯ LOW	CRITICAL
								2%		3 fewer per 1000 (from 7 fewer to 4 more)		
								50%		65 fewer per 1000 (from 185 fewer to 95 more)		
Death due to TB (follow-up median 30–36 months; assessed with clinical or verbal autopsy or hospital records)												
2	Randomized trials	serious[7]	no serious inconsistency	serious[3]	no serious imprecision	none	4/1345 (0.3%)	8/1333 (0.6%)	OR 0.52 (0.17 to 1.64)	3 fewer per 1000 (from 5 fewer to 4 more)	⨁⨁◯◯ LOW	CRITICAL
								0.1%		0 fewer per 1000 (from 1 fewer to 1 more)		
								15%		66 fewer per 1000 (from 121 fewer to 74 more)		

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous IPT	Six-month IPT	Relative (95% CI)	Absolute		
Tuberculosis or death (follow-up 30–47 months; assessed with all TB (confirmed, probable, possible)												
3	Randomized trials	serious[2]	no serious inconsistency	serious3[4,5]	no serious imprecision	none	107/1509 (7.1%)	160/1660 (9.6%)	RR 0.76 (0.6 to 0.96)	23 fewer per 1000 (from 4 fewer to 39 fewer)	⨁⨁◯◯ LOW	CRITICAL
								2%		5 fewer per 1000 (from 1 fewer to 8 fewer)		
								50%		120 fewer per 1000 (from 20 fewer to 200 fewer)		
Adverse events – not reported												
0	–	–	–	–	–	none	–	–	–	–		CRITICAL
Adherence – not reported												
0	–	–	–	–	–	none	–	–	–	–		IMPORTANT

[1] Median follow-up period varied from 2.5 years (30 months) in the 36 months isoniazid arm and 2.6 years in the 6 months isoniazid plus ethambutol arm in the Swaminathan et al. 2012 study, and 3.9 years (47 months) for both the continuous and six-month isoniazid groups in the Martinson et al. 2011 study. Median follow-up was not reported for the Samandari et al. 2011 study but is probably close to 36 months.

[2] Swaminathan et al. 2012 and Martinson et al. 2011 studies were not blinded, and the allocation concealment in the Samandari et al. 2011 study was not clearly described and might have led to selection bias.

[3] The control group in the Swaminathan et al. 2012 study received 300 g isoniazid + 800 g ethambutol.

[4] Differences in included patient population: Martinson et al. 2011 excluded patients eligible for ART; median CD4 count at baseline was 484 cells/mm3. In Samandari et al. 2011 study 2% were on ART before enrolment and 47% were on ART by month 36. Median CD4 count at baseline was 297 cells/mm3. Swaminathan et al. 2012 study included ART-naïve patients with a median CD4 count of 325 cells/mm3.

[5] Martinson et al. 2011 study included only patients with positive TST (> 5 mm).

[6] Martinson et al. 2011 and Swaminathan et al. 2012 studies were not blinded.

[7] Swaminathan et al. 2012 study was not blinded, and the allocation concealment in the Samandari et al. 2011 study was not clearly described and might have led to selection bias.

Author(s): Saskia den Boon
Date: 2014-02-19
Question: Should continuous IPT versus six-month IPT be used for TB prevention in people living with HIV who have a positive TST (> 5 mm)?
Settings: South Africa, Botswana, India
Bibliography: Martinson et al. 2011, Samandari et al. 2011, Swaminathan et al. 2012

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous IPT	Six-month IPT	Relative (95% CI)	Absolute		
Active TB (confirmed, probable, possible) (follow-up 30–47 months;1 assessed with culture, smear, signs and symptoms of TB + response to treatment)												
3	Randomized trials	serious[2]	no serious inconsistency	serious[3,4]	no serious imprecision	none	18/548 (3.3%)	47/684 (6.9%)	RR 0.51 (0.3 to 0.86)	34 fewer per 1000 (from 10 fewer to 48 fewer)	⨁⨁◯◯ LOW	CRITICAL
								2%		10 fewer per 1000 (from 3 fewer to 14 fewer)		
								50%		245 fewer per 1000 (from 70 fewer to 350 fewer)		
Confirmed TB (follow-up 30–47 months; assessed with culture positive for MTB)												
2	Randomized trials	serious[5]	no serious inconsistency	serious[3]	no serious imprecision	none	8/296 (2.7%)	25/468 (5.3%)	OR 0.51 (0.22 to 1.14)	25 fewer per 1000 (from 41 fewer to 7 more)	⨁⨁◯◯ LOW	CRITICAL
								2%		10 fewer per 1000 (from 16 fewer to 3 more)		
								50%		162 fewer per 1000 (from 320 fewer to 33 more)		
Death (follow-up 36–47 months; assessed with clinical or verbal autopsy, hospital records, or death certificates)												
2	Randomized trials	serious[6]	no serious inconsistency	serious[7]	no serious imprecision	none	13/416 (3.1%)	38/543 (7%)	RR 0.5 (0.27 to 0.91)	35 fewer per 1000 (from 6 fewer to 51 fewer)	⨁⨁◯◯ LOW	CRITICAL
								2%		10 fewer per 1000 (from 2 fewer to 15 fewer)		
								50%		250 fewer per 1000 (from 45 fewer to 365 fewer)		
Death due to TB (follow-up mean 36 months; assessed with clinical or verbal autopsy or hospital records)												
1	Randomized trials	no serious risk of bias[8]	no serious inconsistency	no serious indirectness	serious[9]	none	0/252 (0%)	3/989 (0.3%)	OR 0.56 (0.03 to 10.84)	1 fewer per 1000 (from 3 fewer to 29 more)	⨁⨁⨁◯ MODERATE	CRITICAL
								2%		0 fewer per 1000 (from 1 fewer to 10 more)		
								50%		60 fewer per 1000 (from 145 fewer to 507 more)		

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous IPT	Six-month IPT	Relative (95% CI)	Absolute		
Tuberculosis or death (follow-up median 36–47 months; assessed with all TB (confirmed, probable, possible))												
2	Randomized trials	serious[6]	no serious inconsistency	serious[7]	no serious imprecision	none	24/416 (5.8%)	67/543 (12.3%)	RR 0.51 (0.33 to 0.79)	60 fewer per 1000 (from 26 fewer to 83 fewer)	⨁⨁◯◯ LOW	CRITICAL
								2%		10 fewer per 1000 (from 4 fewer to 13 fewer)		
								50%		245 fewer per 1000 (from 105 fewer to 335 fewer)		
Adverse events – not reported												
0	–	–	–	–	–	none	–	–	–	–		CRITICAL
Adherence – not reported												
0	–	–	–	–	–	none	–	–	–	–		IMPORTANT

[1] Median follow-up period varied from 2.5 years (30 months) in the 36 months isoniazid arm and 2.6 years in the 6 months isoniazid and ethambutol arm in the Swaminathan et al. 2012 study, and 3.9 years (47 months) for both the continuous and six-month isoniazid groups in the Martinson et al. 2011 study. Median follow-up was not reported in the Samandari et al. 2011 study but is probably close to 36 months.

[2] Swaminathan et al. 2012 and Martinson et al. 2011 studies were not blinded, and the allocation concealment in the Samandari et al. 2011 study was not clearly described and might have led to selection bias.

[3] The control group in the Swaminathan et al. 2012 study received 300 g isoniazid + 800 g ethambutol.

[4] Differences in included patient population: Martinson et al. 2011 study excluded patients eligible for ART; median CD4 count at baseline was 484 cells/mm3. In the Samandari et al. 2011 study, 2% were on ART before enrolment and 47% were on ART by month 36. Median CD4 count at baseline was 297 cells/mm3. Swaminathan et al. 2012 study included ART-naïve patients with a median CD4 count of 325 cells/mm3.

[5] Swaminathan et al. 2012 and Martinson et al. 2011 studies were not blinded.

[6] Martinson et al. 2011 study was not blinded, and the allocation concealment in the Samandari et al. 2011 study was not clearly described and might have led to selection bias.

[7] Differences in included patient population: Martinson 2011 et al. study excluded patients eligible for ART; median CD4 count at baseline was 484 cells/mm3. In the Samandari et al. 2011 study, 2% were on ART before enrolment and 47% were on ART by month 36. Median CD4 count at baseline was 297 cells/mm3.

[8] Although allocation concealment in the Samandari et al. 2011 study was not clearly described, it is not sufficient to downgrade for risk of bias.

[9] Very few.

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Date: 2014-03-27
Question: Should continuous isoniazid versus six-month isoniazid be used for tuberculosis prevention in people living with HIV and with a negative TST (< 5 mm)?
Settings: South Africa, Botswana, India
Bibliography: Martinson et al. 2011, Samandari et al. 2011, Swaminathan et al. 2012

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous IPT	Six-month IPT	Relative (95% CI)	Absolute		
Active TB (confirmed, probable, possible) (follow-up 30–36 months; assessed with culture, smear, signs and symptoms of TB + response to treatment)												
2	Randomized trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	22/929 (2.4%)	30/932 (3.2%)	RR 0.73 (0.43 to 1.26)	9 fewer per 1000 (from 18 fewer to 8 more)	⨁⨁◯◯ LOW	CRITICAL
								2%		5 fewer per 1000 (from 11 fewer to 5 more)		
								50%		135 fewer per 1000 (from 285 fewer to 130 more)		
Confirmed TB (follow-up median 30 months; assessed with culture positive for MTB)												
1	Randomized trials	serious[3]	no serious inconsistency	serious[2]	no serious imprecision	none	2/207 (0.97%)	3/203 (1.5%)	OR 0.65 (0.11 to 3.93)	5 fewer per 1000 (from 13 fewer to 41 more)	⨁⨁◯◯ LOW	CRITICAL
								2%		7 fewer per 1000 (from 18 fewer to 54 more)		
								50%		106 fewer per 1000 (from 401 fewer to 297 more)		
Death (follow-up mean 36 months; assessed with clinical or verbal autopsy, hospital records, or death certificates)												
1	Randomized trials	no serious risk of bias[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	32/722 (4.4%)	25/729 (3.4%)	RR 1.29 (0.77 to 2.16)	10 more per 1000 (from 8 fewer to 40 more)	⨁⨁⨁⨁ HIGH	CRITICAL
								2%		6 more per 1000 (from 5 fewer to 23 more)		
								50%		145 more per 1000 (from 115 fewer to 580 more)		
Death due to TB (follow-up mean 36 months; assessed with clinical or verbal autopsy or hospital records)												
1	Randomized trials	no serious risk of bias[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/722 (0.55%)	3/729 (0.41%)	OR 1.35 (0.3 to 6.05)	1 more per 1000 (from 3 fewer to 20 more)	⨁⨁⨁⨁ HIGH	CRITICAL
								2%		0 more per 1000 (from 1 fewer to 5 more)		
								50%		42 more per 1000 (from 100 fewer to 366 more)		
Tuberculosis or death (follow-up median 36 months; assessed with all TB (confirmed, probable, possible)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous IPT	Six-month IPT	Relative (95% CI)	Absolute		
1	Randomized trials	no serious risk of bias[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	47/722 (6.5%)	45/729 (6.2%)	RR 1.05 (0.71 to 1.57)	3 more per 1000 (from 18 fewer to 35 more)	⨁⨁⨁⨁ HIGH	CRITICAL
								2%		1 more per 1000 (from 6 fewer to 11 more)		
								50%		25 more per 1000 (from 145 fewer to 285 more)		
Adverse events – not reported												
0	–	–	–	–	–	none	–	–	–	–		CRITICAL
Adherence												
0	No evidence available	–	–	–	–	none	–	–	–	–		IMPORTANT

[1] Swaminathan et al. 2012 study was not blinded, the allocation concealment in the Samandari et al. 2011 study was not clearly described and might have led to selection bias.

[2] The control group in the Swaminathan et al. 2012 study received 300 g isoniazid + 800 g ethambutol.

[3] Swaminathan et al. 2011 study was not blinded.

[4] Although allocation concealment in the Samandari et al. 2011 study was not clearly described, it is not sufficient to downgrade for risk of bias.

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Definitions for ratings of the certainty of the evidence (GRADE)**

Ratings	Definitions
⨁⨁⨁⨁ **High**	This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low.
⨁⨁⨁◯ **Moderate**	This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different4 is moderate.
⨁⨁◯◯ **Low**	This research provides some indication of the likely effect. However, the likelihood that it will be substantially different4 is high.
⨁◯◯◯ **Very low**	This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different4 is very high.

*Substantially different: large enough difference that it might have an effect on a decision

**The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group began in the year 2000 as an informal collaboration of people with an interest in addressing the shortcomings of present grading systems in health care. The working group has developed a common, sensible and transparent approach to grading quality of evidence and strength of recommendations. Many international organizations have provided input into the development of the approach and have started using it.

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