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Use of Isoniazid Preventive Therapy for Tuberculosis Prophylaxis Among People Living with HIV/AIDS: A Review of the Literature

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Abstract

Background—Tuberculosis (TB) is the leading preventable cause of death in persons living with HIV (PLHIV), accounting for over a quarter of all HIV-associated deaths in 2012. Isoniazid preventive therapy (IPT) has the potential to decrease TB-related cases and deaths in PLHIV; however, implementation of this has been slow in many high HIV- and TB-burden settings.

Methodology—We performed an assessment of the evidence for the use of IPT in adults living with HIV based on a review of literature published from 1995 to 2013. Eligible articles included data on mortality, morbidity, or retention in care related to the provision of IPT to adults with HIV in low- or middle-income countries. Cost-effectiveness information was also abstracted.

Results—We identified 41 articles involving over 45,000 persons living with HIV. While there was little evidence to demonstrate that IPT reduced mortality in PLHIV, there was substantial evidence that IPT reduced TB incidence. While these findings were consistent irrespective of CD4 or antiretroviral therapy (ART) status, studies frequently demonstrated a greater benefit among patients with a positive TB skin test (TST). Duration of effectiveness and benefits of prolonged therapy varied across settings.

Conclusions—This analysis supports the WHO recommendations for the provision of IPT to PLHIV to reduce TB associated morbidity, and serves to highlight the need to strengthen IPT implementation. While there appears to be a greater benefit of IPT among PLHIV who are TST positive, IPT should be provided to all PLHIV without presumptive TB when TST is not available.

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Background

HIV is the strongest risk factor for developing tuberculosis (TB) disease among those infected with *Mycobacterium tuberculosis*. The risk of developing TB is 20 to 37 times greater in people living with HIV (PLHIV) than among those who do not have HIV infection.[1] In 2012, of 8.6 million people who developed TB, 1.1 million were HIV-infected; 320,000 deaths from HIV-associated TB accounted for approximately a quarter of all HIV-associated deaths.[2] TB thus remains the leading preventable cause of morbidity and mortality in PLHIV. If not adequately addressed, TB has the potential to undermine the great strides made globally in rapidly expanding HIV care and treatment. Therefore prevention of TB is one of the most important measures needed to reduce morbidity and mortality among PLHIV, especially in countries with a high TB and HIV burden.

Multiple strategies are available for preventing TB disease. Early initiation of antiretroviral therapy (ART) is the most effective TB prevention intervention among PLHIV.[3–5] A meta-analysis of multiple observational cohort studies in countries with both high and low TB incidence rates reported TB risk reduction of 54% to 92% among PLHIV on ART compared to PLHIV not on ART.[6] However, a 5-year follow-up study suggested that despite the dramatic reduction in TB risk among PLHIV on long-term ART, this risk remains several times higher than the risk of TB among persons without HIV infection living in the same communities.[7] These findings highlight that, for long-term reduction of TB among PLHIV, including those on ART, other adjunctive strategies such as isoniazid preventive therapy (IPT) should be implemented.

Isoniazid (INH) has long been used for both TB treatment and prevention. Initial studies demonstrating the effectiveness of IPT in preventing TB disease in persons with latent TB infection were published in the late 1950s and early 1960s.[8] Although most of the early studies were among immunocompetent adults, they appeared to show that a 6- to 12-month course of INH provided up to 90% protection from TB.[9] Studies demonstrating the benefit of IPT to prevent TB in PLHIV began to be published in the early 1990s, with the World Health Organization (WHO) first recommending the use of IPT to prevent TB in PLHIV in 1998.[10]

In 2008, WHO published guidance incorporating the use of IPT as part of a focused strategy for reducing HIV-associated TB, along with intensified TB case finding (ICF) and TB infection control (known as the “3Is” interventions).[11] The ICF/IPT guidelines released in 2011 included specific evidence-based recommendations on determining eligibility for IPT in settings where TB skin tests (TST) are programmatically challenging and extending the duration of therapy in high TB-burden settings.[1] Specifically, the WHO strongly recommends providing at least 6 months of IPT for PLHIV without active TB, including those receiving ART, and those who have successfully completed TB treatment; and conditionally recommends providing isoniazid for 36 months (as a proxy for lifelong treatment) for PLHIV who are living in settings with high TB prevalence and transmission.[1] The guidelines recommend that these interventions be offered to patients who are TST positive, in settings where TST is used, and to all eligible patients where TST use is not logistically feasible. Despite the existing WHO recommendations, implementation of IPT

remains sub-optimal, with only 30% of PLHIV newly enrolled in HIV care initiated on IPT in 2012.[2]

Given the gaps in program implementation of IPT, we undertook a review of the literature on the benefit of IPT for PLHIV in resource-limited settings, as part of a larger review of 13 care and support interventions for PLHIV.[12] For this review, we assessed the impact of the provision of a minimum of 6 months of INH on (1) mortality, (2) morbidity, and (3) retention in HIV care, and assessed the cost-effectiveness of IPT among PLHIV in terms of these outcomes.

Methodology

We conducted a literature search of 6 medical literature databases—Medline, Embase, Global Health, CINAHL, SOCA, and African Index Medicus (AIM). Articles eligible for inclusion were those that 1) evaluated IPT provision in adults living with HIV, 2) were conducted in low- or middle-income countries, 3) described use of IPT for 6 months or more to prevent development of TB disease, including the use of INH after completion of TB treatment to prevent recurrence, and 4) were published between 1995 and August 2014. While the other articles in this supplement included 5 outcomes (mortality, morbidity, retention in care, quality of life, and reduction of HIV transmission), we focused only on 3 (mortality, morbidity, and retention in care), as it was felt that these 3 could be logically tied to IPT use and were of greatest relevance. For the purpose of this review only articles presenting primary data or unique analyses (e.g., a meta-analysis) were included. A detailed description of the search terms and geographic filters used for the overall review of care and support interventions for PLHIV is presented in Ref 12. For our review, we utilized the additional IPT-specific search terms shown in Table 1.

Article titles and abstracts identified by the search terms were reviewed sequentially by 2 different reviewers to identify relevant articles. Articles that appeared to meet the inclusion criteria after both reviews were selected for full-text review. On full-text review, articles that were confirmed as meeting the inclusion criteria were abstracted, summarized, and categorized based on the outcome. Information abstracted from each article included the study design (expressed as hazard ratios, odds ratios, relative risk, etc., with the respective 95% confidence intervals if available), comparison group(s), number of participants, and assessment of impact on the outcome(s) of interest (expressed as hazard ratios, odds ratios, relative risk, etc. and the respective 95% confidence intervals, if available). Additional information recorded included adherence to IPT, adverse events, and any stratification of results by CD4 or TST status.

For each study, the internal and external validity were rated as “good,” fair,” or “poor” based on the design, loss-to-follow-up rate, and relevance to the population of interest today (i.e., PLHIV in resource-limited settings with increasing access to ART), and the overall quality of evidence was rated as “strong,” “medium,” or “weak.” Specific criteria for each of these ratings are included in Tables 2–4 of the introduction to this supplement.[12] Cost-effectiveness studies were assessed based on the level of evidence presented and categorized as “Level 1” – full economic evaluation, “Level 2” – partial economic evaluation, or “Level

3" – randomized trials and studies with limited cost information. For the purpose of this review, cost-effectiveness studies reporting on life expectancy, years of life saved (YLS), and quality of life years saved (QALYs) were grouped with the mortality studies and those reporting on TB cases averted were grouped with the morbidity studies.

Because of the heterogeneity of study populations, study methods, settings, and outcomes, we did not attempt quantitative synthesis of study results overall. However, studies were grouped together based on the outcome assessed (mortality, morbidity, or retention in care) and the overall quality of the body of evidence for each outcome was rated as "good," fair," or "poor" based on criteria agreed on *a priori* and described in the introductory paper. Similarly, the overall potential impact of the intervention was rated as "high," "moderate," "low," or "uncertain" for each of the outcomes assessed.

Results

Our search identified a total of 2,228 articles (Figure 1). Review of the abstracts led to the exclusion of 2,132 articles. Of the remaining 96 articles, 55 were determined not to meet inclusion criteria after full-text review and 41 articles were included in the final analysis. Of these, 30 provided data on mortality (including 3 cost evaluations), 38 on morbidity (including 3 cost evaluations) and 1 on retention in HIV care. These categories were not mutually exclusive, as most studies presented on multiple outcomes. Table S1 (See Supplemental Digital content) lists a summary of each of the articles included, grouped by outcome. For each outcome, the overall findings, assessment of the quality of the data, and the rated impact of the interventions are presented below.

Mortality

There were a total of 18 studies (9 randomized control trials [RCTs],[13–21] 6 cohort/non-randomized studies,[22–27] and 3 systematic reviews[28–30]) that reported on mortality in adults receiving IPT as compared to no IPT (or placebo). Fourteen of these found no significant reduction in all-cause mortality.[13–21,25–29] Of the 4 articles that found a significant mortality reduction with IPT, 2 were conducted exclusively among individuals who were TST positive.[23,24] In addition, the only systematic review that reported a significant reduction in mortality with IPT in PLHIV found the reduction to be significant among persons who were TST positive, but not those who were TST negative.[30]

One additional trial assessed the provision of IPT to TST positive patients as part of a multi-component intervention in Brazil.[31] This study found a 31% reduction in tuberculosis or mortality (adjusted hazard ratio [aHR] 0.69; 0.57–0.83) among participants attending a clinic where health care workers had received training on administering TSTs, providing IPT and treating TB, as compared to participants who attended a clinic where no intervention had occurred. A follow-up assessment modeled the potential impact of this intervention when scaled-up throughout Rio de Janeiro (population 4.1 million). It found that scale up of IPT over the course of 5 years, with 20% coverage of those eligible each year, had the potential to reduce TB-related mortality by 14% amongst PLHIV and by 4% amongst the general population.[32]

There were 2 studies included in this review that assessed the benefit of extending the duration of IPT in regards to mortality.[33,34] The first study was a double-blind placebo-controlled RCT that compared 6 months of INH to 36 months of INH among 1,995 PLHIV in Botswana. In this setting, the researchers found that the overall benefit of IPT appeared to decline about 200 days after the regimen was completed, and continuing IPT for 36 months resulted in a significant decrease in mortality when compared to 6 months of IPT (aHR 0.32; 0.11–0.90). However, this was only true for participants who were TST positive.[33] There was no significant difference between the groups in adherence or adverse events in that study. A similar RCT comparing 6 months of INH plus ethambutol to 36 months of INH alone in India found no significant difference in mortality, irrespective of TST status.[34]

Eight RCTs and one systematic review compared at least 6 months of INH to a shorter course of a rifamycin-based regimen.[16,17,19,20,26,28,35–37] In each of the studies, the overall morality was not significantly different between the INH and rifamycin-based regimens, though in the systematic review only INH plus rifampin resulted in a significant reduction in mortality (relative risk [RR] = 0.69, 0.50–0.95).[28] Two studies and one review noted a higher rate of adverse events in the rifamycin-based regimens,[20,28,35] while one study noted increased adverse events with either 6-month or “continuous” INH when compared to the shorter combination regimens.[37]

Two additional observational studies reported mortality data from IPT programs without comparison groups; findings from these are included in Table S1 (See Supplemental Digital content).[38,39] Overall, across the studies reporting mortality data, IPT adherence (mean, median, or completion rate) ranged from 63% to 92%, though the definition and method of measuring adherence varied. Adverse events were more common in the intervention group than the placebo group in multiple studies, though serious adverse events requiring discontinuation of INH were rare.

Three studies reported on costs of IPT and outcomes in terms of life expectancy, YLS, and, QALYs.[40–42] One of the studies evaluated 3 different prophylactic regimens; all 3 extended life expectancy and QALYs.[40] While rifamycin plus pyrazinamide resulted in the greatest extension in life expectancy/QALYs, the 6-month course of INH was the most cost effective.[40] Another study evaluated different strategies of providing IPT. This showed that while use of TST screening prior to IPT reduced the cost per QALY gained, using a “treat-all” strategy of providing IPT without using TST first resulted in a higher overall number of QALYs saved.[42]

This review included numerous studies of good internal quality, but the external generalizability was limited due to the fact that many of these studies occurred prior to the widespread availability of ART. In addition, although there was a large body of evidence reporting on mortality in IPT, the findings varied greatly among studies, many of which were powered to detect TB incidence and may not have had sufficient power to detect mortality. As a result, we rated the overall quality of evidence on the use of IPT to reduce mortality in adults living with HIV as “fair” (See Table 2). Based on the evidence that exists, IPT is expected to have a “low/uncertain” impact on reducing mortality in adults living with HIV. While there is more evidence supporting the benefit of IPT in persons who are TST positive

than persons who are TST negative, the majority of studies showed no significant impact on mortality, irrespective of TST status.

Morbidity

A total of 22 studies (8 RCTs,[13–16,18–21] 9 cohort studies,[23–27,43–46] 2 case-control studies,[47,48] and 3 systematic reviews[28–30]) reported on TB incidence in persons receiving IPT as compared to no IPT (or placebo). Seven of these did not find a statistically significant reduction in TB incidence[14–16,18,24,45,48], whereas 15 studies, including all 3 systematic reviews, reported a significant reduction in TB incidence with IPT.[13,19–21,23,25–30,43,44,46,47] In addition, 2 RCTs looked at IPT as part of a multi-component intervention.[31,49] In both of these studies, TB incidence was significantly reduced in persons attending clinics that had received an IPT and TB training intervention as compared to control clinics. As described above, a study modeling the effects of scale-up of the intervention, predicted a potential 15% reduction in TB incidence amongst PLHIV and 4% reduction in TB in the general population.[32]

Of the studies that reported a significant decrease in TB incidence with IPT, 6 of them were conducted in populations that were mainly (>75%) TST-positive individuals,[23,25,31,32,43,44] and one RCT and follow-up cohort study noted a larger decrease in TB incidence in participants who were TST positive as compared to TST negative.[19,26] In the 2 systematic reviews that reported results stratified by TST status, IPT significantly reduced TB incidence by 60% to 62% in the sub-group of persons who were TST positive but had no significant benefit in the TST negative sub-group, with TB incidence reductions of 11% to 16%. In both of these reviews, the benefit of IPT remained significant, with a reduction in TB incidence of 33% to 44% even when TST status was not taken into consideration.[29,30] One RCT that evaluated 12 months of INH in ART-treated patients in South Africa, reported a greater benefit of IPT in persons who were TST negative (aHR 0.43; 0.20–0.96) as compared to TST positive (aHR 0.55; 0.26–1.24).[21] This study was published after the aforementioned reviews.

When reported, the median baseline CD4 for most of the studies was between 200 and 400.[15,21,31,43–46,49] Most of the studies adjusted for CD4 in their analysis, and only 2 studies reported a differential benefit based on CD4. One study, Churchyard et al found a greater benefit of IPT in those with CD4 <200, whereas the other, Yirdaw et al. found that the benefit was greatest in those with a CD4 ≥350.[27,46] There were few studies directly reporting on the interaction between IPT and ART. Those that did stratify by ART status demonstrated an additive benefit when IPT and ART were used combined compared to either intervention alone.[22,33,43,44,46]

Four studies in different settings assessed the duration of effectiveness of IPT after discontinuation of therapy.[16,25,26,33] A study in Thailand found that the benefit was significant 6 months after completion of therapy, but then steadily waned thereafter. In this setting, the reduction in TB incidence was no longer significant at 4 years post treatment.[25] In Uganda, an initial study demonstrated a 68% reduction in TB incidence in TST-positive participants after an average of 12 months of data collection.[16] However, there was no longer any significant difference in TB incidence between IPT and placebo after 3 years of follow-

up. In Zambia, the reduction in TB incidence was significant during 2.5 years of follow-up; however, the benefit declined steadily after the first 1.5 years.[26] Lastly, in Botswana, the benefit of IPT appeared to disappear approximately 200 days after discontinuation of therapy.[33]

Three studies compared effectiveness of IPT for 6 months versus longer regimens.[33,34,50] Two of the studies, the study from Botswana mentioned above and a second study in Haiti, found significant reductions in TB incidence in those receiving the longer course of therapy.[33,50] In Botswana, this benefit was statistically significant only among participants who were TST positive.[33] A study in India comparing 6 months of INH plus ethambutol to 36 months of INH found no statistically significant difference in TB incidence, irrespective of TST status.[34]

Eight studies compared 6 months of INH to shorter rifamycin-based regimens.[16,17,19,20,26,35–37] In 7 of the studies, there was no difference in efficacy between INH and the shorter regimens. In one study, a significant difference was noted between regimens, primarily in the duration of benefit, with continued efficacy noted at 3 years for the rifamycin-based regimens but not for standard IPT.[16] Five additional studies reported on TB incidence in adults without a comparison group;[38,39,48,51–53] findings from these are included in Table S1 (See Supplemental Digital content).

Three cost-effectiveness studies reported on costs of IPT and outcomes in terms of TB cases averted.[40,41,54] In a study that evaluated 3 different prophylactic regimens compared to no prophylaxis, all 3 regimens resulted in a lower estimated TB incidence and prevented secondary infections. Taking into account medical costs, “social” costs, and secondary infections, they estimated that IPT resulted in a cost savings of $24.16 per person. A separate study evaluating IPT administration using a TST-based targeting vs. “treat-all” strategy found that the TST strategy was more cost-effective at $157 per case of latent TB infection treated, compared to $482 per case treated using a “treat-all” or non-TST-based strategy. This study, however, did not report costs in terms of TB cases averted.[54]

Given the large body of well-designed studies and relatively consistent results supporting an initial significant benefit of IPT in reducing TB incidence in PLHIV, we rated the overall quality of evidence of this intervention as “good,” and the likely impact of this intervention as “high.”

Retention in Care Data

There was only one study that reported on the effect of IPT on retention in HIV care[25] and this study found no benefit of IPT on retention in care. Given the low number of studies reporting on this outcome, we rated the quality of evidence on this outcome as “poor” and the impact of IPT on retention in care in people living with HIV as “low/uncertain.”

Discussion

In total, 41 articles that included over 45,000 PLHIV addressed the intervention. While there was little evidence to demonstrate the benefit of IPT in reducing overall mortality in PLHIV,

there was substantial data demonstrating the effectiveness of IPT in reducing TB incidence. Available data also indicates that IPT is cost-effective and potentially cost-saving for health systems in terms of TB cases averted and/or QALYs saved. Although the overall findings were largely consistent irrespective of CD4 or ART status, results frequently differed based on TST status with a greater benefit reported in TST positive as compared to TST negative patients in the majority of studies. In addition, findings with regards to duration of effectiveness and benefits of prolonged therapy varied across settings.

Programmatic Considerations for Implementation

The substantial evidence of the benefit of IPT in reducing TB incidence in PLHIV demonstrated in this literature review underscores the importance of IPT as a core component of clinical care services for PLHIV in resource-limited settings. Despite long-standing recommendations from WHO to incorporate IPT as part of comprehensive TB/HIV activities in resource-limited settings, scale-up of IPT among PLHIV has been slow. National efforts in Namibia and South Africa demonstrate that national-level scale-up is possible;[2] however, countries must take into account multiple programmatic considerations in order to implement a successful IPT program.

Many countries have taken the first step toward scaling up IPT programs for PLHIV by incorporating this into national-level guidance. However, widespread implementation of IPT programs has proven difficult, often due to the complexities involved in coordination of national and subnational TB and HIV programs (i.e., for supply-chain management and monitoring and evaluation). In some settings, persons eligible for IPT are identified in HIV clinics, but referred to TB clinics for provision of prophylaxis and for ongoing monitoring. In others, HIV clinics are expected to deliver IPT but are faced with challenges around maintaining a steady supply of IPT due to separate procurement mechanisms.

IPT is part of the clinical cascade of TB/HIV collaborative activities; intensified case finding (ICF) helps identify PLHIV who need to be evaluated for TB disease as well as those who can be started on IPT. However, in order for this cascade to function effectively, clinicians must feel confident in the ability of the ICF algorithm to rule out TB disease. A 2011 study from Getahun et al demonstrated that asking just 4 questions (current cough, fever, night sweats, or weight loss) had a negative predictive value of 98% in places with a TB prevalence of 5%.[55] While the negative predictive value goes down slightly in higher-burden TB settings, the WHO determined that just asking these 4 questions was sufficiently effective at ruling out TB, and that any person with HIV who does not have any of these symptoms should be eligible for IPT if no contraindications exist.[1] This guidance greatly simplified recommendations and answered many questions that previously existed at the programmatic level concerning whether TST or chest radiograph was required to determine who is eligible for IPT. Furthermore, the WHO guidelines emphasize that these questions should be asked at every clinic visit, both to improve TB case detection among PLHIV as well as to identify patients eligible for IPT.

When assessed, the majority of articles included in this review report a greater benefit of IPT in patients who are TST positive as compared to TST negative. Although recommendations currently state that TST should be implemented where feasible to target IPT use towards

those who would have the greatest benefit, many resource-limited settings have not routinely incorporated TST into evaluations of PLHIV due to a number of programmatic challenges. These include having adequate and consistently available supplies, staff trained to administer and interpret the TST, and concerns with missed opportunities for treatment when patients do not return to have their TST results read. In addition, one RCT included in this review reported a slightly greater benefit of IPT in TST negative as compared to TST positive individuals.[21] Notably, this study was performed exclusively among ART-treated patients using universal sputum culture to rule-out pre-existing TB, which should ensure that their study did not include any partially treated TB cases amongst their TST positive sub-group. Unless replicated, this study is unlikely to change the current guidance on TST use, but it does highlight a need to further assess the effect of using TST to target IPT in ART-treated populations. In the interim, the summary data presented in this and previous reviews demonstrates that there is sufficient evidence to recommend providing IPT irrespective of TST status, especially in locations where TST use is determined not to be feasible.

Finally, many countries have not developed systematic methods for monitoring and evaluating individual- or aggregate-level outcomes of IPT implementation. HIV recording and reporting systems should capture information about IPT provision so that this is more easily assessed. IPT registers could also be employed to monitor IPT initiation, adherence, and any adverse events during treatment. Individual patients should be monitored for occurrence of symptoms consistent with active TB disease at every follow-up visit and tracked to ensure that they complete the full course of IPT. This data should be reported to the national level.

Limitations

This analysis was limited in that it was based on existing published literature and did not include a meta-analysis or evaluation of unpublished data. The scope of this supplement was intentionally limited to adults with HIV in low- and middle-income settings. In addition, while we focused specifically on the evidence behind IPT in terms of mortality, morbidity, and retention in care, we did not aim to address issues such as the optimal prophylactic regimen, duration of IPT efficacy, IPT adherence, or adverse events as independent outcomes. Another major area not discussed as part of this review was emergence of INH resistance, although a review of this was included in the WHO 2011 guidance.[1]

Interpretation of the mortality data reviewed may be limited by the age of the studies and the study designs. Most of the studies were performed in the 1990s and early 2000s prior to the widespread availability of ART. In addition, many of the studies were designed to detect differences in TB incidence and may have been underpowered to detect differences in mortality. The small number of studies reporting on the effect of IPT on retention in HIV care also limited our ability to assess the impact of IPT on this outcome.

Research Gaps

There are several key research gaps related to provision of IPT in PLHIV that were identified. The duration of the protective effect of IPT appears to vary by location, which may be related to the local burden of TB. While there is a clear benefit of prolonged and

possibly lifelong therapy in places with very high TB and HIV burden (e.g., Botswana), the optimal administrative schedule (e.g., short course, lifelong, or repeated) is not well defined in all settings. In addition, there is still a need to assess the possible emergence of INH drug resistance within a context of routine, programmatic use. Although not included in this review, the literature search for this topic identified 5 applicable articles on IPT in pediatric HIV populations, with results ranging from no benefit to substantial benefit of IPT; this highlights the need for work to evaluate the benefit of IPT and barriers to implementation for this vulnerable population. Lastly, the articles included in this review highlighted a number of alternative shorter-course regimens that have comparable efficacy and adverse event profiles to INH. Determining in what settings these regimens should be scaled up and the potential implications of this on resistance and duration of effectiveness merits further investigation.

Conclusions

In general, these findings support the provision of IPT to PLHIV for the reduction of TB incidence and associated morbidity. Our review confirms that while there appears to be a greater benefit of IPT among PLHIV who are TST positive, IPT should be provided to all PLHIV without TB disease or presumptive TB when TST is not available, regardless of CD4 count or ART. The benefit of IPT appears to wane within 1 to 4 years in high TB burden settings and future studies are needed to assess the population and individual-level benefit of longer courses of IPT. In order to reduce the incidence and morbidity of TB among PLHIV and ensure success of the global HIV/AIDS response, further effort should be exerted in ensuring that high-quality evidence-based IPT programs are scaled up in countries with high burdens of both TB and HIV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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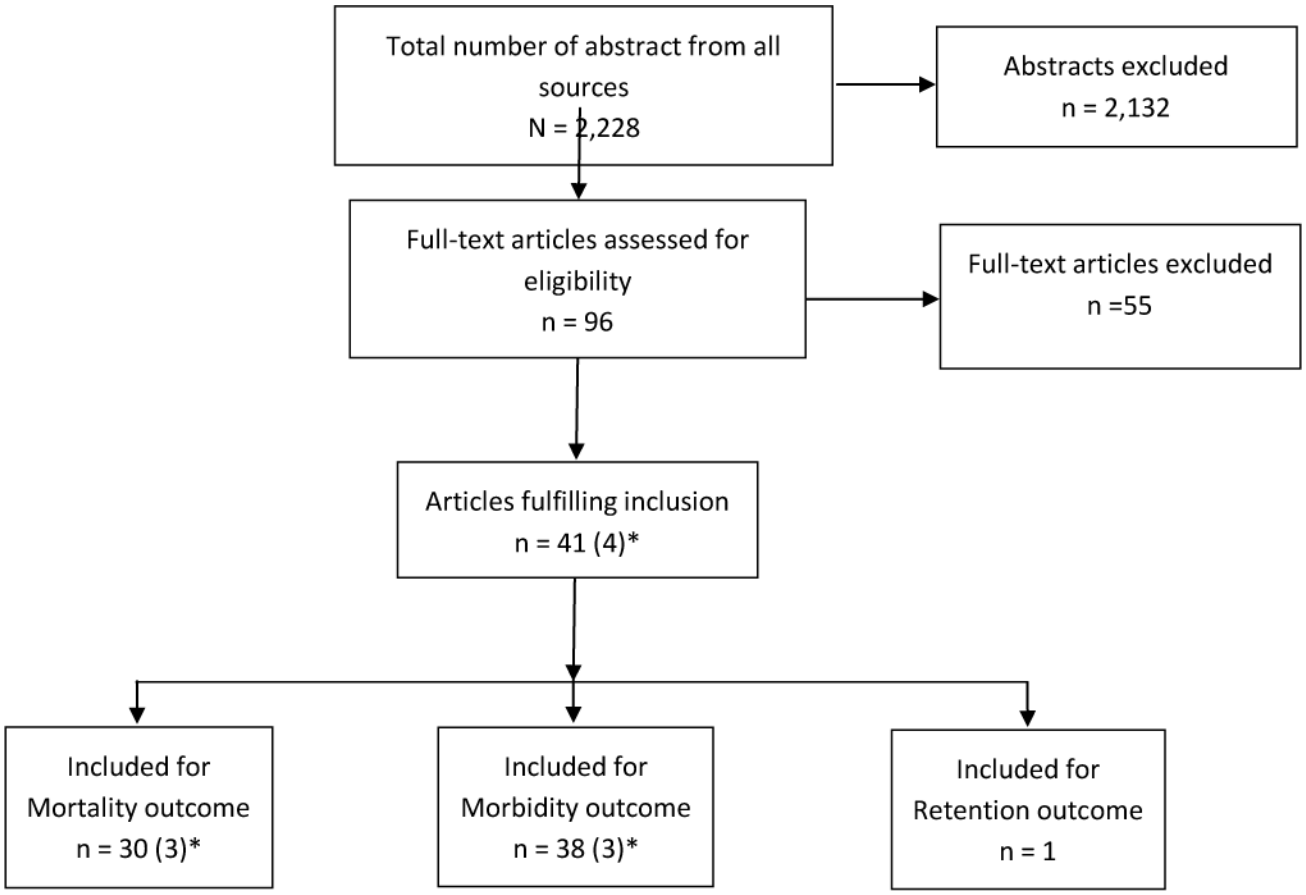

Figure 1. Study Flow Diagram

*Number of studies in each category including costing data listed in parentheses

Table 1

Keyword Search Terms

Isoniazid Preventive Therapy-Specific Search Terms	
Tuberculosis	Latent TB
Isoniazid	Isoniazid Preventive Therapy
INH	IPT
Prevention	Primary Prevention

Table 3

Summary of Evidence From All Studies Addressing an Outcome

Outcome	Overall Quality of Evidence		Impact of the Intervention	Evidence from Economic Evaluation		Comments
	Studies (# Studies addressing each outcome and references)	**Overall Quality of the Body of Evidence** ***(For all studies addressing each outcome) (1 = Good; 2 = Fair; 3 = Poor) (Score and narrative)***	**Expected Impact of the intervention*** ***(Based on the main findings from good quality studies addressing the intervention) (1 = High; 2 = Moderate; 3 = Low; 4 = Uncertain)***	**Studies (# Studies with cost effectiveness data addressing each outcome)**	**Quality of Evidence from Economic Evaluation** ***(Summary assessment)***	
Mortality	18 studies of IPT vs. no IPT (or placebo) in adults with HIV 2 studies evaluating IPT as part of a multi- component intervention 2 RCTs on the optimal duration of IPT 8 RCTs comparing INH to rifamycin-based chemoprophylaxis 2 studies on IPT with no comparison group	**Fair** While there are a large number of studies reporting on mortality in HIV-positive individuals receiving IPT vs. no IPT (or placebo), the methods, regimen, follow-up, and results were variable.	**Low/Uncertain** 4 of 18 studies found a significant reduction in mortality with IPT.	3 studies addressing cost and life expectancy and/or quality-of life years (QALYs) saved.	2 studies found that prophylaxis (INH or multiple regimens) extended life expectancy, and 2 found that IPT programs increased QALYs saved. In the study comparing different regimen, INH resulted in the most cost-savings (had the lowest cost per QALY saved).	Most studies were performed prior to widespread availability of ART. In addition, many were powered to detect changes in TB incidence and not mortality.
Morbidity	22 studies of IPT vs. no IPT (or placebo) in adults with HIV 3 studies evaluating IPT as part of a multi-component intervention 3 RCTs on the optimal duration of IPT 8 RCTs comparing INH to rifamycin-based chemoprophylaxis 5 studies on IPT with no comparison group	**Good** There is a large body of high-quality studies comparing IPT to no IPT (or placebo) in adults with HIV	**High** 15 out of 22 reported a statistically significant reduction in TB incidence with IPT	3 studies addressing cost and reduction in TB incidence	All prophylactic regimens assessed were less expensive than no prophylaxis	TB incidence was decreased even after adjusting for CD4 and TST status in multiple studies. In studies that stratified by TST status, TB incidence was significantly reduced in TST positive, but not TST negative individuals
Retention in Care	1 study on retention in HIV care as a potential outcome of IPT	**Poor**	**Low/Uncertain**	No studies available		

*[1]The expected impact of the intervention was rated as; **High** = Intervention expected to have a high impact on the outcome; **Moderate** = Likely to have a moderate impact on the outcome; **Low** = Intervention expected to have a low impact on the outcome; **Uncertain** = Available information is not adequate to assess estimated impact on the outcome.

Note: Assessment of the **expected impact** of the intervention was based on published evidence. Additional considerations that would inform implementation decisions would have to take into account the cost-effectiveness information and country-specific contextual considerations.