**Table S1: Summary Table: Assessment of Individual Studies by Outcome**

| **Study Characteristics** | | | | **Key Findings** [Magnitude of effect (HR, OR, RR, RD & 95% CI) or other description] | **Quality of Evidence for Individual Studies** | | | **Evidence from Economic Evaluation (e.g., cost-effectiveness)** *(Yes or No; if Yes, brief description and rating of quality of study (Level 1, 2, or 3)***) | **Comments** [Including comments on: 1) WHO staging/CD4 count and ART status 2) Duration of efficacy 3) Adherence 4) Adverse events] |
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| | | | | | **External and Internal Validity** *(1 = Good; 2 = Fair; 3 = Poor)* | | **Overall Quality of Evidence Rating*** *(1 = Strong; 2 = Medium; 3 = Weak)* | | |
| Citation | Study Design (e.g., RCT) | Country, Study Period | No. Participants | | **Internal Validity** (Bias) | **External Validity** (Generalizability) | | | |
| **Mortality** | | | | | | | | | |
| Akolo, C., et al., 2010.[1] | Meta-analysis | Multi-country Update of previous review, studies from 1993 through April 2008 | 12 RCTs with a total of 8,578 PLHIV ≥13 years without active TB, randomized to TB preventive therapy and placebo or alternative regimens | No evidence that preventive therapy reduced all-cause mortality, RR= 0.94 (0.85–1.05) or mortality amongst those who were PPD positive, RR = 0.80 (0.63–1.02). No differences in the effect on death by study drug with the exception of INH+RIF, which was associated with a significant reduction in the risk of death, OR = 0.69 (0.50–0.95). | 1-Good | 1-Good | 1-Strong | No | Adherence: Some evidence that adherence improves with shorter duration of prophylaxis. Adverse events: Preventive therapy led to more adverse events compared to placebo (6 trials; 5,525 participants; RR = 2.55, (1.70–3.85). The likelihood of stopping treatment due to adverse effects was higher for combination therapies than for INH monotherapy. |
| Bucher, H.C., et al., 1999.[2] | Meta-analysis | Multi-country Articles published from 1993 to 1998; Mean | 7 RCTs included in the meta-analysis: 2,367 PLHIV received INH and 2,162 | No difference in death rate for INH vs. placebo group: RR = 0.94 (0.83–1.07) For 5 trials with TST results: TST positive RR = 0.79 (0.37–1.70) TST negative RR = 1.02 | 2-Fair | 2-Fair | 1-Strong | No | Adverse events: No significant difference in all side effects from 4 trials (INH vs. placebo), RR = 1.36 (1.00-1.86) or drug-limiting toxicity, RR = 1.66 (0.83-3.32). There was |

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| | | follow-up; 0.4-3.2 years | received placebo | (0.90–1.17).<br>No statistically significant difference between RR of death among TST positive and TST negative (p = 0.52). | | | | | noted to be an increase in hepatotoxicity, defined as twofold increase in AST, RR = 1.80 (1.05-3.10). |
| Charalambous, S., et al., 2010.[3] | Cohort study | South Africa<br>Jan. 2004 – Dec. 2007; 12-month follow-up period | 3,270 ART-naïve adults starting ART as part of workplace ART program | IPT in combination with ART reduced mortality compared to ART alone in ART-naïve population, uOR = 0.32 (0.24–0.49), aOR= 0.50 (0.32–0.80). | 2-Fair | 2-Fair | 2-Medium | No | Note that the two cohorts (receiving INH and not) were statistically different across various demographic and clinical characteristics.<br>No significant difference in mortality noted when results stratified by CD4. |
| Churchyard, G.J., et al., 2003.[4] | Cohort study | South Africa<br>Enrollment Dec. 2000 for IPT cohort and July 2001 for control cohort; time at risk median 0.91 years for IPT group and 0.41 years for control group | 559 HIV-infected miners with history of successfully treated TB; 338 men getting secondary IPT and 221 control cohort | Mortality not significantly reduced in IPT cohort (mortality rate ratio = 0.7, 0.39–1.24), even after accounting for CD4/cotrimoxazole provision.<br>Number of person-years of IPT required to prevent 1 case of recurrent TB among individuals with a CD4 cell count < 200 x 106 cells/l, and > or = 200 x 106 cells/l was 5 and 19, respectively. | 2-Fair | 2-Fair | 2-Medium | No | Secondary prophylaxis study<br>Adverse events: IPT interrupted and then restarted because of rash (n = 2), nausea (n = 1) and abdominal pain (n = 1); stopped and not restarted in 3 patients because of rash; no episodes of hepatitis or peripheral neuropathy. |
| de Pinho, A.M., et al., 2001.[5] | Prospective cohort analysis | Brazil<br>Enrollment Jan 1991 to Dec. 1994; enrollment follow-up Sept .1998; median follow-up | 297 TST-positive PLHIV; 128 given anti-TB chemoprophylaxis (83 INH, 45 RIF+PZA); | Chemoprophylaxis associated with significantly lower risk of death, HR = 0.31 (0.13–0.75) including after adjusting for baseline CD4 aHR 024 (0.09–0.65) | 1-Good | 1-Good | 2-Medium | No | Chemoprophylaxis included 2 groups: 1) INH x 12 months and 2) RIF+PZA x 2 months. |

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| | | 43.6 months | 169 did not receive either. | | | | | | |
| Fitzgerald, D.W., et al., 2000.[6] | Randomized, placebo-controlled trial | Haiti Enrollment completed July1998, follow-up completed July 1999; | 233 adults (≥18 years) 142 PLHIV completing treatment for TB; 74 given placebo and 68 given INH. | No difference in mortality noted with 17 deaths in each group. RR = 0.93 (0.51–1.65). | 2-Fair | 2-Fair | 2-Medium | No | Secondary prophylaxis study: Used 12 months of post-treatment INH. |
| Fitzgerald, D.W., et al., 2001.[7] | Randomized, placebo-controlled trial | Haiti Enrollment completed Dec. 1998, follow-up completed Dec. 1999; mean follow-up 2.4-2.5 years | 237 PPD-negative PLHIV (≥18 years) | No difference in mortality for INH x 12 months vs. placebo, RR = 1.05 (0.55–2.03). | 2-Fair | 2-Fair | 1-Strong | No | >90% of persons who were PPD negative (n = 146) responded to candida/MMR (n = 133), so anergy did not appear to be common. |
| Hawken, M.P., et al., 1997.[8] | Randomized, double-blind, controlled trial | Kenya April 1992-March 1994; median follow-up 1.83 years | 684 PLHIV (age 14-65) | Mortality of INH vs. placebo cRR = 1.11 (0.77–1.68); aRR = 1.18 (0.79–1.75);<br>If TST positive, aRR = 0.33 (0.09–1.23);<br>If TST negative, aRR = 1.39 (0.9–2.12) | 2-Fair | 1-Good | 1-Strong | No | Median CD4 = 322 (INH) and 346 (placebo); Lack of significance partly attributed to small numbers and poor adherence..<br>Adherence: Based on tablet count: 42% missed <1 wk, 31% missed >52 wks;<br>Adverse events: No significant difference in adverse events for INH vs. placebo, RR = 1.41 (0.78-2.54). |
| Johnson, J.L., et al., | Randomized, double- | Uganda March 1993 | 2,736 PLHIV (2,018 PPD- | No difference in mortality among the treatment arms | 1-Good | 2-Fair | 1-Strong | No | Continuation study as follow-up to Whalen et al. |

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| 2001.[9] | blind, controlled trial | - April 1995, mean follow-up 1.6 in anergic cohort and 2 years among PPD-positive individuals | positive, 718 anergic) | for either the PPD-positive or anergic cohorts. | | | | | Compared three regimens: INH daily x 6 months, INH+RIF x 3 months, and INH+RIF+PZA x 3 months.. |
| Kabali, C., et al., 2011.[10] | Cohort study nested within a randomized trial | Tanzania Sept. 2001-Jan. 2008 | 588 TST-positive PLHIV in cohort of PLHIV with baseline CD4 >200, 488 completed 6 months of IPT and 70 did not | Completion of IPT associated with increased survival in HIV-infected adults with CD4>200 and positive TST, crude HR=0.4 (0.2–0.8) and equivalent adjusted HR. | 1-Good | 1-Good | 2-Medium | No | |
| Khawcharoenporn, T., et al., 2012.[11] | Prospective, non-randomized intervention trial | Thailand Jan. 2004-Jan. 2008, 4 years | 400 PLHIV, 200 underwent TST and received IPT if positive; 200 not screened | No difference in all-cause mortality (3%) between those receiving IPT and those not. | 2-Fair | 2-Fair | 2-Medium | No | Adherence: In IPT group only 17 participants (9%) had reactive TST< and of these, 14 (82%) completed IPT.<br>Adverse events: No significant adverse drug reactions or treatment interruptions reported. |
| Lim, H.J., et al., 2006.[12] | Randomized, double-blind, placebo-controlled trial | Uganda Enrollment period: March 1993-April 1995; follow-up: last clinic visit before Aug. 1998 | 2,736 PLHIV randomized based on PPD status | No difference noted in relative hazard of AIDS Progression or death when comparing placebo to INH (HR = 1.02, 0.80–1.3); INH+RIF x 3 months (HR = 0.91, 0.71–1.17); or INH+RIF+PZA x 3 months (HR = 0.90, 0.72–1.12). | 2-Fair | 2-Fair | 1-Strong | No | Study was designed so that PPD positive (>5mm) pts assigned to INH daily x 6 months (n = 536), INH+RIF daily x 3 months (n = 556), INH+RIF+PZA x 3 months (n = 464) or placebo (n = 323). Patients with cutaneous anergy randomly assigned to INH |

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| | | | | | | | | | (n = 395) or placebo (n = 323) daily x 6 months. |
| Mohammed, A., et al., 2007.[13] | Randomized, double-blind, placebo-controlled trial | South Africa Study end: Dec 2004; Median follow-up 350 days in INH group, 358 days in placebo group and 1,130 days in INH open-label arm | 118 PLHIV, 20 TST positive (received open-label INH) 98 TST negative (randomized to INH vs. placebo) | No significant differences in death rate between INH and placebo groups (14/48 vs.18/50, p = 0.318). | 1-Good | 1-Good | 1-Strong | No | Adherence: Median adherence was 85% in randomized trial arms (similar for INH and placebo) and 92% in open-label INH arm.<br>Adverse events: 3 cases of peripheral neuropathy occurred in the INH arm and none in the placebo arm (p = 0.114). |
| Mwinga, A., et al., 1998.[14] | Randomized, double-blind, controlled trial | Zambia Aug. 1992-July 1994; Median follow-up 1.8 years | 1,053 PLHIV (age≥ 15 years), 352 on placebo, 350 on INH, and 350 on RIF+PZA | No significant difference noted in mortality rate for either group:<br>INH vs. placebo: Mortality cRR = 1.05 (0.73–1.50);<br>RIF+PZA vs. placebo: Mortality cRR = 1.24 (0.87–1.76); | 2-Fair | 2-Fair | 1-Strong | No | Adherence: Overall compliance was 74%.<br>Adverse events: 29 subjects (3%) taken off of regimen due to adverse events.. |
| Quigley, M.A., et al., 2001.[15] | RCT converted to cohort study | Zambia Aug. 1992-July 1994; Mean follow-up 3 years (up to 1999) | 1,053 PLHIV originally enrolled: 112 initial placebo patients placed on INH x 6 months; 44 placebo patients refused or ineligible for IPT | No significant difference noted in mortality rate for either group:<br>For INH vs. placebo mortality RR = 0.95 (0.71–1.28);<br>For RIF+PZA vs. placebo mortality cRR = 1.24 (0.94–1.65). | 2-Fair | 2-Fair | 2-Medium | No | Follow-up study to Mwinga et al. Analysis done as ITT using original randomized arms. |
| Rangaka M.X., et | Randomized, placebo- | South Africa | 1,369 ART-treated | No significant difference noted in all-cause mortality | 1-Good | 1-Good | 1-Strong | No | Median CD4 = 216<br>Adherence: No difference |

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| al., 2014.[16] | controlled trial | Jan 2008-Sept 2011; Median follow-up 2.5 yrs | PLHIV (age≥ 18 years), 667 on placebo, 662 on INH | for INH vs. placebo: HR = 0.72 (0.34-1.34) | | | | | in median months on study drug or total doses dispensed<br>Adverse events: No difference in discontinuation of study drug due to adverse events |
| Whalen, C.C., et al., 1997.[17] | Randomized, placebo-controlled trial | Uganda March 1993-April 1995; designed for 3-year follow-up, but stopped due to success of interven-tion | 2,736 PLHIV randomized based on PPD status | Cumulative mortality rate was 20%. Mortality did not differ between groups:<br>INH vs. placebo, RR = 0.9 (0.6–1.2);<br>INH+RIF vs. placebo, RR = 0.8 (0.5–1.2);<br>INH+RIF+PZA vs. placebo, RR = 0.96 (0.7–1.4);<br>Overall mortality was higher in anergic cohort (p = 0.001), INH vs. placebo RR = 1.05 (0.77–1.42). | 1-Good | 2-Fair | 1-Strong | No | Study compared 3 different prophylactic regimens with placebo for PPD positive participants: INH daily x 6mo, INH+RIF daily x 3 months, INF+RIF+PZA daily x 3 months<br>Adherence: Of 90% of participants tested for INH urine metabolites (scheduled and random) 75% tested positive.<br>Adverse events: Discontinuation rate of 0.2% for placebo, 0.6% for INH, 2.3% for INH+RIF, and 5.6% for INH+RIF+PZA. |
| Wilkinso n, D., 1998.[18] | Meta-analysis | Multi-country Articles from 1989-1997; follow-up 15-33 months | 4 trials with 4,055 PLHIV (from U,S., Haiti, Kenya, Uganda) comparing INH to placebo | Mortality was significantly reduced in TST-positive individuals, but not TST negatives:<br>INH + other prophylaxis vs. placebo, mortality RR = 0.93 (0.83–1.05);<br>For TST positives, RR = 0.73 (0.57–0.95);<br>For TST negatives RR = 1.02 (0.89–1.17). | 2-Fair | 2-Fair | 1-Strong | No | Adherence: Adherence estimated at 63-75%.<br>Adverse events: Adverse drug reactions higher in treatment group, but not significantly RR = 1.45 (0.98–2.14). |
| Durovni, B., et al., 2013.[19] | Stepped-wedge, cluster-randomized trial | Brazil Sept. 2005-Aug. 2009 | 12,816 PLHIV seen in one of 29 city health department clinics | The multi-component intervention reduced the combination of TB and death in participants, HR = 0.76 (0.66–0.87), aHR = 0.69 (0.57–0.83) | 2-Fair | 2-Fair | 2-Medium | No | Intervention in this study had multiple components, including training on TB screening, use of TST, IPT, and TB treatment. Median CD4 at first visit was 426. |

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| | | | during study period | | | | | | Adherence: Of patients that tested TST positive, 82% began IPT, and 85% of these completed IPT.<br>Adverse events: 22 (1.5%) of participants experienced treatment interruptions due to adverse events. |
| Dowdy, D.W., et al., 2014.[20] | Modeling study | Brazil<br>Modeled 5 year period | Population of 4.1 million; | Providing IPT to 20% of eligible PLHIV per year decreased TB-related mortality by 14% over the course of 5 years | 2-Fair | 2-Fair | 2-Medium | | Follow-on to Durovoni et al estimating impact of intervention if continued expansion at same rate over 5 years. |
| Samandari, T., et al., 2011.[21] | Randomized, double-blind, placebo-controlled trial | Botswana<br>Nov. 2004-July 2006 with 3 years of follow-up | 1,995 PLHIV randomly assigned to 6 months INH+30 months of masked placebo (989) or 6 months INH+30 months of masked INH (1006). | Death rate was not significantly decreased in all patients who received 36 months vs. 6 months of treatment, but was significantly decreased in participants who were TST positive:<br>Overall HR = 1.00 (0.64–1.56)<br>TST positive HR = 0.32 (0.11–0.90)<br>TST negative HR = 1.28 (0.76–2.15). | 1-Good | 2-Fair | 1-Strong | No | Duration study: Benefit of 6-months of INH decreased approx. 200 days after completion.<br>Adherence: 821/989 (83%) persons completed INH x 6 months + placebo x 30 months, 834/1,006 (83%) persons completed INH x 36 months.<br>Adverse events: 1% of participants in placebo group vs. 1.3% in intervention group had severe adverse events during the 30-month extension period (p =0.36). |
| Swaminathan, S., et al., 2012.[22] | Randomized, open-label controlled trial | India<br>March 2001-October 20025 | 712 PLHIV randomized to INH 300 mg+etham-butol 800 mg for 6 months; or INH 300 mg for 36 months | There was no difference in crude mortality for INH+ethambutol vs. INH x 36 months, irrespective of TST status:<br>Overall mortality aIRR = 1.20 (0.66–2.18)<br>For TST positive: aIRR = 1.51 (0.56–4.02)<br>For TST negative: aIRR = 1.10 (0.50–2.41). | 1-Good | 2-Fair | 2-Medium | No | |

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| Gordin, F., et al., 2000.[23] | Randomized, open-label controlled trial | Multi-country Sept. 1991-May 1996; follow-up Oct 1997; mean follow-up 37 months | 1,583 TST-positive PLHIV ≥13 years in U.S., Mexico, Haiti and Brazil | No significant difference in the risk of death between the two regimen, uRR = 0.87 (0.69–1.09), aRR=0.86 (0.68–1.08). | 1-Good | 1-Good | 2-Medium | No | Median CD4 on entry: 426. No difference noted when stratified by presence or absence of AIDS. Adherence: 80% completed RIF+PZA compared to 69% IPT completion (p = <0.001). Adverse events: Study drug discontinued in 10% of RIF+PZA and 6% of INH group (p = 0.01), though abnormal LFTs more common in INH group (p = 0.02). |
| Halsey, N.A., et al., 1998.[24] | Randomized clinical trial | Haiti Enrollment April 1990-July 1992; follow-up up to 4 years | 730 TST-positive PLHIV assigned to INHx6 (370) or RIF+PZA x 2 months (380) | No difference in mortality rate with 72 and 71 deaths respectively (p = 0.85). | 2-Fair | 2-Fair | 1-Strong | No | Adherence: Identical number of patients dropped during the first two months of therapy, but adherence was better in the RIF+PZA group compared to INH due to duration of therapy. Adverse events: No serious adverse reactions or discontinuations reported. |
| Martinson, N.A., et al., 2011.[25] | Randomized clinical trial | South Africa Sept. 2002-June 2005 with a median follow-up of 4 years | 1,528 TST-positive PLHIV. 1,150 randomized to INH+RFP x 3 months (329), INH+RIF x 3 months (329), INH x 6 months (328), and continuous INH (up to 6 years) (164) | No significant difference in the risk of death between the 2 regimens, uRR = 0.87 (0.69–1.09), aRR = 0.86 (0.68–1.08). | 2-Fair | 2-Fair | 1-Strong | No | Adherence: Proportion taking at least 90% of study medications varied by group (96% for INH+RFP, 95% for INH+RIF, 83% for INH x 6 months, and 89% for continuous INH during follow-up) . Adverse events: Rates of serious adverse events also varied by group (8.7 per 100 person-years in the INH+RFP group, 10.6 in the INH+RIF group, 15.4 in the |

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| | | | | | | | | | INH x 6 months group and 18.4 in the continuous-INH group). |
| Alaei, K., et al., 2002.[26] | Prospective cohort study | Iran October 1997-April 1998, with 3-year follow-up | 246 TST-positive, HIV-infected male prisoners with history of injection drug use | During the 3-year follow-up, 41 (17%) of participants died. | 3-Poor | 3-Poor | 2-Medium | No | No comparison group. 94 cases (38%) were loss to follow-up. |
| Mosimaneotsile, B., et al., 2010.[27] | Cohort study | Botswana Enrollment Nov. 2004-June 2006 | 1,995 PLHIV (age≥ 18 years) without acute illness, or history of TB/previous receipt of IPT | 20 patients (1%) died while on IPT<br>9 of 16 (56%) deaths with sufficient information were due to AIDS-defining illnesses. (Three deaths were categorized as possible TB deaths.) | 2-Fair | 2-Fair | 2-Medium | No | No comparison group.<br>Adherence: 86% of clients completed the 6-month course of IPT, and 91% of those with pill count data (1375/1511) to ≥80% of their pills.<br>Adverse events: 28 (1.4%) of participants were reported as having serious adverse events including 1 death from hepatic encephalopathy. |
| Bell, J.C., et al., 1999.[28] | Markov model | Uganda | Hypothetical cohort of 100,000 TST-positive PLHIV | All three regimens extend life expectancy and QALYs. RIF+PZAx2 months resulted in better health outcomes than INH x 6months months and INH/RIF x 3 months. | NA | NA | NA | Yes – Level 2 All 3 regimens were less expensive than no preventive therapy. Providing INH x 6 months saves $24.16 per person, relative to the other regimens. | Modeled comparison of INH x 6 months vs. INF+RIF x 3 months vs. INH+RIF+PZA x 2 months vs. no prophylaxis. Separate estimates made based on: 1) TB cases, 2) TB + social costs, 3) TB + social costs + secondary infections. The cost-effectiveness ratios are sensitive to assumptions about costs, effectiveness of intervention, and number of secondary cases. |

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| Pho, M.T., et al., 2012.[29] | Trial-based cost-effectiveness analysis | India Modeled period of 3 and 10 years and projected life expectancy | Hypothetical cohort of 100 person-years (PY) | Six months of INH+ethambutol resulted in an estimated increased life expectancy of 0.8 months (at a cost of $100). 36 months of INH increased life expectancy by 0.2 months at a cost of $55. | NA | NA | NA | Yes-Level 2 INH+etham-butol was deemed cost-effective with an incremental cost-effectiveness ratio (ICER) of $1,490/year of life saved (YLS). 36 months of INH had an ICER of $3120/YLS | Evaluated life expectancy, TB incidence, cost, and ICER in patients receiving INH+ethambutol x 6 months vs. INH x 36 months in India; WHO suggests that an IPT strategy is "cost-effective" when the ICER is <3x the GDP per capita (which is $980 in India). |
| Shrestha, R.K., et al., 2007.[30] | Markov cohort simulation | | Modeled | IPT program targeted based on TST resulted in an additional 11 quality-adjusted life years (QALYs) per 100-HIV infected clients. Providing IPT without using TST screening resulted in an additional 30 QALYs per 100-HIV infected clients. | NA | NA | NA | Yes-Level 2 Cost-utility was $83 per QALY gained using TST and $89 per QALY gained without using TST at 6 months if 6 months of IPT were provided | Information modeled effect on QALYs using actual program data (patient outcomes and costs) collected from IPT program that was implemented using the TST strategy at the AIDS Information Center in Uganda; TST sensitivity and specificity were based on published literature. |
| **Morbidity** | | | | | | | | | |
| Akolo, C., et al., 2010.[1] | Meta-analysis | Multi-country Update of previous review, studies from 1993 through April 2008 | 12 RCTs with a total of 8,578 PLHIV ≥13 years without active TB, randomized to TB | INH reduced incidence of active TB by 33% compared to placebo: RR=0.67, 0.51–0.87. For TST positive, INH reduced the risk of active TB by 62%: RR=0.38, 0.25–0.57. No significant effect noted | 1-Good | 1-Good | 1-Strong | No | Adherence: Some evidence that adherence improves with shorter duration of prophylaxis Adverse events: Preventive therapy led to more adverse events compared to placebo (6 trials; 5525 participants; RR=2.55, |

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| | | | preventive therapy and placebo or alternative regimens | in TST negative persons: R= 0.89, 0.64–1.24.<br>No significant difference in effectiveness of INH compared to other preventive regimens (including RIF+PZA, INH+RIF, and INH+RIF+PZA). | | | | | (1.70–3.85). The likelihood of stopping treatment due to adverse effects was higher for combination therapies than for INH monotherapy. |
| Bucher, H.C., et al., 1999.[2] | Meta-analysis | Multi-country Articles published from 1993 to 1998; mean follow-up, 0.4-3.2 years | 7 RCTs included in the meta-analysis: 2,367 PLHIV received INH and 2,162 received placebo | Significant reduction in TB incidence noted for all patients combined (RR = 0.58, 0.43–0.8), and TST positive individuals (RR = 0.40, 0.24–0.65), but not TST negative individuals, (RR = 0.84, 0.54–1.30) | 2-Fair | 2-Fair | 1-Strong | No | Adverse events: No significant difference in all side effects from 4 trials (INH vs. placebo), RR = 1.36 (1.00-1.86) or drug-limiting toxicity, RR = 1.66 (0.83-3.32); There was noted to be an increase in hepatotoxicity, defined as twofold increase in AST, RR = 1.80 (1.05-3.10). |
| Churchyard, G.J., et al., 2003.[4] | Cohort study | South Africa Started Dec. 2000 for IPT cohort and July 2001 for control cohort, time at risk median 0.91 years for IPT group and 0.41 years for control group | 559 HIV-infected miners with hx of successfully treated TB; 338 men getting secondary IPT and 221 control cohort | Recurrent TB reduced by 55% in persons receiving IPT, IRR = 0.45 (0.26–0.78). IPT had greater effect in men with only 1 past episode of TB vs. more episodes (p=0.03) and in men with previously culture confirmed MTB (p=0.001). | 2-Fair | 2-Fair | 2-Medium | No | Secondary prophylaxis study<br>Adverse events: IPT interrupted and then restarted because of rash (n = 2), nausea (n = 1) and abdominal pain (n = 1); stopped and not restarted in 3 patients because of rash; no episodes of hepatitis or peripheral neuropathy. |
| de Pinho, A.M., et al.,. | Cohort study | Brazil Enrollment Jan 1991 | 297 TST-positive PLHIV; 128 | Chemoprophylaxis was associated with significant reduction in risk of | 1-Good | 1-Good | 2-Medium | No | Chemoprophylaxis included 2 groups: 1) INH x 12 months and 2) RIF+PZA |

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| 2001.[5] | | to Dec. 1994; enrollment follow-up Sept. 1998; median follow-up 43.6 months | given anti-TB chemoprophylaxis (83 INH, 45 RIF+PZA); 169 did not receive either. | developing TB (OR = 0.43, 0.18–0.99) and similar result observed after adjustment for CD4 count (OR = 0.38, 0.14–1.04). | | | | | x 2 months. |
| Fitzgerald, D.W., et al., 2000.[6] | Randomized, placebo-controlled trial | Haiti 1998 | 233 adults (≥18 years) 142 PLHIV completing treatment for TB; 74 given placebo and 68 given INH. | TB incidence was significantly reduced in HIV-positive individuals with rate of 7.8 vs 1.4 in patients on INH vs. placebo, RR=0.18 (0.4–0.83) | 2-Fair | 2-Fair | 2-Medium | No | Secondary Prophylaxis Study: Used 12 months of post-treatment INH. |
| Fitzgerald, D.W., et al., 2001.[7] | Randomized, placebo-controlled trial | Haiti Enrollment completed Dec. 1998, follow-up completed Dec. 1999; mean follow-up 2.4-2.5 years | 237 PPD-negative PLHIV (≥18 years). | No difference in incidence of TB disease noted for INH x 12 months, RR=1.27 (0.36–4.37) | 2-Fair | 2-Fair | 1-Strong | No | >90% of persons who were PPD negative (n = 146) responded to candida/MMR (n = 133), so anergy did not appear to be common. |
| Golub, J.E., et al., 2007.[31] | Retrospective cohort study | Brazil Sept. 2003-Sept. 2005 | 11,026 PLHIV; Comparison made based of time on therapy, time on IPT only, time on ART only, | Both IPT and ART led to a reduction in TB incidence, but the two combined were significantly more likely to reduce TB incidence: ART-only RH = 0.55 (0.45–0.68) IPT only, RH = 0.36 (0.15–0.89) | 2-Fair | 2-Fair | 2-Medium | No | Median CD4 cell count was 365. 74% of patients received ART. ~80% of those receiving IPT were TST positive. Adherence: IPT completion rate 76%. |

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| | | | and time on both. | IPT+ART, RH = 0.23 (0.12–0.45).<br>After adjusting for age, CD4, and previous TB, IPT alone does not remain significant, but IPT+ART does:<br>IPT only, aRH = 0.57 (0.18–1.82)<br>IPT+ART, aRH = 0.24 (0.11–0.53) | | | | | |
| Golub, J.E., et al., 2009.[32] | Prospective cohort study | South Africa June 2003–Dec. 2007 | 2,778 PLHIV (≥18 years); Total 4,287 person-years follow-up (2,815 treatment-naïve, 954 HAART only, 427 IPT only, 132 both IPT and HAART) | IPT alone did not significantly reduce TB in patients who were not on ART, but did significantly reduce TB incidence when combined with ART:<br>IPT only (no ART), HR = 0.71 (0.45-1.10); aHR = 0.87 (0.55–1.36)<br>IPT+ART vs. ART alone: HR = 0.14 (0.02–1.03) vs. 0.62 (0.4–0.87); aHR = .11 (0.02–0.78) vs. 0.36 (0.25–0.51). | 2-Fair | 2-Fair | 2-Medium | No | Median baseline CD4 = 266. 79% had TST done, and 96% of them were TST positive.<br>Adherence: Completion rate was 59%; ITT analysis done. |
| Hawken, M.P., et al., 1997.[8] | Randomized, double-blind, controlled trial | Kenya April 1992-March 1994; median follow-up 1.83 yrs | 684 PLHIV (age 14-65) | TB incidence was not significantly reduced in INH vs. placebo for any group: Overall cRR = 1.11 (0.64–1.98); aRR = 0.92 (0.49–1.71).<br>For TST positive aRR = 0.6 (0.23–1.6), and for TST negative aRR = 1.23 (0.55–2.76). | 2-Fair | 1-Good | 1-Strong | No | Median CD4=322 (INH) and 346 (placebo); Lack of significance partly attributed to small numbers and poor adherence.<br>Adherence: Based on tablet count: 42% missed <1 week, 31% missed >52 weeks;<br>Adverse events: No significant difference in adverse events for INH vs. |

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| | | | | | | | | | placebo, RR = 1.41 (0.78-2.54) |
| Johnson, J.L., et al., 2001.[9] | Randomized, double-blind, controlled trial | Uganda March 1993-April 1995; mean follow-up 1.6 in anergic cohort and 2 years among PPD-positive individuals | 2,736 PLHIV (2,018 PPD-positive, 718 anergic) | No difference using IPT, but combination regimens did reduce TB incidence. PPD-positive group (3 regimen vs. placebo):<br>INH, RR = 0.76 (0.48–1.20), aRR = 0.67 (0.42–1.07)<br>INH+RIF, RR = 0.46 (0.48–0.77) , aRR = 0.49 (0.29–0.82)<br>INH+RIF+PZA, RR = 0.47 (0.26–0.86), aRR = 0.41 (0.22–0.76)<br>Anergic group (INH vs. placebo):<br>RR = 0.67 (0.42–1.07), aRR = 0.61 (0.32–1.16). | 2-Fair | 2-Fair | 1-Strong | No | Continuation study as follow-up to Whalen et al. Compared three regimens: INH daily x 6 months, INH+RIF x 3 months, and INH+RIF+PZA x 3 months. Duration of efficacy: Noted that for INH x 6 months vs. placebo aRR was 0.11 (0.01-0.93) at 9 months, 0.49 (0.16-1.51) at 12 months, and 0.68 (0.35-1.35) at 24 months |
| Kabali, C., et al., 2011.[10] | Cohort study nested within a randomized trial | Tanzania Sept. 2001–Jan..2008 | 588 TST-positive PLHIV in cohort of PLHIV with baseline CD4 >200, 488 completed 6 months of IPT and 70 did not | Completion of IPT associated with increased survival in HIV-infected adults with CD4 counts >200 and positive TST, but protective effect did not extend to incidence of active TB (crude HR 0.7, 0.3–1.5; adjusted HR 0.6, 0.3–1.3). | 1-Good | 1-Good | 2-Medium | No | Authors offered several reasons why reduction in mortality but not in TB incidence:<br>1. IPT therapy may have been partially effective, but were underestimated in "non-completers"<br>2. Smear-negative TB tend to be common among patients at advanced stage of HIV<br>3. Study was statistically underpowered to detect an effect of magnitude seen in this study. |
| Khawcharoenporn, T., et al., 2012.[11] | Prospective, non-randomized intervention trial | Thailand Jan. 2004–Jan. 2008, 4 years | 400 total PLHIV; one group of TST-positive persons who | Incidence of pulmonary TB was significantly higher during the first 6 months in the non-IPT group than in the IPT group (8.60 vs. 0 | 2-Fair | 2-Fair | 2-Medium | No | Duration study: Effect noted only during first 6 months of treatment, and waned there-after. Adherence: In IPT group |

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| | | | received IPT and one group who received no IPT | cases/100 py, p = 0.01), regardless of initial CD4 count (though all cases occurred in patients with CD4<200); however, the 4-year incidence of pulmonary TB was not statistically different for the IPT and non-IPT groups (0.80 vs. 1.76 cases/100,000 person-years). | | | | | only 17 participants (9%) had reactive TST, and of these, 14 (82%) completed IPT. Of note: None of the patients that received IPT subsequently developed TB.<br>Adverse events: No significant adverse drug reactions or treatment interruptions reported. |
| Khongphatthanayothin, M., et al., 2012.[33] | Prospective cohort study | Thailand Jan. 2003-April 2008 | 4,339 PLHIV; 4,111 (95%) underwent TST, 1157 (28%) were TST positive, 799 (69%) initiated IPT | Outcomes only assessed in 358 (8.5%) of patients with TST test. TB not reported in any patients completing IPT compared to 2 TB cases (2%) amongst TST positive patients who did not complete IPT (p=0.084) and 34 TB cases (2%) amongst patients who were originally TST negative. | 3-Poor | 2-Fair | 2-Medium | No | Baseline CD4 of 304 (405 for TST positive and 267 for TST patients); 23% of patients on ART at the time of TST. Very high loss to follow-up noted.<br>Adherence: Of 799 patients that initiated IPT, 633 (79%) completed 6 months of IPT and 551 (69%) completed 9 months of IPT.<br>Adverse events: 1.2% developed grade 3 or higher liver enzyme elevations at 3 months and 1% at 6 months; all returned to baseline after IPT discontinued. |
| Lahey, T., et al., 2013[34] | Case control (Secondary analysis of randomized placebo-controlled vaccine trial) | Tanzania Enrollment from 2001-2005 with follow-up through Jan. 2008; mean follow-up 3.2 years | 979 PLHIV (age≥ 18 years), with CD4 >200 enrolled in placebo arm of TB vaccine trial | Definite TB diagnosed in 52 (5%) and probable TB in 92 (9%). 20 (39%) of those with definite TB completed 180 days of INH, 29 (32%) of those with probable TB completed 180 days of INH, and 216 (24%) of patients without TB completed IPT, p = .072. Likelihood of TB associated with history of | 2-Poor | 2-Fair | 2-Medium | No | All TST-positive participants (and only TST-positive participants) were offered IPT.<br>Adherence: 88% completed 6 months of IPT. |

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| | | | | prior active TB irrespective of TST status of IPT administration. | | | | | |
| Kibret, K.T., et al., 2013.[35] | Case control | Ethiopia Dec. 2011–Feb. 2012 | 593 PLHIV ≥18 years, (196 cases, 397 controls). Cases were PLHIV with TB after ART initiation; controls were PLHIV without TB after ART initiation | INH significantly reduced the risk of TB infection in PLHIV, (AOR=0.35, 0.13–0.29). | 2-Fair | 1-Good | 2-Medium | No | Note: Cotrimoxzaole was also significant in reducing TB incidence (AOR = 0.19, 0.06-0.62). |
| Mohammed, A., et al., 2007.[13] | Randomized, double-blind, placebo-controlled trial | South Africa Study end date: Dec 2004; Median follow-up 350 days in INH group, 358 days in placebo group and 1130 in INH open-label arm | 118 PLHIV: 20 TST-positive (received open-label INH), 98 TST-negative (randomized to INH vs. placebo) | No significant between placebo and INH arms in TB incidence (HR = 1.59, 0.57–4.49; aHR = 2.02, 0.65–5.23), hospitalization (p = 0.999) or decline in lymphocyte count (p = 0.311). | 1-Good | 1-Good | 1-Strong | No | Adherence: Median adherence was 85% in randomized trial arms (similar for INH and placebo) and 92% in open-label INH arm.<br>Adverse events: 3 cases of peripheral neuropathy occurred in the INH arm and none in the placebo arm (p=0.114). |
| Mwinga, A., et al., 1998.[14] | Randomized, double-blind, controlled trial | Zambia Aug. 1992-July 1994; median follow-up 1.8 years | 1,053 PLHIV (age≥ 15 years), 352 on placebo, 350 on INH, and 350 on RIF+PZA | Prophylaxis led to significant reductions in TB (If probable TB included)<br>INH vs. placebo: cRR = 0.62 (0.38–0.99);<br>RIF+PZA vs. placebo, cRR = 0.58 (0.35–0.95);<br>Either chemoppx vs. | 2-Fair | 2-Fair | 1-Strong | No | TB reduction was noted to be higher in persons with higher lymphocyte count.<br>Adherence: Overall compliance was 74%.<br>Adverse events: 29 subjects (3%) taken off of regimen due to adverse |

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| | | | | placebo: cRR = 0.60 (0.40–0.89);<br>Effect significant in participants with positive TST (RR = 0.27, 0.08–0.87) but not negative TST (RR = 1.06, 0.46–2.46). | | | | | events. |
| Quigley, M.A., et al., 2001.[15] | RCT converted to cohort study | Zambia Aug .1992-July1994; mean follow-up 3 years (up to 1999) | 1,053 PLHIV originally enrolled: 112 initial placebo patients placed on INH x 6 months; 44 placebo patients refused or ineligible for IPT | Noted diminishing effect over time, though reduction in TB incidence significant for first 2.5 years: INH vs. placebo, cRR = .52 (0.27–1.00); RIF+PZA vs. placebo, cRR = 0.58 (0.3–1.09); Either chemo ppx vs. placebo cRR = 0.55 (0.32–0.93). | 2-Fair | 2-Fair | 2-Medium | No | Follow-up study to Mwinga et al (See regimen above). Analysis done as ITT using original randomized arms. Duration study: Cumulative benefit was present in first 2.5 years only. |
| Rangaka, M.X., et al., 2014.[16] | Randomized, placebo-controlled trial | South Africa Jan 2008-Sept 2011; Median follow-up 2.5 years | 1,369 ART-treated PLHIV (age≥ 18 years), 667 on placebo, 662 on INH | Significant reduction in TB incidence in patients who received INH vs. placebo; aHR=0.64 (0.42-0.96)<br>Difference higher among TST negative than TST positive perons:<br>TST negative: aHR = 0.43 (0.21-0.86)<br>TST negative: aHR=0.86 (0.37-2.0) | 1-Good | 1-Good | 1-Strong | No | Median CD4 = 216<br>Adherence: No difference in median months on study drug or total doses dispensed<br>Adverse events: No difference in discontinuation of study drug due to adverse events |
| Whalen, C.C., et al., 1997.[17] | Randomized, placebo-controlled trial | Uganda March 1993-April 1995; Designed for 3-yr follow-up, but stopped | 2,736 PLHIV randomized based on PPD status | Among TST-positive cohort, TB incidence was significantly decreased in all groups vs. placebo:<br>INH: aRR = 0.32 (0.14–0.76);<br>INH+RIF: aRR = 0.41 (0.19–0.89);<br>INH+RIF+PZA: aRR = 0.43 | 1-Good | 2-Fair | 1-Strong | No | Adherence: Of 90% of participants tested for INH urine metabolites (scheduled and random) 75% tested positive.<br>Adverse events: Discontinuation rate of 0.2% for placebo, 0.6% for INH, 2.3% for INH+RIF, and |

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| | | due to success of interventi on | | (0.20–0.92).<br>Among anergic cohort, there was no statistically significant benefit:<br>INH vs. placebo: aRR = 0.75 (0.30–1.89). | | | | | 5.6% for INH+RIF+PZA |
| Wilkinso n, D., et al., 1998.[18] | Meta-analysis | Multi-country Articles from 1989-1997; follow-up 15-33 months | 4 trials with 4,055 PLHIV adults (from U.S., Haiti, Kenya, Uganda) comparing INH to placebo | Found significant reduction in TB incidence with prophylaxis:<br>INH or other ppx vs. placebo, RR = 0.57 (0.41–0.79);<br>For TST positives, RR = 0.32 (0.19–0.51);<br>For TST negatives, RR = 0.82 (0.50–1.36). | 2-Fair | 2-Fair | 1-Strong | No | Adherence: Adherence estimated at 63-75%.<br>Adverse events: Adverse drug reactions higher in treatment group, but not significantly RR = 1.45 (0.98–2.14). |
| Yirdaw, K.D., et al., 2014.[36] | Retrospectiv e cohort analysis | Ethiopia Sept 2007-Aug 2010; Median follow-up 2 years | 5, 407 PLHIV 2,131 of whom received IPT | IPT significantly reduced incidence of TB, both alone and in combination with ART:<br>IRT only: aHR = 0.36 (0.19-0.66)<br>IPT before ART: aHR = 0.18 (0.08-0.42)<br>IPT after ART: aHR = 0.08 (0.05-0.15)<br>ART only: aHR = 0.32 (0.24-0.43) | 2-Fair | 1-Good | 2-Medium | No | Analysis compared patients during IPT and ART treatment with same patients prior to initiation of either (reference).<br>Adverse events: IPT completion only documented in 24% |
| Durovni, B., et al., 2013.[19] | Stepped-wedge, cluster-randomized trial | Brazil Sept. 2005-Aug. 2009 | 12,816 PLHIV seen in 1 of 29 city health department clinics during study period | The multi-component intervention reduced the incidence of TB after adjustment for potential confounders, HR = 0.87 (0.69–1.10), aHR = 0.73 (0.54–0.99). | 2-Fair | 2-Fair | 2-Medium | No | Intervention in this study had multiple components, including training on TB screening, use of TST, IPT, and TB treatment. Median CD4 at first visit was 426.<br>Adherence: Of patients that tested TST positive, 82% began IPT and 85% of these completed IPT.<br>Adverse events: 22 (1.5%) of participants experienced treatment interruptions |

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| | | | | | | | | | due to adverse events. |
| Dowdy, D.W., et al., 2014.[20] | Modeling study | Brazil Modeled 5 year period | Population of 4.1 million; | Providing IPT to 20% of eligible PLHIV per year decreased TB incidence by 15% over the course of 5 years | 2-Fair | 2-Fair | 2-Medium | | Follow-on to Durovoni et al estimating impact of intervention if continued expansion at same rate over 5 years. |
| Grant, A.D., et al., 2005.[37] | Intervention study with randomized incremental recruitment | South Africa 1999-2001; median follow-up 22 months | 1,655 HIV-infected males Inclusion criteria: Employee at South African-based mining company | Enrollment into a work-related HIV clinic that provided IPT (among other interventions) reduced incidence of TB: IRR = 0 .62 (0.43–0.89). The effect was even greater after adjusting for potential confounders: IRR = 0.54 (0.35–0.83). | 2-Fair | 2-Fair | 2-Medium | No | Median CD4 count was 371 in those who started IPT and 278 in those who hadn't started IPT. Adverse events: 9 patients discontinued IPT because of adverse events |
| Fitzgerald, D.W., et al., 2000.[6] | Retrospective cohort study | Haiti 1992-1998 | 1,005 PLHIV who had completed IPT | 14 (1.4%) of 1,005 PLHIV developed TB disease after IPT. Median time to TB diagnosis was longer for persons who received IPT for longer time periods at 8 months for 6 patients receiving 6 months of INH, 22 months for 5 patients receiving 12-24 months of INH, and 40 months for 3 patients receiving 24-36 months of INH (p = 0.026). | 2-Fair | 2-Fair | 2-Medium | No | Duration study: Evaluation looked at time to development of TB in patients receiving different courses of INH (6 months-3 years. The median CD4 count at TB diagnosis was 240 cells/mm3. |
| Samandari, T., et al., 2011.[21] | Randomized, double-blind, placebo-controlled | Botswana Nov. 2004-July 2006 with 3 years of | 1,995 PLHIV randomly assigned to 6 months INH+30 | TB incidence was significantly decreased in patients who received 36 months vs. 6 months of treatment: HR=0.57 (0.33– | 1-Good | 2-Fair | 1-Strong | No | Duration study: Benefit of 6-months of INH decreased approx. 200 days after completion. Adherence: 821/989 |

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| | trial | follow-up | months of masked placebo (989) or 6 months INH+30 months of masked INH (1,006) | 0.99).<br>When stratified by TST status, only those with positive TST benefited significantly:<br>TST positive HR=0.26 (0.09–0.80);<br>TST negative HR=0.75 (0.38–1.46). | | | | | (83%) persons completed INH x 6 months + placebo x 30 months, 834/1,006 (83%) persons completed INH x 36 months.<br>Adverse events: 1% participants in placebo group vs. 1.3% in intervention group had severe adverse events during the 30-month extension period (p = 0.36). |
| Swaminathan, S., et al., 2012.[22] | Randomized, open-label controlled trial | India March 2001-Oct. 2005 | 712 PLHIV randomized to INH 300 mg + ethambutol 800 mg for 6 months; or INH 300 mg for 36 months | There was no difference in TB incidence between the INH+ethambutol vs. INH x 36 months groups, irrespective of TST status:<br>Overall aIRR = 1.15 (0.68–1.95)<br>For TST positive, aIRR =1.66 (0.63–4.30)<br>For TST negative, aIRR =1.48 (0.55–3.96). | 1-Good | 2-Fair | 2-Medium | No | Adverse events: 2 patients in the 36 month INH arm had severe peripheral neuropathy. |
| Gordin, F., et al., 2000.[23] | Randomized, open-label controlled trial | Multi-country Sept. 1991-May 1996; follow-up Oct 1997; mean follow-up 37 months | 1,583 HIV-positive persons ≥13 years with positive TST in U.S., Mexico, Haiti and Brazil | No significant difference in the risk of TB between the two regimen, uRR = 0.72 (0.40–1.31), aRR = 0.67 (0.36–1.24) | 1-Good | 1-Good | 2-Medium | No | Median CD4 on entry: 426. No difference noted when stratified by presence or absence of AIDS<br>Aherence: 80% completed RIF+PZA compared to 69% IPT completion (p=<0.001)<br>Adverse events: Study drug discontinued in 10% of RIF+PZA and 6% of INH group (p=0.01), though abnormal LFTs more common in INH group (p=0.02) |
| Halsey, N.A., et al., 1998.[24] | Randomized clinical trial | Haiti Enrollment April 1990-July | 730 TST-positive PLHIV assigned to | Overall, no significant difference noted in TB incidence for RIF+PZA vs. INH, HR=1.3 (0.68–2.70). | 2-Fair | 2-Fair | 1-Strong | No | Adherence: Identical number of patients dropped during the first two months of therapy, but |

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| | | 1992; follow-up up to 4 years | INHx6 (370) or RIF+PZA x 2 months (380) | | | | | | adherence was better in the RIF+PZA group compared to INH due to duration of therapy. Adverse events: No serious adverse reactions or discontinuations reported. |
| Martinson, N.A., et al., 2011.[25] | Randomized clinical trial | South Africa Sept. 2002-June 2005 with a median follow up of 4 years | 1,528 TST-positive PLHIV 1,150 randomized to INH+RFP x3 months (329), INH+RIF x 3 months (329), INH x 6 months (328), and continuous INH (up to 6 years) (164) | Incidence rate for RFP & INH 2.0 per 100 person years, RIF & INH 2.0, Continuous INH 1.4, and INH 6 months 1.9. TB incidence rate ratios were 1.05 (0.56-1.97), 1.02 (0.55-1.91), and 0.74 (0.29-1.73) with INH 6 months as the reference group. | 2-Fair | 2-Fair | 1-Strong | No | Adherence: Proportion taking at least 90% of study medications varied by group (96% for INH+RFP, 95% for INH+RIF, 83% for INHx6months, and 89% for continuous INH during follow-up). Adverse events: Rates of serious adverse events also varied by group (8.7 per 100 person-years in the INH+RFP group, 10.6 in the INH+RIF group, 15.4 in the INHx6 months group and 18.4 in the continuous-INH group). |
| Alaei, K., et al., 2002.[26] | Prospective cohort study | Iran Oct. 1997-April 1998, with 3-year follow-up | 246 TST-positive, HIV-infected male prisoners with history of injection drug use | Of 111 patients followed for 3 years receiving IPT (excluding deaths and LTFU), 12 developed TB (rate 3.5/100 person-years). | 3-Poor | 3-Poor | 2-Medium | No | No comparison group. High loss to follow-up. Authors concluded that TB incidence was lower than anticipated TB incidence in absence of IPT. |
| Bakari, M., et al., 2000.[38] | Nested cohort study | Tanzania 1994-1998 2-year follow-up | 143 HIV-infected police officers from cohort of 2,899 officers evaluated for | 2/19 developed TB, 1 who defaulted on IPT and developed TB 1 month later and a second 2 years after completing 6 months of INH. | 3-Poor | 3-Poor | 2-Medium | No | Low participation rate. Of 400 eligible HIV-infected officers, 143 (36%) received HIV test results, 87 of these agreed to IPT and only 37 (43%) of these came for their evaluation. Adherence: 19/29 (66%) |

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| | | | HIV-vaccine trial | | | | | | patients who started IPT completed the course.<br>Adverse events: No serious side effects noted. |
| Mosiman eotsile, B., et al., 2010.[27] | Cohort study | Botswana Enrollment Nov. 2004- June 2006 | 1,995 PLHIV (age≥ 18 years) without acute illness, or history of TB/previous receipt of IPT | During 6 months of follow-up on IPT, 8 (0.40%) developed TB disease. INH resistance was not detected among any TB cases. | 2-Fair | 2-Fair | 2-Medium | No | No comparison group.<br>Adherence: 86% of clients completed the 6-month course of IPT, and 91% of those with pill count data (1375/1511) to ≥80% of their pills.<br>Adverse events: 28 (1.4%) of participants were reported as having serious adverse events, including 1 death from hepatic encephalopathy. |
| Souza, C.T., et al., 2009.[39] | Non-randomized clinical trial | Brazil Aug. 2002-April 2007; Mean follow-up 2.8 years | 138 TST-positive PLHIV | Only 1 person developed TB, equating to a rate of 0.3 per 100 person years. | 2-Fair | 2-Poor | 2-Medium | No | 74% of participants were on ART and mean CD4 was 539.<br>Adherence: 88% adherence.<br>Adverse events: Minor side effects noted in 17 (12%) of participants, 7 (5%) required discontinuation. |
| Bell, J.C., et al., 1999.[28] | Markov model | Uganda | Hypothetical cohort of 100,000 HIV-infected individuals with positive TST | All three regimens reduced TB incidence in PLHIV and secondary infections. | NA | NA | NA | Yes – Level 2<br>All 3 regimens were less expensive than no preventive therapy. Providing INH x 6 months saves $24.16 per person, relative to the other regimens. | Modeled comparison of INH x 6 months vs. INF+RIF x 3 months vs. INH+RIF+PZA x 2 months vs. no prophylaxis.<br>Separate estimates made based on: 1) TB cases, 2) TB + social costs, 3) TB + social costs + secondary infections. The cost-effectiveness ratios are sensitive to assumptions about costs, effectiveness of intervention, and number of secondary cases. |

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| Pho, M.T., et al., 2012.[29] | Trial-based cost-effectiveness analysis | India Modeled period of 3 and 10 years and projected life expectanc y | Hypothetical cohort of 100 person years (PY) | 6 months of INH+ethambutol resulted in an estimated increased life expectancy of 0.8 months (at a cost of $100). 36 months of INH increased life expectancy by 0.2 months at a cost of $55. | NA | NA | NA | Yes - Level 2 INH+ethambut ol was deemed cost-effective with an ICER of $1,490/YLS 36 months of INH had an ICER of $3,120/YLS | Evaluated life expectancy, TB incidence, cost, and ICER in patients receiving INH+ethambutol x 6 months vs. INH x 36 months in India. WHO suggests that an IPT strategy is "cost-effective" when the ICER is <3x the GDP per capita (which is $980 in India). |
| Shrestha, R.K., et al., 2006.[40] | Markov cohort simulation | Uganda Jan. 2001-Jan. 2003; 2-year follow-up | 7,073 HIV-infected patients | | NA | NA | NA | Yes - Level 2 If 6 months of IPT were provided, ICER of providing IPT based on TST result was $157 per case treated; ICER for providing IPT without using TST was $482 per case treated | Information modeled effect on TB cases using actual program data (patient outcomes and costs) collected from IPT program that was implemented using the TST strategy at the AIDS Information Center in Uganda. TST sensitivity and specificity were based on published literature. |

* Acronyms:
GDP = gross domestic product
HR = hazard ratio
ICER = incremental cost effectiveness ratio
INH = isoniazid
IPT = isoniazid preventive therapy
IRR = incident rate ratio
OR = odds ratio
PZA = pyrazinamide
QALYs = quality adjusted life years saved
RCT = randomized control trial
RH = relative hazard
RIF = rifampin
RFP = rifapentine
RR = relative risk
YLS = years of life saved
a = adjusted (e.g. aHR = adjusted hazard ratio)
c = crude (e.g. cRR = crude rate ratio)
u = unadjusted (e.g. uOR = unadjusted odds ratio)

**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 |
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| | **Studies**<br>(# Studies addressing each outcome and references) | **Overall Quality of the Body of Evidence**<br>*(For all studies addressing each outcome)*<br>*(1 = Good; 2 = Fair; 3 = Poor)*<br>*(Score and narrative)* | **Expected Impact of the intervention***<br>*(Based on the main findings from good quality studies addressing the intervention)*<br>*(1 = High; 2 = Moderate; 3 = Low; 4 = Uncertain)* | **Studies**<br>(# Studies with cost effectiveness data addressing each outcome) | **Quality of Evidence from Economic Evaluation**<br>*(Summary assessment)* | |
| **Mortality** | 18 studies of IPT vs. no IPT (or placebo) in adults with HIV<br>2 studies evaluating IPT as part of a multi-component intervention<br>2 RCTs on the optimal duration of IPT<br>8 RCTs comparing INH to rifamycin-based chemoprophylaxis<br>2 studies on IPT with no comparison group | **Fair**<br>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**<br>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.<br>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. |

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| **Morbidity** | 22 studies of IPT vs. no IPT (or placebo) in adults with HIV<br>3 studies evaluating IPT as part of a multi-component intervention<br>3 RCTs on the optimal duration of IPT<br>8 RCTs comparing INH to rifamycin-based chemoprophylaxis<br>5 studies on IPT with no comparison group | **Good**<br>There is a large body of high-quality studies comparing IPT to no IPT (or placebo) in adults with HIV | **High**<br>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** | 1 study on retention in HIV care as a potential outcome of IPT | **Poor** | **Low/Uncertain** | No studies available | | |

[*i] *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.*

**References:**


1. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *The Cochrane database of systematic reviews.* 2010(1):CD000171.
2. Bucher HC, Griffith LE, Guyatt GH, et al. Isoniazid prophylaxis for tuberculosis in HIV infection: a meta-analysis of randomized controlled trials. *Aids.* Mar 11 1999;13(4):501-507.
3. Charalambous S, Grant AD, Innes C, et al. Association of isoniazid preventive therapy with lower early mortality in individuals on antiretroviral therapy in a workplace programme. *Aids.* Nov 2010;24 Suppl 5:S5-13.
4. Churchyard GJ, Fielding K, Charalambous S, et al. Efficacy of secondary isoniazid preventive therapy among HIV-infected Southern Africans: time to change policy? *Aids.* Sep 26 2003;17(14):2063-2070.
5. de Pinho AM, Santoro-Lopes G, Harrison LH, Schechter M. Chemoprophylaxis for tuberculosis and survival of HIV-infected patients in Brazil. *Aids.* Nov 9 2001;15(16):2129-2135.
6. Fitzgerald DW, Desvarieux M, Severe P, Joseph P, Johnson WD, Jr., Pape JW. Effect of post-treatment isoniazid on prevention of recurrent tuberculosis in HIV-1-infected individuals: a randomised trial. *Lancet.* Oct 28 2000;356(9240):1470-1474.
7. Fitzgerald DW, Severe P, Joseph P, et al. No effect of isoniazid prophylaxis for purified protein derivative-negative HIV-infected adults living in a country with endemic tuberculosis: results of a randomized trial. *Journal of acquired immune deficiency syndromes.* Nov 1 2001;28(3):305-307.
8. Hawken MP, Meme HK, Elliott LC, et al. Isoniazid preventive therapy for tuberculosis in HIV-1-infected adults: results of a randomized controlled trial. *Aids.* Jun 1997;11(7):875-882.
9. Johnson JL, Okwera A, Hom DL, et al. Duration of efficacy of treatment of latent tuberculosis infection in HIV-infected adults. *Aids.* Nov 9 2001;15(16):2137-2147.
10. Kabali C, von Reyn CF, Brooks DR, et al. Completion of isoniazid preventive therapy and survival in HIV-infected, TST-positive adults in Tanzania. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease.* Nov 2011;15(11):1515-1521, i.
11. Khawcharoenporn T, Apisarnthanarak A, Manosuthi W, Sungkanuparph S, Mundy LM. Isoniazid preventive therapy and 4-year incidence of pulmonary tuberculosis among HIV-infected Thai patients. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease.* 2012;16(3):336-341.
12. Lim HJ, Okwera A, Mayanja-Kizza H, Ellner JJ, Mugerwa RD, Whalen CC. Effect of tuberculosis preventive therapy on HIV disease progression and survival in HIV-infected adults. *HIV clinical trials.* Jul-Aug 2006;7(4):172-183.
13. Mohammed A, Myer L, Ehrlich R, Wood R, Cilliers F, Maartens G. Randomised controlled trial of isoniazid preventive therapy in South African adults with advanced HIV disease. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease.* Oct 2007;11(10):1114-1120.
14. Mwinga A, Hosp M, Godfrey-Faussett P, et al. Twice weekly tuberculosis preventive therapy in HIV infection in Zambia. *Aids.* Dec 24 1998;12(18):2447-2457.
15. Quigley MA, Mwinga A, Hosp M, et al. Long-term effect of preventive therapy for tuberculosis in a cohort of HIV-infected Zambian adults. *Aids.* Jan 26 2001;15(2):215-222.
16. Rangaka MX, Wilkinson RJ, Boulle A, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. *Lancet.* Aug 23 2014;384(9944):682-690.
17. Whalen CC, Johnson JL, Okwera A, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda-Case Western Reserve University Research Collaboration. *The New England journal of medicine.* Sep 18 1997;337(12):801-808.
18. Wilkinson D, Squire SB, Garner P. Effect of preventive treatment for tuberculosis in adults infected with HIV: systematic review of randomised placebo controlled trials. *Bmj.* Sep 5 1998;317(7159):625-629.

**19.** Durovni B, Saraceni V, Moulton LH, et al. Effect of improved tuberculosis screening and isoniazid preventive therapy on incidence of tuberculosis and death in patients with HIV in clinics in Rio de Janeiro, Brazil: a stepped wedge, cluster-randomised trial. *The Lancet infectious diseases.* Oct 2013;13(10):852-858.

**20.** Dowdy DW, Golub JE, Saraceni V, et al. Impact of isoniazid preventive therapy for HIV-infected adults in Rio de Janeiro, Brazil: an epidemiological model. *Journal of Acquired Immune Deficiency Syndromes: JAIDS.* Aug 15 2014;66(5):552-558.

**21.** Samandari T, Agizew TB, Nyirenda S, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. *Lancet.* May 7 2011;377(9777):1588-1598.

**22.** Swaminathan S, Menon PA, Gopalan N, et al. Efficacy of a six-month versus a 36-month regimen for prevention of tuberculosis in HIV-infected persons in India: a randomized clinical trial. *PloS one.* 2012;7(12):e47400.

**23.** Gordin F, Chaisson RE, Matts JP, et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. Terry Beirn Community Programs for Clinical Research on AIDS, the Adult AIDS Clinical Trials Group, the Pan American Health Organization, and the Centers for Disease Control and Prevention Study Group. *JAMA : the journal of the American Medical Association.* Mar 15 2000;283(11):1445-1450.

**24.** Halsey NA, Coberly JS, Desormeaux J, et al. Randomised trial of isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection. *Lancet.* Mar 14 1998;351(9105):786-792.

**25.** Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. *The New England journal of medicine.* Jul 7 2011;365(1):11-20.

**26.** Alaei K, Alaei A, Mansouri D. Reduction of clinical tuberculosis in HIV-infected males with isoniazid prophylaxis. *Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit.* Nov 2002;8(6):754-757.

**27.** Mosimaneotsile B, Mathoma A, Chengeta B, et al. Isoniazid tuberculosis preventive therapy in HIV-infected adults accessing antiretroviral therapy: a Botswana Experience, 2004-2006. *Journal of acquired immune deficiency syndromes.* May 1 2010;54(1):71-77.

**28.** Bell JC, Rose DN, Sacks HS. Tuberculosis preventive therapy for HIV-infected people in sub-Saharan Africa is cost-effective. *Aids.* Aug 20 1999;13(12):1549-1556.

**29.** Pho MT, Swaminathan S, Kumarasamy N, et al. The cost-effectiveness of tuberculosis preventive therapy for HIV-infected individuals in southern India: a trial-based analysis. *PloS one.* 2012;7(4):e36001.

**30.** Shrestha RK, Mugisha B, Bunnell R, et al. Cost-utility of tuberculosis prevention among HIV-infected adults in Kampala, Uganda. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease.* Jul 2007;11(7):747-754.

**31.** Golub JE, Saraceni V, Cavalcante SC, et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. *Aids.* Jul 11 2007;21(11):1441-1448.

**32.** Golub JE, Pronyk P, Mohapi L, et al. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. *Aids.* Mar 13 2009;23(5):631-636.

**33.** Khongphatthanayothin M, Avihingsanon A, Teeratakulpisarn N, et al. Feasibility and efficacy of isoniazid prophylaxis for latent tuberculosis in HIV-infected clients patients in Thailand. *AIDS research and human retroviruses.* Mar 2012;28(3):270-275.

**34.** Lahey T, Mackenzie T, Arbeit RD, et al. Recurrent tuberculosis risk among HIV-infected adults in Tanzania with prior active tuberculosis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Jan 2013;56(1):151-158.

**35.** Kibret KT, Yalew AW, Belaineh BG, Asres MM. Determinant factors associated with occurrence of tuberculosis among adult people living with HIV after antiretroviral treatment initiation in Addis Ababa, Ethiopia: a case control study. *PloS one.* 2013;8(5):e64488.

**36.** Yirdaw KD, Jerene D, Gashu Z, et al. Beneficial effect of isoniazid preventive therapy and antiretroviral therapy on the incidence of tuberculosis in people living with HIV in Ethiopia. *PloS one.* 08 Aug 2014;9(8).

**37.** Grant AD, Charalambous S, Fielding KL, et al. Effect of routine isoniazid preventive therapy on tuberculosis incidence among HIV-infected men in South Africa: a novel randomized incremental recruitment study. *JAMA : the journal of the American Medical Association.* Jun 8 2005;293(22):2719-2725.

**38.** Bakari M, Moshi A, Aris EA, et al. Isoniazid prophylaxis for tuberculosis prevention among HIV infected police officers in Dar es Salaam. *East African medical journal.* Sep 2000;77(9):494-497.

**39.** Souza CT, Hokerberg YH, Pacheco SJ, Rolla VC, Passos SR. Effectiveness and safety of isoniazid chemoprophylaxis for HIV-1 infected patients from Rio de Janeiro. *Memorias do Instituto Oswaldo Cruz.* May 2009;104(3):462-467.

**40.** Shrestha RK, Mugisha B, Bunnell R, et al. Cost-effectiveness of including tuberculin skin testing in an IPT program for HIV-infected persons in Uganda. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease.* Jun 2006;10(6):656-662.