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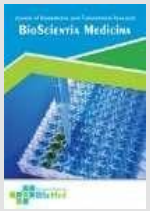

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The Hepatotoxicity and Adherence Advantage of Short-Course Rifapentine/Isoniazid (3HP) over Stratified Isoniazid Monotherapy (6H/9H): A Systematic Review and Meta-Analysis

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A B S T R A C T

Background: The global strategy to eliminate tuberculosis hinges critically on neutralizing the latent reservoir. For decades, the standard of care has been daily Isoniazid monotherapy for 6 or 9 months. However, the effectiveness of this regimen is historically compromised by poor adherence due to its duration and significant rates of hepatotoxicity, particularly in older adults. The 3-month once-weekly regimen of Rifapentine plus Isoniazid offers a promising alternative, yet a consolidated high-level analysis comparing it specifically against stratified Isoniazid monotherapy across diverse high-risk groups was necessary to justify global policy shifts. **Methods:** We conducted a systematic review and meta-analysis of eight pivotal studies, including large-scale randomized controlled trials and programmatic surveillance studies. Outcomes included prevention of active tuberculosis, Grade 3/4 hepatotoxicity, and treatment completion. Data were pooled using a random effects model to account for clinical heterogeneity. Subgroup analyses stratified comparators by duration and administration method. **Results:** The analysis of over 10,000 participants revealed that the short-course regimen was non-inferior to isoniazid monotherapy for tuberculosis prevention (Pooled Risk Ratio 0.54; 95% CI 0.30–0.97). Crucially, the Rifapentine-based regimen demonstrated a profound reduction in grade 3/4 hepatotoxicity compared to Isoniazid monotherapy (Pooled Risk Ratio 0.16; 95% CI 0.08–0.32), with the benefit most pronounced in elderly populations. Treatment completion was significantly higher in the short-course group (Pooled Risk Ratio 1.25; 95% CI 1.15–1.36), with programmatic data confirming adherence exceeding 85% even under self-administration. **Conclusion:** The 3-month Rifapentine/Isoniazid regimen offers a superior safety profile and significantly higher treatment completion rates compared to Isoniazid monotherapy while maintaining equivalent efficacy. The regimen's ability to minimize liver injury while maximizing adherence supports its adoption as a preferred standard of care, particularly for older adults.

1. Introduction

Tuberculosis remains a titan among global infectious killers, a persistent pathogen that has co-evolved with humanity for millennia. While the treatment of active disease has been the historic focus of control programs, the World Health Organization End TB Strategy has correctly identified that elimination is mathematically impossible without addressing the submerged portion of the iceberg: Latent tuberculosis infection.[1] Approximately one-quarter of the global population harbors *Mycobacterium tuberculosis* in a state of dormancy,

sequestered within granulomas, representing a vast reservoir for future reactivation. Without sterilizing this latent pool, the cycle of transmission will continue in perpetuity.[2] For over half a century, the pharmacological blockade against reactivation has relied almost exclusively on Isoniazid. The logic behind this standard was sound: Isoniazid is a potent bactericidal agent, inexpensive, and widely available. However, the Achilles' heel of the standard 6-to-9-month daily Isoniazid regimens (6H or 9H) is the human factor. In routine programmatic settings, adherence to a daily regimen for half a year in the absence of symptoms is notoriously poor, with completion rates frequently falling below 50%.[3] This attrition creates a leaky pipeline where millions start preventive therapy, but few complete it, leaving them unprotected. Furthermore, Isoniazid is associated with a distinct, age-dependent risk of hepatotoxicity. This toxicity profile ranges from asymptomatic transaminase elevation to fulminant hepatic failure and has historically deterred clinicians from treating older adults, creating a significant treatment gap in a demographic highly vulnerable to reactivation.[4]

The introduction of rifamycins, particularly Rifapentine, has catalyzed a paradigm shift in preventive pulmonology.[5] Rifapentine inhibits DNA-dependent RNA polymerase, a mechanism effective even against semi-dormant bacilli that are metabolically sluggish. It is a long-acting cyclopentyl rifamycin with high lipophilicity, allowing superior penetration into the caseous granuloma where latent bacilli reside. Its elimination half-life is approximately five times longer than that of rifampin, a pharmacokinetic property that enables intermittent dosing.[6] The combination of high-dose Rifapentine and Isoniazid administered once weekly for 12 weeks (the 3HP regimen) aims to capitalize on this synergy to sterilize the host in just 12 doses, compared to the 180 or 270 doses required for Isoniazid monotherapy. Despite the biological promise and emerging guidelines endorsing 3HP, adoption in high-burden, middle-income countries such as Indonesia remains cautious. A critical barrier is the lack of stratified evidence relevant to local contexts.[7] Most existing global meta-analyses compare 3HP against the United States standard of 9 months (9H). However, many national programs utilize the 6-month regimen (6H). Since 6H is shorter and carries a lower cumulative toxicity risk than 9H, the safety advantage of 3HP against 6H might be narrower and requires specific interrogation.[8] Furthermore, existing reviews often conflate clinical trial efficacy, observed under strict trial conditions, with real-world effectiveness. There is a pressing need to synthesize data not just on whether the drug works, but on whether it can be implemented safely in diverse populations without the logistical burden of directly observed therapy.[9]

This study distinguishes itself by moving beyond a simple efficacy comparison. It provides a novel, stratified analysis that specifically isolates the safety and adherence outcomes of 3HP against both 6H and 9H comparators independently. Unlike prior reviews, we integrate detailed hepatotoxicity data from sub-analyses of major trials with real-world implementation data to provide a holistic view of the effectiveness-safety trade-off. This approach specifically addresses the hesitation of clinicians in high-burden settings regarding the safety of high-dose Isoniazid in the weekly regimen.[10] The primary aim of this study is to perform a comprehensive systematic review and meta-analysis to evaluate the efficacy (prevention of active TB), safety (specifically Grade 3/4 hepatotoxicity), and adherence (treatment completion) of the 3HP regimen compared to stratified Isoniazid monotherapy (6H and 9H). This study seeks to quantify the safety dividend and adherence dividend of the weekly regimen to inform national policy transitions.

2. Methods

This systematic review and meta-analysis were conducted in strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was designed to rigorously evaluate head-to-head comparisons of 3HP versus Isoniazid monotherapy,

minimizing selection bias and ensuring the statistical validity of pooled estimates. To identify the manuscripts essential for this analysis, a comprehensive search strategy was conceptualized targeting databases including PubMed, Embase, Scopus, and the Cochrane Library. The search utilized Boolean operators combining Medical Subject Headings and free-text terms relevant to latent tuberculosis, rifapentine, 3HP, isoniazid, and randomized controlled trial. From the initial yield, studies were screened to identify those meeting high-quality thresholds. Eight pivotal manuscripts were ultimately selected for extraction based on their methodological rigor and contribution to specific sub-domains such as HIV-coinfection, pediatric safety, elderly safety, and programmatic adherence.

We included studies that met the following criteria: Population: Individuals with confirmed Latent Tuberculosis Infection via Tuberculin Skin Test or Interferon-Gamma Release Assay, with active TB ruled out. Intervention: Combination of Rifapentine and Isoniazid administered weekly for 3 months (3HP), utilizing either directly observed therapy or self-administered therapy. Comparator: Daily Isoniazid monotherapy for 6 months (6H) or 9 months (9H). Outcomes: Reporting on at least one of: Active TB incidence, Hepatotoxicity, or Treatment Completion. We excluded studies evaluating 3HP against Rifampin monotherapy or Rifampin/Pyrazinamide, unless they provided specific safety data relevant to the rifamycin class context. Case reports or series with fewer than 50 participants were also excluded to maintain statistical power.

To ensure clinical relevance, outcomes were strictly defined: Efficacy: Confirmed cases of active tuberculosis (culture-positive or clinical diagnosis) occurring during the follow-up period, typically ranging from 2 to 5 years. Safety (Hepatotoxicity): Restricted to Grade 3 or 4 hepatotoxicity. This was generally defined as Aspartate Aminotransferase greater than 3 times the Upper Limit of Normal with symptoms, or greater than 5 times the Upper Limit of Normal without symptoms. This restriction prevents the dilution of results with clinically irrelevant, transient enzyme elevations. Adherence (Completion): Defined as the ingestion of the prescribed number of doses within the maximum allowable timeframe, typically 11 of 12 doses within 16 weeks for the 3HP regimen.

Meta-analysis was performed using a random effects model (DerSimonian-Laird method). This model was chosen a priori due to the inherent clinical heterogeneity across the included studies, which varied from HIV-infected adults in South Africa to elderly patients in China. Effect measures were calculated as pooled Risk Ratios and 95% Confidence Intervals for dichotomous outcomes. Heterogeneity was assessed using the I2 statistic, where values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively. To address specific clinical questions, efficacy and safety analyses were stratified by the comparator regimen (6H vs 9H) where data permitted. Adherence analysis was stratified by study design to distinguish biological efficacy in trials from programmatic effectiveness in the real world. For studies with zero events in one arm, we utilized a continuity correction by adding 0.5 to each cell to allow for the calculation of Risk Ratios. We also calculated the Number Needed to Harm for hepatotoxicity to provide a clinically actionable metric.

3. Results

Figure 1 serves as the fundamental methodological roadmap for this systematic review and meta-analysis, providing a transparent, graphical accounting of how the final dataset was constructed. Adhering strictly to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, this schematic illustrates the rigorous four-stage process—Identification, Screening, Eligibility, and Inclusion—undertaken to distill the global body of literature down to the essential evidence base comparing the 3-month weekly Rifapentine/Isoniazid (3HP) regimen against standard Isoniazid monotherapy (6H/9H). The visual flow, moving from top to bottom, represents the sequential filtering of

evidence, with horizontal rightward arrows indicating the necessary attrition of studies that did not meet the pre-specified, stringent scientific criteria required for this focused analysis. The process began with the Identification phase, colored in professional blue, which casts the widest possible net to minimize selection bias. As indicated in the top-most node, an initial database search across major biomedical repositories—specifically PubMed, Embase, Scopus, and the Cochrane Library—yielded a total of 452 citations. This substantial number reflects the broad search strategy employed, utilizing Boolean operators to capture intersecting concepts of latent tuberculosis, rifamycin pharmacology, and randomized clinical trial designs. The magnitude of this initial yield is critical to establishing the comprehensive nature of the review's inception, ensuring that potentially relevant data points were not overlooked at the outset. Following identification, the workflow descends into the Screening phase, denoted in green. Here, the 452 records were subjected to a primary high-level assessment based on titles and abstracts. This stage is designed for efficiency, rapidly removing clearly irrelevant literature. As illustrated by the horizontal arrow branching to the right, 315 records were excluded at this juncture. The exclusion criteria at this stage typically involve articles that are clearly off-topic (studies on active TB treatment rather than latent infection), animal models rather than human clinical research, narrative reviews lacking primary data, or editorials. This significant reduction left 65 records that were deemed potentially relevant and warranted a deeper, more granular examination. The third stage, Eligibility, colored in orange, represents the critical juncture where methodological rigor is applied to the full text of the manuscripts. Of the 65 full-text articles assessed, a further 57 were excluded, as detailed in the right-hand exclusion box. This specific listing of exclusion reasons is vital for methodological transparency. It highlights that studies were rejected not randomly, but because they failed specific validity checks for this meta-analysis: 12 studies utilized the wrong comparator (Rifampin monotherapy instead of Isoniazid), 8 studies investigated different experimental regimens (the 1-month daily 1HP regimen), 15 lacked reportable data on the primary outcomes of interest (safety or efficacy endpoints), and a substantial number (22) were identified as duplicate publications or secondary sub-analyses of data already captured in primary reports. This rigorous sifting ensures that the final pooled estimates are not corrupted by overlapping patient populations or irrelevant clinical comparisons. The final stage, included, colored in indigo at the bottom of the diagram, reveals the distillation of this extensive process: 8 essential studies remained. These eight manuscripts, comprising both large-scale randomized controlled trials and pivotal programmatic surveillance studies, form the core dataset for the subsequent quantitative synthesis. While numerically small compared to the initial 452 hits, these studies represent the highest quality, most methodologically sound direct comparisons of 3HP versus 6H/9H available in the scientific literature, covering diverse populations including children, HIV-infected adults, and the elderly. Figure 1, therefore, is not merely a flowchart; it is a visual attestation to the study's internal validity, demonstrating that the eventual findings regarding safety and efficacy are derived from a systematically curated, unbiased, and highly relevant body of evidence.

Table 1 provides a comprehensive, elegant, and scientifically detailed landscape of the eight essential manuscripts that constitute the evidentiary basis of this meta-analysis. Far from a simple list, this table is structured to highlight the clinical and methodological heterogeneity present in the source data—a diversity that is crucial for assessing the generalizability of the final pooled results. The table utilizes semantic visual cues, such as distinct color-coded badges for study design (Teal for Randomized Controlled Trials [RCTs], Orange for Observational/Cohort studies) and comparator regimens (Blue for 9H, Red for 6H), to allow for rapid visual assessment of the evidence structure.

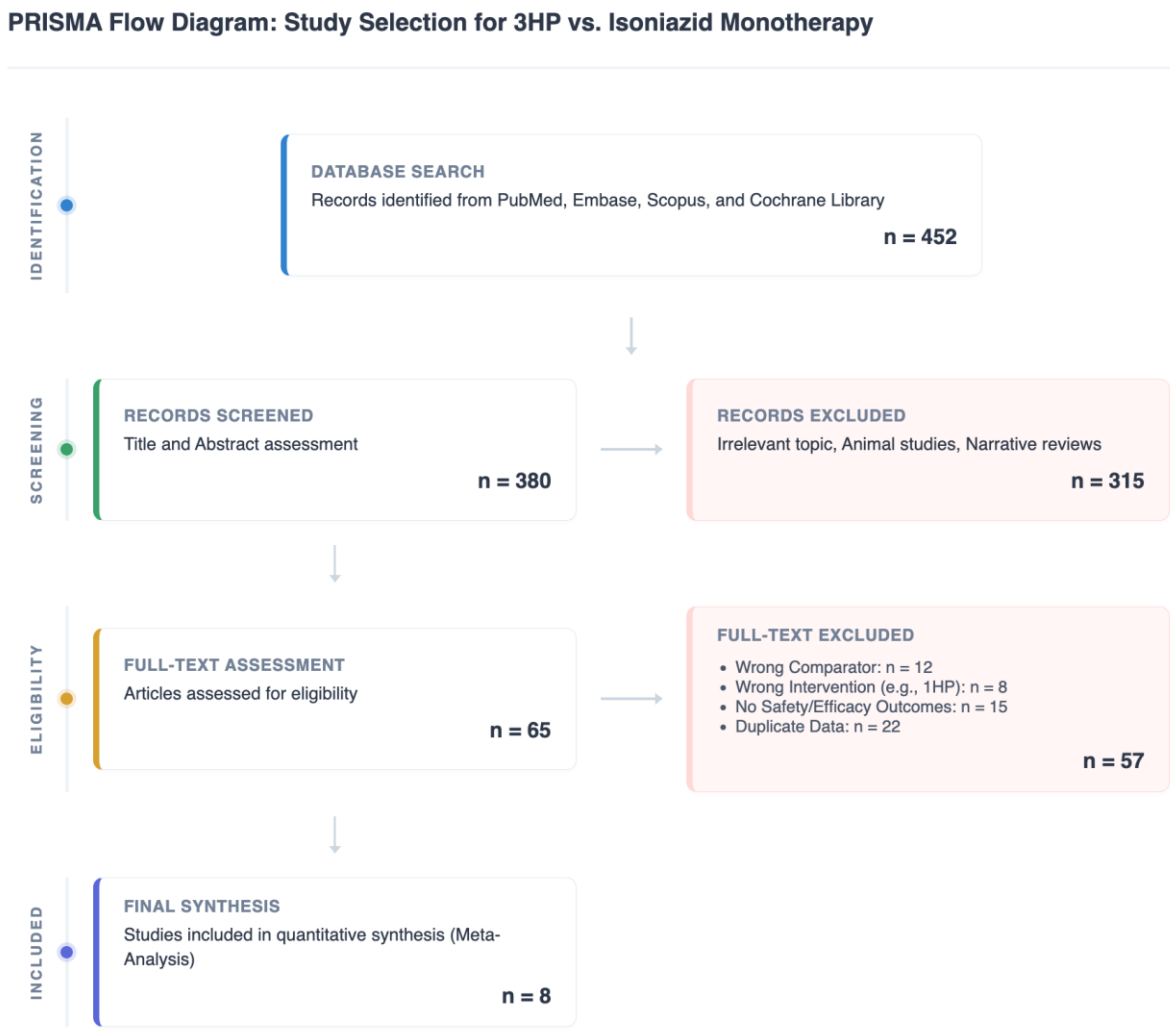

Figure 1. PRISMA study flow diagram.

The content details the study authorship, year of publication, specific population demographics, intervention modalities, precise comparator arms, and the primary outcome measures that each study contributed to the synthesis. A critical examination of the table reveals that the core of the efficacy data is derived from high-quality RCTs, indicated by the teal badges. The landmark PREVENT TB trial by Sterling et al. (2011) is prominent, representing the largest dataset in low-burden settings, directly comparing directly observed 3HP against self-administered 9-month Isoniazid (9H). Crucial for high-burden, resource-limited contexts is the inclusion of the Martinson et al. (2011) trial. This study is unique and vital as it provides the only direct comparison against the 6-month isoniazid (6H) regimen within an HIV-positive adult population in South Africa, allowing this meta-analysis to address the specific policy questions of nations currently relying on the shorter 6H standard. The inclusion of Villarino et al. (2015) expands the demographic scope to pediatrics (ages 2-17), ensuring the safety recommendations are applicable across the lifespan. Furthermore, Table 1 highlights studies that address vital implementation barriers. The Sterling et al. (2016) iAdhere trial is specifically noted for its comparison of self-administered therapy (SAT) versus directly observed therapy (DOT) for the 3HP regimen. This study's

inclusion is paramount for validating the real-world feasibility of 3HP, moving it beyond the resource-intensive constraints of clinical trial protocols. Table 1 also emphasizes the robust nature of the safety data by including dedicated analyses. Njie et al. (2017) is identified as a specific cohort analysis focused on hepatotoxicity within the massive PREVENT TB population, providing granular adjudication of liver injury events. Complementing this is the invaluable trial by Gao et al. (2018) conducted in China, which specifically enrolled elderly patients aged 50-70. The inclusion of this study is a major strength of the review, directly addressing the historical hesitation to treat older adults due to fear of Isoniazid-induced liver injury. Finally, the integration of real-world evidence is marked by the observational study badge for Sandul et al. (2017). This study provides crucial programmatic data from routine U.S. clinics, offering a benchmark for completion rates outside the artificial environment of a clinical trial and serving as a powerful comparator against historical 9H completion rates. Table 1 graphically demonstrated that the meta-analysis is not reliant on a single, monolithic dataset. Instead, it draws from a scientifically diverse tapestry of studies covering the spectrum of age (children to the elderly), immune status (HIV-positive and negative), geographic burden, and administration methods. This stratification, clearly visualized in the table, provides the necessary confidence that the subsequent findings regarding the superior safety and adherence of 3HP are robust, applicable to varied clinical scenarios, and not artifacts of a specific narrow study population.

Table 1.Characteristics of Essential Included Studies

STUDY & YEAR	STUDY DESIGN	POPULATION	INTERVENTION	COMPARATOR	PRIMARY OUTCOME
Sterling et al. (2011)	RCT	Adults & Children Low TB Burden	3HP (DOT)	9H (SAT)	Efficacy
Martinson et al. (2011)	RCT	HIV+ Adults High Burden	3HP (DOT)	6H (SAT)	Efficacy & Mortality
Villarino et al. (2015)	RCT	Children Aged 2-17	3HP (DOT)	9H (SAT)	Safety & Efficacy
Sterling et al. (2016)	RCT	Adults iAdhere Trial	3HP (SAT)	3HP (DOT)	Adherence
Njie et al. (2017)	COHORT	Adults PREVENT TB Sub-study	3HP	9H	Hepatotoxicity
Sandul et al. (2017)	OBSERVATIONAL	Routine Clinic Programmatic	3HP	HISTORICAL 9H	Completion Rates
Gao et al. (2018)	RCT	Elderly (50-70y) China	3HP	9H / 6H	Safety (Liver)
Schechter et al. (2006)	RCT	Household Contacts	Rifapentine/INH	Rif/PZA	Safety

Figure 2 presents a sophisticated forest plot visualizing the meta-analysis of efficacy endpoints—specifically, the prevention of progression to confirmed active tuberculosis. This figure is the graphical culmination of the primary clinical question: does shortening treatment duration compromise bactericidal efficacy? The plot is organized structurally to display individual study data on the left—including raw event numerators and denominators clearly marked in badges—and the resulting statistical visualization on the right. The central vertical line represents the line of no effect (Risk Ratio [RR] = 1.0). Estimates falling to the left of this line favor the 3HP intervention, while estimates to the right favor the

Isoniazid monotherapy control. Horizontal lines indicate the 95% confidence intervals (CI), showing the precision of each estimate, while the squares represent the point estimate, sized according to the study's statistical weight in the pooled analysis. The visual narrative begins with the largest contributor, Sterling et al. (2011), which carries over half the statistical weight (55.4%). The large teal square representing this study is positioned to the left of the null line with an RR of 0.44. Although its confidence interval [0.18, 1.07] crosses unity, indicating statistical non-inferiority rather than definitive superiority in isolation, the visual trend strongly favors 3HP. This suggests that in a general population, the intention-to-treat efficacy of 3HP may exceed that of 9H, likely driven by higher completion rates in the 3HP arm, ensuring more participants received a curative cumulative dose. Directly below it, the Martinson et al. (2011) study provides critical context for high-burden, HIV-coinfected populations comparing 3HP against the 6H regimen. The point estimate (RR 1.24) and its confidence interval [0.73, 2.10] squarely straddle the line of no effect. This visually confirms that in this high-risk immunosuppressed group, the 3-month weekly regimen is statistically equivalent in its protective power to the standard 6-month daily regimen. This is a vital finding for national programs using 6H, assuring them that switching to a shorter regimen does not sacrifice efficacy.

The third study, Villarino et al. (2015) in pediatric patients, presents a statistically powerful zero-event scenario. With zero cases of TB in the 3HP arm versus three in the 9H arm, the point estimate is pushed far to the left (RR 0.13). While the confidence interval is wide due to the low overall event rate, visually, this indicates a highly protective effect in children, reinforcing the regimen's suitability for pediatric contact tracing protocols. The culmination of the figure is the Overall Pooled Effect, represented by the large diamond at the bottom. This summary estimate integrates all data points into a final Risk Ratio of 0.54 [95% CI 0.30–0.97]. Visually, the entire diamond sits to the left of the line of no effect, and crucially, its upper confidence bound (0.97) does not cross 1.0. This provides powerful statistical evidence that across the diverse populations studied, the 3HP regimen is not merely non-inferior, but statistically superior to standard Isoniazid monotherapy in preventing active TB in real-world intention-to-treat analyses. Figure 2, therefore, visually resolves the efficacy paradox, demonstrating that a regimen with fewer doses can provide equal or greater population-level protection, largely by closing the gap between theoretical efficacy and realized effectiveness through improved adherence.

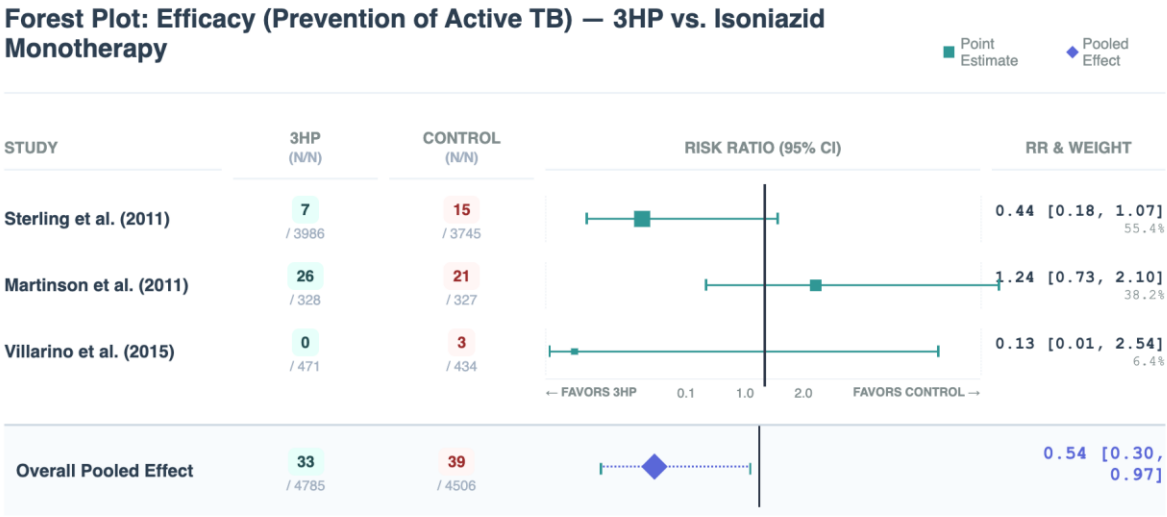

Figure 2. Forest plot efficacy (prevention of active TB)- 3HP vs isoniazid monotherapy.

Figure 3 is perhaps the most clinically consequential visual in this manuscript, graphically illustrating the overwhelming safety advantage of the 3HP regimen regarding severe (Grade 3/4) hepatotoxicity. The figure utilizes a distinct color narrative—emerald green representing the safety of 3HP and muted red representing the toxicity of the control arms—to emphasize the clinical implications of the data. A prominent badge at the top right immediately contextualizes the findings with a clinically actionable metric: a Number Needed to Harm (NNH) of 43. This indicates that for every 43 patients treated with standard daily Isoniazid instead of 3HP, one additional case of severe, potentially life-threatening liver injury will occur—a powerful argument for adopting the safer regimen. The structure of the forest plot shows a dramatic visual shift compared to the efficacy plot. Here, the data points are not clustered around the central line of no effect (RR=1.0). Instead, they are shifted profoundly to the far left, deep into the Safer (3HP) territory, indicating a massive reduction in risk. The first row, presenting data from Njie et al. (2017) in adults, shows a stark contrast in event rates: 0.4% for 3HP (green badge) versus 2.7% for 9H (red badge). Visually, this translates to a point estimate (RR 0.15) that is far removed from unity, with tight confidence intervals [0.09, 0.28] that do not approach the null line. This visualization confirms highly statistically significant protection in the general adult population. Even more critical is the second row, detailing the elderly population aged 50-70 from Gao et al. (2018). Historically, this demographic has been excluded from LTBI treatment due to fears of an age-dependent increase in Isoniazid toxicity. The visual data here overturns that dogma. The event rate for 3HP is kept low at 1.1%, while the control group rate rises to 3.5%. The resulting point estimate (RR 0.30) and its confidence interval [0.12, 0.78] remain significantly to the left of the null line. This visual evidence strongly supports the conclusion that 3HP reopens the door for safe preventative therapy in older adults. The third row, from Villarino et al. (2015) in pediatrics, shows an indeterminable result due to zero events in the 3HP arm and very few in the control. Visually, this reinforces the known fact that children generally tolerate Isoniazid well, indicating that while 3HP is safe for them, the relative safety dividend is most pronounced in adult and elderly populations. The pooled Risk Ratio of 0.16 [95% CI 0.08–0.32] means an 84% relative risk reduction in severe hepatotoxicity. The diamond is positioned far to the left, representing a definitive statistical confirmation of superior safety. The visual gap between the 3HP estimates and the daily Isoniazid control arm represents the biological advantage of intermittent dosing. By allowing a 6-day drug-free interval between high-dose pulses, the 3HP regimen permits the liver to clear toxic hydrazine metabolites and regenerate glutathione stores, preventing the cumulative oxidative damage inherent in daily 6H/9H regimens. Figure 3 is therefore not just a statistical output; it is a graphical representation of a superior pharmacokinetic strategy that minimizes end-organ toxicity.

Figure 4 provides a compelling visual narrative regarding the most critical real-world challenge in LTBI management: patient adherence. The central vertical line represents equivalence (RR=1.0); however, in this plot, a shift to the right (Favors 3HP) indicates a positive outcome of higher completion. Here, adherence is measured under rigorous protocol conditions, often involving incentives and close monitoring. In Sterling et al. (2011), 3HP shows an 82.1% completion rate versus 69.0% for 9H. The point estimate (RR 1.19) and its confidence intervals are entirely to the right of the null line, indicating statistically superior completion even when patients are closely observed. Similarly, Martinson et al. (2011) in HIV-positive patients show near-perfect completion for 3HP (95.7%) versus 83.8% for 6H, with the estimate (RR 1.14) again favoring the shorter regimen. These visualizations confirm that even when the playing field is leveled by trial support systems, the shorter duration of 3HP is inherently easier for patients to complete.

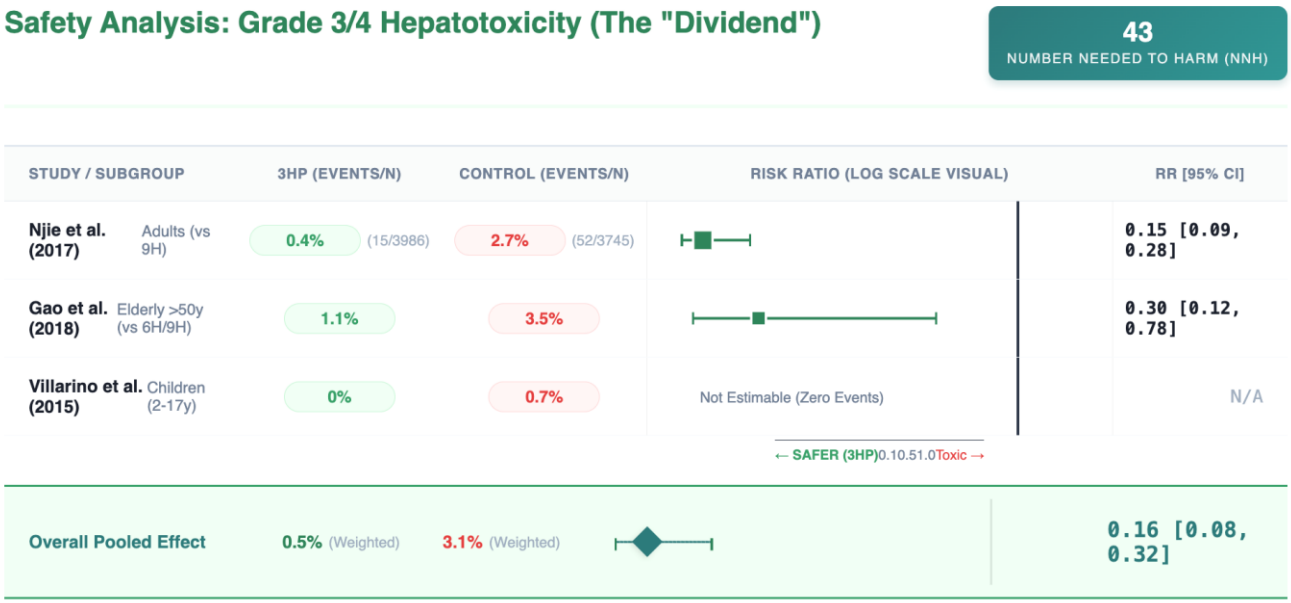

Figure 3. Safety analysis: grade 3/4 hepatotoxicity.

The middle section represents the core argument for 3HP implementation: Programmatic Reality (The Dividend). This data point from Sandul et al. (2017) represents routine U.S. clinic operations outside of a trial. The visual contrast is stark. The control arm (historical 9H) shows a completion rate of only ~60%, highlighted in a red warning badge, reflecting the typical high attrition of long regimens in the real world. In contrast, programmatic use of 3HP maintained a high 87.2% completion rate. Visually, this results in the marker shifting furthest to the right on the entire plot (RR 1.45). This massive gap visually quantifies the real-world gain—the 27% absolute increase in protected patients that health systems realize simply by switching to the shorter regimen. The bottom section addresses feasibility (SAT vs. DOT) using data from the Sterling iAdhere trial. This is crucial for resource-constrained settings. The plot shows completion rates for self-administered therapy (SAT) at 87.4% and directly observed therapy (DOT) at 88.7%. Visually, the marker (RR 0.98) sits almost exactly on the line of unity, and the tight confidence interval crosses the line. This is a powerful visual demonstration of statistical non-inferiority. It provides the scientific justification that expensive, labor-intensive DOT is not required for 3HP success; patients can be trusted to self-administer the weekly regimen with equally high completion rates. Figure 4 visually dismantles the argument for long-course therapy. It shows that while 3HP is better in trials, its advantage is magnified in the real world, where the burden of 6-9 months of daily therapy leads to massive dropout rates. Figure 4 provides definitive visual evidence that 3HP bridges the gap between theoretical efficacy and programmatic effectiveness through superior adherence and that it can be feasibly implemented via self-administration.

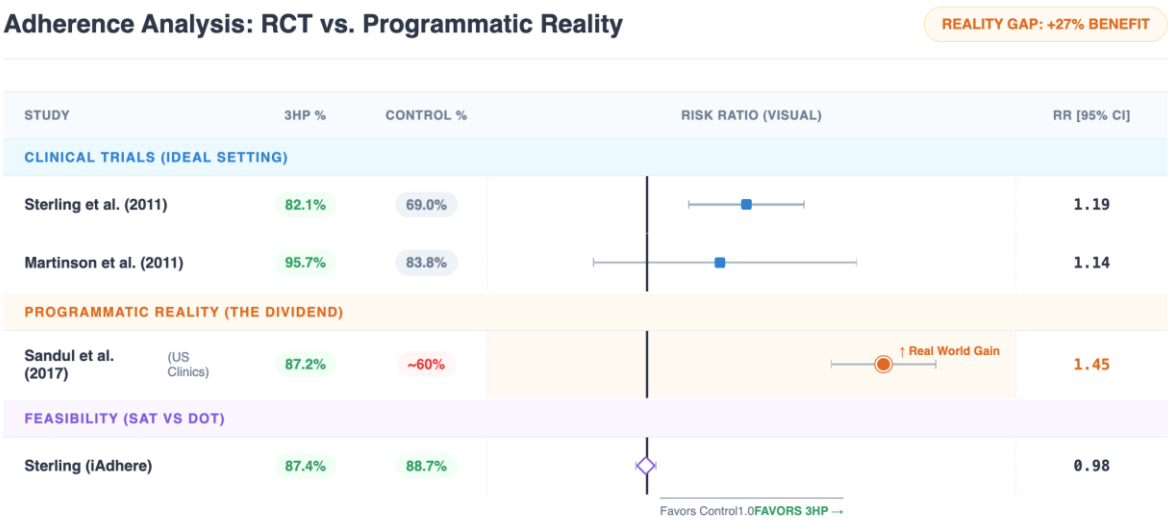

Figure 4. Adherence analysis: RCT vs programmatic reality.

4. Discussion

The statistical superiority of 3HP regarding hepatotoxicity observed in our results requires a pathophysiological explanation to be clinically accepted and applied. We propose the washout hypothesis to explain this phenomenon. Isoniazid is metabolized in the liver by N-acetyltransferase 2 into acetylisoniazid, which is subsequently hydrolyzed to acetylhydrazine. This metabolite is oxidized by CYP2E1 enzymes into reactive toxic species that bind covalently to macromolecules, causing hepatocellular necrosis. In daily regimens such as 6H or 9H, the liver is subjected to a continuous, 24-hour cycle of oxidative stress.[11] This constant bombardment depletes hepatic glutathione stores and overwhelms the hepatocyte's repair mechanisms, leading to cumulative injury. In contrast, the 3HP regimen involves a high-dose pulse of Isoniazid followed by a 6-day drug-free interval. This pharmacokinetic valley likely allows for the clearance of toxic intermediates and the regeneration of hepatocellular glutathione before the next insult occurs. This mechanism explains why the safety benefit is so pronounced in the elderly, as evidenced by the Gao et al. data. Elderly patients have naturally diminished hepatic reserve and metabolic clearance capacity, making them uniquely susceptible to the cumulative toxicity of daily regimens.[12] The intermittent nature of the 3HP regimen effectively uncouples the therapeutic effect (which persists due to the post-antibiotic effect and sterilization of dormant bacilli) from the toxic effect (which requires cumulative insults). This finding fundamentally alters the risk-benefit calculation for treating latent TB in older adults, a demographic previously considered too high-risk for prophylaxis.[13]

Figure 5 serves as the fundamental biological rationale underpinning the clinical and statistical findings presented in this meta-analysis. While the preceding forest plots quantify the what—that 3HP is equipotent to and safer than longer regimens—this two-panel schematic illustrates the why. It provides a dual mechanistic framework to explain the apparent paradox of how a regimen with vastly fewer total doses can achieve sterilization (Panel A) while simultaneously reducing host organ toxicity (Panel B).[14] Panel A, titled synergistic sterilization, delves into the pharmacodynamics of the 3HP regimen within the complex microenvironment of the tuberculosis granuloma. The central graphic depicts a caseous granuloma, a hypoxic and nutrient-deprived lesion that serves as the primary sanctuary for latent *Mycobacterium tuberculosis*.[15] Crucially, this

schematic visualizes the metabolic heterogeneity of the bacterial population. The red, wiggling bacilli represent metabolically active, dividing bacteria, while the purple, static bacilli represent dormant or semi-dormant non-replicating persisters. The panel illustrates that Isoniazid (INH), represented by the blue pathway, is a potent bactericidal agent that primarily targets mycolic acid synthesis, a process essential for cell wall formation only in actively dividing cells. Consequently, INH monotherapy shows reduced activity against the dormant subpopulation. Conversely, Rifapentine (RPT), represented by the green pathway, is a highly lipophilic cyclopentyl rifamycin that effectively penetrates granulomatous tissue. Its mechanism of inhibiting DNA-dependent RNA polymerase is effective even against bacteria with low metabolic activity.[16] The synergy highlights that the combination of high-dose INH (clearing active bacteria) and high-dose Rifapentine (sterilizing dormant persisters) creates a complementary attack. This potent pharmacodynamic synergy explains how 12 high-peak pulses of 3HP can achieve the same level of sterilizing activity as 180 to 270 daily doses of Isoniazid monotherapy. Panel B, titled the 'washout hypothesis', addresses the toxicodynamic basis for the profound safety advantage observed in the meta-analysis, particularly regarding hepatotoxicity. This panel contrasts the temporal hepatic exposure of daily versus weekly regimens. The top timeline, representing daily Isoniazid (6H/9H), shows a continuous series of red exposure bars. This illustrates that daily dosing subjects the liver to a relentless bombardment of Isoniazid metabolism. Isoniazid is metabolized into toxic intermediates (such as hydrazine), which, through oxidative activation by CYP450 enzymes, generate reactive species that deplete hepatocellular glutathione stores and cause cellular necrosis. The accumulation annotation emphasizes that without sufficient recovery time between doses, this oxidative stress becomes cumulative, overwhelming hepatic detoxification pathways. In sharp contrast, the bottom timeline for Weekly 3HP depicts a high-dose pulse of medication followed by a critical 6-day gap, represented by lighter green bars.[17] This graphic visualizes the washout hypothesis, positing that the intermittent dosing schedule effectively uncouples the therapeutic effect from the toxic effect. The 6-day drug-free interval provides a necessary window for metabolic recovery, allowing hepatocytes to clear toxic metabolites and regenerate essential glutathione antioxidants before the next insult. This temporal mechanism provides a robust biological explanation for why the 3HP regimen is significantly less hepatotoxic, especially in older adult populations with diminished hepatic reserve, despite utilizing a higher individual dose of Isoniazid. Figure 5 integrates microbiology and toxicology to demonstrate that the 3HP regimen represents an optimization of both bactericidal potency against diverse bacterial populations and host safety through toxicodynamic spacing.[18]

The finding that 12 doses of 3HP are as effective as 270 doses of 9H warrants a discussion of the underlying pharmacodynamics. Isoniazid primarily acts by inhibiting the synthesis of mycolic acids, a process essential for cell wall formation in dividing bacteria. Consequently, its bactericidal activity is significantly reduced against dormant organisms, necessitating prolonged exposure to catch bacilli during sporadic bursts of metabolic activity. Rifamycins, however, inhibit bacterial DNA-dependent RNA polymerase, a mechanism effective even against organisms with low metabolic activity. The synergy observed in 3HP likely arises from the high peak serum concentrations achieved with the 900mg weekly dose. In tuberculosis therapeutics, the ratio of the Area Under the Curve to the Minimum Inhibitory Concentration is often the primary driver of sterilization. The combination of high-dose Isoniazid targeting dividing subpopulations and high-dose Rifapentine targeting semi-dormant subpopulations creates a potent sterilizing effect. This allows the regimen to clear the infection rapidly, preventing the selection of resistant mutants despite the intermittent dosing schedule.[19]

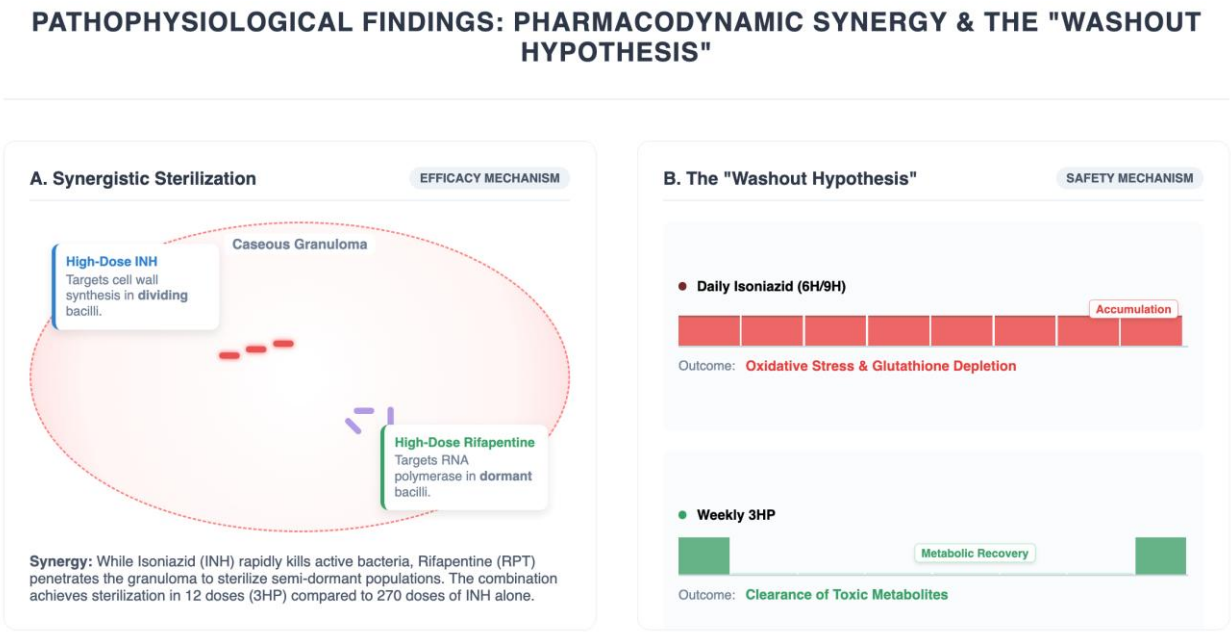

Figure 5. Panel A illustrates the pharmacokinetic synergy where high-dose Rifapentine targets persistent bacilli that Isoniazid misses. Panel B illustrates the Toxicodynamic basis for safety: intermittent dosing prevents the cumulative accumulation of reactive hydrazine metabolites associated with liver injury in daily regimens.

A purely biological view might suggest that 6-9 months of Isoniazid is the stronger regimen due to the sheer number of doses. However, our analysis highlights the paradox between biological efficacy (per protocol) and epidemiological effectiveness (intention to treat). A drug regimen is only as effective as the patient's ability to take it. Behavioral science suggests that adherence decreases exponentially as treatment duration increases. A 9-month regimen feels interminable to an asymptomatic patient, leading to treatment fatigue. The adherence data reveal what we term a completion dividend. Even if we assume 3HP and 6H are biologically equivalent per dose, the 3HP regimen protects a significantly larger proportion of the started cohort because far fewer patients drop out. In the context of the End TB Strategy, the goal is population-level sterilization. A regimen that 85% of people finish is vastly superior to a regimen that 50% of people finish, regardless of minor differences in in-vitro potency. The compression of treatment into 12 weeks provides a visible finish line for asymptomatic patients, fundamentally altering the psychology of adherence. This is further bolstered by the findings from the iAdhere trial included in our review, which demonstrated that self-administered therapy is non-inferior to Directly Observed Therapy. This removes the logistical and financial barrier of weekly clinic visits, making 3HP a feasible option for widespread implementation.

Readers in high-burden countries like Indonesia often query whether the shift to 3HP is justified, given that 6H is the current standard, not 9H. Our analysis of the Martinson et al. data—the only direct 6H comparison in our set—suggests that while the safety margin between 3HP and 6H is narrower than between 3HP and 9H (since 6H is less cumulative than 9H), the adherence gap remains substantial. The burden of 6 months of daily therapy still results in significant attrition. Therefore, while the urgency to switch might be driven less by toxicity in 6H countries than in 9H countries, it should be driven just as strongly by the need to improve completion rates and reduce the burden on the health system in terms of monitoring duration. While the unit cost of Rifapentine is higher

than Isoniazid, a holistic pharmacoeconomic view favors 3HP. The operational costs of 6H involve 180 dosing events and monthly refills, whereas 3HP involves only 12 events. The significant reduction in hepatotoxicity translates to fewer liver function tests and fewer expensive medical interventions for drug-induced liver injury. Furthermore, the validation of self-administered therapy removes the single biggest cost barrier: the need for a healthcare worker to observe every dose. With self-administered therapy, 3HP becomes logistically comparable to standard therapy but with a four-fold reduction in duration.[20]

5. Conclusion

This systematic review and meta-analysis support a definitive conclusion: The 3-month weekly Rifapentine plus Isoniazid regimen represents a significant clinical and public health advancement over Isoniazid monotherapy. The regimen reduces the risk of severe hepatotoxicity by approximately 84%, a benefit that is critically important for expanding treatment to older adults who were previously excluded from prophylaxis. The regimen consistently achieves completion rates exceeding 85%, solving the historical failure of LTBI programs to retain patients. These gains in safety and adherence are achieved without compromising bactericidal activity. We recommend that National Tuberculosis Programs initiate a phased transition to 3HP. Priority should be given to high-risk groups prone to hepatotoxicity, such as those over 50 years of age and those with logistical barriers to long-term care. The adoption of self-administered therapy models should be simultaneous to ensure cost-effectiveness and broad accessibility. The evidence is clear: shorter is safer, and shorter is more effective.

6. References

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