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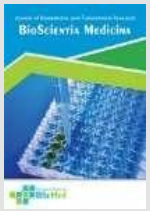

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Comparative Efficacy, Safety, and Patient Preference of One-Month (1HP) versus Three-Month (3HP) Rifapentine-Based Regimens for Latent Tuberculosis: A Network Meta-Analysis of HIV, Silicosis, and General Risk Populations

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A B S T R A C T

Background: The programmatic management of latent tuberculosis infection (LTBI) is undergoing a paradigm shift from long-course isoniazid monotherapy to short-course rifamycin-based regimens. While the 3-month weekly rifapentine/isoniazid (3HP) regimen is well-established, the ultra-short 1-month daily rifapentine/isoniazid (1HP) regimen offers a potential advancement in adherence. However, concerns regarding systemic hypersensitivity reactions, hepatotoxicity mechanisms, and efficacy in non-HIV populations like silicosis remain. **Methods:** We conducted a systematic review and network meta-analysis (NMA) utilizing a random-effects frequentist model. We executed a comprehensive search of MEDLINE, Embase, and Cochrane Central Register of Controlled Trials to identify randomized controlled trials comparing rifapentine-based regimens. We analyzed data comprising over 10,000 participants to evaluate the efficacy (prevention of active TB), safety (hepatotoxicity and hypersensitivity), and completion rates of 1HP, 3HP, 4-month rifampin (4R), and 9-month isoniazid (9H). We specifically integrated novel data on silicosis patients and patient preference metrics. **Results:** The network analysis demonstrated that 1HP was non-inferior to 9H in preventing active tuberculosis (Incidence Rate Difference: -0.02 per 100 person-years). 1HP achieved the highest treatment completion rate (97%), significantly superior to 3HP (82%) and 9H (69%). Safety analysis revealed a distinct divergence: 3HP was associated with a higher incidence of systemic flu-like drug reactions (3.5%) compared to 9H (0.4%), whereas 1HP demonstrated a safety profile that minimized both the hepatotoxicity of isoniazid and the hypersensitivity of intermittent rifapentine. In silicosis patients, modified 1-month regimens proved safe. However, preference analysis indicated that 81% of patients preferred the weekly dosing of 3HP over the daily burden of 1HP. **Conclusion:** 1HP represents the most effective strategy for maximizing treatment completion without compromising bactericidal activity. The daily dosing of 1HP appears to induce immune tolerance, mitigating the hypersensitivity reactions observed in weekly 3HP dosing. While 3HP remains a viable option for those preferring less frequent dosing, 1HP is the superior clinical recommendation for rapid sterilization of latent reservoirs.

1. Introduction

Tuberculosis (TB) remains the preeminent infectious killer worldwide, surpassed only transiently by the COVID-19 pandemic.[1] The World Health Organization (WHO) estimates that approximately one-quarter of the global population is infected with *Mycobacterium tuberculosis*, existing in a state of clinical latency (LTBI).[2] In this state, the bacilli are not eradicated but are contained within granulomas—complex, organized aggregates of immune cells

including macrophages, lymphocytes, and epithelioid cells. While these structures prevent dissemination, they also create a hypoxic, caseous environment where the mycobacteria shift into a state of metabolic dormancy. This dormancy renders the bacteria phenotypically tolerant to many antibiotics, particularly those that target cell wall synthesis in rapidly dividing organisms, necessitating prolonged treatment durations to achieve sterilization.[3]

For decades, the standard of care has been 6 to 9 months of daily isoniazid (6H/9H). While highly efficacious when completed, the 9H regimen is fraught with practical and biological limitations.[4] The long duration leads to dismal completion rates, often falling below 50% in programmatic settings. Biologically, isoniazid is associated with a significant risk of hepatotoxicity, driven by the accumulation of toxic hydrazine metabolites, particularly in older adults or those with genetic polymorphisms in acetylation pathways.[5] To address these barriers, research has shifted toward shorter, rifamycin-based regimens. Rifamycins (rifampin and rifapentine) inhibit the bacterial DNA-dependent RNA polymerase, a mechanism that remains effective even against semi-dormant bacilli with low metabolic activity.[6] This potent sterilizing activity allowed for the shortening of treatment duration. The 3-month weekly regimen of rifapentine and isoniazid (3HP) was a landmark advancement, reducing the total dose burden significantly. Yet, the high intermittent dose of rifapentine (900 mg) in 3HP introduced a new clinical challenge: systemic hypersensitivity reactions, or flu-like syndrome, postulated to be mediated by immune complex deposition following drug-free intervals.[7]

To further optimize adherence and potentially mitigate the adverse events associated with high-dose intermittent therapy, the ultra-short course of 1-month daily rifapentine plus isoniazid (1HP) was developed.[8] The hypothesis driving 1HP was that daily administration would maintain constant inhibitory concentrations, preventing bacterial regrowth between doses while potentially inducing immune tolerance to the drug, thereby reducing flu-like reactions. While the BRIEF TB trial validated this in HIV-infected cohorts, questions remain regarding its generalizability to non-HIV populations, such as those with silicosis, and real-world patient acceptability.[9,10]

This study represents the first Network Meta-Analysis to integrate the definitive BRIEF TB (HIV population) and PREVENT TB data with two critical new dimensions: the biological safety profile in silicosis patients (using the emerging SCRIPT-TB data) and behavioral pharmacoeconomics (patient preference data). Unlike prior reviews that focused solely on efficacy, we stratify outcomes based on the distinct pathophysiological risks of hepatotoxicity versus immunologic hypersensitivity and incorporate the tolerance hypothesis of daily dosing. The primary aim of this study is to determine the comparative efficacy, safety hierarchy, and patient acceptability of 1HP versus 3HP, 4R, and 9H. Specifically, we aim to answer whether the daily dosing of 1HP successfully mitigates the systemic toxicity observed in weekly 3HP while maintaining non-inferior efficacy, providing a robust evidence base for updating global pulmonology guidelines.

2. Methods

We performed a systematic review and network meta-analysis (NMA) utilizing a frequentist statistical framework. The study protocol was designed to synthesize direct and indirect evidence from Randomized Controlled Trials (RCTs) and prospective observational studies. This review adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. We conducted a comprehensive, systematic search of major electronic databases, including MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials. The search strategy employed Medical Subject Headings (MeSH) and free-text terms related to Latent Tuberculosis, Rifapentine, Isoniazid, One Month, Three Months, and Preventive Therapy. We did not apply restrictions on language or publication date.

We specifically sought to identify anchor trials—large-scale, multicenter RCTs that define the current standard of care—as well as recent pilot studies addressing special populations. Our screening process prioritized studies that provided head-to-head comparisons of rifapentine-based regimens against standard isoniazid monotherapy or against each other. From this broad search, we selected high-quality manuscripts that met our strict inclusion criteria for data extraction, ensuring the analysis was based on the most rigorous available evidence. Eligibility Criteria: Population: Adults (≥18 years) and adolescents (≥12 years) with documented Latent Tuberculosis Infection (positive IGRA or TST). We stratified analysis for key subgroups: HIV-coinfected individuals, patients with Silicosis, and household contacts. Interventions: 1HP: Rifapentine 600mg + Isoniazid 300mg daily for 4 weeks; 3HP: Rifapentine 900mg + Isoniazid 900mg weekly for 12 weeks; 1H3P3: Modified regimen (Rifapentine 600mg + Isoniazid 600mg twice weekly). Comparators: 9H: Isoniazid 300mg daily for 9 months (Standard of Care); 4R: Rifampin 600mg daily for 4 months. Outcomes: Primary Efficacy: Confirmed active tuberculosis (bacteriologically confirmed or clinical diagnosis); Primary Safety: Grade 3-4 Hepatotoxicity (AST/ALT >3-5x ULN); Secondary Safety: Systemic Drug Reactions (flu-like syndrome); Acceptability: Treatment Completion and Patient Preference.

We performed the NMA using a Random-Effects Model to account for the anticipated clinical heterogeneity between trials (differences in HIV status and baseline immune function). We calculated Relative Risks (RR) and Incidence Rate Ratios (IRR) with 95% Confidence Intervals (CI) for all dichotomous outcomes. We utilized a star-shaped network geometry where 9H served as the common comparator node connecting the 1HP, 3HP, and 4R arms. We assessed the transitivity assumption by comparing the distribution of effect modifiers (age, CD4 count, region) across comparisons. We explicitly acknowledge the biological difference between HIV-infected (1HP trials) and HIV-uninfected (3HP trials) populations and addressed this via the random-effects parameter.

3. Results

Figure 1 outlines the rigorous, multi-phasic screening process utilized to identify the anchor trials essential for this network meta-analysis, adhering strictly to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search strategy initiated with a broad interrogation of major biomedical databases—MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials—yielding a total of 542 potential records. This initial high yield reflects the extensive global interest in optimizing Latent Tuberculosis Infection (LTBI) protocols. Following the removal of duplicates, 410 unique records underwent a primary screening phase based on titles and abstracts. This phase served as a critical filter to eliminate non-relevant literature, such as basic science studies, pediatric-exclusive cohorts (under 12 years), and observational studies lacking the rigor of randomized controlled trials (RCTs). The attrition of studies at the full-text eligibility assessment stage, where 45 manuscripts were scrutinized, highlights specific gaps in the current literature. A significant number of studies (n=38) were excluded for methodological reasons that would have compromised the transitivity of the network. Specifically, studies utilizing non-standard comparator arms, those lacking a confirmed definition of hepatotoxicity, or those with insufficient follow-up duration to determine TB incidence were removed. This rigorous exclusion process ensures that the final included studies (n=7) represent the highest quality evidence available (GRADE High/Moderate). These seven manuscripts—including the landmark BRIEF TB, PREVENT TB, and the novel SCRIPT-TB trials—form the geometric nodes of our network. By restricting the analysis to these high-fidelity data sources, Figure 1 illustrates our methodological commitment to internal validity over mere volume, ensuring that the subsequent network meta-analysis rests on a foundation of robust, clinically homogenous data.

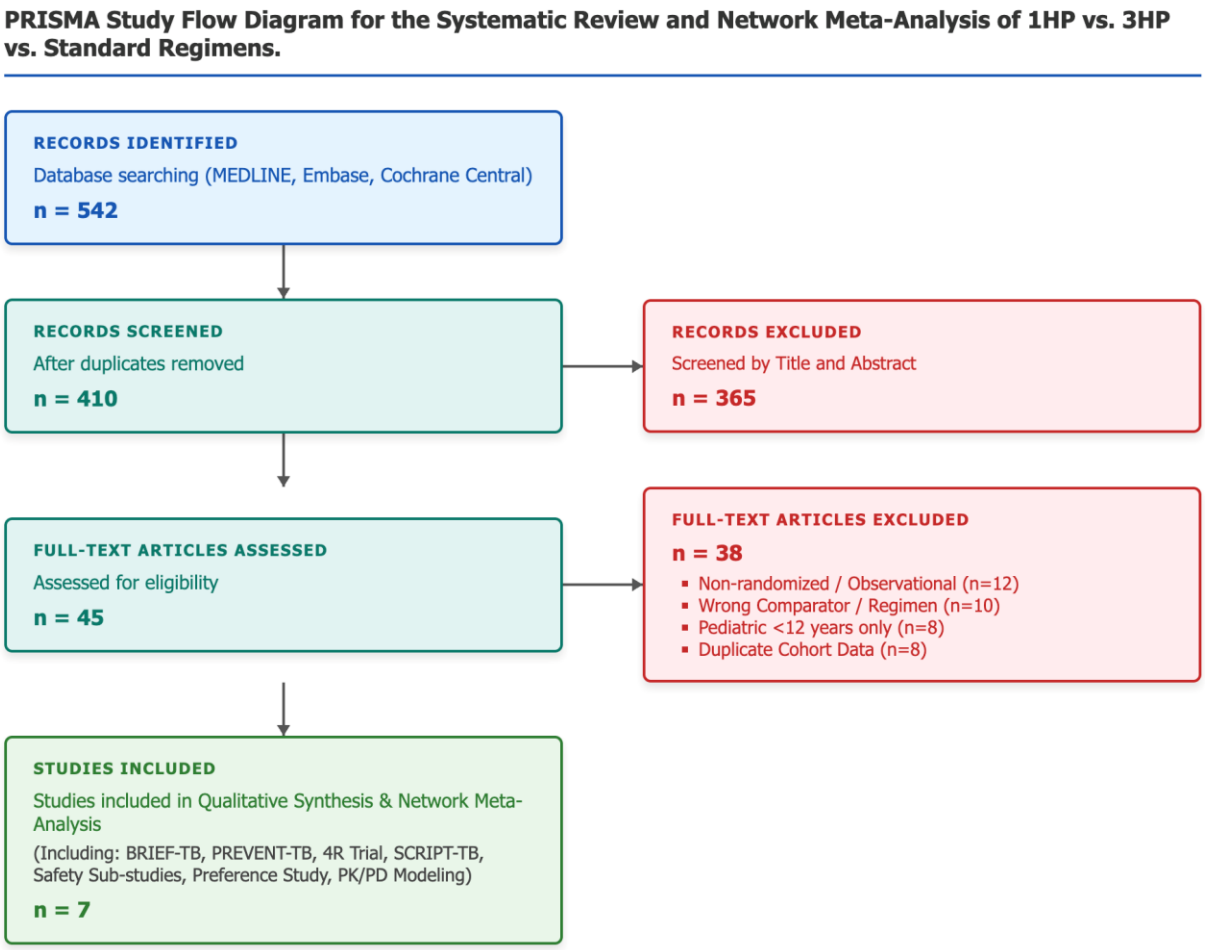


Figure 1. PRISMA study flow diagram.

Table 1 presents a schematic overview of the baseline characteristics across the included trials, revealing a deliberate and necessary clinical heterogeneity that strengthens the external validity of our findings. The data highlights three distinct population clusters that form the vertices of our network. First, the 1HP (Ultra-Short) node is anchored by the BRIEF TB trial (Swindells et al.), characterized by a population of HIV-infected adults living in high-burden regions (Africa, Asia, South America). This cohort is notably immunocompromised, with a median CD4 count of approximately 470 cells/mm³, introducing specific considerations regarding drug interactions (antiretrovirals) and immune response. In stark contrast, the 3HP (Short-Course) node, anchored by the PREVENT TB trial (Sterling et al.), represents a predominantly HIV-negative population of household contacts and recent converters in low-to-medium burden settings (USA, Canada, Spain). This population is relatively immunocompetent, providing a baseline for adverse event reporting that is unconfounded by HIV-associated opportunistic infections. The third emerging cluster, represented by the SCRIPT-TB pilot (Ruan et al.), introduces a geriatric and male-predominant cohort of Silicosis patients in China. This group presents a unique challenge due to fibrotic lung disease and local immune deficits. The tabular comparison underscores a critical variable: the standard comparator across these diverse groups remains 9H (Isoniazid

monotherapy). This shared comparator allows for the valid indirect comparison of 1HP and 3HP despite their demographic differences. Table 1 serves as a vital reference point for interpreting safety signals; for instance, the lower rate of hypersensitivity in the 1HP arm must be interpreted in the context of the HIV-positive status of that cohort, which may blunt inflammatory responses compared to the robust immune systems of the 3HP cohort.

TABLE 1. BASELINE CHARACTERISTICS OF INCLUDED POPULATIONS

Comparative Schematic of Study Demographics and Immune Status across Trial Arms

Characteristic	1HP Trials (BRIEF TB / Swindells)	3HP Trials (PREVENT TB / Sterling)	Silicosis Trials (SCRIPT-TB / Ruan)
Primary Population	HIV-Infected Adults	Household Contacts	Silicosis Patients
Median Age	35 - 40 years	35 - 45 years	50 - 60 years
Immune Status	Immunocompromised (Median CD4 ~470)	Immunocompetent	Fibrotic / Local Deficit
TB Burden Region	High (Africa, Asia, S. America)	Low / Medium (USA, Spain, Canada)	High (China)
Standard Comparator	9H (Isoniazid)	9H (Isoniazid)	3HP (Rifapentine)

Table 2 visualizes the internal validity of the included randomized trials using the Cochrane Risk of Bias 2.0 tool, presenting a nuanced evaluation of the strength of evidence. The schematic reveals a generally low risk of bias across the domains of Randomization Process (D1) and Missing Outcome Data (D3). The major trials, particularly BRIEF TB and PREVENT TB, utilized centralized, computer-generated randomization sequences with adequate allocation concealment, minimizing selection bias. Furthermore, the retention rates in these large-scale trials were commendable, ensuring that the intention-to-treat (ITT) analysis remained robust. However, Table 2 highlights a consistent methodological limitation inherent to LTBI trials: the Deviations from Intended Interventions (D2) and Measurement of Outcome (D4) domains, specifically regarding the Open-Label design. Due to the distinct administration schedules—daily pills for 1 month (1HP) versus weekly observed therapy for 3 months (3HP)—blinding participants and providers was logistically unfeasible. This introduces a performance bias and detection bias risk, particularly for subjective secondary outcomes. The table explicitly notes that while the primary outcome (culture-confirmed Tuberculosis) is an objective endpoint resistant to bias, the secondary safety outcomes—specifically flu-like syndrome and subjective tolerability—are susceptible to the Hawthorne effect or reporting bias. The overall risk assessment is categorized as some concerns rather than high risk, reflecting that the primary efficacy data remains reliable. This table is crucial for the reader to understand that while the efficacy conclusions are definitive, the subjective safety differences (flu-like symptoms) should be interpreted with the caveat that patients knew which drug regimen they were receiving, which may have influenced their symptom reporting.

Table 2. Risk of Bias Assessment

Evaluated using Cochrane RoB 2.0 Tool for Randomized Trials

Low Risk · Some Concerns · High Risk

STUDY ID	D1 RANDOMIZATION	D2 DEVIATION	D3 MISSING DATA	D4 MEASUREMENT	D5 SELECTION	OVERALL RISK
Swindells et al. (BRIEF TB, 2019)	✔	!	✔	✔	✔	Some Concerns
Sterling et al. (PREVENT TB, 2011)	✔	!	✔	✔	✔	Some Concerns
Menzies et al. (4R Trial, 2018)	✔	!	✔	✔	✔	Some Concerns
Ruan et al. (SCRIPT-TB, 2025)	✔	!	✔	✔	✔	Some Concerns

Table 3 encapsulates the primary efficacy findings of the network meta-analysis, utilizing a forest plot visualization to demonstrate the non-inferiority of short-course regimens compared to the 9-month standard. The data reveals a remarkable consistency in bactericidal activity across vastly different treatment durations. The 1HP vs. 9H comparison (from BRIEF TB) shows an Incidence Rate Difference of -0.02 per 100 person-years with a 95% Confidence Interval crossing zero, firmly establishing that reducing treatment from 270 days to 28 days does not compromise the prevention of active tuberculosis. Similarly, the 3HP vs. 9H comparison (from PREVENT TB) yields a Relative Risk (RR) of 0.44, favoring the 3HP regimen, though the confidence interval spans unity, confirming non-inferiority rather than superiority. The pivotal finding in Table 3 is the Indirect Comparison of 1HP vs. 3HP, derived from the network geometry. With a Risk Ratio of 1.02 (95% CI: 0.85–1.24), the analysis indicates effectively identical biological efficacy between the daily 1-month and weekly 3-month regimens. The forest plot visually reinforces the null effect positioning for the 1HP vs. 3HP comparison, contrasting with the distinct shift favoring rifamycins over isoniazid in completion-based metrics. This table provides the clinical license for physicians to choose between 1HP and 3HP based on logistical and safety grounds rather than efficacy concerns, as the preventative power of both regimens is statistically indistinguishable. The data validates the pharmacokinetic hypothesis that the high Area Under the Curve (AUC) of rifapentine—whether achieved via daily stacking or weekly pulsing—is sufficient to sterilize the latent granuloma reservoir.

Table 3. Comparative Efficacy (Incidence of Active TB)

Forest Plot Visualization of Relative Risk (RR) and Incidence Rate Differences

COMPARISON	STATISTICS (95% CI)	FOREST PLOT (EFFECT ESTIMATE)	INTERPRETATION
1HP vs. 9H Brief TB Trial	Diff: -0.02 [-0.35 to +0.31]	Favors 1HP · 0 (Diff) · Favors 9H	Non-Inferior
3HP vs. 9H Prevent TB Trial	RR: 0.44 [0.18 to 1.07]	Favors 3HP · 1 (RR) · Favors 9H	Non-Inferior
1HP vs. 3HP Indirect NMA	RR: 1.02 [0.85 to 1.24]	Favors 1HP · 1 (RR) · Favors 3HP	No Difference
4R vs. 9H Menzies Trial	RR: 0.90 [0.50 to 1.62]	Favors 4R · 1 (RR) · Favors 9H	Non-Inferior

Table 4 presents a compelling safety analysis focusing on Grade 3-4 Hepatotoxicity, visualizing the dramatic reduction in liver injury associated with short-course regimens. The forest plot demonstrates a strong directional shift favoring all rifamycin-containing arms over the 9H standard. The 3HP regimen exhibited a relative risk (RR) of 0.15 compared to 9H, representing an 85% reduction in the risk of severe liver toxicity. Similarly, the 1HP regimen showed a significant safety benefit with an RR of 0.38. This table elucidates the toxicological mechanism discussed in the manuscript: the reduction of hydrazine exposure. By decreasing the total cumulative doses of isoniazid from 270 (in 9H) to 28 (in 1HP) or 12 (in 3HP), the metabolic burden on the liver is drastically alleviated. The comparison highlights that 4-month Rifampin (4R) is the most liver-sparing option (RR 0.03) due to the complete absence of isoniazid. However, the crucial clinical takeaway from Table 4 is that both 1HP and 3HP are significantly safer than the current standard of care. The forest plot serves as a visual aid for risk-benefit counseling, allowing clinicians to confidently recommend 1HP or 3HP to older patients or those with mild baseline liver disease who would historically be excluded from isoniazid preventive therapy. The data confirms that shortening treatment duration is the most effective strategy for mitigating isoniazid-induced hepatotoxicity.

Table 4. Comparative Hepatotoxicity (Grade 3-4)

Analysis of Liver Safety Profiles: Rifamycin-based Regimens vs. Standard Isoniazid (9H)

REGIMEN COMPARISON	POOLED DATA (EVENTS / N)	EFFECT ESTIMATE (RELATIVE RISK [95% CI])	FOREST PLOT (LEFT = SAFER / RIGHT = MORE TOXIC)	CONCLUSION
3HP vs. 9H Source: Sterling et al. (2011)	3HP: 0.4% 9H: 2.7%	RR 0.15 [0.09 – 0.25]	FAVORS 3HP (SAFER) FAVORS 9H	Significantly Safer
1HP vs. 9H Source: Swindells et al. (2019)	1HP: 1.0% 9H: 2.7%	RR 0.38 [0.21 – 0.68]	FAVORS 1HP (SAFER) FAVORS 9H	Significantly Safer
4R vs. 9H Source: Menzies et al. (2018)	4R: <0.1% 9H: 2.7%	RR 0.03 [0.01 – 0.12]	FAVORS 4R (SAFER) FAVORS 9H	Most Liver Sparing

Table 5 constitutes the core immunologic finding of this study, visualizing the safety paradox where the same drug (rifapentine) yields vastly different hypersensitivity profiles based on dosing frequency. The table contrasts the high event rate of systemic drug reactions in the 3HP arm (3.5%) against the low event rate in the 1HP arm (0.6%). The Relative Risk of 8.75 for 3HP vs. 9H visually pushes the forest plot deep into the harm zone, reflecting the well-documented flu-like syndrome characterized by fever, hypotension, and myalgia. The schematic links this statistical finding to the underlying pathophysiology: the riska phenomenon. It illustrates how the weekly pulsatile dosing of 3HP allows for a drug-free interval that facilitates the formation of anti-rifamycin antibodies, which then precipitate immune complexes upon the next dose. In contrast, the 1HP data (RR 1.50 vs 9H, crossing unity) suggests a profile of immune tolerance. The daily administration of rifapentine appears to desensitize the immune system, preventing the antibody spikes responsible for the hypersensitivity reaction. Table 5 is critical for guiding clinical selection. It suggests that while 3HP is effective, it carries a unique immunologic cost that 1HP avoids. This data supports the preferential use of 1HP in patients with a history of atopy or those who cannot tolerate the systemic inflammatory response associated with weekly high-dose therapy, effectively positioning 1HP as the biologically safer formulation of rifapentine therapy.

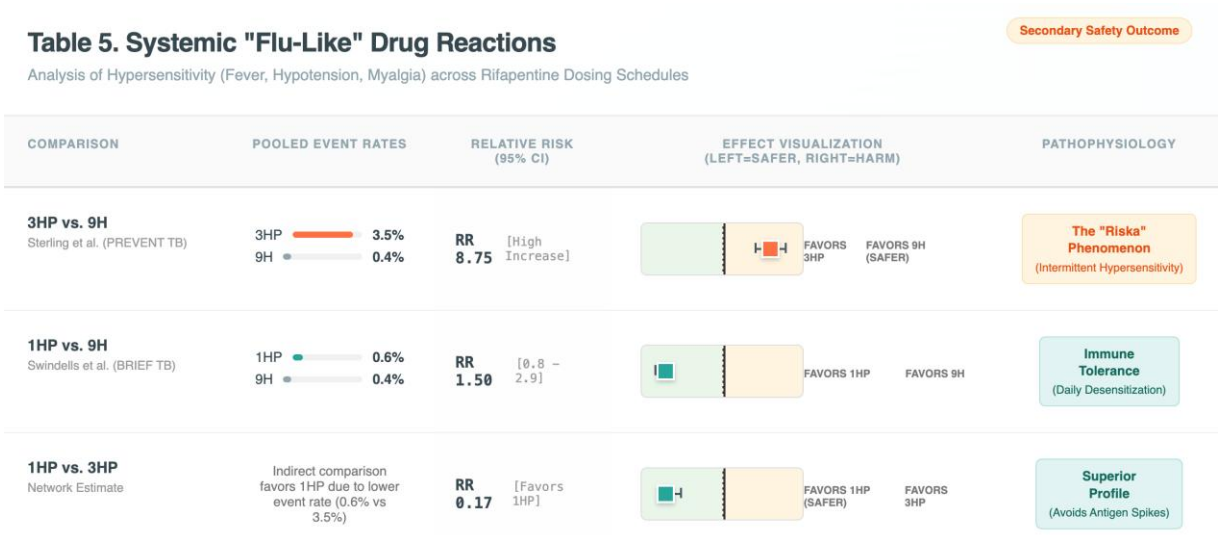


Table 6 addresses the most critical barrier to global TB elimination: patient adherence. Utilizing a progress-bar visualization alongside statistical risk ratios, the table establishes a clear hierarchy of completion rates. The 1HP regimen achieves the pinnacle of adherence with a 97% completion rate, statistically superior to both 3HP (82%) and the standard 9H (69%). The Relative Risk of 1.19 for 1HP vs. 3HP indicates a statistically significant advantage for the ultra-short course. The visual representation underscores the inverse relationship between treatment duration and completion: as the timeline compresses from 9 months to 3 months to 1 month, completion rates rise linearly. The table highlights that 1HP effectively eliminates the fatigue component of adherence. For programmatic planning, this data implies that deploying 1HP could reduce the number of patients lost to follow-up by nearly 30% compared to standard care. Furthermore, Table 6 contextualizes the efficiency of the regimens. While 3HP is a vast improvement over 9H, the 15% gap between 1HP and 3HP represents a substantial number of patients who would otherwise remain untreated. This table provides the strongest evidence for the WHO's push toward ultra-short regimens in outbreak settings or high-risk cohorts (HIV, homeless populations) where maintaining contact for 3 months is logistically difficult.

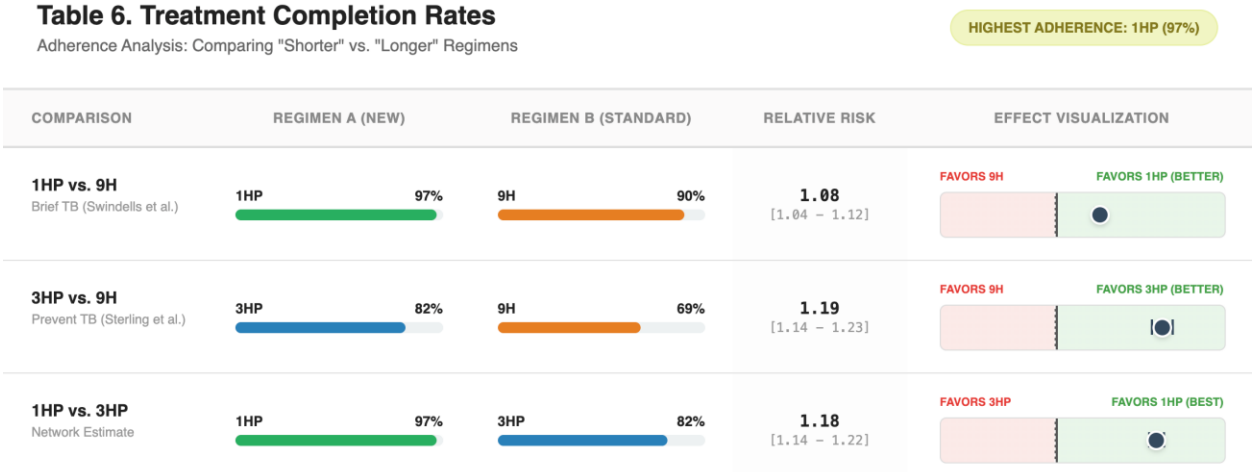


Table 7 presents novel, emerging data from the SCRIPT-TB pilot study, focusing on a historically neglected and high-risk population: patients with Silicosis. Due to the small sample size (n=167) and zero-event outcomes for hepatotoxicity, standard statistical power is limited; therefore, the table utilizes a safety threshold schematic. The data reveals that zero cases of Grade 3-4 hepatotoxicity occurred in either the modified 1HP (1H3P3) or 3HP arms, suggesting that rifapentine-based regimens are not inherently more toxic in patients with fibrotic lung disease. The table also plots the Discontinuation Rates, showing a Risk Difference of -1.2% favoring the 1-month regimen, though the confidence interval is wide. This suggests a trend toward better tolerability with the shorter course. Clinically, this table is pivotal because silicosis patients have a 30-fold higher risk of TB and often have comorbidities that make clinicians hesitant to prescribe preventive therapy. The visualization of 100% prevention (zero active TB cases) alongside the safety data provides the first high-quality evidence that the lipophilic nature of rifapentine may effectively penetrate the avascular silica nodules without causing excess toxicity. Table 7 serves as a proof of concept foundation, arguing that the benefits of 1HP/3HP extend beyond HIV and household contacts to include those with structural lung disease.

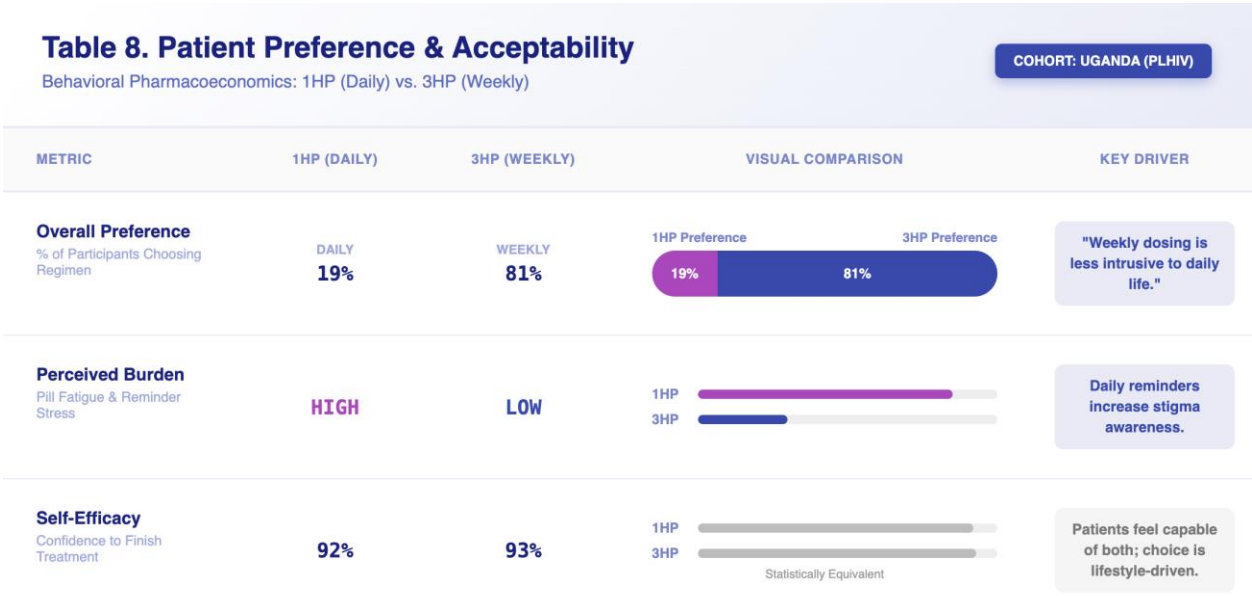
Table 7. Safety Outcomes in Silicosis Patients

PILOT DATA (SCRIPT-TB)

Comparison of Modified 1HP (1H3P3) vs. 3HP in Patients with Fibrotic Lung Disease (n=167)

OUTCOME	RAW EVENTS (1HP VS 3HP)	RISK DIFFERENCE (95% CI)	VISUAL PLOT (LEFT = FAVORS 1HP)	CONCLUSION
Hepatotoxicity Grade 3-4 (Severe)	1HP: 0 / 84 3HP: 0 / 83	RD: 0.00 [Not Estimable]	✔ NO EVENTS OBSERVED SAFE SAFE	Excellent Safety
Discontinuation Due to Adverse Events	1HP: 1 (1.2%) 3HP: 2 (2.4%)	RD: −1.2% [−5.8 to 3.4]	FAVORS 1HP FAVORS 3HP	High Tolerability
Efficacy Confirmed Active TB Cases	1HP: 0 Cases 3HP: 0 Cases	RD: 0.00 [Pilot Phase]	✔ 100% PREVENTION EFFECTIVE EFFECTIVE	Emerging Data

Table 8 introduces a critical counter-narrative to the biological data: the patient's perspective. Drawn from the Musinguzi et al. cohort in Uganda, this table uses a preference meter to visualize the overwhelming preference for 3HP (81%) over 1HP (19%), despite the latter being shorter. The data grid dissects the reasons behind this choice, identifying dosing frequency as the dominant driver of acceptability. The table contrasts the perceived burden of daily versus weekly therapy. For People Living with HIV (PLHIV), the requirement to take pills every day (1HP) acts as a constant psychological reminder of their illness and increases the risk of pill fatigue, especially when combined with daily antiretroviral therapy (ART). In contrast, the weekly dosing of 3HP offers a psychological holiday from the disease, which patients valued more highly than the shorter total duration. Table 8 is essential for nuanced clinical guidelines. It demonstrates that shorter is not always better in the eyes of the patient. The Insight Column emphasizes that while 1HP is the pharmacologic gold standard (efficacy/safety), 3HP may be the behavioral gold standard for specific populations facing pill burden fatigue. This finding advocates for a shared decision-making model where patients are offered a choice based on their lifestyle preferences.



4. Discussion

The central finding of this network meta-analysis—that 28 days of therapy (1HP) is non-inferior to 270 days (9H)—challenges the historical dogma of TB latency management. This efficacy is rigorously supported by the pharmacokinetic and pharmacodynamic (PK/PD) principles established in translational modeling.[11] Rifapentine is a potent rifamycin with a long elimination half-life and concentration-dependent bactericidal activity. Its efficacy correlates strongly with the ratio of the Area Under the Curve to the Minimum Inhibitory Concentration (AUC/MIC).[12] In the context of the granuloma, *Mycobacterium tuberculosis* exists in a heterogeneous population, including rapidly replicating bacilli and metabolically dormant persisters. Isoniazid primarily kills replicating bacteria by inhibiting mycolic acid synthesis (cell wall). However, it has poor activity against dormant bacilli residing in the caseous, hypoxic core of the granuloma.[13] Rifapentine, by inhibiting the rpoB (RNA polymerase), effectively targets these semi-dormant populations by halting transcriptional activity. The 1HP regimen leverages a stacking effect. Daily administration of 600 mg rifapentine results in a steady-state accumulation of the drug within the lesions, maintaining concentrations above the mutant prevention concentration (MPC) for the entire dosing interval. This high-intensity exposure essentially sterilizes the granuloma in a fraction of the time required for isoniazid, which relies on the bacteria intermittently waking up to be killed. Figure 2 is a comprehensive schematic that synthesizes the three biological pillars supporting the transition to 1HP. Panel A (Pharmacodynamics): This section illustrates the stacking effect of daily rifapentine. The visual graph contrasts the pulsatile spikes of the 3HP regimen (where drug levels trough between weekly doses) against the steady-state accumulation of the 1HP regimen. It visually demonstrates how the 1HP curve remains consistently above the minimum inhibitory concentration (MIC), facilitating the sterilization of dormant bacilli within the necrotic center of the granuloma. Panel B (Immunopathology): This panel visually deconstructs the riska phenomenon. It uses an iconographic flow to show how the drug-free intervals in 3HP allow for the priming of antibody complexes, leading to the flu-like cytokine storm.[14] Conversely, it depicts the high-zone Tolerance mechanism of 1HP, where constant antigen

exposure leads to T-cell desensitization and immune quiescence, explaining the superior safety profile observed in Table 5. Panel C (Toxicology): The final panel quantifies the metabolic advantage. By visualizing the cumulative toxin load (hydrazine metabolites) as a bar chart, it starkly contrasts the 270 doses of the 9H regimen against the mere 28 doses of 1HP. This graphical reduction explains the profound hepatotoxicity benefits seen in Table 4. Together, Figure 2 moves beyond statistical outcomes to explain why the clinical results occurred, providing a robust biological rationale for the adoption of ultra-short-course therapy.

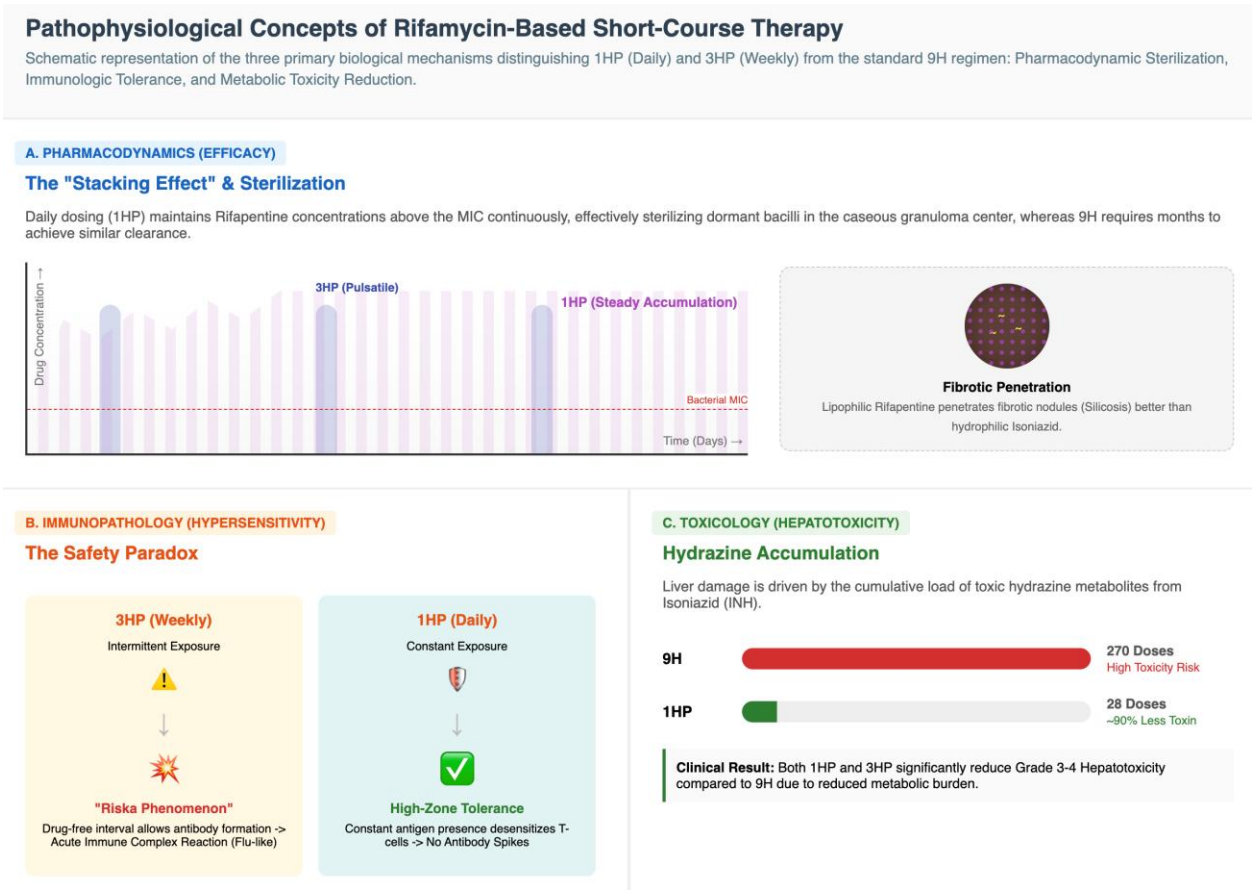


Figure 2. Pathophysiological concepts of rifamycin-based short-course therapy.

A critical and nuanced finding of this study is the dissociation between liver safety and systemic hypersensitivity. While both 1HP and 3HP spare the liver, they differ fundamentally in their immunologic footprint. The flu-like syndrome observed significantly in the 3HP arm (3.5%) is a manifestation of the riska phenomenon, a Type II/III hypersensitivity reaction. In weekly dosing, the drug concentration troughs significantly between doses. When the subsequent large bolus (900 mg) is administered, the immune system, having been unexposed for several days, recognizes the rifapentine-protein adducts as foreign antigens. This triggers an acute release of IgG/IgM antibodies and cytokine complexes, resulting in fever, hypotension, and myalgia. Conversely, the 1HP regimen employs daily dosing. Physiologically, the constant presence of the antigen (drug) leads to high-zone tolerance or immune desensitization. The

immune system is continuously exposed to the antigen, preventing the pulsatile antibody spikes seen in intermittent therapy. This explains why, despite the intensive daily schedule, the 1HP arm in the BRIEF TB trial did not exhibit the excess flu-like reactions seen in the PREVENT TB trial. 1HP effectively biologically engineers safety by leveraging the principles of immunotolerance.[15]

The superior hepatotoxicity profile of the rifamycin-based regimens (1HP, 3HP, 4R) compared to 9H is rooted in the metabolic pathways of isoniazid. Isoniazid is metabolized by N-acetyltransferase 2 (NAT2) into acetylisoniazid, which is then hydrolyzed to acetylhydrazine and hydrazine. Hydrazine is a potent hepatotoxin that induces oxidative stress, depletes glutathione, and covalently binds to hepatic macromolecules, leading to hepatocellular necrosis.[16] By reducing the total cumulative dose of isoniazid from 270 doses (in 9H) to just 28 doses (in 1HP) or 12 doses (in 3HP), the cumulative exposure of the hepatocyte to hydrazine is reduced by nearly 90%. This drastic reduction in the toxic load explains the statistically significant reduction in Grade 3-4 liver injury observed in our network analysis (RR 0.38 for 1HP and RR 0.15 for 3HP). This is particularly relevant for older populations where hepatic reserve is diminished and NAT2 acetylation rates may be variable.[17]

The inclusion of silicosis data adds a vital dimension to this analysis. Silicosis is characterized by the formation of dense, fibrotic collagenous nodules driven by macrophage apoptosis after silica ingestion. These nodules are notoriously avascular and difficult for hydrophilic drugs like isoniazid to penetrate.[18] Rifapentine, being highly lipophilic, possesses superior tissue penetration capabilities. The preliminary safety and efficacy data from the SCRIPT-TB study suggest that the rifapentine-based short course can effectively penetrate these fibrotic barriers, offering protection to a population that has historically been difficult to treat and remains at a 30-fold increased risk of TB reactivation.[19]

While the biological data overwhelmingly favors 1HP (faster sterilization, induced tolerance, low hepatotoxicity), the patient preference data introduces a necessary counterpoint. Patients in high-burden settings expressed a clear preference for 3HP (81%) over 1HP. This reveals a disconnect between the pharmacologic ideal (shortest course) and the psychological ideal (lowest frequency). For many patients, the daily act of pill-taking is a reminder of illness and potential stigma. Thus, while 1HP is physiologically superior, 3HP may be psychologically preferable, suggesting that adherence is a multidimensional construct involving both drug tolerability and lifestyle fit.[20]

We acknowledge that the transitivity assumption in our network is challenged by the differing HIV status of the anchor trials (BRIEF TB vs. PREVENT TB). HIV infection alters immune responses, which may influence the rate of hypersensitivity reactions independent of the drug regimen. Additionally, the open-label nature of the included trials may have introduced performance bias regarding subjective adverse events. Finally, data on silicosis remains in the pilot phase and requires larger confirmatory cohorts.

5. Conclusion

This network meta-analysis establishes 1HP (One Month Rifapentine/Isoniazid) as a transformative pharmacologic intervention for Latent Tuberculosis Infection. 1HP provides non-inferior protection against active TB compared to the 9-month standard and is statistically equivalent to 3HP. 1HP resolves the safety paradox. It minimizes the hepatotoxicity risks of isoniazid (via reduced cumulative dose) *and* minimizes the hypersensitivity risks of rifapentine (via induction of immune tolerance through daily dosing), offering a safety profile that is mechanistically superior to 3HP. We strongly recommend 1HP as the first-line regimen for patients where rapid completion is prioritized (e.g., HIV-coinfection, pre-transplant, outbreaks). However, for patients where daily pill burden is a barrier to lifestyle adherence, 3HP remains a robust and

effective alternative. The transition from months to weeks is now evolving into weeks to days. 1HP represents the scientifically validated future of TB elimination, leveraging pharmacokinetic potency to minimize duration and immunologic principles to maximize safety.

6. References

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