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REVIEW ARTICLE

THE ROLE OF ISONIAZID IN THE TREATMENT OF TUBERCULOSIS: MECHANISMS, EFFICACY AND CLINICAL CHALLENGES: A REVIEW

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Abstract

Tuberculosis (TB) remains one of the leading causes of mortality from infectious diseases worldwide, with *Mycobacterium tuberculosis* (Mtb) infecting one-quarter of the global population. Isoniazid (INH), a cornerstone of first-line anti-TB therapy for over 70 years, continues to play a central role in both treatment of active TB and preventive therapy for latent infection. This review provides an analysis of the mechanisms of action, clinical efficacy, pharmacological properties, and emerging challenges associated with isoniazid in modern TB management. Isoniazid is a prodrug that requires activation by the mycobacterial catalase-peroxidase enzyme KatG to form reactive species that inhibit InhA, an essential enoyl-acyl carrier protein reductase involved in mycolic acid biosynthesis. This inhibition disrupts the mycobacterial cell wall and leads to bactericidal activity, particularly against actively replicating bacilli. The review further evaluates the clinical efficacy of isoniazid within standard 6-month regimens for drug-susceptible TB, as well as its role in 3HP and 6H preventive therapy regimens. Despite its potency and low cost, the widespread emergence of INH resistance, primarily mediated by mutations in katG and inhA, poses a significant threat to TB control programs. The molecular basis of resistance, diagnostic approaches, and current World Health Organization (WHO) recommendations for managing INH-resistant TB was elaborated. Additional clinical challenges addressed include hepatotoxicity, drug-drug interactions, and adherence issues linked to long treatment durations. Finally, future directions, including novel drug delivery systems, combination therapies, and strategies to overcome resistance while preserving the utility of isoniazid in TB elimination efforts was highlighted.

Keywords: drug delivery, drug resistance, isoniazid, hepatotoxicity, *Mycobacterium tuberculosis*.

INTRODUCTION

Tuberculosis (TB) is an ancient infectious disease caused by *Mycobacterium tuberculosis* (Mtb) that continues to impose a major burden on global public health[1]. Despite advances in diagnostics and therapeutics, TB remains the leading cause of death from a single infectious agent, with an estimated 10.6 million new cases and 1.3 million deaths reported in 2024. The persistence of TB is driven by factors including poverty, co-infection with HIV, emergence of drug-resistant strains, and incomplete treatment adherence[2]. Effective chemotherapy is therefore central to TB control, and among the available anti-TB agents, isoniazid (INH) has remained indispensable since its introduction into clinical practice in 1952. Isoniazid, also known as isonicotinic acid hydrazide, is a low-cost, orally bioavailable prodrug that exhibits potent bactericidal activity against actively replicating *M. tuberculosis*. It forms the backbone of all standard first-line treatment regimens recommended by the World Health Organization (WHO), including the 6-month 2HRZE/4HR regimen for drug-susceptible pulmonary TB[3]. Beyond treatment, INH is also the mainstay of preventive therapy for latent TB infection (LTBI), with regimens such as 6-9 months of daily INH (6H/9H) and the shorter 3-month weekly rifapentine plus INH (3HP) widely implemented in high-burden settings[4].

The widespread use of INH in both active disease and prevention underscores its unique position as the single most important anti-TB drug developed to date. The antitubercular activity of INH stems from its selective targeting of mycobacterial cell wall synthesis. As a prodrug, INH requires activation by the mycobacterial catalase-peroxidase enzyme KatG. The activated intermediates then form a covalent adduct with NADH, which binds with high affinity to InhA, the enoyl-acyl carrier protein reductase involved in the biosynthesis of mycolic acids. Inhibition of InhA disrupts the synthesis of the mycobacterial outer membrane, leading to cell death[5]. This mechanism confers high specificity for mycobacteria and accounts for INH's excellent early bactericidal activity. However, the dependence on KatG activation also represents a critical vulnerability, as mutations in katG and in the inhA promoter region are the primary drivers of INH resistance. Pharmacologically, INH is rapidly absorbed and widely distributed, including into caseous granulomas and cerebrospinal fluid. Its metabolism is primarily governed by hepatic N-acetyltransferase 2 (NAT2), resulting in genetically determined fast, intermediate, and slow acetylator phenotypes that influence both drug exposure and risk of adverse effects[6]. The most significant toxicity associated with INH is drug-induced hepatotoxicity, which, along with peripheral neuropathy, requires clinical monitoring during therapy. Additional challenges include numerous drug-drug interactions, particularly with antiretrovirals and anticonvulsants, and the need for pyridoxine supplementation to prevent neurotoxicity. Despite its clinical success, the utility of INH is increasingly threatened by drug resistance. INH monoresistance is the most common form of resistance globally and can lead to treatment failure and amplification to multidrug-resistant TB (MDR-TB) if not detected early. The rise of INH-resistant TB has prompted revisions to treatment guidelines, including the use of longer regimens and the inclusion of additional drugs such as levofloxacin[6]. At the same time, efforts are underway to preserve and enhance the role of INH through novel formulations and drug delivery systems. Nanoparticles, liposomes, and biopolymer-based scaffolds, including chitosan, are being investigated to improve INH bioavailability, enable controlled release, and reduce toxicity[7].

Isoniazid (INH) is a first line bactericidal agent against *Mycobacterium tuberculosis* whose activity depends entirely on intracellular activation and selective inhibition of mycolic acid biosynthesis[8]. Although highly effective, its clinical utility is increasingly compromised by resistance, which arises primarily through mutations that prevent drug activation or increase the abundance of its target enzyme[9]. Understanding both the mechanism of action and the molecular basis of resistance is therefore essential for optimizing INH use in current TB treatment regimens. The antitubercular activity of isoniazid stems from its role as a prodrug that, following activation by the mycobacterial catalase-peroxidase KatG, forms an adduct that inhibits InhA and disrupts cell wall synthesis in *M. tuberculosis.* However, this dependence on a single activation pathway and targ*et al*so makes INH vulnerable to resistance. Mutations in katG, inhA, and related genes are now the leading cause of INH resistance worldwide and represent a major challenge to TB control[10]. Despite being in use for over 70 years, isoniazid remains the most potent early bactericidal drug in TB therapy due to its specific inhibition of mycolic acid synthesis in *M. tuberculosis*. Paradoxically, this same mechanism underlies its greatest weakness: resistance develops readily through single-step mutations that block activation by KatG or alter the drug target InhA. As INH resistance continues to rise globally, a detailed understanding of its mechanism of action and resistance pathways is critical for both diagnosis and drug development.

Absorption and distribution of isoniazid

INH is rapidly and almost completely absorbed from the gastrointestinal tract, with peak plasma concentrations occurring 1-2 hours after oral administration. Food, particularly carbohydrates, can delay absorption but does not significantly reduce overall bioavailability[11]. The drug is water-soluble, has low protein binding (<10%), and distributes widely into all body tissues and fluids. Critically for TB, INH penetrates well into caseous granulomas, macrophages, and the cerebrospinal fluid, achieving concentrations that exceed the MIC for *M. tuberculosis*. This broad distribution underlies its efficacy in pulmonary, extrapulmonary, and central nervous system TB.

Metabolism and acetylator phenotype

The primary route of INH metabolism is hepatic acetylation by N-acetyltransferase 2 (NAT2) to form N-acetyl isoniazid, which is then hydrolyzed to acetylhydrazine and isonicotinic acid[12]. NAT2 activity is genetically polymorphic, giving rise to three phenotypes: slow, intermediate, and fast acetylators. Fast acetylators clear INH 2-3 times faster than slow acetylators, resulting in lower drug exposure (AUC) but also a reduced risk of hepatotoxicity. In contrast, slow acetylators maintain higher plasma levels and are at greater risk of adverse effects. This genetic variability has implications for both efficacy and safety, particularly in populations with a high prevalence of slow acetylators.

Elimination

INH and its metabolites are primarily excreted in urine. The elimination half-life ranges from 1-2 hours in fast acetylators to 3-4 hours in slow acetylators[13]. Renal impairment has minimal effect, but dose adjustment may be needed in severe hepatic dysfunction due to the risk of drug accumulation and toxicity.

Pharmacodynamics of isoniazid

INH exhibits concentration-dependent bactericidal activity against rapidly dividing extracellular *M. tuberculosis*, and time dependent activity against semi-dormant intracellular *bacilli*. Its pharmacodynamic index most closely linked to efficacy is the ratio of the area under the curve to MIC (AUC/MIC) and the peak concentration to MIC (C_{max}/MIC).

Bactericidal activity (EBA) of isoniazid

INH has the highest EBA of all first-line TB drugs, reducing sputum bacillary load by ~0.5 log10 CFU/mL per day in the first 2 days of therapy. This rapid kill is

attributed to inhibition of mycolic acid synthesis in actively replicating bacilli[14].

Post-antibiotic effect and sterilizing activity

INH also contributes to the sterilizing activity of TB regimens by killing slowly metabolizing bacilli in acidic environments, although to a lesser extent than rifampicin and pyrazinamide[14]. The combination of rapid kill and sterilizing activity is why INH is indispensable for shortening treatment duration to 6 months. The mutant prevention concentration for INH is low, meaning subtherapeutic exposures readily select for katG and inhA mutants. Maintaining adequate C_{max} and AUC is therefore critical to prevent amplification of resistance, particularly in INH mono-resistant strains where higher doses may retain some activity.

Clinical roles of isoniazid in TB management

Treatment of active drug-susceptible TB

INH is a core component of the standard 6-month regimen: 2 months of INH, Rifampicin, Pyrazinamide, and Ethambutol followed by 4 months of INH and Rifampicin (2HRZE/4HR)[15]. In this regimen, INH provides the early bactericidal effect while rifampicin and pyrazinamide contribute sterilizing activity. Daily dosing is preferred, but thrice-weekly dosing is also effective in directly observed therapy programs. The main clinical challenge with INH is hepatotoxicity, which occurs in 1-3% of patients and is more common in slow acetylators, those >35 years, and patients with alcohol use or concomitant hepatotoxic drugs[16]. Peripheral neuropathy is prevented by pyridoxine supplementation. Drug-drug interactions, particularly with antiretrovirals and anticonvulsants, also require clinical attention. The clinical success of isoniazid in TB management is rooted in its favorable PK profile, potent PD activity, and versatility across treatment and prevention. However, interindividual variability in metabolism, the narrow margin between efficacy and toxicity, and the ease with which resistance emerges necessitate careful dosing, pharmacogenetic consideration, and adherence support. As TB programs move toward shorter, safer regimens and personalized medicine, optimizing INH exposure through therapeutic drug monitoring and novel delivery systems remains a priority. Tuberculosis remains a major global health threat, and the emergence of drug-resistant *Mycobacterium tuberculosis* strains has significantly complicated control efforts. Drug-resistant TB (DR-TB) arises primarily from chromosomal mutations selected by inadequate treatment, poor adherence, or transmission of resistant strains. Resistance to isoniazid (INH) is the most common form of first-line drug resistance and is a key predictor of progression to multidrug-resistant TB (MDR-TB), defined as resistance to at least INH and rifampicin. For decades, INH was the backbone of TB therapy due to its potent early bactericidal activity and ability to sterilize lesions. However, the rising prevalence of katG and inhA mutations has forced a reevaluation of its role.

In INH-susceptible TB, INH remains essential to the standard 6-months regimen for its rapid bacterial kill. In INH-monoresistant TB, WHO now recommends replacing INH with a fluoroquinolone while retaining rifampicin, shifting INH from a core drug to a conditional one. For MDR-TB, INH is generally omitted due to high-level resistance, though high-dose INH may still be considered for low-level inhA mutations[17]. Thus, the role of INH is evolving from a universal first-line agent to a stratified drug whose use depends on rapid molecular diagnostics and resistance patterns. Preserving INH efficacy through optimized dosing, novel formulations, and drug delivery systems has become critical to prevent further resistance amplification and to support shorter, more effective TB regimens. Drug-induced liver injury (DILI) is the most serious adverse effect of INH. The incidence of symptomatic hepatitis is 0.5-3%, but asymptomatic transaminitis is much more common. Toxicity is thought to arise from hydrazine metabolites produced during INH metabolism, and risk is increased by slow acetylator status, age >35 years, alcohol consumption, malnutrition, and concomitant hepato-toxic drugs such as rifampicin and pyrazinamide[18]. Clinically, hepato-toxicity often necessitates treatment interruption, dose reduction, or permanent disconti-nuation of INH. In TB/HIV co-infected patients on antiretrovirals, the risk of liver injury is further compounded[19]. This creates a difficult balance: stopping INH jeopardizes regimen efficacy, but continuing it risks severe liver damage. Routine liver function monitoring is recommended but is not feasible in many high-burden, resource-limited settings.

CONCLUSION

Isoniazid's legacy in TB treatment is unmatched. Its mechanism underpins the success of modern TB therapy, and its efficacy in susceptible disease remains essential. Yet its clinical utility is now constrained by resistance, toxicity, and pharmacokinetic variability. Preserving the role of INH in the 21st century, will require moving beyond empirical use toward personalized, resistance-guided, and formulation-optimized approaches.

AUTHOR'S CONTRIBUTION

Ezegbe CA: conceptualization, writing original draft, revision. **Emeka-Obi OR:** conceptualization, writing original draft, revision. **Okorafor EC:** conceptual-lization, revision. **Onuaja CG**: editing. **Amadi NA:** editing, revision. **Amadi RG:** writing original draft. Final manuscript was checked and approved by all authors.

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DATA AVAILABILITY

The related author can provide the empirical data supporting the study's conclusions upon request.

CONFLICT OF INTEREST

There are no conflicts of interest in regard to this project.

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