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AN UPDATE AND REVIEW OF ISONIAZID IN TUBERCULOSIS

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Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. These organisms produce a silent, latent infection or an active disease characterized by fever, night sweats, and weight loss, leading to progressive tissue destruction and possibly death. The World Health Organization (WHO) estimates 9.4 million incident cases, 14 million prevalent cases, and 1.68 million deaths (with 0.38 million in HIV-positive individuals) in 2009.[1] Poverty, HIV coinfection, and drug resistance continue to be major contributors to the global endemic. Although 95% of TB cases are found in developing countries, the United States continues to import new cases from countries where TB remains out of control.[2] Tuberculosis remains a significant health problem worldwide.

Approximately one third of the world's population, including more than 11 million persons in the United States, is latently infected with *M. tuberculosis*. About 80% of U.S. TB cases are due to reactivated latent infection (LTBI). Once infected with *M.tuberculosis*, a person's lifetime risk of active TB is approximately 5-10%.[3] The greatest risk for active disease occurs during the first two years of infection. A targeted approach of screening is recommended over random screening (**Table 1**).[2,3,4]

Isoniazid (INH, isonicotinylhydrazide) is a synthetic antibiotic first introduced in 1952. Due to its efficacy and low cost, INH is considered a first-line agent in treatment of susceptible replicating *M. tuberculosis* and should be considered once treatment is indicated. INH is available generically as oral tablets (100mg, 300mg), oral syrups (50mg/5mL) or solutions (50mg/5mL), and intramuscular solutions (100mg/mL). INH (Nydrazid®) is only available as an IM solution. For LTBI, INH monotherapy for 9 months is the treatment of choice for most patients.[4] INH should be used in multi-drug regimens in patients with active TB in order to achieve bacterial clearance, to reduce risk of transmission and to prevent emergence of drug resistance.[5] This article will review the current and various roles INH plays in the management of latent and active TB.

Pharmacology and Pharmacokinetics

Despite its rather simple chemical structure, the mechanism of action of INH is complex. INH is a prodrug that is activated by the catalase-peroxidase enzyme KatG to form an INH-NAD adduct. The adduct inhibits InhA (the enoyl-ACP reductase of the fatty acid synthase type II system), responsible for mycolic acid biosynthesis. Since this process is specific to *Mycobacterium*, inhibition causes cell wall disruption and ultimately bacterial cell death. INH is bactericidal against rapidly dividing cells, which are usually found in extracellular cavitary lesions. It also has bacterio-

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static activity against organisms found within closed caseous lesions and macrophages that divide slowly and intermittently.[6]

Pharmacokinetic properties of the drug are listed in **Table 2**. INH is often administered orally and is absorbed rapidly in the GI tract. The rate and extent of absorption following oral therapy can be delayed by foods and antacids. The primary route of INH metabolism is hepatic acetylation. Polymorphisms in the expression of the enzyme system primarily responsible for this process, *N-acetyltransferase-2* (*NAT2*), result in trimodal elimination (slow, intermediate, and fast).[9]

Kim et al. evaluated genetic polymorphisms of drug-metabolizing enzymes (CYP2C9, CYP2C19, CYP2D6, CYP2E1, NAT2, UGT1A1, and UGT1A3) and anti-TB drug-induced hepatotoxicity in a Korean population. All patients received the standard four-drug regimen indicated for active pulmonary TB, and underwent the same monitoring schedule for hepatotoxicity. Patients with genetic variants in the *NAT2* promoter region (variant allele of -9796T>A) were found to have decreased serum acetyl-INH levels (metabolite of INH). The ratio of acetyl-INH:INH in subjects carrying the minor allele was significantly lower compared with those with the wild-type genotype. Moreover, the minor allele homozygotes showed significantly lower ratios compared with heterozygotes ($p = 0.009$). These findings suggest genetic variations are linked with slow acetylation of INH.[10]

Patients with *NAT2* genotypes (-9796T>A, R197Q and ht2) that had high INH levels, low acetyl-INH:INH ratio and low INH clearance showed a higher rate of anti-TB drug-induced hepatitis. These findings suggest that genetic variants in the promoter and exons of *NAT2* increase the risk of anti-TB drug-induced hepatitis by altered gene expression. No significant gene associations were revealed in any of the CYP enzymes studied, suggesting that there is no essential role for genetic mutation of the other metabolizing enzymes in the development of this adverse reaction. There were no significant differences in serum drug levels of rifampin (RIF), ethambutol (EMB) and pyrazinamide (PZA) with *NAT2* variants.[10]

Drug interactions with INH result from the inhibitory effects on the hepatic isoenzymes. The most commonly affected include CYP2C19, CYP3A4, and CYP2C9. Results are conflicting for CYP1A2, and INH is theorized to have a dual effect on inhibitory and inducing actions on CYP2E1. Potent inhibitory effects of INH on CYP3A4 increase serum concentrations and decrease clearance of agents such as benzodiazepines, corticosteroids, paricalcitol, ranolazine, dronedarone, cyclosporine, theophylline, and telithromycin. Anticonvulsants (phenytoin, valproic acid) metabolized by CYP3A4 should also be used with caution, and appropriate adjustments to the anticonvulsant dose should be made. INH also inhibits hepatic oxidative metabolism of warfarin, increasing warfarin concentrations (CYP3A4, CYP1A2, CYP2C19). When INH exerts an inducing effect on CYP2E1, toxic metabolites of certain compounds (i.e. acetaminophen) can accumulate in the liver. Simultaneous use with such agents should be avoided to prevent potentiation of hepatotoxicity.[11]

Table 1 | High Risk Populations Needing Targeted Tuberculin Testing and Treatment of LTBI[2,3,4]

Persons at highest risk of exposure to and infection with *Mycobacterium tuberculosis*

- Persons in close contact with individuals with confirmed active TB
- Foreign-born persons from endemic countries (and have been living in the U.S. for less than 5 years)
- Residents and employees of congregate settings (correctional facilities, LTCF, homeless shelters)

Persons at high risk of progression from LTBI to active TB

- HIV-coinfected persons
- Persons infected with M. tuberculosis within the past 2 years
- Children younger than 4 years old
- Adults older than 65 years old
- Immunosuppressed persons (DM, ESRD, Cancer, Prolonged steroid use, Organ transplants)

DM = diabetes mellitus; ESRD = end-stage renal disease; HIV = human immunodeficiency virus infection; LTBI = latent tuberculosis infection; LTCF = long-term care facilities TB = tuberculosis

Table 2 | Pharmacokinetics of INH

Property	
Tmax	0.5-2hours
Bioavalibility	90%
Protein Binding	<10%
Metabolism	Acetylation
Excretion	75-96% urine unchanged
Vd	06-1.2 L/kg
Elimination half life	1-1.8 hrs (FA) 3-4 hrs (SA)
Clearance[7*,8]	50 l/h (FA) 15 l/h (SA)

FA=fast acetylators; hrs=hours; l/h=liters per hour; L/kg=liters per kilogram; SA=slow acetylators

*Study conducted in healthy North American males; similar data of fast versus slow acetylators found in South African population.

Adverse Events

INH is most frequently associated with adverse reactions affecting the nervous system and the liver. Slow acetylators may be at increased risk of hepatotoxicity and peripheral neuropathy. Gastrointestinal, hematologic, and hypersensitivity reactions have also been reported.[11,12] Because TB is often diagnosed in HIV-coinfected patients, interactions with antiretroviral drugs can potentiate toxicities even more (**Table 3**).

Peripheral neuropathy is a dose-related toxic effect of INH. INH competes with vitamin B6 (pyridoxine) in its action as a cofactor in the synthesis of synaptic neurotransmitters. Those at highest risk include the malnourished, those predisposed to neuritis (alcoholics, diabetics), HIV-seropositive patients, and pregnant/breastfeeding women. Supplementation with pyridoxine (vitamin B6) should be used to prevent neurotoxicity, with the usual dose of 10 mg (patients not included in the high-risk populations) to 50 mg/day (for patients with one or more high-risk features).[4]

INH-induced hepatotoxicity is associated with metabolites of INH and is not correlated with serum concentrations of the parent compound. The onset of INH -induced hepatotoxicity is observed within the first two months of therapy in approximately 50 percent of patients. Risk for clinical hepatitis reactions increase when INH is taken together with other anti-TB medications such as RIF (**Table 4**).[4]

Clinical Trials

Role of INH in LTBI Regimens

The American Thoracic Society, the Centers for Disease Control and Prevention, and the Infectious Diseases Society of America (ATS-CDC-IDSA) recommend INH as standard treatment for LTBI.[2-5,14] Randomized trials show that approximately 90% protection is provided by completion of 9-month course of INH and 60 to 80% protection is provided by completion of a 6-month course.[14] A major difficulty associated with the use of standard therapy with INH for LTBI is poor patient adherence because of the prolonged course required. Shorter courses of therapy have been proposed as an alternative, including rifampin (RIF) monotherapy as well as INH plus RIF combination therapy.

In one randomized trial in which patients received RIF alone for 3 months, 60% protection was conferred.[15] A four-month course of RIF (4RIF) is also recommended by ATS-CDC-IDSA as an alternative, but this shorter course of therapy has not been directly compared to nine months of INH (9INH). A randomized trial conducted by Aspler et al. found that four months of RIF alone would be cost saving and prevent more cases within 2 years if efficacy exceeded 74%, and cost saving could be maintained if efficacy exceeded 65% (**Table 5**).[16] RIF monotherapy appears to be less expensive per patient with better completion (74% 4RIF vs. 60% 9INH) and fewer adverse events (grade 3-4 adverse events: 1.7% (4RIF) vs. 4% (9INH), p=0.003). The health system costs included scheduled and unscheduled visits, investigations and drugs.[16] A clinical trial comparing adverse events from a 4-month course of RIF to a 9-month course of INH is currently ongoing (NCT00170209).[17]

Three months of INH plus RIF combination therapy (with the same dosing as recommended for standard monotherapy of either drug) may be an alternative treatment option in select patients, but risk of hepatotoxicity may increase.[4] In a meta-analysis of five trials by Ena and Valls, three months of INH+RIF was found

Table 3 | Potentially overlapping toxicities of antiretroviral drugs and isoniazid [13]

Antiretroviral Drugs	Potential Toxicities
Stavudine, Didanosine	Peripheral neuropathy
Efavirenz	Psychiatric symptoms
Nevirapine Ritonavir-boosted PIs Efavirenz Etravirine Maraviroc	Hepatitis
Zidovudine PIs Didanosine	Gastrointestinal intolerance

PIs=protease inhibitors

Table 4 | Clinical Hepatitis in persons taking isoniazid and rifampin[4]

Drug	Number of Studies	Patients	Clinical Hepatitis (%)
INH	6	38,257	0.6
INH + RIF	19	6,155	2.7
INH + Drug other than RIF	10	2,065	1.6
RIF + Drug other than INH	5	1,264	1.1

Table 5 | Summary of Clinical Trials with Isoniazid in Tuberculosis

Study	Design & Endpoint	Results	Conclusions
Aspler et al. [16] 2010	OL, RCT 420 adults w/ (+) TST Compared: 4RIF/9INH Primary EP: total health system costs**	Total health system cost PP: $854 (4RIF) vs. $970 (9INH) (p<0.0001) Avg cost PP: $1094 (4RIF) vs. $1625 (9INH) (p<0.0001) Management of AEs: $25,684 (RIF) vs. $48,142 (9INH) (p=0.008)	4RIF regimen would be cost saving and prevent more cases due to better completion and fewer AEs
Ena J and Valls V [18] 2005	Meta-analysis of 5 RCTs Compared: 3RIF+INH/9INH Primary EP: development of active TB, severe ADRs, and death	All primary endpoints equivalent with both regimens.	3RIF+IN was equivalent to 9INH in efficacy, proportion of ADRs, and mortality.
Madhi et al. [22] 2011	DB, R, PC Preexposure INH Tx in HIV and non-HIV children exposed to HIV during perintal period Compared: INH/PCB x 96 weeks Primary EP: TB-disease-free survival and TB-infection-free survival.	HIV-infected children with TB or death: 19% vs. 19.3% (p=0.93) Combined incidence of TB infection, TB disease, or death: 10% vs. 11% (p=0.44)	Primary INH prophylaxis did not improve TB-disease free survival or TB-infection-free survival.
Swaminathan et al. [23] 2010	OL, RCT 334 HIV pts w/ newly dx TB Compared: Intermittent Reg6M [ETH 1,200 mg; INH 600 mg; RIF 450 or 600 mg; and PZA 1,500 mg] for 2 mos; followed by 4 mo of INH+RIF (at same doses)] / Reg9M [same doses as Reg6M except followed by 7 mos of INH+RIF] Primary EP: percentage of pts responding to anti-TB tx	Reg6M – 83% vs. Reg9M – 76% (p not SIG) Bacteriological recurrence: Reg6M vs. Reg9M (15 vs. 7%; P < 0.05); overall recurrences not SIG (Reg6M, 19% vs. Reg9M, 13%)	In tx naïve HIV pts, Reg9M resulted in a similar outcome at the end of tx but a significantly lower bacteriological recurrence rate compared with Reg6M thrice-weekly regimen. ARR was high w/ these intermittent regimens and neither mortality nor ARR was altered by lengthening TB tx.
Johnson et al. [26] 2009	R, OL, PROS 370 pts w/ noncavitary TB* Compared: 2-mos INH+RIF/4-mos INH+RIF during continuation phase Primary EP: relapse rate of TB after neg sputum culture post-2 mos of anti-TB tx	4-mos (total tx) vs. 6-mos (total tx) resulted in 7% vs. 1.6% relapse rate (p=0.054)	Shortening treatment from 6 to 4 mos in adults with non-cavitary disease and culture conversion after 2 mos using current drugs resulted in greater relapse rate and is not considered optimized tx.
Katiyar et al. [29] 2008	DB, RCT 134 pts w/MDR-TB Compared: High-dose INH/normal-dose INH/PCB+second-line drugs Primary EP: sputum culture conversion and proportion of pts w/ sputum culture neg after 6 mos of tx.	High-dose INH pts became sputum neg 2.38 times more rapidly than the other 2 comparators combined. (p=0.001) High-dose INH pts had 2.37 times higher likelihood of sputum-neg at 6 mos (p<0.001)	In low-resource scenarios where a standardized therapeutic protocol is used for MDR-TB, high-dose INH may be used as an adjuvant agent.

9INH=isoniazid (9-month course); ADR=adverse drug reactions; AE=adverse events; ARR= acquired rifamycin resistance; Avg=average; DB=double-blind; Dx=diagnosed; EP=Endpoint; ETH=ethambutol; HIV=human immunodeficiency virus; MDR-TB=multidrug-resistant tuberculosis; Mo=month; Neg=negative; OL=Open-label; PBC=placebo; PP=per person; PROS=prospective; Pt=Patient; PZA=pyrazinamide; R=randomized; RCT=randomized controlled trial; Reg6M=6 month regimen; Reg9M=9 month regimen; RET=Retrospective; RIF=rifampin; SIG=significant; TB=tuberculosis; TST=tuberculin skin test; Tx=therapy;
*Enrollment stopped by safety monitoring committee due to increased risk for relapse in the 4 mo arm
**Costs include scheduled and unscheduled visits, investigations and drugs.

to be equally efficacious to nine months of INH, have equal proportions of adverse drug reactions, and comparable rates of mortality compared to nine months of INH.[18] Acceptable treatment options for LTBI are listed in **Table 6**.[3,4,14]

Another short course option for LTBI consists of a 3-month course of INH plus rifapentine administered once weekly. This regimen caused relatively lower rates of grade 3 or 4 hepatotoxicity when compared to RIF plus PZA (1% vs. 10%, respectively, P<0.001) in treatment of LTBI.[19] It is important to note, however, that the INH/rifapentine combination was administered weekly while the RIF/PZA combination was administered daily. Although the RIF plus PZA regimen is only for two months, it is no longer recommended for treatment of LTBI due to significant hepatotoxicity in the setting of preventive therapy.[18,20] A direct comparison of this regimen to a 9-month course of INH is still ongoing (NCT00023452).[21]

INH prevents progression of TB disease in children with known contact to persons with infectious TB, but its role in preexposure prophylaxis has not been evaluated. In a double-blind, randomized, placebo-controlled study, Madhi et.al evaluated the safety and efficacy of INH versus placebo for preexposure prophylaxis against TB in HIV-infected children and uninfected children exposed to HIV during the perinatal period.[22] Among 548 HIV-infected children (91-120 days of age), half of the infants were assigned to receive INH, the other half to receive placebo. Within the same study, half of the non-HIV-infected infants were also assigned to receive INH, the other half to receive placebo. All treatments were started at 3-4 months of age and continued for 96 weeks. This study found that primary INH prophylaxis did not improve TB-disease-free survival among HIV-infected children (19.0% (INH group) vs. 19.3% (placebo group), p=0.93), nor did it improve TB-infection-free survival among HIV-uninfected children immunized with BCG vaccines (10% (INH group) vs. 11% (placebo group), P=0.44).[22]

Duration of INH therapy in Active TB

Treatment of active TB with combination drug therapy remains the cornerstone of mycobacterial killing. Multiple agents help achieve bacterial clearance, reduce the risk of transmission, and prevent the emergence of drug resistance. First-line drugs used to treat active TB include INH, a rifamycin derivative [RIF (Rifadin®, Rimactane®), rifabutin (Mucobutin®), or rifapentine (Priftin®)], ETH, and PZA. Second-line drugs in treatment of active TB are aminoglycosides (streptomycin, kanamycin, and amikacin); capreomycin; p-aminosalicylic acid; cycloserine; thioamides (ethionamide and prothionamide); and fluoroquinolones (moxifloxacin, levofloxacin, gatifloxacin).[5] The ATS-CDC-IDSA have issued a joint statement on the treatment of active TB in the United States to include two stages of therapy, beginning with two months of an initial or "intensive phase," followed by four or seven months of a "continuation phase" (**Figure 1**).[4] Extending the continuation phase of treatment reduces the rate of relapse. Most medications are administered five to seven times per week via directly observed therapy (DOT), which involves direct observation of patients ingesting anti-TB medications. DOT is the preferred management strategy for all patients being treated for TB.[5]

The International Union Against Tuberculosis (IUAT) trial concluded that 6 months was the optimal duration (compared to 3- and 12-months) of INH therapy as it prevented the greatest number of TB infections per episode of hepatitis caused.[14] A 2010 randomized clinical trial by Swaminathan et.al evaluated the efficacy of a 6- or 9-month intermittent treatment regimen (Reg6M vs Reg9M) in antiretroviral therapy-naïve HIV-infected patients with TB.[23] All subjects had two months of the intensive phase (INH + RIF + ETH + PZA), followed by either a four or seven month course of INH + RIF, totaling either a six or nine month treatment regimen, respectively.[23,24] Bacteriological recurrence was detected more often in Reg6M than Reg9M (15 vs. 7%, respectively, P<0.05), with overall occurrence not statistically significant. These data further underline the message to recommend a 9-month course of INH therapy against active TB.[23]

Role of INH in HIV-coinfected patients

Human immunodeficiency virus (HIV) infection is the strongest risk factor for progression from TB infection to active TB disease; the risk for progression is more than 10-fold for persons with combined TB and HIV infection versus those without HIV, irrespective of CD4 cell count.[25] Tuberculosis is an acquired immunodeficiency syndrome (AIDS)-defining illness in patients with HIV, in which the diagnosis of one necessitates the screening for the other.[3] Treatment for TB in patients with or without HIV consists of the same multidrug therapies. However, INH and rifapentine together should not be used intermittently (once- or twice-weekly dosing) in HIV positive patients during the continuation phase due to higher rate of treatment failure and relapse.[4] In a recent prospective study by Johnson et.al, duration of anti-TB treatment was studied in HIV-non-infected individuals with drug-susceptible non-cavitary pulmonary TB.[26] All subjects had two months of the intensive phase treatment with the same four standard drugs for therapy (INH + RIF + ETH + PZA). After 2 months, those with negative spu-

Table 6 | Treatment Options for LTBI [3,4,14]

Drug	Daily dosage (maximum)	Adult intermittent dosage (maximum)	Pediatric Doses	Duration
INH	5mg/kg (300mg)	15mg/kg (900mg/dose) 2x/wk	10-20 mg/kg BW daily or 20-40 mg/kg twice weekly	6 or 9 mos
RIF (Rifadin®)	10mg/kg (600mg)	10mg/kg (600mg/dose)	10-20 mg/kg	Daily dosing req'd when used alone; 4 mos in adults; 6 mos in children
INH + RIF*	300mg INH + 600mg of RIF daily	---	10-20 mg/kg INH + 10-20 mg of RIF/kg daily	3 mos

BW = body weight; INH = isoniazid; kg = kilograms; mg = milligrams; mos = months; req'd = required; RIF = rifampin
*INH+RIF combination therapy with intermittent dosing schedule is not recommended.

tum cultures continued either a regimen of INH + RIF for 2 more months or 4 more months (totaling 4 versus 6 months of therapy). Authors found that shortening treatment from 6 to 4 months in these individuals resulted in a greater relapse rate (1.6% vs. 7.0%, respectively, p=0.05), and concluded that better biomarkers, optimized dosing with current drugs, and novel drugs with new mechanisms of action are likely needed to shorten current anti-TB treatment.[26]

Multidrug-resistant (MDR-) and extensively drug-resistant (XDR-) TB

The most recent WHO summary report of the global burden of MDR-TB released in 2010 estimated 3.6% of incident TB cases are resistant.[1] MDR-TB is characterized by resistance to at least INH and RIF, while XDR-TB is resistant to at least INH and RIF (among the first-line drugs), to any one fluoroquinolone (ciprofloxacin or ofloxacin), and to at least one second-line injectable drug (amikacin, capreomycin, or kanamycin). [1,27] MDR- and XDR-TB requires at least 18 to 24 months of therapy, depending on patient's response to treatment.

INH resistant (INH-R) TB is a significant issue because loss of effectiveness of this drug compromises both the preventive therapy and treatment of disease.[28] INH-R occurs through several different mechanisms. Alterations or overexpression of *katG* confer INH resistance through loss of catalase peroxidasae activity, an INH-activating enzyme. Loss of NADH de-

Initial phase			Continuation phase			Range of total doses (minimal duration)	Rating* (evidence)†	
Regimen	Drugs	Interval and doses‡ (minimal duration)	Regimen	Drugs	Interval and doses‡§ (minimal duration)		HIV−	HIV+
1	INH RIF PZA EMB	Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)¶	1a	INH/RIF	Seven days per week for 126 doses (18 wk) or 5 d/wk for 90 doses (18 wk)¶	182–130 (26 wk)	A (I)	A (II)
			1b	INH/RIF	Twice weekly for 36 doses (18 wk)	92–76 (26 wk)	A (I)	A (II)#
			1c**	INH/RPT	Once weekly for 18 doses (18 wk)	74–58 (26 wk)	B (I)	E (I)
2	INH RIF PZA EMB	Seven days per week for 14 doses (2 wk), then twice weekly for 12 doses (6 wk) or 5 d/wk for 10 doses (2 wk),¶ then twice weekly for 12 doses (6 wk)	2a	INH/RIF	Twice weekly for 36 doses (18 wk)	62–58 (26 wk)	A (II)	B (II)#
			2b**	INH/RPT	Once weekly for 18 doses (18 wk)	44–40 (26 wk)	B (I)	E (I)
3	INH RIF PZA EMB	Three times weekly for 24 doses (8 wk)	3a	INH/RIF	Three times weekly for 54 doses (18 wk)	78 (26 wk)	B (I)	B (II)
4	INH RIF EMB	Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)¶	4a	INH/RIF	Seven days per week for 217 doses (31 wk) or 5 d/wk for 155 doses (31 wk)¶	273–195 (39 wk)	C (I)	C (II)
			4b	INH/RIF	Twice weekly for 62 doses (31 wk)	118–102 (39 wk)	C (I)	C (II)

Definition of abbreviations: EMB = Ethambutol; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; RPT = rifapentine.
* Definitions of evidence ratings: A = preferred; B = acceptable alternative; C = offer when A and B cannot be given; E = should never be given.
† Definition of evidence ratings: I = randomized clinical trial; II = data from clinical trials that were not randomized or were conducted in other populations; III = expert opinion.
‡ When DOT is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.
§ Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31 week; either 217 doses [daily] or 62 doses [twice weekly]) continuation phase.
¶ Five-day-a-week administration is always given by DOT. Rating for 5 day/week regimens is AIII.
# Not recommended for HIV-infected patients with CD4+ cell counts <100 cells/μl.
** Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on initial chest radiograph (see text). For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

Reproduced from: American Thoracic Society, Centers for Disease Control and Prevention, Infectious Diseases Society of America. Treatment of Tuberculosis. ATS -CDC-IDSA 2003. Available at http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf

Figure 1 | Treatment Options for Culture-Positive Pulmonary TB caused by drug-susceptible organisms [4]

hydrogenase II (*ndh*) activity or mutations in the *inhA* S94A allele confer coresistance to INH and ETH in *M. tuberculosis* by inhibiting InhA enzyme enoyl-ACP reductase, an enzyme within the FASII system crucial in synthesizing mycolic acids.[6] Optimized treatment includes rapid initiation of MDR-TB treatment in a stepwise approach, as recommended by the WHO guidelines, to include at least four drugs based on a stepwise process of selecting drugs from five different groups based on relative efficacy.[13,25]

Katiyar et.al conducted a double-blind randomized control trial to evaluate effectiveness of high-dose INH compared to normal dose INH or placebo (plus second -line drugs) in MDR-TB patients.[29] High-dose INH patients became sputum negative 2.38 times more rapidly than the other two comparators combined and had 2.37 times higher likelihood of being sputum-negative at 6 months of treatment.[29] These findings encouraged Van Deun et.al to include high-dose INH as an adjunctive agent in their observational study to evaluate effectiveness of six standardized regimens in patients with proven MDR-TB not previously treated with second-line drugs.[30] These authors learned that a 9-drug combination, which includes high-dose INH during the intensive phase of treatment (for four out of nine months), appeared to be the most effective regimen for MDR- or XDR-TB (relapse-free cure in 87.9% of 206 patients; major AE manageable).[30] This regimen includes use of many second-line drugs, including fluoroquinolones. The fluoroquinolones are the only new class of anti-TB drugs introduced after RIF, and so rational use of this class of drugs is critical.[24]

Summary

INH is the highly effective in prevention as well as treatment of INH-susceptible TB. INH is used in every drug-susceptible regimen used to treat active TB in the intensive and the continuation phase. If MDR-TB is suspected, a high-dose INH course may be used as an adjunct to other therapies. Shorter courses of therapy are often being studied compared to the standard nine months course of INH in an attempt to increase patient adherence, decrease healthcare costs as well as drug toxicities due to the long duration of therapy. Peripheral neuropathy and drug-induced hepatotoxicity are the two most common adverse reactions from the use of INH, and known drug interactions should be adjusted accordingly.

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Clinical Trial Update

Dual antiplatelet therapy duration and clinical outcomes following treatment with zotarolimus-eluteing stents [1] | In an analysis of the Endeavor trials, which evaluated a zotarolimus-eluting stent, discontinuation of dual antiplatelet therapy (DAPT) with aspirin and clopidogrel at six months was not associated with worse ischemic outcomes compared to longer durations of therapy. Patients enrolled in the Endeavor series underwent percutaneous coronary intervention (PCI) and received a minimum of three months of DAPT; extended duration DAPT was at the discretion of the physician. Patients were followed for up to three years after PCI and stent placement for ischemic events including myocardial infarction (MI), stroke, cardiac death, all-cause death, and stent thrombosis (ST). Patients who had an ischemic or bleeding event prior to 6 months were excluded from the analysis. Remaining patients were then stratified based on duration of DAPT therapy: on at 6 months (but not 12 months), on at 12 months, on at 24 months, and on at 12 months but not at 24 months. Results showed that treatment for 6 months did not increase the risk death, MI, or ST thrombosis when compared to greater than 12 months and greater than 24 months (Table 1); risk for bleeding was not different between groups. Randomization was not maintained for the analysis and therefore these results can only be considered as hypothesis generating and must be interpreted cautiously. Also, as the patients in the analysis only received a zotarolimus-eluting stent it is uncertain whether these results can be applied to patients who receive bare metal or other drug-eluting stents. The analysis adds to other observational evidence suggesting DAPT may not indicated in all patients for a full 12 months. Results of randomized placebo controlled trials will be needed to clearly define the optimal duration of therapy.

Table 1 | Duration of DAPT therapy and ischemic outcomes.

Outcome	Duration of DAPT Therapy	
	6 mo vs. ≥ 12 mo	6 mo vs. ≥ 24 mo
MI	0.3% vs. 1.1%	0.4% vs. 1.2%
Death	2.7% vs. 2.2%	1.6% (for both)
ST	0.3% vs. 0.0%	0.1% vs. 0.2%

DAPT = dual antiplatelet therapy; MI = myocardial infarction; ST = stent thrombosis

1. Kandzari DE, Barker CS, Leon MB, et al. Dual antiplatelet therapy duration and clinical outcomes following treatment with zotarolimus-eluting stents. JACC Cardiovasc Interv 2011; 4:1119-1128.

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