Chapter 10

Latent Tuberculosis Infection: Patho-Biology and Treatment

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Additional information is available at the end of the chapter

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Abstract

Tuberculosis continues to be an epidemic disease worldwide especially in the developing countries. One of the main reasons behind the continuation of this epidemic is latent tuberculosis infection. Globally, 2–3 billion people have latent TB infection. Prevention of reactivation TB is now considered as one of the important strategies of TB prevention and is one of the main pillars for the WHO "End TB Strategy." Biostatistical modeling has shown that protecting 8% of persons with latent tuberculosis every year can bring down the global incidence rate by 14 times by 2050 as compared to that in 2013 without any other intervention. One of the most effective strategies recommended by WHO has been Isoniazid preventive therapy for 6–9 months. Chemoprophylaxis for LTBI can prevent 60–90% of reactivation TB. Isoniazid preventive therapy is considered safe; however, it can occasionally result in significant adverse effects like hepatitis and rarely mortality. In conclusion, chemoprophylaxis of LTBI can be considered an important intervention being done to curb the epidemic of TB especially in high-risk group and reduce the morbidity and mortality associated with active TB disease.

Keywords: latent tuberculosis infection, World Health Organization, chemoprophylaxis, isoniazid therapy

1. Introduction

The medical, economic and social impact of the dual epidemics of human immunodeficiency virus (HIV) and tuberculosis (TB) will continue to remain one of the biggest public health challenges of the twenty-first century. According to the World Health Organization (WHO) Global Status Report, 11% of 10.4 million new cases of TB in 2015 were HIV-positive [1]. This is

an increase in the number of new TB cases from 9.2 million in 2014 [1]. Sixty percent of the new TB cases are reported from India, Indonesia, China, Nigeria, Pakistan and South Africa [1]. It has been difficult to rein in the TB epidemic, and there are many reasons for it. One of the main reasons for spread of TB in low TB/HIV burden countries is the reactivation of latent tuberculosis. In high TB/HIV burden countries, the main factors are lack of accessible health facilities where timely and effective treatment of TB can be given and the burgeoning numbers of drug-resistant TB cases. Another significant factor in the failure of TB control programmes in the developing countries has been the ongoing HIV epidemic. HIV-infected patients are at increased risk of new TB infection as well as reactivation of latent TB infection (LTBI). Prevention of reactivation TB in those with LTBI is now considered as one of the key strategies of TB prevention and is one of the pillars for the WHO "End TB Strategy" [1]. The WHO aims to implement LTBI detection and treatment in the 30 high-TB burden countries first. In these countries, it has set out an ambitious target of bringing 90% of children under 5 years who are TB contacts and PLHA under the chemoprophylaxis programme by 2025 [1]. Biostatistical modeling shows that if 8% of persons with latent tuberculosis could be permanently protected each year, the global incidence in 2050 would be 14 times lower than incidence in 2013, with no other intervention needed [2].

2. LTBI

Latent tuberculosis infection (LTBI) is a state of persistent immune response to *Mycobacterium tuberculosis* (Mtb) antigens without evidence of clinically manifested active TB [3]. In simpler terms, LTBI is infection with viable bacilli of Mtb complex but without symptoms of the disease. LTBI has great public health significance because a significant proportion of these people can develop active TB and contribute to spread and persistence of TB in the population. About 2–3 billion people, that is, one-third of the world's population, has TB infection but no TB disease. Among the people with LTBI, the lifetime risk of developing TB disease is 5–15% [4–6]. In HIV-infected, the annual risk of developing reactivation TB is 5–15% [7]. The risk is similar in people on anti-TNF-α therapy, patients on dialysis and those undergoing solid organ or hematological transplant [3]. Another similar high-risk group is that of children under 5 years of age who are household contacts of pulmonary TB cases [3].

Operational constraints and unfounded fears of increased incidence of drug-resistant TB have been the two main reasons for the poor implementation of LTBI programme in high-TB burden countries. Only 87,236 children under 5 years age who were household contacts of TB cases were initiated on TB chemoprophylaxis in 2015 [1]. The best chemoprophylaxis coverage was from the Americas (67%, range 63–71%) and European Region (42%, range 40–44%). In high TB or HIV/TB burden countries, the figures ranged from 2.6% in Cameroon to 41% in Malawi. These numbers belie the actual magnitude of the problem. The total number of children on TB chemoprophylaxis (87236) is only 7.1% (range 6.9–7.4%) of the 1.2 million children who are eligible for treatment. PLHA have a higher coverage with TB chemoprophylaxis, especially in the African region. In 2015, TB chemoprophylaxis was being offered to PLHA enrolling for HIV care in 57 countries. These countries represent 61% of the global TB burden. These data

are encouraging because in 2014 there were only 49 countries where TB preventive treatment was available. South Africa, Malawi, Mozambique and Kenya have the largest number of PLHA on TB chemoprophylaxis. Much more needs to be done. Of the 30 high TB/HIV burden countries, no preventive treatment was available in 21 countries. Even in nine that did report so, coverage of people newly enrolled in HIV care varied from 2% in Indonesia to 79% in Malawi. The National AIDS Control Organization (NACO) in India issued new TB management guidelines in 2016 [8]. TB care has now been integrated into the services provided by the ART centres and isoniazid preventive therapy (IPT) has also been included in it [8].

3. Pathobiology of LTBI

Ninety percent of people infected with Mtb are able to successfully contain the microbe and ward of clinical disease. It should be realized that Mtb infection cannot be eradicated but only contained even in healthy immune-competent people and a key pathological mechanism in this is formation of tubercular granuloma.

Mtb infection occurs via the respiratory tract and on entry, mycobacteria encounter alveolar macrophages in the airways and immediately infect them. Macrophages can provide an intracellular sanctuary for mycobacteria, and Mtb has evolved numerous mechanisms to survive within macrophages. A characteristic set of pro-inflammatory cytokines and chemotactic factors for macrophages are released and cause granuloma formation. The granuloma is composed of various cells including macrophages, lymphocytes, dendritic cells, neutrophils, and sometimes fibroblasts, often with a necrotic centre. This structure serves to contain the bacilli and acts as an immune microenvironment that limits *M tuberculosis* replication. However, formation of a granuloma is not enough to control infection, as it has been seen that persons with active TB can have multiple granulomas in the lungs and possibly other tissues. Instead, granulomata must have optimal immunologic function to contain or eliminate the bacilli [9]. When they fail to do so, they release anti-inflammatory cytokines which aim to prevent tissue destruction but at the same time trigger fibrosis.

Structural or functional disruption of the granuloma is likely to lead to reactivation of latent *M. tuberculosis* infection, dissemination, and active disease [9]. Research in HIV-TB has given insight into some of the mechanisms involved in reactivation of TB [10]. The cause of disruption can be understood as general and overlapping processes, including increase in the HIV viral load within involved tissue, a reduced number of CD4 T cells, a defective macrophage function, and perturbation of Mtb-specific T-cell function [9]. They can all lead to detrimental changes within granulomas.

Depletion of CD4 cell population leads to an inability to mount an effective cell-mediated immune response against Mtb. Studies on macaques infected with simian immunodeficiency virus (SIV) have shown that reactivation of LTBI is directly associated with depletion of CD4+ T cells [10–12]. Critical decline in the number of CD4+ T cells is associated with a decrease in the number of memory CD4+ T cells (CD27+ CDRO45+) that can recognize Mtb antigens, decrease in polyfunctional antigen-specific CD4+ T cells and a relative increase in interferon

gamma + CD 8+ T cells [10–12]. Other mechanisms include suppression of cell-mediated responses of regulatory T cells (Tregs) and impairment of TNF-α- mediated apoptosis of Mtb-infected cells [13].

4. Diagnosis of LTBI

Prior to putting people on chemoprophylaxis for LTBI, active TB has to be first excluded by standard case finding methods. Latent tuberculosis infection (LTBI) is most often diagnosed by the tuberculin skin test (TST), and the Mantoux TST is the standard method of determining *Mycobacterium tuberculosis* infection. This test is performed by injecting 0.1 ml of tuberculin purified protein derivative (PPD) (equivalent to 1 TU of PPD RT 23 or 2.5 TU of PPD- S) into the inner surface of the forearm. In India, PPD-RT 23 with Tween 80 of strength 1 TU and 2 TU are standardized tuberculins available which is supplied by the Bacillus Calmette-Guérin (BCG) vaccine Laboratory, Guindy, Chennai. CDC recommended strength is 5 TU of PPD-S. The injection is given intradermally with a tuberculin syringe, with the needle bevel facing upward. The injection should produce a pale wheal 6–10 mm in diameter and the skin test reaction should be read between 48 and 72 hours after administration. The reaction should be measured in millimeters of the induration (palpable, raised, hardened area or swelling) across the forearm (perpendicular to the long axis) and not the erythema (redness).

Classification of positive TST results

Induration size/Patient profile	**≥5 mm**	**≥10 mm**	**≥15 mm**
	HIV-infected persons • A recent contact of a person with TB disease • Persons with fibrotic changes on chest radiograph consistent with prior TB • Patients with organ transplants • Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF- alpha antagonists)	• Recent immigrants (<5 years) from high-prevalence countries • Injection drug users • Residents and employees of high-risk congregate settings • Mycobacteriology laboratory personnel • Persons with clinical conditions that place them at high risk • Children <4 years of age • Infants, children, and adolescents exposed to adults in high-risk categories	Any person, including persons with no known risk factors for TB

In interpreting a positive TST, it is important to consider much more than only the size of the induration. Rather, the TST should be considered according to three dimensions: size of induration, pre-test probability of infection and risk of disease if the person were truly infected [14].

There are two important causes of false-positive results: nontuberculous mycobacterial (NTM) infection and prior BCG vaccination [15]. NTMs are not a clinically important cause of false-positive TST results, except in populations with a high prevalence of NTM sensitization and a very low prevalence of TB infection [15]. The impact of BCG on TST specificity depends on when BCG is given and on how many doses are administered. If BCG is administered at birth or infancy and not repeated, then its impact on TST specificity is minimal and can be ignored while interpreting the results [15]. In contrast, if BCG is given after infancy (e.g., school entry) and/or given multiple times (i.e., booster shots), then TST specificity is compromised [15].

Tuberculin skin tests are subject to variability when repeated tuberculin tests are given. Chance variation should result in differences of less than 6 mm (representing two standard deviations) in 95% of subjects. This supports the adoption of 6 mm as a criterion to distinguish increases in reaction size due to random variation alone from true biologic phenomena, which could be either conversion or boosting [16]. Boosting is best distinguished from conversion on clinical grounds. One can attribute an increase in reaction size to boosting when the increase in reaction is seen after an interval of 1–5 weeks during which there has been no possibility of exposure, such as pre-employment testing of a health care worker [16]. Conversion can be confidently stated to have occurred when a previously tuberculin-negative individual becomes tuberculin test positive after receiving BCG vaccination, or following significant exposure such as during an outbreak or as a result of close contact with a highly contagious index case [17, 18]. Among subjects vaccinated in infancy, and tested after an interval of 5 years or more, prevalence of initial tuberculin reactions is the same in vaccinated and unvaccinated reference populations but prevalence of boosting was 7% higher in vaccinated than unvaccinated [19].

The other method of detecting LTBI is based on IFNγ release assays (IGRA). These tests detect a set of Mtb genes that are present in Mtb complex but not present in BCG immunized or in a setting of NTM infection. In this test, the sera of patients is incubated with Mtb specific T lymphocytes. The T cells respond to Mtb-specific gene products by secretion of pro-inflammatory cytokines that are detected. Two IGRAs are commercially available today. QuantiFERON-Gold In Tube test (QFT; Germany) uses whole blood and is ELISA based. The T-SPOT.TB test (Oxford Immunotec, Abingdon, UK) uses peripheral blood mononucleated cell (PBMC) and ELISPOT technique. Both IGRAs incorporate the region of difference 1 (RD1)-encoded 6 kDa early secretory antigenic target (ESAT-6) and 10 kDa culture filtrate protein (CFP10) antigens, whereas an additional single peptide from TB7.7, encoded in RD11, is added to the QFT [20]. The selections of antigens for these tests are critical. Natural immunity to *M. tuberculosis* is highly individual, multi-epitopic and multiantigenic, and more than 80 antigens are necessary to capture 80% of the MTB-specific T-cell response [21]. The currently used antigens ESAT-6, CFP10 and TB7.7 were selected for their high immunogenicity and specificity for *M. tuberculosis* infection, not for their predictive potential. ESAT-6 is considered among the most immunogenic proteins, but it has a drawback when used to detect LTBI. It is secreted through the entire spectrum of latency and also in active stages of the infection. Therefore, disease stage-specific diagnosis is impossible using ESAT-6 [22].

Various studies have evaluated the utility of IGRAs and TST. A study from Turkey published in 2007 seems relevant to countries like India as Turkey is also a country with high prevalence of TB

and high BCG vaccination coverage [23]. The workers compared TST with QuantiFERON®-TB in three population groups: household contacts of smear-positive TB cases, community members who had been exposed to index smear-positive TB cases and healthcare workers dealing with TB cases or handling TB specimens. They did a Kappa analysis to look for agreement between the tests. They found that QuantiFERON®-TB values were higher in the first group of patients when compared to the other two groups. In case of TST, there was no difference among the three groups. Evaluation for agreement rates between the groups showed poor agreement in all three groups. The authors concluded that while Quantiferon Gold was more objective, practical and gave quantitative values, it was more expensive and required a well-equipped laboratory and thus did not have a programmatic role in detection of LTBI in a country will high TB prevalence and high BCG coverage [23].

In a Japanese study, the specificity of IGRA was studied in healthy low-risk individuals with history of BCG vaccination [24]. It was seen that TST was positive (≥ 10 mm) in 64.6% (specificity 35.4%) while QuantiFERON®-TB test was positive in 1.9% (specificity 98.1%,) [24]. Similar results were obtained in another study done in Korea [25].In this study, 273 participants were included, 220 (95.7%) had received BCG vaccine. Participants were grouped according to their risk of infection: group 1, no identifiable risk of *M. tuberculosis* infection (n = 99); group 2, recent casual contacts (n = 72); group 3, recent close contacts (n = 48); group 4, bacteriologically or pathologically confirmed TB patients (n = 54). They studied the levels of agreement between the TST and the IFN-gamma assay and the likelihood of infection in the various groups and found out that the overall agreement between the TST and the IFN-gamma assay in healthy volunteers was a kappa value of 0.16. The odds of a positive test result per unit increase in exposure across the four groups increased by a factor of 5.31 (95% confidence interval [CI], 3.62–7.79) for the IFN-gamma assay and by a factor of 1.52 (95% CI, 1.20–1.91) for the TST (P < .001). In another study of 590 HIV-infected patients, QuantiFERON® -TB Gold test correlated with known risk factors for LTBI or past history of TB [26].

Both TST and IGRAs are acceptable but imperfect LTBI tests, with advantages and disadvantages [27]. In some situations, neither test is appropriate (e.g., active TB diagnosis in adults) and in some situations, both the tests may be necessary to detect *M. tuberculosis* infection (e.g., immunocompromised populations), and there are situations where one test may be preferable to another. For example, IGRAs may be preferable to the TST in populations where BCG is given after infancy or given multiple times. In contrast, TST may be preferable to the IGRAs for serial testing of health care workers. Both TST and IGRAs have reproducibility challenges, and dichotomous cut-offs are inadequate for interpretation [27]. The ability of tuberculin skin tests and IGRAs to identify persons at highest risk of progressing to active tuberculosis is poor. Neither test reliably predicts future disease among persons with positive tests nor do strongly positive tests mean a higher risk. In one meta-analysis, the pooled positive predictive value for progression to active tuberculosis was 2.7% (95% confidence interval [CI], 2.3–3.2) for IGRAs and 1.5% (95% CI, 1.2–1.7) for the tuberculin skin test [28]. A meta-analysis of only longitudinal studies of IGRAs, with a median follow-up of 4 years, showed a moderate association between positive tests and subsequent tuberculosis (unadjusted incidence ratio, 2.10 [95% CI, 1.42–3.08]) [29]. The other limitations of these tests are inability to distinguish reactivation from reinfection, reduced accuracy in immunocompromised patients, and inability to discriminate the various stages within the spectrum of LTBI [30]. To maximize the positive predictive value

of existing LTBI tests, LTBI screening should be reserved only for those who are at sufficiently high risk of progressing to disease. The recommendations for systematic testing for LTBI as per WHO 2015 guidelines are as follows [31]:

Population groups	Test	Quality of recommendation
PLHA, child contacts of TB cases, patients being initiated on anti-TNF treatment, patients receiving dialysis, patients preparing for organ/haemotologic transplant and patients of silicosis	IGRA/TST	Strong recommendation, low/very low quality evidence
Prisoners, health-care workers, immigrants from high TB-burden countries, homeless persons and illicit drug users	IGRA/TST	Conditional recommendation, low/very low quality evidence

In the long term, highly predictive biomarkers need to be identified. This is an active area of research, and future generations of LTBI tests should overcome the limitations of current assays. A great endeavor is on to discover reliable, low-cost biomarkers. Gene signatures can distinguish between active and latent TB [32]. A lot of works have been done to identify differential expression of cytokines and chemokines in active TB and LTBI. It has been shown that plasma levels of the CXC chemokine IP-10 and soluble TNF receptor type 2 (sTNFr2) can significantly differentiate active TB from the LTBI group, irrespective of HIV status [33]. Another study showed that serum IL-2, IL-9, IL-13, IL-17, TNF-α, sCD40L and VEGF-A levels may be adjunctive biomarkers for differential diagnosis of active TB, LTBI, and NTM disease [34]. Assessment of serum sCD40L and Mtb antigen-specific IFN-γ, TNF-α, and IL-2 levels could also help predict successful anti-TB treatment in conjunction with Mtb clearance [31]. Achkar et al. looked at biomarkers to distinguish active TB and LTBI from no TB infection in HIV positive and negative populations [35]. They did so because inflammatory response and repair are both blunted in PLHA. They identified a set of biomarkers which reliably predict active TB. The biomarkers identified are shown in **Table 1** [32]:

Functional category	HIV-Positive TB	HIV-Negative TB
Immune response	CD14, SEPP1, SELL	CD14, SEPP1, PGL YR P2
Tissue development & repair	TNXB, LUM, PEPD, QSOX1, COMP	PFN1, VASN
Lipid metabolism	APOC1	
Other	GP1BA	CPN2, TAGLN2, IGFBP6

SEPP, selenoprotein P; SELL, selectin L; TNXB, tenascin XB; LUM, lumican; PEPD-peptidase D; QSOX1, quiescin sulfhydryl oxidase 1; COMP, cartilage oligomeric matrix protein; APOC1, apolipoprotein C-I; GP1 BA-glycoprotein 1 BA; VASN, vasorin; PFN 1, profilin1; CPN 2, chaperon 2; TAGLN2, transgelin 2; IGFBP 6, insulin-like growth factor binding protein 6; PGLYRP2, peptidoglycan recognition protein 2.

Table 1. Newer biomarkers for diagnosis of active TB.

5. Treatment of LTBI

Treatment of LTBI reduces the risk for active disease and hence various authorities have recommended treatment for this entity. Chemoprophylaxis for LTBI can prevent 60–90% of

reactivation TB [36]. But chemoprophylaxis cannot be considered as a universal approach due to the inherent toxicity of all TB drugs. However, in vulnerable populations, the benefits far outweigh the risks [33].

The International Union against Tuberculosis (IUAT) trial, conducted in Eastern Europe, randomized approximately 28,000 individuals with positive tuberculin skin tests (TST) and fibronodular changes on chest X-ray [37]. Approximately 7000 participants each were randomized to placebo, 3, 6 or 12 months of INH. Compared to participants who took placebo, participants who completed 3 months INH had 31% reduction in TB; those who completed 6 months INH (6INH) 69% reduction and the subjects who completed 12 months INH (12INH) had 93% reduction in TB. The efficacy of 6INH and 12INH waned during 5 years of follow-up but remained significantly better than the placebo. It is to be noted that fewer people completed 12 INH regimens as compared to 6INH [34].

Concerns regarding the relatively low efficacy of 6INH, and equally serious concerns regarding the poor completion of 12INH resulted in recommendations for 9 months INH by the American Thoracic Society in 2000 [38]. The optimal duration of INH was recommended as 9 months, with estimated efficacy of 90% and no significant gain with extension to 12 months [35].

In another trial, in Hong Kong, people who had pulmonary silicosis with a positive TST were randomized to placebo, 6INH, 3 m INH + Rifampin, or 3 m Rifampin alone [39]. During 5 years of follow-up, 27% of those randomized to placebo arm developed active TB, compared to 16, 13, and 10% for the three regimens respectively [36]. The estimated effectiveness of 3-months rifampin was approximately 65%; this was better than the other regimens although the differences between active regimens were not significant, and all were significantly better than placebo [36].

A series of randomized trials have demonstrated that the efficacy of 3-4INH + RIF to be equivalent to that of 6INH (four studies) or 9INH (one study) although adverse events are significantly more frequent [40, 41].

For adults, the recommended duration of treatment is at least 6, and preferably 9, months. Children younger than 18 years and persons with HIV infection should be treated for 9 months [42]. In HIV TB setting, IPT has been shown to slow the progression to active disease. A Cochrane systematic review of 12 trials, published in 2010 among 8578 patients showed that IPT reduced the risk of active TB by 64% among TST positive HIV-infected participants [43]. WHO has recommended that in resource-limited countries and other middle-income countries, people living with HIV and children below 5 years of age who are household or close contacts of people with TB and who, after an appropriate clinical evaluation, are found not to have active TB but have LTBI should be treated. WHO has recommended the following regimens for the treatment of LTBI which are similar to current CDC guidelines [26, 44–46].

The 9-month regimen with isoniazid is preferred because it is more efficacious. However, treatment of LTBI for 6 months rather than 9 months may be more cost-effective and result in greater adherence by patients.

Regimen	Dose isoniazid	Dose rifapentine or rifampicin	Maximum dose
6 m or 9 m isoniazid daily	Adults = 5 mg/kg Children = 10 mg/kg		isoniazid - 300 mg
3 m rifapentine + isoniazid weekly	Adults & children isoniazid - 15 mg/kg	Rifapentine (wt band): 10.0–14.0 kg = 300 mg; 14.1–25.0 kg = 450 mg; 25.1–32.0 kg = 600 mg; 32.1–49.9 kg = 750 mg; ≥50.0 kg = 900 mg	isoniazid - 900 mg Rifapentine - 900 mg
3 or 4 m isoniazid + rifampicin daily	Isoniazid: Adults - 5 mg/kg Children - 10 mg/kg	Rifampicin: Adults & children - 10 mg/kg	isoniazid-300 mg Rifampicin - 600 mg
3 or 4 m rifampicin alone daily	Adults & children 10 mg/kg		Rifampicin - 600 mg

Directly observed once-weekly regimen of isoniazid and rifapentine is recommended as an option equal to the standard INH 9-month daily regimen for treating LTBI. The regimen may be used in otherwise healthy HIV-infected persons, 12 years of age and older, who are not on antiretroviral medications. It may also be considered for children aged 2–11 years if completion of 9 months of INH is unlikely and hazard of TB disease is great.

The regimen using 4 months of rifampicin can be considered for persons who cannot tolerate INH or who have been exposed to INH-resistant TB. It should also not be used to treat HIV-infected persons taking some combinations of ART especially protease inhibitors.

The National Aids Control Organization guidelines for LTBI in PLHA published in 2016 recommends the following strategy [8]

- Adults and adolescents living with HIV should be screened for TB with a clinical algorithm and those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered Isoniazid Preventive Therapy (IPT).
- Children living with HIV (more than 12 months of age) who do not report poor weight gain, fever, current cough or history of contact with a TB case, are unlikely to have active TB and should be offered IPT.
- Additional investigations will help in ruling out active TB (X-ray chest and tuberculin skin test) but are not mandatory.
- The treatment recommended in adult and adolescent is Isoniazid 300 mg + Pyridoxine 50 mg (Vitamin B6) per day for 6 months and for children above 12 months is Isoniazid 10 mg/kg + Pyridoxine 25 mg (Vitamin B6) per day for 6 months.

6. Chemoprophylaxis after contact with MDR-TB

Treatment of close contacts of drug-resistant active TB cases is difficult and yet is an increasingly common clinical problem. For contacts of INH-resistant index cases, INH will be ineffective, so 4RIF is recommended [47, 48].

In a prospective study, two of 41 children receiving tailored preventive therapy developed TB (confirmed and probable TB) compared to 13 of 64 children not receiving preventive treatment (OR 0.2, 95% CI 0.04–0.94) [49]. However, WHO has not recommended any form of preventive therapy for MDR contact cases. Based on the available evidence and the probability of increased likelihood to develop active TB disease following recent infection, strict clinical observation and close monitoring for the development of active TB disease for at least 2 years is preferred over the provision of preventive treatment for contacts of MDR-TB cases [1].

Clinical management of latent tuberculosis infection should also address such concomitant risk factors as illicit-drug use, alcohol abuse, and smoking through opioid-substitution treatment and counseling about alcohol and smoking cessation, respectively. Acceptance of and adherence to the full course of latent tuberculosis treatment must be encouraged. In a study conducted in the United States and Canada, 17% of persons who were offered treatment for latent infection refused it [1]. Treatment completion varies widely (from 19 to 96%), and the reasons for non-completion need to be fully assessed [1]. The use of various incentives to promote treatment initiation and adherence, depending on the specific need of the person being treated, should be considered. Peer education, counseling, people-friendly services, and properly trained service providers boost confidence and may improve adherence to treatment [1].

7. Adverse effects of LTBI treatment

The lengthy duration of treatment reduces patient compliance, while the potential occurrence of serious adverse events such as hepatitis, further discourages patients' and providers' acceptance of this therapy [50–52].

INH has the major disadvantage of potential serious adverse events. Of particular concern is hepatotoxicity, as this is difficult to detect, and can be fatal. Surveillance studies have confirmed that hepatotoxicity is quite common in patients taking INH and can be severe resulting in up to 1 per cent mortality in older patients [53].The relative risk for developing hepatotoxicity associated with isoniazid compared with placebo were 3.45 (95% CI, 1.49–7.99) for 12 weeks of treatment, 4.59 (95% CI, 2.03–10.39) for 24 weeks of treatment, and 6.21 (95% CI, 2.79–13.79) for 52 weeks of treatment in the IUAT trial [34].

In another randomized trial, rates of grade 3 and 4 adverse events were significantly lower with 4RIF than 9INH [54]. Grade 3–4 hepatotoxicity occurred in 4% of patients taking 9INH compared to less than 1% in those taking 4RIF [54].

Comparison of drug toxicity of INH and Rifampicin has been studied in many trials. Rates of hepatotoxicity among patients receiving isoniazid were 5.2, 3.7, 34 and 11.4% compared to rates among patients treated with rifampicin (0.0, 0.7 and 4.4%, respectively) [55, 56].

In PREVENT TB study, rates of grade 3 and 4 hepatotoxicity were 4.9 and 1.0% in the rifapentine plus isoniazid arm and 5.5 and 1.1% in the isoniazid-only arm, respectively [57]. The RR for grade 3 or 4 hepatotoxicity was 0.90 (95% CI, 0.75–1.08). Mortality from hepatotoxicity was reported to be 1.0% among patients on isoniazid and 0.8% on those on isoniazid plus

rifapentine (RR, 0.83 [95% CI, 0.51–1.35]) [57]. Therefore, unless the index TB case has INH-resistant TB or an abbreviated regimen is required in a special situation, there is no reason not to use INH for LTBI chemoprophylaxis.

8. Conclusion

Identification and early chemoprophylaxis for LTBI can prevent reactivation TB and thus reduce both TB morbidity and transmission of TB in the community. In low TB-burden countries LTBI detection and IPT are important strategies for TB eradication. Diagnosis of LTBI is based on either TST or TB IGRA. The test preferred usually depends on the financial support available for public health programmes. In high TB- burden countries, LTBI detection and treatment can contribute to decreasing TB burden and transmission and also emergence of drug resistant TB. Here the guidelines are pretty straightforward and IPT should be offered to all children less than 5 years who have contact with pulmonary TB cases or HIV-positive individuals. INH is the preferred drug for LTBI and a 9-month regimen is considered optimal. However, careful clinical monitoring is required to detect drug induced liver injury early and also to ensure adherence to therapy. Clinical trials in different parts of the world have shown that this effort is worth it.

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