



Review Article

Management of Latent Tuberculosis Infection in People Living with HIV in Resource Constrained Nations

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ABSTRACT

Tuberculosis has been a public health challenge from time immemorial, and its significance, during last three decades has been enhanced by HIV. In view of significant morbidity and mortality due to tuberculosis in people living with HIV, World Health Organization has recommended treatment of latent tubercular infection by isoniazid preventive therapy. This article briefly reviews the public health importance of HIV-TB co-infection, pathogenesis, and treatment regimen available for latent tubercular infection. Guidelines recommended by World Health Organization on the issue are discussed with an objective to initiate a wider debate to reach consensus on an issue that has potential to improve quality and quality of life of millions of people living with HIV

Key Words: Latent Tubercular infection, HIV-TB co-infection, Isoniazid preventive therapy, People Living with HIV

INTRODUCTION

Tuberculosis (TB) has been a public health challenge for centuries, and continues to contribute considerable morbidity and mortality especially in high prevalence countries of African and Asian continents. Although the incidence of tuberculosis is declining, mortality due to TB is second only to HIV/AIDS due to a single infectious agent worldwide. ⁽¹⁾ Two important factors i.e. association of TB with the human immunodeficiency virus (HIV) infection, and increasing resistance of Mycobacterium tuberculosis to anti-tubercular drugs have revived the interest of public health experts towards prevention, diagnosis and treatment of TB. These factors have also posed new

challenges to resource-constrained countries that will have to plan and implement strategies for management of latent tubercular infection (LTBI) in high risk groups, much before the battle against the active disease could be stabilized in their favour. The credit of bringing LTBI to the centre stage goes to acquired immune deficiency, although iatrogenic immune suppression (organ transplant, steroid therapy, blocking agents against Tumor Necrosis Factor-Alpha) has joined forces with the virus. ^(2,3,4)

It is estimated that one-third of the total world population is latently infected with M tuberculosis ⁽⁵⁾ and 5%–10% of the infected individuals will develop active TB

disease during their life time. This risk increases to 5-15% every year in HIV co-infected individuals with lifetime risk approaching 50% in this group. ⁽⁶⁾ World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) have included diagnosis and treatment of LTBI in people living with HIV in resource constrained countries and United States respectively. ^(7,8)

This article briefly reviews the public health challenge of TB in People Living with HIV (PLH), pathogenesis, diagnosis and treatment regimens for LTBI, and summarizes the guidelines recommended by WHO for management of LTBI in PLH in resource constrained nations.

The Magnitude of the Challenge: LTBI in People Living with HIV ⁽⁹⁾

The risk of developing tuberculosis (TB) is estimated to be between 21-34 times higher in PLH than among those without HIV infection.

The magnitude of the challenge can be appreciated by following data released by WHO for the year 2010 :-

- There were 8.8 million new cases of TB, of which 1.1 million (13%) were among people living with HIV.
- Of the 1.1 million people who died from TB 350,000 (24%) were living with HIV.
- There were 34 million people living with HIV with 2.6 million becoming newly infected with HIV.

However, in vast majority of infected individuals, an effective cell-mediated immune response develops 2–8 weeks after infection and succeeds in stopping multiplication of the bacilli. The activated T-lymphocytes, macrophages, and other immune cells form granulomas that wall off the growing necrotic tissue limiting further spread of the tubercle bacilli. Most of the

- Of the 1.8 million HIV-related deaths, 350,000 were due to TB.
- Of the 1.5 million people reported to have newly enrolled in HIV care, just about 180,000 (12%) were put on isoniazid preventive therapy (IPT).
- With 24% of all TB deaths being associated with HIV, 13% of new TB cases being among people living with HIV, and 22% of HIV-related deaths caused by TB, TB represents a serious health risk and is a leading cause of morbidity and mortality among people living with HIV

Transmission of M. tuberculosis Infection

Tubercular infection is initiated by inhalation of droplet nuclei (1–5 µm in diameter) containing *M. tuberculosis*, expectorated by patients with active pulmonary TB. The risk of infection is dependent on several factors mainly the infectiousness of the source case, closeness of contact, bacillary load, and immune status of the host. Small size favours entry of droplet nuclei into terminal alveoli where they are engulfed by phagocytic immune cells (macrophages and dendritic cells), as well as nonphagocytic cells in the alveolar space. *M. tuberculosis*, internalized by phagocytic immune cells, replicates intracellularly, and the bacteria-laden immune cells may cross the alveolar barrier to cause systemic dissemination.

bacilli are killed in the caseating granulomas, and disease progression is arrested. However, the pathogen is not completely eradicated in some individuals as *M. tuberculosis* has evolved effective strategies to evade the immune response resulting in survival and persistence of some bacilli in a non-replicating state in the host (LTBI). A subsequent defect in cell-

mediated immunity may result in reactivation of dormant bacilli causing

active disease many years after the infection (reactivation TB).⁽¹⁰⁾

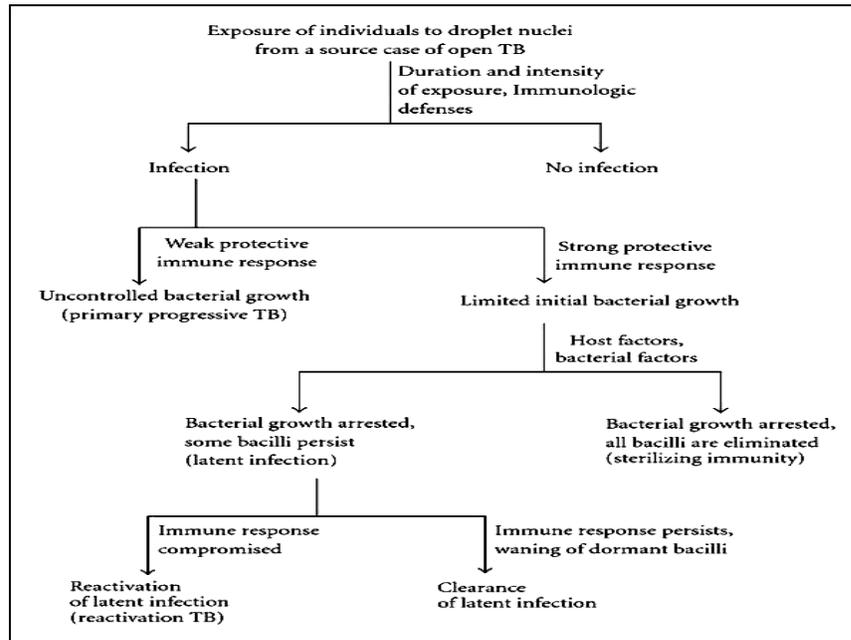


Table 1: Pathogenesis of Tuberculosis in immunocompetent⁽¹⁰⁾

Dynamic Model of Dormant M tuberculosis in Immune Competent Hosts

The classical model of LTBI mentioned above, does not explain how the bacilli evade progressive cellular turnover and the regenerative processes involved in reconstituting the injured tissues. It also fails to explain why a nine month course of isoniazid that is effective only against actively dividing bacilli has a 90% efficacy in the treatment of LTBI. The dynamic model of latent infection has been proposed in which endogenous reactivation as well as damage response occurs constantly in immunocompetent individuals. The model suggests that during initial stages (developing granuloma) of infection, *M. tuberculosis* grow well inside phagosome and then escape from phagosome/phagolysosome and are released in extra cellular milieu due to macrophage necrosis. Some of the extra cellular bacilli stop

replicating due to hypoxic and acidic environment, nutrient limitation and presence of bactericidal enzymes released from destruction of immune cells, even before an effective immune response is fully developed. With the development of an effective immune response, the actively growing bacilli are easily killed, however, the metabolically inactive, non-replicating (dormant) bacilli resist killing and may survive. The model also assigns an important role to foamy macrophages that emerge during chronic inflammatory processes (such as TB) due to phagocytosis of cellular debris rich in fatty acids and cholesterol in the dissemination and/or waning of infection. The model suggests that as foamy macrophages phagocytose extracellular non-replicating lipid-rich *M. tuberculosis* along with other cellular debris, the bacilli are not killed due to their non-replicating, metabolically inert (dormant)

state. At the same time, tubercle bacilli also do not grow in the intracellular environment as the macrophages are now activated. As the foamy macrophages containing non-replicating bacilli drain from lung granuloma towards bronchial tree, they lodge *M. tuberculosis* into a different region of lung parenchyma due to aerosols generated by inspired air and the bacilli get another chance to begin the infection process at this new location. In this infection-control of growth-reinfection process, bacilli getting lodged in the upper lobe may have the chance to cause cavity lesion. This is due to higher oxygen pressure in upper lobes that can support rapid extracellular bacillary growth resulting in bacillary concentration that cannot be controlled by the optimum immune response mounted by the host. The subsequent much stronger inflammatory response leads to tissue destruction, liquefaction and extracellular bacillary growth which amplifies the response further and causes cavitations. (11-13)

The dynamic infection model, involving drainage and destruction of non-replicating bacilli over a period of time, proposes slow clearance (waning) of latent infection in a sub-set of infected individuals who are not at risk of re-infection. A recent study carried out in Norway, a country with a low risk of active transmission of infection or re-infection, has shown that rates of reactivation of TB, among patients previously exposed to *M. tuberculosis* progressively declines with passage of time. (14) Furthermore, the prevention of re-infection by bacilli resuscitated from dormancy by isoniazid, during infection-control of growth re-infection cycles, also explains how therapy with a single drug, effective only against actively dividing bacilli, is highly effective for a latent infection. (15)

Diagnosis of latent M. tuberculosis infection

Diagnosis of LTBI is constrained by a low bacillary load that limits the role of direct microscopy and weak humoral response that makes serological testing unreliable. Till beginning of 21st century only test available for diagnosis of LTBI for almost 100 years was tuberculin skin test (TST), which detects a cutaneous delayed-typed hypersensitivity response to purified protein derivative (PPD). The sensitivity of TST is compromised by its inability to evoke positive results in immunocompromised (PLH, iatrogenic immunosuppressant, overwhelming tubercular infection), and its specificity is limited by cross reactivity of the PPD with environmental mycobacteria and BCG vaccination. (15)

Newer Tests for Diagnosis of LTBI

Newer tests for diagnosis of LTBI are in vitro T cell-based interferon-gamma release assays (IGRAs) and are based on the principle that T cells of individuals sensitized with *M. tuberculosis* antigens produce high levels of IFN- γ in response to a reencounter with these antigens. The performance of IGRA tests has been evaluated extensively, and FDA in US has approved the tests for diagnosis of LTBI in high risk groups. IGRAs have better specificity (higher than TST) as they are not affected by prior BCG vaccination since the antigens used in these assays are not present in *M. bovis* BCG and cross reactivity with environmental mycobacteria are less likely. Furthermore, the sensitivity of IGRAs is also higher than TST in immunocompromised individuals. However, the IGRAs technology has not undergone evaluation in high prevalence countries. Other limitations of IGRAs are their inability to distinguish LTBI from active TB disease (similar to TST), and higher cost. Both these factors are important in high TB

incidence countries where latent infection is widespread, reinfections happen frequently, and resources to use a costly test for mass

screening programmes may not be available. (16-22)

Regimens for Treatment of LTBI. (10, 23, 24)

The regimens recommended for treatment of LTBI are tabulated below:-

Drug	Dose (Adult)	Schedule	Remarks
Isoniazid	5 mg/kg (max 300 mg)	Daily x 12 months (365 doses)	Preferred regimen by International Union Against Tuberculosis (IUTA)
Isoniazid	5 mg/kg (max 300 mg)	Daily x 9 months (270 doses)	Preferred regimen by CDC, except in cases where Isoniazid resistance is suspected
Isoniazid	15 mg/kg (max 900 mg)	Twice weekly x 9 months (76 doses)	Under DOT
Isoniazid	5 mg/kg (max 300 mg)	Daily x 6 months (180 doses)	Regimen recommended by WHO for implementation in resource constrained nations (25)
Isoniazid	15 mg/kg (max 900 mg)	Twice weekly x 6 months (52 doses)	Under DOT
Isoniazid and Rifampicin	INH 5 mg/kg max 300 mg Rfm 450/ 600 mg	Daily x 3 months (90 doses)	Rifampicin has drug-drug interaction with Many NNRTIs and PIs.
Isoniazid and Rifapentine	INH 15 mg/kg (max 900 mg) Rfp (max 900 mg)	Once weekly x 3 months (12 doses)	Under DOT (26)
Rifampicin	10 mg/kg (max 600 mg)	Daily x 4 months (120 doses)	Recommended regimen if isoniazid resistance is confirmed. See note above regarding drug-drug interaction.
Rifabutine	300 mg per day	-do-	Preferred regimen for PLH on ART, but dosage adjustment of both rifabutine and ART drugs required.

Table 2 : Regimens Recommended for treatment of LTBI

Regimen of Rifampicin and Pyrazinamide for treatment of LTBI is not recommended due to risk of drug induced hepatitis and death (27)

Guidelines for Management of LTBI in PLH in Resource Constrained Countries (28)

HIV is the strongest risk factor for developing TB disease in those with LTBI, or new M tuberculosis infection. The risk of developing TB is between 21 to 34 times greater in PLH than among those who do not have HIV infection. TB is also responsible for more than a quarter of deaths in PLH. In response to the dual epidemic of HIV and TB, WHO has recommended twelve collaborative TB/HIV activities.

The recommendations specifically related with diagnosis and treatment of LTBI is summarized below:

- a. 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). IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, who have previously been treated for TB.

- b. People living with HIV who have a positive TST benefit more from IPT; TST can be used where feasible to identify such individuals. WHO recommends inclusion of TST in detection of LTBI in countries that can ensure resources for mass screening of PLH by TST. However, TST is not a requirement for initiating IPT in people living with HIV. IGRAs are not recommended for to screen PLH for eligibility to receive IPT
- c. Pregnancy in PLH: After TB disease is excluded; daily Isoniazid with supplementation with pyridoxine is indicated, after exclusion of Tubercular disease by clinical algorithm.
- d. IPT in Children.
 - Children living with HIV who have any one of the following symptoms – poor weight gain, fever, current cough or contact history with a TB case – may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, and all children who have no symptoms suggestive of TB should be offered IPT regardless of their age.
 - All children living with HIV who have successfully completed treatment for TB disease should receive INH for an additional six months.
 - Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening, and have no contact with a TB case should receive six months of IPT (10 mg/kg/day) as part of a comprehensive package of HIV prevention and care services.
- Children living with HIV who are less than 12 months of age, only those children who have contact with a TB case and who are evaluated for TB (using investigations) should receive six months of IPT if the evaluation shows no TB disease.
- e. Breastfeeding: Breastfeeding is not contraindicated in women taking INH. However, supplementation with pyridoxine is recommended.
- f. IPT and Drug Resistance. Providing IPT to people living with HIV does not increase the risk of developing isoniazid-resistant TB. Therefore, concerns regarding the development of INH resistance should not be a barrier to providing IPT.
- g. PLH with symptoms suggestive of TB. Adults and children living with HIV who have any one of the symptoms of TB may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, such patients should be offered IPT regardless of their age.

Recommendations

HIV has significantly enhanced the need for diagnosis and treatment of LTBI, even in resource constrained nations. WHO recommends creation of a collaborative organization for coordinating efforts against HIV-TB. ⁽²⁴⁾ The risk of morbidity and mortality due to tuberculosis is an issue in PLH, hence National HIV/AIDS Control Programme (NACP) should be primarily responsible for diagnosis, prevention and treatment of tuberculosis infection (LTBI) as well as disease among PLH. This will require resource support to NACP for diagnosis (including extra-pulmonary TB), treatment (including regimens for patients on ART), follow-up, data management, training and research. National TB Control Programme (NTCP) should be upgraded to diagnose HIV in confirmed and suspected

TB patients, and referring the co-infected to the nearest NACP Centre for management. At grass root level facilities of DOT worker should be shared by both programmes. Frequent cross referrals between NACP and NTCP must be avoided in HIV-TB co infected as it will require duplication of resources, and also lead to increased non-adherence to treatment.

Technical issues like diagnostic trials to compare the efficacy and cost effectiveness of IGRAs versus TST, especially in immune compromised, and children recently immunized with BCG, and clinical trials for the most suitable (effective, affordable, safe and acceptable) regimen for treatment of LTBI among PLH not on ART, on ART, pregnant and breast feeding mothers, infants, infected with isoniazid resistant and MDR-bacilli should be undertaken.

National Programmes require enormous resources that need political will, and it is imperative for public health experts to debate the issue to arrive at a consensus on the need, technical and operational issues. NGOs and corporate sector (including pharmaceutical sector) obviously are important stakeholders, and should be collaborated from the beginning.

CONCLUSION

It is high time that low and middle income nations that have high TB and HIV incidence and prevalence rates debate the issue of treatment of LTBI in HIV infected persons, and develop national protocols based on public health burden of HIV-TB coinfection. Some experts have voiced concerns regarding implementation of universal treatment of PLH due to high prevalence of isoniazid resistance and re-infection,⁽²⁹⁾ while others⁽³⁰⁾ have recommended its implementation through integrated counseling centres and anti-retroviral treatment centres. The guidelines

of WHO are broad based for countries with wide disparity in their load of HIV-TB coinfection patients, and resources available. National programmes obviously will depend on 'local' factors. 'Nipping the TB in bud' by treating LTBI in PLH is likely to be a cost effective exercise in resource constrained nations as it will improve the quantity and quality of life of millions of PLH, and decisions regarding the same should be arrived through co-operation and co-ordination of all stakeholders.

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