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Ethical issues in expanding latent TB management in high burden countries

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To cite: Basu S, Sharma N, Mase S, Sachdeva KS. Ethical issues in expanding latent TB management in high burden countries. *Indian J Med Ethics*. 2020 Jan-Mar; 5(1) NS:53-6. DOI:10.20529/IJME.2020.020.

Manuscript Editor: Vijayaprasad Gopichandran

Peer Reviewers: Two anonymous reviewers

Abstract

Global efforts are being made to eliminate tuberculosis (TB) as a public health problem by 2030. These efforts are being thwarted by the challenge of effective management to minimise the progression of latent TB infection (LTBI) to TB, thereby interrupting the chain of transmission. Approximately 5%–10% LTBI cases eventually develop TB in their lifetime with the risk being higher in children, people living with HIV/AIDS (PLHIV), undernourished people, and patients with diabetes, chronic kidney disease, silicosis, and other comorbid conditions. Apart from operational barriers, complex ethical issues govern decision-making processes in either retaining current LTBI management practices or advocating implementation of the latest World Health

Organization guidelines, which suggest extending treatment to vulnerable groups who have a higher risk of progression to TB.

Newer LTBI treatment regimens have a diminished risk of toxicity that allays threats to patient safety. Public health justification for treating LTBI can also override patient autonomy, but the lack of a patient-centred approach is associated with poor adherence and treatment outcomes.

Cost-effectiveness studies need to evaluate the gains and losses accruing from funding treatment of LTBI versus similar costs in nutritional interventions for managing undernutrition. Similarly, the impact of diverting resources available for management of the existing active TB control programmes to expanding LTBI treatment also needs to be assessed.

In conclusion, a comprehensive LTBI treatment strategy built on the basis of high-quality evidence is the best way forward for resolving the ethical considerations at the heart of LTBI management in the developing world.

***Keywords**: Tuberculosis; India; Latent TB; Medical ethics*

Background

Global efforts are being made to eliminate tuberculosis (TB) as a public health problem by 2030. These are thwarted by challenges to effective management to minimise the progression from latent TB infection (LTBI) to TB disease. An estimated two billion people have LTBI, which is a state of an asymptomatic, persistent immune response to *Mycobacterium tuberculosis* (1). From this last group of infected people, nearly 5%–10% of people will eventually develop TB during their lifetime, with the risk being highest in the first two years after contracting the infection (2). Effectively managing LTBI is, therefore, necessary to interrupt the chain of transmission and accelerate the reduction in TB incidence rates from the current rate of 2% per year (3). However, in India, a country with one-fourth of the global TB burden, LTBI is treated only in children below six years of age and in PLHIV (4).

In this context, the latest World Health Organization (WHO guidelines advocate extension of treatment of LTBI in vulnerable groups who have a higher risk of progression to TB. These groups include all household contacts to infectious TB, silicosis patients, chronic kidney disease patients on dialysis, organ transplant recipients, and patients on immunosuppressant medications such as TNF-alpha antagonists (1, 5, 6). Some other groups like undernourished adults with low body mass index and people with diabetes having LTBI may also benefit from the treatment (6).

Several operational barriers and challenges to implementing and scaling LTBI treatment in high risk populations have already been identified. These include the reduced availability and affordability of LTBI screening tests (TST/IGRA), difficulty in implementing effective and thorough contact tracing in high migration settings, convincing asymptomatic people with LTBI to accept and complete its treatment, the spectre of drug-resistant TB, and the presumed risk of LTBI reinfection (6). However, the complex ethical issues, both from an individual and a societal public health perspective, that impact decision-making processes in either restricting LTBI treatment or pursuing models of expansion have not so far received adequate attention.

Ethical challenges in recommending LTBI treatment in a high burden setting

The fundamental ethical dilemma in advocating LTBI treatment, from the perspective of the individual, pertains to attaining a favourable balance of beneficence (benefit to the patient) and non-maleficence (avoiding harm to the patient) because of the possible side-effects from LTBI drugs. Although isoniazid preventive therapy (IPT) for LTBI treatment increases the risk of hepatotoxic reactions, the cumulative risk of side effects from a four-drug first-line anti-TB regimen used for treating TB is much higher especially with increasing age and among women (7). Moreover, newer LTBI treatment regimens, like the once weekly twelve-dose INH-Rifapentine regimen (3HP), are significantly less likely to cause adverse effects compared to IPT (1). With these newer shorter regimens, LTBI management is more likely to be successfully implemented with reduced potential to harm the patient, fulfilling the condition of non-maleficence.

Nevertheless, people with LTBI are asymptomatic without TB disease, and more than nine in ten persons will never develop TB disease in their lifetime, although the risk is significantly elevated amongst high-risk groups (1). This indicates that in advocating LTBI treatment, the principle of patient beneficence is likely to be more effective in individuals belonging to the high-risk groups compared to the others.

Public health ethics in expansion of LTBI treatment: Justification versus concerns

The public health justification for treating asymptomatic conditions with chronic medication therapy is well established in cases where the condition contributes to a high burden of disease, disability, and death. For instance, treating a common medical problem like mild hypertension that is usually asymptomatic is more beneficial, from a population perspective, as it lowers the burden related to anticipated disease complication in comparison to an individual high-risk approach strategy (8, 9). Furthermore, in contrast to hypertension, that requires lifelong treatment and affects only the individual at risk, LTBI can be cured with six months of IPT or twelve doses of 3HP. Consequently, it also prevents the development of TB, an airborne communicable disease that affects the community at large and requires a sustained public health response.

This need to promote the collective good of society can also override concerns for patient autonomy, the ethical principle of the right to control what happens to one's body and whether to initiate or refuse any treatment. Although people with LTBI are non-infectious, each individual with LTBI who develops TB may infect 10–15 other people within a year (10), unless

the TB is detected and anti-TB therapy initiated. Moreover, according to one estimate, treating 14% of individuals with LTBI per year is likely to reduce TB incidence from 1280 cases per million recorded in 2010 to 20 cases per million by 2050 without any additional intervention (11). Theoretically, TB eradication can be achieved by universal treatment of people with LTBI to eliminate the large reservoir of infection. Nevertheless, to tackle the complex issue of LTBI management, there is need for a patient-centred approach that preserves patient autonomy, builds patient confidence, and promotes patient-provider collaboration in the decision-making process. Treating unwilling or unconvinced people is likely to be counterproductive because of the risk of low adherence to the LTBI treatment regimen. Moreover, the long treatment duration in IPT is associated with lower medication adherence and chances of early discontinuation of therapy, ultimately negatively impacting the potential benefits of LTBI treatment in preventing TB disease progression (12, 13). However, newer anti-LTBI regimens like 3HP involve only an intake of 12 cumulative doses that significantly reduces concerns relating to adherence and also promotes treatment completion (1). LTBI management should include a comprehensive patient education component delineating the disease process, the importance of treatment completion, adherence support, and the recognition and management of the potential side effects of treatment (14). The presence of stigma related concerns on LTBI detection also need assessment and redressal.

Finally, there are currently disparities in LTBI treatment recommendations, resulting from advocacy of different treatment strategies for low versus high TB burden settings, which may compromise the principles of justice and equity. Low-burden, low-incidence countries have universally adopted a comprehensive LTBI treatment strategy (1). Paradoxically, however, most high burden, high incidence countries restrict LTBI treatment by eligibility and drug regimens because of concerns about reinfection, resource availability, and individual country-specific feasibility. This is a double whammy since the proportion of demographic groups at high risk of progression to TB disease is also the highest in these low and middle-income countries that lack effective LTBI management strategies (5). Nevertheless, there are exceptions, like Vietnam, a high TB burden country, which has made considerable progress in adopting the WHO (2018) LTBI recommendations. In contrast to India, the Vietnamese public health system provides LTBI treatment to HIV negative household contacts including children ≥ 5 years, adolescents, and adults, patients on TNF-alpha antagonist treatment, patients on dialysis, and those scheduled for any organ transplant. Prisoners and healthcare workers in Vietnam are also eligible for LTBI therapy (15).

However, the extension of LTBI treatment, to adhere to WHO or similar recommendations in developing countries, will involve significant investment of scarce resources in public health. The health costs involved are expected to be higher in case the more sensitive interferon gamma (IFN-y) release assay (IGRA) test is preferred over the cheaper Tuberculin Skin Test (TST) as the former is more expensive but also demonstrates higher specificity in BCG vaccinated individuals, although the economics of scale will lower costs with time (16). Consequently, there exists the risk of diversion of funds from other aspects of TB control, especially active case finding, which will be detrimental to objectives of the programme. Furthermore, from a counterfactual position, it could be argued that the additional financial resources required for LTBI treatment expansion could be more judiciously utilised instead for treating undernutrition in children and adults. The process would also render these groups more immune against infectious diseases, including TB, apart from improving their quality of life. On the other hand, despite the short-term increase in costs involved in expanding LTBI testing and treatment, enormous long-term cost savings can be realised by preventing new cases of TB.

Another potential argument against LTBI expansion in high-burden settings is the presumed lack of benefit resulting from tubercular reinfection as the annual risk of TB infection in a high burden country like India is only 1.5% (17), which is expected to decline further with reduction in the incidence of disease.

Conclusion

In conclusion, public health policies for TB control and elimination, need to have an effective LTBI management strategy and remove disparities in its universal accessibility and availability. A comprehensive LTBI treatment strategy built on the substructure of high-quality evidence is the best way forward for resolving the ethical considerations at the heart of LTBI management in the developing world (1, 6). These include cost-effectiveness studies factoring the number of LTBI to be treated to prevent an active TB case, while also accounting for costs of treating LTBI drug-related adverse effects to model the estimated long-term cost savings, and also compare the health outcomes with alternative nutritional and behavioural interventions. Furthermore, the rate of reinfection in successfully treated LTBI cohorts needs to be assessed through survival analysis. Failure to do so involves the risk of inappropriate diagnosis and management of LTBI, failure to end TB, and overlooking of the potential health needs of a large proportion of the global population.

***Sources of support**: Nil*

***Conflict of interest**: Nil*

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