Published in final edited form as:
Int J Tuberc Lung Dis. 2012 August ; 16(8): . doi:10.5588/ijtld.12.0364.

Short-course untargeted isoniazid preventive therapy in South Africa: time to rethink policy?

Stephen D. Lawn[a,b] and **Robin Wood**[a]

[a]The Desmond Tutu HIV Centre, Institute for Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

[b]Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK

Keywords

HIV; tuberculosis; prevention; isoniazid preventive therapy; TST

South Africa has the worst HIV-associated tuberculosis (TB) epidemic in the world with 300,000 cases each year. Previous national TB control policies have failed, confirming the fact that we cannot treat our way out of this epidemic using TB case management alone. Implementation of preventive interventions is therefore imperative and these include antiretroviral therapy (ART) and isoniazid preventive therapy (IPT).

Whereas ART has been scaled up rapidly in much of sub-Saharan Africa, implementation of IPT has in contrast been very poor. Recognising that the process of tuberculin skin testing (TST) was a stumbling block to implementation of IPT, the World Health Organization (WHO) in 2011 revised the IPT guidelines and made a strong explicit recommendation that "TST is not a requirement for initiating IPT in people living with HIV" although it "can be used where feasible".[1]Eliminating the need for assessment of TST status may be an important factor underlying recent gains in implementation.

In line with WHO policy, South Africa revised national IPT policy in 2010 [2] and in this issue of the journal, Bristow and colleagues report on the impressive gains in numbers of HIV-infected patients being started on IPT in South Africa over the subsequent year.[3] In a country where service delivery often falls well short of desired levels, this is highly commendable. However, as the authors clearly point out, their analysis simply presents numbers of patients started on IPT but not the numbers completing treatment or the benefit derived. Two key features of the current South African policy may greatly limit the impact of scale-up, namely the lack of targeting of IPT and the use of courses of relatively short duration.

While IPT benefits those who are TST-positive, there is strong evidence from a meta-analysis of controlled trials that included 2,490 patients with negative or anergic TST reactions that these patients derive no significant benefit from IPT.[4] While eliminating the need for TST assessment simplifies implementation of IPT, the downside is that the

Correspondence Stephen D. Lawn, Desmond Tutu HIV Centre, Institute of Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Anzio Road, Observatory 7925. Cape Town, South Africa. Tel +27 21 650 6970 Fax +27 21 650 6963, stevelawn@yahoo.co.uk.

Conflicts of interest
The authors have no conflicts of interest to declare

intervention no longer targets the minority of patients who stand to gain benefit. Thus, large numbers of patients are treated needlessly, undermining cost-effectiveness. Moreover, a small proportion of those unlikely to benefit might actually be harmed. In neighbouring Botswana, just 24.4% of 1,891 HIV-infected patients assessed for IPT were TST-positive and [5] and untargeted therapy would therefore potentially benefit just 1 in every 4 patients treated.

The South African guidelines recommend that IPT should be given for 6 months either continuously or over a 9 month period.[2] However, increasing data from carefully conducted trials show that the duration of benefit is largely limited to the actual period of treatment.[5,6,7] Once treatment has stopped, TB risk rapidly increases again. The likely explanation for this is that the prevailing force of *Mycobacterium tuberculosis* infection in South Africa and neighbouring countries is extremely high. Even when administered as mass treatment to whole working communities associated with the South African mines, short-course IPT had no impact on TB incidence or prevalence.[8] As Nardell and Churchyard rightly stated, unless the force of transmission can be reduced, durable benefits from prevention strategies are likely to be elusive.[9]

Life expectancy of people living with HIV-infection may now be extended for many decades by ART and so a 6-month course of IPT is likely to have minimal impact on lifetime TB risk. Growing evidence therefore suggests that if IPT is used, to do so on a long-term basis would be a more rational approach.[5] This option is included in the WHO guidelines.[1] A shift in policy towards long-term or even life-long therapy, however, would provide an even stronger rationale for targeting IPT according to TST status. Indeed, targeted provision of IPT for 36 months to TST-positive individuals in Botswana has been found to be more cost-effective than providing IPT without TST assessment or providing IPT for 6 months only.[10]

In conclusion, the current rapid scale-up of IPT in South Africa under national guidelines reported by Bristow and colleagues is not being targeted in patients who will benefit and is being given for too short a duration that will not provide durable prevention. This policy is inefficient use of scarce health-care resources. Current scientific evidence suggests that if this intervention is to be appropriately tailored to the local epidemiological situation, it should be given to patients who are confirmed to be TST positive and on a long-term basis.

Acknowledgments

SDL was funded by the Wellcome Trust, London, UK. RW is funded in part by the International Epidemiologic Database to Evaluate Aids with a grant from the National Institute of Allergy and Infectious Diseases (NIAID: 5U01AI069924-02); Cost-Effectiveness of Preventing AIDS Complications (CEPAC) funded by the National Institutes of Health (NIH, 5 R01AI058736-02); USAID Right to Care (CA 674 A 00 08 0000 700) and the South African Centre for Epidemiological Modeling and Analysis (SACEMA).

References

(1). World Health Organization. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. World Health Organization; Geneva, Switzerland: 2010. from the following URL:http://whqlibdoc.who.int/publications/2011/9789241500708_eng.pdf. [Accessed on 07 December 2010]

(2). Department of Health. Guidelines for tuberculosis preventive therapy among HIV infected individuals in South Africa. Department of Health; Republic of South Africa: 2010.

(3). Bristow C, Larson E, Vilakazi-Nhlapo K, Wilson M, Klausner J. Scale up of isoniazid preventive therapy in PEPFAR-assisted clinical sites in South Africa. Int J Tuberc Lung Dis. 2012 in press.

(4). Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV-infected persons. Cochrane Database of Systematic Reviews. 2010; (1) Art. No.: CD000171. DOI:10.1002/14651858.CD000171.pub3.

(5). Samandari T, Agizew TB, Nyirenda S, Tedla Z, Sibanda T, Shang N, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. Lancet. 2011; 377:1588–98. [PubMed: 21492926]

(6). Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med. 2011; 365:11–20. [PubMed: 21732833]

(7). Samandari, T.; Agizew, T.; Nyirenda, S.; Tedla, Z.; Sibanda, T.; Mosimaneotsile, B., et al. TB incidence increase after cessation of 36 months isoniazid prophylaxis in HIV+ adults in Botswana; Abstracts of the 19th Conference on Retroviruses and Opportunistic Infections; Seattle, WA, USA. March 2012; Abstract #147

(8). Churchyard, GJ.; Fielding, KL.; Lewis, JJ.; Coetzee, L.; Corbett, EL.; Godfrey-Faussett, P., et al. Community-wide isoniazid preventive therapy does not improve tuberculosis control among gold miners in South Africa: the Thibela TB study; Abstracts of the Conference on Retroviruses and Opportunistic Infections; Seattle, WA, USA. March 2012; Abstract #150aLB

(9). Nardell E, Churchyard G. What is thwarting tuberculosis prevention in high-burden settings? N Engl J Med. 2011; 365:79–81. [PubMed: 21732840]

(10). Smith T, Samandari T, Abimola T, Marston B, Sangrujee N. Cost-effectiveness of alternative policies to reduce TB disease and death in HIV-infected persons in Botswana. Am J Respir Crit Care Med. 2011; 183:A5310.