

TAC

TREATMENT ACTION CAMPAIGN

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Isoniazid Preventive Therapy in the context of HIV: An intervention that can save lives¹

Summary:

- Isoniazid preventive therapy (IPT) for tuberculosis consists of taking one pill daily for 6-9 months to prevent the development of active TB.
- Isoniazid (INH) preventive therapy has proven to be safe and effective at reducing the risk of active TB in people living with HIV.
- Patients with active TB must be given the appropriate treatment and not IPT.
- Successful IPT implementation requires expanded screening tools and the improved use of existing screening tools to rule out active TB. This means routine clinical screening for TB in all settings and greater access to chest X-ray, smear microscopy and culture.
- Once active TB has been excluded, adherence support, community and patient education is the only way to ensure that isoniazid resistance is prevented.
- While WHO recommends IPT for all people living with HIV in areas with latent TB infection greater than 30%, IPT is part of policy but not implemented in South Africa.
- IPT for people living with HIV should be implemented in South Africa.

The Crisis of Tuberculosis in South Africa

1. HIV is a powerful risk factor for the progression of latent TB infection to active disease. Today in South Africa, HIV-related TB is the leading cause of death.² HIV uninfected people with latent TB have a one-in-ten risk of developing active disease in their lifetime. However, this risk increases to one-in-ten per year for HIV-infected people. People living with HIV have a weakened immune system, which allows TB to spread to other parts of the body and cause active TB disease. Additionally, HIV-positive people have a higher risk of reactivation, as well as an increased risk of death from active disease.³

¹ This policy briefing for the Treatment Action Campaign was written by Hannan Braun with comments from Zackie Achmat, Paula Akugizibwe, Gregg Gonsalves, Katie Flannery and Lesley Odendal. Released for first SA TB Conference Durban 01 July 2008.

² Mortality and causes of death in South Africa, 2005: Findings from death notification. P0309.3. Available at <http://www.statssa.gov.za/publications/P03093/P030932005.pdf>

³ Basu S, Maru DSR, Poolman E, Sharma SK, Galvani AP, "Primary and secondary tuberculosis preventive therapy in antiretroviral treatment clinics: comparing strategies to maximize benefit and minimize resistance," DRAFT.

2. According to the WHO, South Africa has the fourth-heaviest tuberculosis burden in the world in terms of absolute numbers.⁴ As people living with HIV have a higher risk of developing active TB, national TB statistics can mask the true urgency of TB in HIV-positive populations. A recent study in a township of Cape Town found that the TB notification rate among HIV-positive individuals was 4381 cases per 100 000 people, while the rate among HIV-negative individuals was 656 cases per 100 000 people,⁵ showing the increased burden of TB disease in HIV infected populations.

Preventive Therapy

3. The WHO recommends preventative therapy for TB for all people living with HIV in areas with latent TB infection of greater than 30%,⁶ like South Africa. Preventive therapy is the use of anti-tuberculosis drugs (such as isoniazid) aiming to prevent the progression to active disease.

Isoniazid Preventive Therapy

4. Isoniazid preventive therapy is safe and effective, and it should be part of the standard of care administered to people living with HIV. The treatment, which is a six- to nine-month regimen, greatly reduces the risk of developing active TB, saving lives.

5. The use of isoniazid preventive therapy in South Africa has been very low, reflecting the failure of the Department of Health to address the TB and HIV epidemics with the urgency they require. Resistance to the use of IPT in South Africa is largely due to the difficulty of ruling out patients with active TB. This kind of mistake could lead to the unintended treatment of active TB with isoniazid, which on its own cannot treat active TB. Improperly treating active TB is likely to cause resistant strains. However, evidence shows that with proper clinical screening, chest x-rays and laboratory tests, it is possible to rule out active TB in the majority of patients.

6. IPT is safe and effective in reducing the risk of TB in people living with HIV.

- a) Multiple studies from around the globe confirm the beneficial potential of IPT for HIV-positive people. These studies found that IPT typically reduces the risk of TB disease by between 33% and 62% in people living with HIV.⁷
- b) The latest research suggests that the benefits of IPT for HIV infected people last for up to 48 months.⁸
- c) IPT is also associated with a reduction in mortality. For HIV-positive individuals with a positive PPD test, which detects exposure to infectious TB bacteria, IPT resulted in a 26% reduction in mortality as compared with the placebo arm. However, there was no significant difference observed in PPD negative individuals.⁹

⁴ WHO report 2008 Global tuberculosis control - surveillance, planning, financing. Available at http://www.who.int/tb/publications/global_report/2008/key_points/en/index.html

⁵ Lawn SD, Bekker L, Middelkoop K, Myer L, Wood R. "Impact of HIV Infection on the Epidemiology of Tuberculosis in a Peri-Urban Community in South Africa: The Need for Age-Specific Interventions." *Clinical Infection Diseases* 42: 1040-7, 2006.

⁶ Report from WHO Three I's Meeting: Intensified Case Finding (ICF), Isoniazid Preventive Therapy (IPT) and TB Infection Control (IC) for People Living With HIV, 2-4 April 2008. Available at http://www.who.int/hiv/pub/meetingreports/WHO_3Is_meeting_report.pdf

⁷ Ibid.

⁸ Ibid.

⁹ Churchyard GJ, Scano F, Grant AD, and Chaisson RE. "Tuberculosis Preventive Therapy in the Era of HIV Infection: Overview and Research Priorities." *The Journal of Infectious Diseases* 196:52-62, 2007.

- d) Secondary IPT (administered to HIV-infected people who have recovered from active TB disease) in a setting with a high TB prevalence reduces the incidence of TB by 55%, likely by preventing re-lapse or re-infection.¹⁰ It is therefore recommended that public clinics also expand their services to offer secondary IPT.
- e) IPT is cheaper than treating active TB. Treating the TB disease requires six months of expensive drugs, and the disease can be fatal. As isoniazid is low-cost and safe, IPT must be part of the standard of care for all HIV-infected individuals in South Africa.
- f) IPT is safer to use than other preventive therapies.¹¹ However, clinical monitoring and patient education is essential to address side effects as they arise, to sensitise patients to possible symptoms of active TB and to ensure adherence. IPT must be implemented with a patient- centered approach with increased treatment literacy and community education.

Improved screening for active TB and concerns of developing isoniazid resistance:

7. Ruling out active TB is essential to providing effective preventative therapy. Providing isoniazid alone to a patient with active TB is insufficient to treat the disease. With only using isoniazid, the bacteria causing TB disease will still be able divide, causing drug resistant strains; much reluctance to IPT implementation stems from this valid concern. TAC believes that the benefits of IPT outweigh the risk of potential isoniazid resistance, a risk that is very low if screening tools are used properly, and TB patients are properly identified and have access to care.

- a) If active TB is effectively excluded, very few organisms will be dividing in the body, and therefore there is a low risk of developing drug-resistant TB. The latest research suggests that IPT has a minimal effect on resistance, if screening tools are used properly.¹²
- b) Much of the current debate lies in concerns of the screening methods used to exclude active TB before starting IPT. Indeed, many people living with HIV present as smear negative, even though they have active TB. An algorithm (clinical screening tool) screening for symptoms of night sweats, cough or weight loss will correctly identify active cases of TB 60% of the time; adding chest x-ray increased the sensitivity to 90%.¹³ Having a more extensive clinical screening tool is likely to add sensitivity, and reduce the number of patients with active TB being given IPT.
- c) A meta-analysis of isoniazid resistant TB after IPT in HIV-positive populations found that there was not a statistically significant increase in isoniazid resistance associated with IPT.¹⁴ In any case, standard first-line quadruple therapy has been shown to be effective against isoniazid-resistant TB, should such resistance arise.¹⁵

¹⁰ Churchyard GJ, Fielding K, Charalambous S, et al. "Efficacy of secondary isoniazid preventive therapy among HIV-infected Southern Africans: time to change policy?" *Aids*. 17: 2063-2070, 2003.

¹¹ Churchyard GJ, Scano F, Grant AD, and Chaisson RE. "Tuberculosis Preventive Therapy in the Era of HIV Infection: Overview and Research Priorities." *The Journal of Infectious Diseases* 196:52-62, 2007.

¹² Balcells ME, Thomas SL, Gofrey-Faussett P, Grant, AD. "Isoniazid Preventive Therapy and Risk for Resistant Tuberculosis." *Emerging Infectious Diseases*. 12:744-751. 2006.

¹³ Basu S, Maru DSR, Poolman E, Sharma SK, Galvani AP, "Primary and secondary tuberculosis preventive therapy in antiretroviral treatment clinics: comparing strategies to maximize benefit and minimize resistance," DRAFT.

¹⁴ Balcells ME, Thomas SL, Gofrey-Faussett P, Grant, AD. "Isoniazid Preventive Therapy and Risk for Resistant Tuberculosis." *Emerging Infectious Diseases*. 12:744-751. 2006.

¹⁵ Nolan CM, Goldberg SV. Treatment of isoniazid-resistant tuberculosis with isoniazid, rifampin, ethambutol, and pyrazinamide for 6 months." *International Journal of Tuberculosis and Lung Disease*. 6:952-8. 2002.

- d) Health care workers should be more sensitised to TB symptoms. Expanding training in the diagnosis of active TB, especially extra-pulmonary TB and smear-negative TB, would help to exclude active TB, even without more expensive technologies.
- e) Chest x-rays should be more widely available in the public healthcare system.
- f) Culture testing is critical and needs to be scaled up in South Africa to more accurately detect cases of active TB, given the high numbers of sputum smear negative and extra-pulmonary TB. While this is supported by the Tuberculosis Strategic Plan for South Africa (the Plan), laboratory capacity must be strengthened in South Africa to realise this goal. Individuals who have symptoms of active disease, even if they are smear negative, should be treated for TB presumptively and not put on IPT.
- g) Advocacy for IPT must also be accompanied by advocacy for expanded and improved clinical screening tools.
- h) Once active TB has been excluded, adherence support, community and patient education is the only way to ensure that isoniazid resistance is prevented.

Integration of HIV and TB Services

8. Prevention and treatment of TB in HIV-infected people must be a priority for both HIV and TB programmes. Although South Africa has a national policy of counseling and testing TB patients for HIV, this is not being implemented successfully: only one third of newly diagnosed TB patients also were tested for HIV in 2006.¹⁶ The latest draft of the Department of Health's *Guidelines for the Management of HIV and TB in Health Facilities* confirms that interventions to control TB must be coordinated with strategies to curb the spread of HIV, and that preventive therapy should be offered in the package of care for HIV-infected individuals.¹⁷ However, there is inadequate political commitment to this kind of joint approach.

- a) IPT and ART can be taken together and are more effective in reducing the incidence of TB in people living with HIV than either is alone. It is therefore critical to expand the integration of TB and HIV services at the primary health care level in order to fight co-infection. One study has shown that antiretroviral therapy combined with IPT resulted in a 76% reduction in the development of active TB, compared to 52.5% (ARVs only) and 68.3% (IPT only).¹⁸
- b) The duty of delivering IPT services must be coordinated with services for people living with HIV. HIV support and adherence trainings could be utilised to successfully increase adherence during IPT.
- c) Patients who test positive for HIV should be counseled on TB, and be accurately screened regularly for active TB. Information regarding isoniazid preventive therapy should be made available to all people living with HIV.
- d) HIV-positive individuals who have been administered both stavudine (d4T) and isoniazid have an increased risk of peripheral neuropathy.¹⁹ It is thus important to integrate TB and HIV services as to avoid this interaction if possible and more effectively monitor patients for peripheral neuropathy.

¹⁶ Tuberculosis Strategic Plan for South Africa, 2007-2011, Department of Health, South Africa, p. 17

¹⁷ Guidelines for the Management of HIV and AIDS in Health Facilities, Draft Three, National Department of Health, 2008. p. 96.

¹⁸ Golub JE, Saraceni V, Cavalcante SC, Pacheco AG, Moulton LH, King BS, Efron A, Moore RD, Chaisson RE, Durovni B. AIDS. 2007 Jul 11;21(11):1441-8. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. *AIDS* 2007 Jul 11;21(11):1441-8.

¹⁹ Breen RAM, Lipman MCI, Johnson, MA, "Increased incidence of peripheral neuropathy with co-administration of stavudine and isoniazid in HIV-infected individuals." *AIDS*. 14: 615. 2000

- e) One way to further minimise the risk of starting IPT on patients with active TB would be to administer ART for approximately four months prior to IPT. The benefit of this approach is that active TB is often unmasked during the initial months of ART, allowing it to be more easily identified. This would further enhance the exclusion of active TB during IPT, and make clinicians more comfortable.²⁰

IPT for Health Care Workers

9. Extending IPT to health care workers including cleaners and ancillary staff also provides a beneficial impact, and it is recommended by the Department of Health.²¹ Occupational TB poses a significant risk to these workers, so preventative measures, coordinated with other infection control measures at health care facilities, are critical to protecting the health of these workers.

Conclusion

10. In a properly functioning health care system, TB can be prevented, accurately diagnosed, and cured. Isoniazid preventive therapy is safe and effective, and there should be universal access to isoniazid for people living with HIV. While there has been little evidence of isoniazid resistance caused by IPT, screening efforts must be strengthened to exclude active TB before the initiation of IPT. Therefore, advocacy for strengthened clinical screening tool must also accompany advocacy for IPT. With improved commitments on the part of the government, healthcare workers, the private sector and partners in civil society, IPT can be safely administered over large areas in South Africa, likely saving lives and reversing the devastating effect of TB in our country.

Glossary of Terms:

- Active TB:** When the TB bacteria overcomes the defenses of the immune system and begin to multiply, latent TB infection progresses to active TB. People with active TB have symptoms of Tb such as weight loss, fever, and fatigue and are infectious.
- Extra-pulmonary TB:** When TB is outside the lungs, such as in the head, kidney, bones, abdomen and joints. This is more common among people living with HIV
- Latent TB:** People infected with latent TB do not feel sick or have symptoms of TB but are infected with mycobacterium tuberculosis. They are not infectious and hence cannot spread TB infection to other people
- PPD (purified protein derivative) Test:** The PPD is a substance that stimulates the immune system to fight foreign substances in the body. PPD is taken from dead tuberculosis bacteria. During the test, this substance is injected beneath the skin. If TB bacteria are present, the skin around the injection becomes swollen and red within one to three days.

²⁰ Lawn SD, Wilkinson RJ, Lipman MC, Wood R. “Immune Reconstitution and “Unmasking” of Tuberculosis During Antiretroviral Therapy.” *American Journal of Respiratory and Critical Care Medicine* 177: 680-685, 2008.

²¹ Guidelines for the Management of HIV and AIDS in Health Facilities, Draft Three, National Department of Health, 2008. p. 96.

•Pulmonary TB: When TB is in the lungs, it is called pulmonary TB. It is the most infectious mode of transmission.

•Sputum: Sputum is the secretions produced inside an infected lung. When the sputum is coughed up it can be studied to determine what kinds of infection are present in the lung. This is used in smear microscopy testing. However, smear microscopy is not effective at detecting extra-pulmonary TB, which is more common among people living with HIV.