CLINICAL PRACTICE

Isoniazid preventive therapy in HIV-infected and -uninfected children (0 - 14 years)

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Isoniazid preventive therapy (IPT) prevents tuberculosis (TB) in immunocompetent children <5 years of age after exposure to an infectious TB source case. Routine IPT has been advocated in all HIV-infected children without TB, but has been controversial. Antiretroviral therapy markedly reduces the risk for TB in HIV-infected children, especially when started early in infancy. In HIV-infected children, as in HIV-uninfected children, we recommend post-exposure IPT after each TB exposure episode; but in HIV-infected children, this should be given irrespective of age or antiretroviral therapy. However, evidence for routine IPT without known exposure to TB in HIV-infected children is not convincing and is therefore not recommended.

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Isoniazid preventive therapy (IPT) effectively prevents tuberculosis (TB) in immunocompetent children <5 years of age, but its use in HIV-infected children remains controversial despite many studies and guidelines.

Recent World Health Organization (WHO) guidelines for IPT in HIV-infected children exclude infants (<12 months of age) from pre-exposure IPT (i.e. IPT before known exposure to TB), based mainly on a large randomised double-blinded study that found no benefit in the first years of life.[1,2] IPT is recommended for older children, based on another randomised double-blinded study and supported by a cohort study of the same and additional children over a longer time period.[1,3,4]

However, it is known from the pre-treatment era and from a study in the HIV era in a high TB incidence area that infants infected with *Mycobacterium tuberculosis* in the first year of life are at greatest risk of developing TB.[5,6] If infants <12 months of age showed no benefit from pre-exposure IPT, it would seem unlikely that older children would benefit, although unrecognised exposure from outside the household is more likely in older children than in infants.[7]

The cohort study by Frigati *et al.*[4] showed that the most benefit for preventing TB was from starting antiretroviral therapy (ART), which reduced the risk for TB by 32%. Other studies in children and adults support ART significantly reducing the risk of TB disease after infection.[8-10] The cohort study,[4] a continuation of the study by Zar *et al.*,[3] also suggested a trend towards the benefit of adding IPT, unlike the study by Madhi *et al.*[2] In both studies, children exposed to TB were switched to open-label IPT.[2-4] Children receiving open-label IPT in the Madhi study were discontinued. In the study by Zar *et al.*, while still in the double-blinded phase (isoniazid v. placebo), there was additional benefit in adding IPT as children were re-assigned to isoniazid v. placebo after receiving open-label IPT.[2,4] Other differences between the studies included severity of disease, availability of ART at baseline, ability to closely monitor adherence and size of the studies, which may account for confusion around the IPT policy for South Africa.

Most HIV-infected infants and children in South Africa should access ART as early as 8 - 10 weeks after birth, which should protect them to a large extent from developing TB as they would be immunologically similar to children without HIV infection. Hence,

the possible benefits of IPT need to be weighed against possible risks, especially when considering pre-exposure IPT.

Le Roux *et al.*[11] showed long-term IPT together with ART to be relatively safe in HIV-infected children; only 3.4% of children on ART and IPT developed grade 3 and 4 transaminase response, although none developed jaundice. However, the risk of hepatotoxicity and of developing isoniazid resistance if undiagnosed TB disease is treated with isoniazid alone is real.

Advice from various international and South African guidelines has caused uncertainty as to whether IPT should be given to all children without TB disease at initiation of ART.[1,12-14] Consequently, there is much uncertainty among healthcare workers (HCWs) in terms of IPT implementation. Therefore, the Paediatric Essential Medicines List Committee supported by the National Department of Health's HIV/AIDS, TB and Maternal, Child and Women's Health (HIV/AIDS, TB & MCWH) branch provide (on weighing current evidence and the risks/benefits) the following national guideline for IPT in HIV-infected and HIV-uninfected children:

1. In HIV-infected children, ART should start as early as possible in infancy. Early ART has an important protective effect against the development of TB following infection with *M. tuberculosis*.
2. **Post-exposure** IPT 10 mg/kg daily for 6 months is recommended in the following children after exclusion of TB disease:
   - HIV-uninfected children less than 5 years of age
   - HIV-infected children irrespective of age or ART status.

   Post-exposure means close contact with an infectious pulmonary TB case (defined as a sputum microscopy smear-positive or culture-positive or Genexpert-positive case) **or** the child is Mantoux tuberculin skin test-positive (induration ≥10 mm or, if HIV-infected, ≥5 mm) in the absence of previous IPT or TB treatment.

   IPT should be repeated with **each** significant new exposure (isoniazid has no post-antibiotic effect, therefore no long-term protective effect after completing IPT).

   In this regard, all HCWs should enquire about any new TB contact (new close TB source cases) at **every** follow-up visit, as well as asking caregivers about their own health, to screen for possible TB symptoms.
3. Pre-exposure IPT is **not** recommended in any HIV-infected or -uninfected child.
4. Post-TB disease IPT is **not** recommended. Ensure when treating TB in children that cure is complete. If resolution of TB is incomplete, exclude drug-resistant TB disease (culture and drug susceptibility testing supported by Genexpert tests) and, if no drug-resistant TB is found, consider prolonging the continuation phase to 7 months as provided for in the *Essential Drug List* in case of extensive disease or slow response to TB treatment. Repeated exposure to TB is managed with exclusion of TB disease and IPT as indicated as per point 2 above.
5. Post-exposure preventive therapy in children (HIV-uninfected or HIV-infected) who are exposed to drug-resistant infectious TB cases:
   - 5.1. True rifampicin (RIF) monoresistant contacts (confirmed by culture-based drug susceptibility test results and **not** Genexpert RIF resistance): INH 10 mg/kg daily for 6 months should be provided.
   - 5.2. INH monoresistant contacts: RIF 10 - 15 mg/kg for 4 months as single drug (or in RIF/isoniazid if single drug RIF not available at the same RIF dose).
   - 5.3. Multidrug-resistant and extensive drug-resistant TB contacts: Evidence for preventive therapy is less clear and expert advice should be sought. Two recent publications address this situation.[15,16]

1. World Health Organization. WHO policy on collaborative TB/HIV activities. Guidelines for national programmes and other stakeholders. WHO/HTM/TB/2012.1 and WHO/HIV/2012.1. WHO: Geneva, Switzerland, 2012.
2. Madhi SA, Nachman S, Violari A, et al. Primary isoniazid prophylaxis against tuberculosis in HIV-exposed children. N Engl J Med 2011;365:21-31. [http://dx.doi.org/10.1056/NEJMoa1011214]
3. Zar HJ, Cotton MF, Strauss S, et al. Effect of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV: Randomised controlled trial. BMJ 2007;334(7585):136.
4. Frigati LJ, Kranzer K, Cotton MF, Schaaf HS, Lombard CJ, Zar HJ. The impact of isoniazid preventive therapy and antiretroviral therapy on tuberculosis in children infected with HIV in a high tuberculosis incidence setting. Thorax 2011;66(6):496-501. [http://dx.doi.org/10.1136/thx.2010.156752]
5. Marais BJ, Gie RP, Schaaf HS, et al. The natural history of childhood pulmonary tuberculosis: A critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis 2004;8(4):392-402.
6. Hesseling AC, Cotton MF, Jennings T, et al. High incidence of tuberculosis among HIV-infected infants: Evidence from a South African population-based study highlights the need for improved tuberculosis control strategies. Clin Infect Dis 2009;48(1):108-114. [http://dx.doi.org/10.1086/595012]
7. Schaaf HS, Michaelis IA, Richardson M, et al. Adult to child transmission of tuberculosis: household or community contact? Int J Tuberc Lung Dis 2003;7(5):426-431.
8. Walters LE, Cotton MF, Rabie H, Schaaf HS, Walters LO, Marais BJ. Clinical presentation and outcome of tuberculosis in human immunodeficiency virus infected children on anti-retroviral therapy. BMC Pediatrics 2008;8(1):1. [http://dx.doi.org/10.1186/1471-2431-8-1]
9. Edmonds A, Lusiama J, Napravnik S, Kitetele F, van Rie A, Behets F. Anti-retroviral therapy reduces incident tuberculosis in HIV-infected children. Int J Epidemiol 2009;38(6):1612-1621. [http://dx.doi.org/10.1093/ije/dyp208]
10. Golub JE, Pronyk P, Mohapi L, et al. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: A prospective cohort. AIDS 2009;23(5):631-636. [http://dx.doi.org/10.1097/QAD.0b013e328327964f]
11. Le Roux SM, Cotton MF, Myer L, et al. Safety of long-term isoniazid preventive therapy in children with HIV: A comparison of two dosing schedules. Int J Tuberc Lung Dis 2013;17(1):26-31. [http://dx.doi.org/10.5588/ijtld.11.0820]
12. Cotton MF. INH preventive therapy (IPT) in HIV-infected South African children. S Afr J HIV Med 2011;12(2):27-30. http://www.sahivsoc.org/upload/documents/guidelines_june_2011b.pdf (accessed 22 June 2013).
13. Department of Health. National Tuberculosis Management Guidelines: 2009. Pretoria: Department of Health, 2009. http://familymedicine.ukzn.ac.za/Libraries/Guidelines_Protocols/TB_Guidelines_2009.sflb.ashx (accessed 22 June 2013).
14. Department of Health. Guidelines for Tuberculosis Preventive Therapy among HIV infected Individuals in South Africa: 2010. Pretoria: Department of Health, 2010. http://hivfshealth.org/document/2010/08/17/guidelines-for-tubercolosis-preventative-therapy-among-hiv-individuals-of-south-africa (accessed 31 May 2013).
15. Seddon JA, Godfrey-Faussett P, Hesseling AC, Gie RP, Beyers N, Schaaf HS. Management of children exposed to multidrug-resistant *Mycobacterium tuberculosis*. Lancet Infect Dis 2012;12(6):469-479. [http://dx.doi.org/10.1016/S1473-3099(11)70366-8]
16. European Center for Disease Prevention and Control. Management of Contacts of MDR TB and XDR TB Patients. http://ecdc.europa.eu/en/publications/Publications/201203-Guidance-MDR-TB-contacts.pdf (accessed 20 May 2013.)

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