GUIDELINE

INH PREVENTIVE THERAPY (IPT) IN HIV-INFECTED SOUTH AFRICAN CHILDREN

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HIV-infected children have a high risk of acquiring tuberculosis. The World Health Organization (WHO) has released isoniazid preventive therapy (IPT) recommendations for adults and children living with HIV, based on efficacy studies, mainly in adults. Data from children appear conflicting. IPT guidelines for children were developed in response to WHO guidelines at a local meeting, followed by discussions.

IPT should be given to all HIV-infected children after exposure to a source case if treatment for active disease is not required. For children whose mothers' HIV status was known antentally, when tuberculosis has been actively excluded in mothers and at infant follow-up, and when infants have commenced antiretroviral therapy in the first 3 months of life, IPT is not required. Otherwise, all infants and children should be given IPT for 6 months once active tuberculosis has been excluded.

HIV-infected children are at high risk of contracting tuberculosis (TB). An incidence of 24 cases per 100 HIV-infected children per year was documented in Cape Town during a period of limited access to antiretroviral therapy (ART).[1]

For HIV-infected adults, IPT is a cornerstone of TB management. IPT for HIV-infected adults refers to giving INH to those without active TB. IPT, together with intensified case finding and infection control, is collectively referred to as the '3 Is' strategy of the World Health Organization (WHO).[2] In a recent meta-analysis of 12 trials and 8 578 randomised HIV-infected subjects >13 years of age, TB preventive therapy (any anti-TB drug) versus placebo resulted in a lower incidence of active TB (relative risk (RR) 0.68, 95% confidence interval (CI) 0.54 - 0.85). This effect was more pronounced in individuals with a positive tuberculin skin test (TST) (RR 0.38, 95% CI 0.25 - 0.57). For adults with a negative TST, there was no statistically significant difference between treatment groups as the upper CI was >1 (RR 0.89, 95% CI 0.64 - 1.24). Compared with INH monotherapy, short-course multidrug regimens had more adverse effects. A reduction in mortality with INH monotherapy versus placebo was confined to those with a positive TST (RR 0.74, 95% CI 0.55 - 1.00).[3]

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The meta-analysis did not address the role of ART, which also reduces the risk of acquiring TB disease, as no randomised controlled trials have been reported in patients on ART. Lawn and colleagues have argued that ART and IPT have complementary roles, IPT being important in TST-positive individuals with higher CD4 counts and better immunity, and that ART (together with active case finding) is the most important component in immunosuppressed individuals.[4]

A meta-analysis from 2006 showed that IPT is not associated with production of INH resistance,[5] although resistance is a concern if patients have active disease before commencing IPT. It is also recognised that IPT is unlikely to prevent TB if a patient is infected with *Mycobacterium tuberculosis* resistant to INH.[6]

For children there are fewer data. The benefit of IPT after documented TB exposure or infection (TST positive) is undisputed, with the efficacy derived from studies in HIV-uninfected children.[7] Findings assessing the value of universal IPT before or in the absence of documented exposure to a source case (pre-exposure IPT) seem contradictory. Zar and colleagues showed benefit in a double-blind study comparing INH with placebo in children with limited access to ART in Cape Town.[1] Active TB was excluded at baseline and children already responding to TB treatment were randomised once TB treatment had been completed. Mortality was lower in the INH group (11 (8%) v. 21 (16%)) (hazard ratio (HR) 0.46, 95% CI 0.22 - 0.95, p=0.015). The incidence of TB was also lower in the INH group (5 cases, 3.8%) than in the placebo group (13 cases, 9.9%) (HR 0.28, 95% CI 0.10 - 0.78, p=0.005).[1]

A large multicentre trial set in Soweto, Cape Town and Durban enrolled infants between 3 and 4 months of age, after excluding all children with known TB contact.

It took place during expanding access to ART. There was no benefit from pre-exposure IPT compared with placebo, either in preventing TB or in reducing mortality in HIV-infected and HIV-exposed uninfected infants.[8,9] The apparent contradiction with the study by Zar *et al.*[1] could be explained by differences in the patient populations, excellent surveillance for TB exposure, and rapid institution of open-label INH for any documented exposure to a source case. The benefit of ART in reducing TB disease is well documented in children.[10,11]

New long-term data from Cape Town on children from the original IPT study recently reported additive benefit of ART and IPT over 5 years of follow-up. All children on placebo were switched to open-label INH and accessed ART through the public programme. INH reduced the risk of TB by 0.22 (95% CI 0.09 - 0.53) compared with placebo. ART alone reduced TB risk by 0.32 (95% CI 0.07 - 1.55). INH plus ART reduced the risk of TB by 0.11 (95% CI 0.04 - 0.32). Restricting the analysis to children receiving ART revealed a TB risk reduction of 0.23 (95% CI 0.05 - 1.00) when comparing INH with no INH.[12] This study suggests that IPT and ART have additive benefit in HIV-infected children.

1. WHO RECOMMENDATIONS

The WHO has recently published guidance on IPT for both children and adults, mainly based on adult data.[13] The recommendations for children are as follows:

1.1 Children living with HIV who do not have poor weight gain, fever or current cough are unlikely to have active TB.
Strong recommendation, low quality of evidence

1.2 Children living with HIV and 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. Once TB is excluded, offer IPT regardless of age.
Strong recommendation, low quality of evidence
Comment: All suspected cases MUST be referred for exclusion of TB according to local guidelines. The timing of this screening is important to avoid excessive referrals. A review after 2 weeks may be useful before referral. In the complete absence of symptoms, no additional work-up is required.

1.3 Children living with HIV and >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 6 months of IPT (10 mg/kg/d) as part of a comprehensive package of HIV prevention and care services.
Strong recommendation, moderate quality of evidence
Comment: The implication is that all HIV-infected children should receive IPT once active TB has been excluded, regardless of their underlying condition. This recommendation brings IPT guidelines for children in line with those for adults. However, in adults, while a duration of 6 months is regarded as the minimum period, there is support for 36 months or longer. In children, the duration was limited to 6 months, pending longer-term safety data. The risk for TB disease may not be at the time of giving IPT. Screening for TB must therefore take place at each clinic visit.

1.4 In children <12 months of age living with HIV, only those children in contact with a TB case and in whom active TB is excluded should receive 6 months of IPT.
Strong recommendation, low quality of evidence
Comment: The contradiction here is that children at greatest risk (HIV-infected infants) are not offered the same access to IPT as older children. HIV-infected infants have a 20 times higher incidence of TB than HIV-uninfected infants in a setting of expanding but inadequate early identification and access to ART.[14]

1.5 All children living with HIV who have successfully completed treatment for TB disease should receive INH for an additional 6 months.[15]
Conditional recommendation, low quality of evidence

2. THE IPT WORKING GROUP

The place of IPT for HIV-infected children in Southern Africa was debated at a small meeting held in Cape Town on 14 October 2010, sponsored by the HIV Clinicians Society of South Africa. Paediatricians from South Africa and Botswana and adult infectious diseases specialists with expertise in IPT attended. (During a review process, additional colleagues with expertise in childhood HIV and TB gave invaluable input.) The consensus was that IPT should be supported. There is a need to define the extent to which it should be included. There is a role for operational research on IPT. Integration of maternal and child health with TB and HIV programmes to accompany IPT (Infection control and Intensified case finding) is a key component for elimination of TB in children.
The following should be addressed:
2.1 Who takes responsibility for delivery of IPT?
2.2 How will it be monitored? Key indicators include:
- uptake
- adherence
- development of TB in children on or not on IPT.

3. RECOMMENDATIONS OF THE IPT WORKING GROUP

At each health care visit, every HIV-infected child must be reviewed for possible TB exposure and/or active disease and managed appropriately.
Always check the following:
- contact with a TB source case
- failure to thrive (monitor Road to Health Card (RTHC))
- present cough (non-remitting cough of ≥2 weeks' duration is suggestive of TB).

4. POST-EXPOSURE IPT

IPT should be provided after EACH documented TB exposure, unless the child is CURRENTLY receiving INH or TB treatment (Fig. 1).

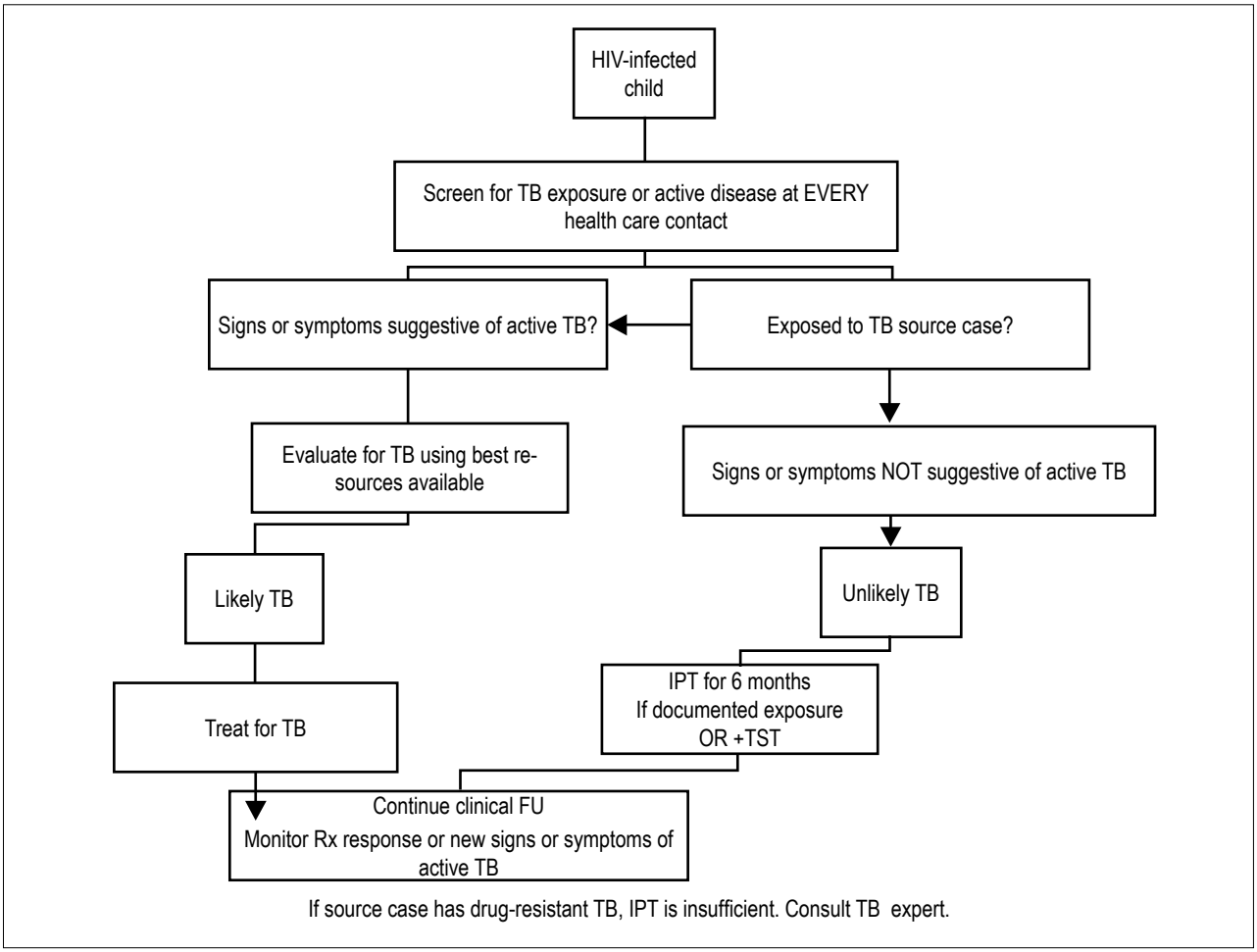

Fig. 1. Management of an HIV-infected child with documented TB exposure or suspected to have TB disease.

4.1 First exclude active TB (see below).
4.2 Give IPT to all HIV-infected children and all children less than 5 years of age, regardless of HIV status, after exposure to a source case of TB.
4.3 Give INH for 6 months (see dosing below).

Before giving post-exposure IPT, first make sure that the child does not have active TB.

- Completely asymptomatic children (no current cough, no failure to thrive, no signs of extrathoracic TB, active and playful) require no further investigation prior to IPT initiation. (All children receiving IPT and/or TB treatment should be followed up clinically while on therapy to evaluate for new symptoms or signs of disease.)
- Any symptomatic child should be carefully assessed (always plot weight and assess RTHC for failure to thrive). In the absence of a convincing clinical picture of TB or lethargy, and without easy access to chest radiography, first treat the most likely alternative diagnosis and re-assess the child after 2 weeks.
- Persistently symptomatic children must be assessed with at least a chest radiograph (antero-posterior or postero-anterior AND lateral). Respiratory specimens (gastric aspirates and/or induced sputa) for *M. tuberculosis* culture must be collected in all children with signs suggestive of TB on chest radiograph (prior to initiation of TB treatment).

NOTE: Evaluate for TB using the best resources available.

5. PRIMARY (PRE-EXPOSURE) IPT

Primary (pre-exposure) IPT should be given for 6 months (Fig. 2).

5.1 Give under the following circumstances:

- Active TB excluded (as for post-exposure IPT).
- Infant/child diagnosed with HIV or ART initiated after 3 months of age (or poor TB exposure screening expected).

5.2. **Do NOT give** if ALL of the following criteria are fulfilled:

- The mother is identified as HIV infected in antenatal clinic and screened for TB.
- No active TB is identified in close contact of the child such as member of the household/plot or a regular visitor.
- Infants are initiated on ART under both of the following circumstances:
  - ART initiated within the 1st 3 months of life when asymptomatic
  - active TB excluded.
- The infant is enrolled in the ART programme and seen at least every month for first 3 months and thereafter at least every 3 months (with screening for TB exposure or signs/symptoms of TB at each visit).

6. CATCH-UP PHASE FOR CHILDREN ALREADY ON ART FOR >6 MONTHS

At the time of implementation of the IPT guidelines (June 2011), there will be 50 000 children on ART. Data support

DOSAGE RECOMMENDATIONS FOR IPT (PRIMARY AND POST-EXPOSURE)		
Weight range (kg)	**100 mg tablets per dose (total dose 10 mg/kg/d)**	**Dose given (mg)**
<5	0.5	50
5.1 - 9.9	1	100
10 - 13.9	1.5	150
14 - 19.9	2	200
20 - 24.9	2.5	250
>25	3	300

Resources for drug-resistant TB: references 16 and 17.

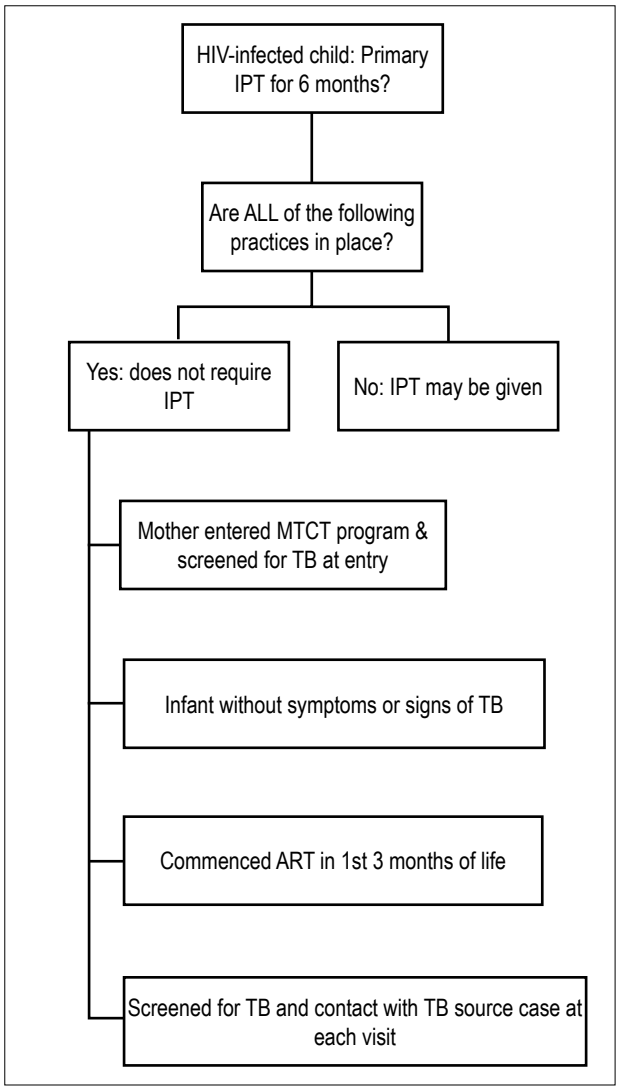

Fig. 2. Considerations for primary (pre-exposure) IPT.

IPT in children.[12] For children already well established on highly active antiretroviral therapy (HAART) (i.e. >3 months) and without active TB, there are two options:

6.1 IPT may be given for 6 months. (Apply guidelines for new contact with potential source case.) This is likely to be most beneficial for those who are TST positive (*note:* in the absence of ART, an induration ≥5 mm denotes a positive TST (Mantoux)).

6.2 Defer IPT and continue monitoring for new TB exposure and signs/symptoms of TB.

7. DOSAGE

7.1 INH 10 - 15 mg/kg/d.

7.2 Also give vitamin B_6 25 mg/d.

8. ADDITIONAL POINTS

8.1 In the absence of obvious TB disease, initiation of HAART takes precedence over IPT.

8.2 IPT must NOT complicate the HAART programme.

8.3 ANY child assessed for TB after contact with a TB source case must be screened for HIV.

Acknowledgements. We thank Natalie Martyn for arranging the meeting and the SA HIV Clinicians Society for sponsoring it.

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