Isoniazid Preventive Therapy (IPT) in HIV-Infected and Uninfected Children

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Background

- Tuberculosis (TB) is a common complication and leading cause of death in HIV infection
- HIV is the strongest risk factor for developing tuberculosis disease in those with latent or new *Mycobacterium Tuberculosis (MTB)* infection
- HIV-infected children are at high risk of contracting 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 ART\(^1\)

Background cont…

- Preventive therapy for TB has been known to reduce incidence in high-risk individuals for more than 40 years
- Isoniazid preventive therapy (IPT) is a key public health intervention for the prevention of TB among people living with HIV (WHO 1998)\(^2\)
- IPT reduces tuberculosis incidence significantly, but is not widely used
‘3 I’s” strategy

- In response to dual epidemics of TB and HIV
  WHO (2008):
  - Intensive case finding for active TB (ICF)
  - Isoniazid Preventive Therapy (IPT)
  - Infection Control for TB

WHO (2011)
- IPT guidelines for adults and children living with HIV, mainly based on adult data
- scale-up implementation
Efficacy of TB Preventive Therapy

- WHO guidelines group: 12 trials (8578 pts >13yo)
- TB preventive therapy (any TB drug) reduced overall risk of developing TB disease by 33% (RR 0.67; CI 0.51-0.87)
- Tuberculin Skin Test (TST) positive: reduction was more pronounced (64%) (RR 0.89; CI 0.64-1.24) not statistically significant as upper CI >1.

- GG conclusion: there is benefit in providing TB preventive therapy to people living with HIV regardless of TST status, with greater protective benefit in those with a positive TST.  

Regimen

- 8 studies comparing INH alone vs multidrug regimens
- Regimens including pyrazinamide, rifampicin and rifapentin as efficacious as INH alone
- More toxicities/adverse events
- Conclusion: INH 300mg/day (adults) or 10mg/kg/day (children) drug of choice
Duration

- No significant difference btw 6 and 9 month duration
- Protective effect decreases with time
- Durability ranges for up to five years
- 36 months in TST positive (high HIV/TB settings)
  *adults only
Immune status and concomitant use of IPT with ART

- ART also reduces risk of acquiring TB disease
- Evidence of benefit of concomitant use of IPT and ART (observational studies)
- Lawn and colleagues: ART and IPT have complementary roles, IPT being important in TST-positive individuals with higher CD4 counts and better immunity, and ART (with active case finding) being the most important component in immunosuppressed individuals

- Brazil: ART + IPT reduced risk substantially, more than either strategy on its own

- Recommendation: IPT should be provided regardless of whether on ART or not
- IPT should not delay ART initiation
HIV uninfected Children

- Benefit of IPT after TB exposure or infection (TST positive) is undisputed\(^5\)
- Six months IPT reduces the risk of developing TB by 60–65% over 5 years’ follow-up\(^6\)
- Prevention of active TB disease, TB meningitis, miliary TB
- WHO and South Africa’s National TB Programme (SANTP) recommend IPT for all children <5 years who are in close contact with an infectious(smear- and/or culture-positive) TB case.

HIV infected Children

- Post-exposure IPT as for uninfected children
- Pre-exposure IPT (absence of a contact with a source case): evidence seems contradictory

- Zar and colleagues showed benefit in a study comparing INH with placebo
  - Findings: Mortality lower in INH group (11 (8%)v 21(16%) (hazard ratio (HR) 0.46, 95% CI 0.22-0.95, p=0.015).
  - Incidence of TB also lower in the INH group (5 cases, 3.8%) \(^1\)
Madhi and colleagues: Large multicentre trial: Soweto, Cape Town and Durban enrolled infants btw 3 and 4 months of age, after excluding all children with a known TB contact.

Findings: **No benefit** from pre-exposure IPT vs placebo, either in preventing TB or in reducing mortality in HIV-infected or HIV-exposed uninfected infants.  

5. Madhi SA et al.;and the P1041 Team. Lack of efficacy of primary isoniazid (INH) prophylaxis in increasing tuberculosis (TB) free survival in HIV-infected South African children. 48th ICAAC/IDSA 46th annual meeting, 2008[G2-1346a]
Recent long-term data (over 5 years of follow-up) from original IPT study

Findings: INH alone reduced the risk of TB by 0.22 (95% CI 0.09-0.53)

ART alone reduced TB risk by 0.32 (95% CI 0.07-1.55)

INH plus ART reduced TB risk by 0.11 (95% CI 0.04-0.32)

In children receiving ART, TB risk was reduced by 0.23 (95% CI 0.05-1.00) when comparing INH with no INH. 6

These findings suggest that IPT and ART have additive benefit in HIV-infected children

WHO Recommendations

1. Children living with HIV who do not have poor weight gain, fever or current cough are unlikely to have active TB and should be offered IPT
   - poor wt gain: reported wt loss \textit{or} wt-for-age less than -2 z-score \textit{or} confirmed wt loss >5% since last visit \textit{or} growth curve flattening

2. Children living with HIV who have any of the above symptoms – poor weight gain, fever, current cough or contact with a TB case – may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB they should be offered IPT.
3. Children living with HIV, >12mo 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.

4. In children living with HIV, <12mo, only those who have contact with a TB case and who are evaluated for TB should receive 6 months of IPT if the evaluation shows no TB.  

IPT Working Group
Recommendations

- All children living with HIV, should be regularly screened for TB exposure and/or active disease at every visit to a health care facility

  - Check contact with a TB source case
  - Check RTHB for poor weight gain/failure to thrive
  - Check presence of current cough

Post-exposure IPT

- IPT should be provided after each TB exposure, unless child currently receiving INH or TB treatment
- First exclude active TB
- Give IPT to all HIV-infected children and all children <5 years of age, regardless of HIV status, after exposure to a source case of TB
- Give INH for 6 months
Fig. 1. Management of an HIV-infected child with documented TB exposure or suspected to have TB disease.
Primary (pre-exposure) IPT

- **Give IPT if:**
  - Active TB excluded
  - Child diagnosed with HIV or commenced ART after 3 months of age

- **Do not give IPT if ALL the following criteria are fulfilled:**
  - Mother identified as HIV infected in antenatal clinic and screened for TB
  - No active TB identified in close contact with child
  - Infants initiated under both of the following circumstances:
    - ART initiated in first 3 months of life when asymptomatic
    - Active TB excluded
  - Infant is enrolled in ART program with close follow-up and screening for TB at each visit.
HIV-infected child: Primary IPT for 6 months?

Are ALL of the following practices in place?

Yes: does not require IPT

No: IPT may be given

Mother entered MTCT program & screened for TB at entry

Infant without symptoms or signs of TB

Commenced ART in 1st 3 months of life

Screened for TB and contact with TB source case at each visit

Fig. 2. Considerations for primary (pre-exposure) IPT.
Catch-up Phase for Children already on ART for >6 months

- 2 options:
  1. Give IPT for 6 months (likely TST positive will have most benefit)
  2. Defer IPT and continue monitoring for new TB exposure signs /symptoms of TB
Dosage

- INH 10-15mg/kg/day (max 300mg/day)
- Pyridoxine (Vit B₆) 25mg/day

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

- **Hepatotoxicity**
  - Transient elevation in LFT's 10-20%
  - Hepatitis <1%, but can be fatal

- **Neurotoxicity**
  - Peripheral neuropathy, ataxia, seizures, psychosis, optic neuritis
  - Reversed by pyridoxine

- **Haematological Effects**
  - Anaemia, thrombocytopenia, neutropenia

- **Skin rashes**
IPT and drug-resistant TB

- No evidence of increased risk of DR in those receiving IPT
- Regular TB screening, prompt TB diagnosis treatment and prevention of drug resistant TB
- IPT not useful if source case has MDR TB → refer to TB expert
Additional points

- TST (mantoux) not required to initiate children on IPT. Should not be routinely used to determine eligibility for IPT
- In the absence of TB disease, ART takes precedence over IPT
- IPT must not complicate the ART programme
- Any child assessed for TB after contact with a TB source case must be screened for HIV
Challenges in Implementation

- Policy-practice gap
- Uptake of and adherence to IPT in children in resource-limited settings remains poor
- Van Wyk and colleagues (2010): Only 21% of children eligible for IPT had documentation of IPT delivery
- Difficulties in screening
- Fear of increasing INH resistance
- Poor acceptability among primary caregivers and healthcare workers
- No standardised management tool
Conclusion

- Screening, management and implementation of IPT programmes have great potential to reduce TB incidence and TB-related mortality in children, both HIV-infected and uninfected

- IPT is a proven and effective intervention
- Barriers are multifactorial but resolvable
- Site-specific gaps need to be addressed
Thank you