How Can We Better Deliver Isoniazid Preventive Therapy (IPT) to Children and to People with HIV?

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Background

• Risk of developing TB disease:
  – 10% \textit{lifetime} risk in healthy people with LTBI
  – 10% \textit{annual} risk in
    • Children with LTBI
    • People living with HIV with LTBI

• WHO recommends: for all PLWH in areas with prevalence of LTBI >30% and documented LTBI or exposure to infectious TB case
  – Screen for TB with simple clinical algorithm
    • If screening positive, evaluate for TB and other OIs
  – Those with unknown or positive TST and unlikely to have active TB should receive at least 6 months of IPT
Current IPT Delivery is Inadequate

• Among eligible
  – Children: only 8% to 20% receive IPT
  – HIV+ patients: Far below global target of 50%
Why is Current IPT Delivery Inadequate?

• Focus has been on treatment of TB (not prevention)
• Difficulties excluding TB disease
• Overestimation of INH side effects
• Concern about generating INH resistance
• Long duration of IPT (6-9 months)
• Inability to ensure IPT adherence and completion
  – Because LTBI patients are asymptomatic, testing and treatment is almost always provider-initiated
  – Motivation to comply with treatment is likely different than for an infection with symptoms
IPT Adherence

• Medication adherence is a complex behavior
• WHO definition: various health-related behaviors that extend beyond simply taking prescribed medications but rather as the extent to which a person’s behavior corresponds with recommendations from a health care provider

• We conducted a systematic review of the literature about IPT adherence to inform improved delivery of IPT in Swaziland among:
  – Children
  – PLWH
Results of our search

- 599 total citations
- 1st screen excluded based on abstract
- 2nd screen excluded based on full text
- We included 6 reviews
Description of 6 Reviews on IPT Adherence

• 6 reviews involving a total of 105 studies:
  – 1 Cochrane review (Lewin 2010)

• All reviews assessed studies that enrolled adults
  – 2 specified inclusion of (but not focus on) children or adolescents (DeFulio 2012, Lewin 2010)

• 3 reviews assessed studies that enrolled PLWH
What Adherence Interventions Were Studied in these 6 Reviews?

• 3 reviews assessed integration of IPT delivery into other health care services:
  – Community care (Al-Darraji 2012, Defulio 2012)
  – HIV care (Uyei 2011)

• 1 review examined impact of a revision of professional roles (Lewin 2010)
  – Use of lay health workers to
    • Support self-administered IPT
    • Provide directly observed therapy

• 2 reviews studied the impact of providing IPT through DOT (Hirsch-Moverman 2008, Zuniga 2012)
Most Relevant Review

- Systematic review by Uyei 2011:
  - Reviewed 6 IPT studies from high TB-burden, low-income settings
    - Botswana, South Africa, Uganda
  - Included PLWH
    - Unclear if children were included
  - Examined the impact of TB and HIV service integration
    - IPT adherence was high across the 6 studies in this review, with completion rates ranging from 47% to 88%
    - TB/HIV service integration appeared be effective
Other Findings of These 6 Reviews: What is the Utility of Incentives?

• Several reviews assessed effectiveness of incentives:
  – Money
  – Food
  – Transportation vouchers or other coupons
  – Other material goods or “treats”

• Conclusions
  – Financial incentives did not improve IPT treatment completion except in vulnerable populations
    • Children, homeless, and impoverished
  – Incentives for these vulnerable populations may improve adherence, but not a robust finding
Overall Conclusions

• Most interventions did not improve IPT treatment completion

• The integration of TB and HIV services yielded high treatment completion rates in some settings

• We need high quality studies performed in high-risk populations in high TB-burden settings to determine the best models of IPT delivery
  – An opportunity for Swaziland teams as IPT implementation rolls out
Individual Studies Not in the 6 Reviews May Inform IPT Delivery in Swaziland

• Searched literature for IPT studies to complement our systematic overview
  – Did not apply same rigorous quality criteria in selecting studies
Interventions – Improving IPT Adherence and Completion

• **Gomes 2011** assessed IPT adherence in 820 children in Guinea-Bissau
  – 76% completed at least 6 months of IPT
  – >80% adherence was observed

• **Rekha 2012** assessed effect of an IPT register and card on IPT delivery among children in India
  – Demonstrated minimal HCW training needed
  – IPT register and card significantly improved IPT
    • Screening and initiation (19% → 61%)
    • Treatment completion rate 74%
Another Study of Integrated TB/HIV Care - in Children

- **Patel 2013** assessed the survival, clinical and immunological outcomes of integrated TB/HIV treatment
  - Studied HIV-infected children ages 3-18 who started anti-TB treatment in primary clinics in Kinshasa, DRC
  - Demonstrated
    - High ART uptake and low mortality
    - Immunological and clinical improvement:
      - 87% of children successfully treated for TB disease
      - Median CD4 increased
      - Median BMI increased
A Study of IPT Adherence in PLWH in Southern Africa

- Rates of adherence were low at ProTEST pilot sites in South Africa, Zambia, and Måalawi
  - 24% to 59%

- Documented reasons for poor adherence
  - Lack of money for transport and food
  - Adverse effects of INH
  - Nondisclosure of HIV status
  - Perception that INH not effective

- These can systematically be addressed

Churchyrd et al. JID 2007;196:S52-62
Studies Documenting IPT Impediments

- Fear of stigmatization, lack of money/food/transport, reluctance to take medicine without symptoms and traditional medication competition (Rowe 2005)

- Difficulty in excluding TB disease and program costs (Lugada 2002)

- (Not documented but from experience: pill burden)
IPT Missed Opportunities Documented

- IPT was initiated in only 2/149 (1.3%) eligible children < age 5 in Cape Town, SA (van Wyk 2011)

- Only 33/365 (9%) of children < age 5 with TB contacts were screened in 44 Malawian hospitals (Claessens 2002)

- Missed opportunities for chemoprophylaxis in 71% of eligible children < age 5 in Cape Town, SA (Du Preez 2011)

- Household support an important factor in retention in IPT in South Africa (Beneri 2013)
  - Young maternal age associated with loss to follow-up
Addressing Concerns: IPT Hepatotoxicity?

- In large reviews, clinically important transaminase elevation has been 0.1 to 0.56%, same in HIV+ & HIV-.*

- IPT is safe in HIV-infected
  - In clinical trials, discontinuation due to adverse events higher for INH than placebo
    - In 5 trials: RR 1.66, 95% CI 1.09 to 2.51**

- IPT is safe in children
  - Hepatotoxicity rates low (<2% severe in children)
  - INH can be reintroduced once transaminases recover (le Roux 2012)

Addressing Concerns: INH Resistance?

Summary RR=1.45 (95% CI=0.85-2.47)
Addressing Other Impediments to IPT

- **Stigma:** stigma from TB disease or HIV, IPT is to prevent progression to TB disease
- **Excluding TB:** WHO symptom screen effective in ruling out TB disease
  - CXR not necessary
- **Cost:** IPT is (likely) cost-effective
- **Training:** training needed but not extensive
  - May need retraining if high staff turnover
- **Scale-up:** *is possible*. Incorporating data collection into standard reporting will aid implementation.
Thank you - Siyabonga

Questions?