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TB CARE II

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

Lisa V. Adams[1], Elizabeth A. Talbot[1], Karen Odato[1], Heather Blunt[1], Karen R. Steingart[2]

[1]Infectious Disease and International Health Section, Geisel School of Medicine at Dartmouth, Hanover, NH, USA
[2]Cochrane Infectious Diseases Group, Liverpool, UK

IPT Indaba | September 4, 2013

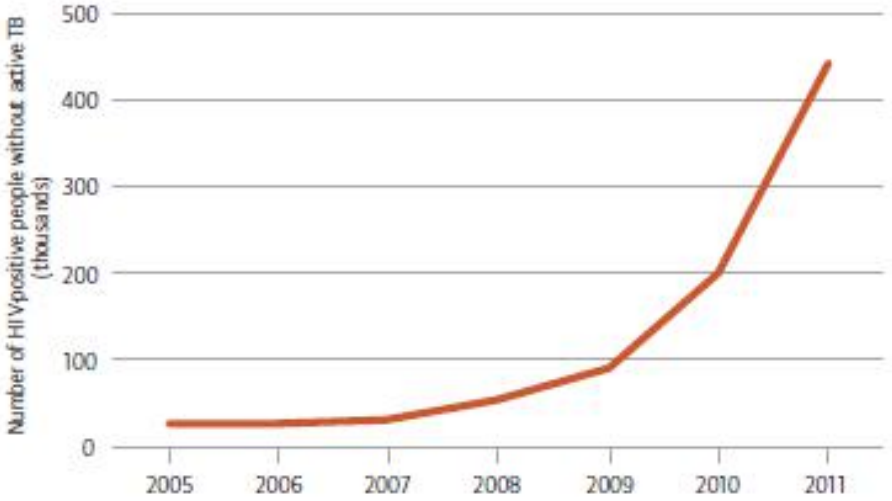
Background

- Risk of developing TB disease:
  - 10% ***lifetime*** risk in healthy people with LTBI
  - 10% ***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%

FIGURE 7.8 **Provision of isoniazid preventive therapy (IPT) to people living with HIV without active TB, 2005–2011**



Why is Current IPT Delivery Inadequate?

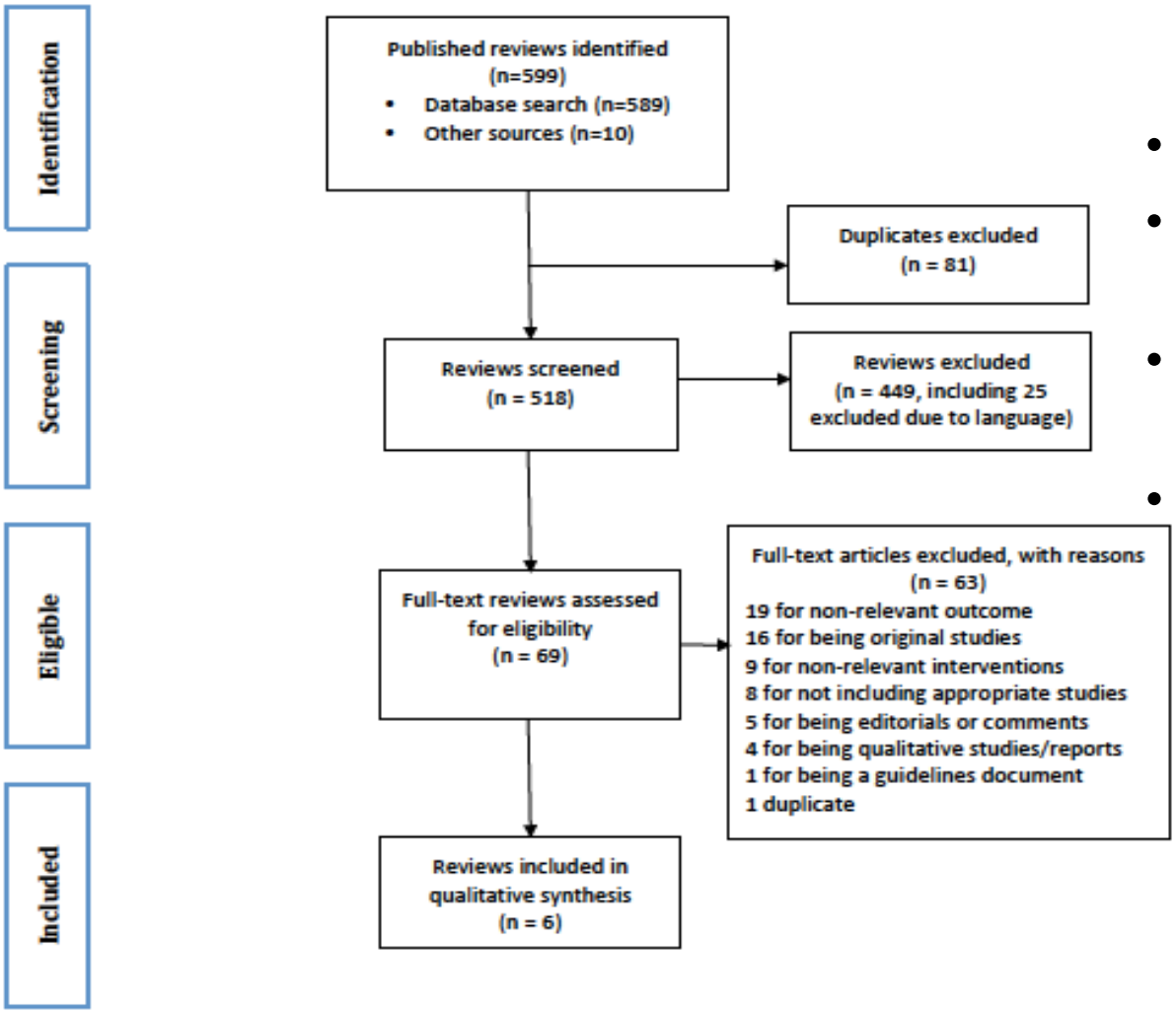
- Focus has been on treatment of TB (not prevention)
- Difficulties excluding TB disease
- Overestimation of INH side effects
- Concern about generating INH resistance
- Long duration of IPT (6-9 months)
- Inability to ensure IPT adherence and completion
  - Because LTBI patients are asymptomatic, testing 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

Figure 1. PRISMA Flow Diagram



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)
  - 5 non-Cochrane reviews (Al-Darraji 2012, Defulio 2012, Hirsch-Moverman, 2008, Uyei 2011, Zuñiga 2012)
- 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
  - Al-Darraji 2012, Hirsch-Moverman 2008, Uyei 2011

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

Churchyard 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

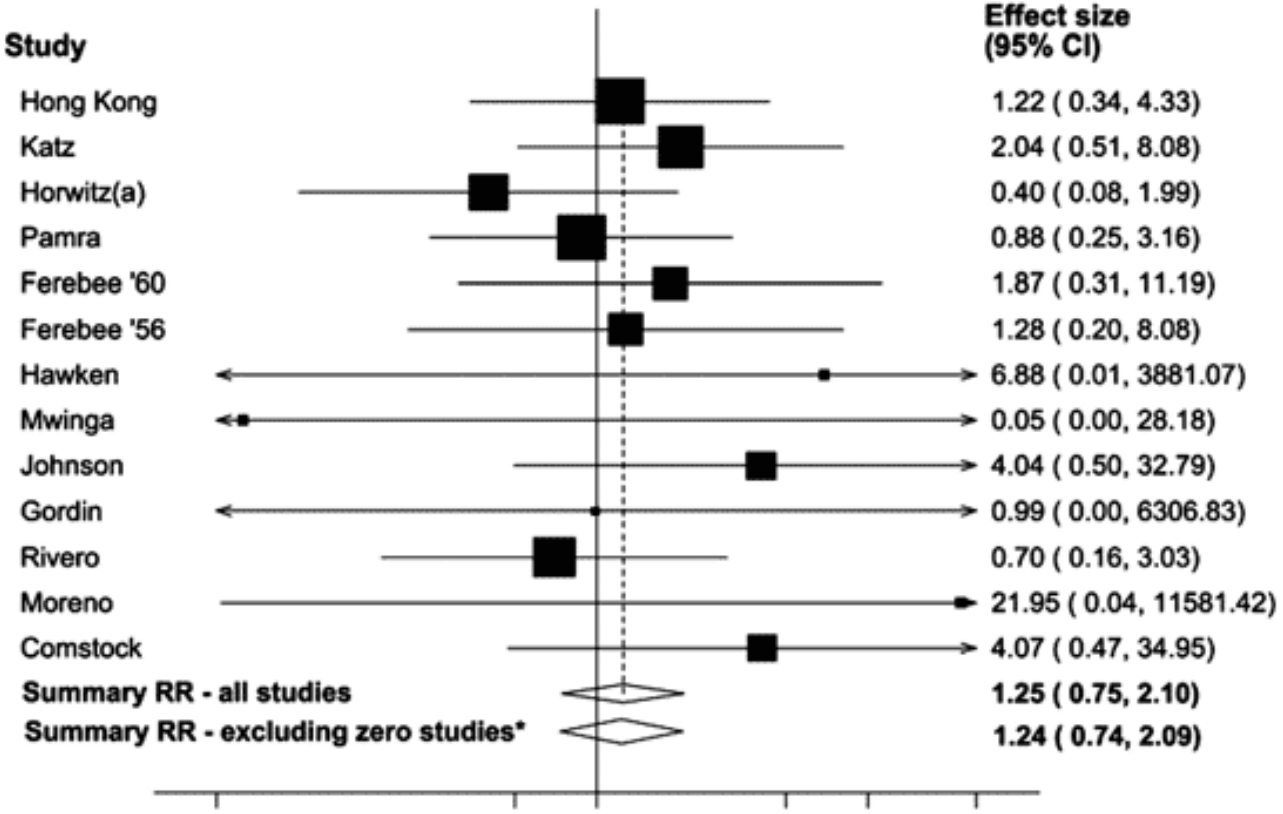
- IPT was initiated in only 2/149 (1.3%) eligible children < age 5 in Cape Town, SA (van Wyk 2011)
- Only 33/365 (9%) of children < age 5 with TB contacts were screened in 44 Malawian hospitals (Claessens 2002)
- Missed opportunities for chemoprophylaxis in 71% of eligible children < age 5 in Cape Town, 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)

*Saukkonen JJ et al. ATS Statement. Am J Respir Crit Care Med. 2006 Oct 15;174(8):935-52
**Wohldehanna et al. Cochrane Database Syst Rev. 2004;(1):CD000171

Addressing Concerns: INH Resistance?



Summary RR=1.45 (95% CI=0.85-2.47)

Balcells et al. Emerg Infect Dis. 2006 May;12(5):744-51

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?