

# A Review of Isoniazid Preventive Therapy (IPT): benefits and challenges

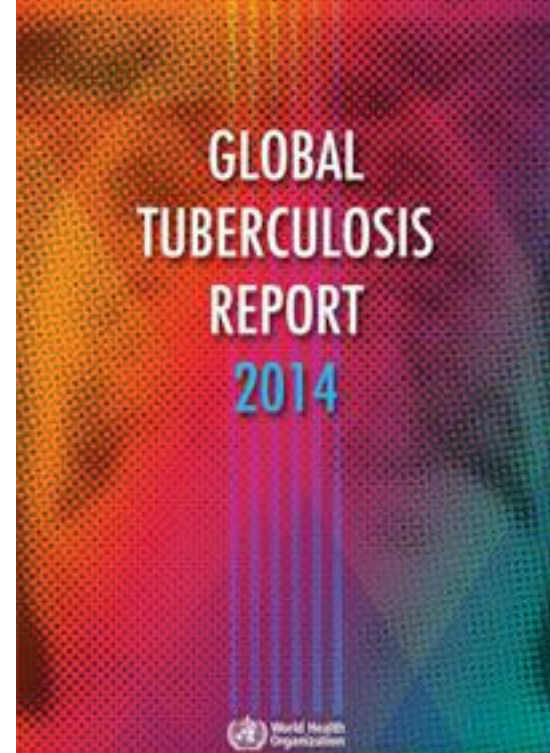
Prepared by:

Dartmouth's Geisel School of Medicine

University Research Council (URC)

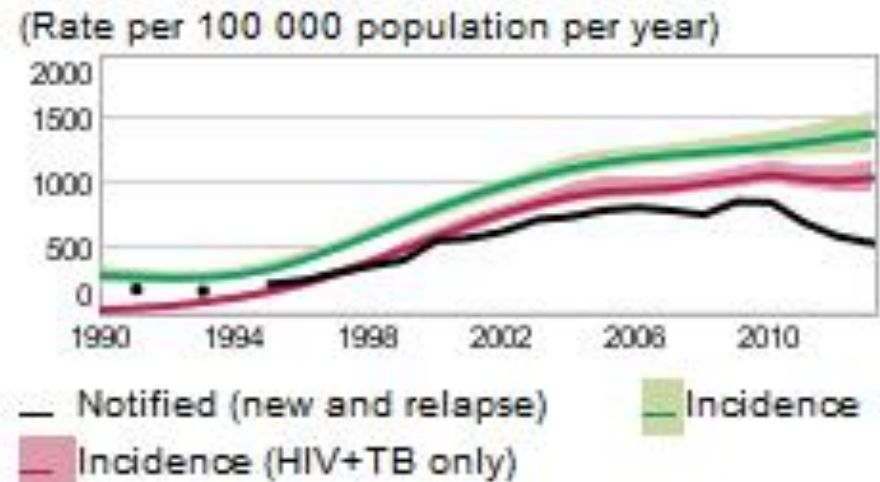
# Tuberculosis Global Epidemiology

- In 2013:
  - 9 million cases
  - 1.4 million deaths
    - 430 000 deaths among HIV+,
  - 500, 000 cases in children < 15 years
- Second only to HIV/AIDS as second killer worldwide



# Swaziland, WHO TB 2014

- In 2013
  - Case notifications: 7,078
    - 10% < age 15
  - TB Incidence: 1,382 per 100,000
  - HIV+ TB patients: 4,747 (74%)
  - HIV+ screened for TB: 100,138
  - HIV+ given INH: 429
  - 5,000 deaths in TB/HIV pts



# Latent Tuberculosis Infection (LTBI)

- *M. tb* contained by the immune system
- Results in a dormant or latent stage of TB
- From this latent stage, the bacteria can reactivate to cause TB disease at any time
- Treatment of latent TB infection (LTBI) can decrease the risk of reactivation

# Isoniazid Preventive Therapy (IPT)

- INH is the mainstay for latent TB treatment
- Effectiveness is 60-90%
  - Due to variable adherence, actual effectiveness is 25-90%
- Trial comparing IPT for 12, 24, 52 weeks
  - 24 weeks decreased TB by 65%
  - Less hepatitis than with 52 weeks

Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. International Union Against Tuberculosis Committee on Prophylaxis. Bulletin of the World Health Organization 1982;60:555-64.

# IPT preventing TB in HIV+ Children

- Frigati et al. 2011, South Africa
  - Double blind, placebo controlled trial in HIV+ children on ART
  - DSMB terminated placebo arm at 4 months due to demonstrated benefit of INH on mortality
  - Children receiving placebo were switched to INH
  - Concluded: IPT reduces the risk of TB in HIV+ children on ART by 0.23 ( 95% CI 0.05-1)

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;66:496-501.

# IPT preventing TB in HIV+ Children

- Further evidence...
- Grey et al. 2014, South Africa
  - RCT to assess the efficacy, tolerability and safety of IPT in HIV+ children on ART
    - 85 received INH, 82 received placebo
  - 4 cases of TB in INH group, 7 in placebo group, all susceptible to INH
  - Conclude: IPT is safe and well tolerated in HIV+ children on ART

Gray DM, Workman LJ, Lombard CJ, Jennings T, Innes S, Grobbelaar CJ, Cotton MF, Zar HJ. Isoniazid preventive therapy in HIV-infected children on antiretroviral therapy: a pilot study. *Int J Tuberc Lung Dis.* 2014 Mar;18(3):322-7.

# IPT in HIV+ Children on ART

- Ayieko et al. Meta-analysis, 2014
  - Included 8 RCTs of IPT in children
  - confirmed that INH is more efficacious in preventing TB
  - Concluded: IPT reduces the risk of developing TB by 59% among children aged 15 years and younger excluding infants (95% CI 0.31-0.55)

Ayieko J, Abuogi L, Simchowitiz B, Bukusi EA, Smith AH, Reingold A. Efficacy of isoniazid prophylactic therapy in prevention of tuberculosis in children: a meta-analysis. BMC infectious diseases 2014;14:91



# Optimal duration of IPT?

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### A Trial of Mass Isoniazid Preventive Therapy for Tuberculosis Control

Gavin J. Churchyard, M.B., B.Ch., Ph.D., Katherine L. Fielding, Ph.D., James J. Lewis, Ph.D., Leonie Coetzee, D.Soc.Sc., Elizabeth L. Corbett, M.B., B.Chir., Ph.D., Peter Godfrey-Faussett, F.R.C.P., Richard J. Hayes, D.Sc., Richard E. Chaisson, M.D., and Alison D. Grant, M.B., B.S., Ph.D., for the Thibela TB Study Team

- 78,744 miners enrolled, randomized into 15 clusters
  - Intervention group: TB screening & IPT x 9 mos
  - Primary outcome: TB incidence during 12 mos after intervention ended

# IPT in high risk populations

- Among 63,174 miners with outcomes:
  - 887 TB cases in the intervention clusters
  - 856 in the control clusters
  - TB incidence: 3.02 & 2.95 cases/100 person-years
- Conclude: Mass screening & treatment for LTBI had no significant effect on TB in South African gold miners
- BUT... IPT was successful in preventing TB during treatment
- Mistake to conclude IPT not beneficial, suggests longer duration indicated while remain at high risk

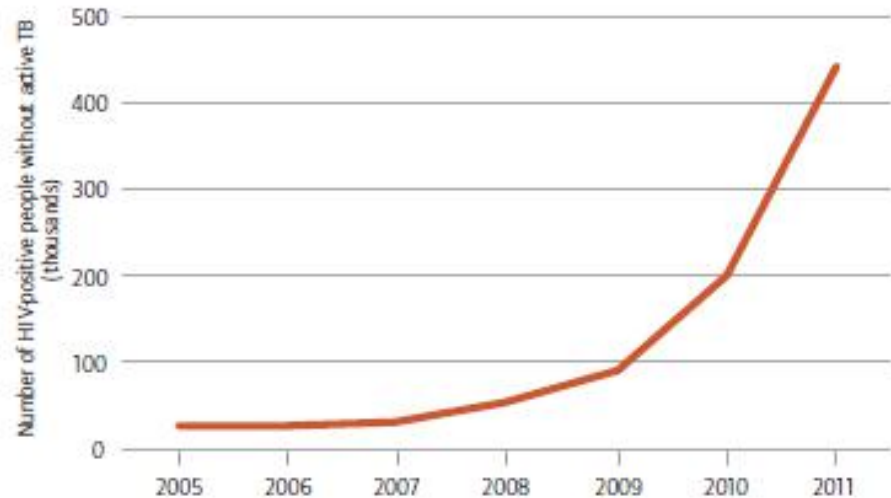
# G Churchyard: “IPT as an Umbrella”



# 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 current IPT delivery is inadequate ?

- Focus historically on TB disease treatment not prevention
- Difficulty excluding TB disease
- Long duration of IPT
- Overestimation of the complications of INH
  - Concerns about toxicity and generation of INH resistant TB are unsubstantiated
- Inability to ensure IPT adherence:
  - LTBI is asymptomatic, therefore testing is provider-initiated
  - Because patients are asymptomatic, less motivated to take long treatment

# Additional References

1. Ayieko J, Abuogi L, Simchowit B, Bukusi EA, Smith AH, Reingold A. Efficacy of isoniazid prophylactic therapy in prevention of tuberculosis in children: a meta-analysis. BMC infectious diseases 2014;14:91.
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