

**SA HIV Clinicians Society
Conference 2012**

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Striving for Clinical Excellence



INH Preventive Therapy in Children

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Prophylactic effect of INH on primary TB in children

RCT: INH vs. Placebo (4-6mg/kg/day)

2 Groups:

- <3y of age – TST 5TU \geq 5mm
- >3y of age - TST 5TU \geq 5mm + CXR evidence Primary TB

| | INH N = 1394 | Placebo N = 1356 |
|-------------------------------|-----------------|---------------------|
| Extra-pulmonary complications | 5 (0.33%) | 26 (1.91%) |

80% cases prevented
P = 0.0002 Fishers Exact 2-tail test

INH reasonably effective for post-exposure prophylaxis

US Public Service TB prophylaxis trial – Am Rev TB 1957; 76: 942-63

How well is post-exposure prophylaxis given to TB-exposed children in public programs?

- Poor
 - Du Preez et al – Ann Trop Paediatr 2011; 31: 301-10
 - Missed opportunities in 70% of 614 children with culture+ TB in Cape Town
 - Pothukuchi et al – Plos One 2011; 6: e225500
 - 56/172 (32%) children <6y of age in households of sputum+ve adults not screened for TB in South India

Post-exposure prophylaxis:

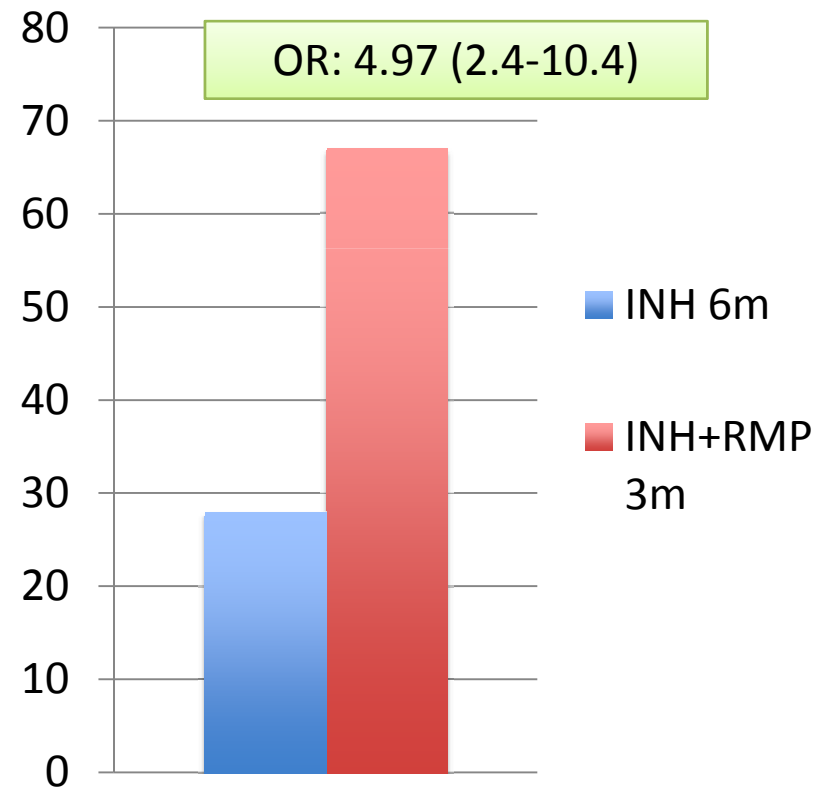
INH X6m vs INH + RMP X3m

National TB Program

- Pre 1996
 - <2y: INH + RMP X3m
 - 2 – 5y: INH X6m
- Post 1996
 - <5y: INH X6m

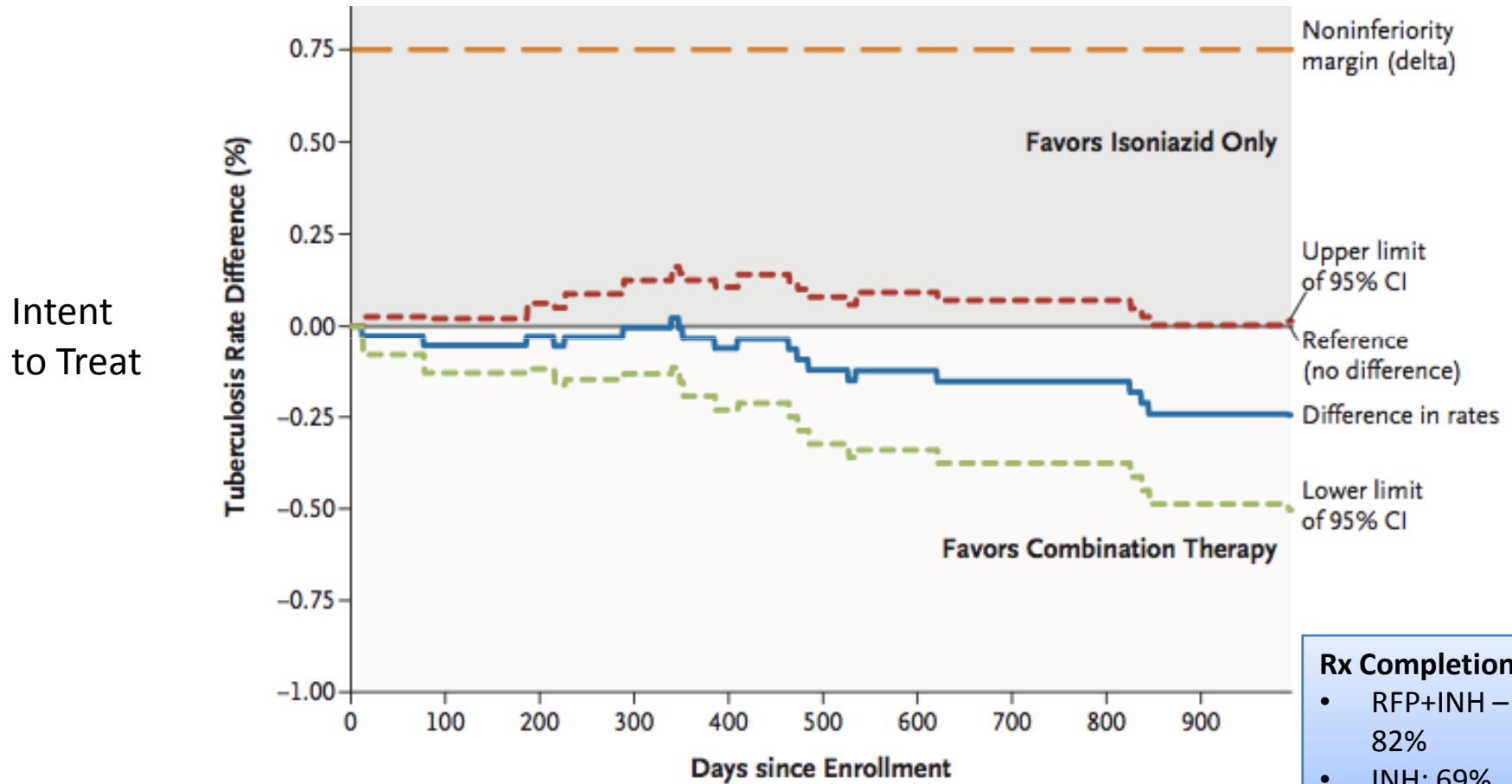
Adherence %: 1996 – 2003

Retrospective study



Van Zyl et al Int J Tuberc Lung Dis 2006
10: 13-18

Weekly rifapentine (RFP) + INH X 12 doses Latent TB infection in adults (vs. INH X 9m)



No. at Risk

Sterling et al N Engl J Med 2011; 365: 2155-66

Role of HIV

- Low TB prevalence settings
- N = 8053
 - HIV - 205
- HIV and TB risk (multivariate analysis)
 - OR 4.1 (1.3 – 3.2)

Post exposure prophylaxis for TB

- After exposure to an adult source case
 - All children <6y
 - All HIV+ children

WHO
NTP - RSA

Post-exposure prophylaxis

INH daily X6m

- For
 - Simple
 - Long period
 - Less complicated if PI for HIV+
- Against
 - Not well implemented

INH + Rifampicin daily X3m

INH + Rifapentine weekly X 12 doses (3m)

- For
 - Shorter period
 - Adherence better
 - 70% vs 29%
 - V Zyl et al Int J Tuberc Lung Dis 2006. 10: 13-18
- Against
 - Few randomized data
 - Rifapentine dosage & formulation issues in children (esp young children)

Post-exposure prophylaxis & HIV in children

- Drug interactions RMP & LPV/r / NVP
- No data on efficacy
- But - INH X6m may be less of a problem in integrated HIV/TB program, if seen monthly

Improving post-exposure prophylaxis for Children

- Separate Register
- Contact clinics
- Same healthcare worker to manage source case & contacts
- Add contact tracing to TB Rx card
- Each child to have own card

Hawkrige A S Afr Med J 2007; 97: 997-1000

Control of TB in HIV+ endemic setting

The 3 I's WHO 2008

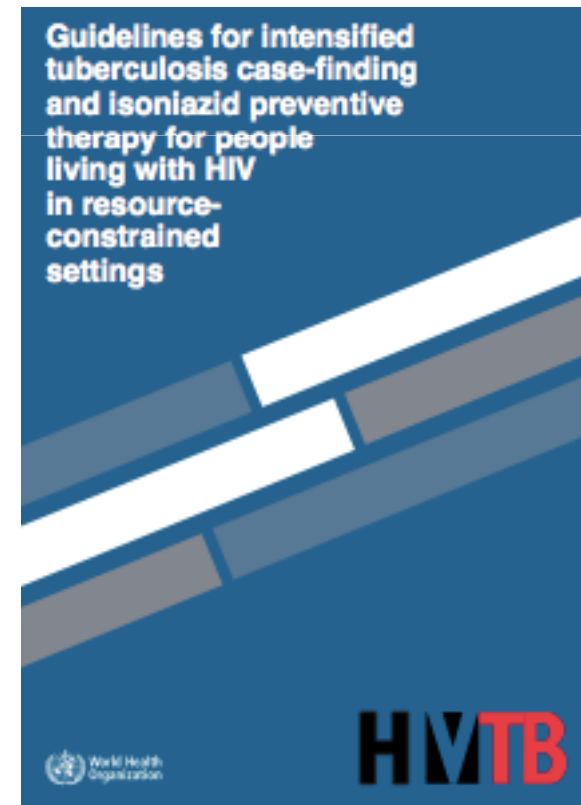
- IPT - all without active TB
- Intensified case-finding
- Infection Control

WHO THREE I's MEETING

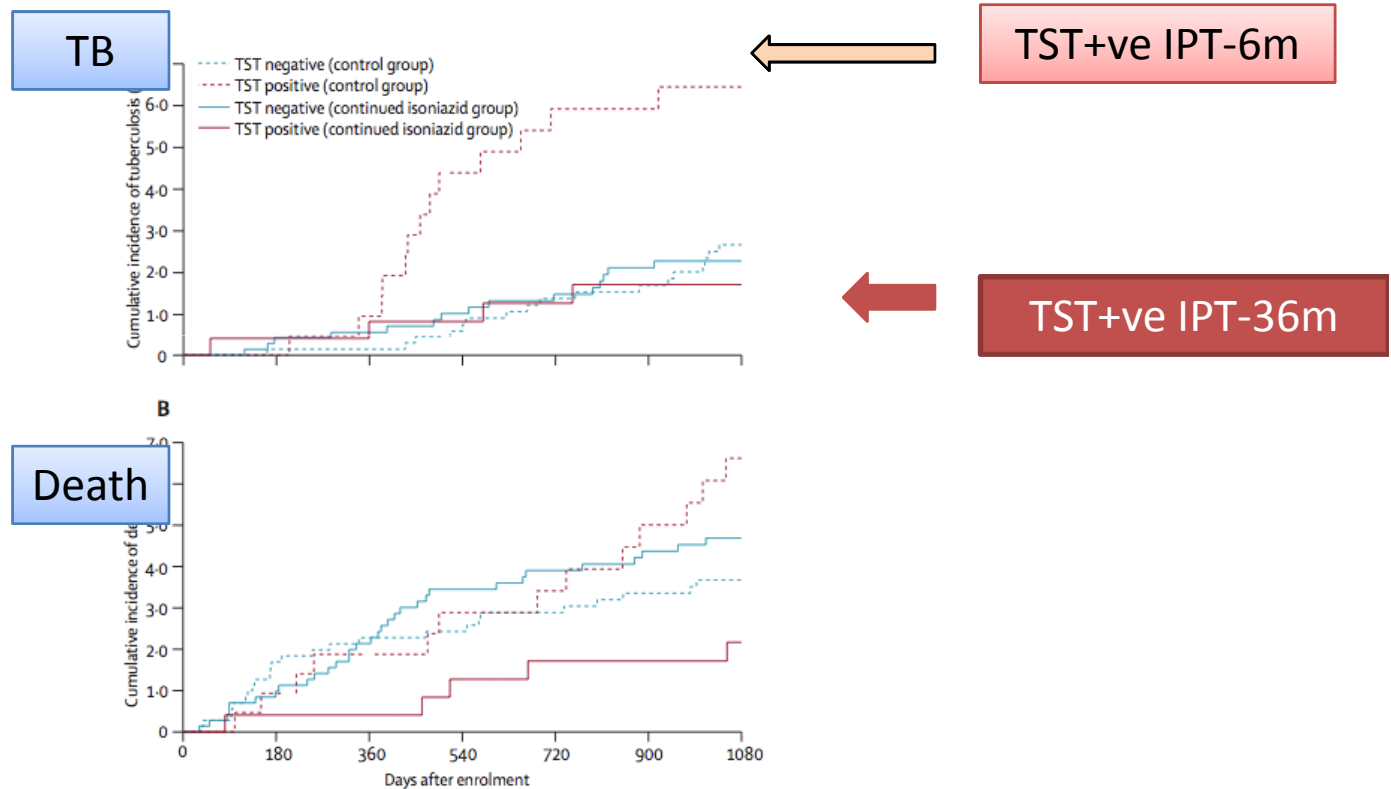
Intensified Case Finding (ICF), Isoniazid Preventive Therapy (IPT)
and TB Infection Control (IC) for people living with HIV

REPORT OF A JOINT WORLD HEALTH ORGANIZATION
HIV/AIDS AND TB DEPARTMENT MEETING

2-4 APRIL, 2008, GENEVA, SWITZERLAND



TB/death with IPT: 6m versus 36m in HIV+ adults, Botswana



| Number at risk | | | | | | |
|--|-----|-----|-----|-----|-----|-----|
| TST negative (control group) | 729 | 704 | 672 | 656 | 637 | 623 |
| TST positive (control group) | 216 | 214 | 206 | 192 | 185 | 180 |
| TST negative (continued isoniazid group) | 722 | 706 | 681 | 658 | 637 | 617 |
| TST positive (continued isoniazid group) | 252 | 246 | 237 | 231 | 226 | 222 |

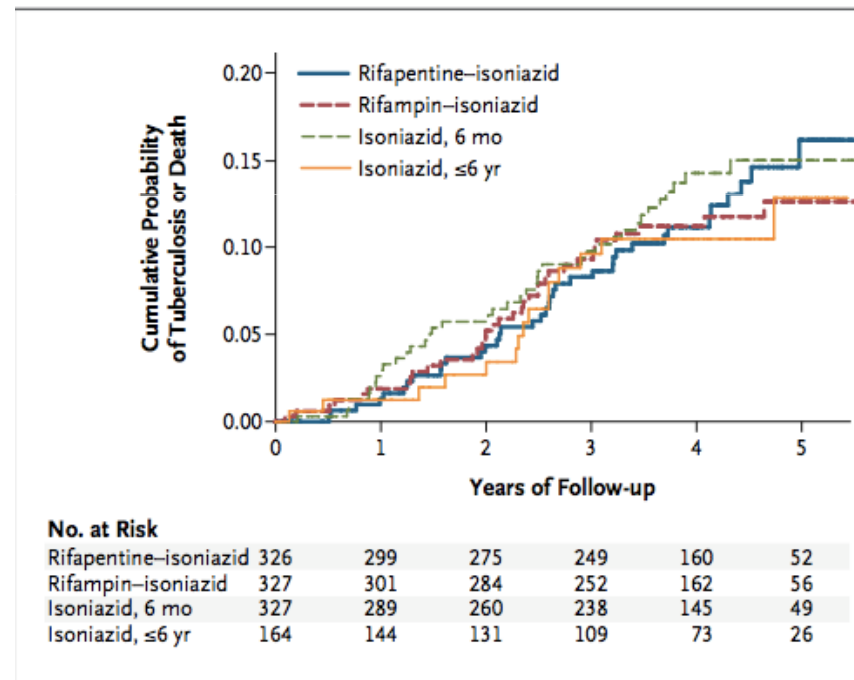
Samdari et al Lancet 2010; 377: 1588-98

But, benefit less obvious in multi-arm study from Soweto in HIV+ adults

Continuous IPT

- Increased
 - Toxicity
 - Temporary / Permanent discontinuation

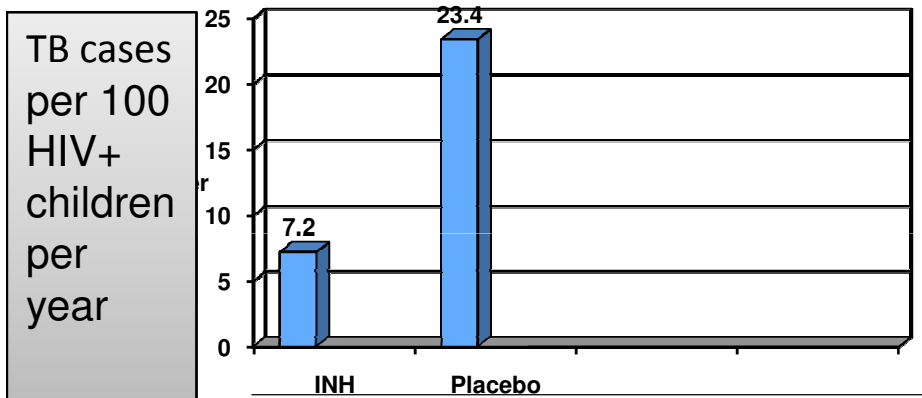
INH6m vs INH continuous vs INH/RMP3m vs INH/RFP3m



IPT for HIV+ infants & children without active TB?

Yes – Zar et al BMJ 2007; 334: 36-43
5/131 vs 13/132 cases

No – Madhi et al N Engl J Med 2011; 365: 21 - 31



Survival

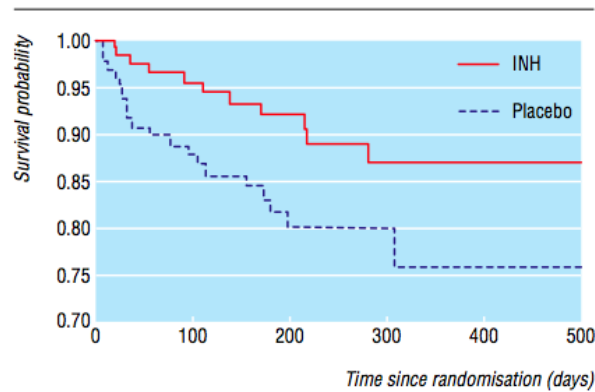
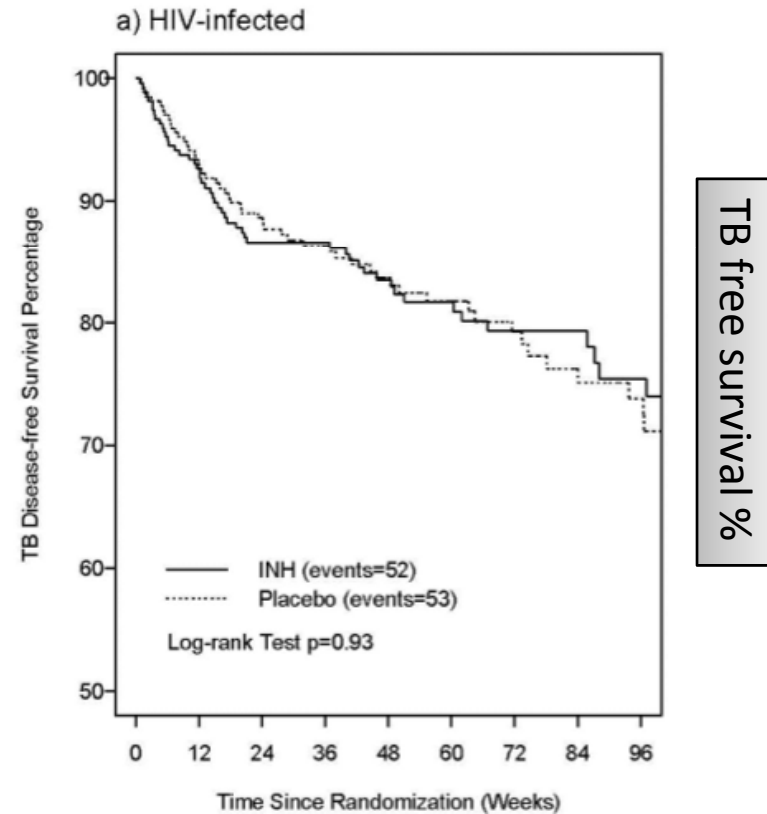


Fig 2 Survival in children on isoniazid (INH) or placebo



Comparisons for HIV+ children

| | Zar et al (Dec 2002 – April 2004) N = 263 | Madhi et al (Dec 2004 – June 2008) N = 547 |
|---------------------------------|---|--|
| Strategy | “All comers” | Pre-exposure prophylaxis |
| INH Dosage mg/kg/day | 10 | 15 - 20 |
| Exclusions | Known TB exposure requiring INH | Any current TB contact |
| ART | Unavailable | Available |
| At baseline (%) | 9 | 31 |
| During trial (%) | 22 | 98.9 |
| Baseline Characteristics | | |
| Median Age (m) | 24.7 | 3-4 |
| CDC N / A (%) | 12 | 90 |
| CD4% | 20 (14-28) | 28 (6-58) |
| <20 | 21.5% | 74% |
| WAZ | -1.6 (-2.5 – 0.4) | -0.58 (-4.3 - 3.1) |
| Prior TB treatment | 17% | None |
| TST +ve | 9% | N/A |

Differences in study conduct & outcome

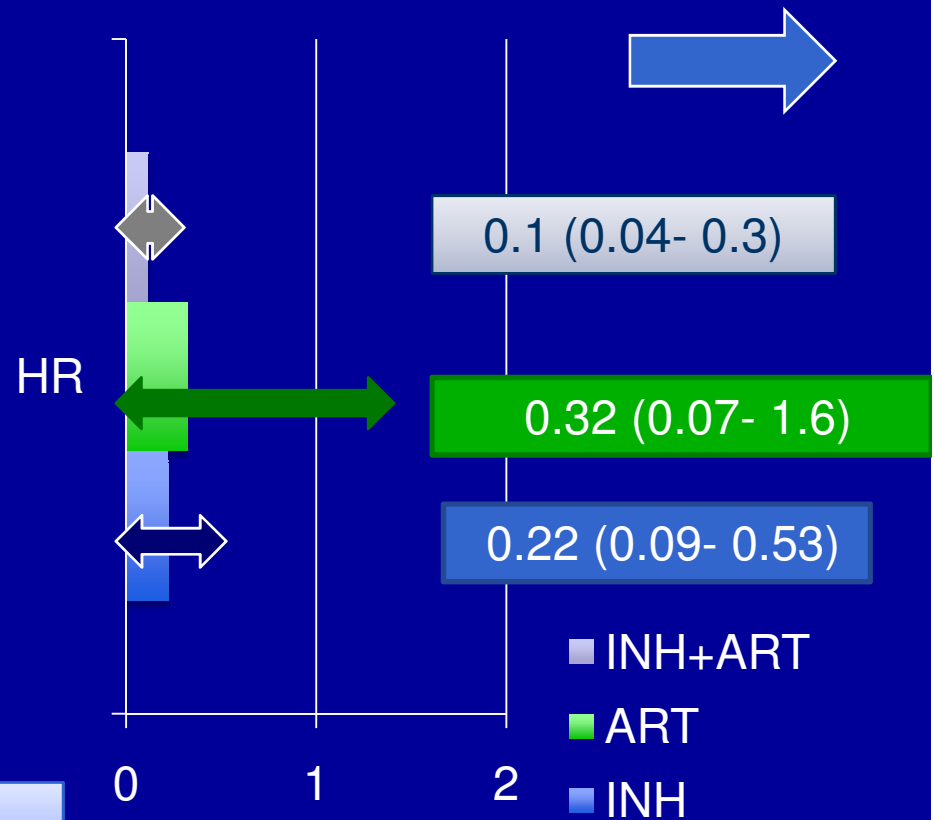
| | Zar et al | Madhi et al (HIV+) |
|-----------------------|---|--|
| Conduct | | |
| Recruitment | 44% recently hospitalized | Very rare |
| TB exposure on trial? | Open-label INH & resume | Open-label INH & Exit |
| TB diagnosis | Regular screening for contacts & TB disease sx, TST CXR Single expert (HS Schaaf) - blinded | Same CXR Algorithm & Endpoint review committee (blinded) |
| Outcome | | |
| Follow-up time (m) | 5.7 (2 – 9.7) | 18 (0.25 – 24) |
| Protocol-defined TB | 18/263 (7%) | 69/547 (12%) |
| TB incidence | Placebo: 23 per 100 children per year | 12.1 per 100 child years |

Continuation Zar study to Dec 2007 (495 person y / 5y)

Background

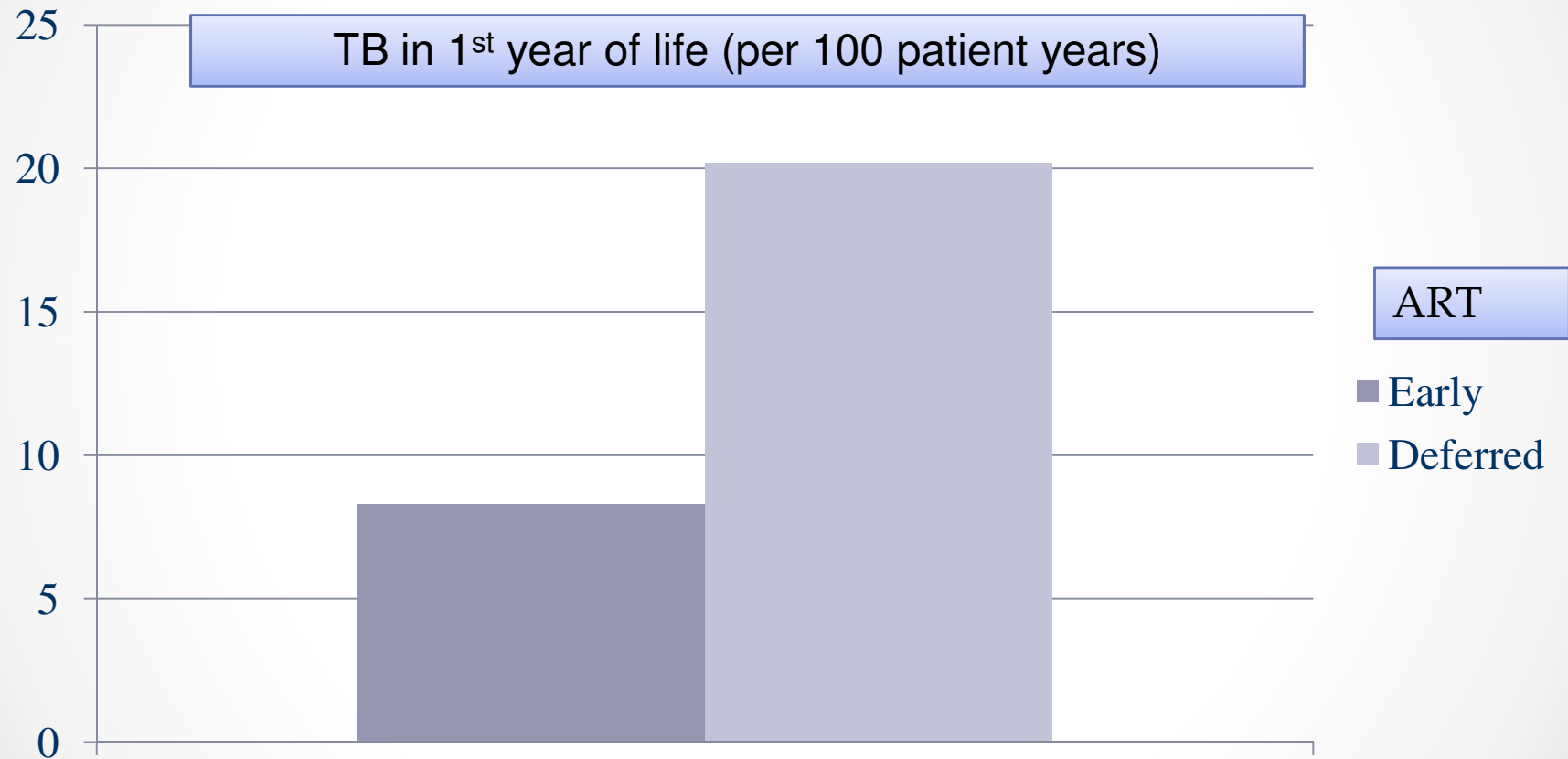
- Dec 2002: Study commenced
- May 2004: switch to open-label INH
- Majority started on ART
- Enrollment continued
- Adjusting for age, nutrition, ART, INH

HR for Reduction in TB incidence (95% CI)



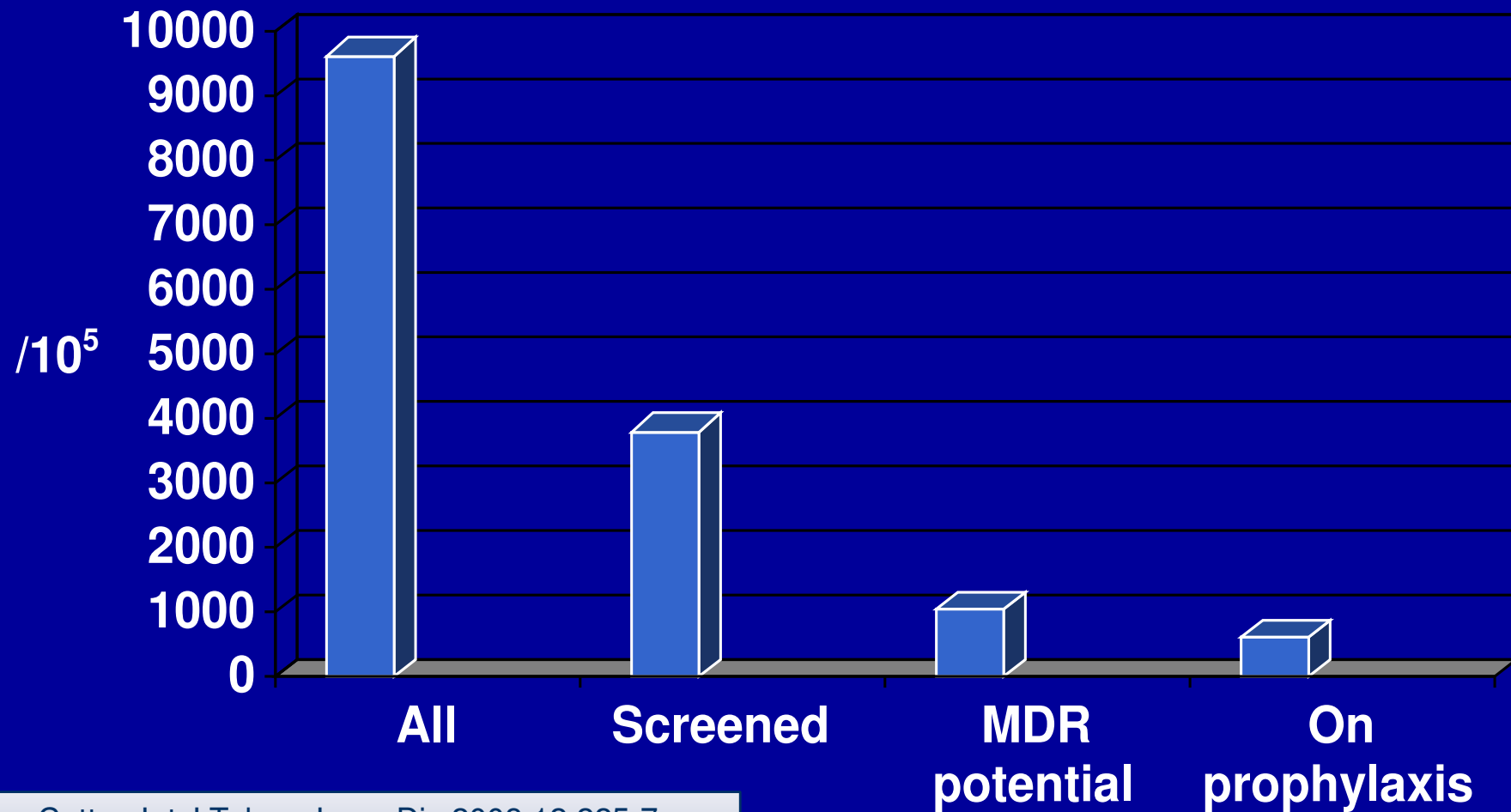
Frigati L et al Thorax 2011;

Impact of early ART on TB



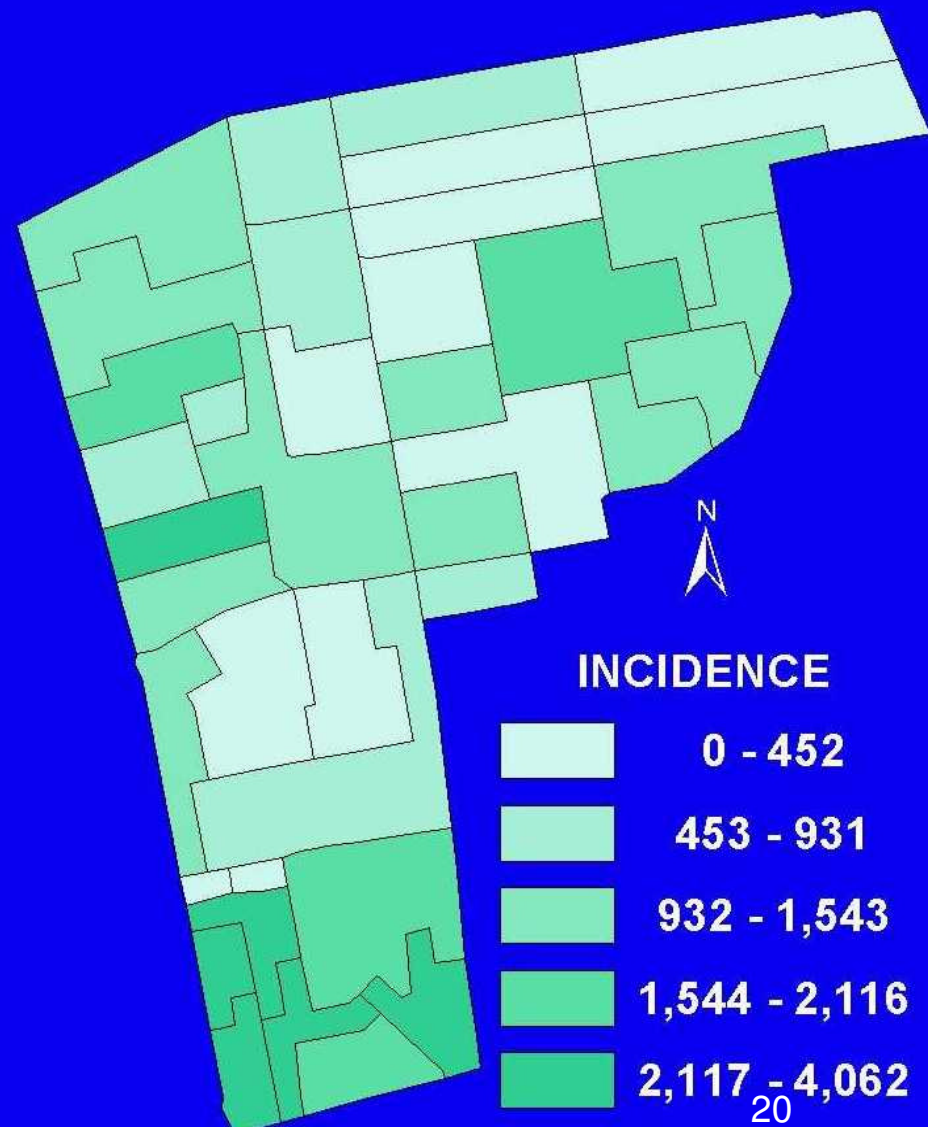
The CHER Trial: Violari et al. N Engl J Med 2008; 359: 2233-44

TB contact per 100 000 HIV-exposed infants 3-4 months of age, excluded from P1041



Cotton Int J Tuberc Lung Dis 2008;12:225-7

Beyers S Afr Med J 1996; 86: 40-1



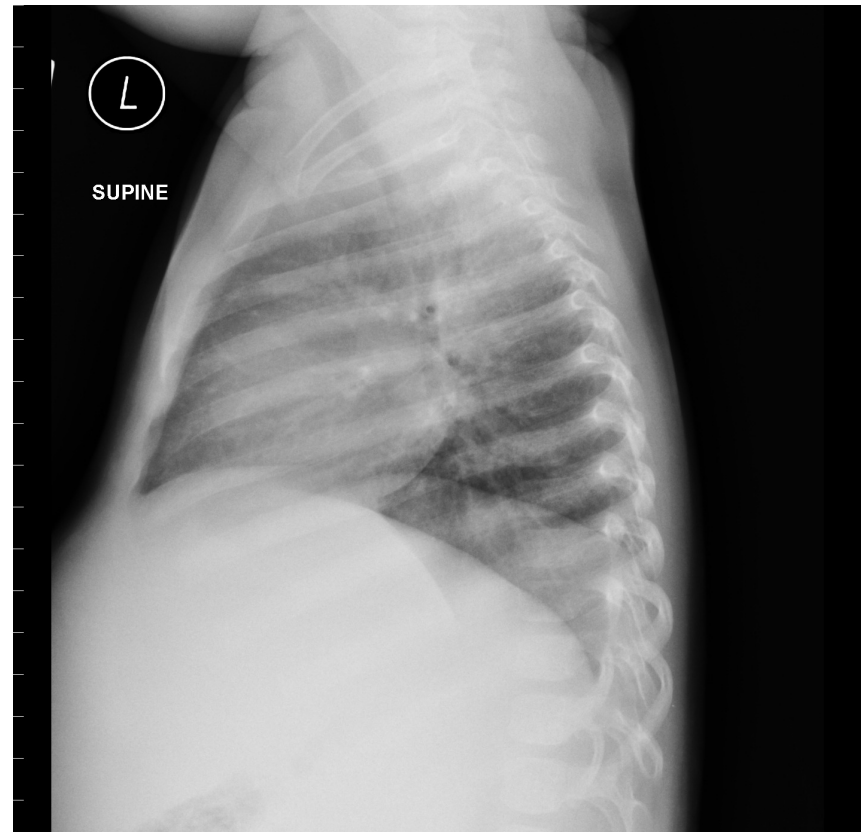
300 150 0 300 600 900 1,200 Meters

How easy is it to diagnose TB in HIV-infected young children?

Not very easy

- Often paucibacillary
- TST often –ve
- Culture yield 30 to 40% in the best circumstances

With delayed ART – 33% have abnormal CXR

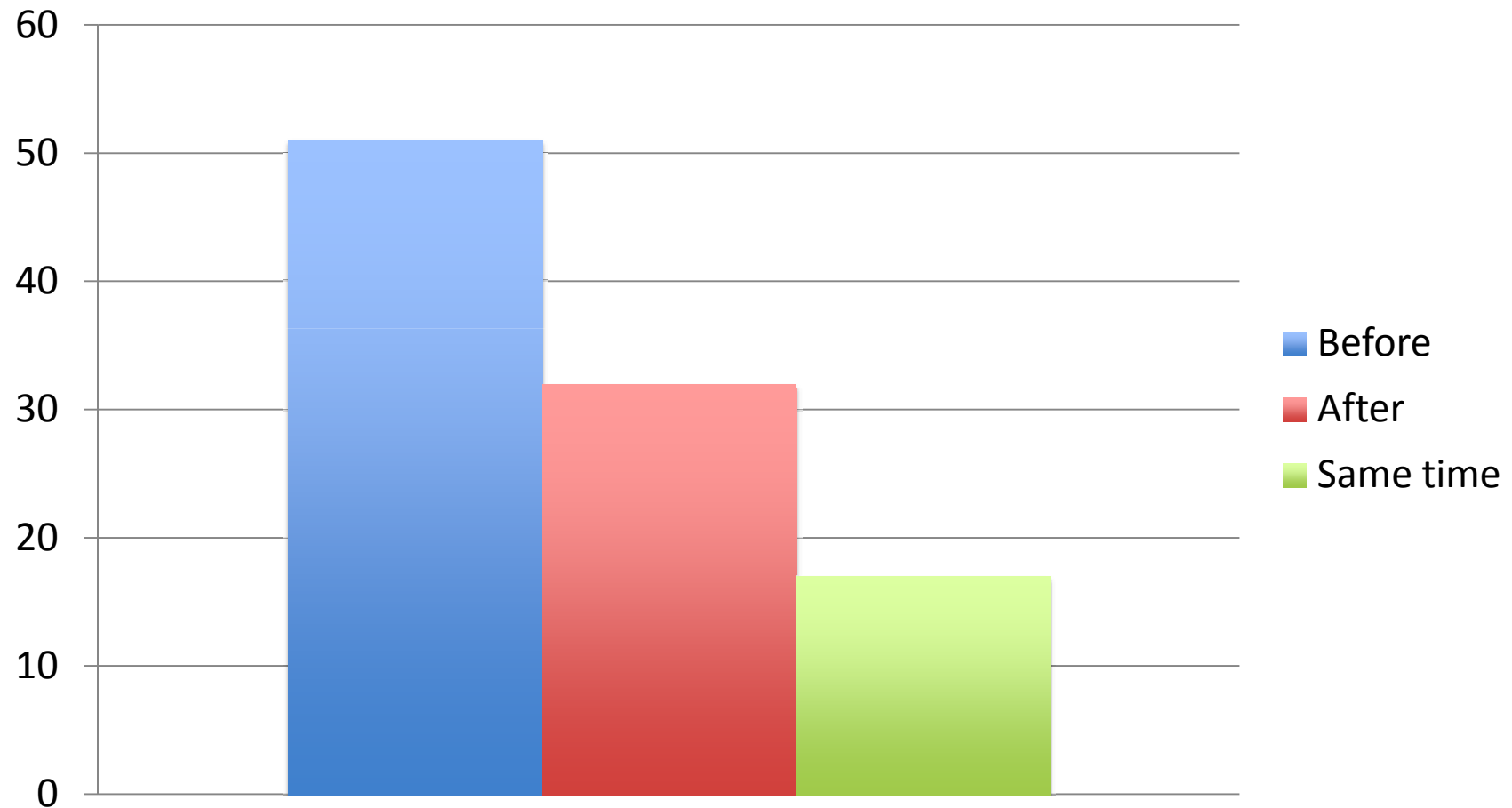


Norton. Am J Roent 2001; 176: 1553-8

Reasons why Zar IPT study showed effect?

- Higher prevalence of TB?
- INH may have treated paucibacillary TB? Mount et al N Engl J Med 1961; 265: 713-721
- Contact with source case often missed
 - 50% contacts not in the household
 - Household contacts not easily identified
 - Cotton et al. Int J Tuberc Lung Dis 2008; 12: 225-7
 - Maritz E – P1041 data Union mtng 2012

At what point is source case identified in children diagnosed with TB? (P1041)



Maritz E et al 43rd Union World Conference on Lung Health, Kuala Lumpur, 13 – 17 Nov 2012

Why & when should IPT be given to HIV+ children?

- TB contact tracing program not working well?
- TB disease cannot be excluded in early phase (despite trying)?
- Absence of early diagnosis of HIV and initiation of ART by 12 weeks of age
- Also, whenever source case is identified.

When should pre-exposure IPT *not* be given?

- Mother identified antenatally & screened for TB
- No TB contacts in house
- Early diagnosis & initiation of ART <12 weeks of age
- Regular follow-up and screening for TB?

Scale-up of IPT in RSA

INT J TUBERC LUNG DIS 16(8):1020–1022
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NOTES FROM THE FIELD

Scale-up of isoniazid preventive therapy in PEPFAR-assisted clinical sites in South Africa

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S U M M A R Y

We reviewed the implementation of isoniazid preventive therapy (IPT) in South Africa from January 2010 to March 2011. The South African National Department of Health distributed revised IPT guidelines in May 2010 to increase IPT use in eligible human immunodeficiency virus (HIV) infected patients. We found a dramatic in-

crease in the absolute numbers of patients reported to have been initiated on IPT (from 3309 in January–March 2010 to 49 130 in January–March 2011), representing an increase in the proportion (1.0–10.5%) of potentially eligible HIV-infected patients started on IPT.

KEY WORDS: IPT; tuberculosis; HIV; PEPFAR
