“Isoniazid preventive therapy for children: impact on mortality and incidence of tuberculosis?”

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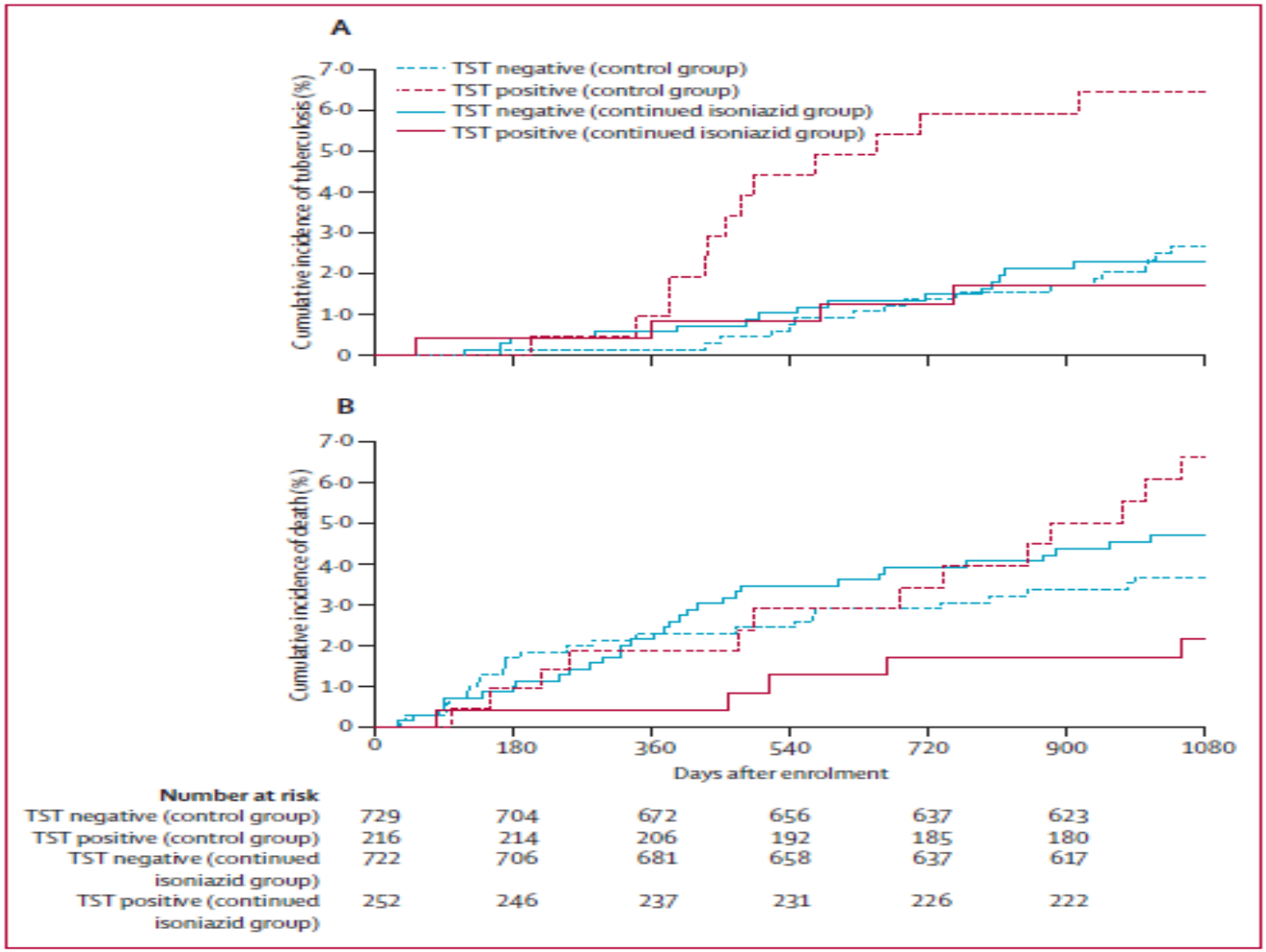
WHO Key Recommendations IPT (Adults)

- Adults and adolescents living with HIV should be screened for TB with a clinical algorithm and those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT.
  - *Strong recommendation, moderate quality of evidence1*
- Adults and adolescents living with HIV and screened with a clinical algorithm for TB, and who report any one of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases.
  - *Strong recommendation, moderate quality of evidence*
- **Adults and adolescents living with HIV who have an unknown or positive TST status and are unlikely to have active TB should receive at least 6 months of IPT as part of a comprehensive package of HIV care. IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women.**
  - *Strong recommendation, high quality of evidence*
- **Adults and adolescents living with HIV who have an unknown or positive TST status and who are unlikely to have active TB should receive at least 36 months of IPT. IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women.**
  - *Conditional recommendation, moderate quality of evidence*
- TST is not a requirement for initiating IPT in people living with HIV.
  - *Strong recommendation, moderate quality of evidence*
- People living with HIV who have a positive TST benefit more from IPT; TST can be used where feasible to identify such individuals.
  - *Strong recommendation, high quality of evidence*



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

***Figure 3*: Cumulative incidence of tuberculosis (A) and death (B) in participants receiving 6 months' open-label isoniazid and 30 months' masked placebo (control group) or isoniazid (continued isoniazid group), by TST status**

TST=tuberculin skin test.

WHO IPT (Adults) Supporting Evidence

Main Results

- **12 trials** [1.] were included with a total of **8578 randomized participants**. TB preventive therapy (any anti-TB drug) versus placebo was associated with a **lower incidence of active TB (RR 0.68, 95% CI 0.54 to 0.85).** This benefit was **more pronounced in individuals with a positive tuberculin skin test (RR 0.38, 95% CI 0.25 to 0.57) than in those who had a negative test (RR 0.89, 95% CI 0.64 to 1.24)**. Efficacy was similar for all regimens (regardless of drug type, frequency or duration of treatment). However, compared to INH monotherapy, short-course multi-drug regimens were much more likely to require discontinuation of treatment due to adverse effects.
- Although there was **reduction in mortality with INH monotherapy versus placebo among individuals with a positive tuberculin skin test (RR 0.74, 95% CI 0.55 to 1.00)** and with INH plus rifampicin versus placebo regardless of tuberculin skin test status (RR 0.69, 95% CI 0.50 to 0.95), overall, there was **no evidence that TB preventive therapy versus placebo reduced all-cause mortality (RR 0.94, 95% CI 0.85 to 1.05).**

WHO Key Recommendations IPT (Children)

- Children living with HIV who do not have poor weight gain, fever or current cough are unlikely to have active TB.
  - *Strong recommendation, low quality of evidence*
- Children living with HIV who have any one of the following symptoms – poor weight gain, fever, current cough or contact history with a TB case – may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, such children should be offered IPT regardless of their age.
  - *Strong recommendation, low quality of evidence*
- **Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening, and have no contact with a TB case should receive six months of IPT (10 mg/kg/ day) as part of a comprehensive package of HIV prevention and care services.**
  - *Strong recommendation, moderate quality of evidence*
- **In children living with HIV who are less than 12 months of age, only those children who have contact with a TB case and who are evaluated for TB (using investigations) should receive six months of IPT if the evaluation shows no TB disease**.
  - *Strong recommendation, low quality of evidence*
- **All children living with HIV who have successfully completed treatment for TB disease should receive INH for an additional six months.**
  - *Conditional recommendation, low quality of evidence*

WHO IPT (Children) Supporting Evidence

- Two studies were considered for the Grading of Recommendations Assessment, Development, and Evaluation(GRADE) criteria assessment of the evidence.

- One study(Zar et al, 2007; Frigati et al, 2011) suggested considerable benefits for children receiving INH, in particular, with regard to significant reductions in mortality.

- A randomized control trial(Madhi et al, 2011, IMPAACT P1041) conducted in South Africa showed that when HIV-infected infants with no known exposure to a TB source case are identified in the first three months of life, given rapid access to ART and carefully monitored for new TB exposure or disease on a monthly basis, there is no benefit from IPT.

Objectives To investigate the impact of INH prophylaxis on mortality and incidence of tuberculosis in children with HIV.

Design Two center prospective double blind placebo controlled trial.

Participants Children aged ≥ 8 weeks with HIV. **Age range: 9.1-51.6 mos**.

Interventions Isoniazid or placebo either daily or three times a week.

Setting Two tertiary healthcare centers in South Africa.

Main outcome measures Mortality, incidence of tuberculosis, and adverse events.

Results 263 children (**median age 24.7 months**) were available when the data safety monitoring board recommended discontinuing the placebo arm; 132 (50%) were taking isoniazid. **Median follow-up was 5.7 (interquartile range 2.0-9.7) months**. **Mortality was lower in the isoniazid group than in the placebo group (11 (8%) *v* 21 (16%), hazard ratio 0.46, 95% confidence interval 0.22 to 0.95, P = 0.015)** by intention to treat analysis. The benefit applied across Centers for Disease Control clinical categories and in all ages. The reduction in mortality was similar in children on three times a week or daily isoniazid. The **incidence of tuberculosis was lower in the isoniazid group (5 cases, 3.8%) than in the placebo group (13 cases, 9.9%) (hazard ratio 0.28, 0.10 to 0.78, P = 0.005). All cases of tuberculosis confirmed by culture were in children in the placebo group.**

Zar et al, BMJ, 2007,

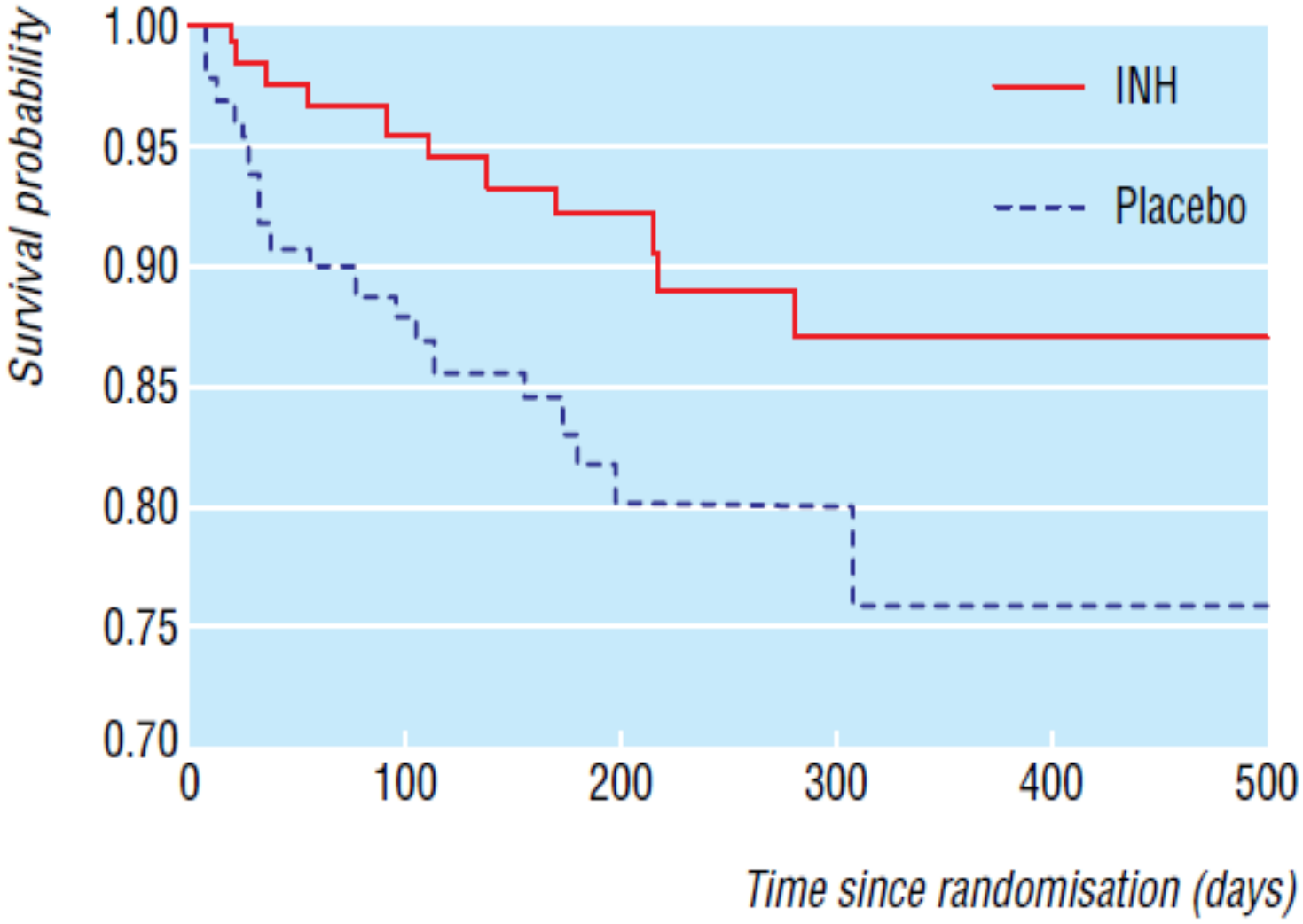


Fig 2 Survival in children on isoniazid (INH) or placebo

Table 3 Incidence of tuberculosis in children allocated to isoniazid prophylaxis or placebo

	Isoniazid n=132 (%)	Placebo n=131 (%)	Total n=263 (%)	HR (95% CI)
Intention to treat	5/132 (4)	13/131 (10)	18/263 (7)	0.28 (0.10 to 0.78)
Frequency of dose:				
Three times a week	3/68 (4)	5/71 (7)	8/139 (6)	0.45 (0.11 to 1.90)
Daily	2/64(3)	8/60(13)	10/124 (8)	0.16 (0.03 to 0.76)
Centers for Disease Control classification:				
A+N	0/14 (0)	1/18 (6)	1/32 (3)	No estimate
B	4/87 (5)	11/86 (13)	15/173 (9)	0.22 (0.07 to 0.70)
C	1/31 (3)	1/27 (4)	2/58 (3)	0.86 (0.05 to 13.8)
Age group (months):				
<12	0/35 (0)	0/42 (0)	0/77 (0)	No estimate
12-24	2/25 (8)	5/26 (19)	7/51 (14)	0.50 (0.10 to 2.60)
>24	3/72 (4)	8/63 (13)	11/135 (8)	0.26 (0.07 to 0.98)
Tuberculin skin test result (n=257):				
Positive	0/15 (0)	1/7 (14)	1/22 (5)	No estimate
Negative	5/113 (4)	12/122 (10)	17/235 (7)	0.32 (0.11 to 0.90)
Receiving HAART at enrolment:				
Yes	0/13 (0)	1/10 (10)	1/23 (4)	No estimate
No	5/119 (4)	12/121 (10)	17/240 (7)	0.31 (0.11 to 0.87)

HAART=highly active antiretroviral therapy.

Objective: To investigate the **combined effect of IPT and ART on TB** risk in children infected with HIV.

Methods: A cohort analysis was done within a prospective, double-blinded, placebo-controlled trial of isoniazid (INH) compared with placebo in children infected with HIV in Cape Town, South Africa, a high TB incidence setting. In May 2004 the placebo arm was terminated and all children were switched to INH. ART was not widely available at the start of the study, but children were started on ART following the establishment of the national ART program in 2004. Data were analyzed using Cox proportional hazard regression.

Results: After adjusting for age, nutritional status and immuno-deficiency at enrolment, **INH alone, ART alone and INH combined with ART reduced the risk of TB disease by 0.22 (95% CI 0.09 to 0.53), 0.32 (95% CI 0.07 to 1.55) and 0.11 (95% CI 0.04 to 0.32) respectively. INH reduced the risk of TB disease in children on ART by 0.23 (95% CI 0.05 to 1.00).**

Frigati et al, Thorax, 2011

Table 2 Effect of INH, ART and INH combined with ART on TB risk

	Univariable		Multivariable	
Variables	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Gender				
Male	1			
Female	1.01 (0.54 to 1.90)	0.970		
Age at follow-up				
0—2	1			
2—5	0.78 (0.37 to 1.66)	0.511	0.74 (0.33 to 1.55)	0.445
>5	0.68 (0.29 to 1.60)	0.384	0.79 (0.33 to 1.91)	0.603
WHO clinical stage at enrolment				
1 or 2	1			
3 or 4	1.52 (0.60 to 3.86)	0.390		
Immunodeficiency at enrolment				
Mild	1			
Advanced/severe	2.44 (0.73 to 8.09)	0.144	2.74 (0.78 to 9.68)	0.117
z-Score (height for age) at enrolment				
Mild	1			
Moderate/severe	1.80 (0.96 to 3.39)	0.068	1.84 (0.99 to 3.42)	0.055
z-Score (weight for age) at enrolment				
Mild	1			
Moderate/severe	1.00 (0.51 to 1.96)	0.098		
z-Score (weight for height) at enrolment				
Mild	1			
Moderate/severe	1.20 (0.40 to 3.57)	0.760		
History of TB disease				
No	1			
Yes	0.83 (0.38 to 1.80)	0.625		
Cotrimoxazole/INH				
Daily	1			
3 times a week	0.89 (0.48 to 1.67)	0.714		
Placebo	1			
ART	0.35 (0.07 to 1.63)	0.179	0.32 (0.07 to 1.55)	0.157
INH	0.24 (0.11 to 0.55)	0.001	0.22 (0.09 to 0.53)	0.001
INH and ART	0.14 (0.05 to 0.35)	<0.001	0.11 (0.04 to 0.32)	<00.01

ART, antiretroviral therapy; INH, isoniazid; TB, tuberculosis.

Background: We conducted a DBRPC trial of **pre-exposure isoniazid prophylaxis** against TB in HIV-infected children and uninfected children exposed to HIV during the perinatal period.

Methods: At **91 to 120 days of age, 548 HIV-infected and 804 HIV-uninfected infants were randomly assigned to isoniazid (10 to 20 mg per Kg/day) or matching placebo for 96 weeks.** All patients received bacille Calmette–Guerin (BCG) vaccination within 30 days after birth. Infants also received oral cotrimoxazole per World Health Organization (WHO) guidelines, and HIV-infected children had access to antiretroviral therapy. **The primary outcome measures were tuberculosis disease and death in HIV-infected children and latent tuberculosis infection, tuberculosis disease, and death in HIV-uninfected children within 96 to 108 weeks after randomization.**

Results: ART was initiated in 98.9% of HIV-infected children during the study. **Among HIV-infected children, protocol-defined tuberculosis or death occurred in 52 children (19.0%) in the isoniazid group and 53 (19.3%) in the placebo group (P = 0.93). Among HIV-uninfected children, there was no significant difference in the combined incidence of tuberculosis infection, tuberculosis disease, or death between the isoniazid group (39 children, 10%) and the placebo group (45 children, 11%; P = 0.44). The rate of tuberculosis was 121 cases per 1000 child-years (95% confidence interval [CI], 95 to 153) among HIV-infected children as compared with 41 per 1000 child-years (95% CI, 31 to 52) among HIV-uninfected children.** There were no significant differences in clinical or severe laboratory toxic effects between treatment groups.

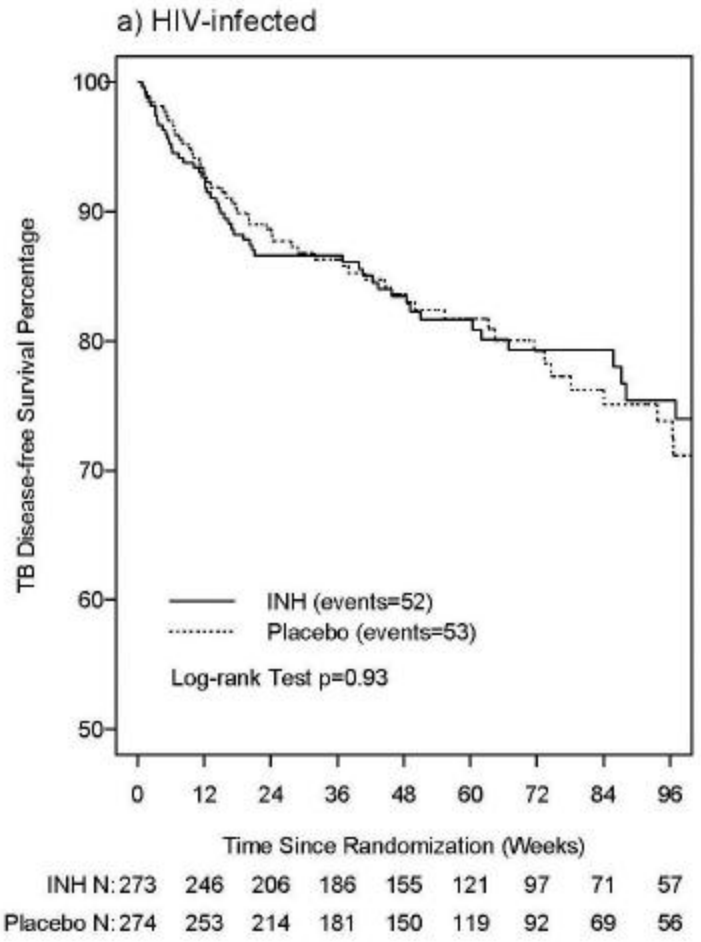
Conclusions: Primary isoniazid prophylaxis did not improve tuberculosis-disease–free survival among HIV-infected children or tuberculosis-infection–free survival among HIV-uninfected children immunized with BCG vaccine

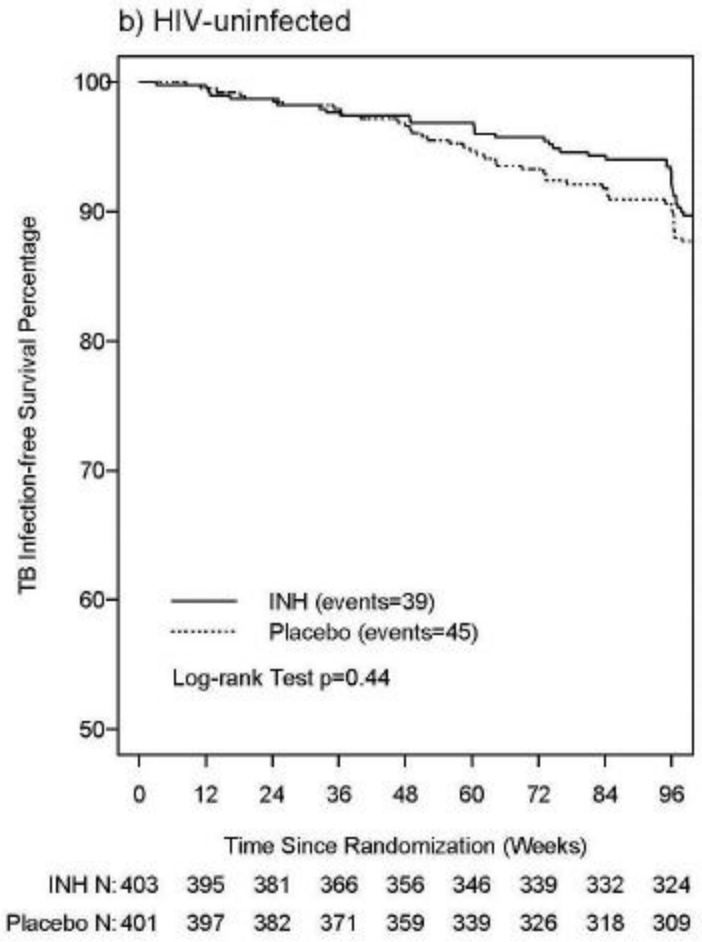
Madhi et al, NEJM, 2011

Table 4. Summary of First End Point Met toward Primary Outcome Measures in Children Randomly Assigned to Isoniazid or Placebo.*

End Point	HIV-Infected Children				HIV-Uninfected Children			
	Total (N=547)	Isoniazid Group (N=273)	Placebo Group (N=274)	P Value†	Total (N=804)	Isoniazid Group (N=403)	Placebo Group (N=401)	P Value†
		no. (%)				*no. (%)*		
Primary end point: tuberculosis disease or death	105 (19.2)	52 (19.0)	53 (19.3)	0.93‡	84 (10.4)	39 (9.7)	45 (11.2)	0.44
Specific end points								
Protocol-defined tuberculosis§	69 (12.6)	31 (11.4)	38 (13.9)	0.40	59 (7.3)	28 (6.9)	31 (7.7)	
Definite PTB	8 (1.5)	5 (1.8)	3 (1.1)		14 (1.7)	8 (2.0)	6 (1.5)	
Probable PTB	8 (1.5)	5 (1.8)	3 (1.1)		9 (1.1)	3 (0.7)	6 (1.5)	
Possible PTB¶	48 (8.8)	21 (7.7)	27 (9.9)		36 (4.5)	17 (4.2)	19 (4.7)	
Definite EPTB	3 (0.5)	0	3 (1.1)		0	0	0	
Probable EPTB and possible PTB	2 (0.4)	0	2 (0.7)		0	0	0	
Death without prior tuberculosis	36 (6.6)	21 (7.7)	15 (5.5)		4 (0.5)	2 (0.5)	2 (0.5)	
Latent tuberculosis‖					21 (2.6)	9 (2.2)	12 (3.0)	

* Percentages for specific outcomes may not add to the total percentages because of rounding.
† P values are for the log-rank test.
‡ P=0.85 in an analysis adjusted for status with respect to antiretroviral treatment at baseline and maternal history of tuberculosis.
§ Protocol-defined tuberculosis included any episode that fulfilled the protocol-specified criteria for possible, probable, or definite tuberculosis, as confirmed by the end-point review committee. EPTB denotes extrapulmonary tuberculosis, and PTB pulmonary tuberculosis.
¶ One HIV-infected participant with possible pulmonary tuberculosis later fulfilled the criteria for probable pulmonary tuberculosis.
‖ Latent tuberculosis was evaluated at 96 weeks of age by means of a tuberculin skin test (with an induration ≥10 mm in horizontal diameter considered to be reactive). The outcome was not evaluated for HIV-infected children because most children had not completed 96 weeks in the study when the study ended.


a) HIV-infected
TB Disease-free Survival Percentage
100
90
80
70
60
50
INH (events=52)
Placebo (events=53)
Log-rank Test p=0.93
0 12 24 36 48 60 72 84 96
Time Since Randomization (Weeks)
INH N: 273 246 206 186 155 121 97 71 57
Placebo N: 274 253 214 181 150 119 92 69 56


b) HIV-uninfected
TB Infection-free Survival Percentage
100
90
80
70
60
50
INH (events=39)
Placebo (events=45)
Log-rank Test p=0.44
0 12 24 36 48 60 72 84 96
Time Since Randomization (Weeks)
INH N: 403 395 381 366 356 346 339 332 324
Placebo N: 401 397 382 371 359 339 326 318 309

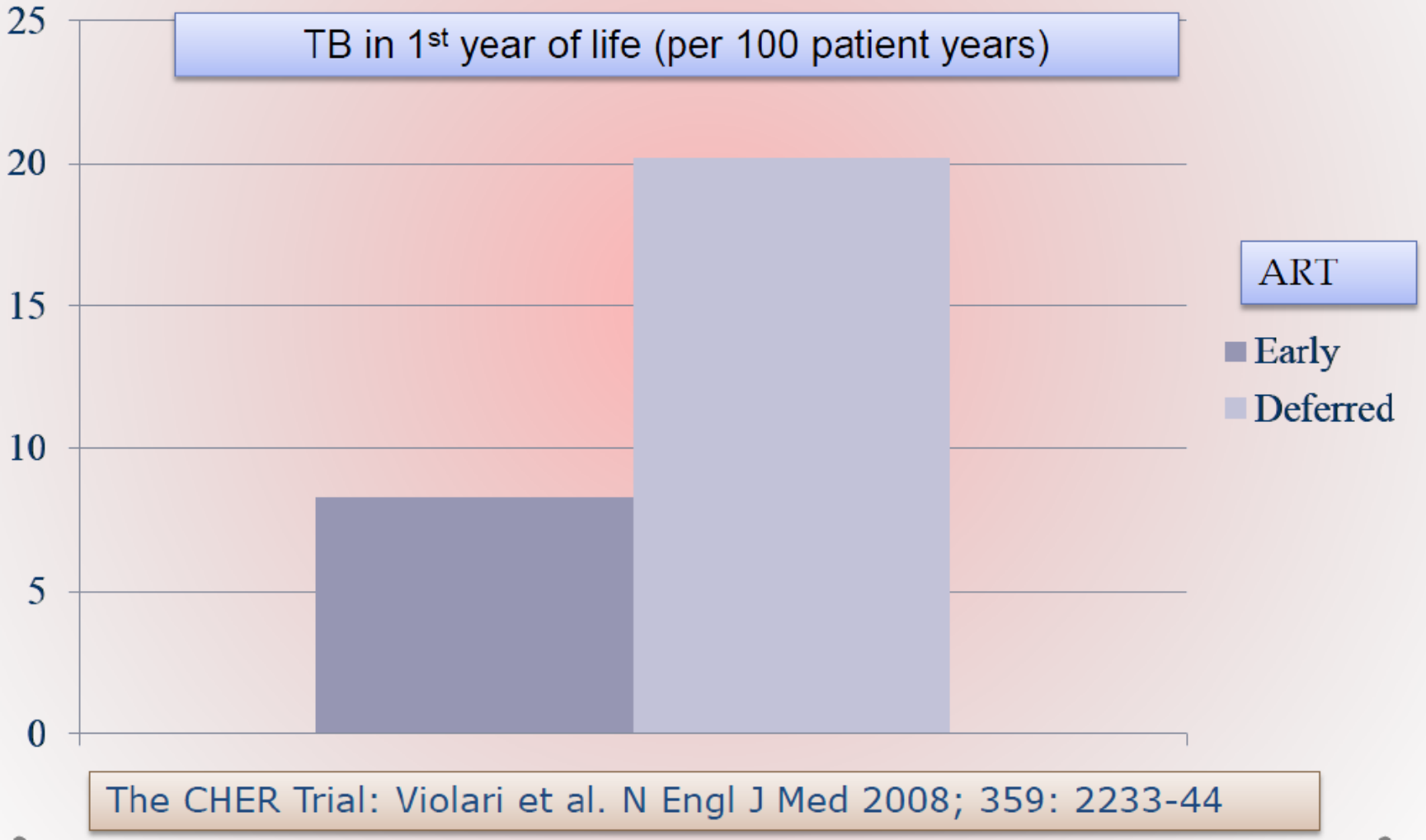
Comparisons

	Zar et al N = 263	Madhi et al (HIV+) N = 547
Strategy	"All comers"	Pre-exposure prophylaxis
Exclusions	Known TB exposure requiring INH	Any current TB contact
ART At baseline (%) During trial (%)	Not available 9 22	Available 31 98.9
Baseline Characteristics Median Age (m) CDC N / A (%) CD4% <20 WAZ Prior TB treatment	 24.7 12 20 (14-28) 21.5% -1.6 (-2.5 – 0.4) 17%	 3-4 90 28 (6-58) 74% -0.58 (-4.3 - 3.1) 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

Impact of early ART on TB



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

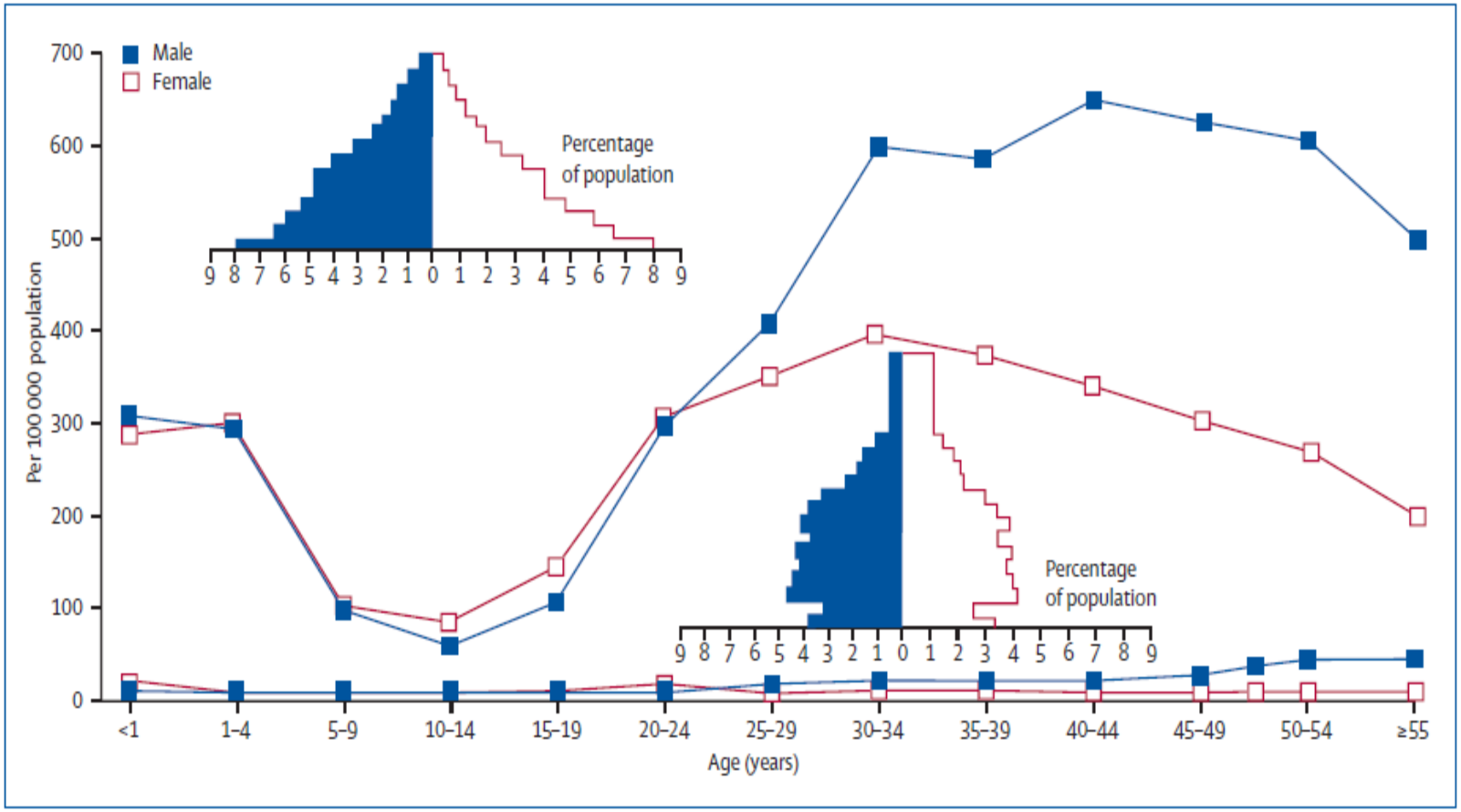


Figure: **Age-related and sex-related incidence of tuberculosis**

Hypothetical communities with high and low incidence of tuberculosis and with different population age structures. Apart from differences in disease frequency, adolescence is marked by sudden emergence of adult-type cavitary lung disease. Reproduced from reference 1.

Table 4 Average age specific risk for disease development following primary infection

Age at primary infection	Immune-competent children (dominant disease entity indicated in brackets)	Risk of disease following primary infection %
<1 year	No disease	50
	Pulmonary disease (Gnon focus, lymph node, or bronchial)	30–40
	TBM or miliary disease	10–20
1–2 years	No disease	70–80
	Pulmonary disease (Gnon focus, lymph node, or bronchial)	10–10
	TBM or miliary disease	2–5
2–5 years	No disease	95
	Pulmonary disease (lymph node, or bronchial)	5
	TBM or miliary disease	0.5
5–10 years	No disease	98
	Pulmonary disease (lymph node, bronchial, effusion or adult-type)	2
	TBM or miliary disease	<0.5
>10 years	No disease	80–90
	Pulmonary disease (effusion or adult-type)	10–20
	TBM or miliary disease	<0.5

TBM = tuberculous meningitis.

The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. B. J. Marais,* R. P. Gie,* H. S. Schaaf,* A. C. Hesseling,* C. C. Obihara,* J. J. Starke,† D. A. Enarson,P. R. Donald,* N. Beyers*; Int.J . Tub., 2004

Assumptions:

1. MTB infections in children under 24 months frequently progress to TB disease.

2. MTB infections in older children (>24 months) rarely progress to TB disease usually resulting in latent TB infection which may subsequently give rise to TB disease.

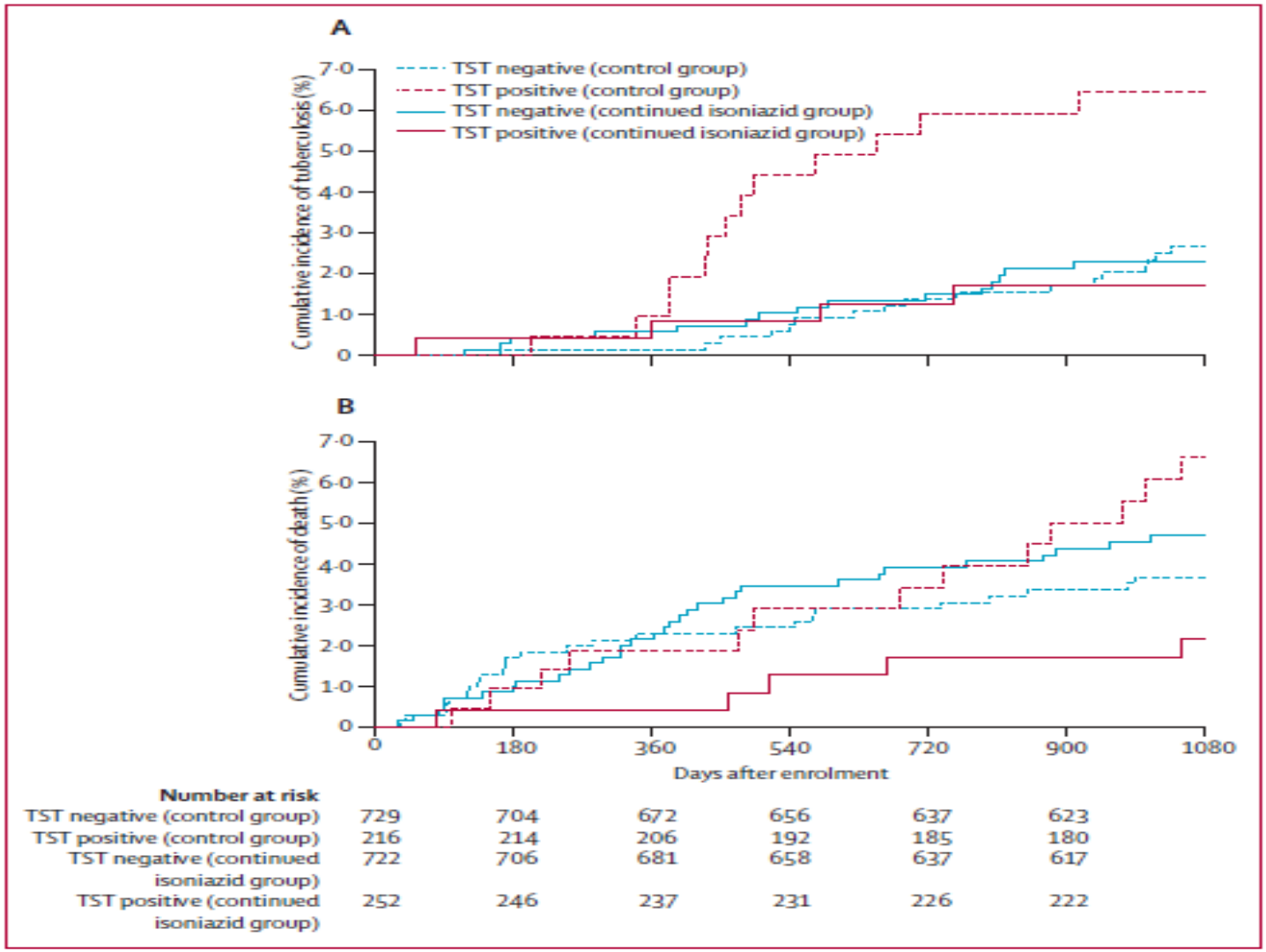
Rational for Discrepant results

Hypotheses:

1. Primary INH prophylaxis is not efficacious in preventing primary TB infection in young HIV-perinatally exposed infants(<12 months) in TB endemic regions .

2. Secondary INH prophylaxis (Treatment of LTBI) is efficacious in preventing TB disease in HIV infected children with latent TB infection over 24 months of age.

Rational for Discrepant results



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TST=tuberculin skin test.

Primary MTB Infection	Primary INH Pro-phylaxis	Age	Innate/ Adaptive Immunity	Intensity of Exposure	Misc. Factors
Frequent progression of infection to TB disease	Lack of Efficacy	<12 months	Immature; not able to contain spread of IC bacilli	High both in terms of pathogen burden and repetitive exposures	Relative resistance of IC bacilli to killing effects of INH.

Scenario 1: Primary MTB infection in a HIV perinatally exposed infant < 12 months in SA.

MTB Infection	Primary INH Pro-phylaxis	Age	Innate/ Adaptive Immunity	Intensity of Exposure	Misc. Factors
Majority of primary MTB infections progress to latent TB infection, TB disease rare	Unknown	>24 months	Innate and Adaptive IR maturing	Still High but decreasing after 4 year of age	Relative resistance of IC bacilli to killing effects of INH.

Scenario 2: Primary MTB infection in an older HIV perinatally exposed infant in SA.

LTBI	Secondary INH Pro-phylaxis (Treat-ment of LTBI)	Age	Innate/ Adaptive Immunity	Intensity of Exposure	Misc. Factors
Reactiva-tion secondary to EC release of IC bacilli	Efficacious	>24 months	Innate and Adaptive IR mature	Decreasing after 4 years of age	INH bacteriocid al against EC rapidly dividing bacilli.

Scenario 3: Secondary (reactivated) MTB disease in an older HIV perinatally exposed infant in SA.

1. Isoniazid is effective as secondary prophylaxis (treatment) in HIV infected adults and children with latent TB in TB endemic regions.
2. Isoniazid does not appear to be effective as primary prophylaxis against new TB disease/ infections in young, HIV-perinatally exposed infants in these same regions.
3. Is Isoniazid effective as primary prophylaxis for adults?

Conclusions

IMPAACT Network and the P1041 Study Team
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