The role of ART and IPT in TB prevention: Latest updates

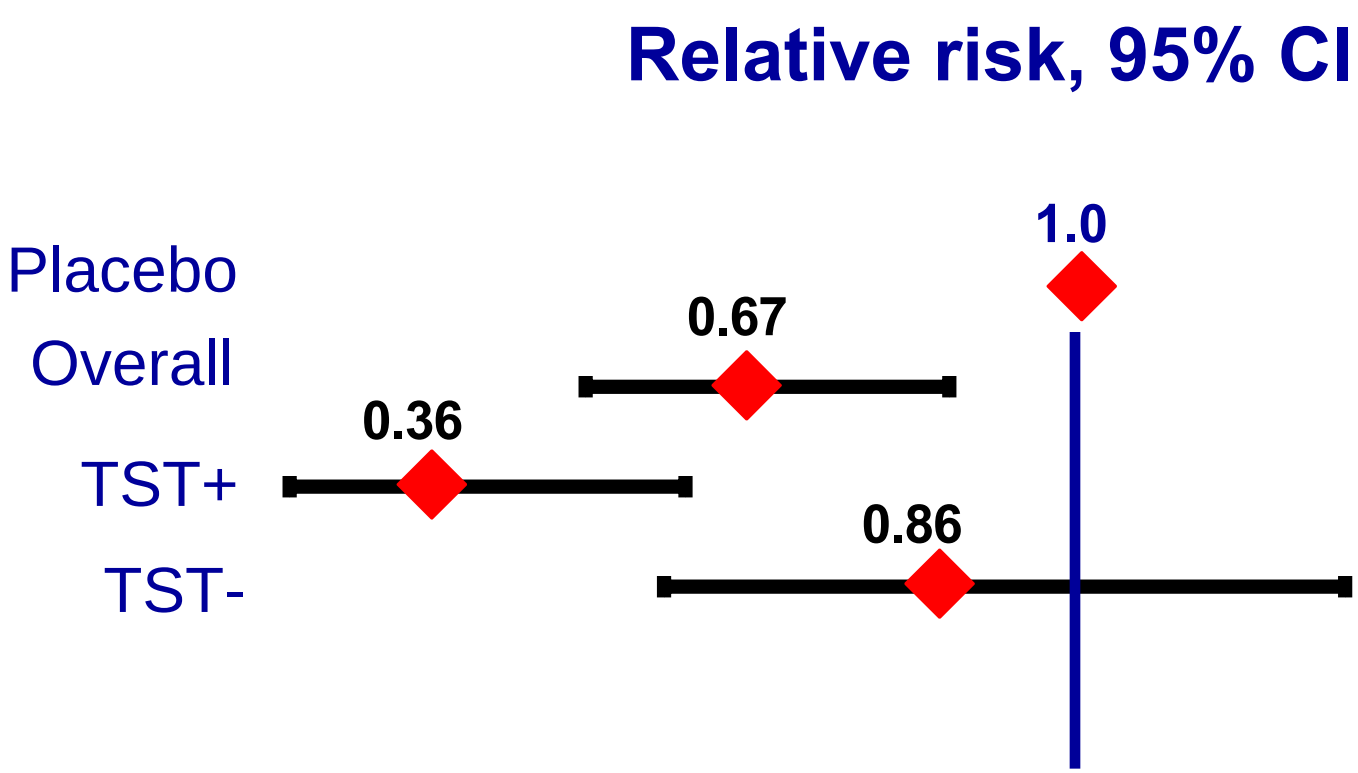
Richard E. Chaisson, MD

Center for Tuberculosis Research
Johns Hopkins University

Consortium to Respond Effectively
To the AIDS-TB Epidemic
(CREATE)

Effect of 6-12 months of IPT on TB:

meta-analysis of clinical HIV trials



Akolo 2010, Cochrane review

2010 WHO Guidelines for TB Preventive Therapy in HIV

- INH preventive therapy (IPT) should be given to all HIV+ patients in high burden areas once active TB is excluded
  - Includes pregnant women, children and those on ART
- TST (PPD) can be used to identify those most likely to benefit from IPT
- Duration of therapy – at least 6 months, 36 months may be more effective (US – 9 months)

Options for Improving Uptake of TB Preventive Therapy

- Strengthen national guidelines and promotion of INH preventive therapy
- New drugs and/or drug regimens
  - Shorter duration of treatment
  - Reduced risk of toxicity
  - Prevention of emergence of resistance
  - Treatment of latent MDR/XDR infections
- Novel treatment delivery strategies

The NEW ENGLAND JOURNAL of MEDICINE

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New Regimens to Prevent Tuberculosis in Adults with HIV Infection

Neil A. Martinson, M.B., B.Ch., M.P.H., Grace L. Barnes, B.S.N., M.P.H., Lawrence H. Moulton, Ph.D., Reginah Msandiwa, R.N., Harry Hausler, M.D., Ph.D., Malathi Ram, Ph.D., James A. McIntyre, M.B., B.Ch., Glenda E. Gray, M.B., B.Ch., and Richard E. Chaisson, M.D.

Project Site – Perinatal HIV Research Unit, Chris Hani Baragwanath Hospital, Soweto, South Africa

Novel Regimens for TB Preventive Therapy for HIV+ Adults with a Positive TST

Short (12 weeks)

- Rifapentine 900mg +INH 900mg weekly – **12 doses**
  - Directly observed in clinic
- Rifampin 600 mg+INH 600mg twice weekly – **24 doses**
  - directly observed, in clinic

Long (throughout duration of trial, up to 6 years)

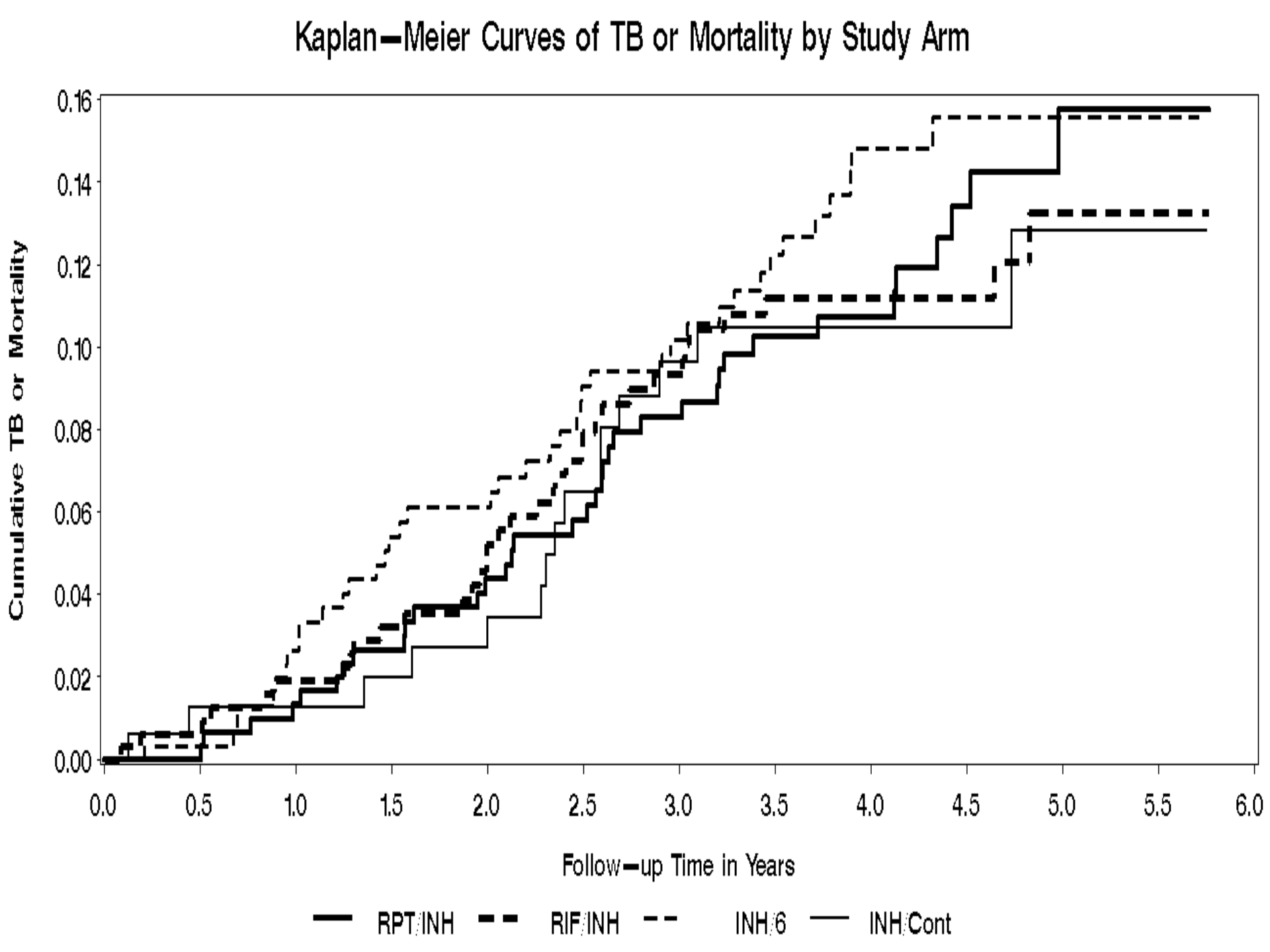
- INH 300mg daily continuously – may be effective to prevent re-infection

Comparator

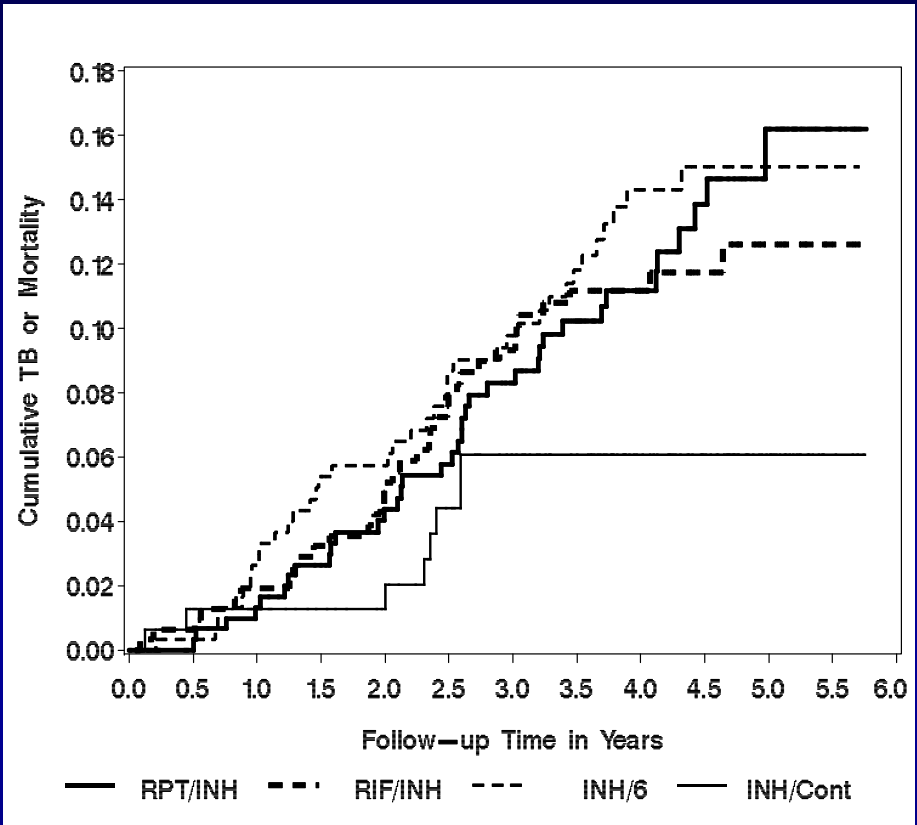
- INH 300mg daily for 6 months – standard of care

Primary Outcomes: Event Rates by Study Arm

Outcome	RPT/INH-3 (N=329)	RIF/INH-3 (N=329)	INH-cont (N=164)	INH-6 (N=328)
Median F/U (yrs)	3.98	3.99	3.81	3.78
TB or death	**3.03**	**2.87**	**2.67**	**3.53**
Rate ratio 95% CI	0.86 0.53-1.4	0.81 0.50-1.3	0.76 0.39-1.4	1 (ref)


Kaplan–Meier Curves of TB or Mortality by Study Arm
Cumulative TB or Mortality
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
Follow–up Time in Years
RPT INH
RIF INH
INH 6
INH Cont

“As treated” analysis – risk of TB or death



Variable		Hazard Ratio	95% CI	P
INH-6	Events: 40	1(ref)		
RPT/INH	Events: 36	0.85	0.54, 1.3	0.48
RIF/INH	Events: 35	0.81	0.52, 1.3	0.37
INH-Cont	Events: 5	0.32	0.12, 0.80	0.015

Resistance Testing of Isolates

Arm	Resistance Testing (N)	MDR (N)	Resistant to			
			INH (N)	R (N)	Strept. (N)	E (N)
RPT/INH-3	20/23	1	2	2	1	1
RIF/INH-3	16/24	0	0	0	0	0
INH-6	14/19	0	0	0	0	0
INH/Cont	7/7	1	1	1	1	0
Total	57/73 (78%)	2	3	3	2	1

- No evidence for selection of resistant strains

Conclusions

- Short courses of RPT/INH or RIF/INH are not superior but appear to be as effective as INH for 6 months
- Lifelong INH is more effective when taken, but non-adherence limits benefit
- All regimens were well tolerated
- There was no evidence of selection for resistance

The Prevent TB Study
TB Trials Consortium Study 26

3 months of once-weekly rifapentine plus INH vs. 9 months of daily INH for treatment of latent TB infection: Results of a multi-center, randomized clinical trial

TR Sterling, ME Villarino, AS Borisov, N Shang, E Bliven-Sizemore, F Gordin, A Kerrigan, M Conde, D Menzies, N Scott, J Hackman, CD Hamilton, CR Horsburgh, RE Chaisson and the TB Trials Consortium

Funded by the Centers for Disease Control and Prevention

Clinical and Demographic Characteristics

MITT Population

Characteristic	9H N=3,745	3HP N=3,986
Indication for TLI		
Close contact	2,609 (70)	2,857 (72)
Recent TST converter	972 (26)	953 (24)
HIV-infected	74 (2)	87 (2)
Fibrosis on CXR	90 (2)	89 (2)
Co-morbid liver disease		
HCV	97 (3)	99 (3)
HBV	60 (2)	42 (1)

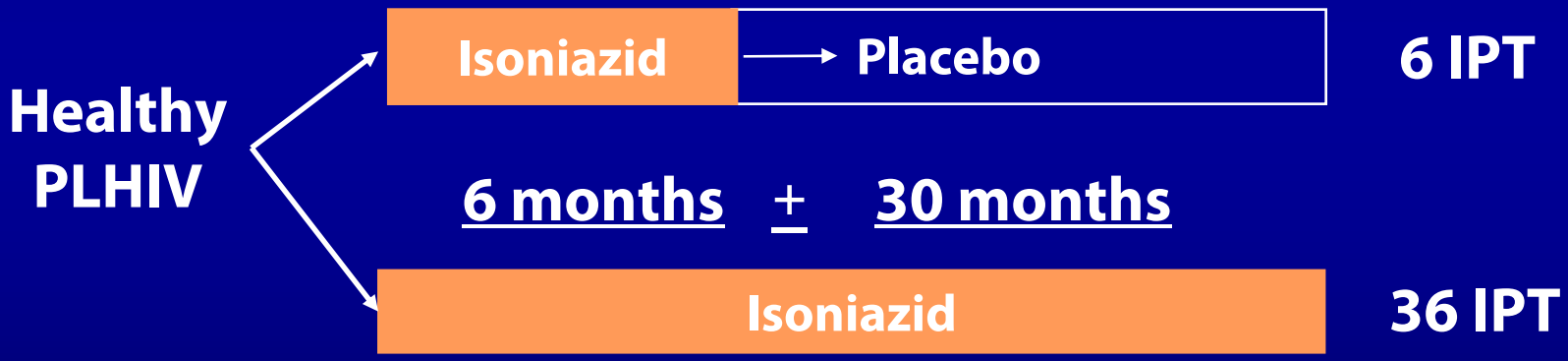
Sterling et al., ATS 2011

Conclusions

- **The effectiveness of 3RPT/INH is non-inferior to 9INH**
  - 97.5% CI of difference = 0.01%; margin = 0.75%
  - There is a suggestion that the 3RPT/INH TB rate (0.19%) is lower than 9INH (0.43%)
- **The completion rate of 3RPT/INH (81.9%) is significantly higher than 9INH (69.5%)**

Botswana IPT Trial 2004–2009

- Randomized, double-blind, placebo-controlled trial
- Approximately 2,000 patients enrolled
- TST+ and TST- patients included
- ART provided as needed through national program
  - When CD4 <200 cells/µL



Samandari et al., Lancet, April 11, 2011

Efficacy of 36 Months IPT vs 6 Months IPT for reducing TB incidence

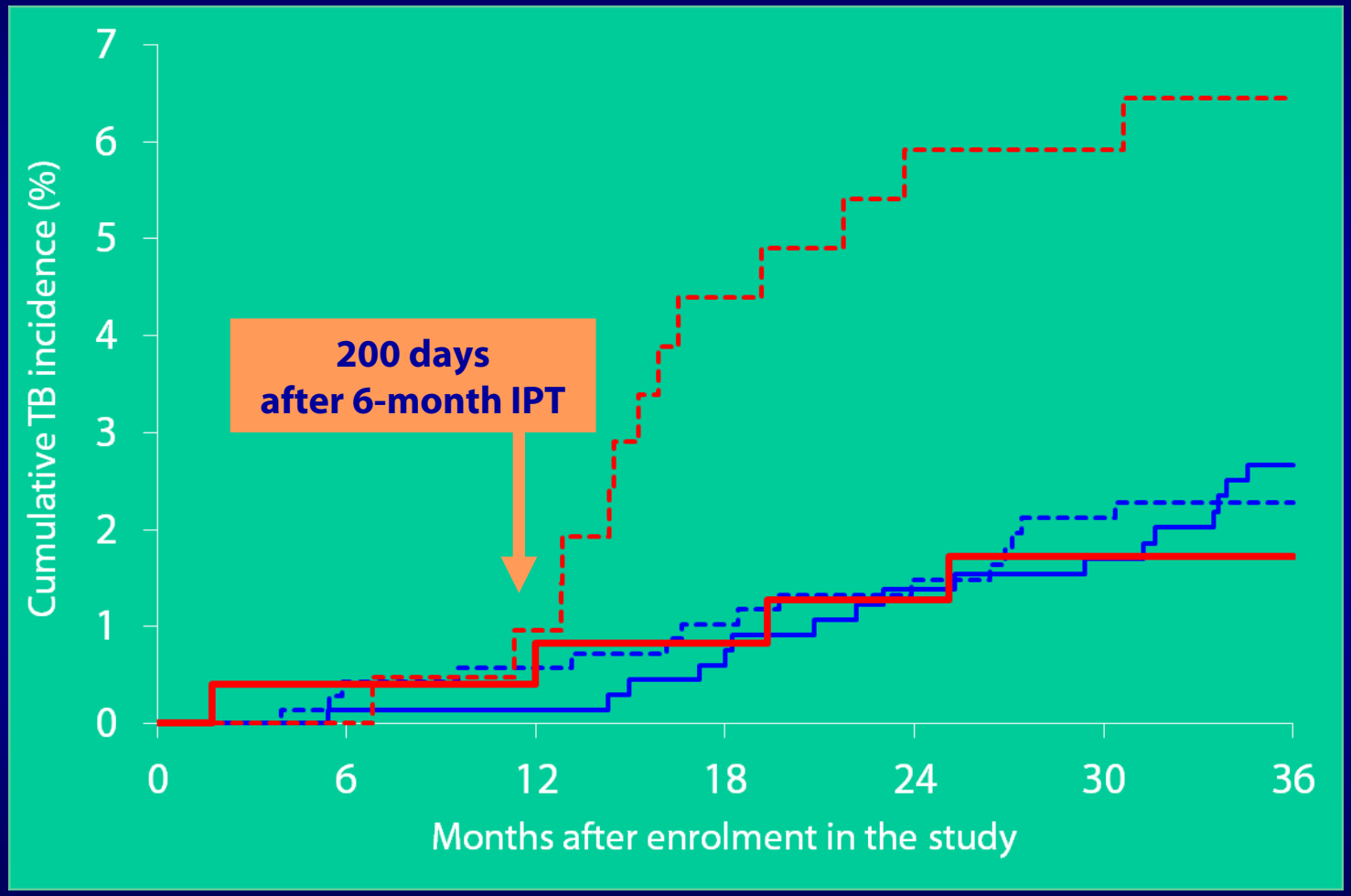
	Sub-group	TB rate 36 IPT	TB rate 6 IPT	Hazard ratio (95% CI)
MITT (N=1,995)	All	0.72	1.26	0.57 (0.33-0.99)*
	TST+	0.57	2.22	0.26 (0.09-0.80)*
	TST-	0.76	1.01	0.75 (0.38-1.46)

TB incidence rate per 100 person-years; * *P*<0.05

ART reduced the risk of TB additively by 50%
in both arms and was independent of IPT's protective effect

Samandari et al., Lancet, April 11, 2011

Continuous IPT for 36 Months Prevents TB Better than IPT for 6 Months in TST-positive PLHIV



Samandari et al., Lancet, April 11, 2011

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ORIGINAL ARTICLE

Primary Isoniazid Prophylaxis against Tuberculosis in HIV-Exposed Children

Shabir A. Madhi, M.D., Ph.D., Sharon Nachman, M.D., Avy Violari, M.D., Soyeon Kim, Sc.D., Mark F. Cotton, M.D., Ph.D., Raziya Bobat, M.D., Patrick Jean-Philippe, M.D., George McSherry, M.D, and Charles Mitchell, M.D., for the P1041 Study Team

Pediatric INH Primary Preventive Therapy Study

- HIV+ and HIV- South African children
  - 91-120 days old
- Vaccinated with BCG at birth
- Access to HAART for HIV+
- INH 10-20 mg/kg or placebo
- Open-label INH if household TB exposure
- Followed for 96-108 weeks

TB or death during follow up

- HIV+
  - INH group – 19.0%
  - Placebo group – 19.3%
  - Overall TB incidence = 12.1 per 100 PY
- HIV-
  - INH group – 10%
  - Placebo group – 11%
  - Overall TB incidence = 4.1 per 100 PY

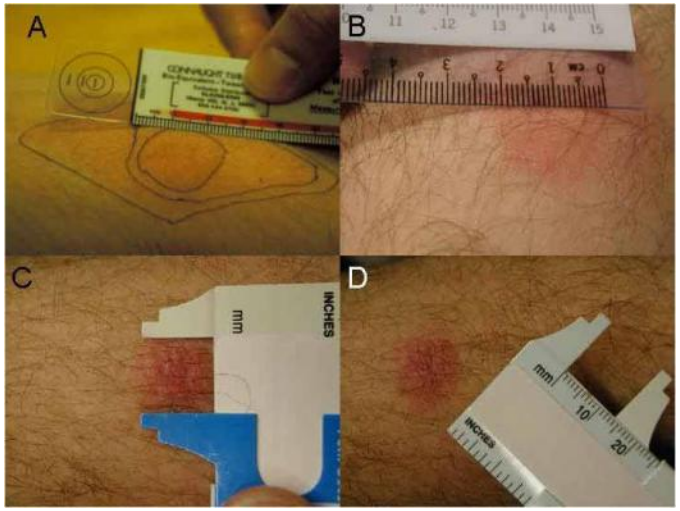
Madhi et al., N Engl J Med 2011;365:21-31

The TB/HIV in Rio Study: A Clinic-Randomized Trial of INH Preventive Therapy in HIV+ Patients

Betina Durovni, Jonathan Golub, Lawrence Moulton, Valeria Saraceni, Richard Chaisson

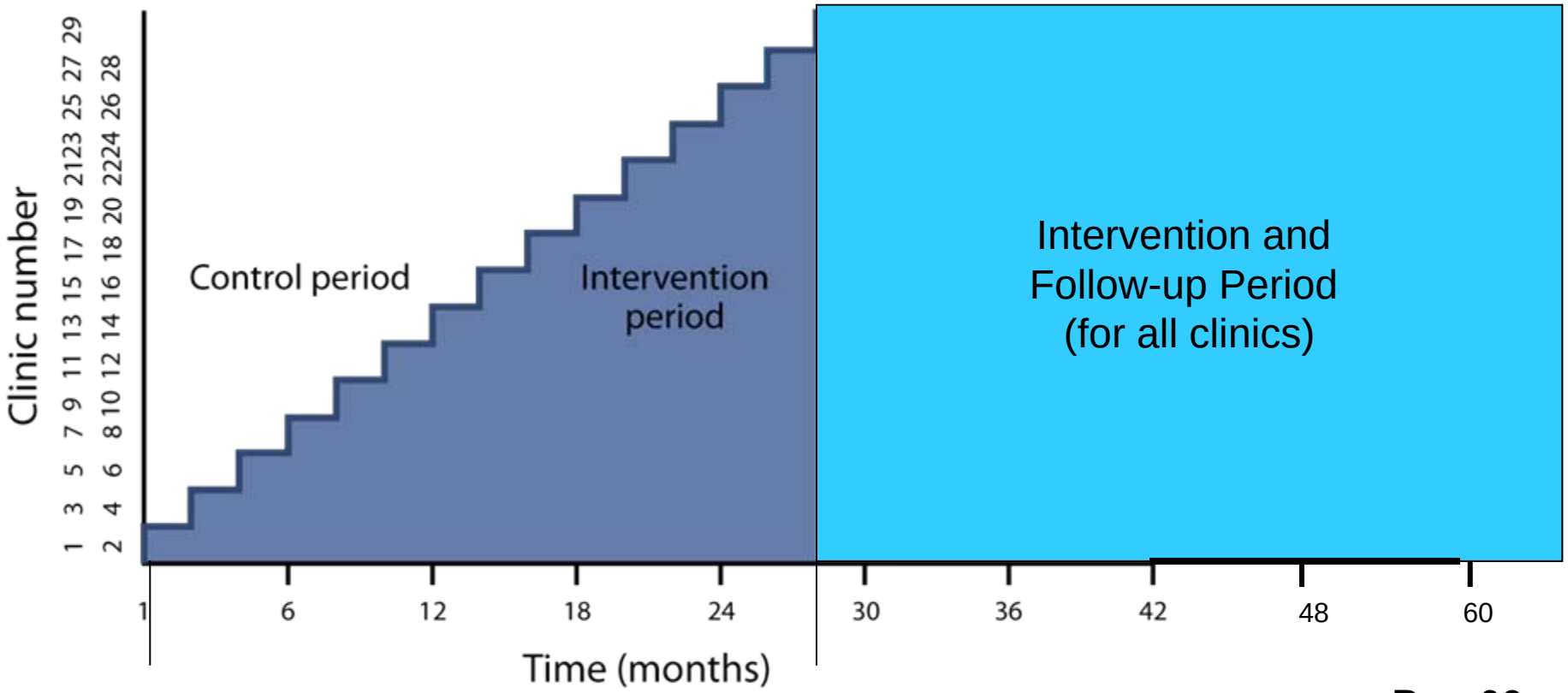
Intervention

- Training for 2 clinics every other month
- Implementation of TB screening and TST policy for all HIV-infected patients
- TST to be done for all eligible clinic patients
  - No prior TB history
  - No prior IPT
  - No prior +TST



- IPT x 6 months for all TST+ without active TB and all contacts of active TB cases

THRio Study Timeline
Stepped-Wedge Design



THRio TB/HIV NO RIO

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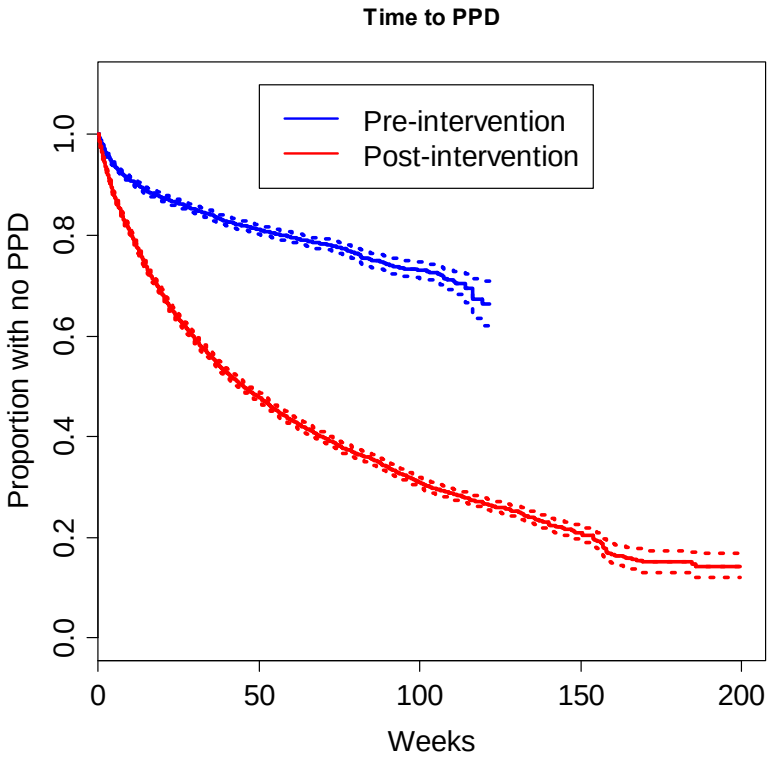
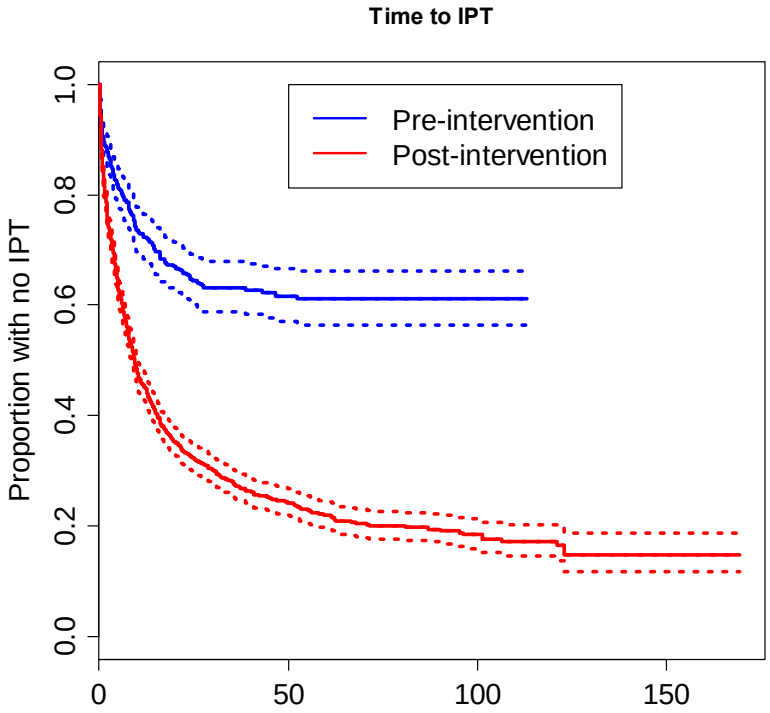
Time to TST and Time to IPT Before and After THRio Intervention

- Time to TST and time to IPT are both markedly improved post-intervention





Durovni et al., AIDS 2010, 24 (suppl 5):S49–S56

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THRio Results: Unadjusted Cox Models

	Outcome	Cases	HR (95% CI)	p-value
Intent To Treat	TB	475	0.87 (0.68-1.10)	0.233
	TB or Death	1313	0.72 (0.62-0.82)	<0.001
Modified Intent To Treat (Stayers)	TB	403	0.57 (0.44-0.76)	<0.001
	TB or Death	1073	0.56 (0.47-0.66)	<0.001

- Intent-to-treat – Among all eligibles
- Stayers – mITT - Among those remaining in clinic contact
  (Patients censored at the moment they go one year without a clinic contact)

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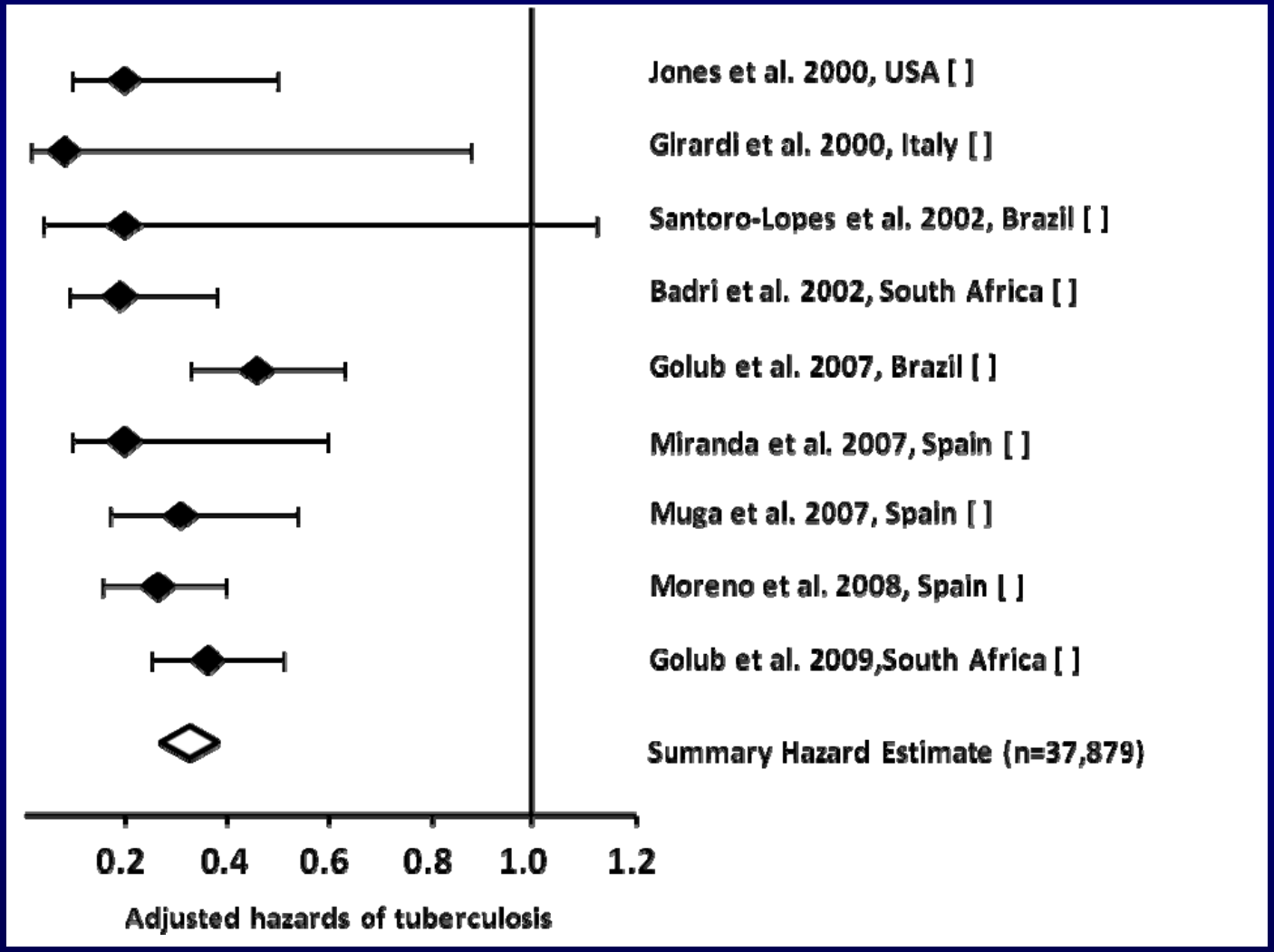
Impact of ART on Risk of TB in Patients with HIV



Lawn et al., Int J Tbc Lung Dis 2011

Impact of early ART on rates of TB in HIV+ adults with initial CD4 counts between 350 and 550 HPTN 052 Trial

Study Arm	TB Events
Early ART	
Pulmonary	14
Extrapulmonary	3
All TB	17/886 (1.9%)
Delayed ART	
Pulmonary	16
Extrapulmonary	17
All TB	33/877 (3.7%)*

***P= 0.03**

Cohen et al., N Engl J Med 2011;on line supplement

General Observations and Conclusions

- TB preventive therapy in high risk adults works and is necessary for TB control
- Short-course, rifapentine-based regimens are effective and well-tolerated
- Long-term INH is more efficacious but may be no more effective than short-course therapy in HIV-infected adults in Africa
- Population-based approaches are promising but challenging
- ART and IPT have additive effects in reducing the risk of TB

Thank you