New horizons in treating latent TB infection

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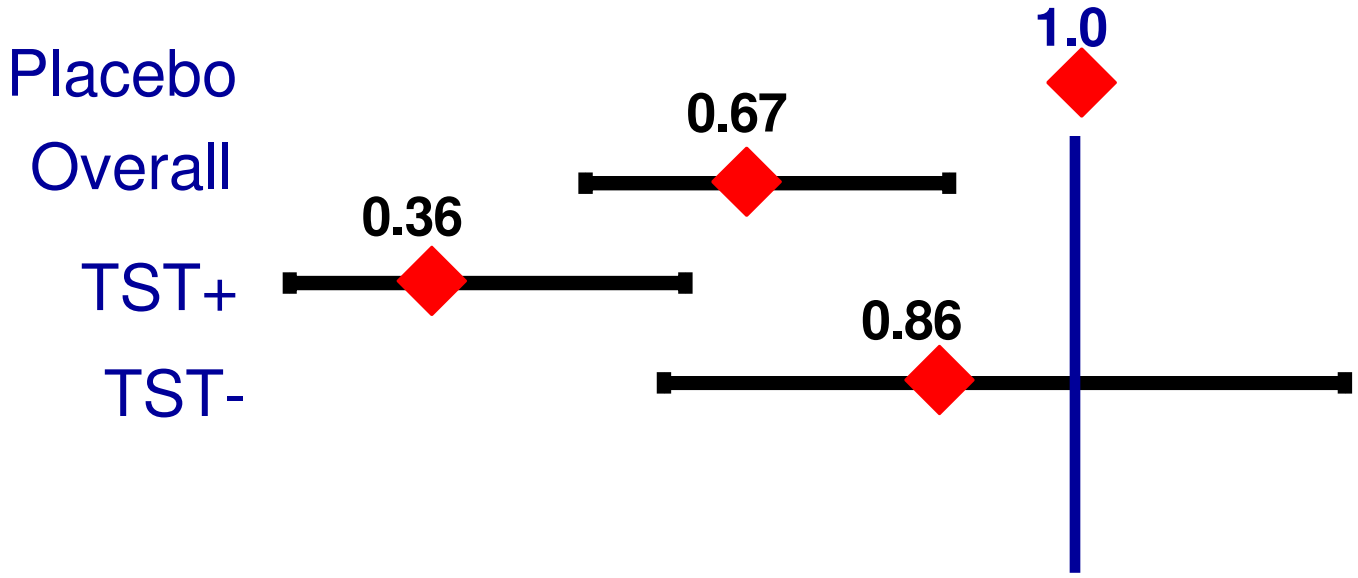
New horizons: outline

- New regimens
- Duration of isoniazid preventive therapy (IPT): is more better?
- IPT and antiretroviral therapy (ART)
- Obstacles to implementation
  - and some solutions

First, the old horizons

- TB preventive therapy works for people with HIV…….

Effect of IPT on TB:
meta-analysis of clinical trials in PWHIV

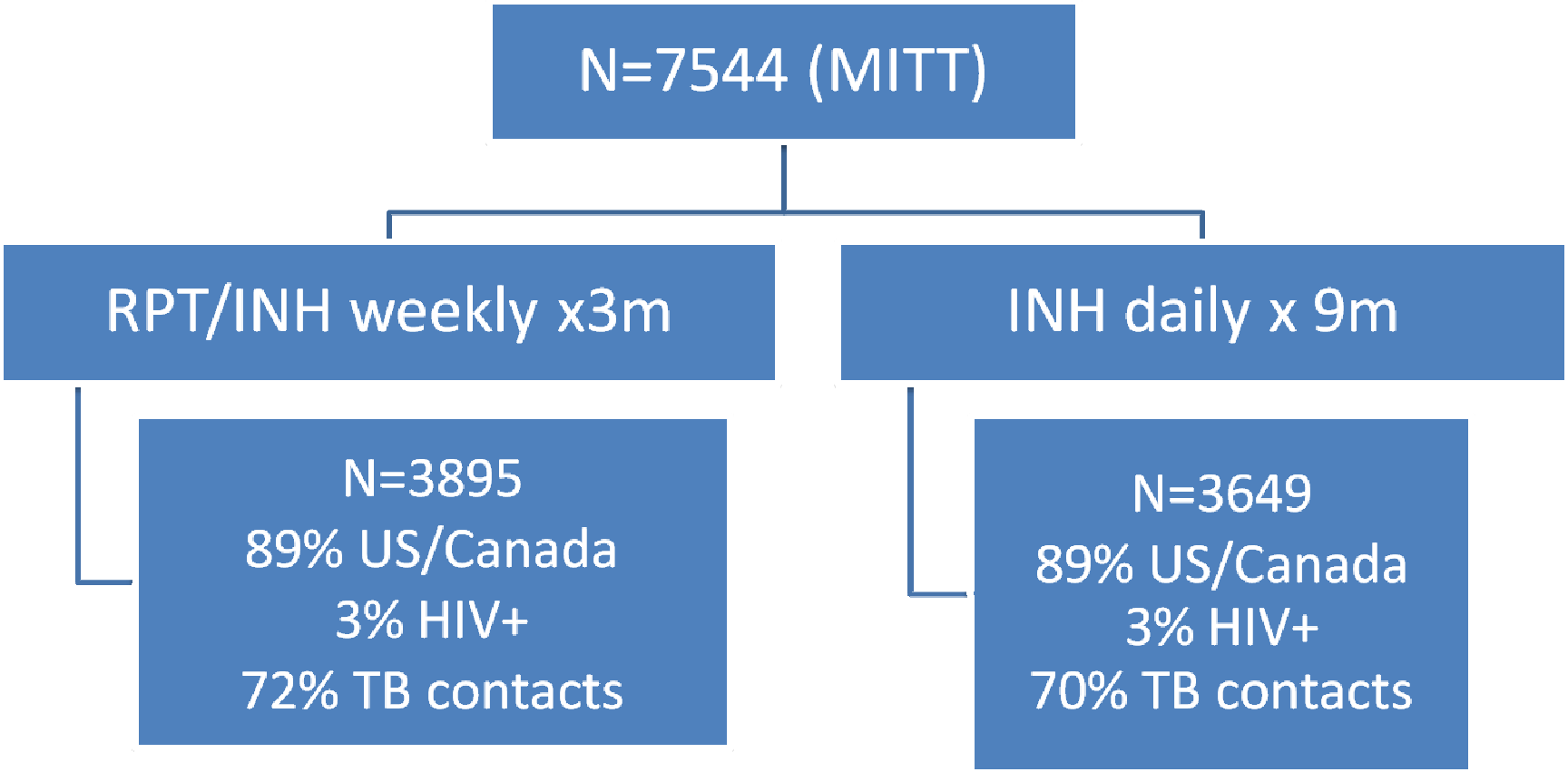


Akolo 2010, Cochrane review

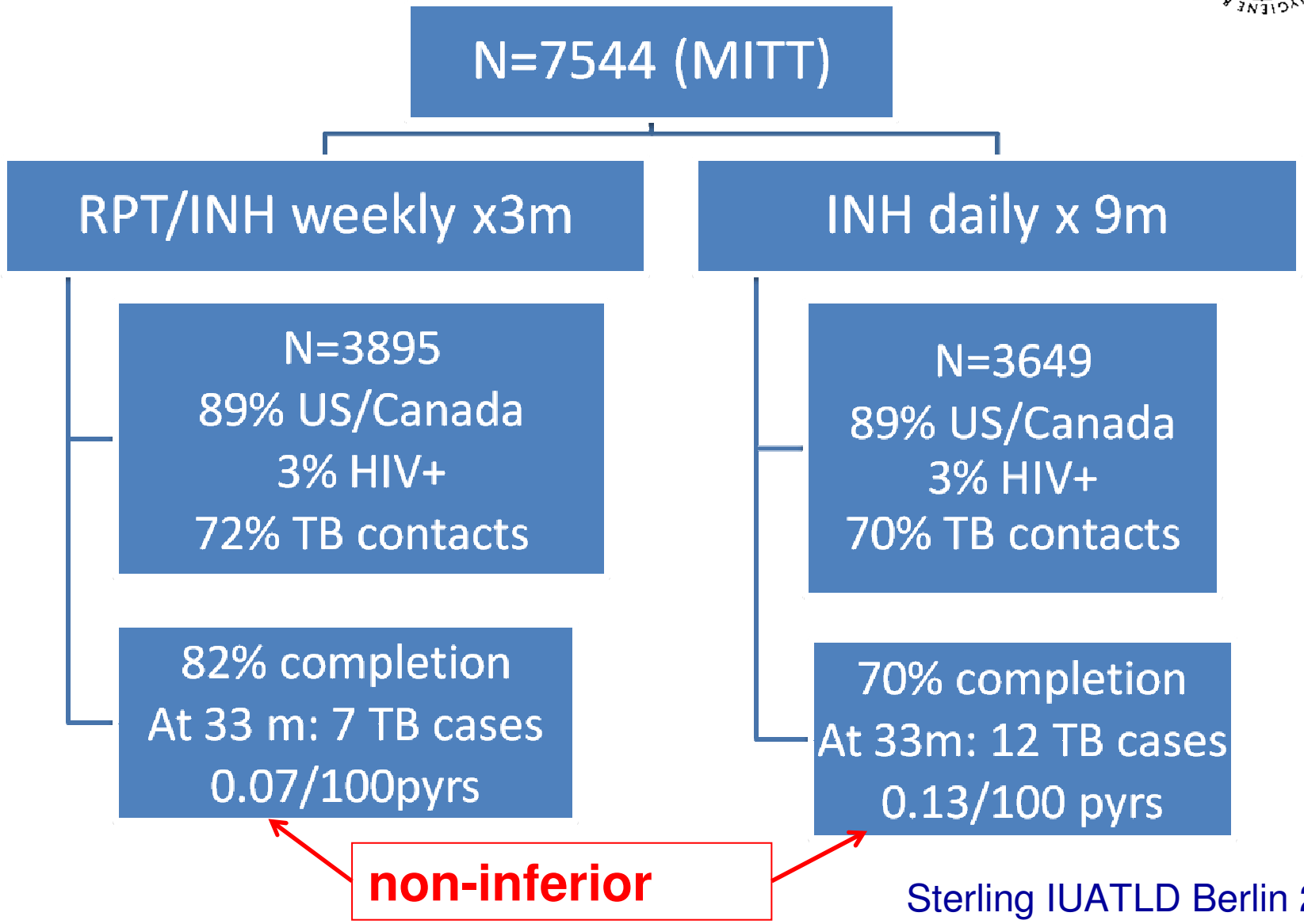
New horizons: where low TB transmission

- treatment of latent TB important in TB control
- INH x 9 months is a long time, completion rates are poor

TBTC26: rifapentine (RPT)/isoniazid (INH) vs. INH

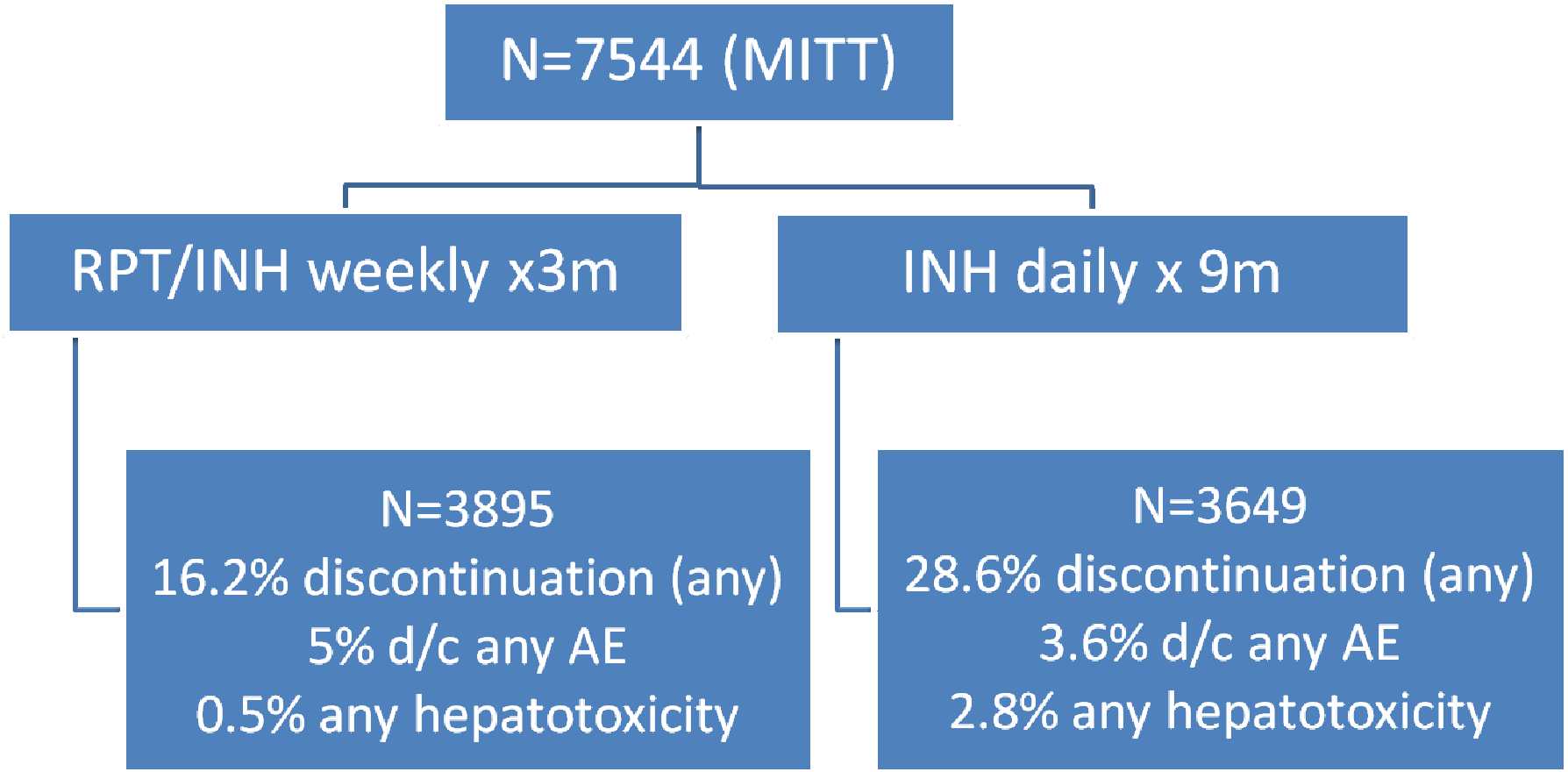


TBTC26: RPT/INH vs. INH



Sterling IUATLD Berlin 2010

TBTC26: RPT/INH vs. INH



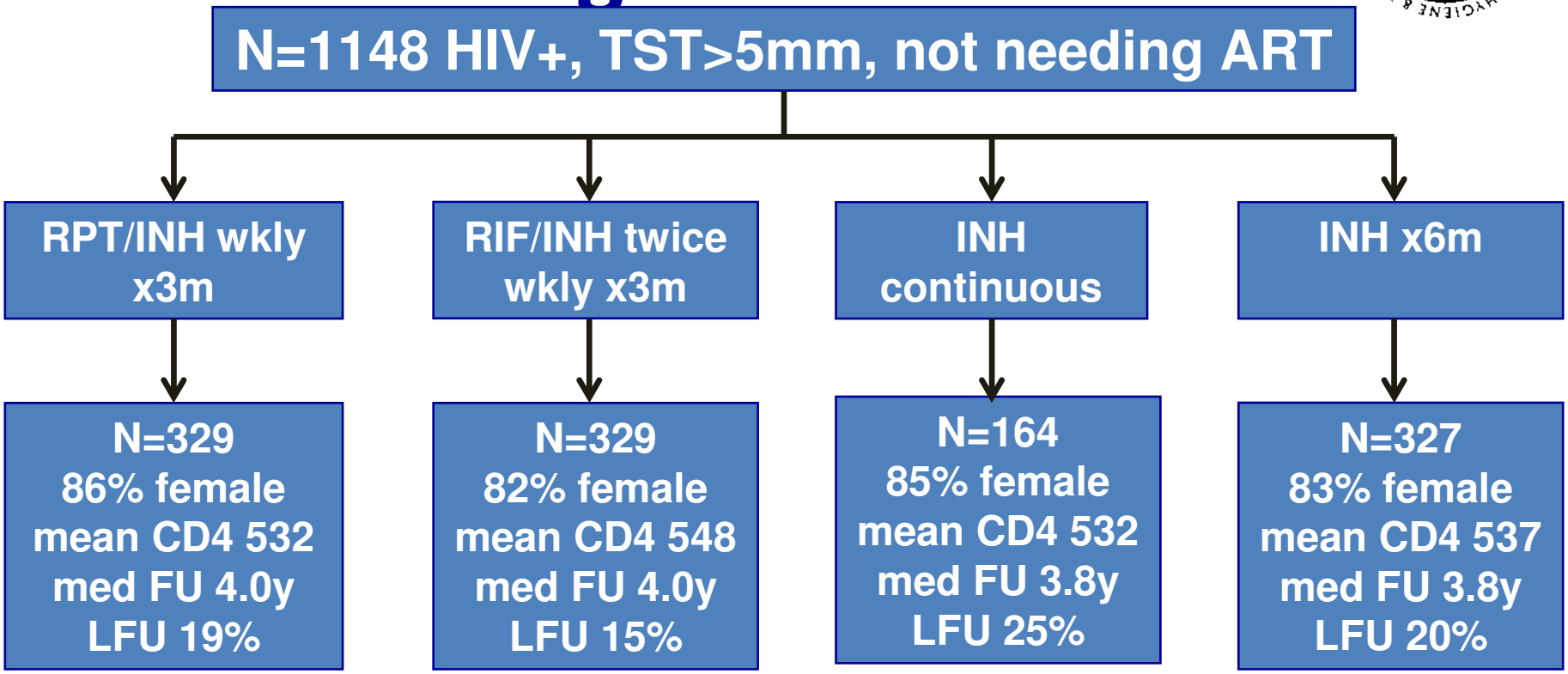
New horizons: shorter regimens

- rifampicin x4m vs. INH x9m
  - adults, TST+ or IGRA+ (excluding HIV+ taking incompatible ART)
  - currently recruiting, high and low burden settings
- ACTG 5279
  - rifapentine/INH daily x1m vs. INH daily x 9m (self-administered)
  - HIV+, TST≥5mm OR IGRA+ OR resident in high burden country
  - due to start 2011

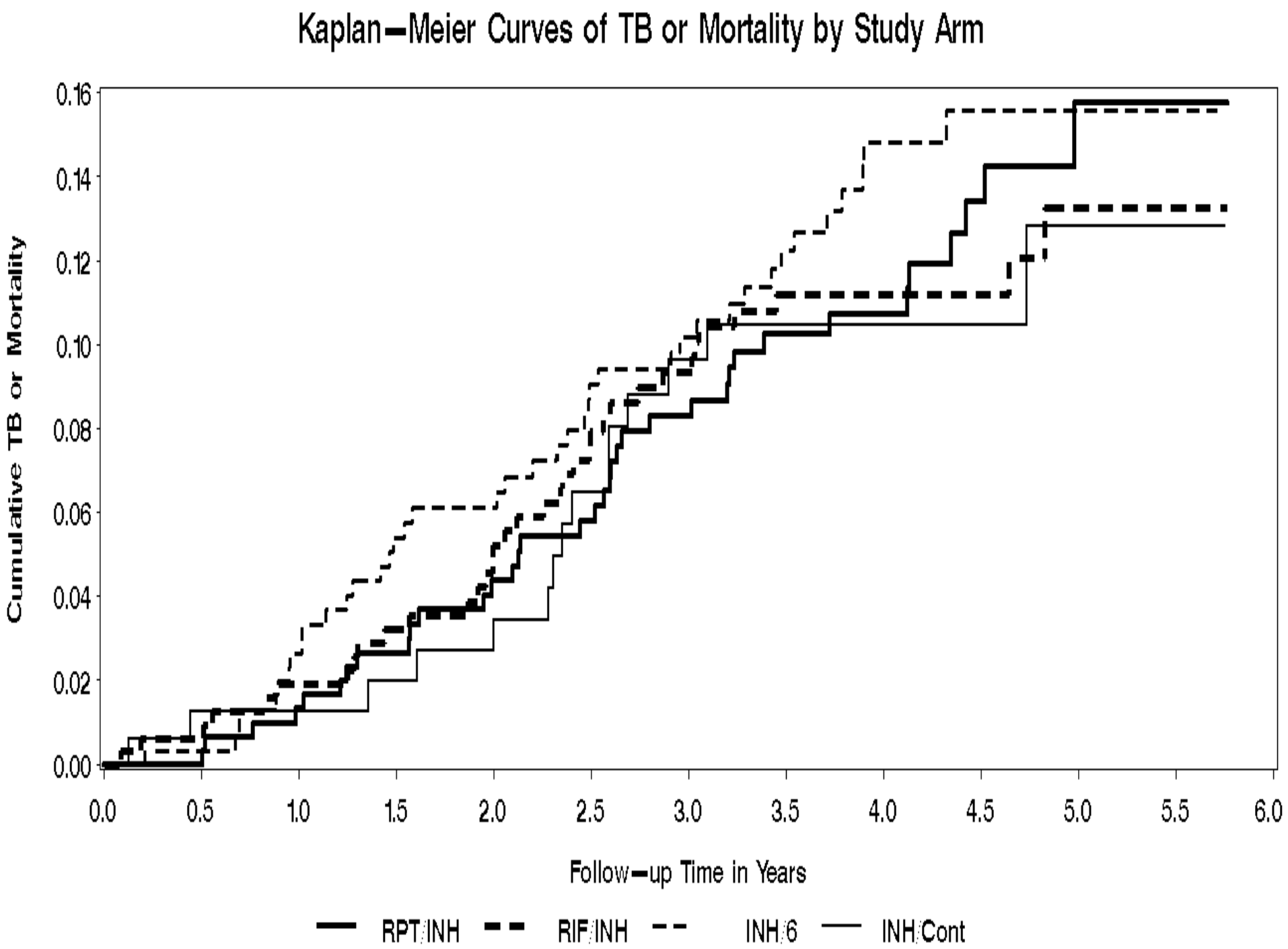
New horizons: high TB transmission

- shorter regimens preferable
- but where high risk re-infection, is longer duration more effective?

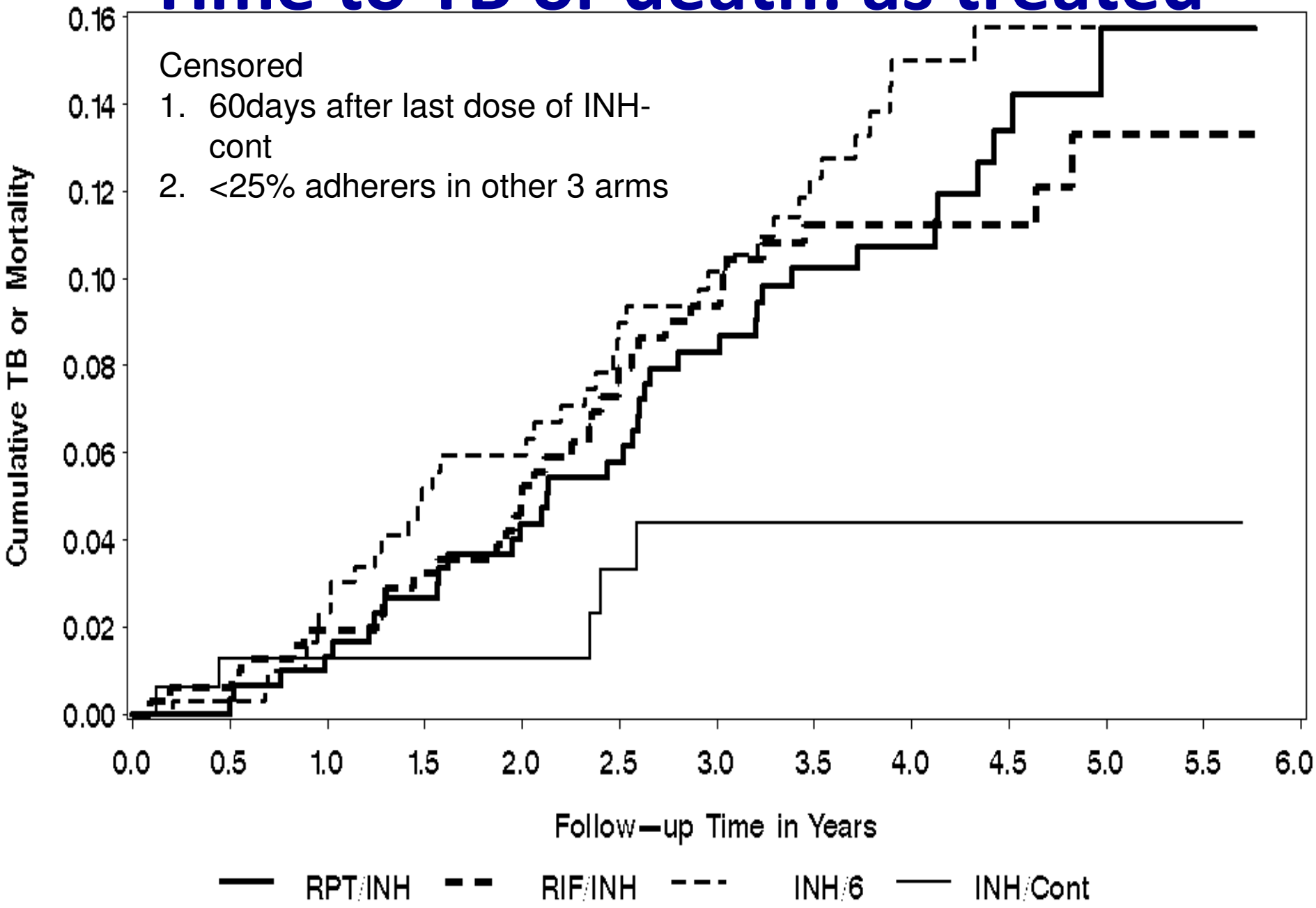
Soweto: novel TLTBI regimens



Martinson CROI 2009


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

Time to TB or death: as treated

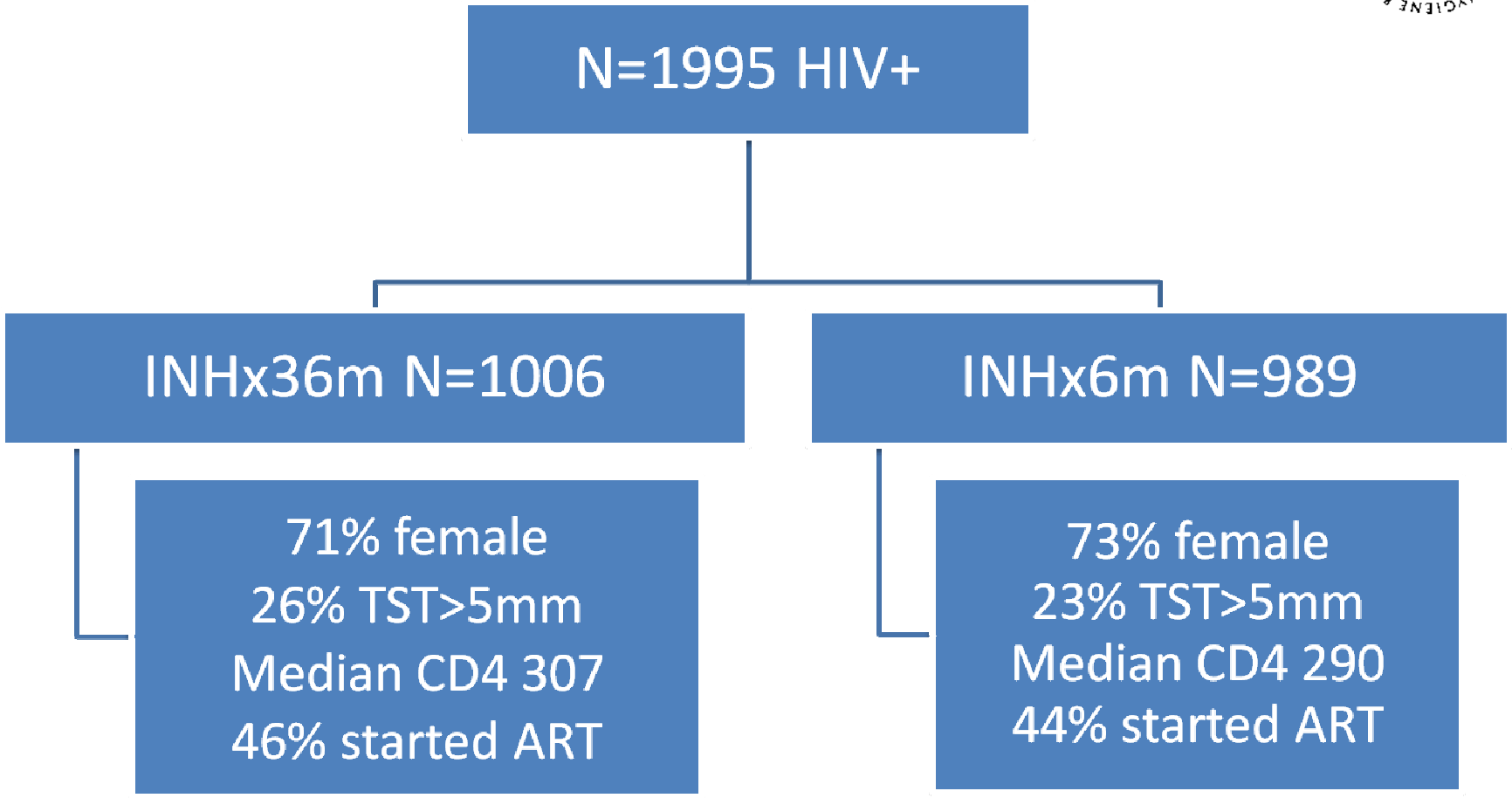


Is longer duration IPT better?

- BOTUSA study, Botswana
  - for PWHIV, is 36 months of INH more efficacious than 6 months?

Samandari CROI 2010; Lancet in press

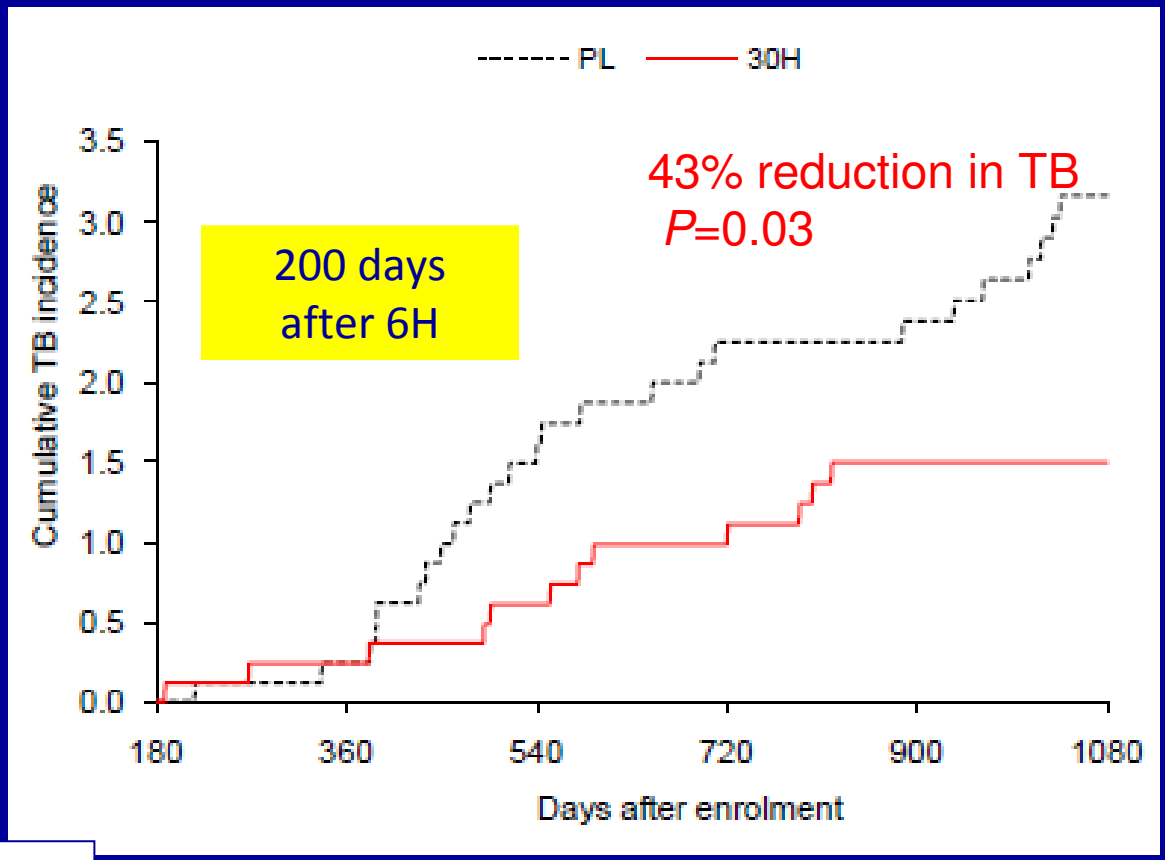
BOTUSA: INH 6 vs. 36m



Samandari CROI 2010; Lancet in press

What was the duration of the benefit of 6 months IPT?

30H=30 additional months of IPT vs PL=placebo

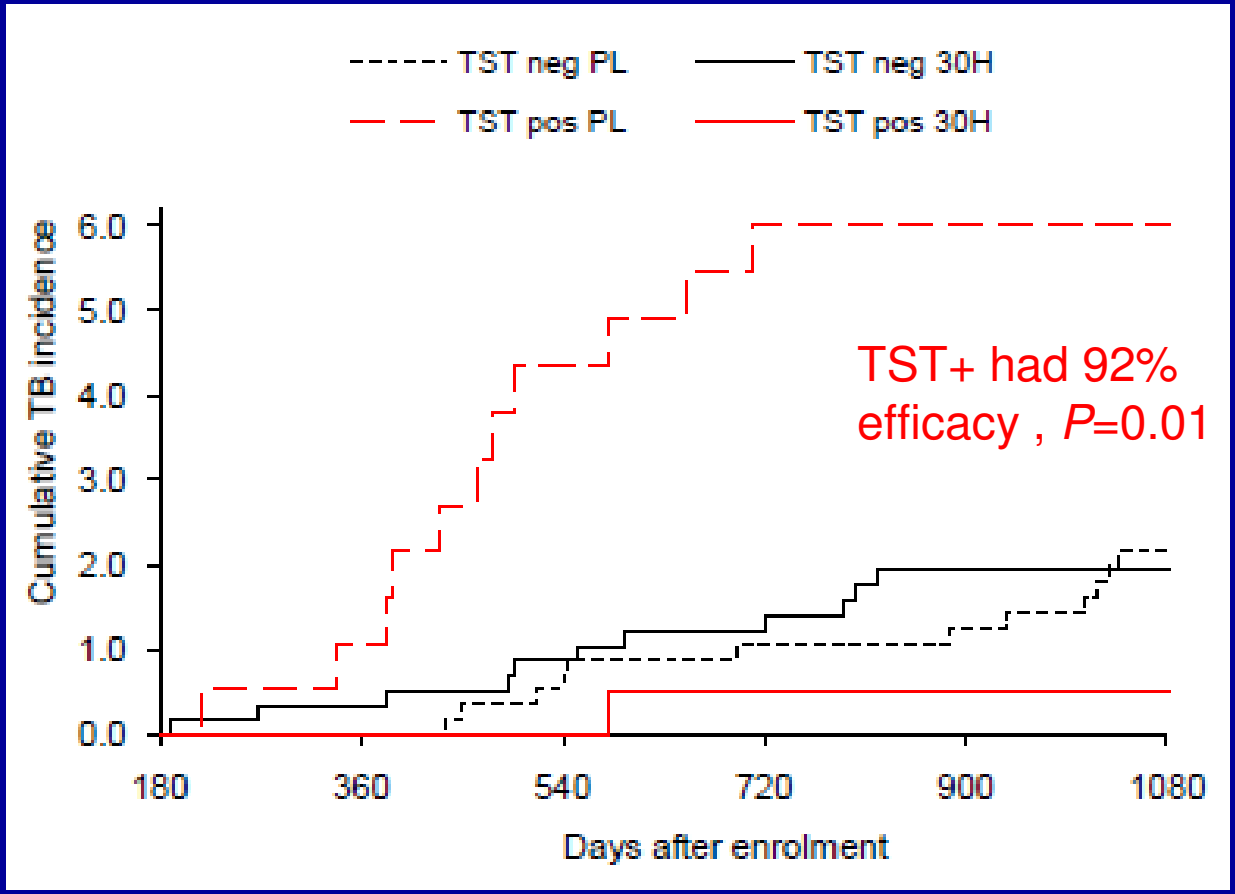


All received 6 months IPT (d0-d180)

Samandari *Lancet* in press

Continuous IPT benefited TST+ only not TST-

30H=30 additional months of IPT vs PL=placebo



TST- effect of IPT P=0.69

Samandari *Lancet* in press

BOTUSA study

- In placebo arm, much higher TB incidence in TST+ vs. TST- over 30m
  - continuing higher TB exposure in TST+?
  - more ART in TST negatives?

Samandari CROI 2010; Lancet in press

IPT and ART for TB prevention?

- Early RCTs of IPT predated ART
- Soweto and BOTUSA studies started ART at CD4<200
- Need to re-evaluate role of IPT in context of wider use of ART, at higher CD4s
  - TB may be proportionally more important cause of morbidity in context of ART
  - IPT adherence may be less of an issue if given with ART

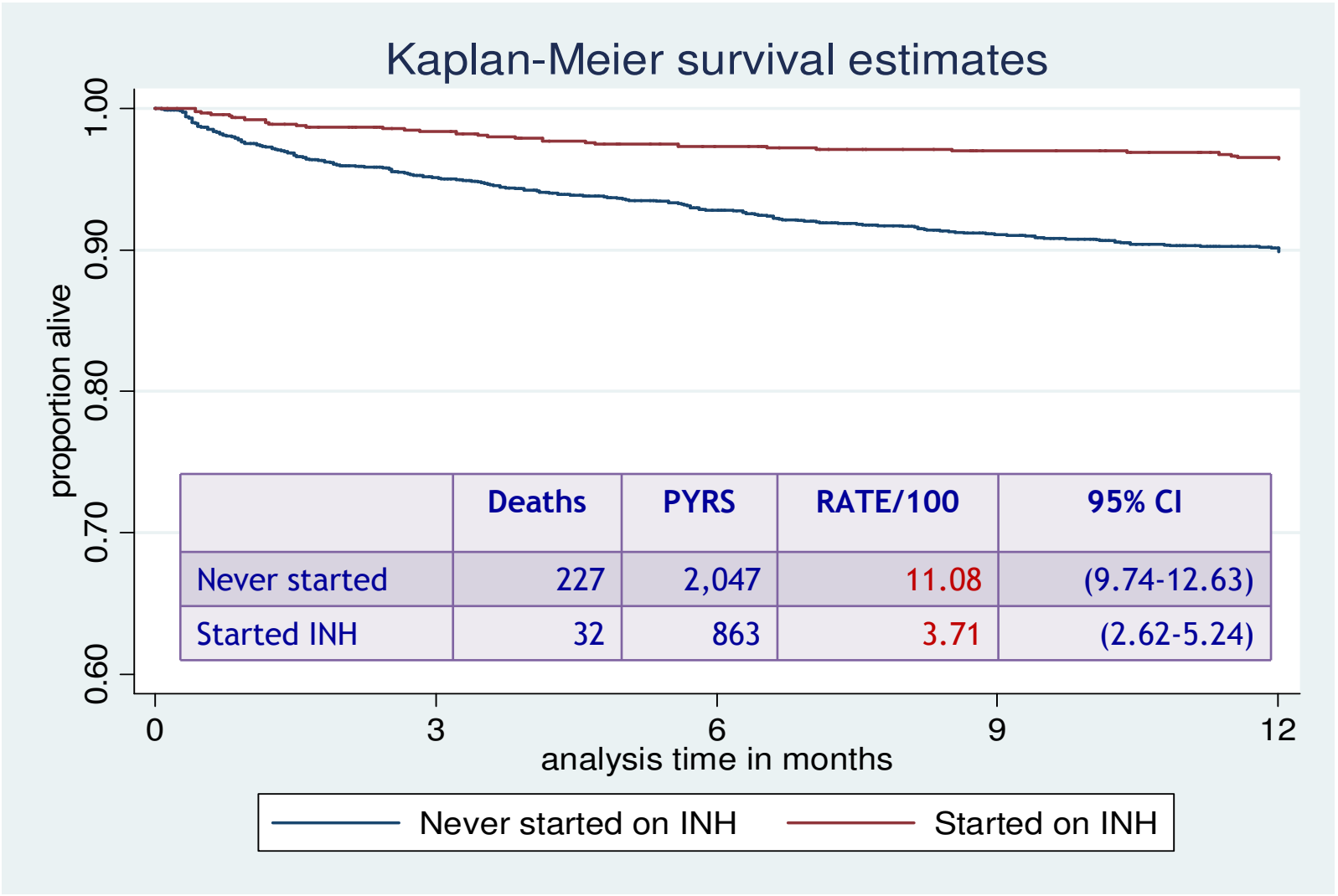
What is the effect of IPT combined with ART?

Association of IPT with mortality among patients taking ART

- Workplace HIV care programme, South Africa
- ART criteria:
  - CD4<250; WHO 4; WHO 3/CD4<350
- IPT recommended if no active or prior TB, but inconsistently implemented
- Retrospective cohort, prospectively-collected data
  - cohort entry: ART start
  - cohort exit: death, leaving employment, 12m post ART start
  - deaths ascertained from clinic and workforce records

Charalambous AIDS 2010;24(s5):S5

KM curve comparing survival among those who started or did not start IPT



	Deaths	PYRS	RATE/100	95% CI
Never started	227	2,047	11.08	(9.74-12.63)
Started INH	32	863	3.71	(2.62-5.24)

Charalambous AIDS 2010;24(s5):S5

IPT vs. no IPT in ART programme – multivariable analysis

		Unadjusted analysis (N=3270)		Adjusted analysis* (N=3094)	
INH	Rate /100py	Hazard Ratio (HR)	95% CI (P value)	Hazard Ratio (HR)	95% CI (P value)
No	11.10	1	(P<0.001)	1	P=0.002
Yes	3.71	0.34	0.24 – 0.49	0.51	0.32 – 0.80

*Adjusted for age group, baseline WHO stage, baseline CD4 count, year started on ART and individual company

Charalambous AIDS 2010(s5):S5

Effect of IPT on death in HIV+:

meta-analysis of clinical trials

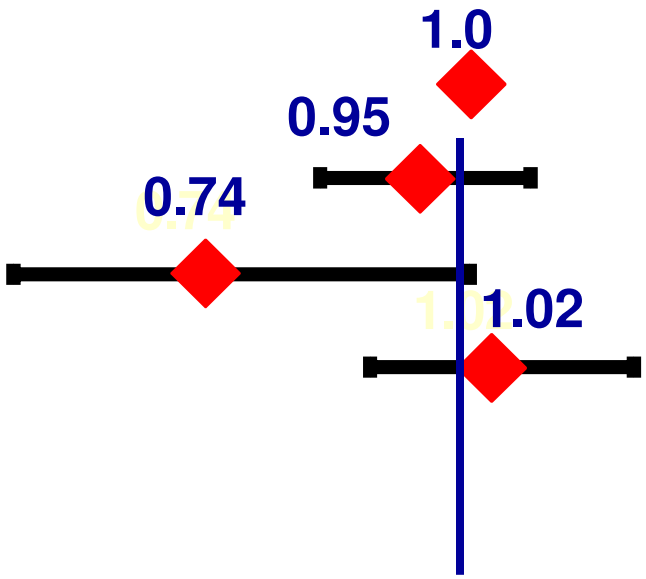
Relative risk, 95% CI

Placebo

Overall

TST+

TST-



Akolo 2010, Cochrane review

Why have IPT trials not shown an effect on mortality?

Screening for TB in IPT trials

Author, country, study period	TB screen pre-enrollment	TB screen during follow-up
Pape, Haiti 1986-9	symptoms CXR	3 monthly
Whalen, Uganda 1993-5	symptoms, physical examination, CXR, sputum M&C x1	monthly, with CXR 6 monthly
Mwinga, Zambia 1992-4	if CXR abnormal, sputum M&C x3	monthly for 6 months, then 3 monthly
Hawken, Kenya 1992-4	symptoms, CXR, sputum M&C x1	monthly for 6 months, then 3 monthly, with CXR 12 monthly
Gordin, US 1991-6	symptoms CXR	at months 1,2,4,6. If symptomatic, CXR and sputum examination
Rivero, Spain 1994-8	symptoms, physical examination, CXR	every 2 weeks for 2 months, then monthly
Fitzgerald, Haiti 1998-9	CXR, sputum microscopy and culture x1	monthly for 12 months, then 3-monthly

Grant AIDS 2010;24(s5):S15

Active case finding reduces TB case-fatality

		Unadjusted		Adjusted	
	Deaths/total	OR	95%CI	OR	95%CI
HIV status					
Negative	17/1628	1		1	
Positive	64/608	11.15	6.3–20.1	15.0	7.4–30.6
How detected					
RSP	12/1225	1		1	
Self presentation	69/1011	7.4	3.9–14.6	5.6	2.6–12.2

Churchyard IJTLD 2000;4:705

Why no effect on death in IPT trials?

- IPT trials have tested
  - intensified case finding vs.
  - intensified case finding plus IPT
- ICF does not reduce risk of TB
- but does reduce risk of TB death
  - equally in both study arms
- hence not detectable with this study design
- early RCTs may have underestimated benefits of IPT plus ICF programme

Grant AIDS 2010;24(s5):S15

What to do for MDR-TB contacts?

- investigate new agents?
- e.g. TMC 207: diarylquinoline, inhibits mycobacterial ATP synthetase

  - phase 2 RCT of 5-drug second line regimen + TMC207 x8w vs. placebo reduced time to culture conversion
  - also has activity in non-replicating mycobacteria

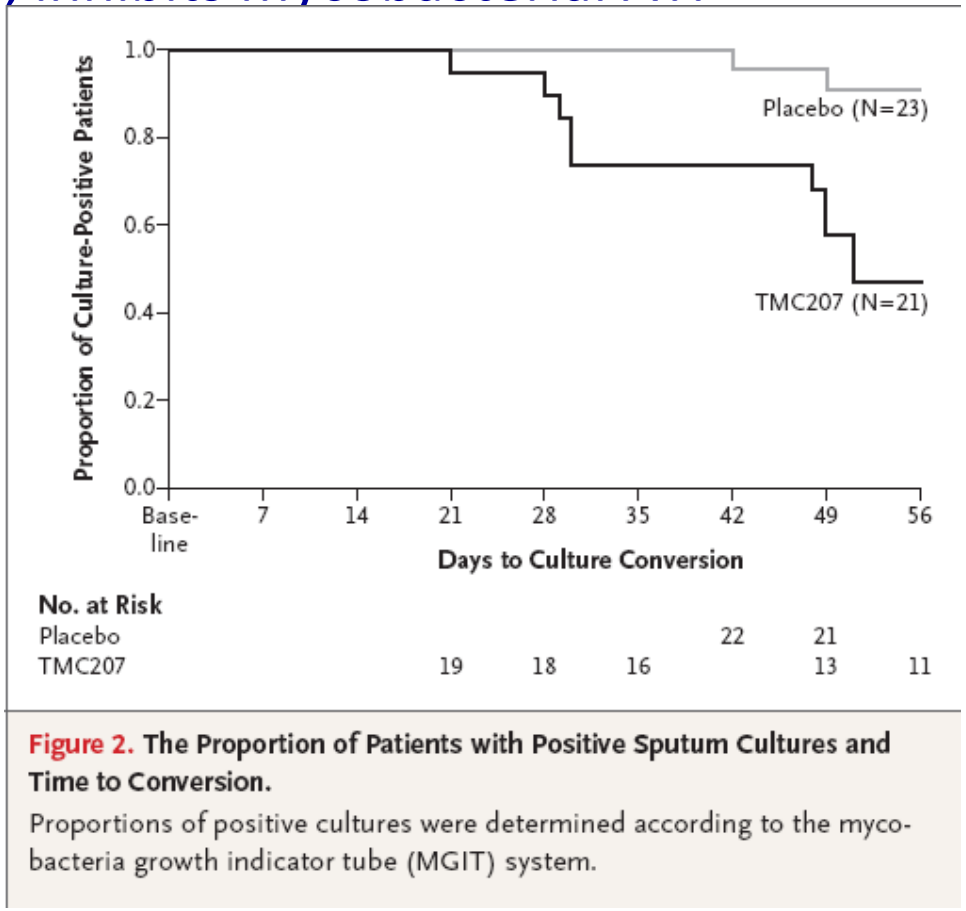


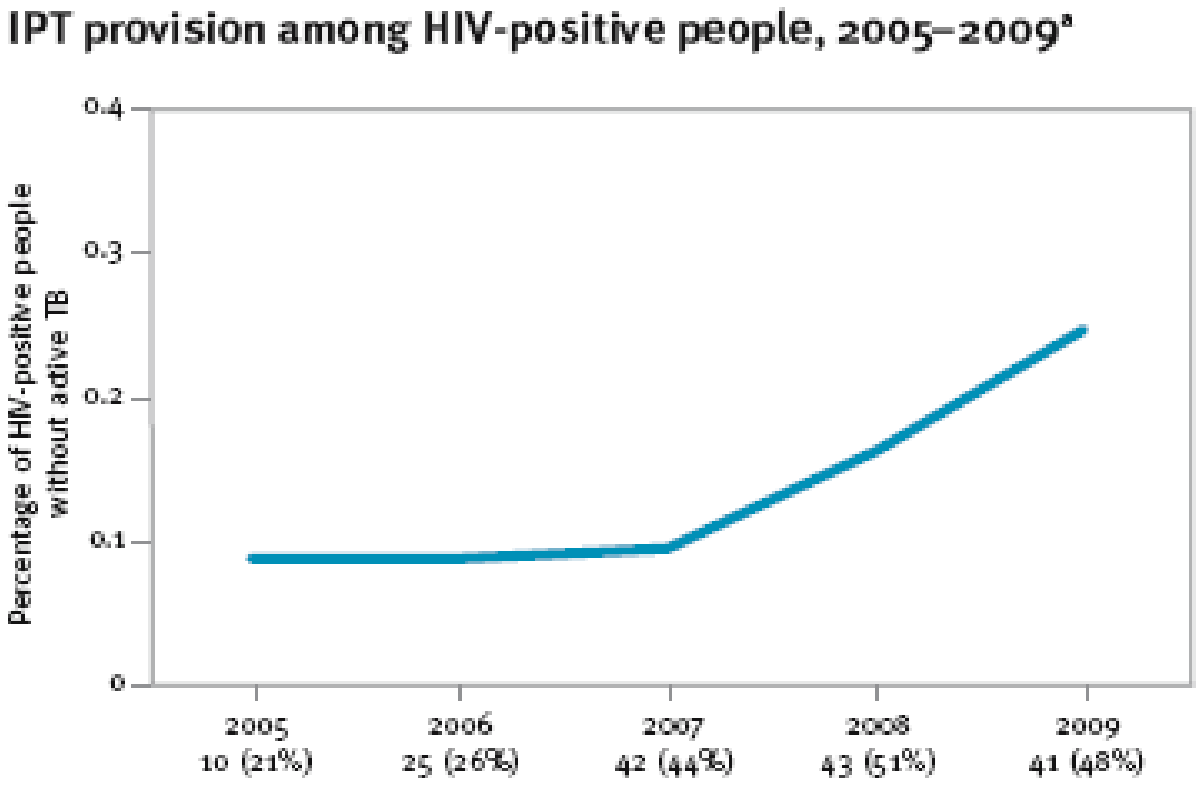
Figure 2. The Proportion of Patients with Positive Sputum Cultures and Time to Conversion.

Proportions of positive cultures were determined according to the mycobacteria growth indicator tube (MGIT) system.

Diacon NEJM 2009;360:2397

IPT implementation for PLHIV

IPT implementation is limited among PLHIV where there is most TB



* Numbers under years show the number of countries reporting data followed by the percentage of total estimated HIV-positive people without active TB accounted for by reporting countries.

WHO TB report 2010

..implementation limited because…

- clinicians (in HIV care programme in SA)
  - lack experience of using IPT
  - uncertain how to exclude active TB
  - worried about side effects
  - worried about promoting resistance
- patients
  - don't know about IPT
  - but think it's a fine idea when you tell them

Lester AIDS 2010;24(s5):S45

Improving IPT implementation

Screening for active TB

OPEN ACCESS Freely available online

PLoS MEDICINE

Development of a Standardized Screening Rule for Tuberculosis in People Living with HIV in Resource-Constrained Settings: Individual Participant Data Meta-analysis of Observational Studies

Haileyesus Getahun[1*], Wanitchaya Kittikraisak[2], Charles M. Heilig[3], Elizabeth L. Corbett[4], Helen Ayles[4,5], Kevin P. Cain[3], Alison D. Grant[4], Gavin J. Churchyard[6], Michael Kimerling[7], Sarita Shah[8], Stephen D. Lawn[4,9], Robin Wood[9], Gary Maartens[10], Reuben Granich[1], Anand A. Date[3], Jay K. Varma[2,3]

- Excluding active TB: symptom screen with any of:
  - cough (any duration)
  - night sweats
  - fever
  - weight loss

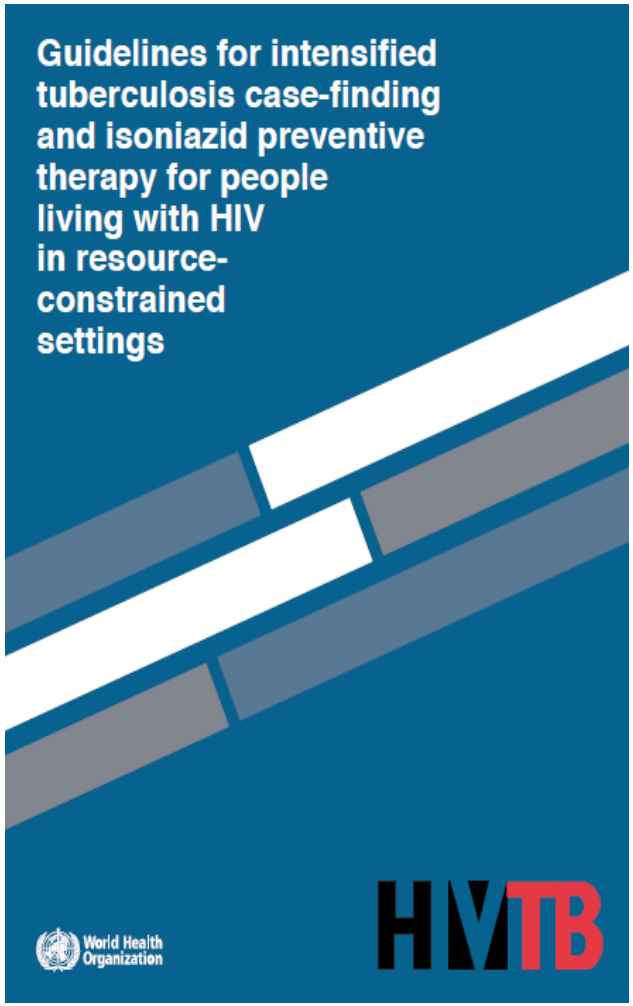
  79% sensitivity, 50% specificity vs. culture pos TB

  NPV 98% at 5% prevalence, 90% at 20% prevalence
- add CXR: sensitivity 91%, specificity 39%

Getahun PLoS Med 2011;8(1):e1000391

New WHO guidelines for TB ICF and IPT for PLHIV

- regular TB screening
- IPT x at least 6m if no active TB
  - regardless of CD4
  - regardless of ART
  - regardless of past history of TB
- Conditional recommendation for 36m IPT if TST pos or unknown
- TST not essential prior to IPT
  - but can identify those who will benefit most
- similar recommendations for children



Improving IPT implementation: experience from large-scale IPT delivery in Thibela TB

Adverse events

Effect of IPT on resistance to INH

Thibela TB

- Aim: to evaluate community-wide IPT in setting of very high TB incidence and high HIV prevalence
- cluster randomised trial
- 15 clusters = gold mine shafts, all employees (total N= 80,000 approx)
- randomised to:
  - intervention (community-wide TB screening, then IPT x9m) vs.
  - control (routine TB control programme activities)
- primary outcome: TB incidence

Thibela TB: adverse events

- AE reporting included these study-defined events:
  - hepatitis (based on clinical monitoring)
  - hypersensitivity
  - peripheral neuropathy
  - convulsions
  - psychosis
  - death from any cause
- occurring between
  - first IPT dispensing date
  - two months after last IPT dispensing date

Thibela TB: adverse events

- 24221 participants started IPT
  - 95% male, median age 40 years
- 130 individuals had132 possible AEs (0.54%)
  - 61 (0.25%) suspected hypersensitivity
  - 50 (0.21%) suspected peripheral neuropathy
  - 17 (0.07%) clinical hepatotoxicity [2 SAEs]
  - 4 (0.02%) convulsions [2 SAEs]
- One hepatotoxicity AE resulted in death: overall risk of death 4 per 100,000 (0.004%)

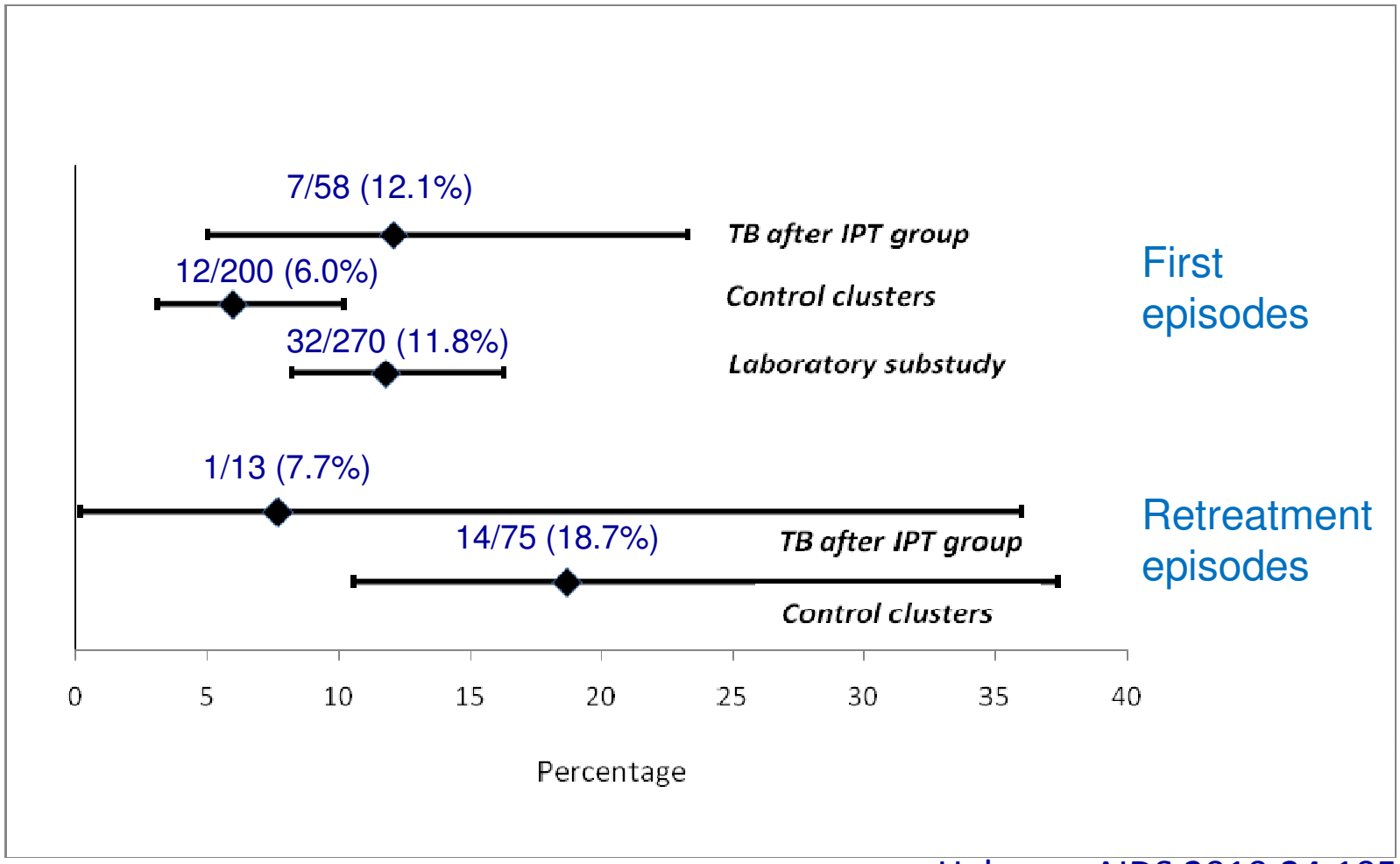
Grant AIDS 2010;24(s5):S29

Isoniazid resistance after IPT

- case series from Thibela TB
  - 126 gold miners (125 men, median 43y) developing active TB after receiving IPT
  - 89/103 (86.4%) had HIV infection
  - median CD4 (n=51) 196 cells/mm^3
  - drug susceptibility results available for 71 (58 new, 13 retreatment)

van Halsema AIDS 2010;24:1051

Prevalence of any isoniazid resistance in TB episodes after IPT (bars=95% CI)



van Halsema AIDS 2010;24:1051

Experience of IPT delivery in Thibela TB

- IPT can be safely delivered by nurses using clinical criteria for adverse event monitoring
- No excess of isoniazid resistance among individuals developing active TB after IPT

Grant AIDS 2010;24(s5):S29
van Halsema AIDS 2010;24:1051

New horizons: low TB transmission

- prospects for effective, shorter, tolerable regimens to treat latent TB

New horizons: high TB transmission

- longer duration of IPT looks better, particularly in TST+
- TB screening simplified to facilitate IPT implementation
- new data support safety of IPT
- need to determine how best to use IPT and ART to maximise TB prevention for PLHIV

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Effect of IPT on prevalence of resistance