LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Isoniazid preventive therapy in the context of drug resistance: challenges and solutions

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Challenges

- Weighing up risks and benefits of isoniazid preventive therapy (IPT) in settings of drug resistance
  - will it work?
  - will it make resistance worse?

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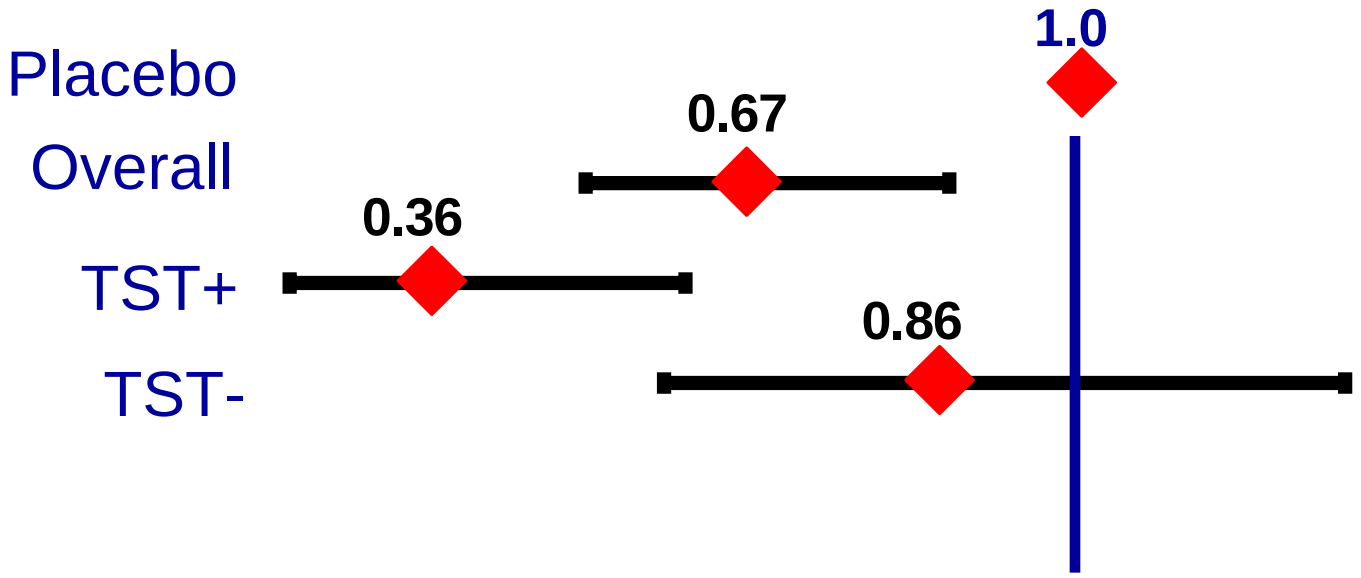
  - will it work?

IPT prevents TB among PWHIV: meta-analysis of RCTs



Akolo 2010, Cochrane review

Does IPT work where there is resistance?

- IPT (probably) ineffective in individual with latent INH-resistant TB
  - though different mutations confer different degrees of resistance
  - *kat* G: high level resistance
  - *inh* A: lower level resistance, can be overcome with high dose INH

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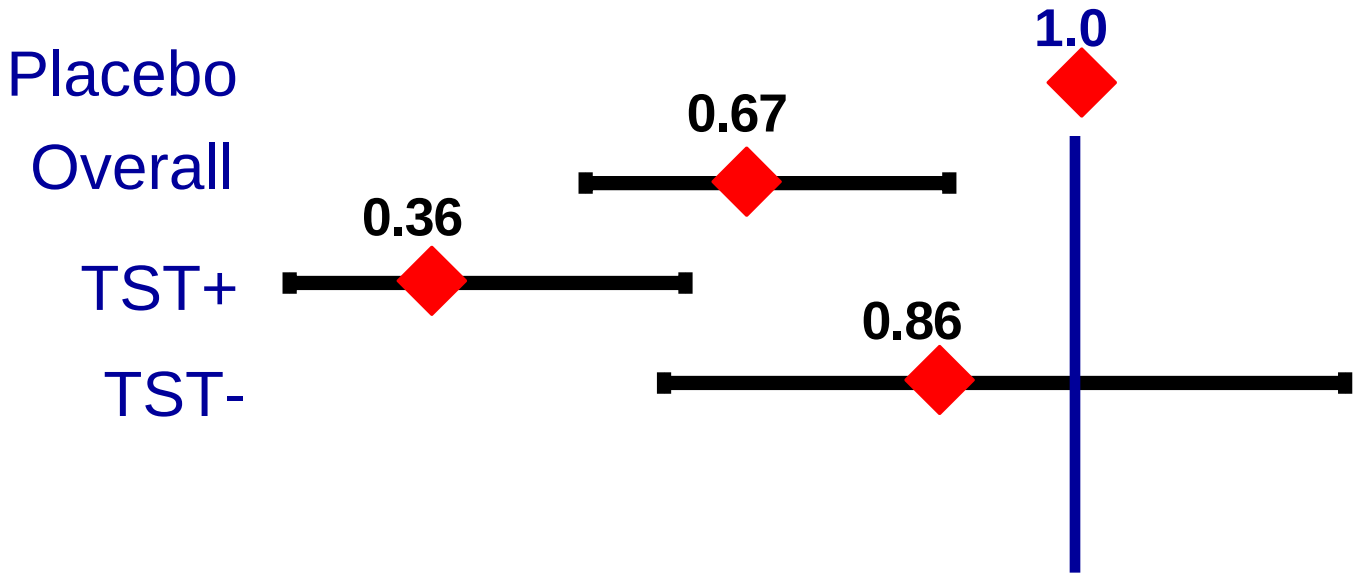


Akolo 2010, Cochrane review

IPT similar to RZ, Haiti, 1990-4

17% any H resistance in new TB cases

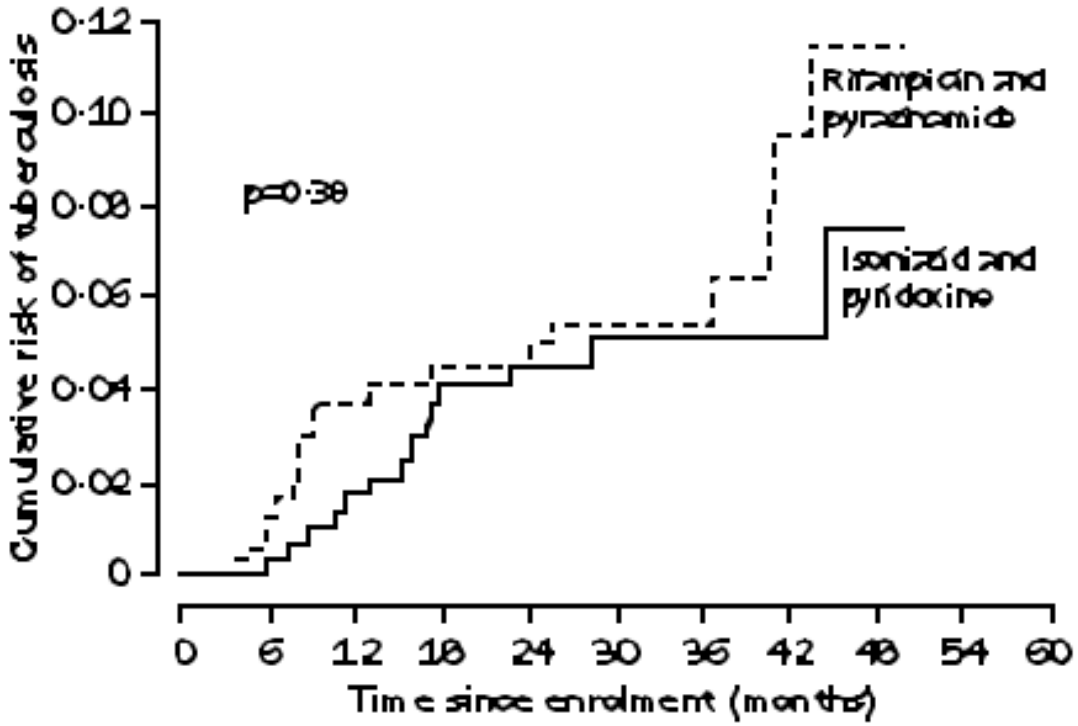
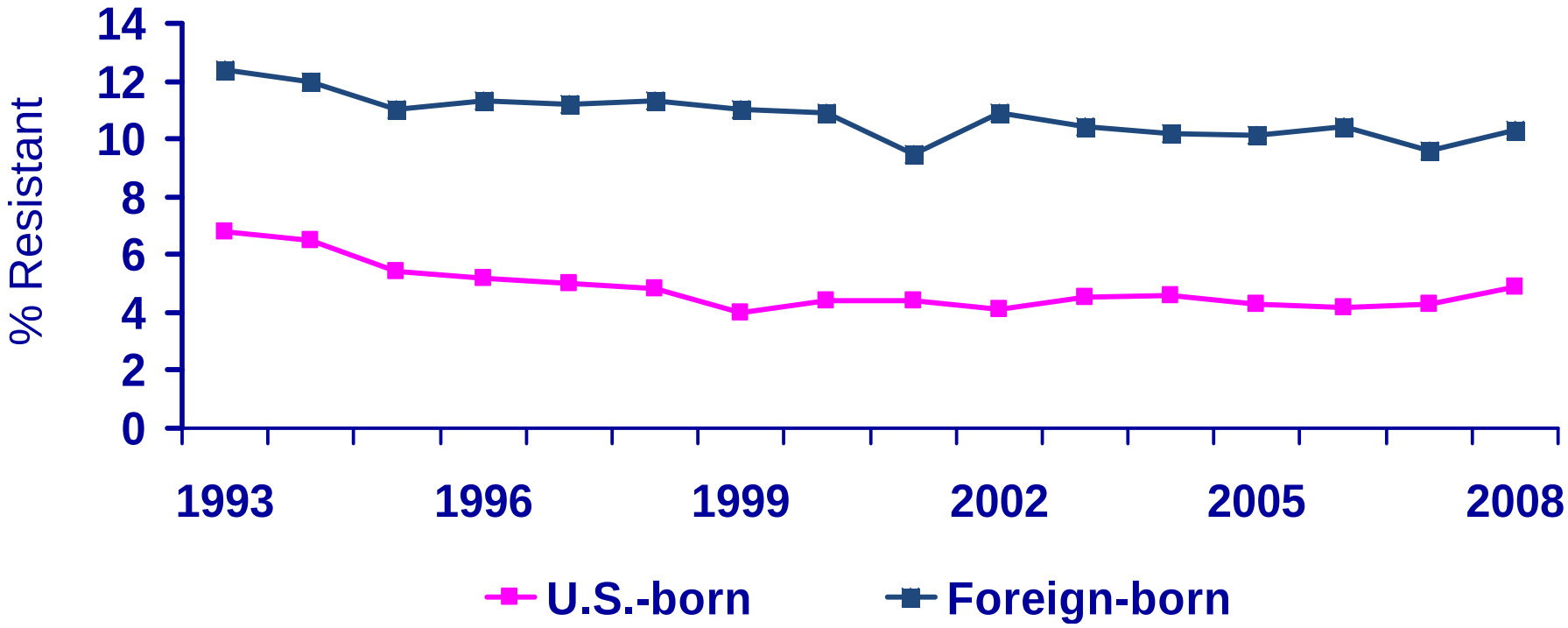


Figure 2: **Kaplan-Meier plot of proportions of patients developing confirmed, probable, or possible tuberculosis by treatment regimen**

Halsey, Lancet 1998;351:786; Chaisson ARRCCM 1996;154:1034

IPT routine for latent TB among US migrants

primary INH resistance in foreign-born 10-12%



*Updated as of May 20, 2009.

Note: Based on initial isolates from persons with no prior history of TB.

Who has drug-resistant latent TB?

- best data from studies of contacts of drug-resistant TB cases
- contacts with latent TB infection may not have the same strain /resistance pattern as the index case

Household contacts may not have the same resistance pattern as index

- Retrospective cohort, Rio de Janeiro, Brazil, 1988-92
- 64 index cases with resistance to >1 drug
- 17/218 HIV neg household contacts developed TB
- 13/17 culture + with DST:
  - 6 (46%) identical DST to index case
  - 4 (31%) resistance, with different pattern
  - 3 (23%) fully susceptible

Kritski AJRCCM 1996;153:331

Household contacts may not have the same resistance pattern as index

	MDR index case	XDR index case
Contacts culture+ with DST	26	29
Fully sensitive	2 (8%)	2 (7%)
MDR	14 (54%)	8 (28%)
XDR	10 (38%)	19 (66%)

data from KwaZulu Natal, South Africa: Moll et al, Union conference, Cancun 2009

IPT may work even in contacts of drug-resistant index cases

- Among TST+ (>10mm) contacts of DR index cases (Brazil, 1988-92):
  - no IPT: active TB in 13/145 (9.0%)
  - IPT: TB in 2/45 (4.4%) (OR 0.46, 95% CI 0.07-2.32)
    - 2 cases post IPT both had MDR strains, as did index cases

Kritski AJRCCM 1996;153:331

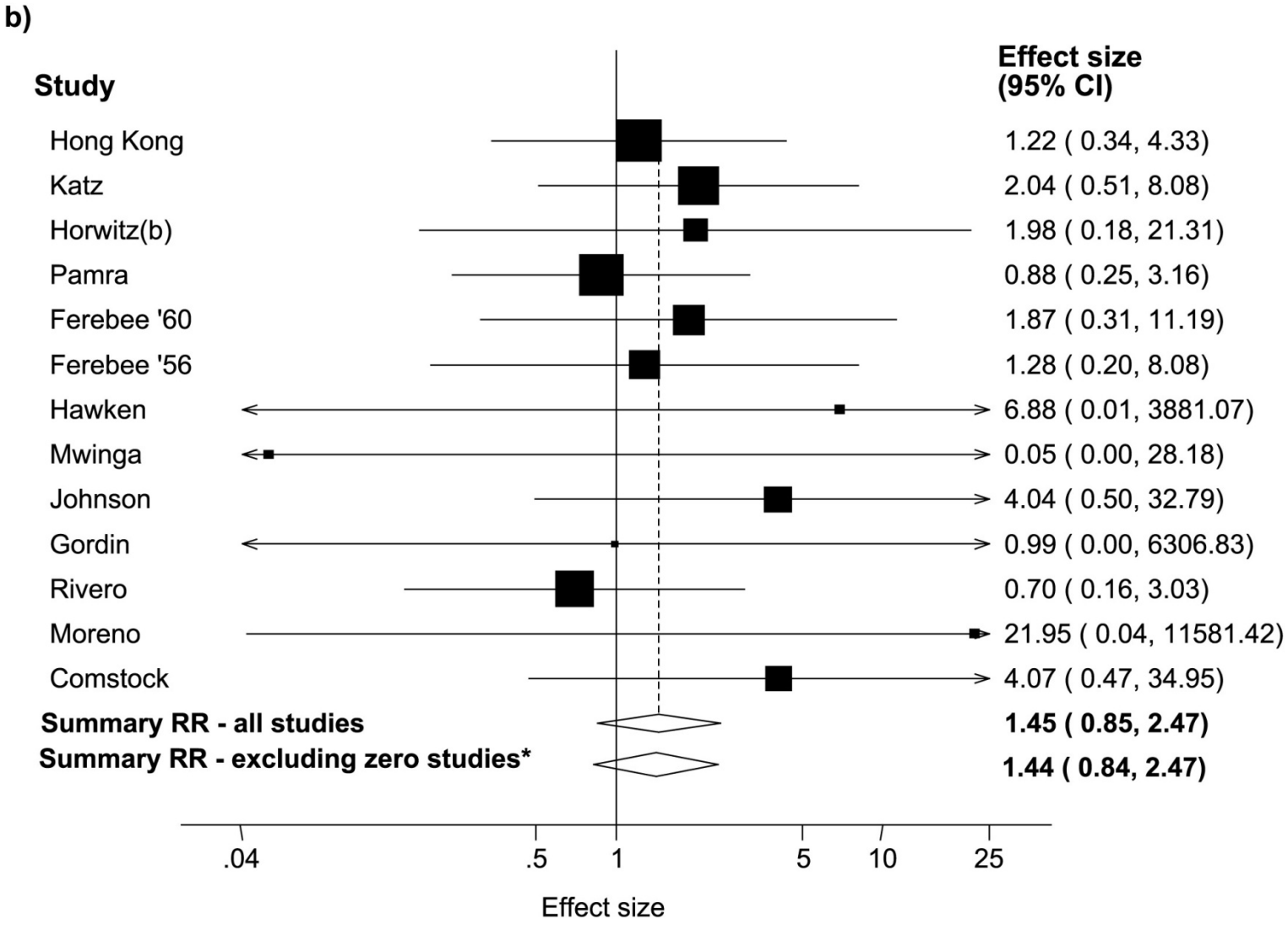
Challenges

- Weighing up risks and benefits of isoniazid preventive therapy (IPT) in settings of drug resistance
  - it will work, for most people
  - will it make resistance worse?

IPT for latent infection does not promote INH resistance

- IPT does not promote isoniazid resistance when used to treat latent TB infection
  - in latent TB few organisms, dividing slowly, hence low risk of selecting drug-resistant mutant

Meta-analysis, incidence of isoniazid resistance, IPT vs. no IPT



Balcells Emerg Infect Dis 2006;**12**:744

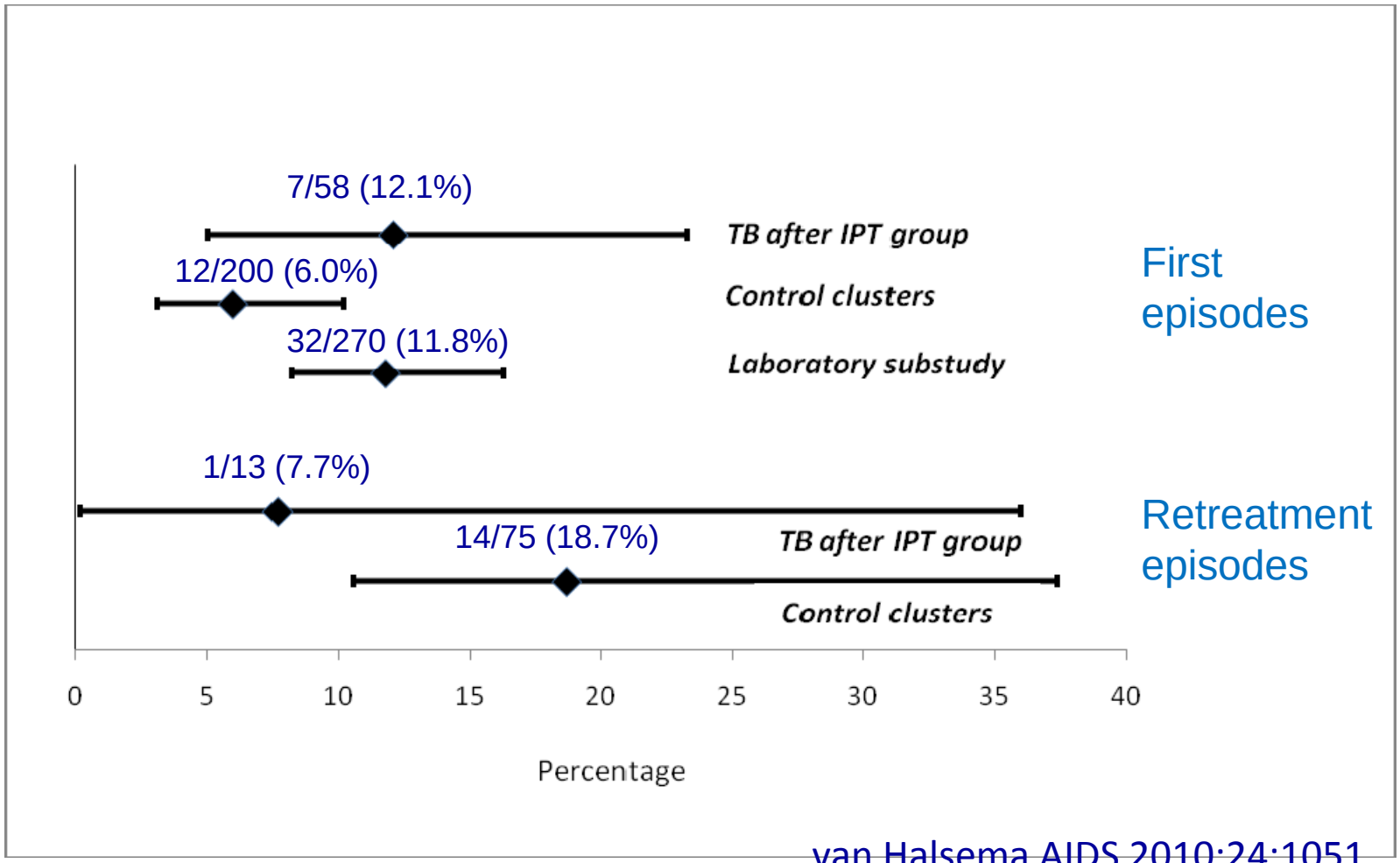
Isoniazid resistance after IPT: data from Thibela TB

Cluster-randomised trial of community-wide IPT: >24,000 gold miners started IPT, South Africa

- substudy of 126 gold miners developing active TB after receiving IPT (125 men, median 43y, 86% HIV+)
- 71 with drug susceptibility results (58 first episodes, 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

Effect of IPT on isoniazid resistance

- IPT does not promote isoniazid resistance when used to treat latent TB infection
  - unless a person with active TB is given inadvertent isoniazid monotherapy
  - thus importance of screening to exclude active TB prior to IPT

Wider benefits of screening plus IPT

- screening (intensified case finding) is an integral part of IPT programme
- benefits all PLWHIV:
  - those with active TB: earlier treatment, better outcomes
  - all clinic attendees [and staff] benefit from less exposure to infectious TB
  - those without active TB may benefit from IPT, will not make resistance worse

Risks vs. benefits of IPT for PWHIV in settings of resistant TB

- no evidence about threshold prevalence of INH resistance at which IPT risks exceed benefits

Solutions: what can we do?

- Review data:
  - outcomes from IPT programmes among PWHIV in settings of high prevalence of isoniazid resistance

IPT use where isoniazid resistance, new cases, >15%

country	year of resistance survey	prevalence any isoniazid resistance, new TB cases	started IPT, 2008
Dominican Republic	1995	19%	443
Georgia	2006	23%	301
Kazakhstan	2001	42.8%	656
Mozambique	1999	16.5%	724
Vietnam	2006	19%	500

WHO drug resistance survey 2008;
IPT data courtesy WHO

Solutions: what can we do?

- Review IPT programmatic outcomes from settings of high resistance
- Decision analysis: modelling risks vs. benefits for range of prevalence of resistance

Sterling Ann Intern Med 1995;155:1622

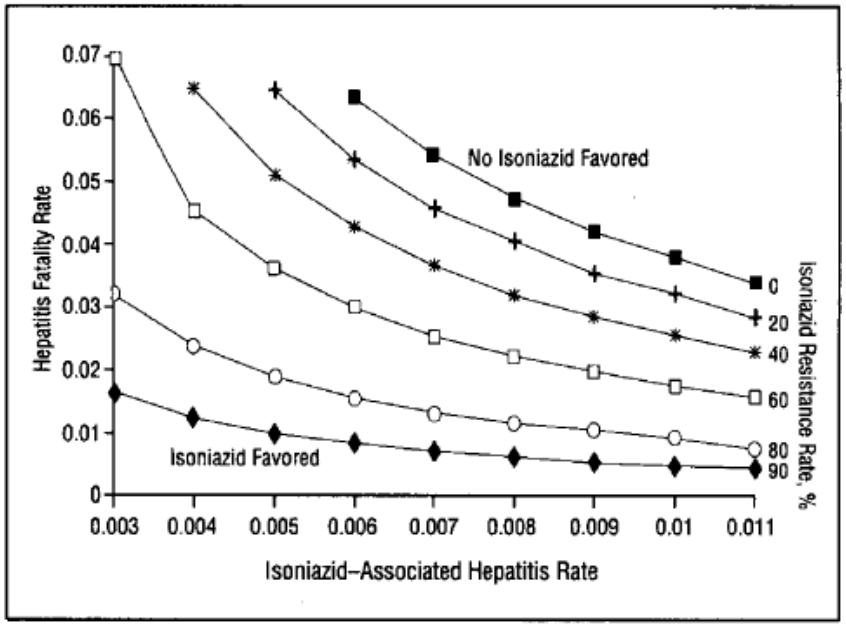


Figure 4. *Three-way sensitivity analysis of isoniazid-associated hepatitis and hepatitis fatality rates in the presence of varied isoniazid resistance rates in tuberculin reactors aged 20 to 34 years.*

Solutions: what can we do?

- Review IPT programmatic outcomes from settings of high resistance
- Decision analysis: modelling risks vs. benefits for range of prevalence of resistance
- Weigh risks and benefits of IPT for PLWHIV:
  - most will benefit from IPT
  - will not promote resistance if active TB excluded
  - screening for active TB is an integral part of an IPT programme
  - clinic-based screening ± IPT benefits all PWHIV

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- Haileyesus Getahun
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Effect of IPT on prevalence of resistance