A randomized trial to compare 4 months Rifampin vs 9 months INH for the treatment of LTBI

Overview of Talk

- The randomized trial of 4RIF vs 9INH
  - Rationale
  - Phases 1 and 2
  - Current trial – key design issues and progress

LTBI treatment – what are the options?

- **6-9 months of INH**
- **2 months RIF-PZA**
- 3-4 months INH-RIF
- 3 months once weekly INH & Rifapentine
- 4 months RIFampin

RCT of 4RIF vs 9INH for TB Prevention

Problems with INH - Summary

1. Length - 6 months minimum, 9 months better
   - Results in poor compliance - less than 50% in most programs, although can be 70%.
2. Side effects of hepatitis - can be fatal although this is now rare
   - Also rash, neuropathies
3. Costs - INH is cheap but close follow up is necessary and this is expensive

LTBI treatment – what are the options?

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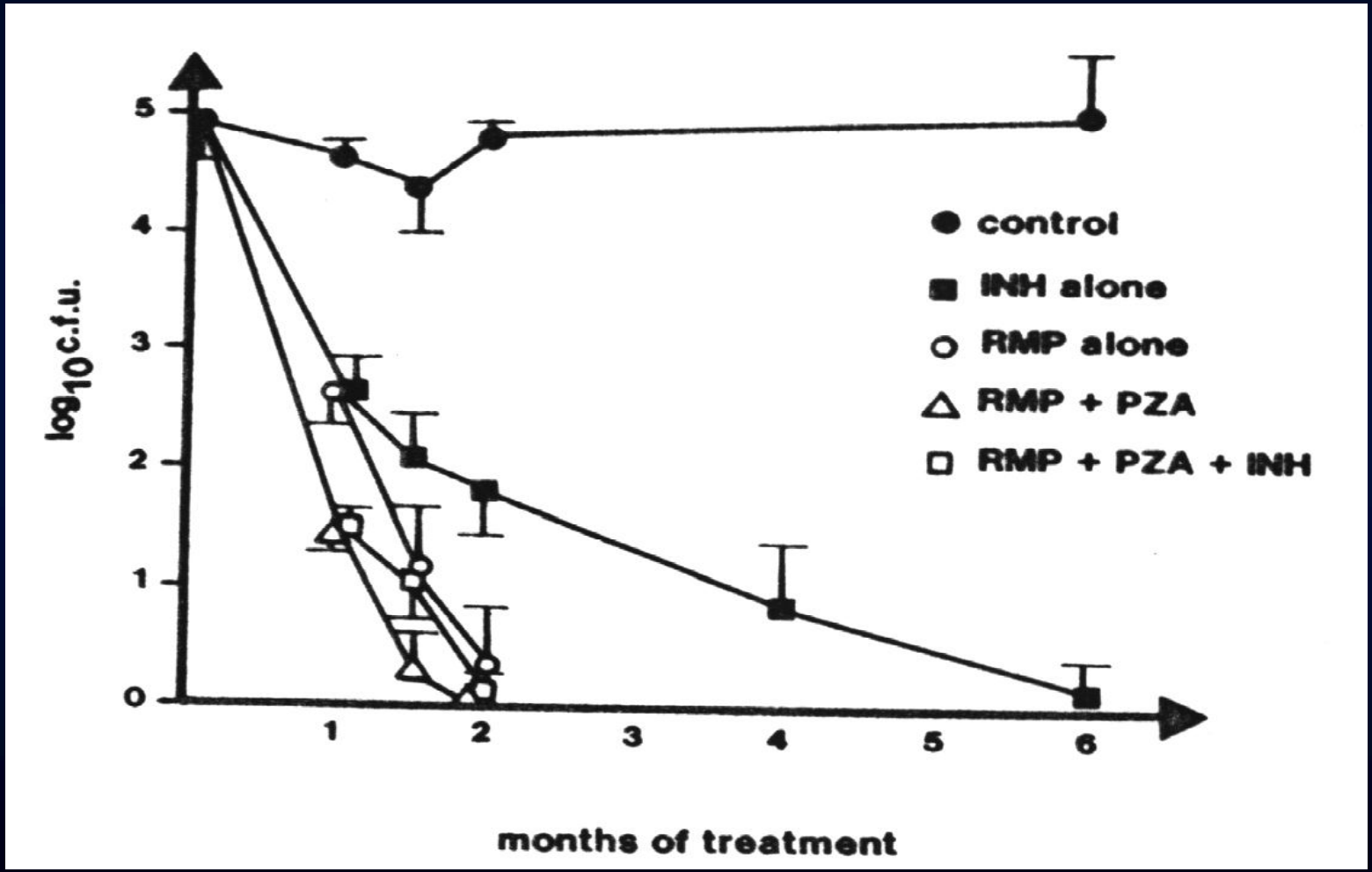
- **2 months RIF-PZA**
- 3-4 months INH-RIF
- 3 months once weekly INH & Rifapentine
- **4 months RIFampin**

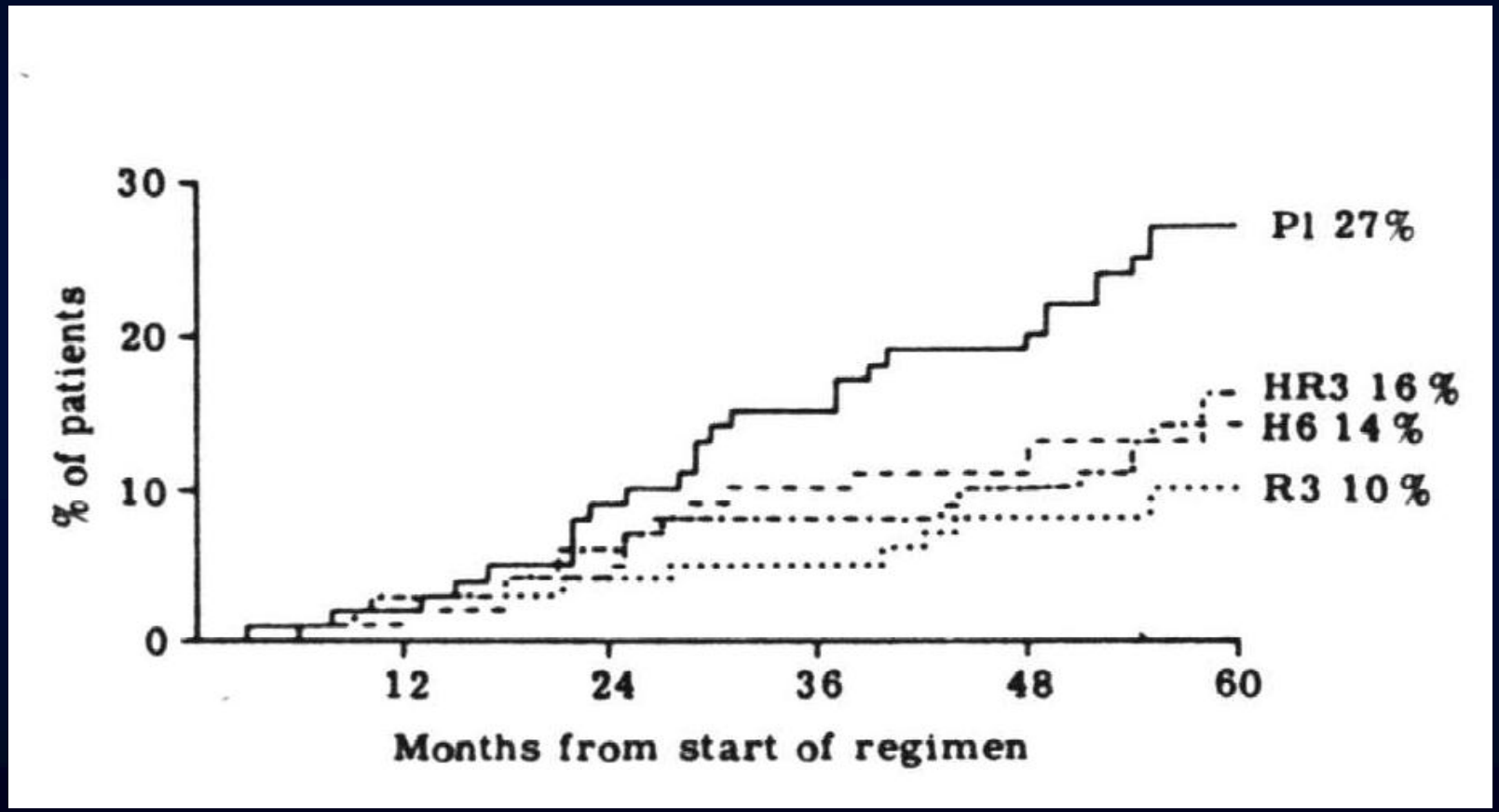
Experimental Study of Short-Course Preventive Therapy in Mice – 2RIF was overlooked



Lecour HF, et.al. Am Rev Respir Dis 1989:140:1189-93

Efficacy of 3 months of Rifampin for the Prevention of TB

Patients with Silicosis



Hong Kong Chest Service. Am Rev Respir Dis 1992;145:36-41

Program Experience with 4RIF and 9INH Maryland 1999-2004

Page et al. Archives Internal Med. 2006: 166; 1863-70

- Patients offered 4 RIF or 9 INH by provider
- Concurrent study but non-randomized

	4 RIF	9 INH
Number Starting	**1,379**	**770**
Completing Therapy	**987 (72%)**	**405 (52%)**
Grade 3 to 4 Hepatitis	**1 (0.1%)**	**12 (2%)**

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Phase 1: Compliance and completion

Completed in 2003

Phase 2 – Adverse events and costs

Completed in 2007

Phase 3: Efficacy and effectiveness

RCT of 9 INH vs. 4 RIF – Phase 1

Completion of therapy among randomized participants

	9 INH (N=58)	4 RIF (N=58)
Completed Rx good compliance, N(%)	36 **(62%)** [1]	50 **(86%)** [1]
Completed Rx poor compliance, N(%)	8 (14%)	3 (5%)
Did not complete Rx, N(%)	14 (24%) [1]	4 (7%) [1]
MD stopped b/o Side effects N(%)	8 (14%)	2 (3%)
< 90% of doses correct at 1 month, N(%)	20 (34%)	12 (21)

[1] P-value = 0.01

RCT of 4RIF vs 9INH for LTBI – Phase 2

Objectives of Phase 2

- Primary objective
  - Compare rate of serious adverse events
- Secondary objectives
  - Compare compliance and completion
  - Compare costs
  - Assess feasibility for phase 3
    - Ability to recruit sufficient numbers

RCT of 4RIF vs. 9INH for LTBI – Phase 2
Completion of Study

	4 RIF (N=420)	9 INH (N=427)	P-value
Completed Therapy N (%)	**339 (81%)**	**259 (69%)**	**<.0001**
Patient Non-compliant (Total) - Drop-out - Intolerance	**61 (14%)** **52 (12%)** **3 (1%)**	**117 (27%)** **82 (20%)** **23 (5%)**	
MD Non-compliant	**6 (1%)**	**12 (3%)**	

RCT of 4RIF vs. 9INH for LTBI – Phase 2

Serious Drug Related Adverse Events

	4 RIF (N=420)	9 INH (N=427)	P-value
All Grades – Total (%) *	**16 (3.8%)**	**24 (5.6%)**	NS
Grade 3 to 4 - Total	**6 (1.5%)**	**17 (4.0%)**	.02
- Hepato-toxicity	**3 (0.7%)**	**16 (3.8%)**	**.003**
- Hematologic	**1**	**1**	-
- Drug Interaction	**1**	**0**	-
- Rash	**1**	**0**	-
Grade 1 to 2 - Total	**11 (2.0%)**	**7 (1.6%)**	NS
- Rash	**8**	**4**	NS
- GI intolerance	**1**	**2**	-
- Hematologic	**2**	**0**	-

* Severity, type + relationship to study drug by independent blinded 3-member panel

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Phase 3 – Effectiveness and efficacy

RCT of 4RIF vs 9INH for LTBI – Phase 3

Objectives of Phase 3

- Primary objective (effectiveness)
  - Compare incidence of confirmed active TB in all randomized in the 28 months post-randomization
  - "Pragmatic" trial – estimate under programme conditions.
- Secondary objectives
  - Compare incidence of confirmed active TB in those who took at least 80% of doses within maximum allowed time (efficacy)
  - Compare incidence of confirmed plus clinical active TB in all randomized
  - Compare serious adverse events

RCT of 9 INH vs. 4 RIF for LTBI – Phase 3

Study design

- Design - open label randomized trial. Pragmatic
- Multi-centre. Randomization – variable blocks, stratified by centre.
- Primary outcome:

  Occurrence of confirmed active TB within 28 months post-randomization.

Planned analyses

- Intention to treat (= effectiveness)
  - All outcomes in those randomized to each arm
  - Regardless of actual compliance
  - Gives idea of public health impact of each arm
- Per protocol (= efficacy)
  - Outcomes in those who took >80% of doses
  - Answers “Doctor, if I take this medicine, how much protection will I have?”
  - BUT – this requires regular assessment of compliance
    - Pill count is protocol mandated method

RCT of 4RIF vs 9INH for LTBI – Phase 3

Study Centres

- 4 in Canada
  - Montreal (Chest), Saskatoon, Edmonton, Vancouver
- International sites
  - Australia (Sydney)
  - Benin (Cotonou)
  - Brazil (Rio de Janeiro - 2 sub-sites)
  - Ghana (Kumasi)
  - Guinee (Conakry)
  - Indonesia (Bandung)
  - Korea (4 sub-sites)
  - Saudi Arabia - Riyadh

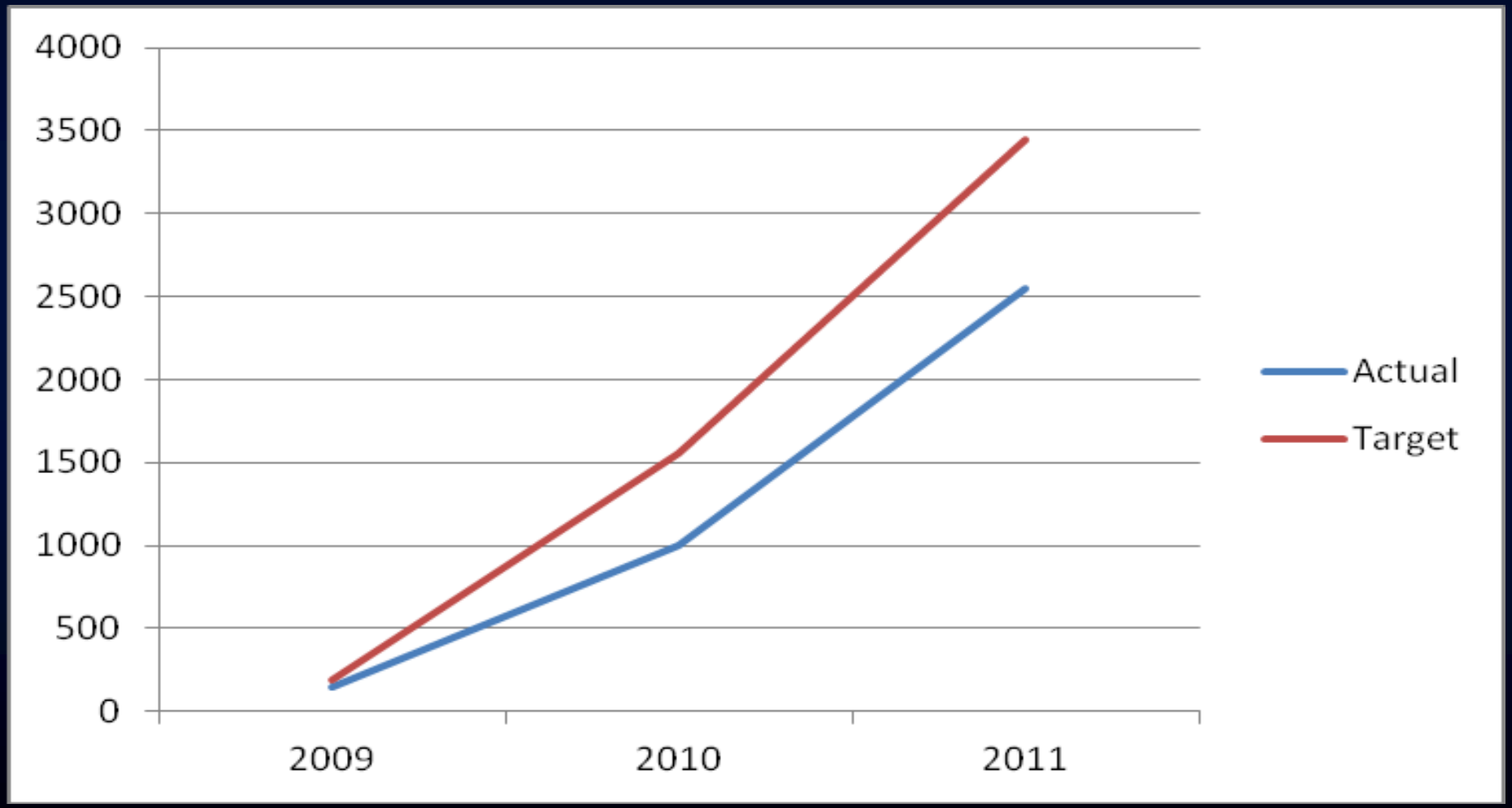
Sites in RCT Phase 3

RCT of 4RIF vs 9INH for LTBI –

Progress

- Study up and running in all sites
- One site never opened
- One very low enrolling site closed
- One low-enrolling site - budget cut in half
- One site – start delayed by a year due to civil unrest (coup / martial law / etc)
- Two new sites identified and opened
- First and second interim analyses for safety – no concerns of DSMB

Planned vs actual enrolment



RCT of 4RIF vs 9INH for LTBI –

Timelines of Phase 3

- Planned enrolment is almost 6,000 persons
  - Feb 15: 4,100 enrolled
- Pediatric trial added – 822 children
  - Feb 15: 398 enrolled
- Enrolment until Dec 2013
- Final follow-up will end in April 2016
- Publication in July 2016
- Wish us luck
  - (even just to survive!!)