Challenges in dealing with the TB epidemic

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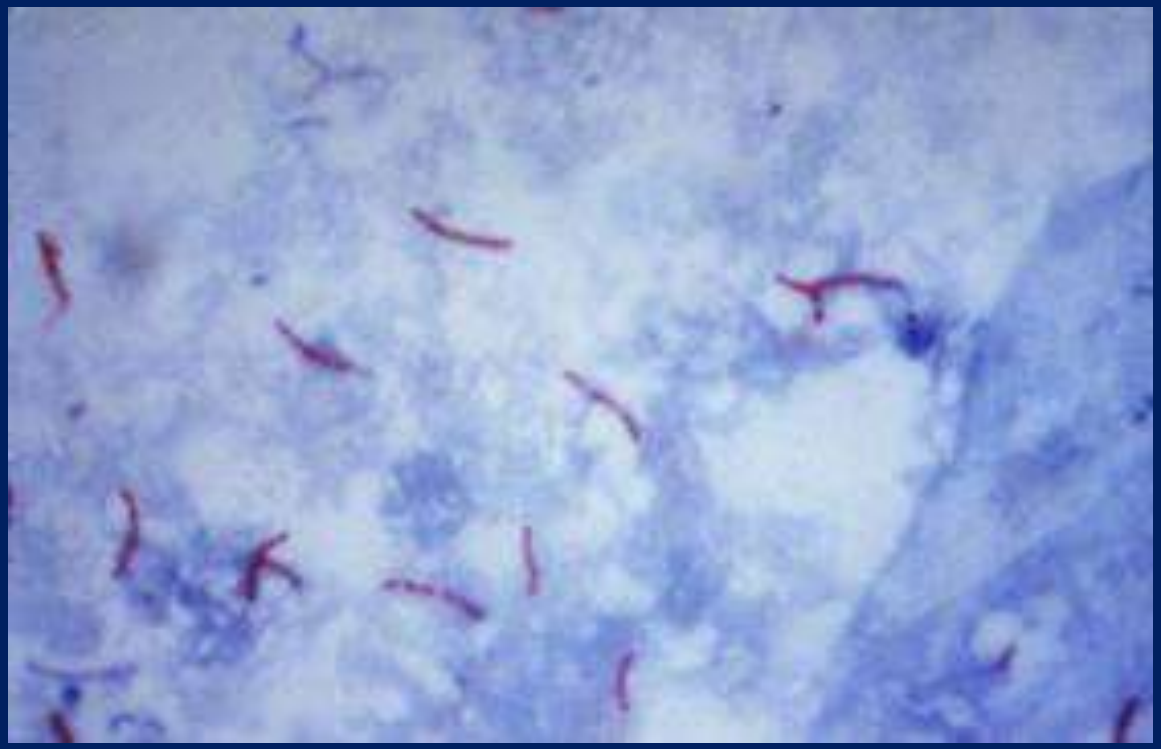
A personal view

Tuberculosis (TB)

- Infectious disease, transmissible through aerosols produced by patients with cavitary pulmonary disease.
- Diagnosis
  - Radiography to detect abnormal shadows
  - Microscopy to detect AFB in the sputum
  - Culture of the microbe and drug susceptibility
  - Molecular methods
- Treatment

  Antibiotic combination that has the possibility to cure >95% of patients

Acid-Fast Bacilli (AFB) after Ziehl-Neelsen staining of a sputum smear



<u>The microbe</u>

- Acid fast staining, a key for rapid diagnosis
- Slow growth (chronicity of the disease)
- High frequency of naturally occurring drug resistant mutants

The current short-course treatment for active tuberculosis

Duration: 6 months

Antibiotics: rifampin (R), isoniazid (H), pyrazinamide (Z), ethambutol (E) for 2 months followed with RH for 4 months (2RHZE/4RH)

Efficacy: > 95% vs. drug-susceptible TB… if

- all drugs are available,
- appropriately prescribed,
- appropriately delivered,
- and actually taken by the patient for the entire treatment duration

… BUT

First, some lessons from the past…

The IUAT trial, 1960

(IUAT Bull. 1964 ; 34 : 82-150)

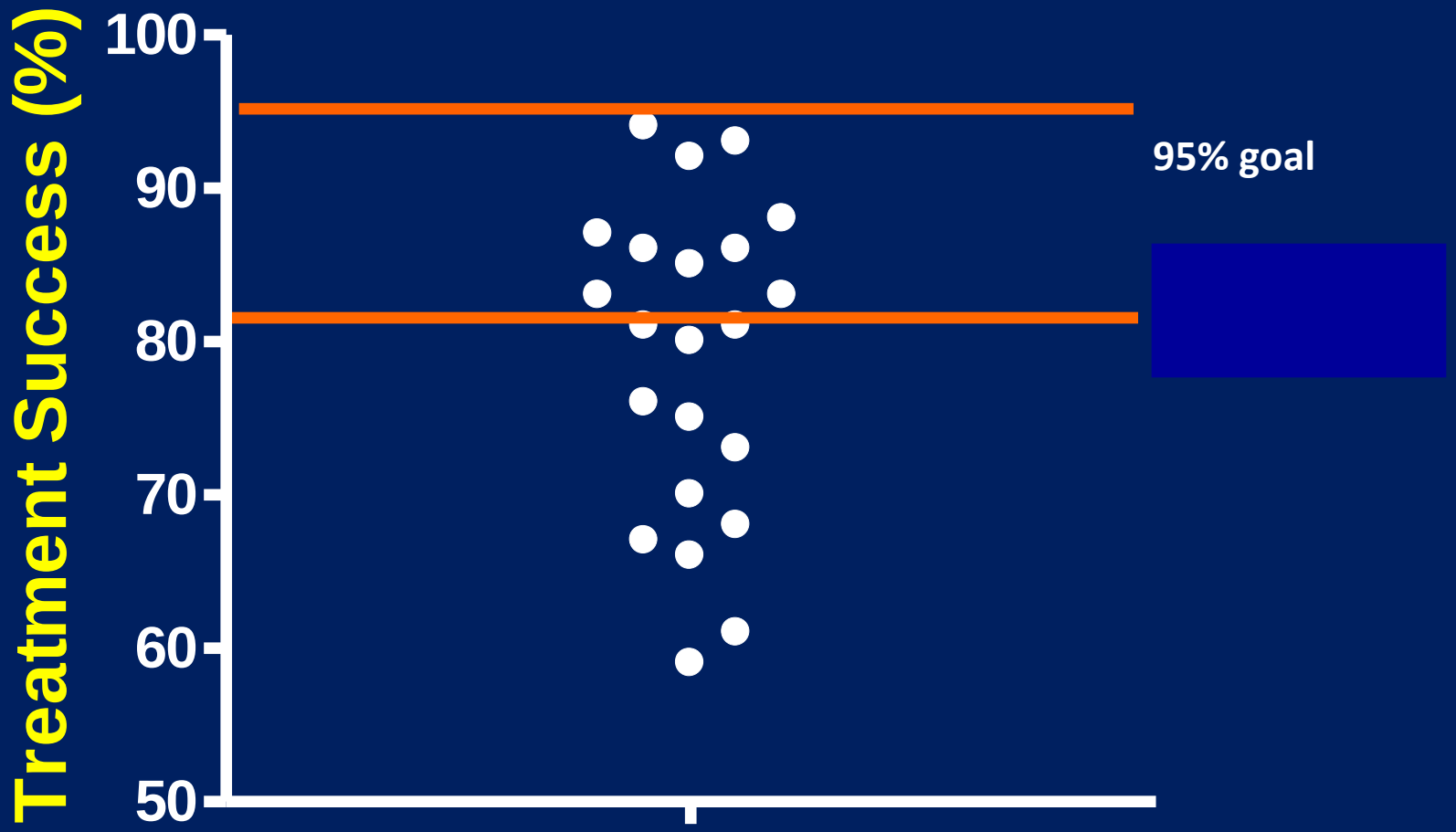
- At the end of the fifties, a majority of TB "experts" were still convinced that once a TB patient, always a TB patient (like a "leper"): a patient can be "stabilized" but never cured
- To convince those in doubt, a multi-center (Europe, Asia, America, Africa) study was conducted under the auspices of IUAT among 581 smear +ve patients with pulmonary TB to study the efficacy of 18 months daily treatment with 3SHP*/15HP
- The results were unambiguous…

*(S, streptomycin 1g IM; H, isoniazid 300mg per os ;
P, PAS 10g per os)

A painful finding

- All of the patients (n= 317) who received the prescribed regimen were cured (not a single failure!)
- But … almost 50% of the patients did not receive or did not take the prescribed regimen for the full duration, and … did not perform as well
- Conclusion: There is a long way between theory and practice! The development of XDR-TB, a man-made phenomenon, was predictable in the sixties!

Treatment Success in the 22 High-Burden Countries



In addition, many TB programs are detecting no more than 50% of estimated number of cases

WHO Global TB Report, 2006

Consequences 1.

Forms of TB	Cases		Deaths
	Incident	Prevalent	
All	9.4 million (1.1 or 12% HIV +ve)	14 million	1.3 (HIV -ve) + 0.4 (HIV +ve)
MDR-TB	440,000 (4.6%)		?
XDR-TB	30,000 (0.3%)		?

*

Global TB 2007-2009 , WHO

Consequences 2. Epidemiological impact of treatment failures

Intervention	Died	Cured	Chronic*	Epidemiological impact
No treatment	50%	25%	25%	0
Adequate treatment	1-5%	≥ 95%	1-5%	Very positive
Inadequate treatment	15%	50%	35%	Negative**

* including failures, treatment abandons, etc. = still sources of infection

** inadequate treatment produces many more chronic patients, i.e. many more sources of infection in the community than no intervention at all, and a proportion of them are drug resistant!

What could we propose?

Innovation, innovation, innovation!

- Innovative techniques in tuberculosis are urgently needed …and thus should be funded and implemented
- However, innovative techniques will not substitute for ensuring regularity of drug-taking, which is the key to success…
- except if we discover a magic bullet (vaccine, drug, or long-lasting fixed drug combination) that would only need to be shot once!

How to innovate?

Some examples…

I. The patients to cure

- While everyone is focused on the treatment of MDR-TB, the exclusive* priority should be given to the cure of the fully drug susceptible new cases
- Why?

  - Because the priority is to cut the vicious circle "Treatment failure of new cases-production of MDR-difficulty in treating MDR"

  - Because it is much easier to cure new cases than MDR

  - Because if we are not able to cure *easy-to-cure* new cases we are not able to cure *difficult-to cure* MDR

*in case of flooding in your bathroom what are you doing?

Ia. Improving cure rate of TB

- Stop talking about care or treatment of patients, talk only of "cure". The only acceptable objective is to cure every diagnosed patient
- How?
- Make complete treatment available and insure that the patients swallow their medicines from initiation to completion of treatment
- How to make patients swallow their medicines?

  - education: +++ (of doctors, health workers, patients)

  - Real Directed Observed Treatment (DOT)

  - In many places, it would require a complete reorganization or re-invention, for example of "hostellization of patients"
- Develop much shorter drug regimens

1b. Develop much shorter TB drug regimens

- Better use of existing drugs
- Use of new drugs

“New” potential drugs for TB

1. Long-lasting rifamycin derivatives (rifapentine)
2. Fluoroquinolones (MXF)

*3. the new diarylquinoline TMC207 or J

*4. the metronidazole derivatives (Pa-824, OPC-67683)

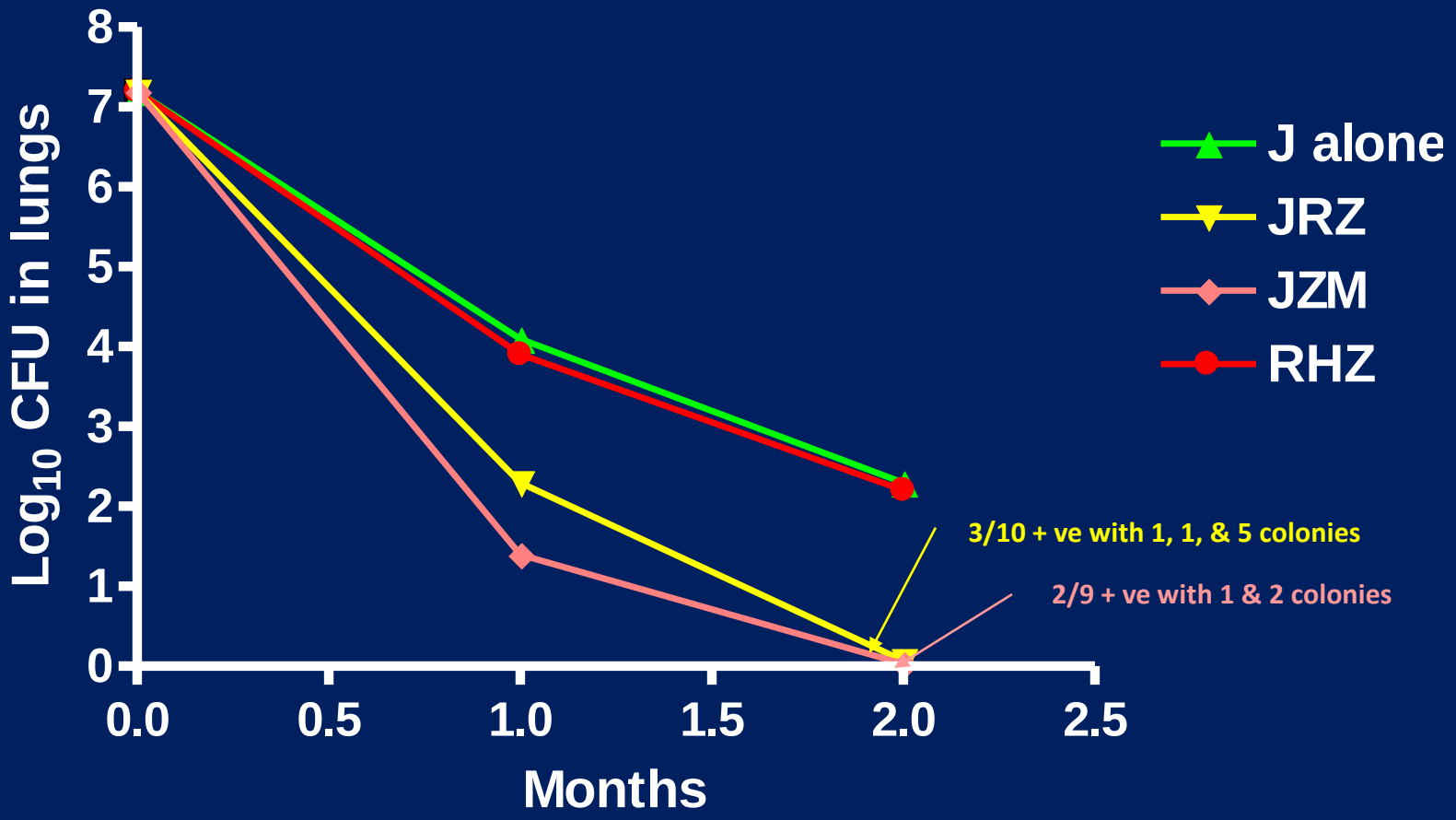
5. Oxazolidinones
6. Benzothiazinones (BTZ)

*7. Clofazimine

Diarylquinoline R207910 or "J"

- MIC for *M. tuberculosis* = 0.06 µg/ml
- C_{max} of 0.5µg/ml and $t_{1/2}$ of 24h: after single dose, serum concentrations are above MIC for 3 days !
- Time-dependent activity: the anti-bacterial starts after several days of exposure in vitro and in humans
- No cross-resistance with known drugs
- Inhibit the proton pump of ATP synthase

Bactericidal activity of J combinations in the mouse model of TB

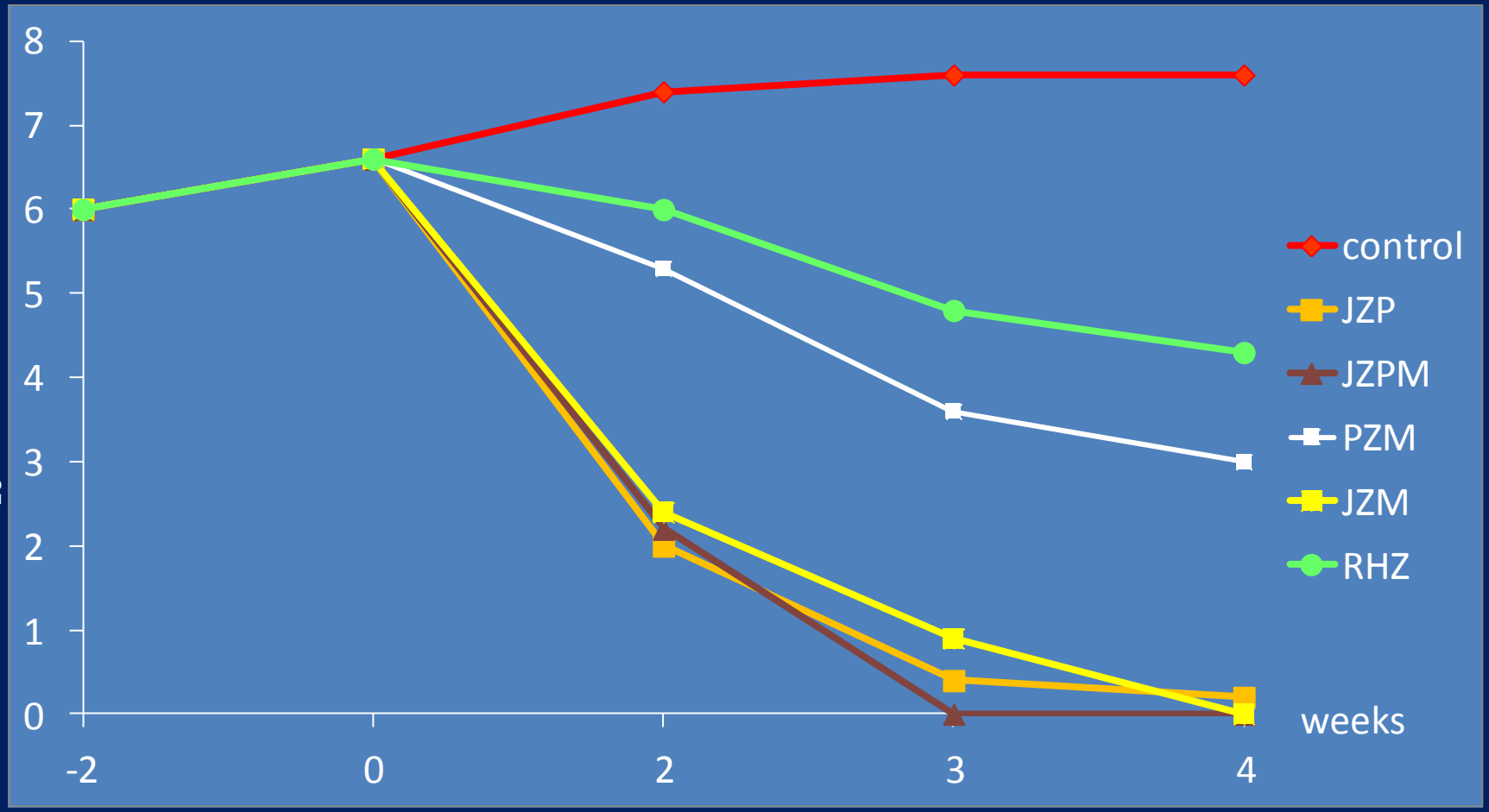


J, diarylquinoline 25mg/kg; R, rifampin 10mg/kg; Z, pyrazinamide 150mg/kg; H, isoniazid 25mg/kg

Daily (5/7) oral treatment; 10 mice per time point

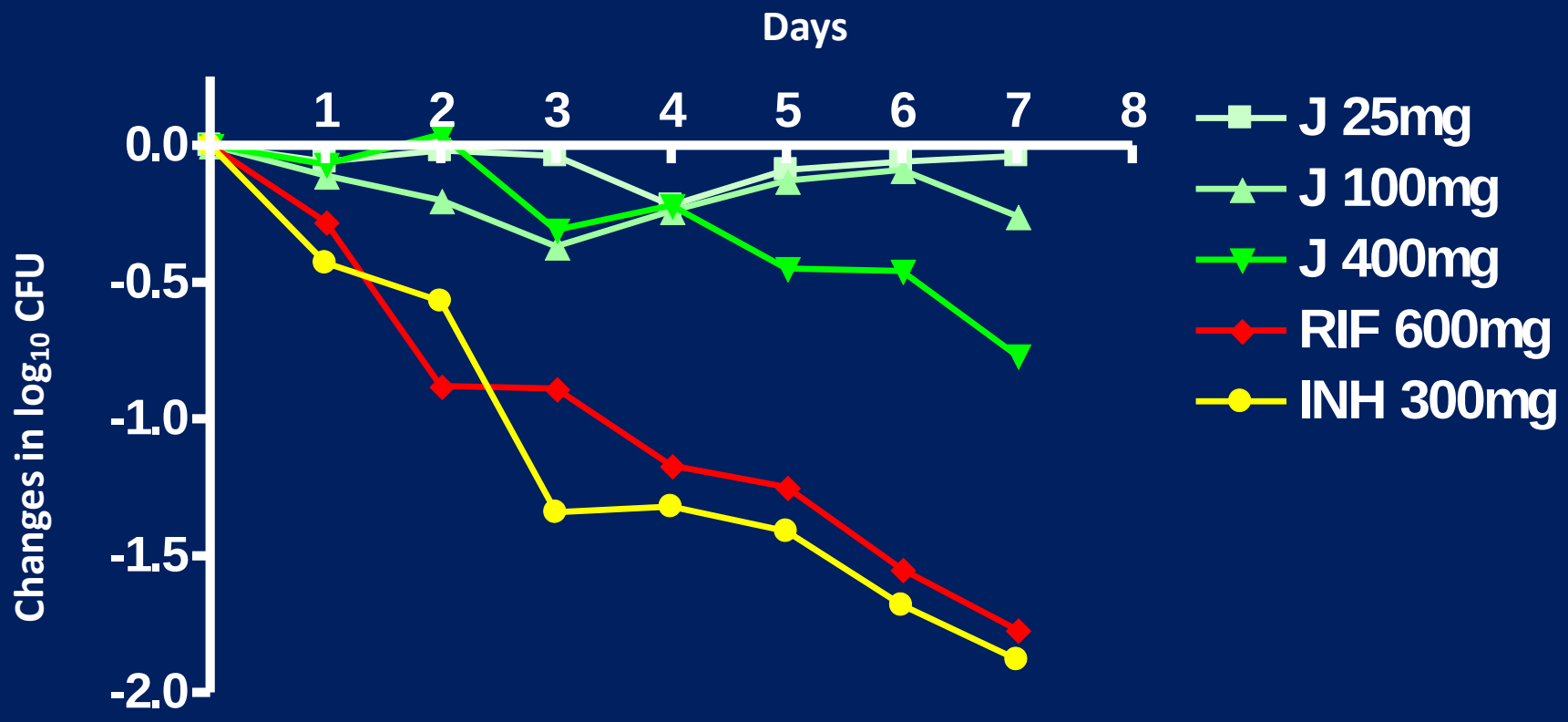
(From Ibrahim et al., AAC 2007; 51:1011-1015)

Early bactericidal activity of J-containing regimens in mice

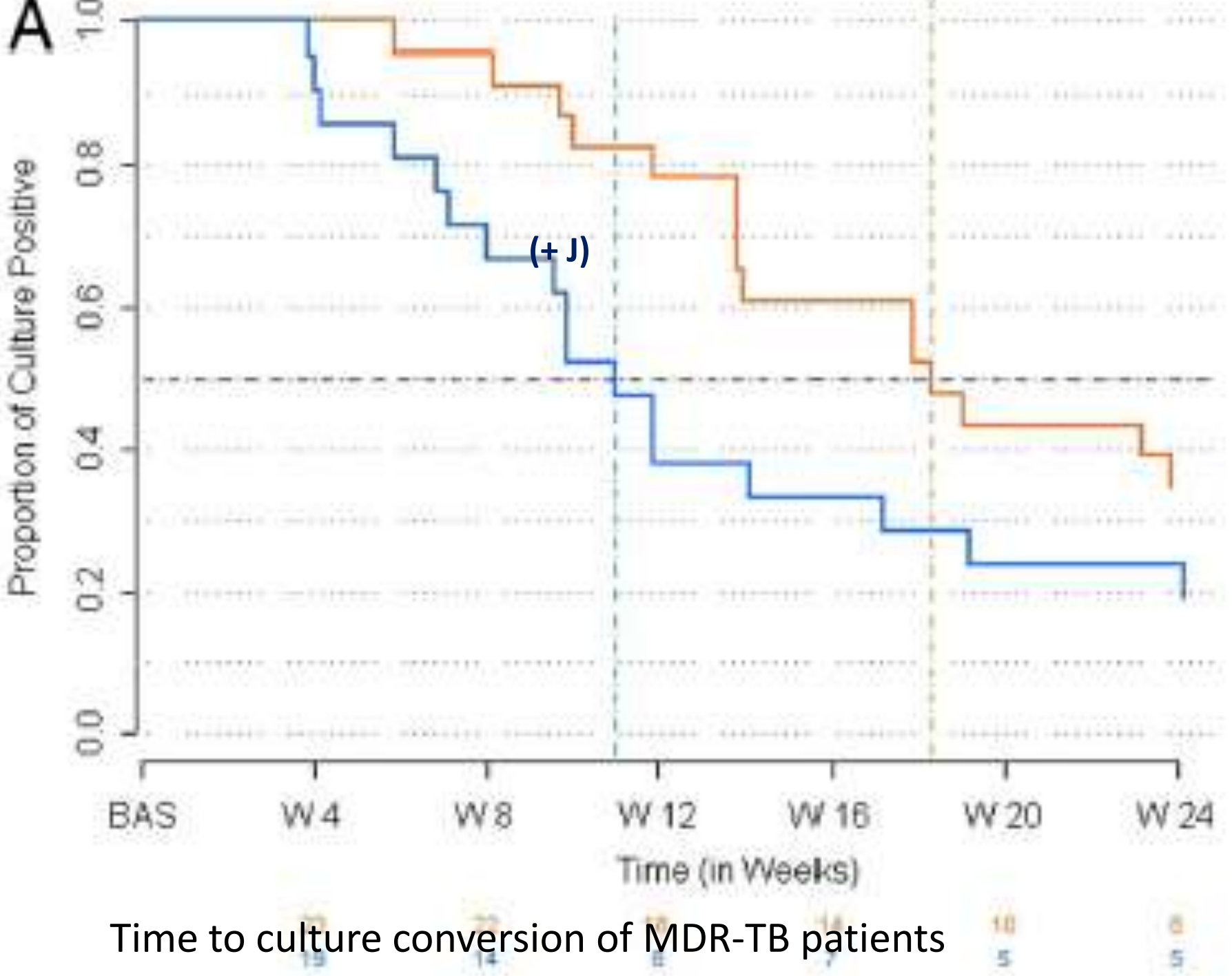


From Andries et al., Antimicrob Agents Chemother 2010; 54: 4540-4544

Early Bactericidal Activity (EBA) of the Diarylquinoline



(From Rustomjee et al. AAC 2008; 52: 2831–2835 **)**

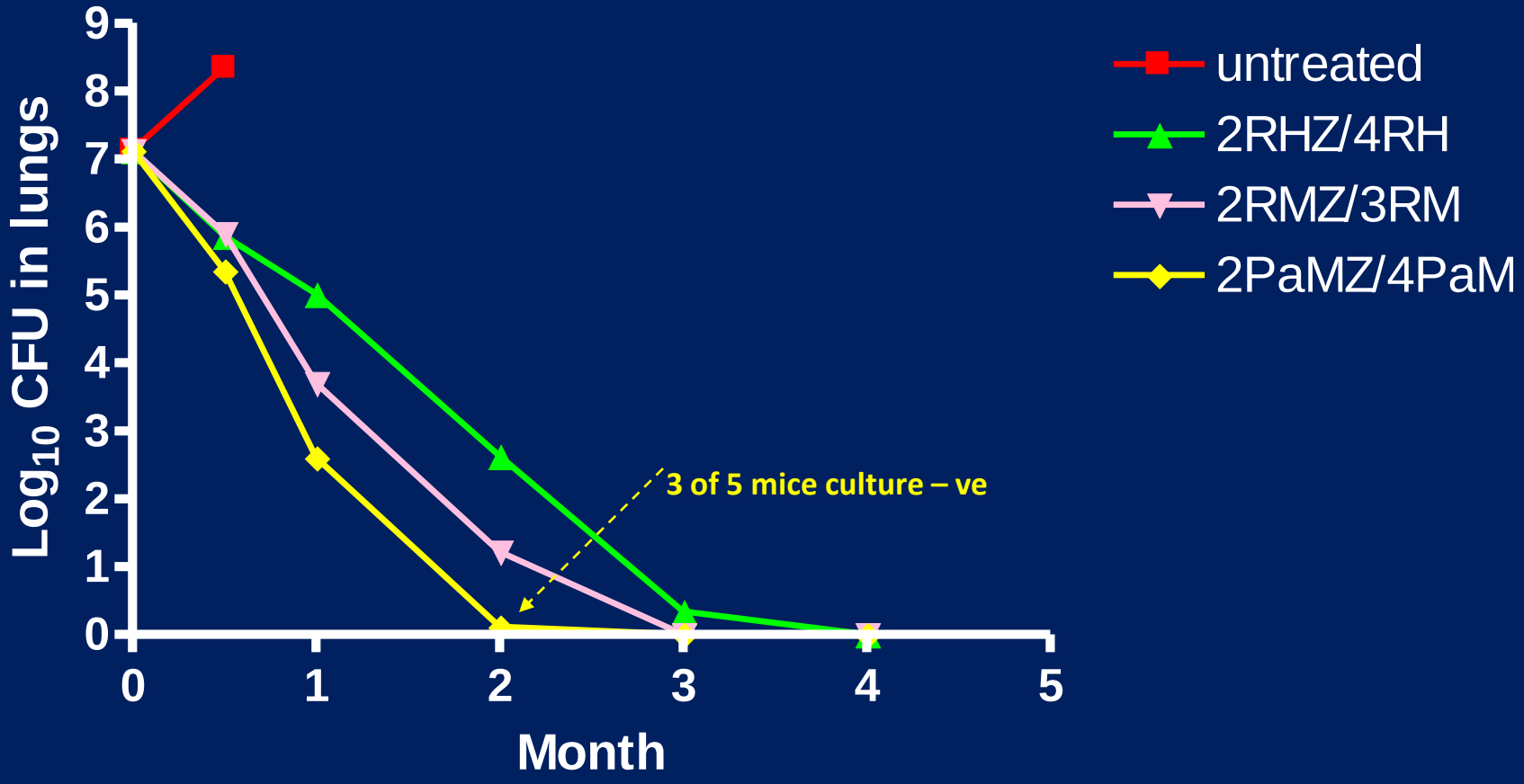


Time to culture conversion of MDR-TB patients

Nitroimidazopyran Pa-824

- MIC of 0.12-0.25 µg/ml for *M. tuberculosis*
- Cmax of 20 µg/ml and $T_{1/2}$ **of** 12 – 14 hr in mice after 100mg/kg dose in mice
- Concentration dependent activity
- Might inhibit protein and cell wall mycolate synthesis

Lung CFU counts in mice treated with Pa without RIF and INH



(Nuermberger & al. AAC 2006;50:2621-2625).

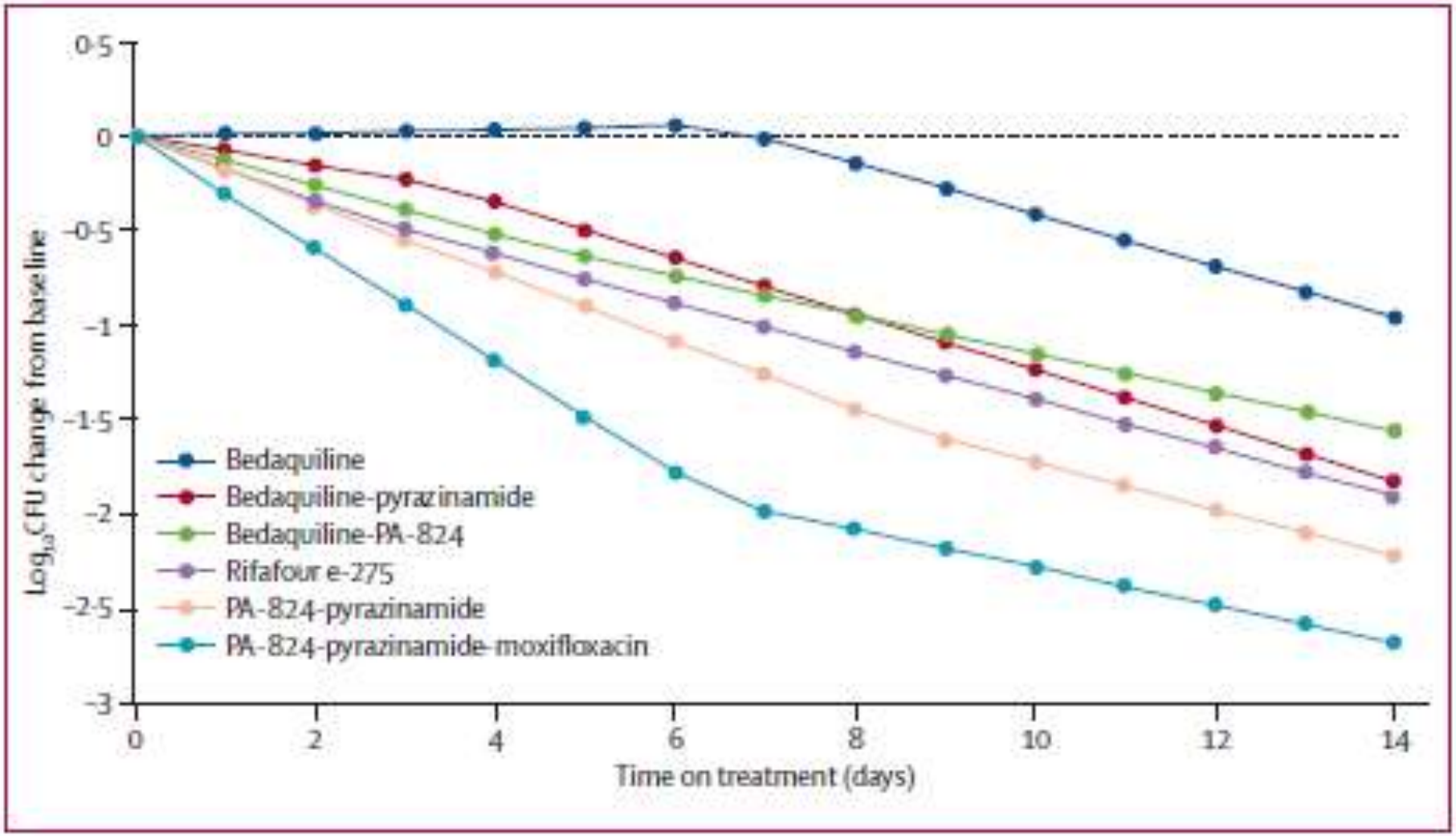


Figure 2: **Bilinear regression showing the fall in mean log_{10}CFU from baseline**

CFU=colony forming unit.

The case of clofazimine

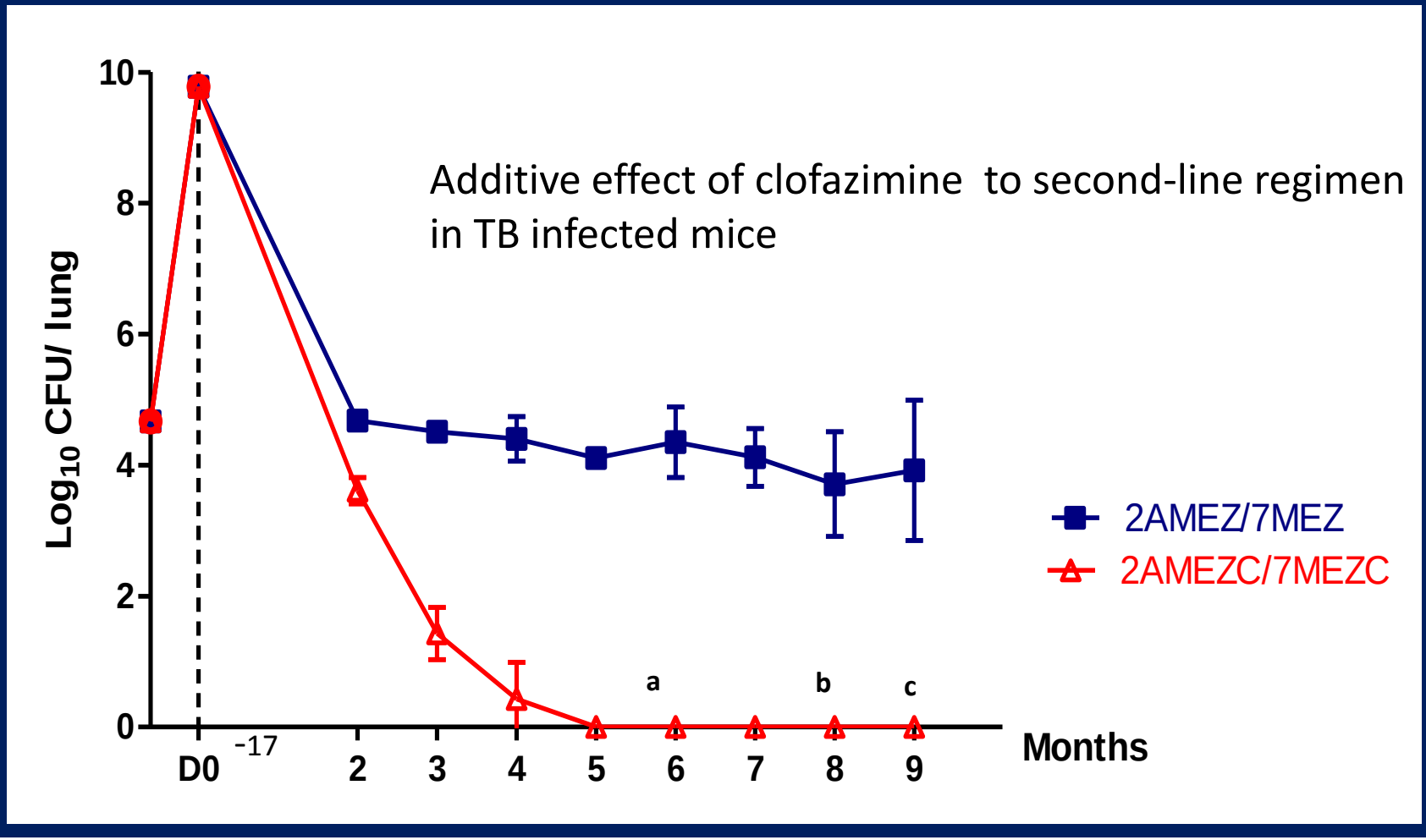
- Clofazimine is a rimino-phenazine dye developed by Vincent Barry in the fifties for treatment of TB that became a leprosy drug (100mg/day):

  - Its MIC for *M. tuberculosis* is 0.5 µg/ml.

  - As its half life is about 70 days, it accumulates in the tissues; after 2 months of treatment, the lung concentration in mice and humans is on average 1000 µg/gm (Grumbach 1960; Mansfield 1974)

  - After stopping treatment, it takes ≥ 2 years for tissue concentration to be less than 0.5µg/gm.

- A 9-month drug regimen including gatifloxacin + ethambutol + pyrazinamide and clofazimine throughout achieved in Bangladesh (Van Deun et al., Am J Respir Crit Care Med 2010; 182: 684–692 close to 90% relapse-free cure rate.



A , Amikacin 100mg/kg; M, Moxifloxacin, 100mg/kg ; E , Ethambutol, 100mg/kg ; Z, Pyrazinamide 150mg/kg, C, Clofazimine 25mg/kg

[a] a single mouse was culture-positive on undiluted charcoal plates with 14 and 17 CFU (drug susceptible)

[b] one mouse was positive on both undiluted plain (14 and 21 CFU) and charcoal (79 and 81 CFU) plates. This isolate was clofazimine resistant but remained moxifloxacin and ethambutol susceptible

[c] one colony each on mouse 1 and mouse 2 lung homogenate at 1:10 dilution

An ultra short-course regimen to test

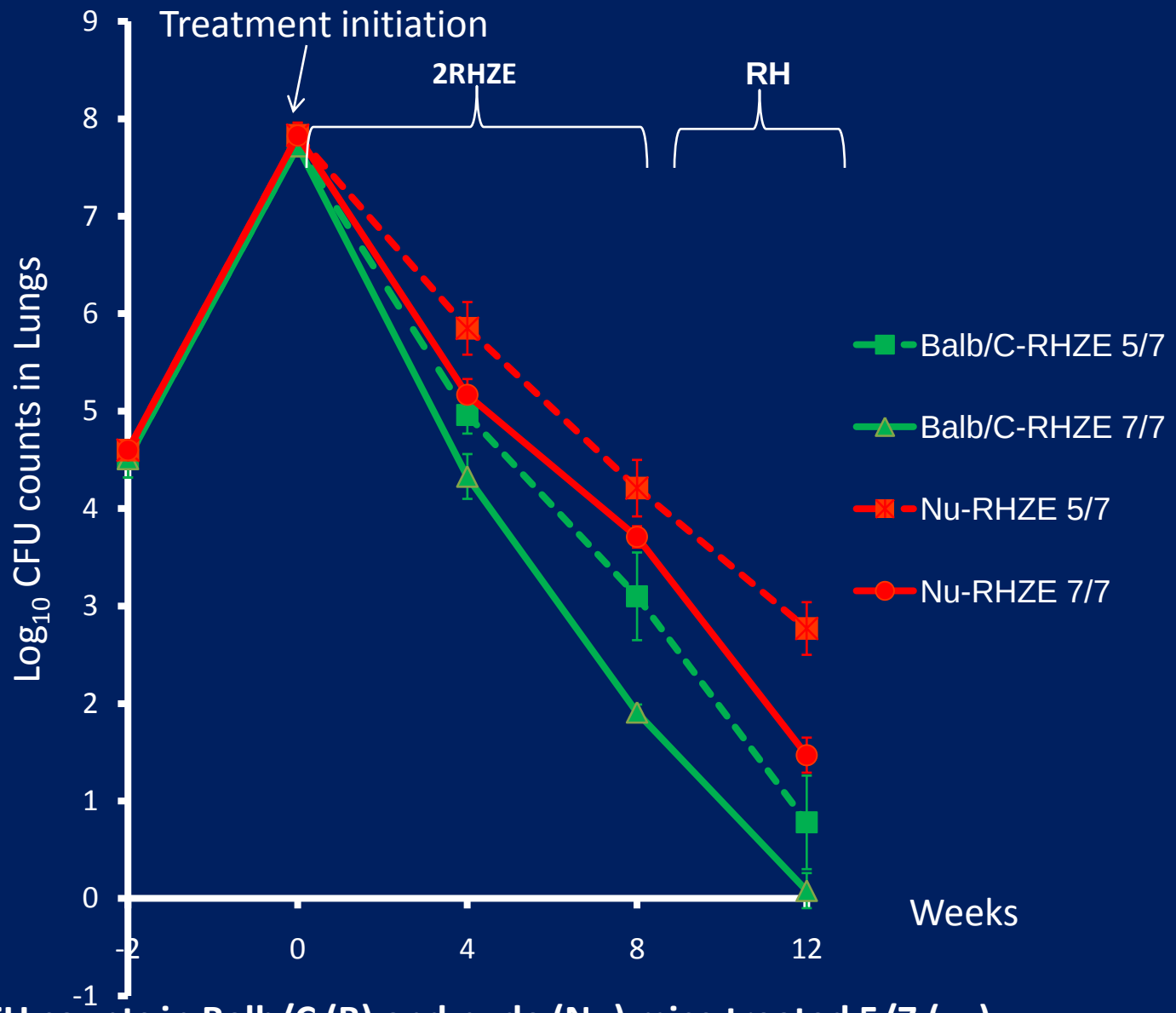
- Rationale: Take advantage of both the potent bactericidal activity of RHZE and the Pk of clofazimine (long half life and accumulation in lung tissue)
- Protocol:

  1. Combine the most effective drug regimen (RHZE) with clofazimine for a relatively short period of time (2-4 months) to kill majority of bacilli, then stop treatment and let the “accumulated” clofazimine do the job of eliminating persisters

  2. Other possibilities: (i) Substitute the diarylquinoline TMC 207 for clofazimine; (ii) Substitute moxifloxacin for isoniazid after the first two days of treatment

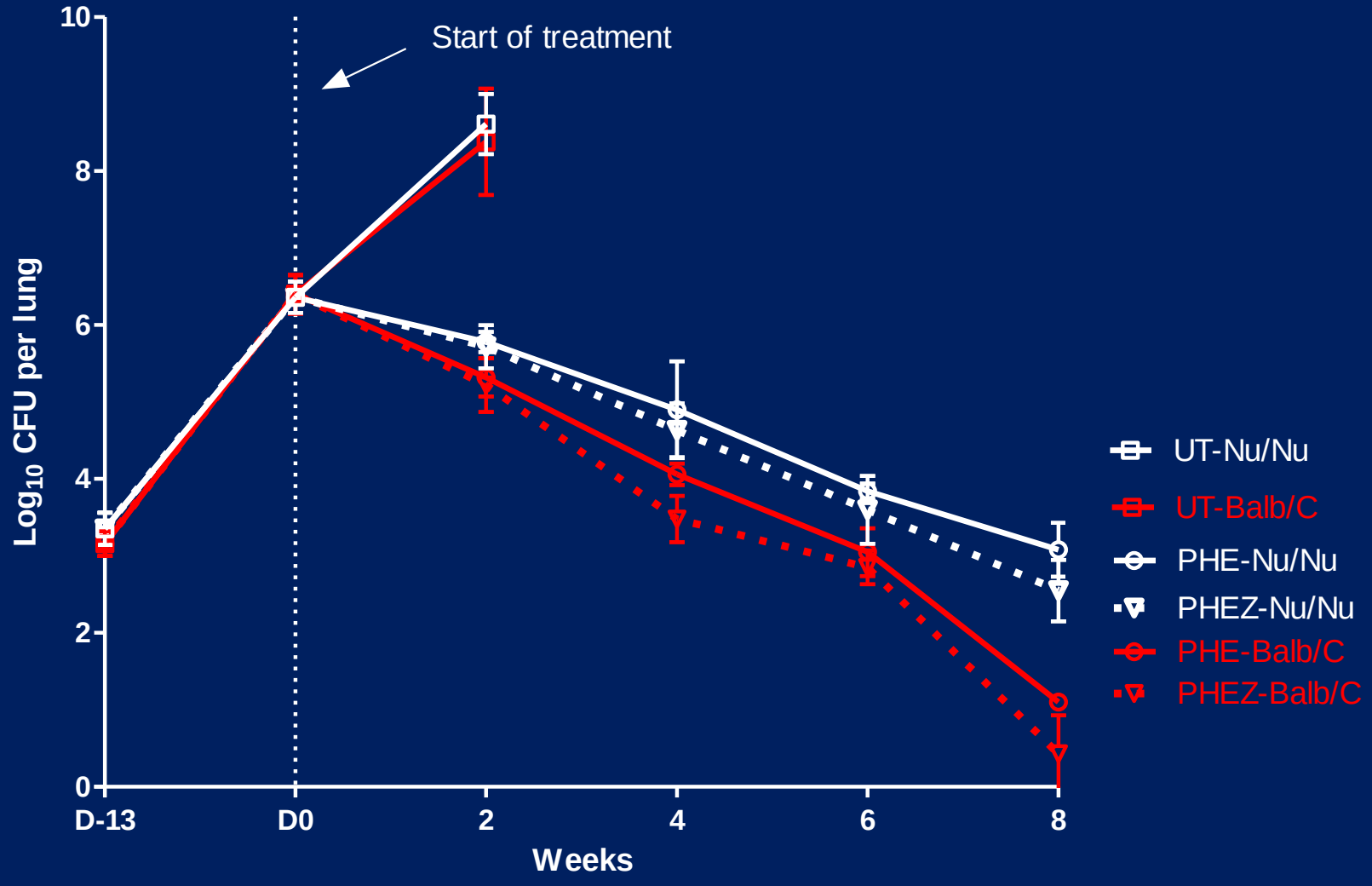
2. Treatment of TB in HIV-infected patients

- HIV-infected TB patients respond as well as immune competent patients to TB treatment
- Is it a dogma or a reality?



Lung CFU counts in Balb/C (B) and nude (Nu) mice treated 5/7 (---) vs 7/7 (—) with RHZE

PHE versus PHEZ in BALB/c and Nude mice



Conclusion 2

- Response to treatment is less active (≤ 1.5 $\log_{10}$ less kill) in immune-deficient than immune-competent mice
- As a consequence, irregularity in drug-taking (5/7) + immune deficiency is a risky combination for failure and drug resistance
- These findings support the earliest antiretroviral treatment in TB patients co-infected with HIV

Final conclusion

- More than ever there is a huge amount of TB research to be performed and the research is more difficult than before. The easiest has been done, the most difficult remains to be done.
- Do not believe in dogma, in short-cuts, in easy-going
- Do remember that implementation in the field is more problematic than pure science in the lab.

Acknowledgments

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