

# Evaluation of high-dose rifapentine plus clofazimine in the first-line regimen for tuberculosis in the mouse model of chemotherapy

**Vikram Saini, MD**

Post-doctoral Fellow

Johns Hopkins University School of Medicine

Baltimore, USA



# The focus of our research is to shorten the duration of tuberculosis treatment

The first-line regimen for drug-sensitive TB treatment is 6 months in duration: “**2RHZE/4RH.**”

A shorter treatment regimen would be beneficial

- for the patient;
- for TB control programmes; and
- **for preventing the development of MDR-TB.**

# The focus of our research is to shorten the duration of tuberculosis treatment

The first-line regimen for drug-sensitive TB treatment is 6 months in duration: “**2RHZE/4RH.**”

In the BALB/c mouse model of TB chemotherapy:

- 2RHZE/4RH is also curative;
- adding clofazimine ( $\geq 12.5$  mg/kg) shortens treatment to 3-4 months<sup>1</sup>; and
- replacing rifampin (10 mg/kg) with high-dose rifapentine (20 mg/kg) shortens treatment to 3 months<sup>2</sup>.

<sup>1</sup>Tyagi *et al.* *PNAS* 2015;112:869. <sup>2</sup>Rosenthal *et al.* *AAC* 2012;56:4331.

# **Hypothesis:**

**Replacing rifampin with high-dose rifapentine**

**AND**

**adding clofazimine**

**in the first-line regimen will further decrease the duration of treatment necessary to achieve relapse-free cure in the BALB/c mouse model of TB chemotherapy.**

# Approach

- BALB/c mice (n = 307) were aerosol-infected with *M. tuberculosis* H37Rv.
- Treatment was initiated 2 weeks after infection with one of the following regimens:
  - RHZE (positive control)
  - RHZEC
  - PHZE
  - PHZEC
  - Untreated (negative control)

---

R, rifampicin 10 mg/kg

Z, pyrazinamide 150 mg/kg

**C**, clofazimine 12.5 mg/kg

H, isoniazid 10 mg/kg

E, ethambutol 100 mg/kg

**P**, rifapentine 20 mg/kg

# Outcomes

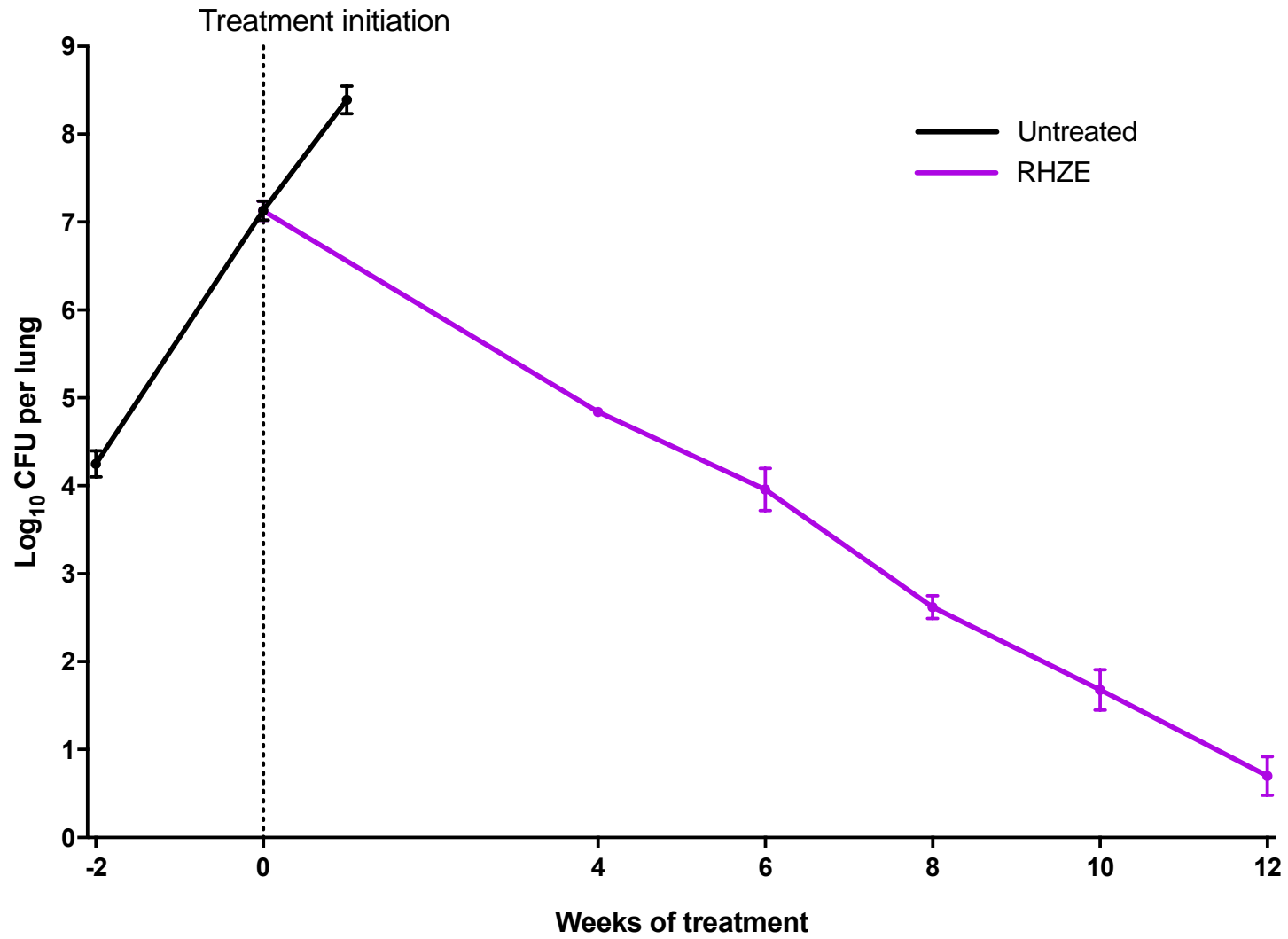
## Bactericidal activity:

The decline in the bacterial burden (CFU counts) in the mouse lungs during treatment (5 mice per group per time point)

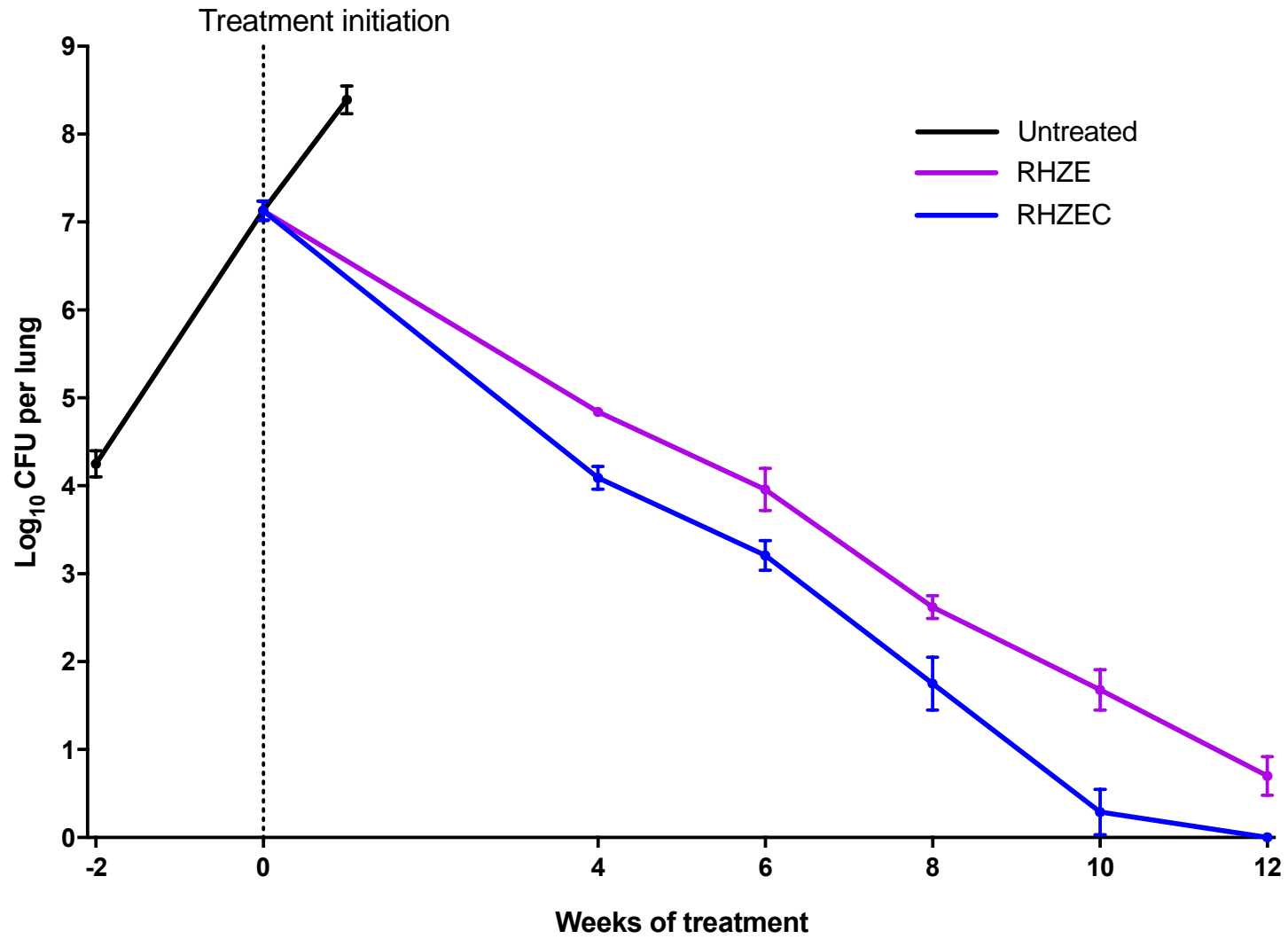
## Sterilizing activity:

The proportion of mice with culture-positive lungs 6 months after stopping treatment (18-20 mice per group per time point)

# Results: Bactericidal activity

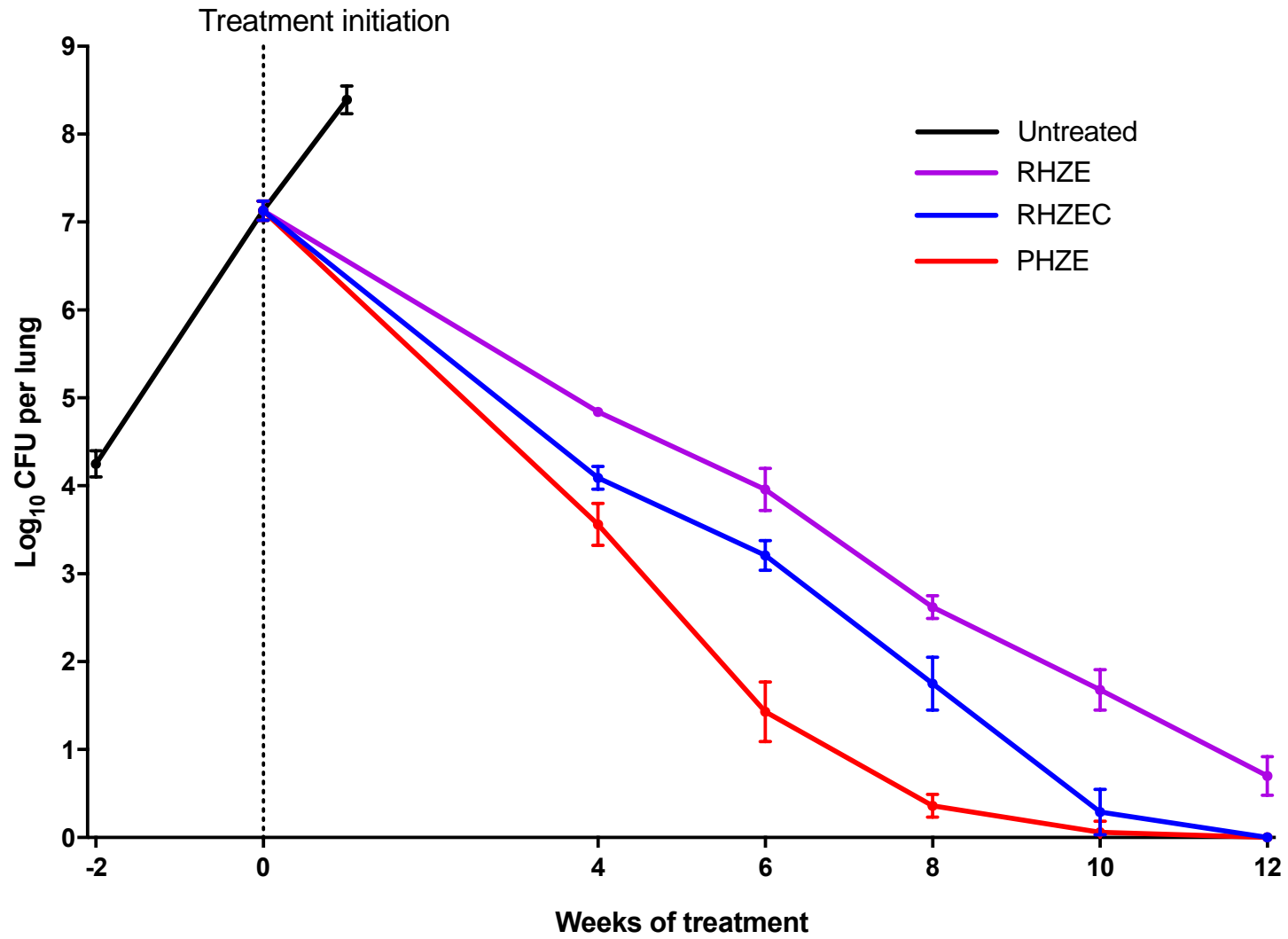


# Results: Bactericidal activity

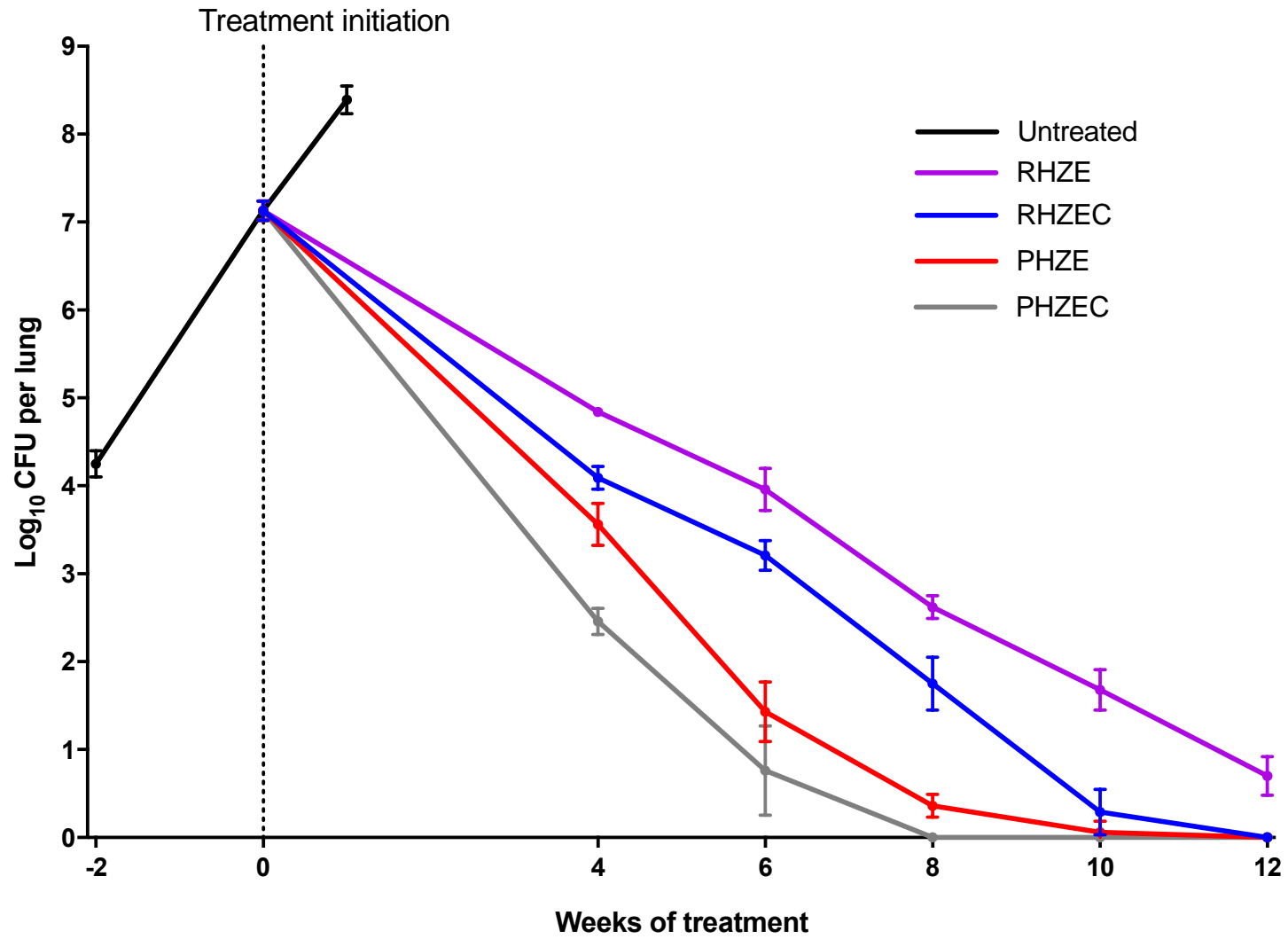




# Results: Bactericidal activity



# Results: Bactericidal activity



## Results: Sterilizing activity

Regimen	Proportion of BALB/c mice with culture-positive lungs 6 months after stopping treatment that was administered for the following duration:			
	6 weeks	8 weeks	10 weeks (pending)	12 weeks (pending)
<b>RHZE</b>	---	---	---	
<b>RHZEC</b>	---	---		
<b>PHZE</b>	---	6/20 (30%)		
<b>PHZEC</b>	5/18 (28%)	0/18 (0%)		

--- not determined

## Results: Sterilizing activity

Regimen	Proportion of BALB/c mice with culture-positive lungs 6 months after stopping treatment that was administered for the following duration:			
	6 weeks	8 weeks	10 weeks (pending)	12 weeks (pending)
RHZE	---	---	---	
RHZEC	---	---		
PHZE	---	6/20 (30%)		
PHZEC	5/18 (28%)	0/18 (0%)		

--- not determined

# Summary to date

In the BALB/c mouse model of TB chemotherapy, high-dose rifapentine and clofazimine both added significant bactericidal activity to the first-line regimen, and when combined result in relapse-free cure after 8 weeks of treatment.

The TBTC study 31 is evaluating the use of high-dose rifapentine to shorten the duration of the first-line regimen to 4 months. Adding clofazimine to the first-line regimen might further reduce the treatment time necessary to achieve relapse-free cure in patients with drug susceptible TB.

# Future Directions

Relapse assessment will be completed in June 2017.

A similar study using the C3HeB/FeJ (Kramnik) mouse model, in which mice develop caseous necrotic TB lung lesions, is ongoing.

# Acknowledgements

- Nicole Ammerman
- Yongseok Chang
  
- Jacques Grosset
- Sanjay Jain
- Eric Nuermberger

## Funding:

- AIDS Clinical Trial Group, NIH
- Bill and Melinda Gates Foundation

