New Tools and New Strategies for Controlling HIV-Related Tuberculosis

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Tools for Treating and Preventing TB in HIV-infected People

Tools	Currently Available	In Development
Diagnostics	Sputum smear (ZN, auramine) Culture (LJ) Rapid culture (MGIT, BACTEC) NAA tests (TMA, RT-PCR)	Simple rapid cultures Immunodiagnostics Antigen-based detection
Treatment	First line drugs (IRZES) Second line drugs for MDR TB (Fluoroquinolones)	Fluoroquinolones Diarylquinolines Nitroimadazopyrans Ethambutol analogues Others
Preventive therapy	INH, INH/RIF	Rifapentine/INH
Other	ARVs Infection Control	?

Strategies for Controlling HIV-Related Tuberculosis: How are tools applied to reduce burden of disease?

Tools	Current Strategies	Future Strategies
Diagnostics	Diagnose symptomatic patients who present to health services. Rely on test (ZN) with 50% sensitivity Algorithm for smear negatives	Active case finding Contact evaluations Use of new technologies Joint TB/HIV case finding
Treatment	DOTS with first line drugs INH/EMB continuation phase in many settings	Shortened treatment Intermittent treatment Avoid drug interactions
Preventive therapy	Primary INH PT for limited time	New regimens (e.g., RPT) Continuous INH Secondary PT Mass PT
Other	ARVs for advanced disease No infection control	Earlier ARVs Enhanced infection control

Need for New Diagnostic Tests and Strategies

- <50% of cases detected in DOTS programs
- Smear sensitivity only 50%, less in HIV+
- High incidence of smear negative TB with high mortality
- Prevalence of active TB in many communities ~1%
- Good yield for active case finding

Rapid(er), simple culture methods

TK Medium

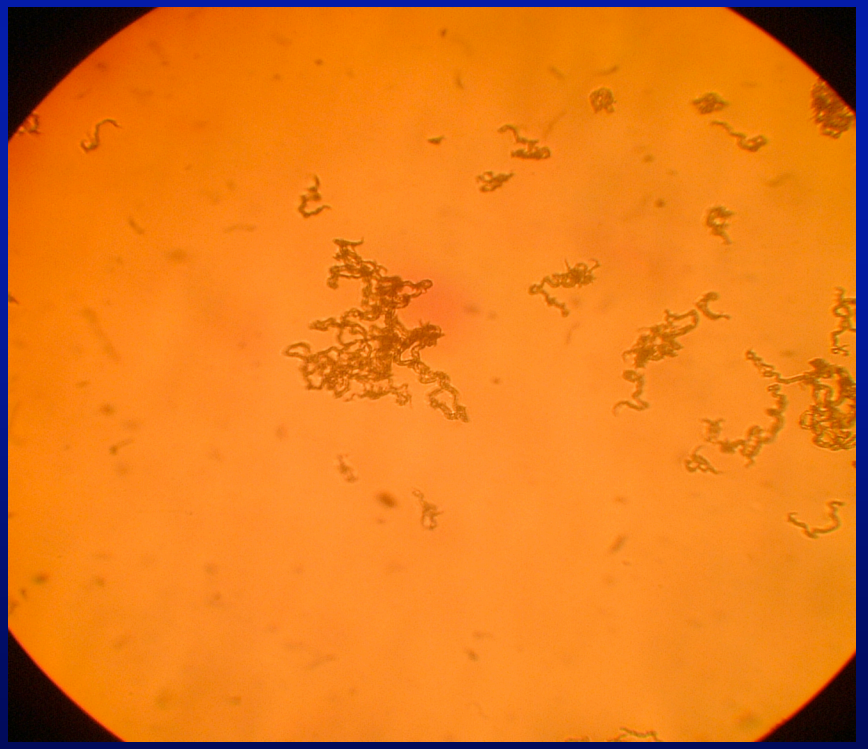
Colorimetric culture system

Results in 7-10 days

MODS System

Microscopic observation

Results in 5-10 days



Active TB Case Finding in HIV+ Women in pMTCT Programs in Soweto, South Africa

Study 1:

438 HIV+ women in nevirapine project given PPD

- 49% of 438 women are PPD+
- 13 have active TB (6% PPD+, 3% total)

Study 2:

366 pregnant women in community pMTCT program assessed by symptoms

- 8 have active TB (2.2%)
- Interview questions added 3 minutes to routine ANC visit

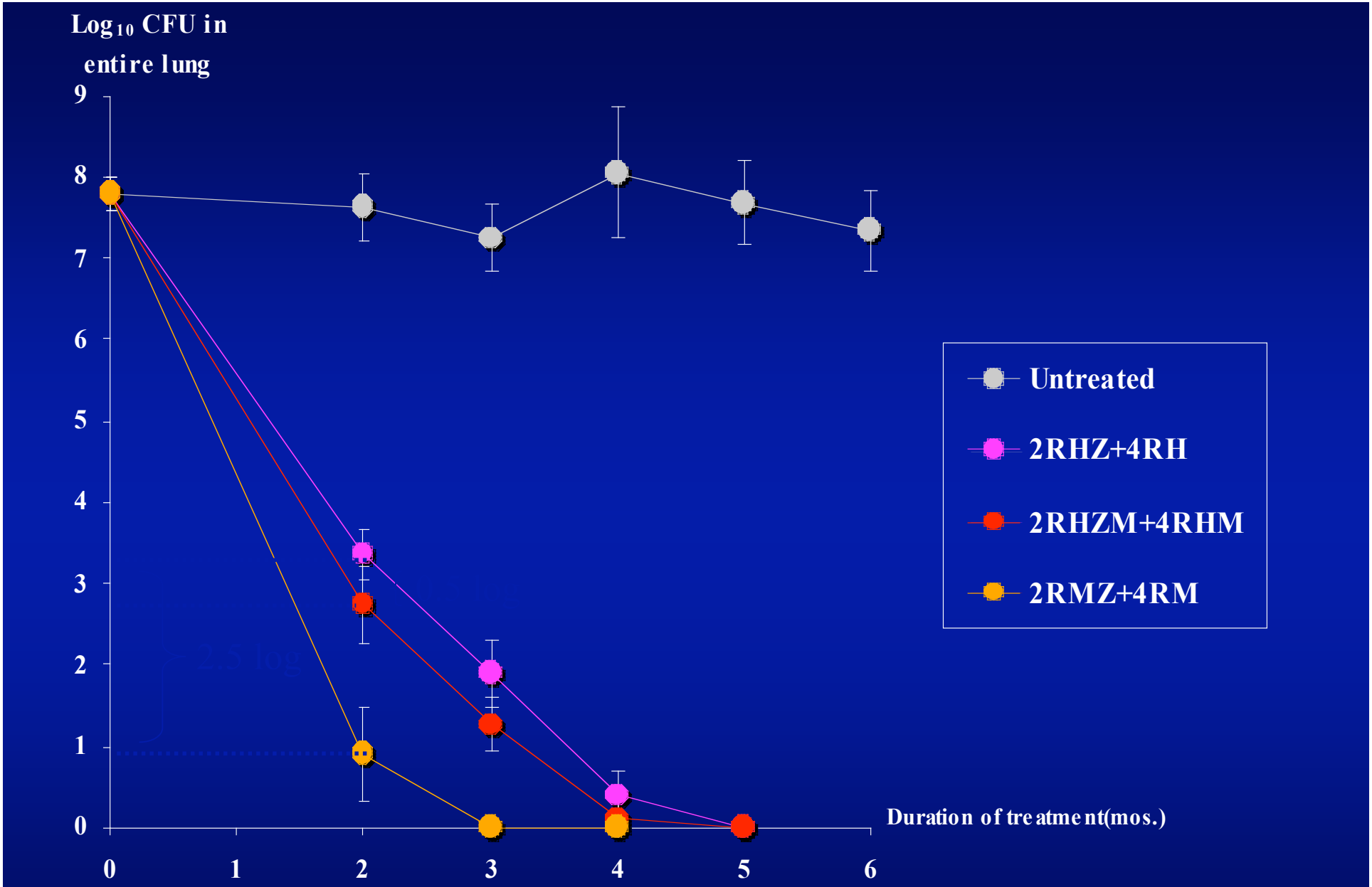
Nachega et al., AIDS 2003; Kali et al., WAC Bangkok, 2005

Improving TB Treatment Options for HIV/TB (and all TB) Patients

- Globally, ~40% of *diagnosed* TB patients fail to complete therapy
- Poor adherence associated with long (6-8 months) regimens
- Shorter duration regimens would improve treatment completion rates
- Regimens that can be easily given with ARVs urgently needed

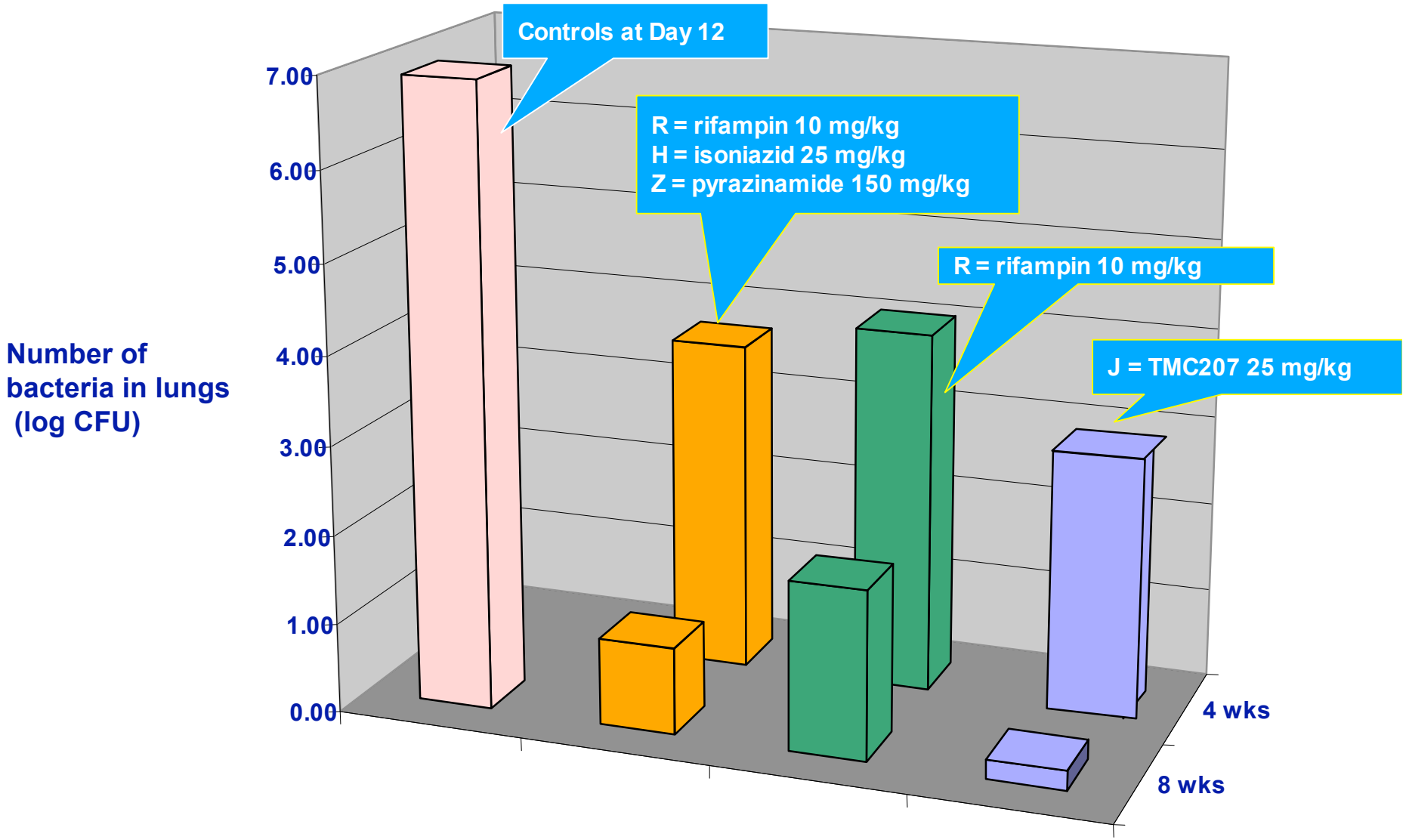
New Drugs for TB

- Fluoroquinolones
  - Moxifloxacin
  - Gatifloxacin
- TMC 207 (diarylquinoline)
- PA-824 (nitroimadopyran)
- Others



Effect of Moxi added or substituted for INH on log_{10} CFU counts from lung in mice with TB (Nuermberger et al., 2004)

TMC207 Activity in Established Mouse Model



Andries et al. Science 2005;307:223

(Treatment for 4 or 8 weeks)

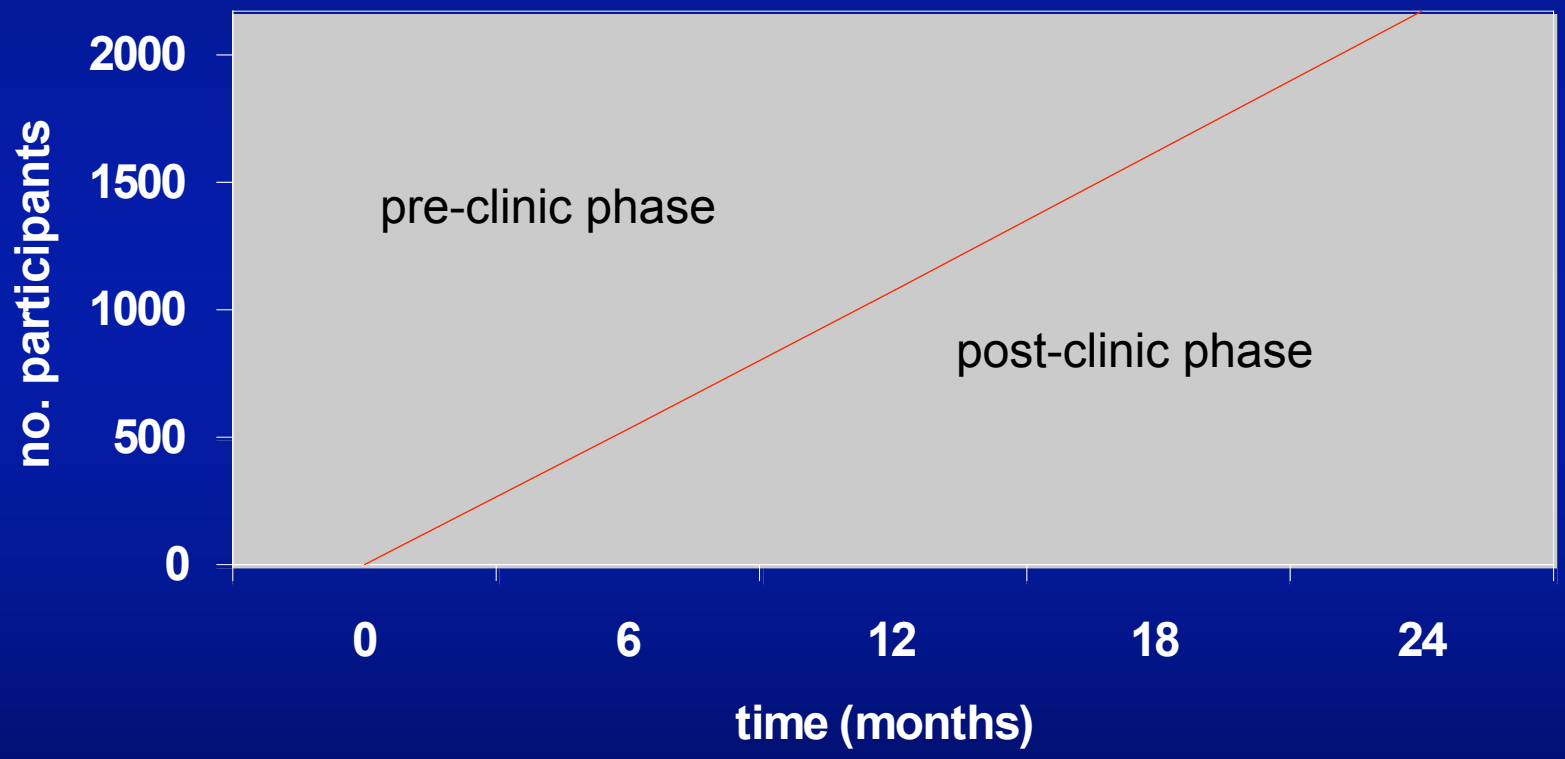
Preventive Therapy of HIV-Related TB

- INH PT reduces TB incidence but not mortality
- Greatest effect among TST+ individuals
- Rifamycin-based regimens as effective as IPT
- Durability limited in high incidence settings
- Growing evidence of efficacy of secondary PT
- PT still not widely used, despite low cost

Preventive Therapy of HIV-Related TB
Unresolved Issues and Opportunities

- What is optimal duration of INH?
- Who should get INH PT?
  - TST+ only, or high prevalence populations?
  - Patients starting ARVs?
  - Patients with prior treatment for TB?
- What are alternative regimens?
  - —Rifapentine/INH weekly x 3 months
  - —INH/Rifampin twice weekly or daily x 2-3 months
- What are alternative public health approaches?
  - —Mass preventive therapy?

Routine INH Preventive Therapy for ~1700 HIV+ Miners: A Randomized Recruitment Trial



Grant et al., JAMA 2005;293:2719-25

Effect of clinic on TB incidence: overall (N=1655)

	IRR (95% CI)
Unadjusted	0.78 (0.58-1.05), P=0.10
Adjusted for:	
calendar period	0.68 (0.48-0.96), P=0.03
calendar period, age	0.67 (0.47-0.96), P=0.03
calendar period, age, WHO stage	0.65 (0.45-0.92), P=0.02
calendar period, age, silicosis	0.62 (0.43-0.89), P=0.009

Grant et al., JAMA 2005;293:2719-25

C R E A E

Mission

To organize, implement and evaluate novel public health strategies to reduce tuberculosis incidence in populations with high rates of HIV and TB co-infection.

Strategies to Reduce TB/HIV in Addition to DOTS

- Active or intensified case finding
  - to identify cases transmitting infection, and who may die without treatment
- Treatment of latent TB infection
  - to prevent disease in HIV+ (and HIV-) persons
- Household HIV/TB interventions linked to cases
  - to promote active case finding, identify candidates for TB preventive therapy (and antiretroviral drugs), and reduce HIV transmission
- Combined ARV and IPT treatment programs
  - to reduce probability of developing primary or reactivation TB

The CREATE Portfolio: Approved Studies

Study/Site	Intervention(s)	Design
Thibela TB SA Gold Mines	Mass preventive therapy	Cluster randomized trial
ZAMSTAR Zambia/South Africa	HH interventions, intensified case finding	Community randomized trial
THRio Rio de Janeiro	Preventive therapy and ARVs	Phased implementation trial

Strategies for Reducing the Burden of TB in HIV-Endemic Areas

- Improved diagnostics (↑ case finding)
  - Simpler tests
  - Find prevalent cases
- Improved therapy (↑ treatment completion)
  - Shorter duration regimens
  - Compatibility with ARVs
  - Effective for MDR TB
- Preventive therapy
  - For high risk populations, broad use essential
- Reduced susceptibility
  - Antiretroviral therapy
- Community level interventions
  - Novel approaches at population level