GLOBAL ALLIANCE FOR
TB DRUG DEVELOPMENT

TB Alliance:
Partnerships of the Future

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HIV/AIDS and TB: A Lethal Convergence

HHMI/CSIS Symposium

May 12, 2005

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The Need for New TB Drugs

TB Defies Current Treatment

- **TB Crisis -- The "Perfect Storm" of Global Health**
  - Latent Reservoir: two billion people
  - HIV-TB co-infections fueling each other
  - Multi-Drug Resistance on rise, getting worse
- **Current tools cannot control the co-epidemic**
  - ≥6 months duration; compliance difficult
  - Drugs developed 40-60 years ago
  - Interact with antiretroviral agents
  - Limited access to standard of care: ~37%

Current TB Drug Therapy

- **Active TB**
  - 6 months of therapy (INH, rifampin, pyrazinamide, ethambutol)
- **TB/HIV co-infection**
  - treatment as in active TB, but drug interactions with ARVs make simultaneous therapy extremely difficult
- **MDR-TB**
  - individualized, prolonged therapy, few available drugs, poorly tolerated and difficult to administer
- **Latent TB**
  - 9 months of INH therapy

The TB Alliance

- Founded in 2000 (Cape Town Declaration)
- Independent Non-Profit Organization
- International Public-Private Partnership
- Based in New York with offices in Brussels and Cape Town

The TB Alliance

Mission

- Develop new, better drugs for TB
- Ensure affordability, access and adoption (AAA)
- Conduct, coordinate and catalyze TB drug development activities worldwide

Active Disease

Impact and Feasibility

- **Objective**: First shorten, then simplify
- **Approach**:
  - Near-term vision
  - Long-term vision

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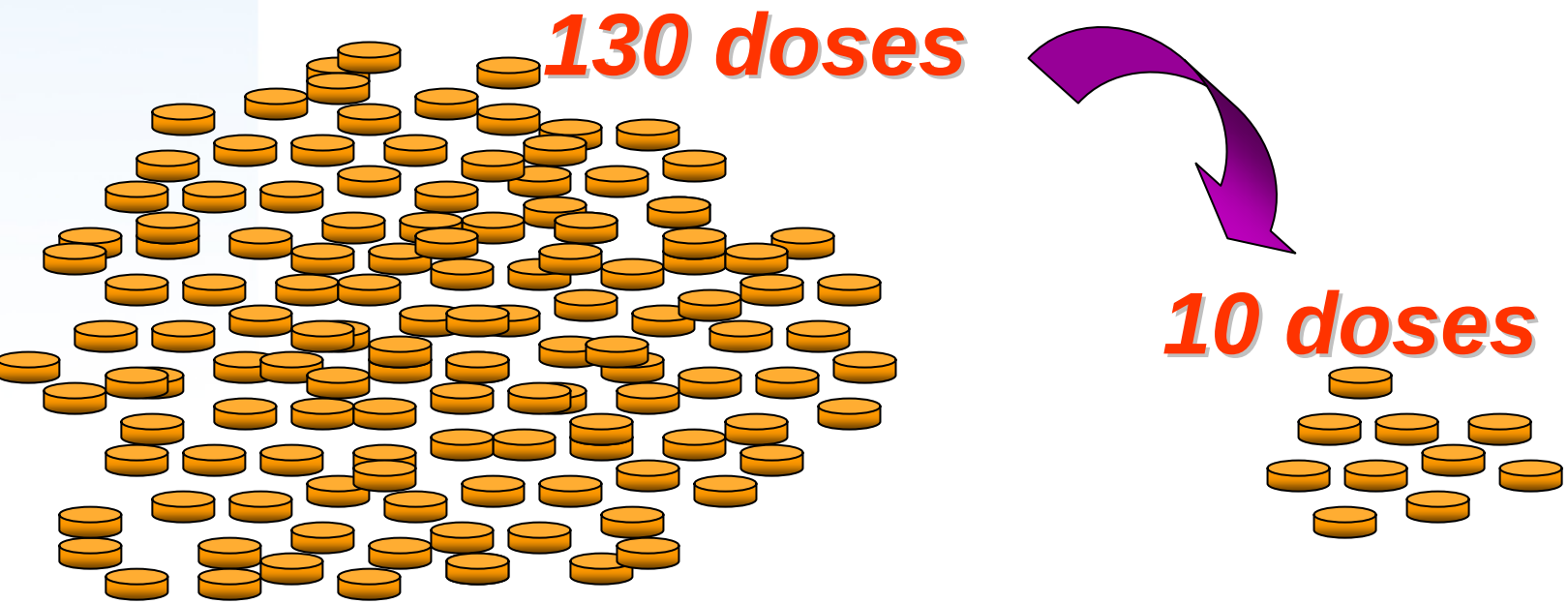
Near-term Vision

Shorten: 6 months to 2-3 months

then

Simplify: daily to weekly



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Shortening and Simplifying Treatment is Feasible

- Treatment has historically already been shortened from 24 to 6 months – general road map available
- Preclinical models predict drugs currently in pipeline could shorten therapy to 2-3 months
- Clinical trials of current drugs demonstrated most patients are cured in 3-4 months (but have no way to identify which ones)

Conclusion: 2-3 month regimens should be achievable with new, more effective drugs

Long-term Vision
Active Disease

7-10 days of treatment

But - very difficult to achieve without advances in understanding the biology of "persistence"

TB/HIV

- **Objective:** Provide safer and more effective TB drugs that can be used simultaneously with anti-retroviral therapy

- **Approach**:
  - Test for and prioritize compounds without P450 interactions
  - Even compounds that do not shorten treatment of active disease may be safe for co-therapy with ARVs

➡ **Success will be a consequence of efforts for active disease**

MDR-TB

- **Objective:** Provide safer and more effective therapy
- **Approach**:
  - Prioritize novel mechanisms of action
  - Screen MDR-TB strains
  - Even compounds that do not shorten treatment of active disease may be efficacious for MDR-TB

➡ **Success will be a consequence of efforts for active disease**

Characteristics of Project Partnerships

- Flexibility (in-license, contracts, sponsored projects, coinvestments, etc)
- Scientific Rigor (SAC, outside reviews)
- Commitment to Affordability, Access and Adoption (AAA)
- Win – Win Proposition

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Global TB Drug Portfolio 2005

	Discovery	Preclinical	Clinical Testing
Compounds, Analogs and Derivatives	Nitroimidazole Analogs (Novartis Institute for Tropical Diseases, NIAID)	Nitroimidazole PA-824 (Chiron)	Moxifloxacin (Bayer Pharmaceutical, EDCTP)
	Carboxylates (Wellesley College)	Pyrrole LL-3858 (Lupin Limited)	Diarylquinoline R207910 (Johnson & Johnson)
	Quinolones (KRICT/Yonsei University)	Quinolone KRQ-10018 (KRICT/ Yonsei University)	Proprietary Compound (Private Sector Partner)
	Macrolides (University of Illinois at Chicago)	Ethambutol Analog (Sequella Inc.)	Gatifloxacin (OFLOTUB - TDR)
	Enoyl ACP reductase inhibitors (GlaxoSmithKline)		
	Isocitrate Lyase inhibitors (GlaxoSmithKline)		
	Focused Screening (GlaxoSmithKline)		
	Pleuromutilins (GlaxoSmithKline)		
	Methyltransferase inhibitors (Anacor Pharmaceuticals)		
	Rifalazil Analogs (ActivBiotics)		
	Alkaloids and Ascididemins (Univ. of Auckland)		
	Screening and Target Identification (AstraZeneca)		

- TB Alliance portfolio
- TB Alliance in discussion
- TB Alliance terminated
- TB Alliance support
- Non-TB Alliance project

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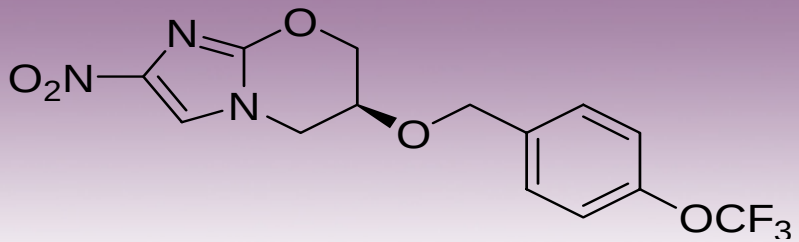

PA-824

- In-licensed from Chiron Corp. in 2002
  - Novel nitromidazole; distinct mechanism of action; no P450 interactions
  - Total, worldwide exclusive rights
- TB Alliance-managed development
- Grant-back option for developed world with royalties to TB Alliance
- No royalties in endemic countries

GSK Partnership

- Co-discovery at Tres Cantos, Spain
  - Joint steering committee
  - ~50 full time researchers
- Mini-portfolio of 4 discovery projects
- Joint commitment to affordability
- Access to Intellectual Property as needed to ensure drug can be developed for TB under “AAA” strategy

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TB Alliance:

Looking Forward

"TB Crystal Ball"

None of present first-line drugs will ultimately be part of an optimized regimen

- All present first-line drugs (HRZE) have poor profiles
- Novel compounds already in development may replace present first-line drugs

H = isoniazid; R = rifampin; Z = pyrazinamide; E = ethambutol

Conventional TB Clinical Paradigm

- Goal of a development program is to substitute one new drug for one of the conventional drugs

  HRZE ⟶ MRZE or HRZM

- Approximate (aggressive) timelines:

Phase I	1 year
Phase II	2 years
Phase III	3 years
	6 years

H = isoniazid; R = rifampin; Z = pyrazinamide; E = ethambutol; M = moxifloxacin

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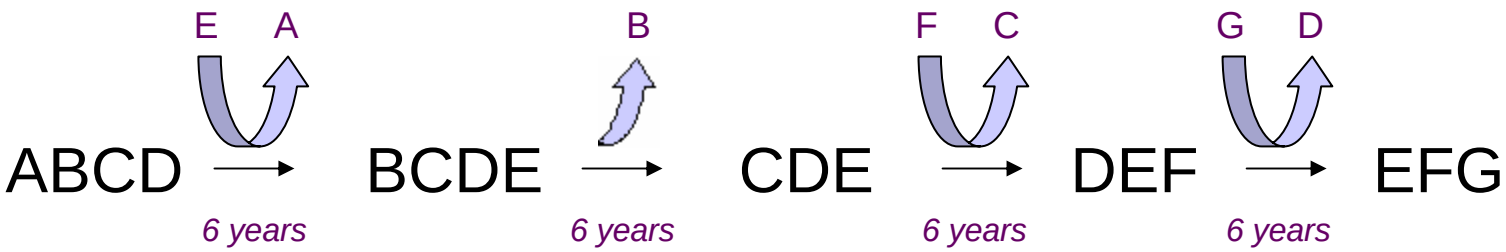
Dilemma

Conventional TB Clinical Development Paradigm



ABCD → *24 years* → EFG

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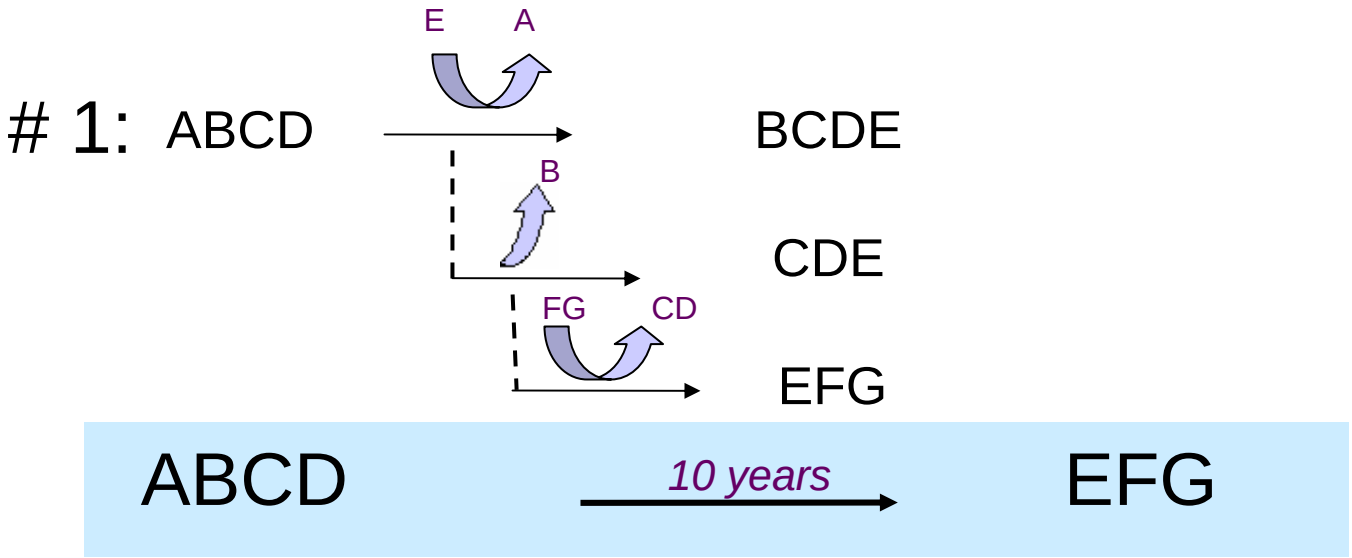
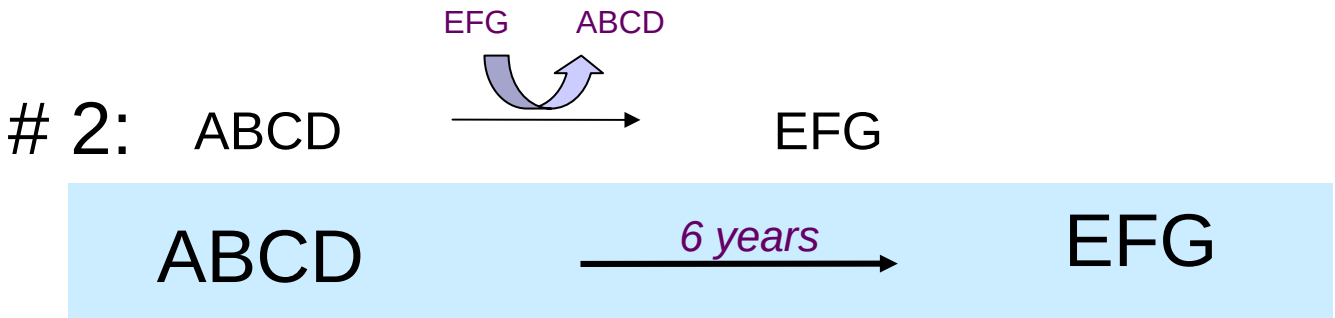
Alternative TB Clinical Development Paradigms





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A New TB Drug Development Paradigm

- Feasible with present technologies
- Based on preclinical evaluation of regimens once individual compounds meet preset criteria, *and*
- New clinical development algorithm for regimens (not compounds)
- Engage major regulatory authorities
- Think and act “comprehensively”– all new compounds are part of one large portfolio

→ **new concepts of partnerships**

Take Home Messages

- New tools are needed, including new TB drugs that can be co-administered with AIDS drugs
- Specific challenges for policymakers include:
  - Adequate resourcing for R&D of new tools
  - Inducements for pharma/biotechs
  - Regulatory buy-in for novel development strategy
  - Adoption in the field
  - Affordable global pricing, including use of novel push-pull mechanisms, such as advance purchase commitments, etc.

Back-ups

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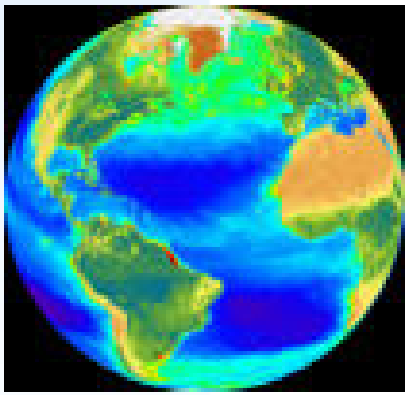
Global Epidemic



- 2 billion people are infected with *M. tb*
- 8 - 9 million new active TB cases a year
- 2 million people die a year
- ~ 400,000 cases of MDR-TB a year
- 12 million persons are TB/HIV co-infected
- Biggest killer of women of childbearing age

→ *TB's economic toll: $16 billion a year*

Latent Infection

- **Objective**: Shorten and simplify treatment
- **Considerations**:
  - Impact immense, success probability low; need better understand of underlying biology
  - Safety profile must be more stringent
  - Clinical evaluation of compounds difficult and expensive
- **Approach:**

  Clinical trials in LTBI with drugs that markedly shorten therapy of active disease and have excellent safety profiles (assumes underlying mechanisms of persistence and latency are similar)

➡ Await scientific advances to enable more rational drug discovery effort

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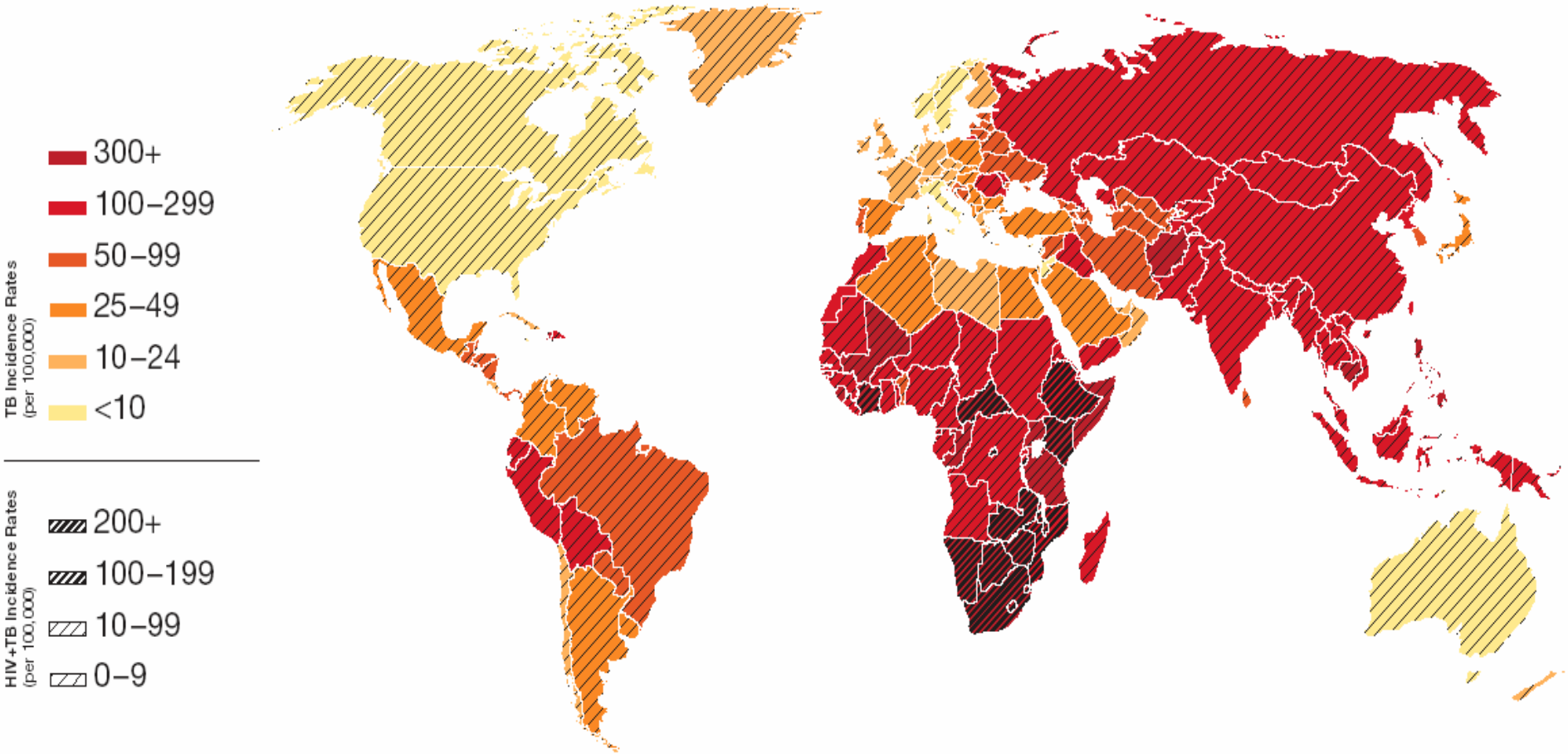
TB-HIV Pandemic

12 million people co-infected



"AAA" in Action

- Affordable pricing guarantees from partners:
  - Novartis - University of Illinois
  - Chiron - KRICT
  - GSK - Johns Hopkins
- Work w/treatment providers to determine drug design
- Select candidates suitable for developing countries
- Coordinate with international organizations
- Partner with endemic countries
  - S. Africa - India
  - Brazil - Peru

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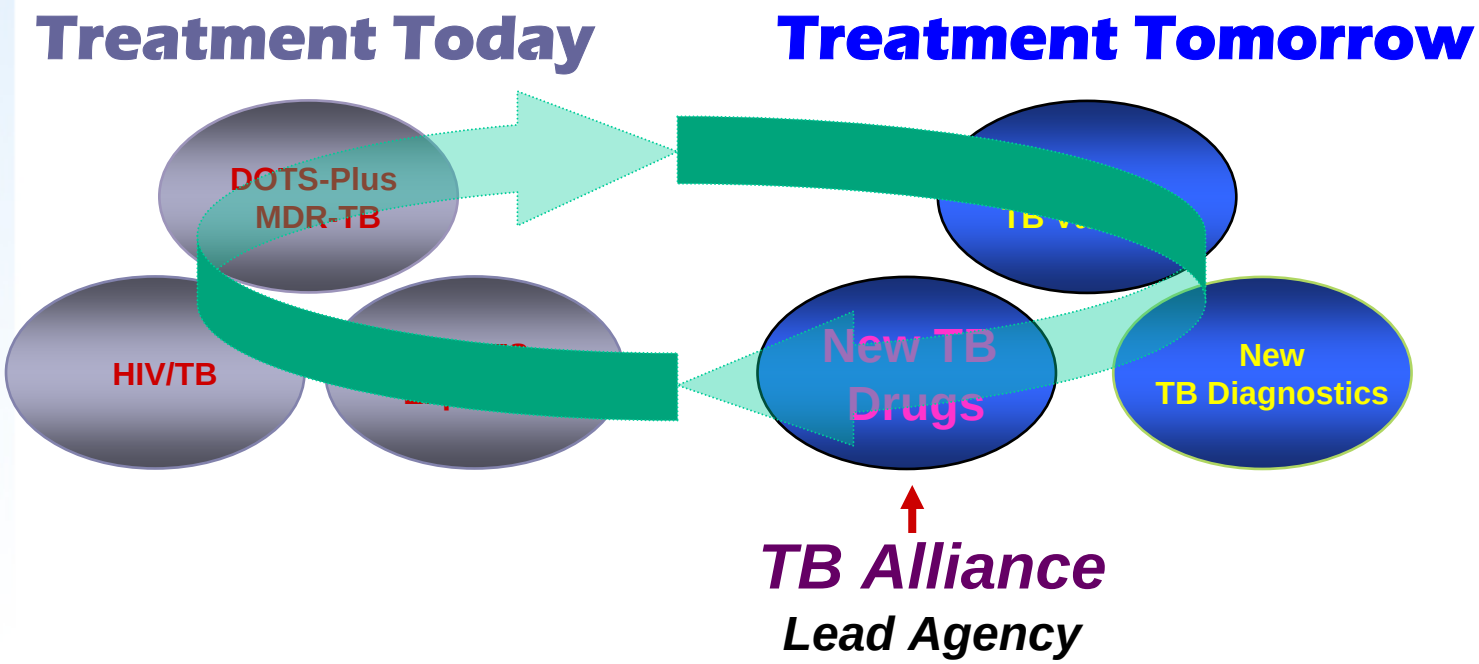
AAA: Global Plan to Stop TB

New Tools Critical to Success



Impact of New Therapeutic Regimen

- Improve compliance and cure rates
- Control MDR-TB
- Stop major cause of death for HIV/AIDS
- Expand TB control/access to DOTS
- Improve efficiency of healthcare systems
- Reduce burdens on patients and providers

Near-term Vision is Achievable

Clinical Evidence

- **BMRC data** – 13% relapse with 3 months therapy using standard drugs
- **TRC (Chennai) trial** – 8% relapse with 3 months OHRZ (ofloxacin less potent fluoroquinolone than moxifloxacin)
- **Pharmacokinetics** – existing compounds have long half-lives consistent with weekly dosing (eg, rifalazil, R207910, moxifloxacin, rifapentine); manipulation of formulation technologically feasible

O = ofloxacin; H = isoniazid; R = rifampin; Z = pyrazinamide

Near-term Vision is Achievable

Preclinical Evidence

- Moxifloxacin (2RMZ/RM) shortens therapy to 3-4 months in Grosset model
- J&J (R207910) and Lupin (LL-3858) compounds: may sterilize lungs in 2 months
- PA-824 has sterilizing activity

Conclusion: 2-3 month regimens should be achievable with new, more effective drugs

R = rifampin; Z = pyrazinamide ; M = moxifloxacin

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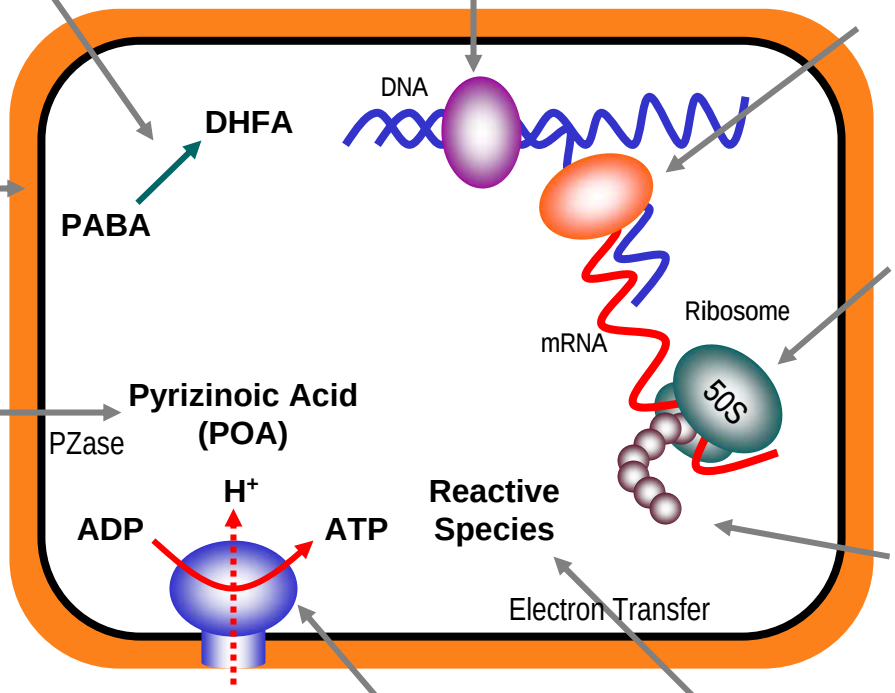
Antimycobacterial Proposed Targets and Relevant Drug Classes

DNA Gyrase
- FQ/NFQ/2-Pyridones
- Novel GyrB inhibitors

Folic Acid Metabolism
- p-Aminosalicylic Acid

RNA Polymerase
- Rifamycins

Cell Wall Synthesis
- Ethambutol
- Cycloserine
- Isoniazid
- Ethionamide
- Thiacetazone
- InhA inhibitors



Ribosome (50S)
- Macrolides/Ketolides
- Pleuromutilins
- Oxazolidinones

Ribosome (30S)
- Aminoglycosides
- Streptomycin
- Capreomycin
- Viomycin

Proton Motive Force
- Pyrazinamide

Peptide Deformylase
- PDF inhibitors

Other Mechanisms
- Pyrroles (Unknown)
- ICL inhibitors

ATP Synthase
- Diarylquinolines

Multiple Targets
- Nitroimidazoles
- Nitrofurans