

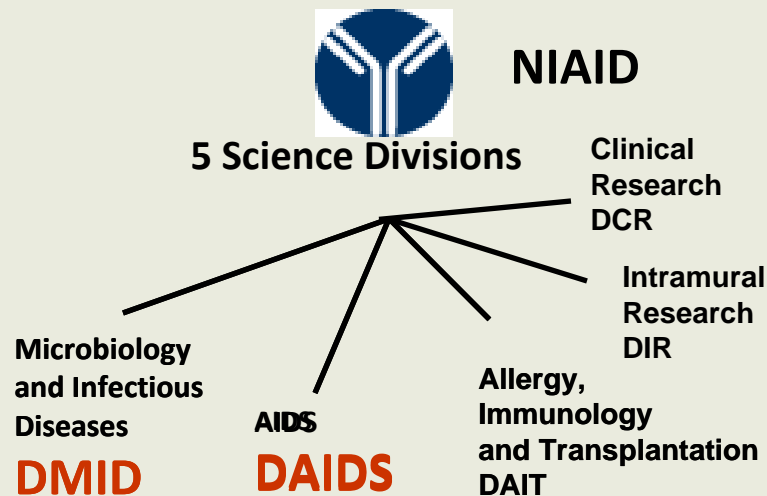
NIAID TB/HIV Clinical Research *Coordination and Collaborations and Global Activities*



NOVEMBER, 2011





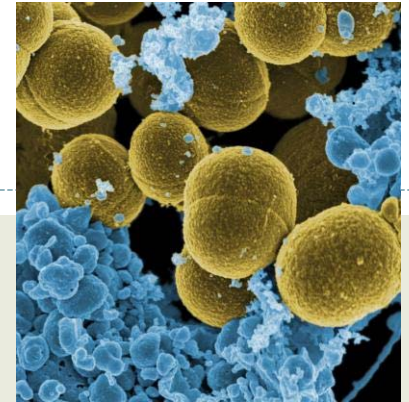


NHLBI





NIAID's Mission



NIAID is the lead NIH Institute for TB Research

- Supports all aspects of TB **biomedical research** - fundamental and applied to further understanding, diagnosis, treatment, and prevention
- Provides critical **resources** to fill gaps in basic, translational, and clinical research in TB, including preclinical and clinical product development/testing

TB Research – 2011 and Beyond

- **We must transform the field of TB research**
- **We are playing “catch up” after decades of neglect and so incremental changes are not sufficient**
- **TB is an ancient disease, but we need to understand it in modern terms, using cutting-edge technologies to ask and answer questions that have never been adequately addressed**

Lessons from AIDS, Applied to TB

- **Commit substantial financial and human resources**
- **Enlist the “best and the brightest” investigators in basic and clinical research, domestically and internationally**
- **Engage with the activist community**
- **Foster cross-sector collaboration with industry, academia, global organizations, philanthropies, NGOs**
- **Garner support of leaders and policymakers**

TB Therapeutic Clinical Research Priorities



- **New drugs and combinations for DS and DR TB:**
 - Efficient Phase I and II evaluations → Phase III
 - Killing Persisters – Sterilizing activity is crucial
- **TB/HIV Therapy**
 - Co-treatment regimens
 - Earlier ART for TB prevention
- Improved diagnostics and DST
- Prognostic biomarkers for treatment response
- Chemoprevention of TB
- Pathogenesis and translational research

Therapeutic Strategy to Address TB/HIV



- **Current focus is on the development of new drugs → optimal combinations**
 - Need for new first line therapy that is:
 - Safe/well tolerated
 - Affordable
 - Effective
 - Reduces treatment time/pill burden
 - Active against DS and resistant TB
 - High barrier to drug resistance
 - **Compatible with ART**

What do we need to get it done?



- **Enhance/adapt existing NIAID clinical research resources for TB**
- **Coordination and Collaborations**
 - **Other sponsors (US/EU and pharmaceuticals)**
 - **International research agencies**
 - **TB/HIV Integration**
- **Innovative research approaches**
- **Develop highly efficient therapeutic research strategies and trial designs**



¹⁰
“I am in the process of exploring the possibility... of utilizing our HIV/AIDS clinical trials networks for the implementation of similar clinical trials capacities for TB as well as other infectious diseases.”

**--- Pacific Health Summit,
June 17, 2009**

NIAID Clinical Trials/Research Infrastructure



DAIDS Cooperative Agreements

- ❑ **AIDS Clinical Trials Group (ACTG)**
- ❑ **International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT)**
- ❑ **HIV Vaccine Trials Networks (HVTN)**

DMID Contracts

- ❑ **Vaccine and Treatment Evaluation Units (VTEU)**
- ❑ **Phase I Clinical Trials Units**
- ❑ **Tuberculosis Research Unit (TBRU)***
- ❑ **Tuberculosis Clinical Diagnostics Research Consortium (CDRC)***

Both Divisions

- ❑ **Support for Unsolicited Clinical Research Projects**

* TB specific

Leadership and Sites for HIV/AIDS Therapeutic Clinical Trials - Renewals



FY 13 DAIDS FOA Objective:

To establish the Leadership of HIV International Clinical Trial Networks to carry out the NIAID therapeutic research agenda in the following four areas:

- **Tuberculosis**
- **Infectious hepatitis**
- **Cure and/or functional cure for AIDS**
- **Non-infectious co-morbidities and novel interventions for HIV-infected individuals**

FY14 DAIDS FOA Objective:

To establish clinical trials units/sites for performance of studies to carry out the NIAID therapeutic research agenda

Coordination Platforms/Forums



- **Therapeutics (Combination Development)**
 - Phase II planning forum and interactions with CPTR
 - Establishment of web site for **posting trials** in development
- **Diagnostics/DST/Biomarker Research**
 - June workshop → establishment of C & C Forum with regular meetings/postings and interactions with CPTR for biomarkers
- **TB Vaccine Research**
 - 1) NIAID TB Vaccine Clinical Research Coordination Committee including IMPAACT, HVTN, ACTG, NICHD, DMID/VTEU
 - 2) Strategic Coordination Forum with Aeras and TBVI, others

Coordination/Collaboration



GATB, ACTG, TBTC Consortium for TB Biomarkers (CTBB)

A collaborative project for standardized sample biobanking

- Contract with repository vendors to establish biobank
- Develop umbrella protocol to specify type, timing, processing, shipping of samples, etc. from selected treatment trials
- Constitute advisory group to review sample use proposals

Other trial sponsors are welcome to join

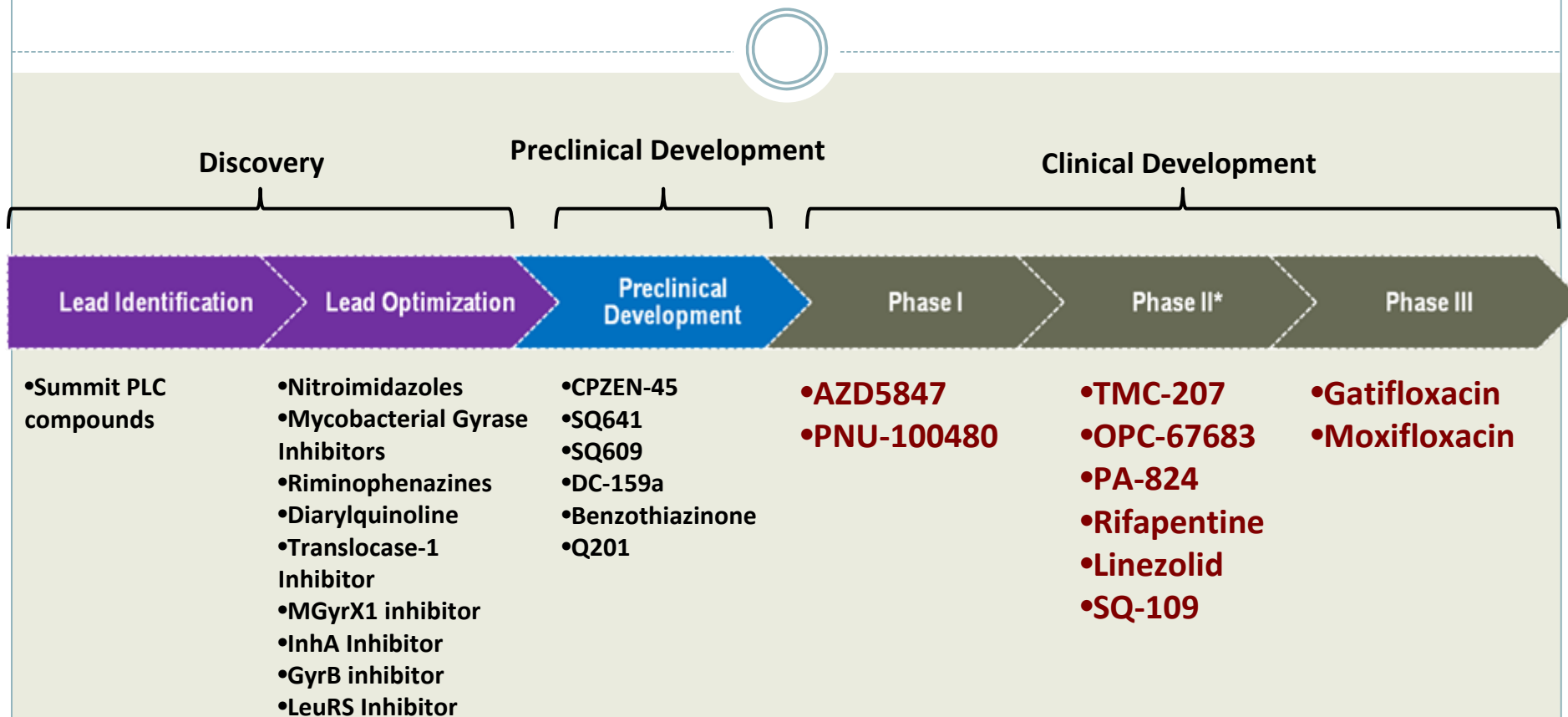
Coordination and Collaborations



Trials Capacity

- **Phase III trials will be large** – require collaborations (CPTR is addressing several aspects)
- *****Phase II planning is reaching a critical stage*****
and needs to be efficient and timely
- No one group has enough resources for any aspect
 - Funding -- This is not the 1990's and this is not HIV!!
 - Site and lab capacity, capabilities, training
 - Sufficient potential study populations
- Sufficient study drug supply to include all promising combinations

Global TB Drug Pipeline¹



¹ Projects that have not identified a lead compound series are considered to be in the screening phase of development and are not included. As of publication, there are 11 screening projects in progress as described on <http://www.newtbdrugs.org/pipeline.php>.

*Initiation of drug combination studies

Possible Combinations – Phase II Trials



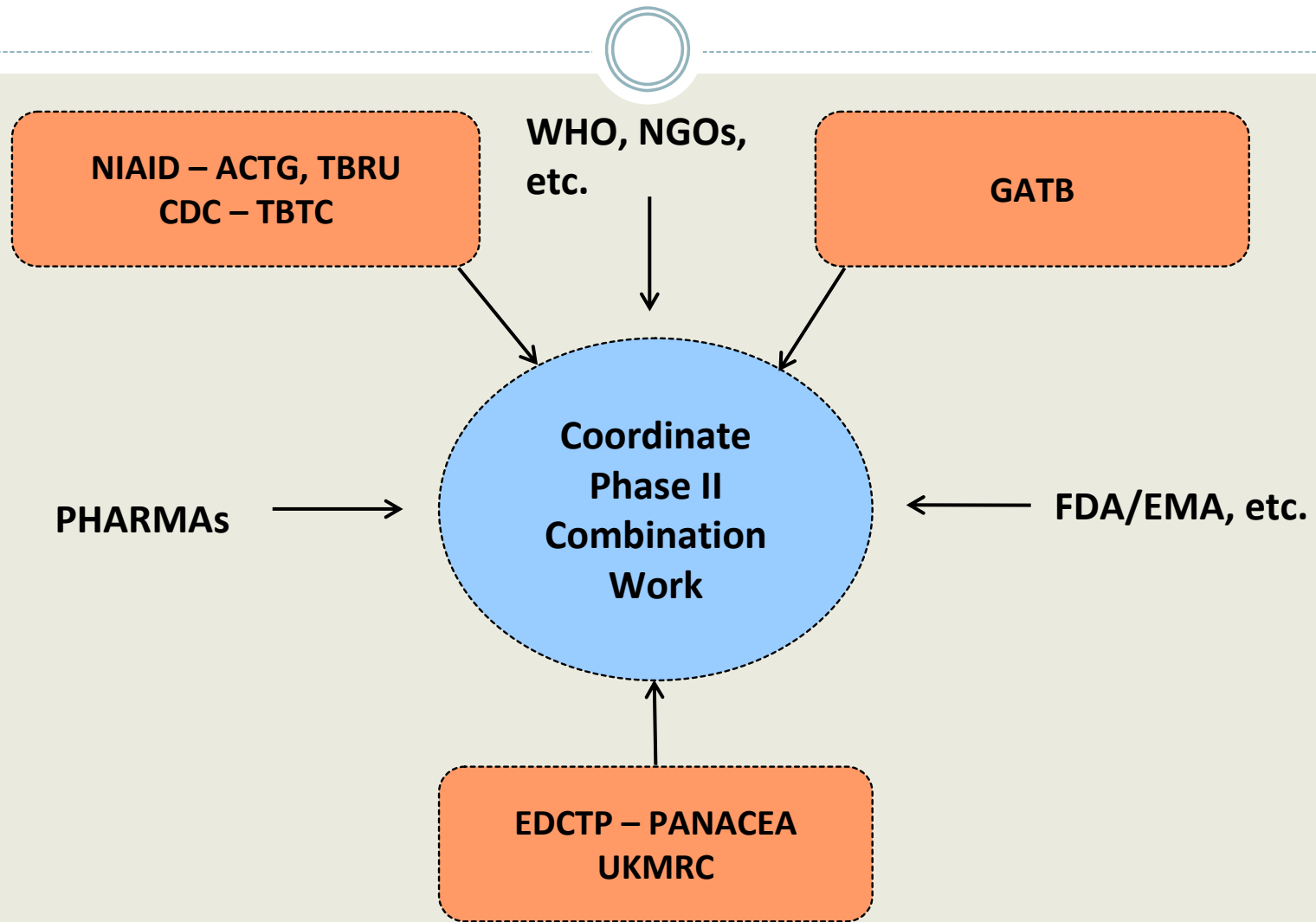
Classes = 8

- Possible 3 drug combos = 56
- Possible 4 drug combos = 70

Classes = 10

- Possible 3 drug combos = 120
- Possible 4 drug combos = 210

Coordination of Phase II Combo Trials



Forum to Coordinate Phase II/III Clinical Trials- Initial Meeting 9/23/11



- **Brief overview of each group's mission, capabilities, AND relevant results from recent studies and plans**
- **Phase II combination study planning coordination**
 - Efficiently/promptly sharing new study results
 - Which combinations would be done by whom/when
 - Anticipate and obtain necessary pre-clinical and clinical data to allow study of specific combos
- **Establish an ongoing Phase II/III Planning Forum**
 - Drafting a proposal for how groups will work to coordinate
 - Quarterly discussions with 1-2 meetings/year

Harmonization



- **Data elements, standards, endpoint definitions, adverse events**
- **Lab procedures for diagnostics/endpoints, DST, quality assurance**
- **Site surveys, qualifications/standards, training, and monitoring**
- **Stored sample collection specifications and procedures**
- **Also, assess opportunities for collaborative conduct of trials**

Global Activities

Building Clinical Trial Capacity



- **Support from the Government, both Central and Provincial**
- **Partner with excellent in-country scientists, institutions, etc.**
- **Construct regulatory process and ethics committee**
- **Identify patient populations with TB and HIV**
- **Assemble laboratory, clinic, and pharmacy facilities**
- **Obtain funding and enhance international collaborations**

Sino-US (Henan) TB prevention and treatment academy

“The success of our joint TB research program would not be possible without the continued support and cooperation of the United States and Chinese governments working at the national and provincial levels to bring together expertise and collaboration opportunities”

“I look forward to a future when US-China leadership in combating TB, through concrete projects such as our joint research partnership in Henan, makes significant, transformative advances in the diagnosis, treatment, and management of TB worldwide”

Anthony S. Fauci
China Daily, 2011-03-24

Current Global Activities/China



- **FY12 Funding Opportunity Announcement**
 - **US-China** Biomedical Collaborative Program on Infectious Diseases Including HIV/AIDS and its Comorbidities, Allergy, Immunology and Cancer
 - Applicants must be senior professional or technical position. Past or present PI of NSFC grant of three years or more

Potential NEW TB/HIV Clinical Research Collaborations in China



Clinical Research Consortium of centers to perform multicenter clinical trials – components

- Leadership/coordination office, operations support
- Training – GCP, GCLP, study-specific
- Site SOPs, QA/QC
- Harmonize and QC key laboratory/sample procedures
- Central data management and statistical functions
- Engage and negotiate with sponsors

NIAID and investigators would give advice and support

Potential NEW TB/HIV Clinical Research Collaborations in China



Close clinical TB/HIV research collaborations with Gates Foundation and partners

- Global Alliance – Treatment (drug combinations)
- Aeras - TB vaccines
- FIND – Diagnostics

Potential NEW TB/HIV Clinical Research Collaborations in China



Establishing Prospective TB/HIV Cohorts

- Determine epidemiology, trends, risk factors, outcomes
- Characterize drug resistance
- Well-characterized samples for biomarker research
- Coordination among sites
- Preparation of new sites for clinical trials

TB-HIV Research Integration



Introduction of “IPT” for HIV+ Why so underutilized?

- How to overcome barriers to use?
- How to best detect active TB?
- Which regimen?
- For how long?
- With ART – use CD4 count to stop?
- Target the PPD+ subset?
- Chemoprevention for MDR Exposure

The New England Journal of Medicine

October 20, 2011

Integration of Antiretroviral Therapy with Tuberculosis Treatment

Salim S. Abdool Karim, et. al.

NEJM, October 20, 2011; 365: p. 1492-1501

The New England Journal of Medicine

October 20, 2011

Timing of Antiretroviral Therapy for HIV-1 Infection and Tuberculosis

Diane V. Havlir, et. al.

NEJM, October 20, 2011; 365: p. 12-21

The New England Journal of Medicine

October 20, 2011

Earlier versus Later Start of Antiretroviral Therapy in HIV-Infected Adults with Tuberculosis

Francois-Xavier Blanc, et. al.

NEJM, October 20, 2011; 365: p. 1471-1481

Current Regimen Development Paradigm:

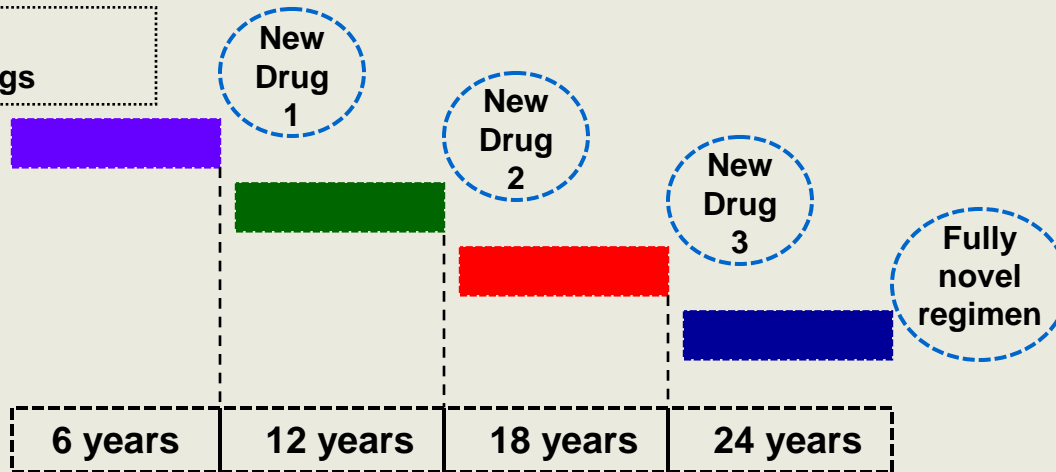
Existing regimen
consists of four drugs

New Drug 1

New Drug 2

New Drug 3

New Drug 4



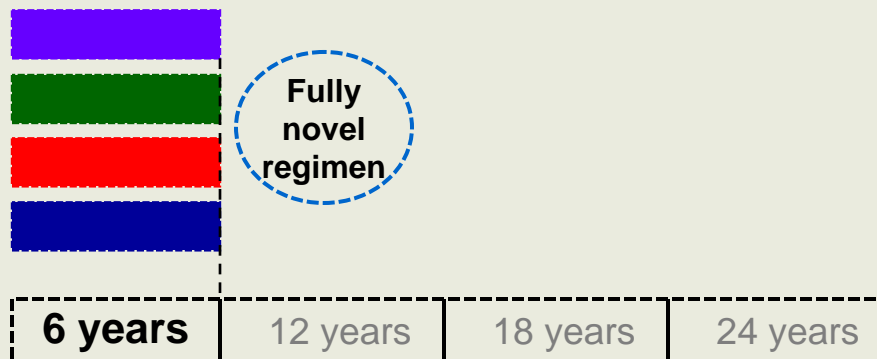
New Combination Approach:

New Drug 1

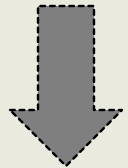
New Drug 2

New Drug 3

New Drug 4

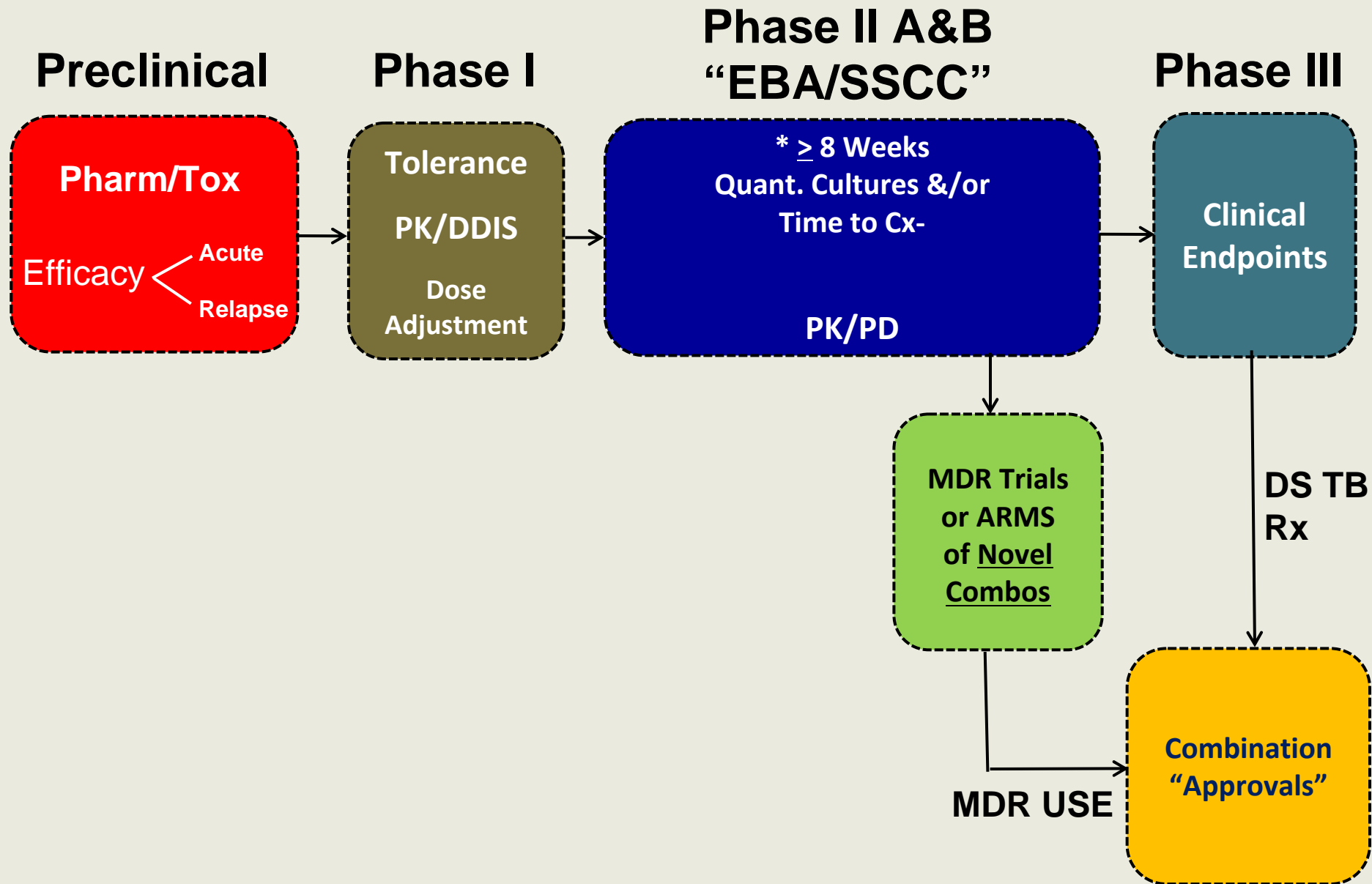


**24
years**



**6
years**

Combination Drug Development



Efficiency in Combination Development - Focus on Phase II



Problem

Serial trials/amendments are much too inefficient-
Delays caused by protocol development (esp. in group setting) and approvals at all levels

Responses

- Innovative, inclusive, new adaptive designs
- Early anticipation and resolution for concerns with new combinations - interactions and safety data
- Coordination of planning/prompt sharing of data

Efficiency in Combination Development - Focus on Phase II



Desirable Features of Adaptive trials

- Multi-arm and may be multi-step (Phase II A → B)
- Seamless transitions, step (IIA → II B)
- Frequent ISMC interim reviews (IRs) – drop arms early if less active than control – but trial continues
- Add new arms as per study criteria
- May include arms for both DS and DR infections

Summary of NIAID Studies for TB - 1



STUDY NUMBER	BRIEF DESCRIPTION
Biomarkers	
A5302	Evaluation of TB biomarkers of treatment response in upcoming ACTG (A5289/A5290) and TBTC (Study 31) clinical trials
Diagnostics	
A5253	Sensitivity and specificity of TB diagnostics
A5255	FASTER: Rapid TB DST study
A5295	Evaluation of Xpert MTG/RIF Assay
DMID 07-0061	Interferon-Gamma Release Assays in TB-HIV co-infected children

Summary of NIAID Studies for TB – 2



STUDY NUMBER	BRIEF DESCRIPTION
HIV/TB	
A5274	REMEMBER: Empiric TB treatment + ART to reduce early mortality following ART initiation
A5284	RIF + GS-9350 (Cobicistat) PK interaction
A5290	Comparison of LPV/r-based ARV \pm RAL with RBT and double dose LPV/r with RIF-based TB RX
LTBI	
A5259	Rifapentine-INH x 3 mos vs SOC for LTBI (TBTC Study 26)
A5279	Ultra-short (1 month) daily course of RPT/INH for LTBI
DMID 07-0083	Phase I Study of Whether Preclearance of LTBI with INH Enhances Specific Immune Responses to MTB following Subsequent BCG Revaccination in Healthy, HIV-uninfected, PPD+ Adults

Summary of NIAID Studies for TB – 3



STUDY NUMBER	BRIEF DESCRIPTION
MDR	
A5300	TMC-207 for preventive therapy for MDR/XDR contacts
A5312	The Early Bactericidal Activity of High-Dose Isoniazid among Adult Patients with inhA-related INH-Resistant Tuberculosis
Harvard CFAR	Inhaled Colistin to Decrease XDR TB Infectivity - Nardell
Optimizing Standard Treatment Regimen	
A5307	Essentiality of INH After Two Doses: Randomized 14-day EBA Comparison of Standard RHZE with Only 2d INH + RZE or Substituting Moxifloxacin for INH (RMZE) During Days 3 and 14
A5311	Phase I Clinical Trial of the Pharmacokinetics of High-dose Daily Rifapentine, Given as a Single Dose or in Divided Doses to Healthy Volunteers

Summary of NIAID Studies for TB – 4



STUDY NUMBER	BRIEF DESCRIPTION
Optimizing Standard Treatment Regimen – continued	
DMID 11-0050	Double Blind randomized dose ranging trial of high dose rifampin (10-15-20 mg/day) for safety and improving treatment outcomes
Pediatrics	
P1073	Study of IRIS in children ≤ 5 years of age
P1078	Safety and Efficacy of Antepartum vs. Postpartum INH Preventive Therapy in HIV-infected Women and Infants
IMPAACT CS	TMC-207 with OBT for treatment of MDR TB in children
Other	
TBRU	EBA Feasibility Study with Standard EHRZ Chemotherapy in Kampala/Mulago

Summary of NIAID Studies for TB – 5



STUDY NUMBER	BRIEF DESCRIPTION
New Drug Development	
A5267	PK interaction study of TMC-207 and EFV
A5306	Safety, tolerability, and PKI study of PA-824 together with Efavirenz or Ritonavir-Boosted Lopinavir or Rifampin
DMID 11-0006	Multiple Dose Extended EBA of Oxazolidinone AZD5847
DMID 10-0043	PK interactions of single-dose TMC-207 with steady-state rifabutin or rifampin
New Combo Development	
A5289	TMC-207 substitution of standard drugs for TB treatment
A5304/ REMox	Two Moxifloxacin containing treatment shortening regimens compared with the standard regimen

THANK YOU



BACKUP SLIDES



Division of AIDS



- **Established in 1986 to help ensure an end to the HIV/AIDS epidemic by:**
 - Increasing basic knowledge of the pathogenesis and transmission of HIV
 - Supporting the development of therapies for HIV infection and its complications and **co-infections**
 - Supporting the development of vaccines and other prevention strategies
- **>150 federal employees and >70 on-site contractors**
- **Annual budget \$1.1B**

NIAID TB → DMID
NIAID HIV → DAIDS

NIAID Clinical Team (TB and TB/HIV)

