NIAID 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

• Prognostic biomarkers for disease progression, treatment response/relapse

• TB/HIV Therapy – Co-treatment regimens
• Chemoprevention of TB
• Improved diagnostics and DST
• Pathogenesis and translational research
What do we need and how to get it done?

- Enhance/adapt existing NIAID clinical research resources for TB
- Coordination and Collaborations
- Develop highly efficient research strategies/agendas and trials designs
  - Target persisters
NIAID Clinical Trials/Research Infrastructure

DAIDS Cooperative Agreements
- AIDS Clinical Trials Group (ACTG)
- International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT)
- International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)
- 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
Coordination of Phase II Combo Trials

NIAID – ACTG, TBRU
CDC – TBTC

WHO, NGOs, etc.

GATB

PHARMAs

EDCTP – PANACEA
UKMRC

FDA/EMA, etc.
Phase II combination development **plan coordination**
- Determine which combinations to be studied - whom/when
- Efficiently/promptly share new study results
- Address necessary pre-clinical and clinical data to allow timely study of specific combos
- Coordination of discussions with Pharmaceutical sponsors

Establish an ongoing Phase II/III **Planning Forum**
- Drafting a proposal for how groups will work to coordinate
- Proposal for support of future activities (conference calls and meetings)
- Quarterly discussions with 1-2 meetings/year
Planning for MDR Trials with New Drugs

- Site surveys
  - Initial – Completed in ACTG and TBTC
- Initial **Observational** studies to better define local drug susceptibility patterns and feasibility issues
- **EARLY coordination** of planning/drug choices
- DR TB Trials
  - Change emphasis to new combos, not single drug additions to OBT
  - Include MDR/XDR into new combo trials as soon as possible
- **Rapid PZA DST** will be essential for next generation of MDR trials – Jump-start pncA sequencing capability
## Summary of NIAID Studies for TB – 2

<table>
<thead>
<tr>
<th>STUDY NUMBER</th>
<th>BRIEF DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV/TB</strong></td>
<td></td>
</tr>
<tr>
<td>A5274</td>
<td>REMEMBER: Empiric TB treatment + ART to reduce early mortality following ART initiation</td>
</tr>
<tr>
<td>A5284</td>
<td>RIF + GS-9350 (Cobicistat) PK interaction</td>
</tr>
<tr>
<td>A5290</td>
<td>Comparison of LPV/r-based ARV ± RAL with RBT and double dose LPV/r with RIF-based TB RX</td>
</tr>
<tr>
<td><strong>LTBI</strong></td>
<td></td>
</tr>
<tr>
<td>A5259</td>
<td>Rifapentine-INH x 3 mos vs SOC for LTBI (TBTC Study 26)</td>
</tr>
<tr>
<td>A5279</td>
<td>Ultra-short (1 month) daily course of RPT/INH for LTBI</td>
</tr>
<tr>
<td>DMID 07-0083</td>
<td>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</td>
</tr>
</tbody>
</table>
really intended to see if pretreatment with INH will improve immune response to BCG
# Summary of NIAID Studies for TB – 3

<table>
<thead>
<tr>
<th>STUDY NUMBER</th>
<th>BRIEF DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MDR</strong></td>
<td></td>
</tr>
<tr>
<td>A5300</td>
<td>TMC-207 for preventive therapy for MDR/XDR contacts</td>
</tr>
<tr>
<td>A5312</td>
<td>The Early Bactericidal Activity of High-Dose Isoniazid among Adult Patients with inhA-related INH-Resistant Tuberculosis</td>
</tr>
<tr>
<td>Harvard CFAR</td>
<td>Inhaled Colistin to Decrease XDR TB Infectivity - Nardell</td>
</tr>
<tr>
<td><strong>Optimizing Standard Treatment Regimen</strong></td>
<td></td>
</tr>
<tr>
<td>A5307</td>
<td>Essentaility 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</td>
</tr>
<tr>
<td>A5311</td>
<td>Phase I Clinical Trial of the Pharmacokinetics of High-dose Daily Rifapentine, Given as a Single Dose or in Divided Doses to Healthy Volunteers</td>
</tr>
<tr>
<td>STUDY NUMBER</td>
<td>BRIEF DESCRIPTION</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------</td>
</tr>
<tr>
<td><strong>Optimizing Standard Treatment Regimen – continued</strong></td>
<td></td>
</tr>
<tr>
<td>DMID 11-0050</td>
<td>Double Blind randomized dose ranging trial of high dose rifampin (10-15-20 mg/day) for safety and improving treatment outcomes</td>
</tr>
<tr>
<td><strong>Pediatrics</strong></td>
<td></td>
</tr>
<tr>
<td>P1073</td>
<td>Study of IRIS in children ≤ 5 years of age</td>
</tr>
<tr>
<td>P1078</td>
<td>Safety and Efficacy of Antepartum vs. Postpartum INH Preventive Therapy in HIV-infected Women and Infants</td>
</tr>
<tr>
<td>IMPAACT CS</td>
<td>TMC-207 with OBT for treatment of MDR TB in children</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>TBRU</td>
<td>EBA Feasibility Study with Standard EHRZ Chemotherapy in Kampala/Mulago</td>
</tr>
</tbody>
</table>
### Summary of NIAID Studies for TB – 5

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

Detection/Quantitation

Drugs Sequencing/Staging

Improved Models/Testing

Immune-Based Therapy

Drug Discovery

N.R. Persisters

Rapid Replicators

Intermittent Replicators

PZA
Dealing with Persisters

- The best targets are NOT necessarily the usual most “vulnerable” or microbe-specific
  - Membrane integrity or critical membrane-function

- More difficult to discover or design agents

- Some potentially sterilizing agents with low activity against active bugs are ignored

- Diagnostics/biomarkers – the TB markers probably differ with changes in subpopulations and disease stage

- Markers for dormant bacilli may be scant to nil at times and change unpredictably as the bugs adapt

- Background NOISE
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 ad safety
- Improved, real-time quantitative response markers
- Coordination of planning/prompt sharing of data
Desirable Features of Adaptive trials

- Multi-arm and may be *multi-step* (Phase II A → B)
- Frequent ISMC interim reviews (IRs) – *drop* arms early if less active than control – but trial continues
- *Add* new arms as per study criteria
- *Seamless* transitions, step (A → B)
- *Flexibility* of entry into Phase A step or Phase B step, depending on how much is known
- May include arms for both *DS and DR* infections
**NIAID TB** → **DMID**  
**NIAID HIV** → **DAIDS**  

**NIAID Clinical Team (TB and TB/HIV)**

---

**Fundamental**  
**DMID Resources**  
- Systems Biology, Biomarker Programs  
- Animal Models (Candidate Selection)  
- Research Reagents  
- "omics" Support Programs  
- Preclinical Services, IND-enabling  
- HIV-TB Basic/Pre-clinical Grants  

**Non-Clinical**  
- **Clinical**  
  - **Ph I**  
  - **Ph IIA**  
  - **Ph IIB**  
  - **Ph III-IV**  

**Clinical Trials Networks**  
- Ph I Units  
- Clinical Trials Networks  
- *Solicited and Unsolicited Grants - R34/U01/BAA*  
- Vaccine & Treatment Evaluation Units  
- *Tuberculosis Research Unit*  
- *TB specific*  

---

*Clinical Diagnostics Research Consortium*
CURRENT REGIMEN DEVELOPMENT PARADIGM:

Existing regimen consists of four drugs:

- New Drug 1
- New Drug 2
- New Drug 3
- New Drug 4

6 years 12 years 18 years 24 years

NEW COMBINATION APPROACH:

- New Drug 1
- New Drug 2
- New Drug 3
- New Drug 4

6 years 12 years 18 years 24 years

Fully novel regimen

24 years

6 years
Combination Drug Development

Pre-clinical
- Pharm/Tox
- Efficacy
  - Acute Relapse

Phase I
- Tolerance
- PK/DDIS
- Dose Adjustment

Phase IIA
- EBA
- ≤ 14 Days Quantitative Cultures

Phase IIB
- “SSCC”
- * ≥ 8 Weeks Quant. Cx or Time to Cx - PK/PD

Clinical Endpoints
- MDR Trials or ARMS of Novel Combos
- Combination “Approvals”
- MDR USE

DS TB Rx
Combination Drug Development

**Preclinical**
- Pharm/Tox
  - Efficacy
    - Acute Relapse
- Tolerance
  - PK/DDIS
  - Dose Adjustment

**Phase I**
- Phase II A&B “EBA/SSCC”
  - * > 8 Weeks Quant. Cultures &/or Time to Cx-
  - PK/PD

**Phase III**
- Clinical Endpoints
  - MDR Trials or ARMS of Novel Combos
    - DS TB Rx
    - MDR USE
    - Combination “Approvals”
Possible Combinations

Classes = 8
• Possible 3 drug combos = 56
• Possible 4 drug combos = 70

Classes = 10
• Possible 3 drug combos = 120
• Possible 4 drug combos = 210
“Re-purposed “ Drugs

- Beta-lactams and clavulanic acid others
- Antifolates/ sulfas (e.g. sulfamethoxazole)
- Nitizoxanide
- Oxyphenbutazone
Initial K-RITH Clinical Studies

- Initial trial, A5307, to open early 2012
- Other Rx concepts (not treatment combo development)
  - Comparison of TB treatment responses among HIV subpopulations vs. non-HIV
  - Efflux pump inhibition
  - Inhaled agents
    - Capreomycin
    - Membrane disrupters - ? Colistin

Substudies to develop:
- Imaging (PET/CT) to evaluate treatment response
- Molecular-based quantitative response assays (rRNA)
Empiric OBT
SPUTUM
# 2016 DHHS/WHO Guidelines for Treatment of Tuberculosis in Adults, Adolescents and Children

<table>
<thead>
<tr>
<th>Antituberculosis Drugs</th>
<th>Approved Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA-dependent RNA Polymerase Inhibitors – DRPIs</td>
<td>Rifapentine, Rifampin, Rifabutin</td>
</tr>
<tr>
<td>Topoisomerase/Gyrase Inhibitors – TGIs</td>
<td>Moxifloxacin, Levofloxacin</td>
</tr>
<tr>
<td>ATP Synthase Inhibitors – ASIs</td>
<td>Bedaquiline (TMC), clofazimine?</td>
</tr>
<tr>
<td>Protein synthesis Inhibitors – PSIs</td>
<td>Oxazolidinones, amikacin and others</td>
</tr>
<tr>
<td>Nitric Oxide Producers/Electron Transport Suppressors – NOPETS</td>
<td>PA-824, Delamanid (OPC)</td>
</tr>
<tr>
<td>Mycolic Acid Synthesis Inhibitors – MASIs</td>
<td>INH, Ethionamide</td>
</tr>
<tr>
<td>Drugs with Unknown Mechanisms of Bacteriolysis – DUMBs</td>
<td>Pyrazinamide, SQ109</td>
</tr>
</tbody>
</table>

DHHS/WHO – available online at [www.curingtb.org.ch-usa](http://www.curingtb.org.ch-usa); ©2011, JHU Center for TB
### Preferred regimens for patients with active and latent tuberculosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred regimens – all patients</td>
<td>DRPI + ASI + TGI + NOPET for 2 months</td>
</tr>
<tr>
<td>Genotypic DRPI resistance</td>
<td>ASI + TGI + NOPET + PSI for 3 months</td>
</tr>
<tr>
<td>Genotypic DRPI + TGI resistance</td>
<td>ASI + NOPET + PI + DUMB for 3 months</td>
</tr>
<tr>
<td>Multiple resistance</td>
<td>Use TB-Phenosense to customize regimen</td>
</tr>
<tr>
<td>Latent TB Infection – DRPI susceptible</td>
<td>Rifapentine/INH for 1 month</td>
</tr>
<tr>
<td>Latent TB – DRPI resistant</td>
<td>Bedaquiline for 3 months</td>
</tr>
</tbody>
</table>
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
Coordination and Collaborations

- Communication/Information Sharing
- Coordination/Harmonization
- Collaborative studies
C & C Platforms/Fora

- **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**
  - I) NIAID TB Vaccine Clinical Research Coordination Committee including IMPAACT, HVTN, ACTG, NICHD, DMID/VTEU
  - 2) Strategic Coordination Forum with Aeras and TBVI, others
• ACTG 5274 (REMEMBER)
• PanACEA PROMPT
  ○ Both are very similar trials that will begin accrual this Summer

• STATIS (SYSTEMATIC EMPIRIC TB TREATMENT IN AIDS PATIENTS TO IMPROVE SURVIVAL)
  ○ In development until aborted in 12/10 when these other trials became known to proposers