Eliminating TB Deaths: Time to Step Up the HIV Response

Perspective from NIAID: The Role of Biomedical Research

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**Tuberculosis (TB) and HIV/AIDS**

- Of the 35 million people living with HIV, ~1/3 are co-infected with TB

- TB is the leading cause of death among HIV-infected people worldwide

- TB accelerates the replication of HIV

- HIV accelerates the progression of TB
May 2014: WHA Endorses Resolution on Post-2015 Strategy for TB Control

Strategy has 3 pillars:

- Integrated, patient-centered care and prevention
- Bold policies and supportive systems
- Intensified research and innovation

Source: WHO (http://www.who.int/tb/features_archive/globaltb_strategy/en/)
Key TB Research Areas in the Era of HIV/AIDS

- Pathogenesis
- Diagnostics
- Therapeutics
- Prevention
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TB Pathogenesis: Selected Challenges

- Gaps in understanding the dynamics of human TB disease

- Understanding the complex interactions between pathogen and host – “systems biology”

- Understanding mechanisms of latency, disease activation, correlates of immunity
TB Pathogenesis – Challenges for HIV Co-Infection

- Higher rates of progression to active TB and accelerated progression of HIV infection
- Different clinical/radiographic manifestations of pulmonary TB
- Reduced immune control and more extrapulmonary TB dissemination
- Limited models of dual infection
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TB Diagnostics: Despite Progress, Severe Limitations

- Most settings have antiquated diagnostics

- Transformative diagnostics needed
  - Point-of-care
  - Simple, accurate, inexpensive
  - Detect TB in clinical specimens from multiple body sites
GeneXpert MTB/RIF: Rapid TB Diagnostic

- Cartridge-based, automated diagnostic

- Detects DNA of TB bacteria and resistance to TB drug rifampicin

- Rapid diagnosis of TB and rifampicin resistance essential for early management of disease

- Time to results: <2 hours
NIAID Large-Scale TB Genome Sequencing Project Launched in 2012

- High-throughput genomic sequencing, bioinformatics analysis & tools (Broad Institute)
  - ~1600 drug-resistant (DR) strains sequenced to date
  - Samples from S. Africa, Korea, Russia, Uganda, Taiwan, Moldova, Mali, India, Iran, Romania & Sweden

- Expanding DR markers for next-generation TB diagnostics, improved therapeutics
TB Diagnosis – Challenges for HIV Co-Infection

- Extrapulmonary and paucibacillary pulmonary disease more common, yet TB diagnosis focused on sputum
- Paucibacillary disease diagnosis requires higher testing sensitivity
- More difficult to “rule out” active TB for chemoprophylaxis
- TB diagnosis in children even more difficult in those with HIV co-infection
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TB Therapeutics: Current Challenges

- Length and complexity of treatment regimens
- Adherence and monitoring
- Side effects
- Drug-drug interactions, e.g., antiretrovirals
Global TB Drug Pipeline

Preclinical Development

CPZEN-45
SQ641
SQ609
Q203
DC-159a
TBI-166
PBTZ169
TBA-354

Clinical Development

Phase I
AZD5847
Bedaquiline*
PA-824
Rifapentine
Linezolid
Sutezolid
SQ109

Phase II
Gatifloxacin
Moxifloxacin
Rifapentine
Delamanid*

Phase III

Novel Combinations

Concepts or candidate drugs to which NIAID has contributed support at some point in development

*Undergoing continued clinical testing to secure full licensure

Updated June 2014. Adapted from Stop TB Partnership
Clinical Trials for MDR/XDR TB

Linezolid for Treatment of Chronic Extensively Drug-Resistant Tuberculosis
M Lee, CE Barry III, et al.

Delamanid for Multidrug-resistant Pulmonary Tuberculosis
MT Gler, CD Wells, et al.

The Diarylquinoline TMC207 [Bedaquiline] for Multidrug-resistant Tuberculosis
AH Diacon, DF McNeeley, et al.
Integration of Antiretroviral Therapy with Tuberculosis Treatment
SS Abdool Karim, Q Abdool Karim et al.

Timing of Antiretroviral Therapy for HIV-1 Infection and Tuberculosis
DV Havlir, I Sanne et al.

Earlier versus Later Start of Antiretroviral Therapy in HIV-Infected Adults with Tuberculosis
F-X Blanc, AE Goldfeld et al.
# FDA-Approved Antiretroviral Drugs

## NRTI
- Zidovudine
- Didanosine
- Zalcitabine*
- Stavudine
- Lamivudine
- Abacavir
- Tenofovir
- Emtricitabine
- 4 multi-drug combinations

## NNRTI
- Nevirapine
- Etravirine
- Delavirdine
- Rilpivirine
- Efavirenz

## PI
- Saquinavir
- Ritonavir
- Indinavir
- Nelfinavir
- Amprenavir*
- Lopinavir + Ritonavir
- Atazanavir
- Fosamprenavir
- Tipranavir
- Darunavir

## Fusion Inhibitor
- Enfuuvirtide (T-20)

## Entry Inhibitor
- Maraviroc

## Integrase Inhibitors
- Raltegravir
- Elvitegravir**
- Dolutegravir

## Multi-Class Combinations
- Atripla
- Complera
- Stribild

*no longer marketed  **currently approved only as part of combination tablet

Source: FDA, 2013
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TB Treatment – Challenges for HIV Co-Infection

- Drug-drug interactions between TB therapy and ART and additive toxicities

- Risk of immune reconstitution inflammatory syndrome (IRIS)

- Limited availability of pediatric drug formulations
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Chemoprevention with isoniazid widely recommended for HIV/TB but still being optimized
TB Vaccines: Modernization Critical

BCG does not prevent adult pulmonary TB, the most transmissible form

Safe and effective vaccines against all forms of TB urgently needed
TB Prevention – Challenges for HIV Co-Infection

- Limited understanding of the mechanisms of interactions between the two pathogens hinders development of preventive measures.

- ART does not completely reverse the increased risk for new or recurrent TB.

- BCG vaccination contraindicated in HIV-infected children.
Expanded Capacity to Conduct TB Clinical Trials
Six Major NIAID-Funded HIV/AIDS Clinical Trials Networks

- AIDS Clinical Trials Group (ACTG)
- HIV Prevention Trials Network (HPTN)
- HIV Vaccine Trials Network (HVTN)
- International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)
- International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)
- Microbicide Trials Network (MTN)
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Expanded to include both TB and TB/HIV
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Biomedical Research:
Develop new and improved interventions

Implementation:
Apply proven interventions and introduce new and improved interventions
“We cannot win the battle against AIDS if we do not also fight TB.”

– Nelson Mandela

XV International AIDS Conference, Bangkok, 2004