Immunology of *M. tuberculosis* infection and disease

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Objectives

• Natural history of MTB infection and disease from host’s perspective
• Basic immunology (innate immune response (IR), T cell, cytokines, immune evasion)
• Applications of TB immunology (IGRA, TB vaccine development, host genetics)
• HIV-TB
Why bother with the immunology or host response to MTB?

- The vast majority of the natural history is pauci-bacillary.
- Exposure, acute and latent infection can be detected by changes in host response.
- So many exposed, infected yet few progress: host response is key.
Natural History of *Mycobacterium tuberculosis* infection
How do we control MTB?

- Innate alone in some? (resistance to infection)
- Innate plus adaptive immune response in most
- (infection to LTBI)
MTB’s initial encounter: Innate immune system (macrophage)

- Lung: alveolar, parenchymal, monocyte
- Multiple receptors on surface & intracellular: CR, TLR, NOD, MR
- Inflammation: cytokines (IL1, TNF, IL12, IL6, etc.)
- Survival: in a unique phagosome
Induction of T cell response to MTB

- Macrophages & Dendritic cells: APC
- MHC-I (HLA-A,B,C) and II (HLA-DR/DP/DQ) Ag processing
- Naïve T cell -> effector, memory, central memory T cell
- IFN-gamma, TNF-alpha, CTL
- Failure of T cells: progression from LTBI to TB
Many human T cell subsets respond to MTB

- CD8 T cell
- CD4 T cell
- γδ T cell
- MΦ

Phos. Ag

CD1 restricted T cell

T reg cell

Th17

MAIT CD8
Cytokines

- Effector molecules of immune system (aka interleukins, lymphokines, chemokines)
- “Immune hormone”
- Proteins (many) secreted by (immune or non-immune) cells
- Binds to surface receptor (IL2-IL2R)
- Cell signaling -> functional change
Mediators of immune response to MTB: Cytokines

- **IFN-γ**
  - IFN-γR deficient humans
  - IFN-γ KO mice

- **TNF-α**
  - TNF-α and TNF-αR KO mice
  - anti-TNF-α antibodies in humans

- **IL-12**
  - IL-12R deficient humans
  - IL-12 KO mice

- **IL-10/TGF-β**
  - Inhibit during active disease
Antigens recognized by MTB-specific T cells?

- 4000 genes = 4000 proteins!
- No immunodominance; lots of diversity
- Some Ags recognized by many: 30 kDa 85B, ESAT-6, CFP-10
What about the rest of the immune system?

- Neutrophils: present in disease
- B cells: may make things worse
- Antibodies: not protective; increased in disease
- NK cells: present; significance
- Others: many cytokines, inflammatory mediators - chicken or egg argument
How do we know all this about the immune response to MTB?

- Animal models: mouse (basic immunology), guinea pig, rabbit, primate
- Limitations: most animal models mimic acute primary infection; no good latency model (primate, rabbit-depends on MTB strain)
How can MTB survive in the heart of the immune system?

Immune Evasion!
Immune Evasion and *M. tuberculosis*

Lung is a unique environment
- Alternatively activated macrophages
- Inhibitory environment for T cell priming & activation
Immune Evasion and *M. tuberculosis* II

Thrives in Macrophages

- Blocks Phagosomal Maturation (no fusion with lysosomes; excludes Proton ATP-ase)
- Inactivates Bactericidal Mechanisms ($O_2^-/H_2O_2/OH^-; NO; Autophagy; Apoptosis$)
Immune Evasion and *M. tuberculosis* III

Avoids Recognition by T cells

- Inhibits MHC II Ag processing for CD4 T cells
- Interferes with TCR signaling, i.e. T cell activation
*M. tb* cell wall: rich source of immune-regulatory molecules
Bottom Line: Key Human Factors

- CD4+ T cells (HIV)
- Interferon-gamma (IFN-\(\gamma\))/IL-12 (IGRA; genetic defects)
- Tumor necrosis factor-alpha (TNF-\(\alpha\)) (Rheumatology)
- Immune response controls but does not eliminate MTB in most (LTBI)
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Questions?
TB immunology: Applications

- IGRA for diagnosis of latent MTB infection (LTBI)
- New/Better TB vaccine
- Immune failure: Progression from LTBI to TB (CD4 T cells & HIV-TB, anti-TNF-α, immunosuppressive Rx)
- Immunodeficiency and other mycobacterial infections (MSMD)
Dx of *M. tuberculosis* Infection (LTBI): TST vs. IGRA?

- Principle for both:
  - No clinical evidence for active TB (CXR-, no symptoms)
  - T cell response to *M. tuberculosis* proteins

- Biological difference:
  - PPD/tuberculin: Mixture of mycobacterial proteins (shared with BCG, environmental myco.)
  - IGRA: peptides of 2 proteins unique to MTB (ESAT-6, CFP-10)
TST or PPD skin test: tried & true

- Low tech
- Cheap in low-cost health care setting
- 2 visits
- Skill & experience in admin. + reading
How did we find IGRA proteins?

*M. tuberculosis* Genetics

- Compare Genomes of MTB and BCG (vaccine)
- Regions of Deletion (RD) in BCG
- RD1: 2 highly immunogenic proteins (ESAT-6, CFP-10)
- Used in IGRA
Most Common IGRA: “QFT Gold” In-Tube Test (Cellestis)

5 easy steps of QFT™ In-Tube

1. Collect 1 mL of blood into NFL, Antigen and Mitogen tubes.
   Shake well.
   Incubate tubes at 37°C for 16-24 hrs.

2. Centrifuge tubes for 15 minutes.

3. Add conjugate, plasma samples and standards to ELISA.
   Incubate for 120 minutes at room temperature.

4. Wash and add substrate.
   Read absorbance after 30 minutes.

5. Software calculates results and prints reports.
Why diagnose and treat LTBI?

5-10% lifetime risk for HIV-uninfected persons; half of this risk is during first 2 yrs. after infection.

Much higher (7 to 10%/year) in HIV/AIDS.

DM, silicosis, ESRD, cirrhosis, TNF inhibitors, immune sup. Rx, etc. increase TB risk.

Reality: LTBI Rx only US/Europe.

Mass treatment before vaccination of adolescents.
Who to test for LTBI?

Close contacts of persons known or suspected to have TB
Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

for the TB Trials Consortium PREVENT TB Study Team*

- 2 pills weekly for 12 doses
  vs.
- 1 pill daily for 270 days
IGRA Summary

- IGRA for Dx LTBI not active TB!
- Not a population screen (i.e. high risk populations only)
- More convenient than TST in US
- False negatives (like TST) in the immunocompromised (anti-TNFα Rx, transplant recipients, HIV)
- Not useful in TB endemic countries (cost, high rate of LTBI)
- LTBI Rx now simple, safe, effective
MDR/XDR TB

Better TB Vaccine is best solution
MDR/XDR TB: 2012 Bleak Reality

Prevalence of and risk factors for resistance to second-line drugs in people with multidrug-resistant tuberculosis in eight countries: a prospective cohort study

Tracy Dalton, Peter Cegielski, Somsoak Akksilp, Luis Asencios, Janice Campos Cavoli, Sang-Nae Cho, Vladislav V Erokhin, Julia Ershova, Ma Torchia Gler, Boris V Kazemy, Hee Jin Kim, Kai Kliiman, Ekaterina Kurbatova, Charlotte Kvasniovsky, Vaira Leimane, Martie van der Walt, Laura E Wa, Grigory V Volchenkov, Martin A Yagui, Hyungi Soon Kang, and the Global PETTS Investigators

Summary
Background The prevalence of extensively drug-resistant (XDR) tuberculosis is increasing due to the expanded use of second-line drugs in people with multidrug-resistant (MDR) disease. We prospectively assessed resistance to second-line antituberculosis drugs in eight countries.

Methods From Jan 1, 2005, to Dec 31, 2008, we enrolled consecutive adults with locally confirmed pulmonary MDR tuberculosis at the start of second-line treatment in Estonia, Latvia, Peru, Philippines, Russia, South Africa, South Korea, and Thailand. Drug-susceptibility testing for study purposes was done centrally at the Centers for Disease Control and Prevention for third-line and second-line drugs. We compared the results with clinical and epidemiological data to identify risk factors for resistance to second-line drugs and XDR tuberculosis.

Findings Among 1278 patients, 43.7% showed resistance to at least one second-line drug, 20.0% to at least one second-line injectable drug, and 12.9% to at least one fluoroquinolone. 6.7% of patients had XDR tuberculosis (range across study sites 0–8–15.2%). Previous treatment with second-line drugs was consistently the strongest risk factor for resistance to these drugs, which increased the risk of XDR tuberculosis by more than four times. Fluoroquinolone resistance and XDR tuberculosis were more frequent in women than in men. Unemployment, alcohol abuse, and smoking were associated with resistance to second-line injectable drugs across countries. Other risk factors differed between drugs and countries.

Interpretation Previous treatment with second-line drugs is a strong, consistent risk factor for resistance to these drugs, including XDR tuberculosis. Representative drug-susceptibility results could guide in-country policies for laboratory capacity and diagnostic strategies.

- # MDR/XDR TB continue to increase
- Inadequate capacity for drug sensitivity testing
- Blind use of second-line TB drugs
- Difficult to reach populations (prisoners, substance abuse, unemployment)
Options for MDR/XDR TB

- New Drugs: only 4-5 in pipeline (#1 approved 12/12; #2 in next 1-2 yrs)
- New uses of existing antibiotics not used in TB: sulfa, beta-lactamase inhibitors, higher doses current TB drugs
- Treat LTBI: regimens don’t treat MDR/XDR strains
- Prevent TB: New Vaccines
New TB Vaccine: What about BCG?

- Oldest vaccine in use
- Over 3 billion doses worldwide
- Massive immunization campaigns worldwide (not USA/Neth)
- Protect Disseminated TB in very young children
- No protection against Pulm. TB in adolescents/Adults
BCG Vaccine Efficacy (%): Clinical Trials

In Brazil 200,000 children (7-14 yr) were +/-BCG revaccinated: 9% BCG efficacy

Functional characterization of proliferating BCG-specific CD4+ T cells

Boost?
Where should new TB vaccines focus?

- BCG
- BCG

Bacterial Load

(TST -)

(TST +)

Innate

Adaptive

Acute

Chronic

Reactivation/Adults

Infection

IO PROGRESSIVE/PEDS

NIAID-DMID - AI70022

OUTCOMES

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Vaccine

What are the two essential components of a vaccine?

How do the vaccines that work well, work?
Current Approaches to TB Vaccine development
(N > 50)*

- Better BCG: add gene (s)
- Weak MTB: knock out gene(s)
- MTB proteins in viral vector: virus (MVA, AD5/35)
- MTB proteins alone with adjuvant (e.g. HepB, HPV)
- Others: nasal BCG, *M. smeg.*, *M. vaccae*, *Streptomyces*, DNA, polysaccharides
### Global TB Vaccine Pipeline: 15 in Clinical Trials

<table>
<thead>
<tr>
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<th>Phase II</th>
<th>Phase IIb</th>
<th>Phase III</th>
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<tbody>
<tr>
<td>AdAg85A</td>
<td>M72+AS01</td>
<td>MVA85A/ AERAS-485</td>
<td>Mw [M. indicus pranii (MIP)]</td>
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<td>McMaster University</td>
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<td>Oxford-Emergent Tuberculosis Consortium (OETC), Aeras, EDCTP, Wellcome Trust</td>
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<td>Max Planck, Vakzine Projekt Mgmt, TBVI</td>
<td>B</td>
<td>IT</td>
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<tr>
<td>H56+IC31</td>
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<td>SSI, TBVI, EDCTP, Intercell</td>
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<tr>
<td>Hyvac 4/ AERAS-404 +IC31</td>
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<td>SSI, sanofi-pasteur, Aeras, Intercell</td>
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<tr>
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<td>RUTI</td>
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<tr>
<td>B</td>
<td>B</td>
<td>B</td>
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</tbody>
</table>

#### TB Vaccine Types
- **Viral-vectored:** MVA85A, AERAS-402, AdAg85A
- **Protein/adjuvant:** M72, Hybrid-1, Hyvac 4, H56
- **rBCG:** VPM 1002, ID93/GLA-SE
- **Killed WC or Extract:** Mw, RUTI

**Source:** Tuberculosis Vaccine Candidates – 2011

**The Foundation for The Gator Nation**
How did we get all these vaccines?

- Known antigens (85B, ESAT6)
- Vector of choice
- Animal model of acute MTB infection (no LTBI)
- Mice, Guinea Pig, Primate
- BCG “Gold Standard”
- Safe in Phase I: arm doesn’t fall off!
- Measure T cell response (i.e. no surrogate)
Vaccines elicit different responses: biomarker for protection?

Modified vaccinia Ankara-expressing Ag85A, a novel tuberculosis vaccine, is safe in adolescents and children, and induces polyfunctional CD4⁺ T cells

Thomas J. Scriba*, Michele Tameris*, Nazma Mansoor¹, Erica Smit¹, Linda van der Merwe¹, Fatima Isaacs¹, Alana Keyser¹, Sizulu Moyo¹, Nathaniel Brittain², Alison Lawrie², Sebastian Gelderbloem¹,³, Ashley Veldsman¹, Mark Hatherill¹, Anthony Hawkridge³, Adrian V. S. Hill², Gregory D. Hussey¹, Hassan Mahomed¹, Helen McShane**² and Willem A. Hanekom**¹

¹ South African Tuberculosis Vaccine Initiative, Institute of Infectious Diseases and Molecular Medicine, and School of Child and Adolescent Health, University of Cape Town, Observatory, South Africa
² Centre for Clinical Vaccinology and Tropical Medicine and The Jenner Institute Laboratories, Nuffield Department of Medicine, Oxford University, Oxford, UK
³ Aeras Global Tuberculosis Vaccine Foundation, Rondebosch, South Africa

The Novel Tuberculosis Vaccine, AERAS-402, Induces Robust and Polyfunctional CD4⁺ and CD8⁺ T Cells in Adults

Brian Abell*, Michele Tameris*, Nazma Mansoor¹, Sebastian Gelderbloem², Jane Hughes¹, Deborah Abrahams¹, Lebohang Makethe¹, Mzwandile Erasmus¹, Marwou de Kock¹, Linda van der Merwe¹, Anthony Hawkridge², Ashley Veldsman¹, Mark Hatherill¹, Giulia Schirru², Maria Grazia Pau², Jenny Hendriks³, Gerrit Jan Weyerling¹, Jaap Goudsmit³, Donata Sizemore⁴, J. Bruce McClain⁴, Margaret Goetz⁴, Jacqueline Gearhart⁴, Hassan Mahomed¹, Gregory D. Hussey¹, Jerald C. Sadoff⁴, and Willem A. Hanekom¹

¹ South African Tuberculosis Vaccine Initiative, Institute of Infectious Diseases and Molecular Medicine and School of Child and Adolescent Health, University of Cape Town, and ²Aeras Global TB Vaccine Foundation, Rondebosch, Cape Town, South Africa; ³Crucell NV, Leiden, The Netherlands; and ⁴Aeras Global TB Vaccine Foundation, Rockville, Maryland
IFN-γ ELISPOT Responses to Ag85A Peptides

MVA85A (AERAS-485): Cumulative Experience

- 14 clinical trials completed or ongoing involving >2500 subjects, at dose levels ranging from $1 \times 10^7$ to $1 \times 10^8$ (healthy adults/adolescents/children/infants; HIV-infected adults; LTBI)

- Acceptable safety profile in all populations studied
  - Site of injection reactions in most subjects

- Preferentially induces CD4+ (some CD8+) T cell responses
  - Appears more immunogenic in adults

- Is currently in phase IIb proof of concept efficacy trials
  - Infants (Univ of Cape Town/SATVI, N~2800) initiated July 2009; over 2400 currently enrolled; data probably available in 2012
  - HIV-infected adults (South Africa, Senegal, N=1400) - March 2011
Failure of first TB vaccine trial (2/13)

Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial


Lancet, 2013
Does Antigen Matter?
How to optimize T cell responses?

- Most current vaccine candidates use well characterized MTB/BCG Antigens
- Mtb has +/- 4000 genes: CD4/CD8 repertoires poorly characterized
- Few adjuvants to boost T cells: TLR4/9 (AS01, IC31)
- Abs. not (thought to be) protective
- Primary T cell vaccines: no track record
GSK M72

- **Rationale**
  - Suboptimal stability of Mtb72F
  - May be due to putative serine protease site (Mtb32A) (Skeiky et al. Inf. & Immun, 1999)
  - M72 = Mtb72F with a point mutation (Ser ⇒ Ala) in active site
  - No predicted T cell epitope in the region of the mutation

- **Preclinical comparison of Mtb72F and M72**
  - Cell-mediated and antibody response comparable in mice
  - Equivalent protection in guinea pigs
GSK M72 Immunogenicity Profile

- Vaccine is immunogenic in target populations
  - Induces an M72-specific Ab response
    - up to 2 years data available in PPD-neg volunteers
    - standard follow-up is 6 months post vaccination
  - Induces M72-specific CD4+ T cells
    - up to 2 years data available in PPD-neg volunteers
    - standard follow-up is 6 months post vaccination
  - Predominantly a polyfunctional CD4+ T cell response
    - Expressing combinations of CD40L, IL-2, TNF-α, and IFN-γ.
  - Comparable magnitude of responses observed after 2 doses in PPD neg, PPD pos and HIV positive subjects
Will MTB Strain Diversity Matter?

Immunogenicity of Novel DosR Regulon-Encoded Candidate Antigens of Mycobacterium tuberculosis in Three High-Burden Populations in Africa

Gillian F. Black,1,† Bonnie A. Thiel,2,† Martin O. Ota,3 Shreemanta K. Parida,4 Richard Adegboyega,5 W. Henry Boom,2,6 Hazel M. Dockrell,7 Kees L. M. C. Franken,1 Anemiek H. Priggen,7 Philip C. Hill,6 Michel R. Klein,5 Mavec K. Labor,9 Harriet Mawanga,5 Gary Schoolnik,5 Kim Stanley,1 Karin Wielinga,6) Stefan H. E. Kaufmann,4 Gerhard Walzl,3 Tom H. M. Ottenhoff,7 and the GCGH Biomarkers for TB Consortium

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TB Vaccines Summary

- Many promising new TB vaccines
- Huge International Effort (NIH, Gates, WHO, World Bank, EEC)
- Challenges:
  - In absence of surrogate marker for protective immunity: large clinical trials (30,000+)
  - Limited global clinical trial capacity for TB vaccines
  - Poor/No track record for T cell vaccines (e.g. HIV vaccine; BCG)
Discussion

- Stuck with BCG? Can/Should we learn more?
- Sterilizing immunity?
- Biomarker for protective immunity?
- Lots of candidates/many vectors-how to proceed?
- Who to vaccinate/boost?
- Protection vs. Immuno-Pathology?
- No human live challenge
- Limited Clinical Trials Capacity
Immunosuppression and mycobacterial infection

- Taught us:
  1. Critical immune components required for control of MTB
  2. In whom to prevent progression from LTBI to TB
M. tuberculosis Infection in Immunocompromised persons

- Bacterial Load
  - Innate (TST -)
  - Adaptive (TST +)
  - Latent Infection
  - Reactivation Disease
  - 1° Progressive Disease

Increased in IC
Unraveling the key interactions of T cells and mononuclear phagocytes to control MTB

- HIV infection: TB directly related to CD4+ T cell depletion (50% >200 CD4/mm³)
- Children with genetic defects in IFNγR, IL12R, STAT1 pathway: dis. inf. with nontuberculous mycobacteria (NTM; e.g. *M. avium*, *BCG*) (MSMD: Mendelian Susceptibility to Mycobacterial Diseases)
- Rx of auto-immune diseases with anti-TNFα drugs: weaken granuloma
**Immunogenetics and MTB**

- **Early evidence**
  - Twin studies: Concordance (32-62% in MZ, 14-18% in DZ)

- **Children with disseminated BCG/NTM (MSMD)**
  - Mutations of the IL-12-IFN-γ-STAT1 pathway

- **Candidate gene studies**
  - Numerous studies but inconsistent, even within study populations

- **Whole genome scans**
  - Promising regions
  - Studies of different stages of TB pathogenesis may be more promising
Adult-Onset Immunodeficiency in Thailand and Taiwan


- Patients in Thailand and Taiwan without a known immunodeficiency who had serious infections with non-tuberculous mycobacteria and other opportunistic infections were identified.

- Immunologic evaluation showed a strong association with autoantibodies to interferon-α.
Common Disease Manifestations in Patients
Clinical Characteristics of the 203 Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (N=52)</th>
<th>Group 2 (N=45)</th>
<th>Group 3 (N=9)</th>
<th>Group 4 (N=49)</th>
<th>Group 5 (N=48)</th>
<th>P Value†</th>
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<tbody>
<tr>
<td>Age — yr</td>
<td><strong>NTM</strong></td>
<td><strong>Other OI</strong></td>
<td><strong>DTB</strong></td>
<td><strong>TB</strong></td>
<td><strong>NL</strong></td>
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<td>Median</td>
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<td>49</td>
<td>38</td>
<td>43</td>
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<td>Male sex — no. (%)</td>
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<td>17 (38)</td>
<td>3 (33)</td>
<td>28 (57)</td>
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<td>Anti–interferon-γ autoantibody—positive — no. (%)</td>
<td>42 (81)</td>
<td>43 (96)</td>
<td>1 (11)</td>
<td>1 (2)</td>
<td>1 (2)</td>
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<td>Associated conditions — no.</td>
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<tr>
<td>Lymphatic obstruction</td>
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<td>9</td>
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<td>Pain or neuropathy</td>
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<td>Hypercalcemia</td>
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</table>

* Patients in group 1 had disseminated, rapidly growing or slowly growing, nontuberculous mycobacterial infection. Patients in group 2 had other opportunistic infections (e.g., Cryptococcus neoformans, Histoplasma capsulatum, Penicillium marneffei, disseminated salmonellosis, or severe varicella–zoster virus infection) with or without nontuberculous mycobacterial infection. Patients in group 3 had disseminated tuberculosis. Patients in group 4 had pulmonary tuberculosis. Group 5 was composed of healthy controls.

† P values were determined with the use of Fisher’s exact test for categorical variables and analysis of variance (F-test) for continuous variables.
Anti–IFN-γ Autoantibody Concentrations in 203 Participants
Neutralizing anti–interferon-γ autoantibodies were detected in 88% of Asian adults with multiple opportunistic infections and were associated with an adult-onset immunodeficiency akin to that of advanced HIV infection.

### Table 2. Isolated Organisms in 97 Patients with Opportunistic Infections.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (N=52)</th>
<th>Group 2 (N=45)</th>
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</thead>
<tbody>
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<td>Organisms isolated (no./patient)</td>
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<td>39</td>
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<td>10†</td>
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<tr>
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<td>Salmonella species</td>
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<td></td>
</tr>
<tr>
<td><em>Burkholderia pseudomallei</em></td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Fungi (no. of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><em>Histoplasma capsulatum</em></td>
<td>7</td>
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</tr>
<tr>
<td><em>Penicillium marneffei</em></td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Varicella-zoster virus (no. of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disseminated</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Parasites (no. of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Strongyloides stercoralis</em></td>
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<td></td>
</tr>
</tbody>
</table>

* Two patients had pulmonary tuberculosis, and two had disseminated tuberculosis.
† Three patients had pulmonary tuberculosis, and seven had disseminated tuberculosis.
Conclusions

• Immune responses to MTB matter!
  – Diagnose LTBI (CD4 T cell/IFN-gamma)
  – Immune failure (CD4 T cell; anti-TNF-α; ?anti-IFN-γ auto-Abs): progression LTBI => TB
  – Vaccine Efficacy (BCG failure/New TB vaccines)
  – Response to TB Rx and relapse (HIV+ higher failure rate)
Southeastern National Tuberculosis Center
SHARE • LEARN • CURE

Questions?
HIV-TB

All about CD4+ T cells
TB Clinical Presentation in HIV+:
Related to immune status

- In Kampala/Uganda 2375 TB cases screened ‘04-present
- 46% TB cases HIV+:
  - 49% CD4 >200 (1/4 rule)
  - 26% CD4 >350
  - range of viral loads
HIV-TB: Clinical presentation and CD4+ T cell count
**M. tuberculosis Infection in HIV+ persons**

- **Bacterial Load**
  - Innate
  - Adaptive
  - Latent Infection
  - Reactivation Disease
  - Progressive Disease

- **TST**
  - TST -
  - TST +

- **Increase in HIV+**
HIV and MTB co-infection: bi-directional interactions

HIV infection:
- loss MTB-specific CD4 T cell,
- loss of CD4 help for CD8, gamma-delta T cells,
- T cells essential for control latent/new MTB infection

HIV +: 5% risk/yr for TB
HIV -: 5% lifetime risk

MTB infection and disease:
- chronic T cell & macrophage activation,
- increased cytokine production (e.g. TNF-alpha),
- increased HIV replication and diversity
HIV and MTB: Approaches to prevention and therapy

- CD4 loss due to HIV
  - MTB replication (Reactivation/Persistence)
  - MTB mediated imm. activation
  - Increased HIV replication
  - CD4 depletion
  - HIV progression

Intervention:
- Inhibit MTB
- Block cytokines
- Reduce HIV replication
Effect of TB Rx vs. TB Rx+ARV on HIV VL

- TB Rx alone (n=38)
- TB Rx+ARV (6mo) (n=38)
TB Rx vs. TB+ARV Rx and Immune Activation: MTB dominant

- TB Rx alone
- TB Rx+ARV (6mo)

Cross-sectional Differences
P-values at Each Time Point

Baseline = 0.73
Month 3 = 0.01
Month 6 = 0.007
Month 9 = 0.90
Month 12 = 0.96
Areas where Rx of TB is Different in HIV+ and HIV-uninfected Patients

- High recurrence rate in HIV+ patients with highly intermittent (once or twice weekly) regimens especially in patients with CD4 < 100
- Increased risk of developing rifampicin resistance in patients with advanced AIDS
Comparison of outcomes by HIV status for 6-month RIF/PZA regimens given as DOT

<table>
<thead>
<tr>
<th>Study</th>
<th>HIV positive</th>
<th>HIV negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment failure (%)</td>
<td>Recurrence (%)</td>
</tr>
<tr>
<td>Haiti (427)</td>
<td>2</td>
<td>5.4</td>
</tr>
<tr>
<td>South Africa (403)</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Baltimore (407)</td>
<td>0</td>
<td>8.3</td>
</tr>
<tr>
<td>South Africa (385)</td>
<td>5.3</td>
<td>22</td>
</tr>
</tbody>
</table>
Relapse vs. re-infection by HIV-serostatus

Lancet 2001;358:1687-93
Summary – Duration of Rx in HIV-TB

• 6 mo regimens have had reasonable results, but concerns remain
  – high risk group for failure/relapse – low CD4
  – unknown whether ARV will correct problem

• role of secondary preventive therapy after treatment in some settings

• need more prospective studies
The Promise of ART for Patients with HIV+TB

- High mortality in pts w/ HIV+TB before ART - 20 to 30% in first yr
- Early deaths due to TB but later mortality due to AIDS & other OIs
- Highest mortality w/ low CD4 (< 100)
- ART decreased deaths & OIs esp in advanced AIDS & should do so in pts w/ TB
Antiretroviral Therapy & TB Treatment

- Many interactions of rifampicin w/ HAART therapy esp protease inhibitors. Less interactions w/ rifabutin but RBT not available in many parts of the world
- The challenge is to use available ART in patients being treated with rifampicin-containing TB regimens.
Timing of Starting ART in Pts w/ TB

Must Balance

- risk of death due to progression of HIV/AIDS vs.
- large # of drugs started at same time
- drug interactions & overlapping side effects
- occurrence of paradoxical/immune reconstitution (IRIS) reactions when ART started early
- worst case is to treat both diseases badly!
<table>
<thead>
<tr>
<th>CD4 Count</th>
<th>Rec Regimen</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 350</td>
<td>Start TB Rx</td>
<td>Defer ART</td>
</tr>
<tr>
<td>200-350</td>
<td>Start TB Rx. Consider ART</td>
<td>Begin ART after intensive phase of TB Rx.</td>
</tr>
<tr>
<td>&lt; 200</td>
<td>Start TB Rx. Start ART as soon as TB Rx underway.</td>
<td>High risk for death.</td>
</tr>
</tbody>
</table>
Which ARV Regimens to Use?

WHO First-line ARV for Adults

- stavudine/lamivudine/efavirenz (d4T/3TC/EFV)
- zidovudine/lamivudine/efavirenz (ZDV/3TC/EFV)
- stavudine/lamivudine/nevirapine (d4T/3TC/NVP)
- zidovudine/lamivudine/nevirapine (ZDV/3TC/NVP)

MORE DATA NEEDED!
Immune Reconstitution Inflammatory Reaction (IRIS; Paradoxical Reactions)

- **Definition:** Worsening signs, symptoms, X-ray after TB Rx
- **Described before HIV-TB**
- +/- 10% HIV-TB on HAART
- **Frequent:** extrapulm. (dissem), low CD4 (2-3 wks on HAART)
- **Immunology:**
  - Rapid decline in VL
  - Return of CD4+ function (not #)
  - Advanced HIV -> large MTB Ag load
  - Reversal of 2 immune-suppressive pathogens: MTB and HIV
Paradoxical or Immune Reconstitution Inflammatory Syndrome (IRIS) Reactions

- transient worsening or new signs, symptoms, or radiographic manifestations of TB after starting TB treatment.
- well-described in TB patients before onset of HIV epidemic. More frequent in patients started on HAART (6 to 36%).
- no diagnostic laboratory tests; must exclude treatment failure, non-adherence, other opportunistic infections
Integration of TB & HIV Care

- TB services part of well-established vertical program
- HIV/ART services in pilot phase
- Both – heavy service load, much cross-referral
- Challenges – overlap of activities, need for trained staff

Key Questions in Management of TB+HIV

✓ How to diagnose TB better especially in patients with advanced HIV/AIDS who often are smear negative or have EPTB
✓ Duration of therapy – Should it be longer? For whom?
✓ Optimal timing of initiation & best ARV regimens for treating patients with TB+HIV
  • Recognition & management of IRIS reactions
  • Secondary prophylaxis after treatment
✓ Provision of effective HIV & TB care in resource-constrained settings
Thank you