Global Trends in TB

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I, Beata Casanas, have the Following commercial and financial interests to disclose to the meeting participants.

- **Pfizer**: speaker
- **Tibotec**: Principal Investigator – TMC 278, TMC 125
- **Napo Pharmaceuticals**: Principal Investigator – Crofelemer
- **GlaxoSmithKline**: Principal Investigator – GW433908, Epzicom
TB Around the World
Global Burden of TB

• 9.2 million new cases in 2006 (139 per 100,000)
• 14.4 million prevalent cases in 2006
• 0.5 million cases of MDR TB

*Data is from the World Health Organization Global Report, 2008.*
Estimated numbers of new cases, 2006

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

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Estimated HIV prevalence in new TB cases, 2006

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For each country or region, the number of incident TB cases arising in people with HIV is shown as a percentage of the global total of such cases. AFR* is all countries in the WHO African Region except those shown separately; AMR* excludes Brazil; EUR* excludes the Russian Federation; SEAR* excludes India.
MDR-TB treatment outcomes in seven countries, 2003 cohort

- Germany (94)
- Lithuania (310)
- Brazil (316)
- Estonia (106)
- Latvia (165)
- Romania (585)
- Peru (1508)

Cured | Completed | Died | Failed | Defaulted | Transferred | Not evaluated
--- | --- | --- | --- | --- | --- | ---
Countries that had reported at least one XDR-TB case by end 2008

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WHO Targets

• Halt and reverse incidence by 2015.

• Detect at least 70% of new smear positive cases.

• Successfully treat at least 85% of detected cases.

*WHO report 2008: Global tuberculosis control - surveillance, planning, financing
Strategies

• DOTS Expansion
• Addressing TB/HIV, MDR TB
• Health system strengthening
• Empowering patients and communities
• Promoting and enabling research

*WHO report 2008: Global tuberculosis control - surveillance, planning, financing
Progress toward Targets

• Case detection rate for new smear-positive cases in DOTS programmes is estimated at 61% as of 2006. Target is 70%.

• The treatment success rate in DOTS programmes was 84.7% in 2005, just short of the 85% target.

• Reduction in incidence, prevalence and death rates.

*WHO report 2008: Global tuberculosis control - surveillance, planning, financing
Progress toward Targets

• While DOTS programmes are reducing death and prevalence rates, a new ecological analysis suggests that they have not yet had a major impact on TB transmission and trends in TB incidence around the world.

*WHO report 2008: Global tuberculosis control - surveillance, planning, financing
TB in the United States
Reported TB Cases*
United States, 1982–2007

*Updated as of April 23, 2008.
## TB Morbidity
### United States, 2002–2007

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*Cases per 100,000, updated as of April 23, 2008.
Factors Contributing to the Increase in TB Morbidity

• HIV epidemic
• Increased immigration from high-prevalence counties
• Transmission of TB in congregate settings
• Deterioration of the health care infrastructure
Reported TB Cases by Age Group, United States, 2007

- <15 yrs (6%)
- 15–24 yrs (12%)
- 45–64 yrs (30%)
- 25–44 yrs (32%)
- >65 yrs (19%)
Reported TB Cases by Race/Ethnicity*
United States, 2007

- Hispanic or Latino (29%)
- Black or African-American (26%)
- Asian (26%)
- White (17%)
- Native Hawaiian or Other Pacific Islander (<1%)
- American Indian or Alaska Native (1%)

*All races are non-Hispanic. Persons reporting two or more races accounted for less than 1% of all cases.
Number of TB Cases in U.S.-born vs. Foreign-born Persons
United States, 1993–2007*

*Updated as of April 23, 2008.
Percentage of TB Cases Among Foreign-born Persons, United States*

1997

2007

*Updated as of April 23, 2008.
Countries of Birth of Foreign-born Persons Reported with TB United States, 2007

- Mexico (24%)
- Philippines (12%)
- Viet Nam (7%)
- India (8%)
- China (5%)
- Haiti (2%)
- Rep. Korea (3%)
- Other Countries (39%)
Primary MDR TB
United States, 1993–2007*

No. of Cases

1993 1995 1997 1999 2001 2003 2005 2007

Percentage

0 1 2 3

No. of Cases

Percentage

*Updated as of April 23, 2008.

Note: Based on initial isolates from persons with no prior history of TB. MDR TB defined as resistance to at least isoniazid and rifampin.
XDR TB Case Count defined on Initial DST† by Year, 1993–2007*

†Drug susceptibility test.
*Reported incident cases as of April 23, 2008.
Extensively drug-resistant TB (XDR TB) is defined as resistance to isoniazid and rifampin, plus resistance to any fluoroquinolone and at least one of three injectable second-line anti-TB drugs.
TB in Florida
Tuberculosis Cases
Florida, 1994-2008

Provisional data from TIMS
(Tuberculosis Information Management System)
Tuberculosis Rates
Florida, 1994-2008

Provisional data from T1MS
Rates are per 100,000 population
Population estimates from Florida Legislature's Office of Economic and Demographic Research (EDR)
TB Cases by Race and Ethnicity
Florida, 2008

- **27%** White, non-Hisp
- **39%** Hispanic-all races
- **22%** Black, non-Hisp
- **10%** Hispanic-all races
- **<1%** Pacific Islander/Nat Hawaiian
- **<1%** Ameri Indian/AK Native
- **<1%** Multi Race

Provisional data from TIMS. *Persons reporting to be American Indian/Alaska Native, Pacific Islander/Native Hawaiian or Multiple races comprised <1% of TB cases.*

Percentages have been rounded and may not equal 100%.
Tuberculosis by Age Group
Florida, 2008

- 45-64 yrs (39%)
- 25-44 yrs (29%)
- 65+ yrs (17%)
- 15-24 yrs (10%)
- 0-4 yrs (4%)
- 5-14 yrs (1%)

N=953

Preliminary data from TIMS
Percentages have been rounded and may not equal 100%
Reported TB Cases by Origin Florida, 2008

- **Foreign-born** (29%)
  - (Other Countries)

- **U.S.-born** (51%)

- **Foreign-born** (20%)
  - (Top 2 Countries)

- **Mexico** (7%)

- **Haiti** (13%)

N=953

Provisional data from TIMS

Percentages have been rounded and may not equal 100%
TB Cases Among Foreign-born Persons
Florida, 1994-2008

Provisional data from TIMS Percentages have been rounded and may not equal 100%
Trend of TB/HIV Co-Infection
Florida, 1994-2008

Provisional data from TIMS Percentages have been rounded and may not equal 100%
TB/HIV Cases by Race & Ethnicity
Florida, 2008

Provisional data from TIMS
All races are non-Hispanic. Hispanic or Latino ethnicity includes ALL races.

Percentages have been rounded and may not equal 100%
TB: Clinical Features
TB Transmission

- **Cough**
  - 1 good cough produces 465 Droplet Nuclei
  - after 30 minutes left: 228 Droplet Nuclei (49%)

- **Speech:**
  - count from 1 to 100 1764 Droplet Nuclei
  - after 30 minutes left 106 Droplet Nuclei (6%)
Latent TB Infection

• Once inhaled, bacteria travel to lung alveoli and establish infection
• 2–12 wks after infection, immune response limits activity; infection is detectable
• Some bacteria survive and remain dormant but viable for years (latent TB infection, or LTBI)
Tuberculin Test

0.1 ml tuberculin (5 TU) injected just under skin surface of forearm. Pale elevation results. Needle bevel directed upward to prevent too deep penetration.

Test read in 48 to 72 h. Extent of induration determined by direct observation and palpation limits marked. Area of erythema has no significance.
Tuberculosis Screening – Skin Tests

- **15mm**
  - Person from LOW prevalence area
  - NO medical risk factors
  - NO known exposure to TB

- **10mm**
  - Person from HIGH prevalence area:
    - Asia, Africa, Latin America ≥1%
    - MEDICAL RISK factors

- **5mm**
  - CLOSE CONTACTS to infectious TB
  - OLD TB LESIONS
  - HIV INFECTION
QuantiFERON-TB Gold test

• QFT-G is a type of blood assay for *M. tuberculosis* (BAMT)
  – Measures the patient’s immune system reaction to MTB via the production of interferon-\textit{gamma} in response to ESAT-6 and CFP-10, two highly immunogenic secreted antigens
  – Blood samples must be processed within 12 hours
Active TB Disease

LTBI progresses to TB disease in
• Small number of persons soon after infection
• 5%–10% of persons with untreated LTBI sometime during lifetime
• About 10% of persons with HIV and untreated LTBI per year
TB: Early Clinical Picture

• General complaints:
  – non-specific
  – excessive fatigue,
  – weight loss,
  – anorexia
  – irritability
• Symptoms of chronic infection:
  – low-grade fever ,
  – night sweats,
  – vague digestive disturbances
  – recurrent headaches
• SPUTUM:
  – at first dry and later productive,
  – purulent sputum
  – hemoptysis,
• Pleuritic pain from TB pleurisy with effusion, may be a presenting symptom in early stages
• Cough rarely associated with pulmonary TB in children.
Acid Fast Bacilli show up a clump or isolated thin pink rods
Severe Pulmonary TB

Most INFECTIOUS CASES

- Extensive cavities
- Positive smear
- High bacilli output
  > 10 /HPField
  or >500,000/ml
- High mortality
- without treatment (75%)
- Very infectious
  50% of close contacts infected
- RAPID evolution
Chest Xrays in TB Control

- **DIAGNOSTIC EXAMINATION** of a suspected case

- **EVALUATION OF A CASE** during treatment
  - **BUT not a substitute to SPUTUM EXAM**
    - only sputum monitors response of MTB to drugs
    - only sputum provides early warning about resistance

- BASELINE XRAY at the end of treatment

- Evaluation of a CONTACT or an INFECTED
TB Treatment

• Start with 4 drugs in all patients
  – INH, RIF, PZA and EMB or SM until sensitivities return
  – If pan sensitive, D/C EMB or SM
  – After 2 months of therapy, D/C PZA
  – Continue INH & RIF for 4 more months for total of 6 months
• Must have culture conversion by 2 months
• 6 month regimen good for HIV(-) and (+)
• Can use BIW regimen / TIW for HIV (+)
• Monitor adherence and toxicity
• DOT, combination pills for self administered (exceptions)
TB Challenges
Primary resistance to any of the 4 major drugs (INH, Rif, Emb, Sm) was estimated at 12% in the USA in 1995. It ranged in 1994-97 from a low of 2.0 in the Czech Republic to a high of 41% in the Dominican Republic (Global surveillance for anti-tb drug resistance. NEJM 1998, 338,23).

Median prevalences were:
- INH 7.3%
- Streptomycin 6.5%
- Rifampin 1.8%
- Ethambutol 1%
- All 4 0.2%
Clinical Significance of Resistance

• If pan sensitive > 95% chance of cure
• If resistant to INH > 90% chance of cure
• If resistant to rifampin > 70% chance of cure
• If resistant to INH and RIF ~ 50% chance of cure
• Before chemotherapy ~ 50% chance of cure
Combating XDR TB

• Diagnostic Laboratory
  – Accurate, reliable and prompt services needed
• Surveillance Epidemiology and Outbreak Investigation
  – Accurate and complete reporting of second line drug susceptibility
  – Real time reporting
  – Active case-finding

Combating XDR TB

- Infection Control
- Clinical and programmatic interventions
- Ethical and Legal Issues
- Communication and education
- Research
- Partnerships
- Cost Analysis

Tuberculosis and HIV
Groups at highest risk of TB disease

- HIV-infected
- Recently infected
- Persons with other medical conditions (diabetes, cancer, immunosuppressed, etc.)
- Persons in a severely malnourished state
- Persons who inject illicit drugs
- Persons with a history of inadequately treated TB infection
Epidemiology of TB and HIV

- Both have afflicted similar populations
- Both are socially stigmatizing
- Globally, TB is the 2nd leading cause of death from an infectious disease (behind HIV)
- TB is the leading cause of death in HIV globally
- Active TB may accelerate HIV replication
TB/HIV: Epidemiology

- Two billion individuals infected worldwide with MTB
- Thirty-three million HIV infected individuals worldwide
- One-third of them co-infected with MTB
- 68%- Sub Saharan Africa, 22%- SEA
- Leading cause of death amongst HIV infected individuals worldwide (half of all persons with AIDS)
- Prevalence of HIV in TB patients (India) 20%
Estimated HIV Coinfection in Persons Reported with TB, United States, 1993–2005*

*Updated as of April 6, 2007.

Note: Minimum estimates based on reported HIV-positive status among all TB cases in the age group.
TB/HIV: Pathogenesis

• Immunity to MTB partly under control of MHC Class II restricted CD4 cells
• Loss of CD4 cells increases risk of
  – Reactivation of latent infection
  – Primary infection
• Active TB up-regulates HIV replication, leading to accelerated progression of HIV
TB/HIV: Pathogenesis

- MTB induces progression of HIV via:
  - inducing replication of HIV in cells of the monocyte lineage and in acutely infected primary macrophages
  - activating transcriptionally latent HIV in alveolar macrophages or in monocytes newly recruited to sites of MTB infection
TB/HIV: Pathogenesis

• MTB induces TNF\textit{alpha} which accelerates HIV replication through:
  - nuclear factor kappa B (NFkB)
  - p38MAP kinase
  - high levels of non-inhibitory \textit{beta}-chemokine MCP1
  - low levels of inhibitory \textit{beta}-chemokines: MIP-1 \textit{alpha}, MIP-1 \textit{beta} and RANTES
TB/HIV: Pathogenesis

- Life time risk in HIV negative persons: 10%
  - 5% within first two years
  - 5% remainder of their lives
- HIV positive persons have 8% risk per year
- HIV+ incidence: 5-16/100 person-years
- Two mechanism
  - Reactivation
  - Re-infection
- Immune reconstitution TB on HAART
HAART and TB incidence

• Observational study in South Africa
• 81% reduction in TB risk with HAART
• Useful across all baseline immunologic, clinical and socio-economic variables
• Greatest reduction in symptomatic patients and those with advanced immune suppression
• Useful in areas with high prevalence of HIV and TB

Badri M Lancet, 359,2002
Managing TB/HIV co-infection

• Concomitant HAART + ATT increases risk of adverse events
• More pill burden
• Paradoxical worsening of TB
• Increases duration of ATT
MDR-TB

• HIV per se not a risk factor for development of MDR TB
• Commonest causes:
  – Poor adherence
  – Poor prescription practice
  – Poor drug quality
• Suspect when re-treatment schedule fails with proper adherence
• Prove by culture-sensitivity
HIV/TB: Treatment

- Do you need to add higher number of drugs?
- Do you need to prolong duration of therapy?
- Can ARV be used concomitantly with ATT (anti-Tuberculosis Therapy)?
- Is there increased incidence of AE’s?
- Is there increased incidence of MDR-TB?
- Should latent tuberculosis be treated? (international)