Eradicating HIV and TB in Sub-Saharan Africa
Pipedream or Possibility?

Umesh G Laloo
Nelson R Mandela School of Medicine
College of Health Sciences
# HIV Prevalence in SA 2001-2010

<table>
<thead>
<tr>
<th>Year</th>
<th>Population 15–49 years</th>
<th>Percentage of the total population</th>
<th>Total number of people living with HIV (in millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percentage of women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>18,7</td>
<td>15,4</td>
<td>9,4</td>
</tr>
<tr>
<td>2002</td>
<td>19,2</td>
<td>15,8</td>
<td>9,6</td>
</tr>
<tr>
<td>2003</td>
<td>19,4</td>
<td>16,1</td>
<td>9,8</td>
</tr>
<tr>
<td>2004</td>
<td>19,6</td>
<td>16,3</td>
<td>9,9</td>
</tr>
<tr>
<td>2005</td>
<td>19,7</td>
<td>16,5</td>
<td>10,0</td>
</tr>
<tr>
<td>2006</td>
<td>19,7</td>
<td>16,6</td>
<td>10,1</td>
</tr>
<tr>
<td>2007</td>
<td>19,7</td>
<td>16,7</td>
<td>10,2</td>
</tr>
<tr>
<td>2008</td>
<td>19,7</td>
<td>16,9</td>
<td>10,3</td>
</tr>
<tr>
<td>2009</td>
<td>19,6</td>
<td>17,0</td>
<td>10,3</td>
</tr>
<tr>
<td>2010</td>
<td>19,7</td>
<td>17,3</td>
<td>10,5</td>
</tr>
</tbody>
</table>

*Source: Statistics SA: Mid-Year Estimates 2010*
<table>
<thead>
<tr>
<th>Adults (15+ years)</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated number receiving ART*</td>
</tr>
<tr>
<td>2005</td>
<td>133 000</td>
</tr>
<tr>
<td>2006</td>
<td>239 000</td>
</tr>
<tr>
<td>2007</td>
<td>424 000</td>
</tr>
<tr>
<td>2008</td>
<td>679 000</td>
</tr>
<tr>
<td>2009</td>
<td>920 000</td>
</tr>
</tbody>
</table>

*Source: Health Information Epidemiology Evaluation and Research, Department of Health (November 09/Report)*
GLOBAL BURDEN OF HIV

UNAIDS REPORT 2010
Adults and children estimated to be living with HIV | 2009

North America 1.5 million
[1.2 million – 2.0 million]

Caribbean 240 000
[220 000 – 270 000]

Central & South America 1.4 million
[1.2 million – 1.6 million]

Western & Central Europe 820 000
[720 000 – 910 000]

Eastern Europe & Central Asia 1.4 million
[1.3 million – 1.6 million]

Middle East & North Africa 460 000
[400 000 – 530 000]

South & South-East Asia 4.1 million
[3.7 million – 4.6 million]

Sub-Saharan Africa 22.5 million
[20.9 million – 24.2 million]

East Asia 770 000
[560 000 – 1.0 million]

Oceania 57 000
[50 000 – 64 000]

Total: 33.3 million [31.4 million – 35.3 million]
Estimated number of adults and children newly infected with HIV | 2009

North America | 70,000
[64,000 – 130,000]

Central & South America | 92,000
[70,000 – 120,000]

Caribbean | 17,000
[13,000 – 21,000]

Sub-Saharan Africa | 1.8 million
[1.6 million – 2.0 million]

Eastern Europe & Central Asia | 130,000
[110,000 – 150,000]

Western & Central Europe | 31,000
[26,000 – 40,000]

Middle East & North Africa | 75,000
[61,000 – 92,000]

South & South East Asia | 270,000
[240,000 – 320,000]

East Asia | 82,000
[68,000 – 140,000]

Oceania | 4,500
[3,400 – 6,800]

Total: 2.6 million [2.3 million – 2.8 million]

Estimated adult and child deaths from AIDS | 2009

North America | 26,000
[22,000 – 44,000]

Central & South America | 59,000
[50,000 – 70,000]

Caribbean | 12,000
[8,000 – 16,000]

Sub-Saharan Africa | 1.3 million
[1.1 million – 1.5 million]

Eastern Europe & Central Asia | 76,000
[60,000 – 90,000]

Western & Central Europe | 8,500
[8,000 – 10,000]

Middle East & North Africa | 24,000
[20,000 – 27,000]

South & South East Asia | 260,000
[230,000 – 300,000]

East Asia | 36,000
[26,000 – 50,000]

Oceania | 1,400
[1,100 – 2,400]

Total: 1.8 million [1.6 million – 2.1 million]
Changes in the incidence rate of HIV infection, 2001 to 2009, selected countries

Source: UNAIDS.
ESTIMATED TB INCIDENCE RATES 2009

SOURCE: WHO TB REPORT 2010
• 8.9–9.9m incident TB cases worldwide
• Africa – 11% of world pop; 30% TB cases
• 0.7m HIV+ TB cases: 85% sub-Saharan Africa
• 1.1–1.7m deaths in HIV–; 0.5–0.8m in HIV+
TB notification rate in 20 African countries* versus HIV prevalence in sub-Saharan Africa, 1990–2004

- Consistently reporting each year: Algeria, Angola, Botswana, Cameroon, Comoros, Congo, Côte d'Ivoire, Democratic Republic of Congo, Ghana, Guinea, Kenya, Malawi, Mauritius, Mozambique, Nigeria, Senegal, South Africa, Uganda, United Republic of Tanzania, Zimbabwe

Risk of developing TB with HIV

- HIV- : lifetime risk of 10%
- HIV+ : risk of 10% per annum
  - Risk of activation 80-200X
- In KwaZulu Natal, South Africa:
  - almost 2/3 TB cases are HIV+
Pathogenesis of TB

Aerosolized bacteria

- Neck lymph node (scrofula)
- CNS spread:
  - Tuberculoma (rare)
  - TB meningitis
    - Headache
    - Stiff neck
    - Coma
- Adrenal TB
  - Addison's disease
    (commonest cause worldwide)
- Pericardium
- GU disease
  - Renal TB
  - Fallopian tube (infertility)
- Bone and joint
  (Pott's disease = TB spine)
- Skin TB
  (lupus vulgaris)
The White Plague

Yet the captain of all these men of death that came against him to take him away was consumption, for it was that that brought him down to the grave.

The life and death of Mr. Badman, presented to the world in a familiar dialogue between Mr. Wiseman and Mr. Attentive

John Bunyan, 1680
Note: PMTCT, Screening transfusions, Harm reduction, Universal precautions, etc. have not been included – this is focused on reducing sexual transmission
Treating HIV and TB

• SAPIT, Stride and Camelia
  - Early or immediate HAART is life saving

• REMEMBER
  - ACTG protocol under development to investigate empiric TB treatment in patients with very low CD4 counts (<100)

• TB / HAART drug interactions
  - A5290: PIs and raltegravir in HIV/TB
What drives TB?

• Spread from person to person
  - Poor infection control
  - Delayed presentation
  - Delayed diagnosis
  - Overcrowding in HC facilities

• Immunosuppression
  - HIV, malnutrition, innate immunity, poor LTBI control

• Lack of convenient treatment strategies, irrational treatment
Natural Ventilation for the Prevention of Airborne Contagion

A. Roderick Escombe 1,2,3, Clarissa C. Oeser 3, Robert H. Gilman 3,4, Marcos Navincopa 5, Eduardo Ticona 5, William Pan 4, Carlos Martinez 5, Jesus Chacaltana 6, Richard Rodriguez 7, David A. J. Moore 1,2, Jon S. Friedland 1,2, Carlton A. Evans 1,2,3,4

CO$_2$ concentration (ppm)

CO$_2$ release

Windows opened

0.5 ACH

12 ACH

368 experiments performed over 2 years
Hospital acquired XDR-TB

12 January 2007
Drug susceptible TB

11 April 2007
XDR-TB

Courtesy: Friedland J
Fundamentals of Infection Control
Hierarchy of Infection Control

Administrative Controls

Environmental Controls

Respiratory Protection

New diagnostics pipeline

- **M. tuberculosis**
- Human host
- Replication of *M. tuberculosis*
- Immune response to *M. tuberculosis*

**Antigen detection tests** (e.g. LAM, ELISA, urinary antigen test, sputum antigen detection)

**Microscopic visualization of bacteria** (e.g. LED microscopy, bleach microscopy)

**Culture based growth detection tests** (e.g. MODS, thin-layer agar, phage-based tests, colorimetric media)

**Nucleic acid amplification tests** (e.g. LAMP, Xpert MTB, Transrenal DNA detection, Genotype MTBDRPlus)

**Volatile organic compounds (VOC) detection** (e.g. E-Nose, biosensors)

**Cellular immune response**: IFN-g assays (e.g. QuantiFERON-TB Gold, T-SPOT.TB); rd ESAT-6 skin test

**Humoral immune response**: Antibody detection tests (e.g. serological tests)

Studies are urgently required to establish the feasibility, utility and effectiveness of sputum induction in HIV-infected patients, particularly, in primary care.
Proportion of Patients with Pulmonary TB Who Have Positive AFB Smears

- HIV Negative
- Early HIV
- Late HIV
Ford Model T 1908-1927

- TST 1890
- Microscopy 1882
- TB culture 1882
- CXR 1896
Epochs in TB and Anti-TB Drug Development

Mycobacterium tuberculosis discovered by Robert Koch as cause of consumption

1880's
- Mycobacterium tuberculosis discovered by Robert Koch

1920's
- The first human trials of the vaccine Bacille Calmette Guérin (BCG), an attenuated version of Mycobacterium bovis (Bovine TB).

1940's
- Large scale BCG immunization

1950's
- Introduction of TB drug regimens

1960's
- First outbreak of drug resistant TB in USA

1970's
- World Health Organisation declares TB a global emergency

1980's
- Rifampycin (Rifapentine)

1990's
- MDR

2000's
- XDR

2010's
- Stop TB strategy (WHO)

Beyond
- PCR for Rif and INH TB drug resistance diagnostics

LEGEND
- Red: Phase 1
- Blue: Phase 2
- Green: Phase 3

A5307 - INH antagonism

Lalloo and Ambaram. Curr HIV AIDS Rep 2010
# Selected studies of TB preventive treatment in HIV

<table>
<thead>
<tr>
<th>Source</th>
<th>Rx Regimen</th>
<th>Rate of TB/100 Person Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haiti</td>
<td>12/12 placebo, 12/12 INH</td>
<td>10, 1.7</td>
</tr>
<tr>
<td>Haiti</td>
<td>LOCATION</td>
<td>1.7, 1.8</td>
</tr>
<tr>
<td>Uganda</td>
<td>6/12 placebo, 6/12 INH, 3/12 INH/rif, 3/12 INH/rif/PZA</td>
<td>3.4, 1.1, 1.3, 1.7</td>
</tr>
<tr>
<td>Kenya</td>
<td>6/12 placebo, 6/12 INH</td>
<td>0.9, 0.4</td>
</tr>
<tr>
<td>USA</td>
<td>6/12 placebo, 6/12 INH</td>
<td>0.9, 0.4</td>
</tr>
</tbody>
</table>
Prevent TB Trial (CDC)

• Once weekly INH and rifapentine for 3 months as good as INH X 9 months
  - Sterling et al. ATS May 16, 2011
## TUBERCULOSIS VACCINE CANDIDATES – 2009

*Stop TB Partnership Working Group on New TB Vaccines*

### SECTION I: Candidates in Clinical Trials - 2009

<table>
<thead>
<tr>
<th>Type of Vaccine</th>
<th>Products</th>
<th>Product description</th>
<th>Sponsor</th>
<th>Indication</th>
<th>Status as of 2009</th>
<th>Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinant Live</td>
<td>VPM 1002</td>
<td><em>rBCG Prague strain expressing listerialysin and carries a urease deletion mutation</em></td>
<td>Max Planck, Vakzine Projekt Management GmbH, TBVI</td>
<td>P</td>
<td>Phase I</td>
<td>[1-3]</td>
</tr>
<tr>
<td></td>
<td>rBCG30</td>
<td><em>rBCG Tice strain expressing 30 kDa Mtb antigen 85B; phase I completed in U.S.</em></td>
<td>UCLA, NIH, NIAID, Aeras</td>
<td>P</td>
<td>Phase I (not active)</td>
<td>[4-8]</td>
</tr>
<tr>
<td></td>
<td>AdAg 85A</td>
<td><em>Replication-deficient adenovirus 5 vector expressing Mtb antigen 85A</em></td>
<td>McMaster University</td>
<td>P B</td>
<td>Phase I</td>
<td>[18-22]</td>
</tr>
<tr>
<td>Recombinant Protein</td>
<td>Hybrid-I+IC-31</td>
<td><em>Adjuvanted recombinant protein composed of Mtb antigens 85B and ESAT-6</em></td>
<td>SSI, TBVI, Intercell</td>
<td>P B P I</td>
<td>Phase IIa</td>
<td>[23-26]</td>
</tr>
<tr>
<td></td>
<td>Hybrid-I+CAF01</td>
<td><em>Adjuvanted recombinant protein composed of Mtb antigens 85B and ESAT-6</em></td>
<td>SSI</td>
<td>P B P I</td>
<td>Phase I</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>M72</td>
<td><em>Recombintant protein composed of a fusion of Mtb antigens Rv1196 and Rv0125 &amp; adjuvant</em></td>
<td>GSK, Aeras</td>
<td>B P I</td>
<td>Phase II</td>
<td>[27-29]</td>
</tr>
<tr>
<td></td>
<td>HyVac 4/AERAS-404</td>
<td><em>Adjuvanted recombinant protein composed of a fusion of Mtb antigens 85B and TB10.4</em></td>
<td>SSI, Sanofi-Pasteur, Aeras, Intercell</td>
<td>B</td>
<td>Phase I</td>
<td>[30, 31]</td>
</tr>
<tr>
<td>Other</td>
<td>RUTI</td>
<td><em>Fragmented Mtb cells</em></td>
<td>Archivel Farma, S.L.; Badalona, Spain</td>
<td>B P I</td>
<td>Phase I</td>
<td>[32-36]</td>
</tr>
<tr>
<td></td>
<td>M. vaccae</td>
<td><em>Inactivated whole cell non-TB mycobacterium; phase III in BCG-primed HIV+ population completed; reformulation pending</em></td>
<td>NIH, Aeras, Immodulon</td>
<td>B P I</td>
<td>Phase III</td>
<td>[37-41]</td>
</tr>
<tr>
<td></td>
<td>M. smegmatis *</td>
<td><em>Whole cell extract; phase I completed in China</em></td>
<td>*communicated by the Wuhan Inst. of Biol.Products</td>
<td>B P I</td>
<td>Phase I (not active)</td>
<td>–</td>
</tr>
</tbody>
</table>
“Now keep your eye on the ball.”
TB and Poverty

- One billion people live on <1 dollar/day
  - Overcrowding
  - Poor ventilation
  - Poor nutrition
  - Increased exposure to biomass fuels
  - Increased exposure to cigarettes
Smoking and TB

- Risk factor for
  - TB infection
  - Development of active pulmonary TB
    - More cavitatory disease, >severity
- 61% of TB deaths attributable to smoking
- Mechanisms:
  - Mechanical disruption of cilia
  - Impairment of macrophage function
  - CD4 lymphopenia

Smoking and TB in the Western Cape

- 1309 smokers (current and ex)
  - 82% PPD +ve
- 1070 never smokers
  - 70% PPD +ve
- Dose response relationship noted

De Boon et al, Thorax 2007
Smoking and risk for HIV

• Systematic review
  - 5/6 studies showed tobacco smoking independent risk factor for HIV infection: OR 1.6-3.5
  - 1/10 related to progression to AIDS 5/6 may be more important in developing countries

Furber et al. Sex Transm Infect 2007
Biomass fuel and TB

- National Family Health Survey
  - India 1992-1993
- TB risk in exposure to BM pollution vs clean burning fuel
  - 2.58 (CI 1.98 – .37)
- 59% of rural and 23% of urban TB attributable to BM pollution

Ministry of Health and Family Welfare
Govt of India, Calverston MD, Macro International. 1998
High risk groups

- Prison populations
- Refugees
- Brothels
Can we eradicate TB in Sub-Saharan Africa

- Do we have the tools?
- What are the obstacles?
- A time to pause and reflect
- We took our eye of the ball
- Bird flu - parallel
Political leadership

- Civil strife
- War
- Poor leadership
Randomized Controlled Trial of the Options Study in 16 DoH Clinics in KZN
Study Design (IMB model*)

- **16 Clinics (8 Matched Pairs)**
  - 8 Intervention Clinics (60% risky sample)
  - 8 Control Clinics (60% risky sample)

- **Ongoing (Intervention Condition Only)**
  - Izindlela Zokuphila/Options for Health intervention sessions
  - Observations of Izindlela Zokuphila/Options for Health sessions
  - Exit interviews

- **BASELINE**
  - ACASI
  - STI testing
  - Chart review (STI, VL, CD4)

- **6-MONTHS**
  - ACASI
  - Chart review (STI, VL, CD4)

- **12-MONTHS**
  - ACASI
  - STI testing
  - Chart review (STI, VL, CD4)

- **18-MONTHS**
  - ACASI
  - STI testing
  - Chart review (STI, VL, CD4)

- **Ongoing (Control Condition Only)**
  - Standard-of-Care HIV Prevention

MDGs

• **Goal 6**: Combat HIV/AIDS, malaria, and other diseases
  - **Target 6A**: Have halted by 2015 and begun to reverse the spread of **HIV/AIDS**
    - HIV prevalence among population aged 15-24 years
    - Condom use at last high-risk sex
    - Proportion of population aged 15-24 years with comprehensive correct knowledge of HIV/AIDS
  - **Target 6B**: Achieve, by 2010, universal access to treatment for HIV/AIDS for all those who need it
    - Proportion of population with advanced HIV infection with access to antiretroviral drugs
  - **Target 6C**: Have halted by 2015 and begun to reverse the incidence of **malaria** and other major diseases
    - Prevalence and death rates associated with malaria
    - Proportion of children under 5 sleeping under insecticide-treated bednets
    - Proportion of children under 5 with fever who are treated with appropriate anti-malarial drugs
    - Prevalence and death rates associated with tuberculosis
    - Proportion of tuberculosis cases detected and cured under DOTS (Directly Observed Treatment Short Course)
IMAGINE

• Imagine there's no heaven (TB)
It's easy if you try
No hell below us (NO MDR OR XDR TB)
Above us only sky
Imagine all the people
Living for today... Imagine
there's no countries (A CURE)
It isn't hard to do
Nothing to kill or die for
And no religion (HIV) too
Imagine all the people
Living life in peace (FREE OF INFECTION)...

• You may say I'm a dreamer
But I'm not the only one
I hope someday you'll join us
And the world will be as one

• Imagine no possessions (TB and HIV)
I wonder if you can
No need for greed or hunger
(TREATMENT FAILURE)
A brotherhood of man
Imagine all the people
Sharing all the world...