Misconception: TB Is a Single Disease

- No TB infection
- TB infection
- TB disease
Misconception: TB Is No Longer a Big Problem

No TB infection 4.6B

TB infection 2.3B

TB disease 9M/year
Misconception: TB Is No Longer a Big Problem

- >2 million deaths every year
- More deaths in women caused by TB than complications of motherhood

**Misconception: TB Is Easy to Diagnose**

<table>
<thead>
<tr>
<th>Common tests for TB</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculin skin test</td>
<td>Neither sensitive nor specific; difficult to use</td>
</tr>
<tr>
<td>Interferon-γ blood test</td>
<td>Difficult to use; expensive</td>
</tr>
<tr>
<td>Signs and symptoms</td>
<td>Nonspecific</td>
</tr>
<tr>
<td>Antibody blood test</td>
<td>Neither sensitive nor specific</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>Sensitive for pulmonary TB, but nonspecific</td>
</tr>
<tr>
<td>Sputum acid-fast smear</td>
<td>Only identifies highly infectious TB cases</td>
</tr>
<tr>
<td>Sputum culture</td>
<td>Sensitive, but difficult to use</td>
</tr>
<tr>
<td>Sputum PCR</td>
<td>Sensitive, easy to use, but expensive and only recently validated</td>
</tr>
</tbody>
</table>

**PCR**, Polymerase chain reaction

γ, gamma
Why HIV and TB Are a Dangerous Duo

- People living with HIV are more likely to develop TB
- In people living with HIV, TB is harder to diagnose and treat
- HIV patients have a high risk of dying during TB treatment

Picture credit: Alex Miranda for WHO
HIV Is the Most Powerful Risk Factor for Progressing from TB Infection to Disease
HIV Is the Most Powerful Risk Factor for Progressing from TB Infection to Disease
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HIV Is the Most Powerful Risk Factor for Progressing from TB Infection to Disease
In People Living with HIV, TB is Harder to Diagnose Many Are Ill, but Don’t Know They Have TB

- Pulmonary TB: Frequently smear and chest X-ray negative
- Extra-pulmonary TB can occur in any anatomic site

<table>
<thead>
<tr>
<th>Setting</th>
<th>No. of studies</th>
<th>Median prevalence of TB disease in HIV patients</th>
<th>No. needed screen to find case to a TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV diagnosis clinics</td>
<td>10</td>
<td>8%</td>
<td>12</td>
</tr>
<tr>
<td>HIV treatment clinics</td>
<td>24</td>
<td>8%</td>
<td>12</td>
</tr>
<tr>
<td>Maternal health clinics for HIV-infected persons</td>
<td>3</td>
<td>2%</td>
<td>44</td>
</tr>
</tbody>
</table>

In People Living with HIV, TB Is Harder to Treat

- Many pills to take several times every day
- Drugs interact with each other
- Drugs have overlapping toxicity
People Living with HIV Have High Risk of Dying during TB Treatment

In people living with HIV, deaths occur early during TB treatment

<table>
<thead>
<tr>
<th>Location</th>
<th>Case fatality rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa</td>
<td>6–39%</td>
</tr>
<tr>
<td>Thailand*</td>
<td>43–50%</td>
</tr>
<tr>
<td>Cambodia</td>
<td>27%</td>
</tr>
<tr>
<td>Vietnam</td>
<td>26–30%</td>
</tr>
</tbody>
</table>

Month of death for 334 HIV-infected TB patients that died during TB treatment

*Multiple provinces, Thailand, 2004–2005

**Six references are available at http://www.cdc.gov/about/grand-rounds/index.htm
TB Can Be Prevented in People Living with HIV

- Find and treat people with TB disease
- Give isoniazid for at least 6 months to people who do not have TB disease
  - Isoniazid preventive therapy (IPT)
  - In 2009, only 0.3% of people with HIV received IPT
    - Finding TB disease is difficult with limited lab resources
    - IPT is not always durable; some develop TB again

IPT, Isoniazid preventive therapy
Improving TB Prevention among PLHIV in Resource-limited Settings

Questions to Answer

- Persons not yet diagnosed with TB
  - Is there a simple clinical algorithm that frontline health care workers can use to identify patients who do not have TB disease?

- Persons screened and found not to have TB disease
  - Can treatment of TB infection for periods longer than 6 months prevent reinfection with TB?
Ruling out TB: The First Step for TB Diagnosis and Prevention

Kevin P. Cain, MD
Division of Tuberculosis Elimination
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention
All people with HIV should be screened for TB
- Screening based on presence of chronic cough
- Diagnosis based on smear microscopy of sputum and chest X-ray
- Based on expert opinion from pre-HIV era and not validated in PLHIV

Problems
- In PLHIV: Small studies suggest low sensitivity of chronic cough, smear microscopy, and chest X-ray
- <5% of PLHIV screened for TB, and <1% started on TB prevention
- In PLHIV with TB: High case-fatality rate
Improving Diagnosis of TB in People Living with HIV Study (ID-TB/HIV)

- 6 sites in Cambodia, Vietnam, and Thailand
- Initiated in 2006
- Funded by USAID
- Conducted at sites supported by PEPFAR
- Goal: Develop simple, sensitive rule for TB screening in PLHIV

PEPFAR, President’s Emergency Plan for AIDS Relief
USAID, US Agency for International Development
PLHIV, People living with HIV
ID-TB/HIV Study
Standardization of Methods across all Sites

- **Standardized laboratory diagnosis:**
  Mycobacterial culture and smear of 6–7 specimens
  - 3 sputum specimens
  - 1 each of urine, stool, blood, and lymph node aspirate (if enlarged)

- **Case definition:** Positive culture for TB from any site

- **Standardized data collection**
  - Clinical signs and symptoms
  - Chest X-ray, CD4 count, complete blood count

- **Calculated performance as individual predictors and >80 million combinations**

- **Calculated yield of different diagnostic tests**
Screening for TB Disease

Ideal screening tool

<table>
<thead>
<tr>
<th>Sensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple</td>
</tr>
</tbody>
</table>

Persons living with HIV

Screen for TB disease

Negative

TB excluded

Positive

Diagnostic evaluation
Screening for TB Disease

1,748 persons living with HIV

- **Perform TB culture**

  - 1,481 Negative
    - TB excluded
  - 267 (15%) Positive
    - TB diagnosed

High prevalence of TB disease in PLHIV

<table>
<thead>
<tr>
<th>Population</th>
<th>TB prevalence per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>5</td>
</tr>
<tr>
<td>Cambodia</td>
<td>700</td>
</tr>
<tr>
<td>ID-TB/HIV study</td>
<td>15,000</td>
</tr>
</tbody>
</table>

PLHIV, People living with HIV
# Sensitivity and Specificity of Predictors

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough ≥2 weeks</td>
<td>33</td>
<td>82</td>
</tr>
<tr>
<td>2 sputum smears for AFB</td>
<td>38</td>
<td>99</td>
</tr>
<tr>
<td>Abnormal chest radiograph</td>
<td>65</td>
<td>85</td>
</tr>
<tr>
<td>Cough</td>
<td>71</td>
<td>53</td>
</tr>
<tr>
<td>Weight loss</td>
<td>73</td>
<td>54</td>
</tr>
<tr>
<td>Fever</td>
<td>74</td>
<td>55</td>
</tr>
<tr>
<td>At least 1 of: Cough or fever of any duration or night sweats ≥3 weeks</td>
<td>93</td>
<td>36</td>
</tr>
</tbody>
</table>

67% of patients with TB will NOT be detected using chronic cough as a screening approach and will have undiagnosed TB.

AFB, Acid fast bacilli
Screening for TB Disease

### Predictor

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Misclassified as not having TB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
</tr>
<tr>
<td>Cough ≥ 2 weeks</td>
<td>67</td>
</tr>
<tr>
<td>Cough, fever, or night sweats ≥ 3 weeks</td>
<td>7</td>
</tr>
</tbody>
</table>

Persons living with HIV

- Negative
  - TB excluded
- Positive
  - Screen for TB disease
    - Diagnostic evaluation

Diagnostic evaluation

Screen for TB disease

Screen for TB disease
Sputum Smears Alone Miss Many TB Cases in PLHIV that Can Be Detected by Culture

This analysis is limited to patients enrolled in Vietnam and Thailand

PLHIV, People living with HIV
Potential Applications Based on ID-TB/HIV Study

- 15% of people with HIV had TB disease
- **Ruling out TB disease**
  - 3-symptom combination (or similar) should be used
  - Chronic cough should not be used for TB screening
  - Patients with none of the 3 symptoms have TB excluded
- **Ruling in TB disease:** Patients with $\geq 1$ symptoms should have $\geq 2$ sputum specimens collected for both smear and culture

Monkongdee P, et al. J Respir Crit Care Med 2009;180(9):903-8
TB Diagnosis: Challenges and Opportunities

- **Challenges**
  - Liquid culture rarely available, difficult to implement
  - Massive scale-up of laboratory services needed

- **An exciting new opportunity: Xpert™ MTB/Rif assay**
  - Endorsed by WHO as the initial diagnostic test of choice for PLHIV
  - Results in >2 hours for both presence of TB and drug resistance
  - Sensitivity approaches that of TB culture
  - Need to demonstrate ability to scale-up

Can Data from the ID–TB/HIV Study Be Extrapolated Globally

- Based on the data from the ID-TB/HIV study, WHO determined that policy change was needed
- WHO and CDC collaborated on a meta-analysis
  - Individual patient-data meta-analysis
  - 12 studies: 9 from Africa, 3 from Asia
- **Best combination: At least 1 of**
  - Current cough
  - Fever
  - Weight loss (subjective)
  - Night sweats (any duration)
- **Sensitivity is 90% in clinical settings**

WHO 2011 guidelines are being implemented globally

- Nearly $150 M in PEPFAR TB/HIV funding allocated in FY2011
- CDC implements TB/HIV activities with PEPFAR funding in 26 countries and 1 regional office

Collaborations are essential to address research questions successfully and to translate research to policy and practice
If Finding TB is So Difficult, Why Not Just Prevent It?

Taraz Samandari, MD, PhD
Division of Tuberculosis Elimination
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention
“An Ounce of Prevention Is Worth a Pound of Cure”
– Benjamin Franklin
TB Infection, TB Disease, and the Tuberculin Skin Test (TST)

- Exposure to TB
- Tuberculin Skin Test (TST) converts to +
- IPT, Isoniazid preventive therapy
- TST, Tuberculin skin test

- NOT INFECTED
- TB INFECTION
- TB DISEASE

TST - - - - - - - - + + + + + + + + + + + + + + +
Anti-retroviral Therapy (ART) for TB Prevention in TB-endemic Settings

- ART reduces the risk of TB in PLHIV by 50–80%
- Increasing use of ART increases CD4 lymphocyte count and thereby reduces the risk of TB
- Rate of TB among PLHIV receiving ART remains unacceptably high in TB-endemic settings
  - 2-7 TB cases per 100 person-years

8 references are available at http://www.cdc.gov/about/grand-rounds/index.htm
PLHIV, People living with HIV
ART, Anti-retroviral therapy
## Isoniazid Preventive Therapy (IPT) for PLHIV

6-month IPT reduces the risk of TB by 64% in TST-positive PLHIV

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment (INH) n/N</th>
<th>Control n/N</th>
<th>Risk ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hawken 1997</td>
<td>5/67</td>
<td>8/69</td>
<td>6.3% 0.64 [0.22, 1.87]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mwinga 1998</td>
<td>4/52</td>
<td>11/60</td>
<td>8.2% 0.42 [0.14, 1.24]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pape 1993</td>
<td>2/38</td>
<td>6/25</td>
<td>5.8% 0.22 [0.05, 1.00]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whalen 1997</td>
<td>7/536</td>
<td>21/464</td>
<td>18.0% 0.29 [0.12, 0.67]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>693</strong></td>
<td><strong>618</strong></td>
<td><strong>38.3% 0.36 [0.22, 0.61]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**6-month IPT reduces the risk of TB by 64% in TST-positive PLHIV**

| TST –             |                     |             |                              |        |                             |
| Subtotal (95% CI) | 1,297               | 1,193       | 43.9% 0.86 [0.59, 1.26]       |        |                             |

6-month IPT does NOT significantly reduce the risk of TB in TST-negative PLHIV

---

INH, Isoniazid
PLHIV, People living with HIV
TST, Tuberculin skin test
# Isoniazid Preventive Therapy (IPT) for PLHIV

Overall IPT reduces the risk of TB by 33% in PLHIV (TST-positive, TST-negative, TST-unknown)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment (INH) n/N</th>
<th>Control n/N</th>
<th>Risk ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (95% CI)</td>
<td>2,152</td>
<td>1,984</td>
<td>0.67 [0.51, 0.87]</td>
<td>100.0%</td>
<td>0.67 [0.51, 0.87]</td>
</tr>
</tbody>
</table>

INH, Isoniazid
PLHIV, People living with HIV
TST, Tuberculin skin test
WHO 1998 Isoniazid Preventive Treatment (IPT) Recommendation

- Provide 6 months daily IPT to HIV-infected adults
- If not feasible and >30% of the population was infected with TB, do not perform tuberculin skin test (TST)
  

- IPT benefit lost in 6-18 months
  - Failure of eradication vs. reinfection
- Later, molecular epidemiology in TB-endemic countries showed infection with new strains of TB is very common (42–88%)

IPT, Isoniazid preventive therapy
TST, Tuberculin skin test
9 additional references are available at http://www.cdc.gov/about/grand-rounds/index.htm
“So Long as It’s Raining, You Need an Umbrella”

TB, Tuberculosis
IPT, Isoniazid preventive therapy
Botswana IPT Trial 2004–2009

- Randomized, double-blind, placebo-controlled trial
- ART provided as needed through national program
  - When CD4 < 200 cells/μL

<table>
<thead>
<tr>
<th>Healthy PLHIV</th>
<th>Isoniazid</th>
<th>Placebo</th>
<th>6 IPT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 months</td>
<td>+</td>
<td>30 months</td>
</tr>
</tbody>
</table>

| PLHIV, People living with HIV |
| ART, Anti-retroviral therapy |

IPT, Isoniazid preventive therapy
Continuous IPT for 36 Months Prevents TB Better than IPT for 6 Months in TST-positive PLHIV


IPT, Isoniazid preventive therapy

PLHIV, People living with HIV

TST, Tuberculin skin test
### Efficacy of 36 Months IPT vs 6 Months IPT

**ART Provided if CD4<200/µL in TST+ PLHIV**

<table>
<thead>
<tr>
<th>Arm</th>
<th>No. of pts</th>
<th>TB cases</th>
<th>TB rate 100 /year</th>
<th>Hazard ratio</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>All enrolled</td>
<td>6 IPT</td>
<td>989</td>
<td>34</td>
<td>1.26</td>
<td>ref</td>
</tr>
<tr>
<td></td>
<td>36 IPT</td>
<td>1006</td>
<td>20</td>
<td>0.72</td>
<td>0.57*</td>
</tr>
<tr>
<td>All TST+ enrolled</td>
<td>6 IPT</td>
<td>216</td>
<td>13</td>
<td>2.22</td>
<td>ref</td>
</tr>
<tr>
<td></td>
<td>36 IPT</td>
<td>252</td>
<td>4</td>
<td>0.57</td>
<td>0.26*</td>
</tr>
</tbody>
</table>

* P<0.05

**ART reduced the risk of TB additively by 50% in both arms and was independent of IPT’s protective effect**

---


PLHIV, People living with HIV
IPT, Isoniazid preventive therapy
TST, Tuberculin skin test
ART, Anti-retroviral treatment
WHO 2011 guidelines for TB screening and prevention in PLHIV

“IPT for a duration of 36 months is conditionally recommended in settings with a high transmission of TB … tuberculin skin testing is not a requirement for initiating IPT … in some settings where it is feasible, [TST] can help to identify those who would benefit most from IPT”

PLHIV, People living with HIV
IPT, Isoniazid preventive therapy
Potential Public Health Impact of Continuous IPT on Annual TB Cases in Botswana

80% of TB patients are HIV+
70% of TB-HIV patients are TST+

Antiretroviral therapy provided to all HIV-infected persons if CD4<250 per µL⁻¹
IPT, Isoniazid preventive therapy
PLHIV, People living with HIV
TST, Tuberculin skin test
Potential Public Health Impact of Continuous IPT on Annual TB Cases in Botswana

45% reduction in all TB cases by prevention in TST+ HIV+ persons

Antiretroviral therapy provided to all HIV-infected persons if CD4<250 /µL

IPT, Isoniazid preventive therapy
ART, Anti-retroviral treatment
PLHIV, People living with HIV
Cost Effectiveness Analysis for TB Prevention
36 Months IPT, TST, and ART

- Initiation of ART at higher CD4 thresholds further reduces tuberculosis disease
  - Is it necessary to include IPT?
  - Is it cost effective to use the TST when implementing IPT?

- Botswana cost analysis for 10,000 PLHIV over 3 years
  - 36 months IPT + ART at CD4<250
    - Equivalent or superior prevention vs. ART initiation at higher CD4 thresholds (350 or 500)
    - Saves $2–4 million
  - Addition of TST to target 36 months IPT for TST-positive PLHIV
    - Reduces TB by 30%
    - At a cost of $80,000

IPT, Isoniazid preventive therapy
ART, Anti-retroviral therapy
TST, Tuberculin skin testing
PLHIV, People living with HIV
Some Additional Research Needs for TB Prevention in PLHIV

- Operationalize TST in resource-limited settings
- Improve control of TB transmission in the communities with high TB endemicity
- Identify better anti-TB drugs and new vaccines to prevent TB
- Determine whether intermittent short courses (6–12 months) of IPT are as efficacious as continuous IPT for TST- positive PLHIV
- Reduce causes of early mortality (such as from TB) in PLHIV initiating ART

TST, Tuberculin skin testing
PLHIV, People living with HIV
ART, Anti-retroviral treatment
From Science to Policy to Impact

Mario C. Raviglione, MD
Director, Stop TB Department
World Health Organization (WHO)
Geneva, Switzerland

With appreciation for support and engagement to Haileyesus Getahun
Stop TB, WHO
Overview

- TB science and policy, hand-in-hand
  - WHO's perspectives on the science of TB/HIV
  - Policies to control TB
  - Potential impact of TB/HIV interventions

- Challenges and opportunities to eliminate TB
Process for Developing WHO Guidelines

- Compose the external guidelines panel; declare COI
- Formulate questions and relevant outcomes
- Assess available evidence
  - Retrieval, evaluation (using GRADE) and synthesis
  - Benefit, equity, and cost
- Develop recommendations (strong, conditional)
- Evaluate impact of recommendations
- Identify areas of further research
- Establish peer review process
- Finalize and define expiration date

COI, Conflict of interest
GRADE, WHO handbook for guideline development 2010 http://www.bmj.com/content/328/7454/1490.full
WHO–CDC Collaboration in the Area of TB/HIV

Inclusion criteria for studies

- Collected sputum specimens from PLHIV regardless of signs or symptoms
- Used mycobacterial culture of at least 1 specimen to diagnose TB
- Collected data about signs and symptoms
Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings
Recommendation 1
Isoniazid Preventive Therapy (IPT)

Adults and adolescents living with HIV should be screened with a clinical algorithm and those who do not report any one of
- Current cough
- Fever
- Weight loss
- Night sweats

are unlikely to have active TB and should be offered IPT

Strong recommendation, moderate quality evidence
Recommendation 2
TB Screening

Adults and adolescents living with HIV should be screened with a clinical algorithm and those who reported any one of

- Current cough
- Fever
- Weight loss
- Night sweats

may have active TB and should be evaluated for TB and other diseases

Strong recommendation, moderate quality evidence
Recommendation 3
Duration of Isoniazid Preventive Therapy

Adults and adolescents who are living with HIV and
- Have tuberculin skin test-positive or unknown status and
- Are unlikely to have active TB
should receive IPT for **at least 6** months

Strong recommendation, high quality evidence
Recommendation 4
Duration of Isoniazid Preventive Therapy

Adults and adolescents who are living with HIV in settings with higher TB transmission and

- Have tuberculin skin test-positive or unknown status and
- Are unlikely to have active TB

should receive IPT for at least 36 months

Conditional recommendation, moderate quality evidence
... Simplicity, simplicity, simplicity! I say, let your affairs be as two or three, and not a hundred or a thousand; instead of a million count half a dozen, and keep your accounts on your thumbnail... Simplify, simplify....

—Henry D. Thoreau, Walden, 1854
Summary
What's New in these Policy Recommendations?

- Screening for TB using only symptom-based algorithm is sufficient to start IPT for PLHIV
- No mandatory chest X-ray and tuberculin skin test requirement for IPT
- Regular screening of those on IPT at every visit
- Pregnant women, children, those on ART, and those who completed TB treatment should receive IPT
- Conditional recommendation of 36 months IPT for settings with high TB transmission among PLHIV

Simplification

PLHIV, People living with HIV
IPT, Isoniazid preventive therapy
ART, Antiretroviral treatment
Can IPT Impact Epidemiology of TB/HIV?

- IPT is highly effective in clinical trials among TB-infected PLHIV (64% reduction in incidence)
- Feasibility of IPT in field conditions is still questioned, although individual benefits are obvious
- New modelling of impact of large-scale IPT is ongoing, whereas previous model showed little impact

Akolo et al Cochrane Database Syst Rev. 2010;Jan 20
Charalambous S, et al AIDS. 2010;24 (sup 5) s5-s13
PLHIV, People living with HIV
IPT, Isoniazid preventive therapy
TB Incidence Rates Falling Globally after Peak in 2004, but Only at <1%/year

Incidence (all forms, including PLHIV)

Peak in 2004

Shaded area = uncertainty band

Notification gap

TB notifications

TB incidence in PLHIV

PLHIV, People living with HIV
Full Implementation of the Global Plan to Stop TB
2015 Millennium Development Goal

Target reached, but TB not eliminated by 2050

Current rate of decline

TB incidence 10x lower than today, but >100x higher than elimination target in 2050

Elimination target: 1/million/year by 2050
Innovative Actions Needed in 4 Areas

TB care and control
- Early & increased case detection: new tools
- Scale-up TB/HIV and MDR-TB interventions
- M&E and impact measurement
- Engage all care providers
- Active screening among at-risk populations

Health systems and policies
- Free services, labs, quality drugs, regulated private care, better M&E

Development agenda
- Socio-economic factors: living conditions, food insecurity, awareness, risk behaviour, access to care

Research sensu lato
- New tools
- Operational research
- Transfer of technology

MDR-TB, Multi drug resistant TB
M&E, Monitoring and evaluation
Conclusions

- **New WHO Guidelines**
  - Incorporate outcomes of latest research and simplify interventions: "Simplicity, simplicity, simplicity"
  - Potential impact of TB/HIV interventions on TB incidence and mortality could be important
  - Need for operational research and field assessment beyond mathematical modelling

- **Fast decline of TB incidence globally will depend on**
  - Quality of core TB control efforts, including rapid detection
  - Bold health system policies
  - Socioeconomic development
  - Availability of new tools
Fundamentals Are Fundamental

Thomas R. Frieden, MD, MPH

Director, Centers for Disease Control and Prevention
Administrator, Agency for Toxic Substances and Disease Registry
What Is the Answer?
What Is the Question?

- Save lives?
- Prevent MDR-TB?
- Reduce incidence?
What Is the Answer?
What Is the Question?

- Save lives?
- Prevent MDR-TB?
- Reduce incidence?


New York City Example
TB Death Rate Declined Dramatically During Most of the 20th Century …

… But Increased Sharply with the HIV Epidemic and Low Rates of TB Diagnosis and Cure

… Until Effective Diagnosis, Treatment, Treatment Observation, and Infection Control Led to a Rapid Decline

TB Control Efforts Are Saving Lives – But We Can Save More Lives

- **Prompt diagnosis of TB and HIV**
  - More rapid and accurate TB diagnosis
    - Many patients who are not diagnosed die of TB
    - TB diagnosis can → HIV testing → ARV Rx

- **Expanded prevention**
  - Reducing TB spread, especially in health care facilities
  - Isoniazid preventive treatment (cf. cotrimoxazole?)
  - Preventing TB and HIV, including testing and early ART (especially if started with CD4>350)
TB Control Efforts Are Saving Lives – But We Can Save More Lives

- More prompt and more effective treatment
  - ART treatment for HIV+ people with TB disease
  - Adjunctive treatments (e.g., steroids for TB meningitis, pericardial effusions)
  - Improved case management of all patients (including direct observation)

Treatment observation prolongs survival of HIV+ people with TB disease

Alwood K, et al. AIDS 1994;8:1103-1108
ART, Anti-retroviral treatment
PLHIV, People living with HIV
SCC, Short-course chemotherapy
“Those who cannot remember the past are condemned to repeat it.”

—Jorge Agustín Nicolás Ruiz de Santayana
What Is the Answer?

What Is the Question?

- Save lives?
- Prevent MDR-TB?
- Reduce incidence?
Clustering of TB cases indicates likelihood that groups of patients are acquiring infection from the same source

In New York City in a one-month study in 1991, molecular epidemiology showed

- About 30% of all TB cases and more than half of MDR-TB cases were clustered
- 41% of HIV-infected patients with TB were in a cluster
- A third of patients in clusters of 4 or more cases had evidence of nosocomial TB acquisition

MDR-TB, Multidrug resistant TB
Preventing MDR-TB

- Treating patients for ethical and public health reasons
  - Ethical: Everywhere, but harm can outweigh the benefits if treatment is not followed through to cure or detracts from treatment of the larger number of patients with drug-susceptible TB
  - Public health, e.g., high HIV prevalence, crowded living conditions

- Testing for drug resistance
  - Can reduce treatment costs and improve outcomes

- Stopping spread in congregate facilities
  - Hospitals, homeless shelters, mines, etc.

No TB control program can treat MDR-TB as fast as a bad program can create it

MDR-TB, Multi drug resistant TB
What Is the Answer?
What Is the Question?

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Global TB incidence
1990–2009
Rates per 100,000 population

Substantial Decrease in TB as More Patients Were Given DOT
New York City, 1978–2008

DOT, Directly observed therapy
DOTS Implementation in India Significantly Accelerated Reduction of TB Prevalence and Risk of Infection
Tiruvallur, India, 1968–2006

ARTI, Annual risk of TB infection
SCC, Short-course chemotherapy

Why is TB Incidence Falling only Gradually
Bad DOTS vs. Reactivation vs. Need for Social Change

☐ Bad DOTS? Continued spread (rain)
  ➢ Insufficient case finding – diagnosing too little, too late
  ➢ Not registering all diagnosed patients
  ➢ Not ensuring treatment continuation/completion
  ➢ Not stopping spread of infection
    ▪ In the community
    ▪ In health care facilities, where many TB infections occur but can be prevented

Implication
☐ Improve diagnosis, treatment, and infection control

DOTS, formerly Directly Observed Treatment Short-course
Why is TB Incidence Falling only Gradually
Bad DOTS vs. Reactivation vs. Need for Social Change

- **Reactivation: Waves crashing on beach**
  - Preventing reactivation of latent TB disease (or disease previously considered cured)
  - Example: In Hong Kong, risk of developing TB from reactivation of previously cured infection is much higher than developing TB from primary infection

**Implication**

- Preventive treatment if indicated
- Research into new ways to identify and treat those most likely to have reactivation of past infection
- Persistence – and recognition that results may not be immediate
Why is TB Incidence Falling only Gradually
Bad DOTS vs. Reactivation vs. Need for Social Change

Need for social change

- Changes in social determinants
  - Poverty
  - Housing
  - Education
- Better control of modifiable risk factors

Implication

- Achieve sustainable long-term change

TB attributable to selected risk factors in 22 high-burden countries*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Proportion of TB attributable to risk</th>
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</thead>
<tbody>
<tr>
<td>Undernutrition</td>
<td>27%</td>
</tr>
<tr>
<td>Indoor air pollution</td>
<td>22%</td>
</tr>
<tr>
<td>Smoking</td>
<td>16%</td>
</tr>
<tr>
<td>HIV</td>
<td>11%</td>
</tr>
<tr>
<td>Alcohol misuse</td>
<td>10%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8%</td>
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</tbody>
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*Multiple risk factors may be present

DOTS, formerly Directly Observed Treatment Short-course
DOTS Is the Foundation of Effective TB Treatment

- **DOTS has been effective**
  - Good quality diagnosis, good-quality treatment, and adherence to treatment through completion
  - Powerful information systems and commitment to observational research
  - Great model for other public health programs

- **Further strengthening and enhancement of DOTS**
  - Optimize TB diagnosis with new tools (e.g., fluorescent LED microscopy)
  - Implement rapid tests for active TB and drug resistance (e.g., GeneXpert)
  - Improve case management (including patient-centered treatment observation)
  - Ensure supplies of high-quality drugs
  - Reinforce program monitoring and supervision

DOTS, formerly Directly Observed Treatment Short-course
LED, Light-emitting diode
“[TB] control programs have been less effective than expected in cutting transmission mainly because patients are not diagnosed and cured quickly enough. The priority now is not to abandon the basic principles of chemotherapy, but rather to implement them with greater vigor.”

Dye C and Williams BG. Science 2010;328:856-861
Challenges for TB-HIV Control

- **HIV continues to drive the TB epidemic in Africa**
  - Expansion of HIV prevention and treatment is critical
  - Isoniazid preventive treatment of people who have both HIV and TB infections could reduce TB

- **Strengthening diagnosis and treatment for TB and HIV**
  - Effective screening and prompt, accurate diagnosis to facilitate early treatment initiation for both TB and HIV
  - Screening of TB patients for HIV
  - Providing ART to all people who have HIV and TB disease

- **Effective case management for both TB patients and people living with HIV**

- **Infection control**

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ART, Anti-retroviral treatment  
PLHIV, People living with HIV  
IPT, Isoniazid preventive therapy
Focus on Basics + New Strategies and Tools = Success in TB Control

- Tremendous progress over the past several decades using current tools and strategies
  - DOTS has saved 6 million lives in the past 15 years – and nearly a million this year alone
- Better application of existing tools can further decrease deaths and, to some extent, incidence
- Persistence, patient-centeredness, and zealous adherence to technical rigor and program excellence are essential
- Current tools and strategies will not eliminate TB
- New approaches will be required to control TB in Africa and, globally, to reduce TB incidence drastically

DOTS, formerly Directly Observed Treatment Short-course