HIV and Drug-Resistant TB

What do we know?
What do we need to know and do?

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HIV & Drug-Resistant TB Epidemic

- Rise of Drug-resistant TB cases in Africa confirms convergence of HIV & drug-resistant TB epidemics
- MDR TB caseload in Botswana has risen consecutively over past decade
- Explosive MDR and XDR TB epidemics seen in South Africa over past 5 years
  - MDR TB prevalence now exceeds 25 cases per 100,000 population in certain areas
Convergence of HIV & MDR/XDR TB

• Why is the convergence of these epidemics concerning?
  – Usual public health implications: drug-resistant TB is more costly, complex & difficult to treat
  – Two factors especially worse with HIV co-infection:
    • Worse outcomes: dramatically greater mortality
    • Potential for explosive spread due to primary transmission
Rise of MDR TB in 1990s

- Numerous outbreaks in congregate settings
- Primarily among HIV co-infected patients
- Characterized by high and rapid mortality

<table>
<thead>
<tr>
<th>Location</th>
<th>HIV co-infection</th>
<th>Mortality</th>
<th>Survival (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Florida</td>
<td>93%</td>
<td>72%</td>
<td>7 weeks</td>
</tr>
<tr>
<td>New York</td>
<td>95%</td>
<td>77%</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Argentina</td>
<td>98%</td>
<td>79%</td>
<td>4 weeks</td>
</tr>
<tr>
<td>New York</td>
<td>91%</td>
<td>83%</td>
<td>4 weeks</td>
</tr>
<tr>
<td>New York</td>
<td>100%</td>
<td>89%</td>
<td>16 weeks</td>
</tr>
<tr>
<td>Italy</td>
<td>98%</td>
<td>95%</td>
<td>6-8 weeks</td>
</tr>
<tr>
<td>Spain</td>
<td>100%</td>
<td>98%</td>
<td>7 weeks</td>
</tr>
</tbody>
</table>

Wells C et al. CID 2007;196:S86-107
Mortality in HIV-Associated XDR TB

Gandhi NR et al. Lancet 2006
HIV-Associated MDR & XDR TB in S Africa

MDR TB (n = 272)

XDR TB (n = 382)

29 days

60 days

Survival in days
Mortality in HIV & MDR/XDR TB

• Successful treatment outcomes possible in low and middle income countries in absence of HIV

• With HIV co-infection, however, drug-resistant TB takes on a different and more aggressive course
  – Nearly two decades of experience demonstrating rapid and high mortality
  – Majority die within 6-8 weeks, before diagnosis can be made by conventional culture and DST

• Thus, majority die before treatment with second-line TB drugs can be initiated
## Predictors of Mortality: HIV & MDR/XDR TB

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Adjusted Hazard Ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 Count: &lt;50 cells/mm³</td>
<td>5.1</td>
<td>0.002</td>
</tr>
<tr>
<td>51-200 cells/mm³</td>
<td>4.0</td>
<td>0.006</td>
</tr>
<tr>
<td>&gt;200 cells/mm³</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>ARVs before MDR/XDR TB diagnosis</td>
<td>0.4</td>
<td>0.027</td>
</tr>
<tr>
<td>Extrapulmonary TB</td>
<td>1.5</td>
<td>0.27</td>
</tr>
<tr>
<td>Admission within last year</td>
<td>1.4</td>
<td>0.30</td>
</tr>
<tr>
<td>Smear Positive</td>
<td>2.1</td>
<td>0.04</td>
</tr>
</tbody>
</table>
How do HIV-infected patients develop MDR/XDR TB?
Acquired resistance: Patient develops resistance due to incomplete or inappropriate treatment
Primary Resistance

**Acquired resistance:**
Patient develops resistance to drugs due to incomplete or inappropriate treatment

**Primary Resistance:**
Patient develops resistance due to transmission of drug-resistant strain
MDR/XDR TB among New TB Cases

Wells C et al. CID 2007;196:S86-107
Four TB Strains in Single Patient

Susceptible TB  $\rightarrow$  MDR TB  $\rightarrow$  XDR TB

Andrews J. et al. JID 2008
Genotypes of Patients with XDR TB Relapse

Andrews J. et al. JID 2008
Transmission of MDR & XDR TB
MDR TB cases in KwaZulu-Natal

SSS Buthelezi. XDR TB Task Force 2008
XDR TB cases in KwaZulu-Natal

![Graph showing XDR TB cases in KwaZulu-Natal from 2001 to 2007 for IALCH and KGV.]
Why is Primary Transmission Occurring?

• Long delays in diagnosis of drug-resistant TB
  – Average time to diagnosis is 6-12 weeks by conventional TB culture and susceptibility testing

• Inadequate treatment options
  – Patients with MDR and XDR TB remain infectious longer

• Lack of Infection control facilities
  – Congregate wards without any isolation possible
What do we need to do?
Comprehensive Response

• Prevention
  – Strengthen TB DOTS program to curb creation of drug resistance
  – Create & Implement comprehensive infection control program to prevent transmission of drug-resistance

• Diagnosis
  – Develop and implement rapid diagnostic assays to reduce time to diagnosis from 6-8 weeks to 1-3 days
  – Use intensified case finding to find patients at earlier stages of disease
Comprehensive Response cont’d

• Treatment
  – Decentralize to reduce referral delay, increase capacity and improve treatment completion rates
  – Use SLDs empirically in HIV-infected patients suspected of MDR or XDR TB
  – Integrate antiretroviral therapy into MDR/XDR TB treatment programs to facilitate early and widespread use
What are the gaps in knowledge?
Research Priorities: Early Mortality

• **Develop and test rapid drug-resistance assays**
  – Must perform well in pauci-bacillary TB and HIV
  – Must be useful in peripheral healthcare settings
    • Ideally, point of care
  – Must provide initial results in 1-2 days

• **Examine the effectiveness and safety of integrated antiretroviral and SLD TB therapy**
  – Impact on mortality
  – Timing of ARV initiation
  – Drug-drug interactions
  – Overlapping toxicities
  – Incidence of IRIS in MDR or XDR TB
Research Priorities: Transmission

• Transmission studies
  – Identify locations of transmission
    • Healthcare settings: both inpatient & outpatient
    • Community transmission
  – Test interventions to interrupt transmission in both healthcare and community settings
• Treatment of contacts exposed to MDR or XDR TB to prevent progression to active disease
Research Priorities: Epidemiology

• Systematic TB drug-resistance surveys in high HIV prevalence settings
  – Actual burden of disease still unknown due to lack of lab capacity
Summary

• Convergence of HIV and Drug-Resistant TB epidemics has highlighted inadequacies in TB control
  – Mortality rates with MDR & XDR TB significantly higher and more rapid than in absence of HIV
  – Emphasize need for better, more rapid diagnostics
  – Use of empiric second-line TB treatment and integration of antiretroviral therapy necessary

• Large pool of vulnerable HIV-infected patients leads to rapid propagation of MDR & XDR TB strains
  – Further studies of transmission dynamics and interruption needed
Implications

• Rise of HIV epidemic in Eastern Europe and MDR/XDR TB epidemics in Africa suggest that we are just at the beginning of this catastrophic convergence

• Significant efforts are needed to understand the implications of these dual diseases and to develop the tools to address them effectively
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