Treatment of resistant TB in HIV infected patients

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Presented at the 8th European HIV Drug Resistance Workshop, March 17-19 2010, Sorrento, Italy
...tuberculosis an emerging disease?

- 3 pandemic (HIV, Malaria e TB) 6 milions deaths/y
- 1,6 milions TB deaths per year
- 5,000 TB deaths day

- 5 outbreaks of SARS per day
- 25 outbreaks of aviarian flu per day
- 50 ebola outbreaks per day

- 3 Titanic per day
- 15 Jambo Boing 747 per day

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Tuberculosis...the “stigma” is going on
XDR-TB: definitions

- XDR (3/06/06) - MDR TB + resistance to > 3/6 of major classes of 2nd-line drugs
  - Need >four 2nd-line drugs for RX

- XDR (since 10/06) – MDR TB + resistance to at least Fq & any injectable 2° -line (amikacin, kanamycin, capreomycin)
  - Treatment outcomes (Latvia) ~ 60% vs <30%
Clinical and operational value of the extensively drug-resistant tuberculosis definition


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Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa

**Neel R Gandhi, Anthony Moll, A Willem Sturm, Robert Pawinski, Thiloshini Govender, Umesh Laloo, Kimberly Zeller, Jason Andrews, Gerald Friedland**

<table>
<thead>
<tr>
<th><strong>Tuberculosis characteristics (n=53)</strong></th>
<th><strong>Number (%)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary tuberculosis alone</td>
<td>40 (75%)</td>
</tr>
<tr>
<td>Pulmonary and extrapulmonary tuberculosis</td>
<td>13 (25%)</td>
</tr>
<tr>
<td>Sputum-smear positive</td>
<td>42 (79%)</td>
</tr>
<tr>
<td>Sputum-smear negative</td>
<td>11 (21%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Previous tuberculosis treatment (n=47)</strong></th>
<th><strong>Number (%)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>No previous treatment</td>
<td>26 (55%)</td>
</tr>
<tr>
<td>Previous treatment: cure or completed treatment</td>
<td>14 (30%)</td>
</tr>
<tr>
<td>Treatment default or failure</td>
<td>7 (15%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Previous admission in past 2 years (n=42)</strong></th>
<th><strong>Number (%)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Admitted for any cause</td>
<td>28 (67%)</td>
</tr>
<tr>
<td>No previous admission</td>
<td>14 (33%)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th><strong>HIV characteristics (n=44)</strong></th>
<th><strong>Number (%)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-infected</td>
<td>44 (100%)</td>
</tr>
<tr>
<td>On antiretroviral therapy</td>
<td>15 (34%)</td>
</tr>
</tbody>
</table>

*Table 2: Characteristics of patients with XDR tuberculosis*
XDR TB in KwaZulu-Natal South Africa

*Figure:* Survival after sputum collection in patients with XDR tuberculosis with confirmed dates of death (n=42)

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XDR TB in KwaZulu-Natal South Africa


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Emergence of *Mycobacterium tuberculosis* with Extensive Resistance to Second-Line Drugs --- Worldwide, 2000--2004
XDR in USA (MMWR, March 2007)

FIGURE. Number of reported cases of extensively drug-resistant tuberculosis (XDR TB)* — United States, 1993–2006

Total = 49 XDR-TB

HIV+

1993-99  14/19 (74%)

2000-2006  2/10 (20%)

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XDR a worldwide issue

Multidrug-Resistant Tuberculosis Treatment Outcomes in Karakalpakstan, Uzbekistan: Treatment Complexity and XDR-TB among Treatment Failures

Helen S. Cox\textsuperscript{1*}, Stobdan Kalon\textsuperscript{2}, Sholpan Allamuratova\textsuperscript{2}, Vinciane Sizaire\textsuperscript{3}, Zinaida N. Tigay\textsuperscript{4}, Sabine Rüscher-Gerdes\textsuperscript{5}, Hamraev A. Karimovich\textsuperscript{4}, Yared Kebede\textsuperscript{6}, Clair Mills\textsuperscript{6}

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Patients XDR infected (Uzbekistan)

Abbreviations: H=isoniazid, R=rifampicin, E=ethambutol, Z=pyrazinamide, S=streptomycin, Km=kanamycin, Ofx=ofloxacin, Cm=cefpodoxime, Eto=ethionamide, Cs=cycloserine, PAS=p-aminosalicylic acid

Figure 2. Drug resistance among 87 MDR-TB patients started on treatment. doi:10.1371/journal.pone.0001126.g002

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XDR a worldwide issue

XDR tuberculosis in India: what’s in a name?
XDR-TB: implication for Global Public Health

Countries that had reported at least one XDR-TB case by end 2008

- Armenia
- Argentina
- Australia
- Azerbaijan
- Bangladesh
- Botswana
- Brazil
- Canada
- Chile
- China, Hong Kong
- Colombia
- Czech Republic
- Ecuador
- Estonia
- France
- Georgia
- Germany
- India
- Iran
- Ireland
- Israel
- Italy
- Japan
- Latvia
- Lesotho
- Lithuania
- Mexico
- Mozambique
- Myanmar
- Namibia
- Nepal
- Netherlands
- Norway
- Oman
- Peru
- Philippines
- Poland
- Portugal
- Qatar
- Rep. of Korea
- Rep. of Moldova
- Romania
- Russian Federation
- Slovenia
- South Africa
- Spain
- Sweden
- Switzerland
- Thailand
- UEA
- Ukraine
- United Kingdom
- United Arab Emirates
- USA
- Uzbekistan
- Viet Nam

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The development of XDR-TB outbreaks in HIV + “a new old story”

<table>
<thead>
<tr>
<th>Facility</th>
<th>% HIV-infected</th>
<th>% Mortality</th>
<th>Median interval (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hosp. Florida</td>
<td>93</td>
<td>72</td>
<td>7</td>
</tr>
<tr>
<td>Hosp. NYC</td>
<td>100</td>
<td>89</td>
<td>16</td>
</tr>
<tr>
<td>Hosp. NYC</td>
<td>95</td>
<td>77</td>
<td>4</td>
</tr>
<tr>
<td>Hosp. NYC</td>
<td>91</td>
<td>83</td>
<td>4</td>
</tr>
<tr>
<td>Hosp. Italy</td>
<td>98</td>
<td>95</td>
<td>6-8</td>
</tr>
<tr>
<td>Hosp. Spain</td>
<td>100</td>
<td>98</td>
<td>7</td>
</tr>
<tr>
<td>Hosp. Argen.</td>
<td>98</td>
<td>79</td>
<td>4</td>
</tr>
</tbody>
</table>

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Nosocomial MDR-TB outbreaks during the pre-HAART period

Transmission of multidrug-resistant tuberculosis among immunocompromised persons in a correctional system--New York, 1991

J Infect Dis 1997 Sep;176(3):637-42
Nosocomial spread of human immunodeficiency virus-related multidrug-resistant tuberculosis in Buenos Aires, 1994-1995

Ann Ital Med Int 1998 Jul-Sep;13(3):139-45

MMWR 1990 Oct 12;39(40):718-22
Nosocomial transmission of multidrug-resistant tuberculosis to health-care workers and HIV-infected patients in an urban hospital--Florida, 1988-1990

J Hosp Infect 2001 Feb;47(2):91-7
Investigation and control of a large outbreak of multi-drug resistant tuberculosis at a central Lisbon hospital, 1995-1996

An outbreak of multidrug-resistant tuberculosis involving HIV-infected patients of two hospitals in Milan, Italy

Maria Luisa Moro, Andrea Gori*, Isabella Errante†, Andrea Infuso, Fabio Franzetti*, Luisa Sodano‡, Enrico Iemoli§ and the Italian Multidrug-Resistant Tuberculosis Outbreak Study Group

Presented at the 8th European HIV Drug Resistance Workshop, March 17-19 2010, Sorrento, Italy
how many drugs do we need?

Nosocomial Spread of Human Immunodeficiency Virus–Related Multidrug-Resistant Tuberculosis in Buenos Aires

Viviana Ritacco, Marta Di Lonardo, Ana Reniero, Marta Ambroggi, Lucia Barrera, Alicia Dambrosi, Beatriz Lopez, Nelida Isola, and Isabel N. de Kantor

Presented at the 8th European HIV Drug Resistance Workshop, March 17-19 2010, Sorrento, Italy

Nosocomial transmission of Mycobacterium bovis resistant to 11 drugs in people with advanced HIV-1 infection

Antonio Guerrero, Javier Cobo, Jesús Fortún, Enrique Navas, Carmen Quereda, Ángel Asensio, José Cariñ, Jesús Blanco, Enrique Gómez-Martínez

Presented at the 8th European HIV Drug Resistance Workshop, March 17-19 2010, Sorrento, Italy
Mortality analysis: HIV+ vs HIV- patients

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Emergence of MDR (XDR)-TB outbreaks (Lombardia, 1993-1998)

MDR M. tb Outbreak
Genotype: Type 1
Hospitals involved: 11
N° cases: 157

MDR M. tb Outbreak
Genotype: Type 20
Hospitals involved: 5
N° cases: 28

MDR M. tb Outbreak
Genotype: Type 65
Hospitals involved: 6
N° cases: 29

MDR M. tb Outbreak
Genotype: Type 23
Hospitals involved: 2
N° cases: 17

MDR M. tb Outbreak
Genotype: Type 580
Hospitals involved: 3
N° cases: 28

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## Spread of MDR e XDR-TB in HIV+

<table>
<thead>
<tr>
<th></th>
<th>Milano 1992-1996 (Franzetti et al.)</th>
<th>SudAfrica 2005 (Gandhi et al.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts with XDR-TB</td>
<td>90</td>
<td>53</td>
</tr>
<tr>
<td>Pts with a previous hospital admission</td>
<td>70%</td>
<td>67%</td>
</tr>
<tr>
<td>Prevalence of XDR-TB</td>
<td>43% (among TB in HIV+ve pts)</td>
<td>39% (among overall TB pts)</td>
</tr>
<tr>
<td>Median CD4 cell count</td>
<td>12</td>
<td>43</td>
</tr>
<tr>
<td>Median survival time</td>
<td>94 days</td>
<td>16 days</td>
</tr>
<tr>
<td>Mortality (at 1 year)</td>
<td>93%</td>
<td>98%</td>
</tr>
<tr>
<td>Clustered strains by genotyping analysis</td>
<td>88%</td>
<td>85%</td>
</tr>
</tbody>
</table>

Franzetti et al. CID, 1999 e Gandhi et al, Lancet 2006

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HIV infection could be successfully treated

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HIV & TB co-infection control

- Which will be the future role of HIV in tuberculosis spreading?

- Which will be the correlation between HIV and MDR TB emergence?

- Did HAART change the role of HIV in tuberculosis epidemiology?
Infections with *M. tuberculosis* among HIV-patients after HAART introduction


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Trends in drug-resistant tuberculosis in the USA, 1993-1996
Incidence of XDR tuberculosis in HIV+ patients (Milano, 1988-2006)

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Incidence of XDR tuberculosis in HIV+ patients (Milano, 1988-2006)

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Factors contributing to the spread of XDR tuberculosis in the Milan

- overcrowded infectious disease wards
- inadequate compliance with infection control procedures
- poor adherence to treatment
- prolonged hospitalisation favouring exposure between patients
- delays in diagnosis
- delays in obtainment of drug susceptibility test results
- No HAART

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Control measurements implementation

- Adherence to basic administrative and source-control measures
- Cough-inducing procedures in TB suspects
- Protocol for early diagnosis
- Placement of patients in single rooms
- Negative pressure rooms was made available for patient isolation

... It is therefore arguable that final eradication of the outbreak was favoured by the use of HAART
Conclusions

XDR outbreaks demonstrate that,

- deficiencies in tuberculosis management, and inadequate infection control procedures can have disastrous results on tuberculosis spread when combined with high concentrations of severely immunosuppressed HIV-infected patients in healthcare environments

- a reduction in the pool of highly susceptible HIV-infected individuals can be brought about by preventing new infections, and by making HAART widely accessible to those in need of it

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Conclusions

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While HIV treatments are becoming more widely available, often many immunosuppressed HIV-infected patients remain in close contact within health facilities, prior to achieving HAART-induced immune reconstitution.

Unless control measures are rapidly implemented, many sub-Saharan countries are likely to experience similarly catastrophic scenarios in the near future.
XDR Tuberculosis — Implications for Global Public Health

Mario C. Raviglione, M.D., and Ian M. Smith, M.B., Ch.B.

Prevalence of MDR tuberculosis among new cases

- ≤ 0.9%
- 1.0%–2.9%
- 3.0%–6.4%
- ≥ 6.5%

Reported cases of XDR tuberculosis

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Efficacy of TB control measurements

“The Case of Peru”

Pulmonary TB cases/100,000

World Health Organization

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One person dies of TB every 15 seconds. TB is preventable and curable.
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  Paolo Fortuna
  Sergio Foresti

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  Paola Meraviglia
  Antonietta Cargnel
  Enrico Iemoli
  Giuliano Rizzardini
  Fabio Franzetti
  Mauro Moroni

Clinic of Infectious Diseases, “San Paolo” Hospital, University of Milan, Italy
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  Villa Marelli Institute
  Luigi Codecasa
  Carla Lacchini

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