TDR-TB in India: lessons and opportunities

THE GLOBAL CRISIS OF DR-TB: IOM WORKSHOP
BEIJING, CHINA. January 2013

Zarir F Udwadia
zfu@hindujahospital.com
Conflicts of interest

• None to declare - -
Introduction

- For 2 weeks in Dec 2011, India coughed and the rest of the world paid attention

- DR-TB languishing from years of neglect was centre-stage again

- TB exists on such an an epic scale in India these coughs would have gone unnoticed

- 130 years after Koch's discovery we have by a combination of ignorance + complacency created a virtually untreatable form of TB
Statutory warning: TB Rx can be dangerous for your health

• 37 year old female: resident of Dharavi, Mumbai.

• History of pulmonary TB since 5 yrs.

• Had consulted multiple physicians for Rx of her TB

• Received multiple 1st and SLDs

• Presented for enrollment in an NIH funded XDR-TB study
Rx history prior to being labeled TDR-TB

- HAD TAKEN > 60 MONTHS OF ATT SINCE 2005:
  - Private: 2005; 4 months U.P.
  - DOTS: 2006; 2 months U.P.
  - Private: 2007-2009; 2 years intermittently U.P.
  - Private: 2010; 3 months Mumbai
  - DOTS-Plus: 2011; 12 months Mumbai
  - Presented to Hinduja Hospital, Mumbai 2011

- Taken almost every available 1st and SLD, often in incorrect doses, and with considerable toxicity
“TREATING A CASE OF MDR-TB TAKES 24 MONTHS AND USUALLY FAILS; CREATING A CASE REQUIRES ONLY A FEW WEEKS.”
THOMAS FRIEDEN
## Drugs taken

<table>
<thead>
<tr>
<th>Drugs taken</th>
<th>Duration</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>28 days</td>
<td>? Peripheral Neuropathy.</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>28 days</td>
<td>-</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>11 months</td>
<td>-</td>
</tr>
<tr>
<td>PZA</td>
<td>18 days</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>202 days</td>
<td>-</td>
</tr>
<tr>
<td>PAS</td>
<td>180 days</td>
<td>Nausea, vomiting, intolerance.</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>11 months</td>
<td></td>
</tr>
<tr>
<td>Kanamycin</td>
<td>95 days</td>
<td>Ototoxicity</td>
</tr>
<tr>
<td>Linezolid</td>
<td>65 days</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>60 days</td>
<td>-</td>
</tr>
</tbody>
</table>
• MULTIPLE DOCTORS
• INNUMERABLE DRUGS
• NEVER A DST
Pre-op CT…..
**DST report**

<table>
<thead>
<tr>
<th>Sample: SPUTUM</th>
<th>MGIT TB DST XDR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test</strong></td>
<td><strong>Result</strong></td>
</tr>
<tr>
<td>MGIT TB DST XDR</td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Resistant 0.1 µg/ml</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Resistant 1 µg/ml</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Resistant 1 µg/ml</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Resistant 2.5 µg/ml</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Resistant 2.5 µg/ml</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Resistant 0.25 µg/ml</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Resistant 2 µg/ml</td>
</tr>
<tr>
<td>Drug</td>
<td>Result</td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Resistant</td>
</tr>
<tr>
<td>PAS</td>
<td>Resistant</td>
</tr>
</tbody>
</table>
Back to the future
Drug option:

- In the absence of all available SLD', a salvage regimen was empirically started:
  - INH (300) 1-0-1.
  - IM Capreomycin 0.75 gm OD.
  - Linezolid (600) 0-1-0.
  - Clofazine (100) 1-0-1.
  - Cycloserine (250) 1-0-1.
Surgery: increasingly the best option in an MDR-TB case

• Surgery was strongly recommended:
  Pros: The disease was still unilateral
    : There were no effective drug options
  Cons: Sputum still +ve at the time (1+)
    : Very low BMI and protein mass

• Relatives counseled re possible high post-op morbidity/mortality: consented
Timing

• Timing is of the essence:

• Compromise chosen was: 2 months of initial treatment

• Hoping to reduce the bacillary load (though not totally sterilize)

• Then proceed with surgery.
Surgery…. 

• Underwent right sided pneumonectomy on 24/08/2011 

• Shifted to ICU with ICD in situ. 

• Was stable on 1st post-op day: breathing spontaneously, SaO2 of 98%
Post-op CXR (Day 1)
Day 2-4 post-op

- Developed fever, hypotension, respiratory failure
- Needed re-intubation, ventilation
- Inotropes: noradrenaline, vasopressin, adrenaline
- Antibiotics: IV Meropenem, Linezolid, Moxifloxacin: chosen also for their anti-mycobacterial effect
- Prone-positioning for refractory hypoxemia
- Died post-op day 4
Day 4 (Before death)

Cause of death: aspiration pneumonia or spill over of TB in the normal lung
Learning points

- Untreatable forms of TB increasingly encountered
- These patients have virtually no drug options
- New drugs are desperately needed
- DST despite expense is money well spent
- Surgery may be the sole option: expensive, high mortality
- In no other disease is prevention more important
3 further cases

- Around this time 3 more cases with the same DST pattern encountered in quick succession

- All seen by me at my free weekly TB OPD run over the last 2 decades at the Hinduja hospital

- One where the changing resistance pattern has been witnessed firsthand
The setting

• The Hinduja Hospital & Research Center
• A large private hospital in Mumbai:
  • An advanced mycobacterial lab
  • RNTCP and CAP accredited
  • LPA accredited by Central TB division, Indian Govt
  • Regular proficiency testing with SNRLs
  • Only Indian lab in initial FIND GeneXpert study (NEJM 2011)
  • Serves as a de facto reference lab for the city of Mumbai for both private and public sectors
Correspondence

Totally Drug-Resistant Tuberculosis in India

To the Editor—Three years after extensively drug-resistant (XDR) tuberculosis was first described in 2006, Velayati et al [1] drew attention to the emergence of totally drug-resistant (TDR) tuberculosis in a cohort of 15 patients from Iran, resistant to all first- and second-line drugs. Since the first cases of XDR tuberculosis in India were reported from the P. D. Hinduja National Hospital and Medical Research Centre, Mumbai, India

individually and often in incorrect doses, from multiple private practitioners (mean, 4 physicians during a 18-month period) in an attempt to cure their multidrug-resistant (MDR) tuberculosis (Table 1). The latest WHO global resistance report estimated 110 132 cases of MDR tuberculosis from India in 2006, which accounts for 20% of the world’s MDR tuberculosis load [3]. Although India’s RNTCP has been a tremendous success, patients with MDR tuberculosis currently

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Zarir F. Udwadia, Rohit A. Amale, Kanchan K. Ajbani, and Camilla Rodrigues

P. D. Hinduja National Hospital and Medical Research Centre, Mumbai, India
<table>
<thead>
<tr>
<th>Pt. no.</th>
<th>Age/Sex</th>
<th>Number of doctors visited</th>
<th>1\textsuperscript{st} line drugs used (with duration in months)</th>
<th>2\textsuperscript{nd} line drugs used (with duration in months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2) 57/M</td>
<td>2 (private)</td>
<td>H (24), R (6), E (6), Z (6), S (1).</td>
<td>Kanamycin (13), Ethionamide (3), Levofloxacin (3), Moxifloxacin (18), PAS (24), Clofazimine (9).</td>
<td></td>
</tr>
<tr>
<td>3) 37/F</td>
<td>4 (private)</td>
<td>H (1), R (1), E (11), Z (1).</td>
<td>Moxifloxacin (7), PAS (6), Clofazimine (12), Kanamycin (3), Linezolid (2), Rifabutin (2).</td>
<td></td>
</tr>
<tr>
<td>4) 31/F</td>
<td>5 (private)</td>
<td>H (16), R (4), Z (4), E (16).</td>
<td>Kanamycin (9), Moxifloxacin (19), PAS (19), Ethionamide (12), Amikacin (9).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pt. no.</th>
<th>Drug susceptibility test results</th>
<th>Hain genotyping MTBDR plus and sL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>Resistant to all 1\textsuperscript{st} and 2\textsuperscript{nd} line drugs</td>
<td>Not done</td>
</tr>
<tr>
<td>2)</td>
<td>Resistant to all 1\textsuperscript{st} and 2\textsuperscript{nd} line drugs</td>
<td>rpo mutant 3, katG mutant 1, inhA, mutant 1, gyrA mutant 3C, rrs mutant 1.</td>
</tr>
<tr>
<td>3)</td>
<td>Resistant to all 1\textsuperscript{st} and 2\textsuperscript{nd} line drugs</td>
<td>rpo mutant 3, katG mutant 2, gyrA mutant 3D, rrs mutant 1.</td>
</tr>
<tr>
<td>4)</td>
<td>Resistant to all 1\textsuperscript{st} and 2\textsuperscript{nd} line drugs</td>
<td>rpo mutant 3, katG mutant 1, gyrA mutant 3C, rrs mutant 1.</td>
</tr>
</tbody>
</table>
Defining TDR: resistance to following 12 drugs

- Resistance to ALL five 1\textsuperscript{st} Line Drugs:
  - H,R,E,Z,S

- Resistance to old and new generation Fluoroquinolones:
  - Ofloxacin, Moxifloxacin

- Resistance to ALL three Aminoglycosides:
  - Kanamycin, Amikacin, Capreomycin

- Resistance to the two most widely used Group 4 drugs:
  - Ethionamide and PAS

- Note: \textit{DST} tested on MGIT 960 (WHO recommended CC)
  - \textit{Molecular tests: Genotype MTBDRplus and MTBDRsl}
First tuberculosis cases in Italy resistant to all tested drugs

GB Migliori (gbmigliori@fsm.it)\textsuperscript{1}, G De Iaco\textsuperscript{2}, G Besozzi\textsuperscript{2}, R Centis\textsuperscript{1}, DM Cirillo\textsuperscript{3}

1. WHO Collaborating Centre for TB and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, Tradate, Italy
2. E. Morelli Hospital, Reference Hospital for MDR and HIV/ TB, Sondalo, Italy
3. Supranational Reference Laboratory, S. Raffaele Institute, Milano, Italy

Emergence of New Forms of Totally Drug-Resistant Tuberculosis Bacilli

Super Extensively Drug-Resistant Tuberculosis or Totally Drug-Resistant Strains in Iran

Ali Akbar Velayati, MD; Mohammad Reza Marjazi, MD; Parsa Farma, PhD; Payam Tabarsi, MD; Jalalein Ghanavi, MD; Abol Hassan ZiaZarif, PhD;

Correspondence

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Indian TDR Timeline

- Dec 21, 2011: Advance E release of article in Clinical Infectious Disease
- Jan 2012 Times of India and Canadian Globe pick up the story
- Jan-Feb 2012: Unprecedented media interest
- Government responses: from the ridiculous to the sublime:
  - Cultures seized from the hospital lab
  - Aspersions on the physicians and the laboratory
- WHO responses more prompt and measured:
  - Jan 2012: WHO webpage with FAQs on TDR
  - March 2012: WHO meeting to discuss nomenclature
DISEASE

India struck by budding strain of 100-per-cent fatal tuberculosis

Article sounds alarm on 'potential epidemic,' blaming drug resistant form of TB on private doctors' prescribing practices

STEPHANIE NOLEN
NEW DELHI

An incurable form of tuberculosis has emerged in India, the first-ever occurrence in a country with a massive epidemic and a highly mobile population that can easily spread the disease.

These are patients with tuberculosis that cannot be cured with any combination of the World Health Organization-recommended drugs, either "first line," the standard treatment, or "second-line," the most powerful, toxic and expensive medications. This form of tuberculosis is 100-per-cent fatal and its emergence here has alarmed public health officials because India has nearly a fifth of the world's TB patients but a health system too frail to respond.

Iran reported the first known cases of totally drug-resistant tuberculosis (TDR-TB) in 15 patients in 2009.

Then in November, doctors in Mumbai concluded four of their patients had it - and after a series of tests, identified eight more cases, which they describe as "unprecedented" in scale.
New, deadlier form of TB hits India

12 Totally Drug-Resistant Cases Of Killer Disease Isolated At Hinduja

‘Deadlier strain arose due to health system’s failure’

Mumbai hospital reports first set of ‘total’ drug-resistant TB cases

TDR: "Triggering Dramatic Responses"
might be responsible for the situation,” said Mhaiskar. “They need to be so and given a protocol to follow when they get a patient with symptoms

GLOBAL HEALTH
India struck by budding strain of incubable tuberculosis

Begam Saikh and her six-year-old daughter Ayesha have both been diagnosed with polio.

Dhar for The Globe and Mail

Goal of a polio-free world hampered by three pockets of disease
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Government responses

• "It's XXDR. There is nothing like TDR. We will hold a meeting to take a final call" Dr Ashok Kumar, Director General TB, Union Health Ministry

• "They spread unnecessary panic in the country using TDR - - a notice will be served on them for creating a fear complex" Dr Prasad, DGHS
Government responses

• “We will hold a quick training course for doctors in how to handle this disease. The course will be short as we don’t have time in hand.” Senior State Health Official

• “We have examined the patients from Mumbai and will do scrotum microscopy on each” Dr Suresh Gupta, DHS
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  - Aspersions on the physicians, hospital and laboratory
  - Pressure to retract the paper, embargo on publications
- WHO responses more prompt and measured:
  - Jan 2012: WHO webpage with FAQs on TDR
  - March 2012: WHO meeting, Geneva to discuss nomenclature
Paul Nunn: "a wake up call for countries to accelerate provision of proper care to MDR patients"

Mario Raviglione: "Indeed, this issue of TDR is a very concerning one, yet anticipated."

Drug-resistant tuberculosis

Frequently Asked Questions
26 January 2012

Note: This page was edited for readability on 24 January 2012. It was originally posted on 13 January 2012.

How does WHO define the recently reported cases of drug-resistant tuberculosis in India?
WHO defines the cases in India as extensively drug-resistant tuberculosis (XDR-TB), a severe form of drug-resistant TB. Other terms used in recent news reports or scientific journals have not been defined by global TB experts.
WHO GENEVA MEETING
March 21st 2012
conclusions - -

• Reports of TB patients with patterns worse than XDR, are increasing and present a formidable challenge

• - -however a new definition of resistance beyond XDR is not recommended given that

• - - this would have a huge impact on lab capacity: at present most labs struggle to diagnose MDR

• Reliability, reproducibility, accuracy and in vivo correlation of DST for SLDs unclear
TDR Timeline: post-script

- May 2nd 2012: National TB Institute verifies that all the strains from Hinduja hospital “are indeed resistant to all 12 drugs as reported”

- January 2013 Hinduja Hospital & Research Centre awarded the “TB Champion of 2013” IUATLD award
Changes at Ground zero

- Free drugs offered to all surviving patients: 6 of whom accept
- Cluster investigation of all their 43 contacts
- Notification of M(X)DR made compulsory in Mumbai: May 7th. MDR cases double in 6 weeks compared to past 18 months
- 2 state labs capacity strengthened: JJ hospital, GT hospital
- RNTCP staff increased from 1 program manager to 24
- Union TB budget increases 70% for TB to Rs 710 crores
- Union Health Secretary writes to each state to scale up DOTS Plus
- Meeting with Maharashtra FDA Commissioner re regulating TB drugs
TDR-TB series

• Since the original publication, 16 more cases

• A total of 20 patients with TDR-TB: holding a mirror to the way MDR-TB is (mis)managed in India

• Mean age: 29

• M:F; 1:1

• Seen an average of 4 doctors, received a mean of 9.45 drugs for an average duration of 26 months prior to being labeled TDR-TB
What's in a name?

What surrounds us we endure better for giving it a name - and moving on.”

Emilie Kioran
What’s in a name?

- XDR-TB
- XXDR-TB
- SXDR-TB
- CDR-TB
- TDR-TB
What’s in a name?

• I have no objection to your giving names any signification you please if you will only tell me what you mean by them. Plato
What's in a name?

• MDR, XDR, TDR - - - each initial we have before DR is a reflection of our failure

• Acknowledge there are forms of MDR: some with even worse prognosis and outcome than others, based on the number of drugs the patient is resistant to
What's in a name?

• TDR-TB seems here to stay:

• 1,700,000 Google results

• It's own Wikipedia page:
  en.wikipedia.org/wiki/Totally_drugresistant_tuberculosis
http://www.google.com/insights/search/?hl=en-GB#cat=0-45&q=TDR+TB&date=today+12-m,&cmpt=date

1,700,000
What’s in a name?

• It's not just about semantics
• It's about treatment
• It's about survival
XDR survival significantly worse than MDR

Hazard ratio of death from XDR 7.9 x of MDR

Figure 1. Survival Rates among Patients with Multidrug-Resistant Tuberculosis and Those with Extensively Drug-Resistant Tuberculosis.
## What’s in a name?

<table>
<thead>
<tr>
<th></th>
<th>MDR-TB</th>
<th>XDR-TB</th>
<th>TDR-TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>H + R</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Other 1st line drugs</td>
<td>√</td>
<td>√</td>
<td>XX</td>
</tr>
<tr>
<td>FQ</td>
<td>√</td>
<td>±</td>
<td>XX</td>
</tr>
<tr>
<td>2nd line injectables</td>
<td>√</td>
<td>±</td>
<td>XX</td>
</tr>
<tr>
<td>Other 2nd line</td>
<td>√</td>
<td>√</td>
<td>±</td>
</tr>
</tbody>
</table>
Countries reporting at least 1 case of XDR-TB as of Jan 2010
Global TB map
Global poverty map
Global malnutrition map: underweight children
MDR – TB PATIENT

PUBLIC

Little choice

Category 2 Rx

Amplify resistance

Chronic MDR-TB Patient

PRIVATE

30%

70%

Many choices

Private allopath (non-specialist)

Homeopath

Ayurvedic

Unani

Chest specialist

Amplify resistance

XDR-TB Patient

Cured (Tiny Fraction)
Dilemma of M(X)DR-TB in India

• Large and ever expanding population
• Accorded status of untreatable and untouchable
• RNTCP has turned a blind eye to them
• WHO focus on DOTS to exclusion of all else
• Individual patient treatment not considered cost-effective
• National strategy: acceptable public health realpolitik
“Our mission must be to treat the sick, not just the sick who can pay. Our mission must be to treat TB regardless of resistance pattern ---

It is failure to treat, not treatment failure, that accounts for the vast majority of MDR-TB deaths.”

• PAUL FARMER, 1998
Diseases desperate grown
By desperate appliances are relieved
Or not at all

William Shakespeare
Hamlet, Act 1V, Scene 111
Rational Classification of Anti-TB Drugs

Group 1: **First Line Drugs, Oral**
(H,R,E,Z)

Group 2: **Quinolones**:
Of, Lf, Mox., Gat

Group 3: **Injectables**:
Sm, Km, Ak, Cm

Group 4: **Other 2nd Line Drugs**:
Et/Pth, Cs, PAS

Group 5: **Reinforcement Drugs**
(poor):
Am/Cl, Clof, Th, High dose INH, Linezolid

- All
- Possible
- 1
- Until
- 4 New
- Exceptional
- If < 4
## Drugs used in 20 TDR cases

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Name of Drug</th>
<th>Number of patients used in</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Clofazimine</td>
<td>18</td>
</tr>
<tr>
<td>2.</td>
<td>Capreomycin *</td>
<td>15</td>
</tr>
<tr>
<td>3.</td>
<td>Linezolid</td>
<td>13</td>
</tr>
<tr>
<td>4.</td>
<td>Cycloserine</td>
<td>12</td>
</tr>
<tr>
<td>5.</td>
<td><em>Isoniazid (300) BD (Double strength)</em></td>
<td>10</td>
</tr>
<tr>
<td>6.</td>
<td>Thioridazine</td>
<td>9</td>
</tr>
<tr>
<td>7.</td>
<td>Ethionamide*</td>
<td>7</td>
</tr>
<tr>
<td>8.</td>
<td>Clarythromycin</td>
<td>6</td>
</tr>
<tr>
<td>9.</td>
<td><em>Moxifloxacin</em></td>
<td>6</td>
</tr>
<tr>
<td>10.</td>
<td><em>Para-amino salicylate</em></td>
<td>5</td>
</tr>
<tr>
<td>11.</td>
<td>Kanamycin *</td>
<td>3</td>
</tr>
<tr>
<td>12.</td>
<td>Rifabutin</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td><strong>SURGERY</strong></td>
<td><strong>4</strong></td>
</tr>
<tr>
<td>No.</td>
<td>Salvage Regimen</td>
<td>Till Nov. 2012</td>
</tr>
<tr>
<td>-----</td>
<td>----------------</td>
<td>---------------</td>
</tr>
<tr>
<td>1.</td>
<td>INH (300) BD, Linezolid (600) OD, Moxifloxacin (400) OD, Clofazimine (100) BD, Cycloserine (250) BD, Capreomycin (750) OD, Ethionamide (250) BD, Thiridazine (25 mg for 1st wk then 50 mg).</td>
<td>11 months.</td>
</tr>
<tr>
<td>2.</td>
<td>INH (300) BD, Capreomycin (500) OD, Clofazimine (100) OD, Clarythromycin (500) BD, Linezolid (600) OD, Cycloserine (250) BD, Rifabutin (150) BD.</td>
<td>11 months.</td>
</tr>
<tr>
<td>3.</td>
<td>Linezolid (600) OD, Capreomycin (1 gm) OD, Cycloserine (250) BD, Clofazimine (100) OD, Amox+clavu (625) BD, Clarythromycin (500) OD.</td>
<td>12 months.</td>
</tr>
<tr>
<td>4.</td>
<td>Capreomycin (750) BD, Clofazimine (100) OD, Linezolid (600) OD, Clarythromycin (250) BD, Amox+Clavulanate (625) BD.</td>
<td>12 months.</td>
</tr>
<tr>
<td>5.</td>
<td>INH (300) BD, Moxifloxacin (200) OD, Clofazimine (100) OD, Ethionamide (250) OD, Linezolid (300) OD, Kanamycin (500) OD.</td>
<td>12 months.</td>
</tr>
<tr>
<td>6.</td>
<td>Cycloserin (250) BD, Clofazimine (100) BD, Clarythromycin (250) BD, Linezolid (600) OD, Capreomycin (750) OD (5/7), Thioridazin (25) OD.</td>
<td>10 months.</td>
</tr>
<tr>
<td>7.</td>
<td>Capreomycin (500), H (300), Clofazimine (100), Ethionamide (250), Z (500)</td>
<td>12 months.</td>
</tr>
<tr>
<td>8.</td>
<td>Linezolid (600), Amox+Clavu (375), Clofazimine (100), INH (300), Clarythromycin (250), Capreomycin (500)</td>
<td>12 months.</td>
</tr>
<tr>
<td>No.</td>
<td>Salvage Regimen</td>
<td>Till Nov. 2012</td>
</tr>
<tr>
<td>-----</td>
<td>-------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>9.</td>
<td>INH (300) OD, PAS (3 gm) BD, Clofazimine (100) OD, Moxifloxacin (400) OD, Linezolid (600) OD, Cycloserine (250) BD, Capreomycin (500) OD.</td>
<td>14 months.</td>
</tr>
<tr>
<td>10.</td>
<td>Lost to follow up</td>
<td>------</td>
</tr>
<tr>
<td>11.</td>
<td>INH (300) BD, Capreomycin (750) OD, Linezolide (600) OD, Clofazimine (100) BD, Cycloserine (250) BD.</td>
<td>------</td>
</tr>
<tr>
<td>12.</td>
<td>Patient Expired.</td>
<td>------</td>
</tr>
<tr>
<td>13.</td>
<td>Linezolid (600) ½ OD, Moxifloxacin (400) 1 OD, Thioridazine (25) 1 OD, Capreomycin (500) IM (5/7), Clofazimine (100) BD, Ethionamide (250) BD, QPAS 1tsf BD.</td>
<td>9 months.</td>
</tr>
<tr>
<td>14.</td>
<td>INH (300) OD, Moxifloxacin (400) OD, Linezolid (600) OD, Ethonamide (250) BD, PAS (3500) OD, Kanamycin (500) OD, Cycloserine (250) BD, Clofazimine (100) BD.</td>
<td>7 months.</td>
</tr>
<tr>
<td>15.</td>
<td>Capreomycin (500) 3times/wk, Clofazimine (100) BD, Cycloserine (250) OD, Ethonamide (250) BD, PAS (3gm) BD, Thioridazine (25mg) at night, Clarythromycin (250) BD.</td>
<td>7 months.</td>
</tr>
<tr>
<td>No.</td>
<td>Salvage Regimen</td>
<td>Till Nov. 2012</td>
</tr>
<tr>
<td>-----</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>16</td>
<td>Capreo. (500) OD except Sat &amp; Sun, Linox (600) ½ OD, Thioril (25) 1OD, Rifabutin (150) 1OD, Clofazimine (100) 1OD</td>
<td>2 months.</td>
</tr>
<tr>
<td>17</td>
<td>QPAS (4500) BD, Moxi (400) OD, Clofa (100) OD, Cyclo (250) BD, Ethiona (250) BD, Thioril (250) OD, Linox (600) OD, Kana (750) OD</td>
<td>2 months</td>
</tr>
<tr>
<td>18</td>
<td>T. Thioril (25) 2 OD, Cap. Cycloserine (250) BD, Cap. Clofazimine (100) BD, Inj. Capreomycin (500) IM 1 OD.</td>
<td>2 months</td>
</tr>
<tr>
<td>19</td>
<td>Capreomycin (500) Mon., Wed., Fri., Clofazimine (100) BD, Rifabutin (300) OD, Linezolid (600) ½ OD, Cycloserine (250) BD, Thiridazin (50) OD.</td>
<td>1 months</td>
</tr>
<tr>
<td>20</td>
<td>Capreomycin (500) OD IM (5/7), Linezolid (600) ½ OD, Clofazimine (100) BD, Thioridazine (25) OD (night), Cycloserine (250) BD.</td>
<td>1 months</td>
</tr>
</tbody>
</table>
### Assessing response: 1 year follow up

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>NUMBER RESPONDING</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL IMPROVEMENT</td>
<td>7/20</td>
</tr>
<tr>
<td>SMEAR CONVERSION</td>
<td>7/20</td>
</tr>
<tr>
<td>CULTURE CONVERSION</td>
<td>5/20</td>
</tr>
<tr>
<td>RADIOLOGICAL IMPROVEMENT</td>
<td>7/20</td>
</tr>
<tr>
<td>LOST TO FOLLOW UP</td>
<td>3/20</td>
</tr>
<tr>
<td>MORTALITY</td>
<td>6/20</td>
</tr>
</tbody>
</table>
TDR patient # 2: before regimen

CXR at time of TDR label
TDR patient: responding well at 1 year

After 1 year of salvage regimen:
Double dose INH, Linezolid, cycloserine, thioridazine, clofazine, capreomycin
TDR patient #4 at diagnosis

30 year old tailor

HIV+ve: on ARVs 7 years, CD4: 370

TB: on Rx for 2 years
Labeled TDR in Dec 2011
Good response at 6 months

Early pneumonectomy + ARVs +
Background regimen of: Capreomycin, Linezolid, Clarithromycin, Clofazamine, Rifabutin

Weight gain of 7 kg
AFB Smear -ve Culture -ve
Relapse at 1 year

TMC 207 applied for on a compassionate basis

Fever, cough
Weight loss 5 kg
AFB smear:+++
“I have to take the injections daily. And I cry every day. Every day I cry for an hour - - the place where they give the injections becomes stone hard - - I can’t lift my legs or walk. If you give me pills I will eat them. As many as you want me to.”

India reports cases of totally drug-resistant tuberculosis

Mismanagement of tuberculosis in Mumbai has led to the emergence of India’s first known cases of a totally drug-resistant form of the disease, say doctors. Samuel Loewenberg reports.

Researchers in Mumbai have identified 12 patients with a virulent strain of tuberculosis that seems to be resistant to all known treatments. The cases of so-called totally drug-resistant tuberculosis (TDR-TB) have been detected in the city in the past 3 months. Worldwide, the only other episodes of TDR-TB reported were in Iran in 2009 and Italy in 2007.

Udwadia says that although the DOTS (Directly Observed Therapy, Short Course) programme has generally been successful for people with normal tuberculosis who do access it, for those with drug-resistant tuberculosis it may not be effective. Research in Mumbai. There is “poor infection control at most of these settings”, said Mistry, and people with resistant tuberculosis could well be infecting patients with a regular tuberculosis infection. A 5-year study done by the Foundation with the Wellcome Trust found that most patients were resistant to two or three of the first-line drugs and were to
We need not new drugs but new regimens

• A single drug is doomed to failure

• New regimens of: existing drugs:
  • Linezolid, thioridazine, moxifloxacin (Abbade)

• Or new regimens of novel agents:
  • TMC207, + OPC67683, + PA824, + PNU100480, + SQ109 ? (Carl Mendel, Global Alliance)

• Drug companies must come together: compassionate use:
  – Potential collaborators: Tibotec, Otsuka, TB Alliance, Pfizer, Sequella
When all else fails - -

• How do we treat XDR-TB patients who have failed treatment?

• What do we do when we have run out of ALL drugs and surgery is not possible?

• Do we continue to treat with the aim of reducing infectiousness rather than curing?

• Should we have a protocol for withdrawal of all drugs as we do in cancer patients?

• What emotional support do we give them?
MDR, XDR, TDR tuberculosis: ominous progression

Zarir F Udwadia

Any man’s death diminishes me because I am involved in mankind, and therefore never send to know for whom the bell tolls; it tolls for thee... (John Donne, Meditation XV(1))

The situation is even worse when it comes to multidrug resistant TB (MDR-TB). Here again India emerges a global hot spot with the latest WHO anti-TB drug treatment recommended. The only way to treat the sick who can pay. Our mission must be to treat TB regardless of resistance pattern. With the very limited treatment options available, we started each patient on a salvage regimen of four new drugs. In addition, aggressive surgery (pneumonectomy) was offered to two patients despite the bilateral nature of their disease. Three patients succumbed to their disease within a few months of being labelled TDR-TB.

TDR-TB is an iatrogenic disease that

Totally drug-resistant tuberculosis in India: Who let the djinn out?

JECH Online First, published on November 15, 2012 as 10.1136/jech-2012-201640

Totally drug-resistant tuberculosis (TDR-TB) in India: every dark cloud has a silver lining

Zarir Udwadia,1 Deepesh Vendoti2

only to further amplify resistance, converting MDR to XDR and then to TDR-TB. A recent study by Dalton et al showed that indiscriminate use of second-line drugs is a strong and consistent factor contributing to resistance to these drugs and the increased XDR rates encountered globally. In no other country are second-line drugs used as freely and prescribed by such a wide and diverse range of medical practitioners as in India.

The 15 patients described above were all started on a variety of salvage regimens,
Suggestions

1. Increase lab capacity

2. Offer DST early to all patients who fail to respond to DOTs instead of subjecting them to Cat 2 Rx

3. Roll out GeneXpert across the country

4. DOTS plus needs to expand country wide

5. Additional funds

6. New drugs needed, but don't squander available ones

7. Private Public Mix (PPM)

8. Legislation to ensure only designated specialists prescribe and treat MDR-TB

"Keep doing what you've always done and you'll get what you always got"

Dixie Snyder
Ayesha: 4 years
"It's not that we can't cure TB, it's that we can't cure TB for poor people. TDR-TB has been present for decades, but instead of pathological resistance the culprits are apathetic governments, broken promises, and non functioning infra-structures that elude accountability. ---TDR-TB reinforces my claim that TB management should be deemed the largest violation of human rights the global health community has ever seen.

Jonathan Smith
“The fate of the worlds poor is due to the inaction of those who are indifferent.”  Peter Small

James Nachtwey