Objectives

- Definitions
- Discuss the epidemiology and pathogenesis of MDR TB
- Discuss MDR TB treatment principles and new drugs
- Review special situations (HIV, Pregnancy, Surgery)
- Present case(s)
1992: Multidrug-resistant (MDR) TB
Definition of Drug Resistant TB

- **MDR TB**
  - A specimen of *M. tuberculosis* isolate that is resistant to at least INH and RIF
  - Can be resistant to other drugs as well

- **ODR TB**
  - Resistant to INH, sensitive to RIF, with or without resistance to other first or second-line drugs
  - Resistant to RIF, sensitive to INH, with or without resistance to other drugs
  - Resistance to any (1 or more) first-line drugs (EMB, PZA, SMN) other than INH or RIF
Killer TB tightens fatal grip

Despite indications that SA is in the forefront of infection, health minister tries to put a clamp on news and snubs global conference

By CHARLES SMITH and LIZ CLARK

At just one hospital in Tygerberg, a third of the patients with HIV who were treated for TB were found to be co-infected with HIV.

The case was reported by the Medical Research Council in June. The council said that TB patients were six times more likely to die if they had HIV.

"We are the most researched country on the continent of Africa," said Lalloo.

"All those in contact with the extensive forms of TB were at risk of developing it, including health personnel," he said.

Patients diagnosed with MDR-TB should be hospitalized to ensure adherence and efficacy, he said. "The support and tracking of such patients is critical to any programme to manage and prevent the spread of MDR-TB."

While all the resources needed were in place, having freely available drugs was a serious problem if they were not issued as part of a well-defined programme. "We are the most researched country on the continent of Africa," he said.

"And the people who are most infected with TB are the medical personnel," he said.

Fifty-two of the 55 patients diagnosed with MDR-TB have already died at Tygerberg Hospital and continuing research points to a strain having spread to other regions of the country.

The extent of this extensively drug-resistant strain is not known, however, as most screening is expensive and difficult to conduct.

Many patients are dying without having been diagnosed. All 55 patients tested so far had XDR-TB.

"And the places where you are most at risk is a South African hospital," he said. "The problem is that the patient is more likely to receive the wrong treatment from the hospital."

"We need to be careful," he said. "We need to be sure that the patient is treated properly and that the treatment is effective."
Definition of XDR TB

- Resistance to at least INH and RIF from among the 1\textsuperscript{st} -line anti-TB drugs (MDR TB)
- \textbf{Plus} resistance to any fluoroquinolone
- \textbf{And} to at least one of 3 injectable 2\textsuperscript{nd}-line anti-TB drugs used in TB treatment
  - Capreomycin
  - Kanamycin
  - Amikacin
2012: Totally drug-resistant TB?
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 Masjedi, MD; Parissa Farnia, PhD; Payam Tabarsi, MD; Jalladein Ghanavi, MD; Abol Hassan ZiaZarifi, PhD; and Sven Eric Hoffner, MD

Background: The study documented the emergence of new forms of resistant bacilli (totally drug-resistant [TDR] or super extensively drug-resistant [XDR] tuberculosis [TB] strains) among patients with multidrug-resistant TB (MDR-TB).

Methods: Susceptibility testing against first- and second-line drugs was performed on isolated Mycobacterium tuberculosis strains. Subsequently, the strains identified as XDR or TDR M. tuberculosis were subjected to spoligotyping and variable numbers of tandem repeats (VNR). Results: Of 146 MDR-TB strains, 8 XDR isolates (5.4%) and 15 TDR isolates (10.3%) were identified. The remaining strains were either susceptible (67%) or had other resistant patterns (20%). Overall, the median of treatments and drugs previously received by MDR-TB patients was two courses of therapy of 15 months’ duration with five drugs (isoniazid [INH], rifampicin [RF], streptomycin, ethambutol, and pyrazinamide). The median of in vitro drug resistance for all studied cases was INH and RF. The XDR or TDR strains were collected from both immigrants (Afghan, 30.4%; Azerbaijani, 8.6%; Iraqi, 4.3%) and Iranian (56.5%) MDR-TB cases. In such cases, the smear and cultures remained positive after 18 months of medium treatment with second-line drugs (ethionamide, para-aminosalicylic acid, cycloserine, ofloxacin, amikacin, and ciprofloxacin). Spoligotyping revealed Haarlem (39.1%), Beijing (21.7%), EAI (21.7%), and CAS (17.3%) superfamilies of M. tuberculosis. These superfamilies had different VNTR profiles, which eliminated the recent transmission among MDR-TB cases.

Conclusions: The isolation of TDR strains from MDR-TB patients from different regional countries is alarming and underlines the possible dissemination of such strains in Asian countries. Now the next question is how one should control and treat such cases.
Emergence of Totally Drug Resistant (TDR) TB

- XDR TB plus cycloserine, PAS, all injectables
- 15 TDR isolates; 56% Iranian, 30% Afghani
- Cases + smear/culture after 18 months Rx
- 95% XDR/TDR had history of prior TB treatment
- 10% had resistance to all second line drugs (Iranian)
  - Believed due to exposure to aminoglycosides and FQ for treatment of other respiratory diseases
- Recent transmission was not the reason for emergence of TDR

*Chest* 2009; 136:420-425
Definitions (3)

- MDR or XDR-TB
  - Primary Resistance: person is exposed to TB which is already drug-resistant and develops disease.
Timebomb
The Global Epidemic of Multi-Drug-Resistant Tuberculosis

Lee B. Reichman, M.D., M.P.H.
with Janice Hopkins Tanne

“A chilling account.” — The New York Times
Impact of MDRTB

- Enormous resource sink
- Prolonged treatment/monitoring required
- Large cost incurred (drugs, hospitalization, DOT, lab testing)
- Major impact to individual health
- Prolonged isolation, inability to work
- Pool of clinical experts diminishing
- Increasingly complex healthcare systems to navigate
- No proven therapy for contacts
Treatment Costs

- Direct costs, mostly covered by the public sector
- $134,000 per MDR TB patient (average)
- $430,000 per XDR TB patient (average)
- $17,000 per non-MDR TB patient

Epidemiology
TB ANYWHERE IS EVERYWHERE

The image

The dandelion is a plant which propagates itself by airborne means. In the same way, social action can spread and take root, carried on the winds of our efforts and the global determination to overcome this disease.

The image also represents the vulnerability of where the disease located anywhere, and everywhere.

Preventable and curable.

WORLD TB DAY

GLOBAL PLAN TO STOP TB.
Percentage of new TB cases with multidrug-resistant tuberculosis

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.


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Percentage of Previously Treated TB Cases with MDR-TB

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Global capacity for drug-susceptibility testing (DST), 2014

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XDR TB

- XDR TB had been reported by 92 countries by the end of 2012
  - 13 countries had >10 XDR TB cases
  - On average, 9.6% of MDR TB cases have XDR TB

- Highest in:
  - Azerbaijan (Baku city: 12.8%)
  - Belarus (11.9%)
  - Lithuania (24.8%)
  - Tajikistan (Dushanbe city and Rudaki district: 21%)

Primary Anti-TB Drug Resistance, United States, 1993 – 2014*

*Updated as of June 5, 2015.

Note: Based on initial isolates from persons with no prior history of TB. Multidrug resistant TB (MDR TB) is defined as resistance to at least isoniazid and rifampin.
Primary MDR TB, United States, 1993 – 2014*

*Updated as of June 5, 2015.

Note: Based on initial isolates from persons with no prior history of TB. MDR TB defined as resistance to at least isoniazid and rifampin.
Primary Isoniazid Resistance in U.S.-born vs. Foreign-born Persons, United States, 1993 – 2014*

*Updated as of June 5, 2015.
Note: Based on initial isolates from persons with no prior history of TB.
Primary MDR TB in U.S.-born vs. Foreign-born Persons United States, 1993 – 2014*

*Updated as of June 5, 2015.
Note: Based on initial isolates from persons with no prior history of TB. MDR TB defined as resistance to at least isoniazid and rifampin.
Extensively drug-resistant TB (XDR TB) is defined as resistance to isoniazid and rifampin, plus resistance to any fluoroquinolone and at least one of three injectable second-line anti-TB drugs.
Which Patients are at Risk of Drug Resistant TB?

- Birth/ residence in country with high incidence of drug resistant TB
- U.S. residents who travel to high risk areas
- Exposure to patient with relapse or failure
- Prior treatment for TB
- Treatment failure
- Relapse in a patient not on DOT
- Poor adherence
- Clinical deterioration during 4 drug therapy
Why Do We Have Drug Resistance?

- Inadequate treatment
  - Incorrect regimen (lack of drugs or knowledge)
  - Poor adherence

Treatment failure / relapse with drug resistant TB

Transmission of drug resistant TB
Transmission of Drug-Resistant TB

- Transmitted same way as drug-susceptible TB

- Drug resistance is divided into two types
  - Primary resistance develops in persons initially infected with resistant organisms
    - Healthcare-associated transmission
    - Community transmission
  - Secondary resistance (acquired resistance) develops during TB therapy
    - Nonadherence to therapy
    - Inappropriate therapy
## Emergence of Resistance
### (Inappropriate Therapy)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>6/09</th>
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<th>2/10</th>
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<tr>
<td>Culture</td>
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### Susceptibility

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<td>Ethambutol</td>
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Emergence of Resistance
(Nonadherence and Inappropriate Therapy)

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<th>12/08</th>
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<th>6/09</th>
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<td>Rifampin</td>
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<td>Ethambutol</td>
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<td>Smear</td>
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<td>Culture</td>
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Susceptibility

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<th>Isoniazid</th>
<th>Rifampin</th>
<th>Ethambutol</th>
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<tbody>
<tr>
<td>6/08</td>
<td>S</td>
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<td>9/08</td>
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<td>3/09</td>
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<tr>
<td>6/09</td>
<td>R</td>
<td>R</td>
<td>R</td>
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</table>
Drug Resistant Mutants Selected by:

- Non-adherence
- Malabsorption
- Inadequate drug regimen
Rates of Natural Resistance in *M. tuberculosis*

- Isoniazid: 1 in $10^6$
- Rifampin: 1 in $10^8$
- Ethambutol: 1 in $10^6$
- Streptomycin: 1 in $10^5$
- INH & RIF: 1 in $10^{14}$

Number of organisms in a TB cavity = $10^9$-$10^{11}$
Spontaneous mutations develop as bacilli proliferate to $>10^8$.

### Pathogenesis of Drug Resistance

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mutation Rate</th>
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<tbody>
<tr>
<td>Rifampin</td>
<td>$10^{-8}$</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>$10^{-6}$</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>$10^{-6}$</td>
</tr>
</tbody>
</table>
Drug-resistant mutants in large bacterial population

Multidrug therapy:
No bacteria resistant to all 3 drugs

INH
RIF
PZA

Monotherapy:
INH-resistant bacteria proliferate

INH
Spontaneous mutations develop as bacilli proliferate to $>10^8$

INH resistant bacteria multiply to large numbers

INH mono-resistant mutants killed, RIF-resistant mutants proliferate $\rightarrow$ MDR TB
What Do Patients with MDRTB Need?

- Patients with MDR TB need to have
  - Accurate and prompt identification
  - Notification to the field staff and provider(s)
  - Appropriate case management
  - Appropriate treatment based on drug susceptibility test results
  - Appropriate infection control measures instituted
MDR TB
## Treatment Strategies

<table>
<thead>
<tr>
<th>Treatment Strategy</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standardized treatment</td>
<td>Regimen is designed based on Drug Resistance Surveillance (DRS) data from a representative patient population</td>
</tr>
<tr>
<td>Empirical treatment</td>
<td>Regimen is individually designed based on patient’s previous history of TB treatment and DRS data as above</td>
</tr>
<tr>
<td>Individualized treatment</td>
<td>Regimen is designed based on the patient’s previous history of TB treatment and individual DST results</td>
</tr>
</tbody>
</table>
# Antituberculosis Drugs

<table>
<thead>
<tr>
<th>First-Line Drugs</th>
<th>Second-Line Drugs</th>
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</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Streptomycin</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Cycloserine</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>p-Aminosalicylic acid</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Ethionamide</td>
</tr>
<tr>
<td>Rifabutin*</td>
<td>Amikacin or kanamycin*</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>Capreomycin</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin*/Moxifloxacin*</td>
</tr>
</tbody>
</table>

* Not approved by the U.S. Food and Drug Administration for use in the treatment of TB
# Drug Activity Against TB

## Bactericidal vs. Bacteriostatic

<table>
<thead>
<tr>
<th><strong>Bactericidal</strong></th>
<th><strong>Bacteriostatic</strong></th>
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</thead>
<tbody>
<tr>
<td>INH</td>
<td>PZA</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Ethambutol</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Levofloxacin <em>(may be bactericidal)</em></td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Ethionamide</td>
</tr>
<tr>
<td>Kanamycin/Amikacin</td>
<td>PAS</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Cycloserine</td>
</tr>
</tbody>
</table>

*Note: Levofloxacin may be bactericidal.*
Third-Line Drugs Used in MDR TB Treatment

- **Linezolid**
  - Used since 2000 in selected cases
    - More recently a 2\textsuperscript{nd} or 3\textsuperscript{rd} line drug
  - Adverse effects of pancytopenia and peripheral/optic neuritis
    - May or may not be reversible
    - May or may not be ameliorated by vitamin B\textsubscript{6}
    - Consider using 600 mg daily (300mg/day being studied)
  - Use with caution with selective serotonin reuptake inhibitors (SSRIs)
  - Lactic acidosis
  - Expensive
Third-Line Drugs Used in MDR TB Treatment -2

- **Clofazimine**
  - More commonly used in patients with leprosy
  - Used in selected cases
  - Needs Investigational New Device (IND) from FDA

- **Bedaquiline**
  - 1\(^{st}\) new class of TB medication approved since RIF
  - New class of antibiotics, diarylquinolones
  - Given as part of MDR combination therapy
  - New mechanism of action: inhibits ATP synthase
Step 1

Use any available

PLUS

One of these

PLUS

One of these

First-line drugs
- Pyrazinamide
- Ethambutol

Fluoroquinolones
- Levofloxacin
- Moxifloxacin

Injectable agents
- Amikacin
- Capreomycin
- Streptomycin
- Kanamycin

Begin with any 1st-line agents to which the isolate is susceptible

Add a fluoroquinolone and an injectable drug based on susceptibilities

Adapted from Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2nd Ed., available from Curry International Tuberculosis Center
Step 1

Begin with any 1st-line agents to which the isolate is susceptible

Add a fluoroquinolone and an injectable drug based on susceptibilities

**First-line drugs**
- Pyrazinamide
- Ethambutol

**Fluoroquinolones**
- Levofloxacin
- Moxifloxacin

**Injectable agents**
- Amikacin
- Capreomycin
- Streptomycin
- Kanamycin

PLUS One of these

PLUS One of these

Step 2

Add 2nd-line drugs until you have 4-6 drugs to which isolate is susceptible (which have not been used previously)

**Oral second-line drugs**
- Cycloserine
- Ethionamide
- PAS

Pick one or more of these

Adapted from *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2nd Ed.*, available from Curry International Tuberculosis Center
Step 1

Begin with any 1st-line agents to which the isolate is susceptible.

Add a fluoroquinolone and an injectable drug based on susceptibilities.

- **First-line drugs**
  - Pyrazinamide
  - Ethambutol

- **Fluoroquinolones**
  - Levofloxacin
  - Moxifloxacin

- **Injectable agents**
  - Amikacin
  - Capreomycin
  - Streptomycin
  - Kanamycin

Step 2

Add 2nd-line drugs until you have 4-6 drugs to which isolate is susceptible (which have not been used previously).

- **Oral second-line drugs**
  - Cycloserine
  - Ethionamide
  - PAS

Step 3

If there are not 4-6 drugs available, consider 3rd-line in consult with MDRTB experts.

- **Third-line drugs**
  - Linezolid
  - Clofazimine
  - Bedaquiline
  - High-dose isonizid
  - Macrolides
  - Imipenem
  - Amoxicillin/Clavulanate

Principles for Managing MDR TB

- MDR TB should never be treated without expert consultation of a specialist in MDR TB treatment.

- Patients must be treated with a regimen of at least 3-5 anti-TB medications to which the strain is likely to be susceptible (4-6 or better).
Principles for Managing MDR TB - 2

- A single new drug should never be added to a failing regimen
- When initiating or revising therapy, always attempt to use at least 3 previously unused drugs to which there is in vitro susceptibility
  - One agent should be an injectable agent
  - A good response does not justify continuation of an inadequate regimen
Injectable agents can be given 5 days/wk initially
  – After culture conversion, dosing can be 2-3x/wk

With extensive disease or slow conversion of sputum cultures, the injectable should be used for longer periods after culture conversion

Capreomycin is the initial injectable agent of choice

Surgery should be considered if a patient’s cultures fail to convert to negative after 4 months of appropriate treatment
Some experts use EMB at a dose of 25 mg/kg daily when used as treatment of patients with MDR TB
- If this higher dose is used, monthly visual monitoring is recommended

Fluoroquinolones:
- Oral agents, well tolerated
- One of the two most important agents in MDR treatment
Specific Drug Resistances

- If isolates show resistance to INH only at a low concentration, INH 900 BIW (high intermittent dose) can be used
  - Do not rely on its effectiveness as a main agent
- There is cross-resistance between amikacin and kanamycin
- Determination of resistance to PZA is problematic, but is uncommon in the absence of resistance to other 1\textsuperscript{st}-line drugs
  - If mono-resistance to PZA is found, consider the specimen may be \textit{M. bovis}, not \textit{M. tb}
Rifampin Resistance

- Resistance to RIF is generally associated with cross-resistance to rifabutin and rifapentine
  - When RIF resistance is present but *in vitro* sensitivity to rifabutin is reported, treatment should still be the same as if RIF-resistant

- For all with RIF-resistance (mono-RIF or MDR TB), consider extended therapy (up to 24 months) if:
  - There is cavitary or extensive disease
  - The patient is HIV-positive or has risk factors for HIV infection
  - The patient is immunosuppressed
  - Time to culture conversion is prolonged
Treatment of HIV-related MDR-TB

- Rapid diagnosis of drug resistance
- Important to treat with the most active anti-TB regimen available
- Initiate antiretroviral therapy based on CD$_4$ count and other individual patient variables
- Use therapeutic drug monitoring when drug interactions are possible or malabsorption is suspected
MDR TB in Pregnancy

- Most medications used to treat MDR TB are known to cause fetal abnormalities or have not been studied adequately regarding their safety in pregnancy.

- PZA can be used as a main agent and is recommended by WHO & ATS.
  - WHO recommends its use in pregnancy even for drug-susceptible TB patients.
  - In the U.S., it is considered a category C agent.
Monitoring Serum Drug Levels

Serum drug level monitoring can be used in patients with the following medical conditions:

- HIV positive/AIDS
- Diabetes
- Malabsorption syndromes
- Renal failure
- Failure to improve on treatment/relapse
- MDR TB
Drug Intolerance

- In general, length of treatment for patients with drug intolerance is the same as for those who have drug resistance
DOT for MDR TB

- Essential that MDR TB patients be treated with Directly Observed Therapy (DOT)
  - Improved overall cure rates
  - Reduction in community prevalence of MDR
- Intermittent regimens should not be used
- All 2\textsuperscript{nd}-line agents must be administered daily
- Twice/day DOT should be used when feasible, and more frequent dosing than twice daily should be avoided
- All doses must be observed
## DOT: Effect on Resistance and Relapse

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<th>DOT</th>
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<tr>
<td>Primary R</td>
<td>13%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Secondary R</td>
<td>10.3%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Relapse</td>
<td>20.9%</td>
<td>5.5%</td>
</tr>
<tr>
<td>MDR relapse</td>
<td>6.1%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

* P < 0.001

*Source: Weis, NEJM 1994; 330, 1179*
New Treatments for MDR TB

- Bedaquiline (Janssen)
- OPC-67683: Delamanid (Otsuka)
- PA 824 (nitroimidazol-oxazine)
- Linezolid
  - NIH and TBTC studies in progress
  - Already in wide use globally
Linezolid for TB

- Used as second and third line treatment for MDRTB
- Has adverse effects:
  - affects the bone marrow
  - peripheral neuropathy
  - optic neuropathy
  - hepatic dysfunction
  - muscle injury

Pts had improved survival with the lower dose of 300mg/day instead of 600mg/day
Bedaquiline (SIRTURO™)
TMC207

- First new TB drug since RIF (1970)
- New class of potent anti-TB drugs: diarylquinolones
  - Accumulates in the body by binding to phospholipids
- Used as part of combination therapy for pulmonary MDR TB in adults (>18 yrs)
- Administered under DOT
- New mechanism of action: inhibits mycobacterial adenosine triphosphate (ATP)-synthase
  - BDQ binds to ATP-synthase, the main energy source for *M. tb* growth
  - Prevents it from supplying energy for the cell, therefore killing the bacterium
OPC-67683: (R)-2-Methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxyethyl}-2,3-dihydroimidazo[2,1-b]oxazole
Delamanid (OPC-67683)

- New mechanism: inhibits cell wall of TB but exact mode of action unclear
- Given along with background MDR regimen
  - Both regimens had sputum culture conversion at 2 months
- Mild adverse effects
- Had prolongation of the QT intervals
- Nov. 2013: European Medicines Agency (EMA) recommended conditional approval
  - Likely effective in treating drug resistant TB over 6 months as it had in the 2 month study
  - Additional studies required for data on long-term benefits and safety
    - Phase III trials currently underway with data expected within next 3 years
Standard MDR-TB regimens currently recommended by WHO

- Intensive phase of 8 months treatment using at least 4 second line drugs with proven effectiveness plus PZA
  - Total treatment of 20 months
  - Recommendation on duration of treatment is subject to adaptation based on patient response to treatment


Shorter Regimens for MDR TB

Shorter regimens for MDR TB:

- Typically last 9-12 months (differs from standard WHO recommended 20 month MDR TB regimen)
- Less costly and likely to be better tolerated by patients
- Evidence on their use reported in Bangladesh with success rates comparable to those for treatment of drug-susceptible TB
- Being introduced by National TB Programs in African countries (Benin, Cameroon, Central African Republic, Cote d’Ivoire, DR Congo, Niger, Swaziland)
Treatment outcomes observed in Bangladesh for MDR-TB cases treated with a 9-month regimen

A regimen consisting of a minimum of 4 months of KmCfzGfxEHZPto, prolonged if necessary until conversion was achieved, followed by 5 months of GfxEZCfz, was reported to give high, relapse-free cure rate in MDR-TB patients [van Deun et al, 2010].

Completion 5.3%
Cure 82.5%
Death 5.35
Default 5.8%
Failure 0.5%
Relapse 0.5%

Km=kanamycin; Cfz=clofazimine; Gfx=gatifloxacin; E=ethambutol; H=high-dose isoniazid; Z=pyrazinamide; Pto=prothionamide

STREAM: standardized treatment regimen of Anti-TB drugs for patients with MDR TB

- Trial is currently taking place in Ethiopia, South Africa and Vietnam, India.
- Plan to recruit at least 400 patients with MDR-TB.
- High dose Fluoroquinolones and clofazimine with a 7 drug regimen for 9 months:
  - Moxi, colfazimine, ethambutol and PZA for 9 months, with supplemental prothionamide, kanamycin and INH during the 4 month intensive phase.
- The trial is expected to run for 2 years, with results available in 2016.
Indications for Surgery - 1

- Adequate 1\textsuperscript{st} and 2\textsuperscript{nd} -line regimens of anti-TB medications have failed to cure or cause \textit{M. tb} cultures to convert to negative within 4 to 6 months
- Sufficient medications are available to treat the patient postoperatively
- Disease is sufficiently localized to allow lobectomy or pneumonectomy
- Remaining lung tissue is relatively free of disease
- Acceptable surgical risk, with sufficient pulmonary reserve to tolerate the resection
Additional possible indications for surgery:

- Major bronchial obstruction
- Severe hemoptysis
- Bronchopleural fistula (BPF)
Surgery for MDR TB Patients

- Even after lung resection, the patient must complete a full course of treatment (i.e., 18-24 months after culture conversion) with medications to which the \textit{M.tb} strain is susceptible.

- If patient is culture negative after surgery, then surgery is considered the conversion episode.
Follow-up of MDR TB Patients after Treatment Completion

- Patients with TB resistant to INH and RIF or treated without RIF/RBT
  - Medical evaluation every 4 months during the 1\textsuperscript{st} year after treatment completion
  - Then every 6 months during the 2\textsuperscript{nd} year

- Months: 4, 8, 12, 18, 24 post treatment

- Educate about relapse and to return if they develop symptoms
Treatment of Contacts to Drug Resistant TB

- Persons exposed to INH-resistant TB:
  - Rifampin:
    - 4 months adults
    - 6 months children

- Persons likely infected with MDR TB:
  - 6-12 months PZA and EMB, or PZA and FQ (i.e., ≥ 2 drugs to which organism is susceptible)
    • Limited experience with FQ as single agent
Principles of Treatment in MDR TB Contacts

- **Always** exclude active TB disease before considering LTBI treatment
  - Evaluate all exposed contacts to identify all active cases and prevent further transmission

- Estimate likelihood of infection with an MDR TB strain

- Consider the risk of progression to active TB disease
  - HIV testing and counseling
Principles of Treatment in MDR TB Contacts

- Tailor LTBI treatment to individual case
  - Regimen should contain 1 to 2 drugs to which source case isolate is susceptible
  - Immunosuppressed individuals should not be treated with monotherapy

- Remember:
  - Efficacy of the regimen largely dependent on adherence and completion of therapy
  - Education of patients is important – adverse effects and importance of adherence
Management of Persons Exposed to Multidrug-Resistant Tuberculosis
# Potential Drug Regimens: Drug-Resistant Tuberculosis

<table>
<thead>
<tr>
<th>Resistance Pattern</th>
<th>LTBI Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>Adults: RIF 4 months; Children: RIF 6 months</td>
</tr>
<tr>
<td>INH, RIF</td>
<td>PZA/EMB or Fluoroquinolone +/- EMB or PZA</td>
</tr>
<tr>
<td>INH, RIF, EMB</td>
<td>Fluoroquinolone +/- PZA</td>
</tr>
<tr>
<td>INH, RIF, PZA</td>
<td>Fluoroquinolone +/- EMB</td>
</tr>
<tr>
<td>INH, RIF, PZA, EMB</td>
<td>Fluoroquinolone +/- Ethionamide*</td>
</tr>
<tr>
<td>INH, RIF, PZA, EMB, injectable</td>
<td>Fluoroquinolone +/- Ethionamide*</td>
</tr>
<tr>
<td>INH, RIF, PZA, EMB, injectable, ethionamide</td>
<td>Fluoroquinolone +/- Cycloserine</td>
</tr>
<tr>
<td>INH, RIF, PZA, EMB, fluoroquinolone</td>
<td>Cycloserine/PAS or PAS/Ethionamide or Ethionamide/Cycloserine</td>
</tr>
</tbody>
</table>

*Better tolerated in children than in adults.

Resources

- **CureTB**: Binational TB Referral Program for TB patients and their contacts who travel between the United States and Mexico
  http://www.curetb.org/

- **TBNet**: A multi-national TB patient tracking and referral project designed to work with mobile, underserved populations
  http://www.migrantclinician.org/network/tbnet

- **National Jewish Medical Center**
Resources

• MDR-TB Service
  - Provides clinical consultation, case management, CI assistance

• CA Microbial Diseases Lab
  - Provides MBs for drug resistance; phenotypic DST for first-line drugs and Amikacin, Levofloxacin, Capreomycin, and Ethionamide; genotyping
Acknowledgements

• CDC
• MDR TB experts at the Regional Training and Medical Consultation Centers
• WHO
Case # 1

• 35-year-old male with chronic cough x 6 months
• Diagnosed with TB in Mexico and treated with a standard four drug treatment regimen 1/97-7/97, but continued to be smear-positive in 1998
• Extensive TB treatment history and history of non-compliance with medications between 10/98-3/00
• Instituto Nacional de Enfermedades Respiratorias (INER) in Mexico City was consulted 3/00 and patient was placed on ethionamide, dapsone, RIF, PZA, and kanamycin from 3/3/00 to 2/01
Case # 1

• 10/00 the patient had a positive smear and culture and susceptibility testing reported 2/01 showed resistance to INH, PZA, and EMB

• Treatment regimen was changed to RIF 600 mg po qd, ethionamide 500 mg po qd, clofazimine 100 mg po qd, streptomycin 1 gram IM QD, erythromycin 300 mg po qd

• Had a positive smear 5/15/03 and was treated with INH/EMB (75mg/400mg) po TID, erythromycin 300 mg po TID, (tionitrozoana) thiocetazone 150 mg po qd, PZA 500 mg po TID

• Returned 9/19/03 and was found to be 5 + smear-positive; emigrated to the U.S. 11/03
Case # 1

- Found to be TST negative at a clinic in the U.S. 12/03 and he discontinued the last TB regimen which was prescribed in Mexico
Next steps

• Tell patient that he does not have TB
• Obtain QFT
• Take a good history, perform symptom review, CXR
• Take a good history, perform symptom review, CXR and obtain sputa for AFB smear and cx x 3
Case # 1

• Evaluated for chronic cough in LHD clinic in 3/04
• CXR obtained
Case # 1

• Found to have 4+ smear-positive, cavitary TB, hospitalized and placed in isolation
• Started initially on INH 300 mg po qd, RIF 600 mg po qd, EMB 1200 mg po qd, PZA 1000 mg po qd, and ethionamide 750 mg po qd on 3/4/04
• MDR-TB service consultation 4/01/04 because patient was on surgery schedule for right pneumonectomy
Recommendations?

- Advise immediate pneumonectomy
- Advise OR staff to wear N95 respirators and proceed with immediate pneumonectomy
- Advise a delay in surgery
- Wait until smear conversion and then proceed with pneumonectomy
- Wait until smear and culture conversion and then proceed with pneumonectomy
Case # 1

• Surgery delayed
• Patient placed empirically (based on treatment history) on moxifloxacin 400 mg po qd, PAS 4 grams bid, capreomycin 750 mg IM qd, cycloserine 250 mg po bid, and linezolid 600 mg po qd on 4/06/04
Case # 1

• Patient culture converted on 4/18/04
• Isolate found to be resistant to all first-line drugs, SM, augmentin, imipenem, clarithromycin, and clofazimine
• Smear negative 5/04
• Presented at San Francisco General Hospital (SFGH) TB case conference and felt to be a good candidate for surgery
• Transferred to SFGH Medical Center for right pneumonectomy on 7/15/04
Case # 1

- Pt feeling “better” since starting TB Rx’s in 4/04. On Directly Observed Therapy. No F/C/cough. Initially gained 12 kg 3/04 – 6/04
- Decreased bilateral hearing prior to starting TB medications (last audiogram 5/04)
- Physical Exam only notable for minimal breath sounds right base
- HIV negative. Capreomycin serum level = 48.3, cycloserine serum level = 35.6
- V/Q: near-complete absence of V&Q to R lung, 97% total to L lung. Right pneumonectomy 7/26
LUNG V/Q SCAN IMAGES - Posterior View

Xe-133 Ventilation Image  Tc-99m MAA Perfusion

97%  3%
Relative Per-cent of Perfusion

Left  Right  Left  Right
Case # 1
Case # 1

- The patient did very well post-operatively, ambulating with minimal pain medications
- Chest tube removed within 1 week
- Discharged to home within 2 weeks of surgery
- Doing well clinically with some weight loss post surgery (5kg)
- Continued on moxifloxacin 400 mg po qd, PAS 4 grams bid, capreomycin 750 mg IM qd, cycloserine 250 mg po bid, and linezolid 600 mg po qd on 4/06/04 all by DOT
Case # 1

• Patient is doing well with weight gain, reported to be asymptomatic, AFB smear, and culture-negative
• Capreomycin discontinued 3/29/05
• No further toxicities to medications
• Completed treatment in 2007
• Recent CXRs from 1/18/05 and 4/18/05
Preventing Acquired Drug Resistance, Case # 2

- 48 year old U.S.-born female, recent onset NIDDM
- Diagnosis 1/5/06 with cough, sputum, 40 lb. weight loss in another state
- 4 (+) AFB sputum, extensive bilateral disease with cavitation
- Treatment: 3 weeks “daily” IRZE given DOT M-F
  - No weekend doses
Case # 2

ADCCOMPACTPLUS
Ex:
PA Chest - 2 View PA GRID
Se: 1/2
Im: 1/1

CHEST

ADCCOMPACTPLUS
Ex:
PA Chest - 2 View LAT
Se: 2/2

CHEST

2006 Jan 01
Acq Tm: 14:28:40

Lat: R

Lin:DCM / Lin:DCM / Id:ID
SIZES ARE APPROXIMATE
W:4135 L:3933

Lin:DCM / Lin:DCM / Id:ID
SIZES ARE APPROXIMATE
W:3843 L:2290
Case # 2

• After 3 weeks, changed to t.i.w. DOT
• At start of week 4, DST = INH resistant
Treatment regimen?

- Continue HREZ tiw, five days a week
- Stop INH and continue REZ tiw, five days a week
- Change regimen to REZ daily by DOT five days a week
- Change regimen to REZ daily by DOT with weekend doses
- Change regimen to Moxi, REZ daily by DOT with weekend doses
Case # 2

- INH d/c’ed, but t.i.w. treatment continued
Case # 2

• Appropriate regimen
• Inappropriate regimen
Case # 2

• Culture still (+) June, 2006, now resistant to INH and Rifampin!

• Why did this patient acquire MDR-TB?
Case # 2

• Why did this patient acquire MDR-TB?
Case # 2

- Patient factors:
  - Extensive cavitary disease
  - 4 (+) AFB on smear
  - DM, with resultant immunocompromise
  - Debilitated state at diagnosis
Case # 2

- Programmatic factors:
  - Policy to give only 3 weeks daily therapy consisting of 15 doses (no option for patient to take weekend doses)
  - Continuing intermittent induction phase despite INH resistance
Case # 2

- DOT for all smear (+) and/or cavitary TB
- Daily therapy throughout induction phase if initial isolate is INH-resistant, or if patient is HIV (+)
- Reminder: CDC and ATS recommend intermittent therapy for drug susceptible TB, there is no recommendation to use intermittent therapy when resistance present
MDR-TB

Preventable!

Treatable!

Curable!
FDA Approval of BDQ

- MDR TB is orphan disease in USA: 98 pts in 2011
- Approved as an orphan drug 12/31/12
- Endpoint: sputum culture conversion
  - Mean culture conversion was 83 days compared to 125 days (79% of patients at 24 weeks)
- Found the drug efficacious
- Concerns about safety – Black Box Warning
  - ↑ risk of QT interval prolongation-can cause arrhythmia
  - ↑ number of deaths: 11.4% (9/79) compared to 2.5% (2/81)
QT Prolongation

- Drugs used to treat TB or NTMs
  - Fluoroquinolones
  - Clofazimine
  - Delaminid
  - PA-824 (nitroimidazol-oxazine)
  - Macrolides

- Electrolyte abnormalities: ↓K, Ca, Mg

- Other drugs that prolong QT interval

- History of Torsade de Pointes

- History of congenital prolonged QT syndrome

- History of hypothyroidism, bradyarrhythmias, uncompensated heart failure

- This effect can be additive
Other Clinically Relevant Information

- EKG at baseline and at least 2, 12, and 24 weeks after starting Bedaquiline
- Serum electrolytes, Ca and Mg
- Monitor LFTs
  - Avoid alcohol and hepatotoxic drugs
- Metabolized by CYP3A4-therapeutic effect may be reduced with inducers of CYP3A4
  - Rifamycins
  - Limited data on HIV/MDR TB co-infected patients
Dosage and Administration

- Given for 24 weeks with an individualized MDR background regimen
  - At least 3 drugs to which isolate susceptible
  - Must be given under DOT
- Should be taken with food
- Oral tablets 100 mg each
  - Weeks 1-2: 400 mg once a day (4 tablets)
  - Weeks 3-24: 200 mg (2 tablets together) 3x/wk
    - At least 48 hours between doses
    - Total dose of 600 mg/week