The Generation of MDR-TB

• Resistance to TB medications is due to chromosomal mutations.
• There is no transmissible resistance factor as is seen in other bacteria (e.g. gram negative rods or some gram positives)
• The mutations occur as independent events and are not associated.
• Mutations occur at low but predictable frequencies $1 \text{ per } 10^{-6} \text{ to } 10^{-8}$ replications.
  – The probability of a bacteria acquiring resistance to two drugs is the product of independent events.
The Creation of MDR-TB

• Because these spontaneous chromosomal mutations rarely occur in the same bacteria, the use of multiple medications protects against acquired resistance.

• Mutations conferring resistance to drug A (e.g. INH) are killed by drug B (Rif) and mutations resistant to drug B (Rif) are killed by drug A (INH)
## MUTATION RATES AND PREVALENCES

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Mutation Rate</th>
<th>Prevalence of Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>$1.8 \times 10^{-8}$</td>
<td>$3.1 \times 10^{-6}$</td>
</tr>
<tr>
<td>Rifampin</td>
<td>$2.2 \times 10^{-10}$</td>
<td>$1.2 \times 10^{-8}$</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>$2.9 \times 10^{-8}$</td>
<td>$3.8 \times 10^{-6}$</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>$1.0 \times 10^{-7}$</td>
<td>$3.1 \times 10^{-5}$</td>
</tr>
</tbody>
</table>
Conditions that select for MDR-TB

• Spontaneous occurrence of a mutant resistant to both Isoniazid and Rifampin would be uncommon: roughly in $10^{-18}$
  
  \[
  \text{the product of } 10^{-8} \times 10^{-10} = 10^{-18}
  \]

• Conditions that increase this possibility are:
  – Low drug levels
  – High numbers of bacilli

Need to ensure proper regimens at appropriate dosages
Generation of MDR-TB: Inadequate therapy

Low levels of drug is most often caused by:

• Patient inability to take the medications
• Physician error
• Lack of drug availability
• Malabsorption

Need to use a systematic approach to designing regimens and delivering care, and have close oversight of patients
• Cavitary lesions contain roughly $10^8$ organisms
  – Rapidly dividing
  – Robust
• Anti-mycobacterial agents may be present at low levels

Need to diagnose TB early before patients advance to cavitary disease
Acquired Resistance to Multiple Drugs: Sequential Mutations

• Acquired resistance is more commonly seen in patients with long standing TB
  – Presence of cavitary lung disease in which large numbers of bacilli proliferate rapidly.
  – Exposure to multiple previous regimens.

• Once patients acquire resistance to a single drug they can then acquire a second spontaneous mutation that confers additional resistance.

Need to ensure that the patient is put on the correct treatment the first time
Transmission and Primary Resistance

• Once a patient has acquired drug resistance the drug resistant strain can be transmitted to close contacts.

• A person who first contracts an already resistant strain is said to have “primary” drug resistance.
DESIGNING A PROPER TREATMENT REGIMEN
Treatment of TB: WHO Category I

- Four drug combination of isoniazid (H), rifampin (R), ethambutol (E) and pyrazinamide (Z) for 6 months given under direct observation and with assistance (incentives, enablers, accompaniment).

- Never use a single agent (mutation rate ~ $1 \times 10^6$ to $1 \times 10^8$ organisms; a typical cavity has $1 \times 10^9$ to $1 \times 10^{10}$ organisms)

First-line

- **INH (H)** — SIX MONTHS
- **RIF (R)** — SIX MONTHS
- **EMB (E)** — TWO MONTHS
- **PZA (Z)** — TWO MONTHS

**2HREZ / 4HR**
The Amplifier Effect of Inadequate Therapy

H R E Z

DOTS

likely
cure
The Amplifier Effect of Inadequate Therapy
The Amplifier Effect of Inadequate Therapy
The Amplifier Effect of Inadequate Therapy

+ heavy mycobacterial burden
+ significant parenchymal destruction
## Previously Treated*: WHO Category II

<table>
<thead>
<tr>
<th>First-line</th>
<th>Injectable</th>
<th>EXPOSED</th>
</tr>
</thead>
<tbody>
<tr>
<td>• INH (H)</td>
<td>EIGHT MONTHS</td>
<td></td>
</tr>
<tr>
<td>• RIF (R)</td>
<td>EIGHT MONTHS</td>
<td></td>
</tr>
<tr>
<td>• EMB (E)</td>
<td>EIGHT MONTHS</td>
<td></td>
</tr>
<tr>
<td>• PZA (Z)</td>
<td>THREE MONTHS</td>
<td></td>
</tr>
<tr>
<td>• SM</td>
<td>TWO MONTHS</td>
<td></td>
</tr>
</tbody>
</table>

**RISK OF SUB-STANDARD THERAPY**

2HREZS / 1HREZ / 5HR

* Failures, relapses and previous defaults (treated for at least one month)
### Multi-drug Resistant Tuberculosis (MDR-TB)

<table>
<thead>
<tr>
<th>First-line</th>
<th>Second-line</th>
<th>Third-line</th>
</tr>
</thead>
<tbody>
<tr>
<td>• INH (H)</td>
<td>Injectable</td>
<td></td>
</tr>
<tr>
<td>• RIF (R)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• EMB (E)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• PZA (Z)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Injectable**
  - • SM
  - • KM
  - • AMK
  - • CM

- **Fluoroquinolone**
  - • OFLOX
  - • LEVO
  - • CPX
  - • MOXI
  - • GATI

- **Other 2nd-line**
  - • ETH
  - • CS
  - • PAS

- **Other agents**
  - • AMX/CLV
  - • Clofazamine
  - • Clarithromycin
  - • Thiacetazone

- **At least 4 active drugs** (with one from each class if possible)
- Previously used/exposed drugs should be viewed with suspicion
Extensively-drug Resistant TB (XDR-TB)

First-line
- INH (H)
- RIF (R)
- EMB (E)
- PZA (Z)

Second-line
- Injectable
- SM
- KM
- AMK
- CM
- OFLOX
- LEVO
- CPX
- MOXI
- GATI
- ETH
- CS
- PAS

Third-line
- AMX/CLV
- Clofazamine
- Clarithromycin
- Other agents
Approach to MDR-TB Therapy

- Identification of MDRTB patients
- Clinical evaluation of MDRTB patients
- Elaboration of an empiric MDR-TB regimen
- Institution of directly observed therapy
- Interpretation of drug susceptibility testing
- Design of definitive MDR-TB regimen
- Surveillance of treatment efficacy
- Determining duration of treatment
- Aggressive side-effect management
- Adjunctive options - surgery
Principles of DOTS-Plus regimen design

• Include first-line drugs to which infecting strain is susceptible
• Include a minimum of four effective drugs
• Utilize parenteral therapy for a minimum of 6 months (ideally 6 months after culture conversion)
• Do not rely on drugs to which resistance is suspected or to which the patient has been previously exposed
• Observe all doses
• Aggressively treat all side effects
Principles of DOTS-Plus regimen design

• When designing a regimen, think of the drugs in five groups:
  – Group 1: Oral first line drugs
  – Group 2: Injectable agents
  – Group 3: Fluoroquinolones
  – Group 4: Weakly or non-bactericidal oral second line agents
  – Group 5: Agents active in vitro but limited data on in vivo activity or third line agents.
Principles of DOTS-Plus regimen design

First-line drugs

• INH
• RIF
• PZA
• EMB

• Whenever possible, include first-line drugs. These are considered the most efficacious and best tolerated.
• Use maximum doses
• High-dose INH (900 mg PO twice weekly) may be used in cases of resistance at low concentrations
Aminoglycosides and capreomycin are bactericidal and should be included whenever possible.

Maximum doses

Ideally until culture negative for six consecutive months

**First line**
- INH
- RIF
- PZA
- EMB

**Injectable**
- SM
- KM
- AMK
- CM
Principles of DOTS-Plus regimen design

First-line drugs
- INH
- Rifampicin (RIF)
- Pyrazinamide (PZA)
- Ethambutol (EMB)

Injectable
- SM
- KM
- AMK
- CM

Fluoroquinolone
- OFLOX
- LEVO
- CPX
- MOXI
- GATI

- Fluoroquinolones (FQ) are highly bactericidal second-line drugs.
- Include whenever infecting strain is susceptible to FQ.
- Cross-resistance is believed not to be complete among Fluoroquinolones.
First-line drugs
• INH
• RIF
• PZA
• EMB

Injectable
• SM
• KM
• AMK
• CM

Fluoroquinolone
• OFLOX
• LEVO
• CPX
• MOXI
• GATI

2nd-line
• ETH
• CS
• PAS

Second-line drugs considered less efficacious than FQs
Maximum doses tolerated
First-line drugs
- INH
- RIF
- PZA
- EMB

Injectable
- SM
- KM
- AMK
- CM

Fluoroquinolone
- OFLOX
- LEVO

2nd-line
- ETH

Other agents
- AMX/CLV
- Clofazamine
- Clarithromycin
- Thiacetazone
Clinical Case:

TK is a 28 year-old failure of category I and has never had DST done. She has no known contacts.

What regimen do you use?
WE PUT HER ON THE FOLLOWING REGIMEN:

AND SENT HER SPUTUM FOR CULTURE AND DST...
Two months after you start therapy, the DST results arrives and the patient is doing poorly and is still smear positive

Resistant = H,R,E, Z, SM ,KM, Ethio
Sensitive = CM, Ofloxacin, CS, PAS

What Regimen do you design?
- Isoniazid (INH)
- Rifampin (RIF)
- Ethambutol (EMB)
- Pyrazinamide (PZA)
- Streptomycin (SM)
- Kanamycin (KM)
- Capreomycin (CM)
- Amikacin (AMK)
- Quinolones (LVX, MOX, OFX)
- Ethionamide (THA)
- Cicloserine (CS)
- Para-aminosalicylic Acid (PAS)
- Clofazimine (CFZ)
- Amoxicillin/Clavulanate (AMX-CLV)
- Clarithromycin (CLR)
• Isoniazid (INH)
• Rifampin (RIF)
• Ethambutol (EMB)
• Pyrazinamide (PZA)
• Streptomycin (SM)
• Kanamycin (KM)
• Capreomycin (CM)
• Amikacin (AMK)
• Quinolones (LVX, MOX, OFX)
• Ethionamide (THA)
• Cicloserine (CS)
• Para-aminosalicylic Acid (PAS)
• Clofazimine (CFZ)
• Amoxicillin/Clavulanate (AMX-CLV)
• Clarithromycin (CLR)
• Isoniazid (INH)
• Rifampin (RIF)
• Ethambutol (EMB)
• Pyrazinamide (PZA)
• Streptomycin (SM)
• Kanamycin (KM)
• Capreomycin (CM)
• Amikacin (AMK) Possible Cross Resistance
• Quinolones (LVX, MOX, OFX)
• Ethionamide (THA)
• Cicloserine(CS)
• Para-aminosalicylic Acid (PAS)
• Clofazimine (CFZ)
• Amoxicillin/Clavulanate(AMX-CLV)
• Clarithromycin (CLR)
- Isoniazid (INH)
- Rifampin (RIF)
- Ethambutol (EMB)
- Pyrazinamide (PZA)
- Streptomycin (SM)
- Kanamycin (KM)
- Capreomycin (CM)
- Amikacin (AMK) (R?)
- Quinolones (LVX, MOX, OFX)
- Ethionamide (THA)
- Cicloserine (CS)
- Para-aminosalicylic Acid (PAS)
- Clofazimine (CFZ)
- Amoxicillin/Clavulanate (AMX-CLV)
- Clarithromycin (CLR)
- Isoniazid (INH)
- Rifampin (RIF)
- Ethambutol (EMB)
- Pyrazinamide (PZA)
- Streptomycin (SM)
- Kanamycin (KM)
- Capreomycin (CM)
- Amikacin (AMK) (R?)
- Quinolones (LVX, MOX, OFX) LVX
- Ethionamide (THA)
- Cicloserine (CS) CS
- Para-aminosalicylic Acid (PAS) PAS
- Clofazimine (CFZ)
- Amoxicillin/Clavulanate (AMX-CLV)
- Clarithromycin (CLR)
• Isoniazid (INH)
• Rifampin (RIF)
• Ethambutol (EMB)
• Pyrazinamide (PZA)
• Streptomycin (SM)
• Kanamycin (KM)
• Capreomycin (CM)
• Amikacin (AMK)
• Quinolones (LVX, MOX, OFX)
• Ethionamide (THA)
• Cicloserine (CS)
• Para-aminosalicylic Acid (PAS)
• Clofazimine (CFZ)
• Amoxicillin/Clavulanate (AMX-CLV)
• Clarithromycin (CLR)

WE PUT HER ON THE FOLLOWING REGIMEN:

CM-LVX-CS-PAS-AMX/CLV

If we had put her on H-R-E-Z-S she would have FAILED TREATMENT

If we had added LVX+KM we would have amplified resistance to include LVX
CASE EXAMPLE: RUSSIAN PRISONER
Patient History

- Patient GV
- Born June 27, 1975
- First diagnosed with TB in February 1997 in the Tomsk prison during a routine x-ray
- His weight was 59 kg with a height of 178 cm
Patient GV: Admission X-ray
Patient History Continued…

- Drug sensitivity testing (DST) showed patient was susceptible to all first-line drugs

- Per local practice, GV was treated with first-line drugs for 11 months from February until November 1997

<table>
<thead>
<tr>
<th>First-line</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH (H)</td>
<td>9 months</td>
</tr>
<tr>
<td>RIF (R)</td>
<td>9 months</td>
</tr>
<tr>
<td>EMB (E)</td>
<td>2 months</td>
</tr>
<tr>
<td>PZA (Z)</td>
<td>2 months</td>
</tr>
</tbody>
</table>

2HREZ / 9HR
• Patient GV was initially feeling fine after completing treatment and was released from prison

• 3 months later he started having fevers, chills and cough

• He noticed blood in his sputum

• Visited the TB physician in February 1998

• His weight had dropped to 53 kg (from 59 kg at start)
Patient History Continued…

- Following international guidelines, GV was treated with WHO category II treatment (2HREZS / 1HREZ / 5HRE) starting in February 1998.
- Drug sensitivity testing from March 1998 (received in May 1998) showed that he was resistant to H and R.

**First-line** + **Injectable**

- **INH (H)**: EIGHT MONTHS
- **RIF (R)**: EIGHT MONTHS
- **EMB (E)**: EIGHT MONTHS
- **PZA (Z)**: THREE MONTHS
- **SM**: TWO MONTHS

2HREZS / 1HREZ / 5HR
• In May 1998, GV was found to still be sputum smear positive
• He continued to have fever and night sweats
• His weight dropped to 49 kg (from 59 kg at start of treatment)
• The TB services ran out of streptomycin and decided to treat him with kanamycin (another aminoglycoside) instead
• He was started on a locally-modified regimen of 3HREZK / 6HREZ in May 1998
• GV continued to have fevers, night sweats, and weight loss over the next six months; his weight dropped to 43 kg (from 59 kg)
• A repeat DST in December of 1998 showed a TB strain resistant to H-R-E-Z-SM-KM

Patient History Continued…

First-line

- INH (H)
- R (R)
- EMB (E)
- PZA (Z)

Injectable

- M
- KM
- XMK
- CM

FQ

Oflox
Levo
Moxi

2nd-line

ETH
CS
PAS
• There were not enough second-line anti-TB drugs available to create a full treatment regimen for MDR-TB, so no appropriate therapy could be provided

• Patient GV was hospitalized in the “chronic ward” and continued on a treatment of HRE indefinitely

First-line

- INH (H)
- RIF (R)
- EMB (E)
In November of 2000 (after almost two years without therapy), second-line anti-TB medications became available.

He was started on the following regimen:

First-line

- INH (H)
- RFP (R)
- EMB (E)
- PZA (Z)

Injectable

- SM
- KM
- AMK
- CM

FQ

- Oflox

2nd-line

- ETH
- CS
- PAS
In early December, GV developed severe nausea and vomiting followed by cramps and seizures.

His Cr was 2.3 (upper limit of normal for men is ~1.5) and his potassium was approximately 6.2. He was diagnosed with renal failure and hyperkalemia.

He was unable to breathe and was started on steroids.

All of his second-line anti-TB medications were stopped.

Patient GV died on December 21, 2000.

**Cause of death:** drug-resistant tuberculosis complicated by renal failure and hyperkalemia
THANK YOU