MODULE THREE

TB Treatment

Treatment Action Group
TB/HIV Advocacy Toolkit
Topics to be covered

• TB treatment fundamentals
• Treatment of TB infection and disease
• TB treatment research
• Advocacy issues
Section 1: TB treatment fundamentals
Goals of TB treatment

- The goals of TB treatment are:
  - to reduce infectiousness
  - to restore health
  - to cure disease
  - to preserve life
  - to prevent relapse
  - to prevent the emergence of drug resistance
Tuberculosis drug discovery/development and its impact on treatment

- Streptomycin/PAS
- Thioacetazone
- Isoniazid
- Cycloserine
- Pyrazinamide
- Kanamycin/amikacin
- Rifampin
- Ethionamide
- Capreomycin
- Ethambutol

Duration of therapy:
- 1944: 24 months
- 1946: 6 months
- 1952: 6 months
- 1955: 6 months
- 1956: 6 months
- 1957: 6 months
- 1965: 6 months
- 1966: 6 months
- 1967: 6 months
- 1968: 6 months
Principles of TB treatment

• The aim of treatment is to provide the safest and most effective therapy in the shortest period of time.

• Three basic principles of TB treatment:
  1. Regimens must contain multiple drugs to which the organisms are susceptible.
  2. The drugs must be taken regularly.
  3. Drug therapy must continue long enough to kill all remaining TB organisms.
Monitoring TB treatment

• Bacteriologic tests detect TB bacteria
  – Smear microscopy
  – Solid and liquid culture

• Clinical monitoring of improvement TB symptoms (e.g., weight loss)

• Radiography relies on chest X-rays
Section 2: Treating TB infection and disease
How do we treat TB?

• Preexposure preventive therapy
  -targets close contacts of someone diagnosed with active TB disease

• Treatment of latent TB infection (LTBI)

• Treatment of drug-sensitive active TB disease

• Treatment of drug-resistant active TB disease
Treating latent TB infection

- 6 months of daily isoniazid (INH) preventive therapy (IPT) is recommended by the WHO for the treatment of LTBI in children and adults.

- There are limited data on alternative regimens for people who are unable to take INH either because of intolerance or resistance, and for contacts of drug-resistant TB contacts.
First-line drugs used to treat drug-susceptible TB

<table>
<thead>
<tr>
<th>Drug</th>
<th>Abbreviation</th>
<th>Initial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>INH</td>
<td>H</td>
</tr>
<tr>
<td>Rifampin*</td>
<td>RIF or RMP</td>
<td>R</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>PZA</td>
<td>Z</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>EMB</td>
<td>E</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>SM</td>
<td>S</td>
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</tbody>
</table>
Treating drug-susceptible TB

• There are two phases of treatment for drug-susceptible TB:
  1. The **initial phase** of treatment is designed to kill actively growing and semi-dormant bacilli.
  2. The **continuation phase** eliminates most (or all) residual bacilli and reduces failures and relapses.
Treating drug-susceptible TB

- The WHO recommends that:
  - New patients with pulmonary TB receive 2 months of isoniazid/rifampin/pyrazinamide/ethambutol followed by 4 months of isoniazid and rifampin or “2HRZE/4RH”
  - Patients with extrapulmonary TB receive streptomycin in place of ethambutol, followed by 4 months of isoniazid and rifampin or “2HRZS/4RH”
  - Retreatment regimens add streptomycin during intensive phase followed, by 1 month of isoniazid/rifampin/pyrazinamide/ethambutol followed by 5 months of isoniazid/rifampin/ethambutol or “2HRZES/1HRZE/5HRE”

*Controversial: if case is resistant, simply adding a fifth drug will only lead to further resistance*
Treating drug-resistant TB

What is multidrug-resistant TB (MDR-TB)?

What is extensively drug-resistant TB (XDR-TB)?
Treating drug-resistant TB

- Drug resistant TB regimens are, ideally, individualized based on drug susceptibility testing (DST).
- When DST is not available, the regimen may be standardized depending on national surveillance data.
  - Standardized treatment regimens are designed on the basis of representative drug resistance surveillance data.
  - Some regimens are standardized until DST results are available, and then treatment is individualized based on results.
- Individualized regimens are designed on the basis of previous TB treatment history and individual DST results.
Why aren’t these drugs sufficient?

• Adherence issues
• Duration of treatment
• Potentially toxic side effects
• Drug availability and quality
• Drug interactions
• Poor cure rates for MDR-TB and XDR-TB
• Little to no evidence on how to treat pediatric TB
Treatment issues: TB/HIV coinfection

• Contraindication of rifampin-based regimens and antiretrovirals
• When to start antiretroviral therapy (ART)
• Risk for immune reconstitution inflammatory syndrome (IRIS)
Treatment issues: childhood TB

- Increased risk for disease progression.
- Lack of evidence to guide correct dosing for infants and children.
- Age and development differences.
- Lack of pediatric formulations.
- Assessing adverse events.
- Difficulty diagnosing and monitoring treatment.
- Uncertainty about the appropriate time to involve children in drug development, and optimal trial designs.
Treatment issues: opioid substitution therapy (OST)

- Methadone and buprenorphine are the most commonly used medications in OST.
- Rifampin can lead to a reduction in circulating methadone and buprenorphine levels, possibly requiring a substantially increased dose.
- There are no reported interactions between methadone and rifabutin.
Section 4:
TB treatment research
TB drug development process

• Preclinical (conducted in laboratories)
  – In vitro (in test tubes).
  – Animal models.

• Clinical trials (conducted in humans)
  – Phase I may evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and early bactericidal activity of a drug.
  – Phase II may evaluate safety and dosing in a larger group of volunteers.
  – Phase III evaluate the efficacy of the drug in a larger group of volunteers.
  – Phase IV: postmarketing.
New drugs in clinical trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Developer</th>
<th>Phase</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZD5847</td>
<td>Oxazolidinone</td>
<td>AstraZeneca</td>
<td>Phase I</td>
<td>To be determined</td>
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<tr>
<td>PNU100480</td>
<td>Oxazolidinone</td>
<td>Pfizer</td>
<td>Phase II</td>
<td>DR-TB</td>
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<tr>
<td>SQ109</td>
<td>Diamine</td>
<td>Sequella/ PanACEA</td>
<td>Phase II</td>
<td>DS- and DR-TB</td>
</tr>
<tr>
<td>PA824</td>
<td>Nitroimidazole</td>
<td>TB Alliance</td>
<td>Phase II</td>
<td>DS- and DR-TB</td>
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<tr>
<td>OPC67683*</td>
<td>Nitroimidazole</td>
<td>Otsuka</td>
<td>Phase II/III</td>
<td>DR-TB</td>
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<tr>
<td>TMC207**</td>
<td>Diarylquinoline</td>
<td>Tibotec/TB Alliance</td>
<td>Phase II</td>
<td>DS- and DR-TB</td>
</tr>
</tbody>
</table>

*OPC 67683 is also referred to as delamanid
*TMC207 is also referred to as bedaquiline

As of December 2011
2010 funding for TB treatment research - $230,540,443

Global Plan target - $740,000,000

- BMGF: $41,871,408 (18%)
- US NIAID, NIH: $20,707,825 (9%)
- Otsuka: $63,648,753 (28%)
- US Other NIH ICs: $5,290,414 (2%)
- USAID: $7,046,029 (3%)
- EC: $7,670,696 (3%)
- UK DfID: $10,775,450 (5%)
- US CDC: $10,968,228 (5%)
- AstraZeneca: $14,023,381 (6%)
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Section 4: Advocacy issues
Advocacy issues

• Research institutions and funders need to ensure the inclusion of people with HIV, children and pregnant women in operational and clinical studies.

• Basic science, later stage clinical trials, and operational research need to be adequately funded.

• The regulatory pathway needs to be defined and harmonized across countries and regions to accelerate the approval of promising treatments.

• Ensuring expanded access/compassionate use to promising treatments preapproval to those in desperate need while ensuring appropriate use of the drugs.
Brief review

• Name a short-term and long-term goal of TB treatment.
• Name the three basic principles of TB treatment.
• Name one method used to monitor TB treatment response.
• Name three types of TB treatment offered.
• What are the two phases of treatment for drug-susceptible TB?
• Name two issues to consider in treating TB/HIV coinfection
• What are the phases of TB research?
• According to The Global Plan to Stop TB 2011-2015 how much investment is needed in TB research to eliminate as public health threat?