The microbiological fundamentals of TB therapy were established between 1950 and 1970.

• **The first principle attempts to respond to the large number of multiplying bacilli present in the tissue of a diseased host, and to the ability of *M. tuberculosis* to mutate after multiple divisions.**

  Thus, several drugs must always be used in combination in order to avoid the development of drug-resistant mutants that can undermine the efficacy of a medication.

• **The second principle attempts to respond to the variable growth capacity of *M. Tuberculosis* in different locations within lesions, which varies depending on metabolic status.**

  For this reason, extended treatments are needed, to allow treatments to act upon the latent bacterial populations that divide very little during treatment because the prevalent surrounding environmental conditions are not conducive for proliferation.
Bacillary populations of *M. tuberculosis*

- Metabolically active and under conditions of continuous growth
- Bacilli in the acid-inhibition phase
- Bacilli in the sporadic multiplication phase
- Persistent or totally dormant populations
Estimated bacterial populations within different TB lesions.

- Smear-positive TB $10^7$-$10^9$ bacilli
- Cavitary $10^7$-$10^9$ bacilli
- Infiltrating $10^4$-$10^7$ bacilli
- Nodules $10^4$-$10^6$ bacilli
- Adenopathies $10^4$-$10^6$ bacilli
- Renal TB $10^7$-$10^9$ bacilli
- Extrapulmonary TB $10^4$-$10^6$ bacilli
TABLE 9. Antituberculosis drugs currently in use in the United States

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

* Not approved by the Food and Drug Administration for use in the treatment of tuberculosis.
Number of bacilli required for the appearance of a mutant resistant to different drugs

- Isoniazide $1 \times 10^5 - 10^6$
- Rifampicin $1 \times 10^7 - 10^8$
- Streptomycin $1 \times 10^5 - 10^6$
- Ethambutol $1 \times 10^5 - 10^6$
- Pyrazinamide $1 \times 10^2 - 10^4$
- Quinolones $1 \times 10^5 - 10^6$
- Others $1 \times 10^3 - 10^6$
Deciding To Initiate Treatment

- Epidemiologic information
- Clinical, pathological, and radiographic findings
- The results of microscopic examination of acid-fast bacilli (AFB)-stained sputum (smears)
- Cultures for mycobacteria.
- A purified protein derivative (PPD)-tuberculin skin test may be done at the time of initial evaluation,
- A negative PPD-tuberculin skin test does not exclude the diagnosis of active tuberculosis.
- However a positive PPD-tuberculin skin test supports the diagnosis of culture-negative pulmonary tuberculosis, as well as latent tuberculosis
Deciding To Initiate Treatment

- If the suspicion of tuberculosis is high or the patient is seriously ill with a disorder, either pulmonary or extrapulmonary, that is thought possibly to be tuberculosis.
- For the diagnosis of tuberculosis. If the diagnosis is confirmed by isolation of M. tuberculosis or a positive nucleic acid amplification test, treatment can be continued to complete a standard course of therapy.
- If the suspicion of tuberculosis is high and the smears or cultures are negative and other disease is excluded then empirical combination therapy should be initiated and if there is a clinical or radiographic response within 2 months of initiation of therapy and no other diagnosis has been established, a diagnosis of culture-negative pulmonary tuberculosis can be made.
**TABLE 7. Priority situations for the use of directly observed therapy**

1. Patients with the following conditions/circumstances:
   - Pulmonary tuberculosis with positive sputum smears
   - Treatment failure
   - Drug resistance
   - Relapse
   - HIV infection
   - Previous treatment for either active tuberculosis or latent tuberculosis infection
   - Current or prior substance abuse
   - Psychiatric illnesses
   - Memory impairment
   - Previous nonadherence to therapy

2. Children and adolescents
Treatment of patients with tuberculosis

• Each regimen has an initial phase of 2 months followed by a choice of several options for the continuation phase of either 4 or 7 months.

• Because of the relatively high proportion of adult patients with tuberculosis caused by organisms that are resistant to isoniazid, four drugs are necessary in the initial phase for the 6-month regimen to be maximally effective.

• The treatment regimen for all adults with previously untreated tuberculosis should consist of a 2-month initial phase of: isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB).
Treatment of patients with tuberculosis

- If drug susceptibility test results are known and the organisms are fully susceptible, EMB need not be included.
- If PZA cannot be included in the initial phase of treatment,
- Or if the isolate is resistant to PZA alone (an unusual circumstance), the initial phase should consist of INH, RIF, and EMB given daily for 2 months.
- Examples of circumstances in which PZA may be withheld include:
  - Severe liver disease
  - Gout
  - Pregnancy
Treatment of patients with tuberculosis

Although clinical trials have shown that the efficacy of streptomycin (SM) is approximately equal to that of EMB in the initial phase of treatment, the increasing frequency of resistance to SM globally has made the drug less useful.

SM is not recommended as being interchangeable with EMB unless the organism is known to be susceptible to the drug or the patient is from a population in which SM resistance is unlikely.

For children whose visual acuity cannot be monitored, EMB is usually not recommended except when there is an increased likelihood of the disease being caused by INH-resistant organisms or when the child has "adult-type" (upper lobe infiltration, cavity formation) tuberculosis
Baseline and Follow-Up Evaluations

Patients suspected of having tuberculosis should have appropriate specimens collected for microscopic examination and mycobacterial culture.

Susceptibility testing for INH, RIF, and EMB should be performed on a positive initial culture, regardless of the source of the specimen.

It is recommended that all patients with tuberculosis have counseling and testing for HIV infection, for hepatitis B or C viruses (e.g., injection drug use).

For all adult patients baseline measurements of serum amino transferases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]), bilirubin, alkaline phosphatase, and serum creatinine and a platelet count should be obtained. Testing of visual acuity and red-green color discrimination should be obtained when EMB is to be used.
Treatment of patients with tuberculosis
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drugs</th>
<th>Initial phase</th>
<th>Continuation phase</th>
<th>Range of total doses (minimal duration)</th>
<th>Rating* (evidence)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Interval and doses‡ (minimal duration)</td>
<td>Interval and doses§ (minimal duration)</td>
<td>HIV−</td>
<td>HIV+</td>
</tr>
<tr>
<td>1</td>
<td>INH</td>
<td>Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)¶</td>
<td>1a INH/RIF</td>
<td>Seven days per week for 126 doses (18 wk) or 5 d/wk for 90 doses (18 wk)¶</td>
<td>182–130 (26 wk)</td>
</tr>
<tr>
<td></td>
<td>RIF</td>
<td></td>
<td>1b INH/RIF</td>
<td>Twice weekly for 36 doses (18 wk)</td>
<td>92–76 (26 wk)</td>
</tr>
<tr>
<td></td>
<td>PZA</td>
<td></td>
<td>1c** INH/RPT</td>
<td>Once weekly for 18 doses (18 wk)</td>
<td>74–58 (26 wk)</td>
</tr>
<tr>
<td></td>
<td>EMB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>INH</td>
<td>Seven days per week for 14 doses (2 wk), then twice weekly for 12 doses (6 wk) or 5 d/wk for 10 doses (2 wk), then twice weekly for 12 doses (6 wk)</td>
<td>2a INH/RIF</td>
<td>Twice weekly for 36 doses (18 wk)</td>
<td>62–58 (26 wk)</td>
</tr>
<tr>
<td></td>
<td>RIF</td>
<td></td>
<td>2b** INH/RPT</td>
<td>Once weekly for 18 doses (18 wk)</td>
<td>44–40 (26 wk)</td>
</tr>
<tr>
<td></td>
<td>PZA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EMB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>INH</td>
<td>Three times weekly for 24 doses (8 wk)</td>
<td>3a INH/RIF</td>
<td>Three times weekly for 54 doses (18 wk)</td>
<td>78 (26 wk)</td>
</tr>
<tr>
<td></td>
<td>RIF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PZA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EMB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>INH</td>
<td>Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)¶</td>
<td>4a INH/RIF</td>
<td>Seven days per week for 217 doses (31 wk) or 5 d/wk for 155 doses (31 wk)¶</td>
<td>273–195 (39 wk)</td>
</tr>
<tr>
<td></td>
<td>RIF</td>
<td></td>
<td>4b INH/RIF</td>
<td>Twice weekly for 62 doses (31 wk)</td>
<td>118–102 (39 wk)</td>
</tr>
<tr>
<td></td>
<td>EMB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
OPTIMUM DURATION OF THERAPY

• The 4-month continuation phase should be used in the large majority of patients
• The continuation phase may be given daily, two times weekly by DOT, or three times weekly by DOT.
• For human immunodeficiency virus (HIV)-seronegative patients with noncavitary pulmonary tuberculosis, and negative sputum smears at completion of 2 months of treatment the continuation phase may consist of rifapentine and INH given once weekly
OPTIMUM DURATION OF THERAPY

• The 7-month continuation phase is recommended only for three groups:
  1) Patients with cavitary pulmonary tuberculosis caused by drug-susceptible organisms and whose sputum culture obtained at the time of completion of 2 months of treatment is positive
  2) Patients whose initial phase of treatment did not include PZA
  3) Patients being treated with once weekly INH and rifapentine and whose sputum culture obtained at the time of completion of the initial phase is positive
OPTIMUM DURATION OF THERAPY

• The once-weekly continuation phase is contraindicated in patients with HIV infection because of an unacceptable rate of failure/relapse, often with rifamycin-resistant organisms.

• For the same reason twice weekly treatment, either as part of the initial phase or continuation phase is not recommended for HIV-infected patients with CD4+ cell counts <100 cells/µl.

• These patients should receive either daily (initial phase) or three times weekly (continuation phase) treatment.
Treatment in special situations

- HIV infection
- Children
- Liver disease
- Pregnancy and breastfeeding
- Renal disease and end stage renal failure
- Extrapulmonary Tuberculosis
- Culture negative pulmonary TBC with radiographic evidence of prior pulmonary TBC
<table>
<thead>
<tr>
<th>Site</th>
<th>Length of therapy (mo)</th>
<th>Rating (duration)</th>
<th>Corticosteroids †</th>
<th>Rating (corticosteroids)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node</td>
<td>6</td>
<td>AI</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
<tr>
<td>Bone and joint</td>
<td>6–9</td>
<td>AI</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
<tr>
<td>Pleural disease</td>
<td>6</td>
<td>AI</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>6</td>
<td>AI</td>
<td>Strongly recommended</td>
<td>AI</td>
</tr>
<tr>
<td>CNS tuberculosis including meningitis</td>
<td>9–12</td>
<td>BIII</td>
<td>Strongly recommended</td>
<td>AI</td>
</tr>
<tr>
<td>Disseminated disease</td>
<td>6</td>
<td>AI</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>6</td>
<td>AI</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>6</td>
<td>AI</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
</tbody>
</table>

† For rating system, see Table 1.

‡ Duration of therapy for extrapulmonary tuberculosis caused by drug-resistant organisms is not known.

§ Corticosteroid preparations vary among studies. See Section 8.3 for specific recommendations.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in frequency?</th>
<th>Recommended dose and frequency for patients with creatinine clearance &lt;30 ml/min or for patients receiving hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>No change</td>
<td>300 mg once daily, or 900 mg three times per week</td>
</tr>
<tr>
<td>Rifampin</td>
<td>No change</td>
<td>600 mg once daily, or 600 mg three times per week</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Yes</td>
<td>25–35 mg/kg per dose three times per week (not daily)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Yes</td>
<td>15–25 mg/kg per dose three times per week (not daily)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Yes</td>
<td>750–1,000 mg per dose three times per week (not daily)</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Yes</td>
<td>250 mg once daily, or 500 mg/dose three times per week*</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>No change</td>
<td>250-500 mg/dose daily</td>
</tr>
<tr>
<td>$\rho$-Aminosalicylic acid</td>
<td>No change</td>
<td>4 g/dose, twice daily</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Yes</td>
<td>12–15 mg/kg per dose two or three times per week (not daily)</td>
</tr>
<tr>
<td>Caprocamycin</td>
<td>Yes</td>
<td>12–15 mg/kg per dose two or three times per week (not daily)</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Yes</td>
<td>12–15 mg/kg per dose two or three times per week (not daily)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Yes</td>
<td>12–15 mg/kg per dose two or three times per week (not daily)</td>
</tr>
</tbody>
</table>

Standard doses are given unless there is intolerance. The medications should be given after hemodialysis on the day of hemodialysis. Monitoring of serum drug concentrations should be considered to ensure adequate drug absorption, without excessive accumulation, and to assist in avoiding toxicity. Data currently are not available for patients receiving peritoneal dialysis. Until data become available, begin with doses recommended for patients receiving hemodialysis and verify adequacy of dosing, using serum concentration monitoring.

* The appropriateness of 250-mg daily doses has not been established. There should be careful monitoring for evidence of neurotoxicity (see Section 3).
Culture negative pulmonary TBC with radiographic evidence of prior pulmonary TBC

**Second Scenario**

- Chest radiograph compatible with pulmonary Tuberculosis
- Smear AFB (-), Culture (-)
- Mantoux test 5mm/ mantoux test 2mm
- Symptoms Free
- Other disease been excluded
Culture negative pulmonary TBC with radiographic evidence of prior pulmonary TBC

First Scenario

- Chest radiograph compatible with pulmonary Tuberculosis
- Smear: AFB (-), NAA (-)
- Quantiferon Test (+)
- Symptoms YES or NO
- Other disease excluded
FIGURE 2. Treatment algorithm for active, culture-negative pulmonary tuberculosis and inactive tuberculosis

Initial cultures negative
No change in CXR

4 months RIF +/- INH
9 months INH
2 months RIF/PZA

Low suspicion
No treatment

At-risk patient
Abnormal CXR
Smears negative
No other diagnosis
Positive tuberculin test

INH/RIF/EMB/PZA

High suspicion

Initial cultures negative
Clinical/CXR improved

2 months INH/RIF

Treatment complete

Initial cultures negative
No change in CXR or Sx

Initial Evaluation
Repeat Evaluation
0 1 2 3 4 6 11

Time (months)
TABLE 14. Summary of evidence* for treatment of persons with radiographic evidence of prior tuberculosis and negative sputum cultures not treated previously

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Rating/evidence</th>
<th>Rating/evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH for 9 mo</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>RIF with or without INH for 4 mo</td>
<td>BII</td>
<td>BIII</td>
</tr>
<tr>
<td>RIF and PZA for 2 mo</td>
<td>CIII</td>
<td>BI</td>
</tr>
</tbody>
</table>

Definition of abbreviations: INH = isoniazid; PZA = pyrazinamide; RIF = rifampin.

*For rating system, see Table 1.
Management of treatment interruptions

- **Duration of Interruption**
  - Yes
    - **Duration of Interruption**
      - < 14 days: Continue treatment; if total not completed in 3 months, restart from beginning
      - ≥ 14 days: Restart from beginning
  - No
    - % planned doses in continuation phase completed
      - < 80%
        - Duration of interruption?
          - < 3 months: Continue treatment; if not completed in 6 mos, start from beginning
      - ≥ 80%
        - Additional treatment may not be necessary

- Additional notes:
  - †: Restart 4-drug regimen from the beginning
Management of treatment interruptions

* Patients who were initially AFB smear-positive should receive additional therapy.

† Recheck smears and cultures (if positive, check drug susceptibility results). Start DOT if not already being used.

‡ If repeat culture is positive, restart four-drug regimen while waiting for drug susceptibility results. If repeat culture is negative, continue therapy to complete regimen within 9 months of original start date.

§ If repeat culture is positive, continue four-drug regimen while waiting for drug susceptibility results. If repeat culture is negative, consider stopping therapy if patient has received a total of 9 months of therapy.
Adverse effects of anti-tuberculosis drugs
### TABLE 10. Clinical hepatitis in persons taking isoniazid and rifampin*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of studies</th>
<th>Patients</th>
<th>Clinical Hepatitis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>6</td>
<td>38,257</td>
<td>0.6</td>
</tr>
<tr>
<td>INH plus other drugs but <em>not</em> RIF</td>
<td>10</td>
<td>2,053</td>
<td>1.6</td>
</tr>
<tr>
<td>INH plus RIF</td>
<td>19</td>
<td>6,155</td>
<td>2.7</td>
</tr>
<tr>
<td>RIF plus other drugs but <em>not</em> INH</td>
<td>5</td>
<td>1,264</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Definition of abbreviations: INH = Isoniazid; RIF = rifampin.

Definition of relapse

Relapse refers to the circumstance in which a patient becomes and remains culture negative while receiving therapy but, at some point after completion of therapy, either becomes culture positive again or has clinical or radiographic deterioration that is consistent with active tuberculosis.
Definition of failure

• Treatment failure is defined as continued or recurrently positive cultures during the course of antituberculosis therapy after 4 months of treatment
Reasons for treatment failure

- Nonadherence to treatment
- Malabsorption
- Not prior drug susceptibility test
- Biological variation of the patient
- Laboratory error
TABLE 6. Epidemiological circumstances in which an exposed person is at increased risk of infection with drug-resistant *Mycobacterium tuberculosis*:

- Exposure to a person who has known drug-resistant tuberculosis.
- Exposure to a person with active tuberculosis who has had prior treatment for tuberculosis (treatment failure or relapse) and whose susceptibility test results are not known.
- Exposure to persons with active tuberculosis from areas in which there is a high prevalence of drug resistance.
- Exposure to persons who continue to have positive sputum smears after 2 months of combination chemotherapy.
- Travel in an area of high prevalence of drug resistance.

*This information is to be used in deciding whether or not to add a fourth drug (usually EMB) for children with active tuberculosis, not to infer the empiric need for a second-line treatment regimen.*
Risk factors for drug resistant TBC

- Exposure to a person who has known drug-resistant tuberculosis
- Exposure to a person with active tuberculosis who has had prior treatment for tuberculosis (treatment failure or relapse) and whose susceptibility test results are not known
- Exposure to persons with active tuberculosis from areas in which there is a high prevalence of drug resistance
- Exposure to persons who continue to have positive sputum smears after 2 months of combination chemotherapy
- Travel in an area of high prevalence of drug resistance
Treatment of relapse and failure

• DOT with a Rifampicin regimen
• DOT with no Rifampicin regimen
• NO prior DOT treatment
• No initial drug susceptibility testing
• Patients with life treatening forms of TBC
Principles of retreatment in drug resistance suspected TBC

• NEVER add a single drug to a failing regimen
• At least 2-3 not previously given agents based on the probability of in vitro susceptibility test should be added
• Empirical retreatment regimens should include a Fluoroquinolone, an injectable agent, one or two of the second line oral agents
• The regimen should be adjusted to the drug susceptibility test results
• Pyrazinamide should not be used with only one other agent when treating active TBC
Treatment of relapse

- **EXPANDED REGIMEN:**
- (INH, RIF, PZA, EMB)
- PLUS
- A fluoroquinolone
- An Injectable agent
- A second line oral agent
  (PAS, Cycloserine, Ethionamide)
Rationale for an ideal initial treatment regimen

IUATLD

- The microbiological bases for TB treatment indicate that the combination 2HRZ/4HR is ideal in all initial cases of the disease where sensitivity to all the drugs can be guaranteed. However, a fourth drug (ethambutol [E]) to this initial phase of therapy is necessary since resistance to isoniazid is found in almost all low- or middle-income countries.

- Moreover, administering these drugs either daily or 2 to 3 times a week has equivalent efficacy, which makes the 2HRZE/4H2R2 or 2HRZE/4H3R3 regimens equally recommendable.

- However, in order to be able to recommend regimens with rifampicin (R) in the second phase, it is essential to ensure adherence to treatment in both phases.

- A regimen 2HRZE/6HE (or 2HRZE/6HT in areas where the prevalence of HIV infection is very low), although somewhat less effective than 2HRZE/4HR, should be recommended as the initial regimen in low and middle-income countries where DOT cannot be guaranteed in the second phase.
• Surgery is only indicated in specific cases for managing the sequelae or complications of pulmonary TB, and in very exceptional cases of multidrug-resistant TB in which the lesions are localised and there are no other drugs to treat the disease.

• In patients with extrapulmonary TB, surgery may be acceptable for obtaining samples for study and for treating certain situations such as constrictive pericarditis, vertebral abscesses that may compress the spinal cord, or superficial and accessible abscesses in cases of osteoarticular TB.

• Corticoid treatment should only be contemplated in four situations: meningeal TB, serious miliary TB, pericardial TB, and TB involving gangliobronchial perforation.
Hospital admission criteria
IUTLD

- **Uncomplicated initial TB is not a criterion for hospital admission**

- **Five conditions warrant hospitalisation:**
  
  - Disease severity. Admission is due to the seriousness of the patient’s condition, not due to the fact that the patient has TB.
  
  - Complications of the disease or its sequelae. Admission is likewise due to complications, and not due to merely having TB.
  
  - Management of serious adverse drug reactions.
  
  - Re-treatment of TB with second-line drugs.
  
  - Due to social reasons (rare).