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

- **The first principle attempts to respond to the large number of multi plying 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

First-line drugs	Second-line drugs
Isoniazid	Cycloserine
Rifampin	Ethionamide
Rifapentine	Levofloxacin*
Rifabutin*	Moxifloxacin*
Ethambutol	Gatifloxacin*
Pyrazinamide	*p*-Aminosalicylic acid
	Streptomycin
	Amikacin/kanamycin*
	Capreomycin

* 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 1x 10^5- 10^6
- Rifampicin 1x 10^7 – 10^8
- Streptomycin 1x10^5-10^6
- Ethambutol 1x10^5-10^6
- Pyrazinamide 1x10^2-10^4
- Quinolones 1x10^5-10^6
- Others 1x10^3-10^6

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

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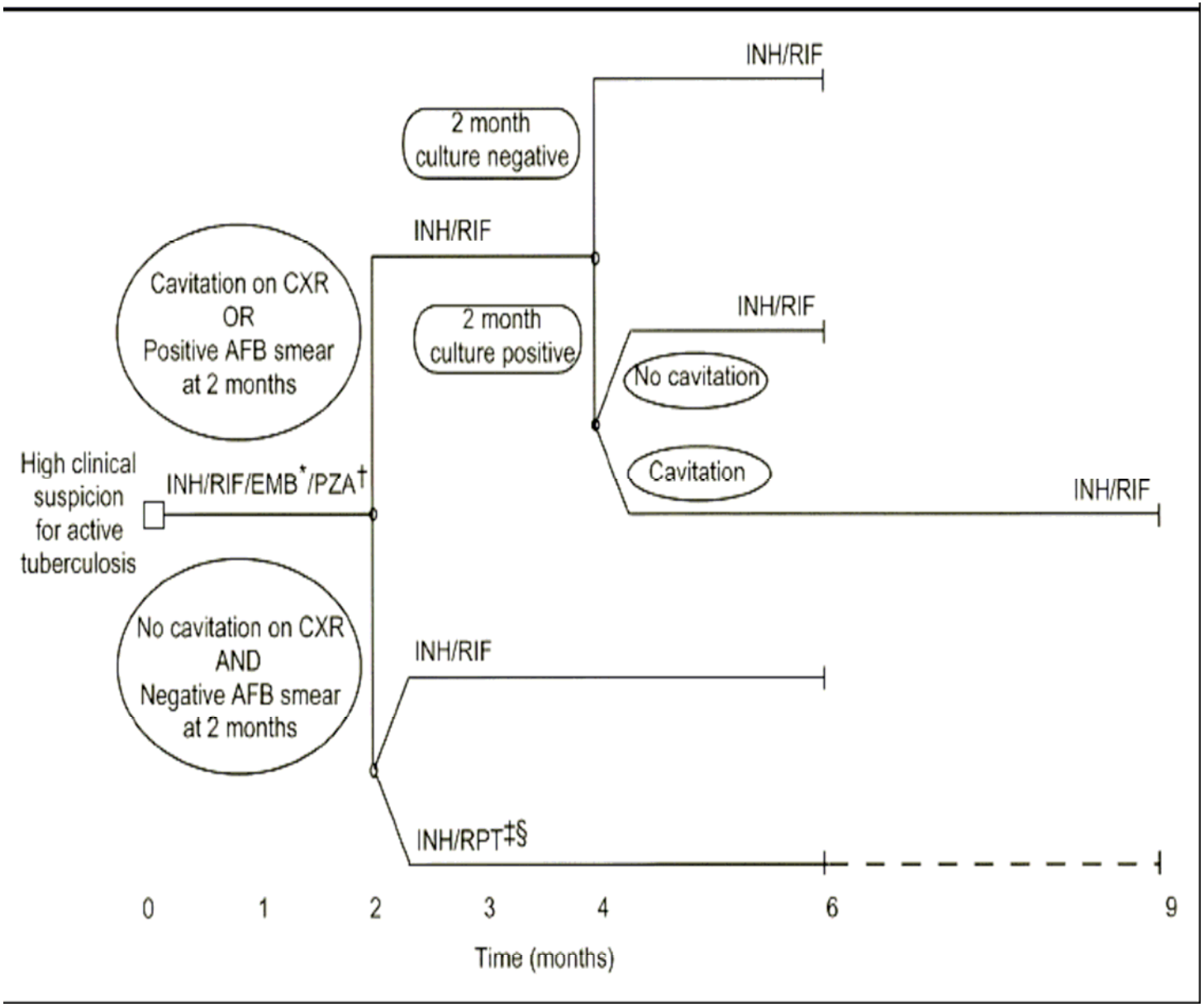
Treatment of patients with tuberculosis



Initial phase			Continuation phase			Range of total doses (minimal duration)	Rating* (evidence)†	
Regimen	Drugs	Interval and doses‡ (minimal duration)	Regimen	Drugs	Interval and doses‡§ (minimal duration)		HIV⁻	HIV⁺
1	INH RIF PZA EMB	Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)¶	1a	INH/RIF	Seven days per week for 126 doses (18 wk) or 5 d/wk for 90 doses (18 wk)¶	182–130 (26 wk)	A (I)	A (II)
			1b	INH/RIF	Twice weekly for 36 doses (18 wk)	92–76 (26 wk)	A (I)	A (II)#
			1c**	INH/RPT	Once weekly for 18 doses (18 wk)	74–58 (26 wk)	B (I)	E (I)
2	INH RIF PZA EMB	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)	2a	INH/RIF	Twice weekly for 36 doses (18 wk)	62–58 (26 wk)	A (II)	B (II)#
			2b**	INH/RPT	Once weekly for 18 doses (18 wk)	44–40 (26 wk)	B (I)	E (I)
3	INH RIF PZA EMB	Three times weekly for 24 doses (8 wk)	3a	INH/RIF	Three times weekly for 54 doses (18 wk)	78 (26 wk)	B (I)	B (II)
4	INH RIF EMB	Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)¶	4a	INH/RIF	Seven days per week for 217 doses (31 wk) or 5 d/wk for 155 doses (31 wk)¶	273–195 (39 wk)	C (I)	C (II)
			4b	INH/RIF	Twice weekly for 62 doses (31 wk)	118–102 (39 wk)	C (I)	C (II)

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 13. Evidence-based* guidelines for the treatment of extrapulmonary tuberculosis and adjunctive use of corticosteriods†

Site	Length of therapy (mo)	Rating (duration)	Corticosteroids‡	Rating (corticosteroids)
Lymph node	6	AI	Not recommended	DIII
Bone and joint	6–9	AI	Not recommended	DIII
Pleural disease	6	AII	Not recommended	DI
Pericarditis	6	AII	Strongly recommended	AI
CNS tuberculosis including meningitis	9–12	BII	Strongly recommended	AI
Disseminated disease	6	AII	Not recommended	DIII
Genitourinary	6	AII	Not recommended	DIII
Peritoneal	6	AII	Not recommended	DIII

*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 15. Dosing recommendations for adult patients with reduced renal function and for adult patients receiving hemodialysis

Drug	Change in frequency?	Recommended dose and frequency for patients with creatinine clearance <30 ml/min or for patients receiving hemodialysis
Isoniazid	No change	300 mg once daily, or 900 mg three times per week
Rifampin	No change	600 mg once daily, or 600 mg three times per week
Pyrazinamide	Yes	25–35 mg/kg per dose three times per week (not daily)
Ethambutol	Yes	15–25 mg/kg per dose three times per week (not daily)
Levofloxacin	Yes	750–1,000 mg per dose three times per week (not daily)
Cycloserine	Yes	250 mg once daily, or 500 mg/dose three times per week*
Ethionamide	No change	250-500 mg/dose daily
p-Aminosalicylic acid	No change	4 g/dose, twice daily
Streptomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)
Capreomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)
Kanamycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)
Amikacin	Yes	12–15 mg/kg per dose two or three times per week (not daily)

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 Senario

- 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 Senario

- Chest radiograph compatible with pulmonary Tuberculosis
- Smear: AFB (-), NAA (-)
- Quantiferon Test (+)
- Symptoms YES or NO
- Other disease exluded

FIGURE 2. Treatment algorithm for active, culture-negative pulmonary tuberculosis and inactive tuberculosis

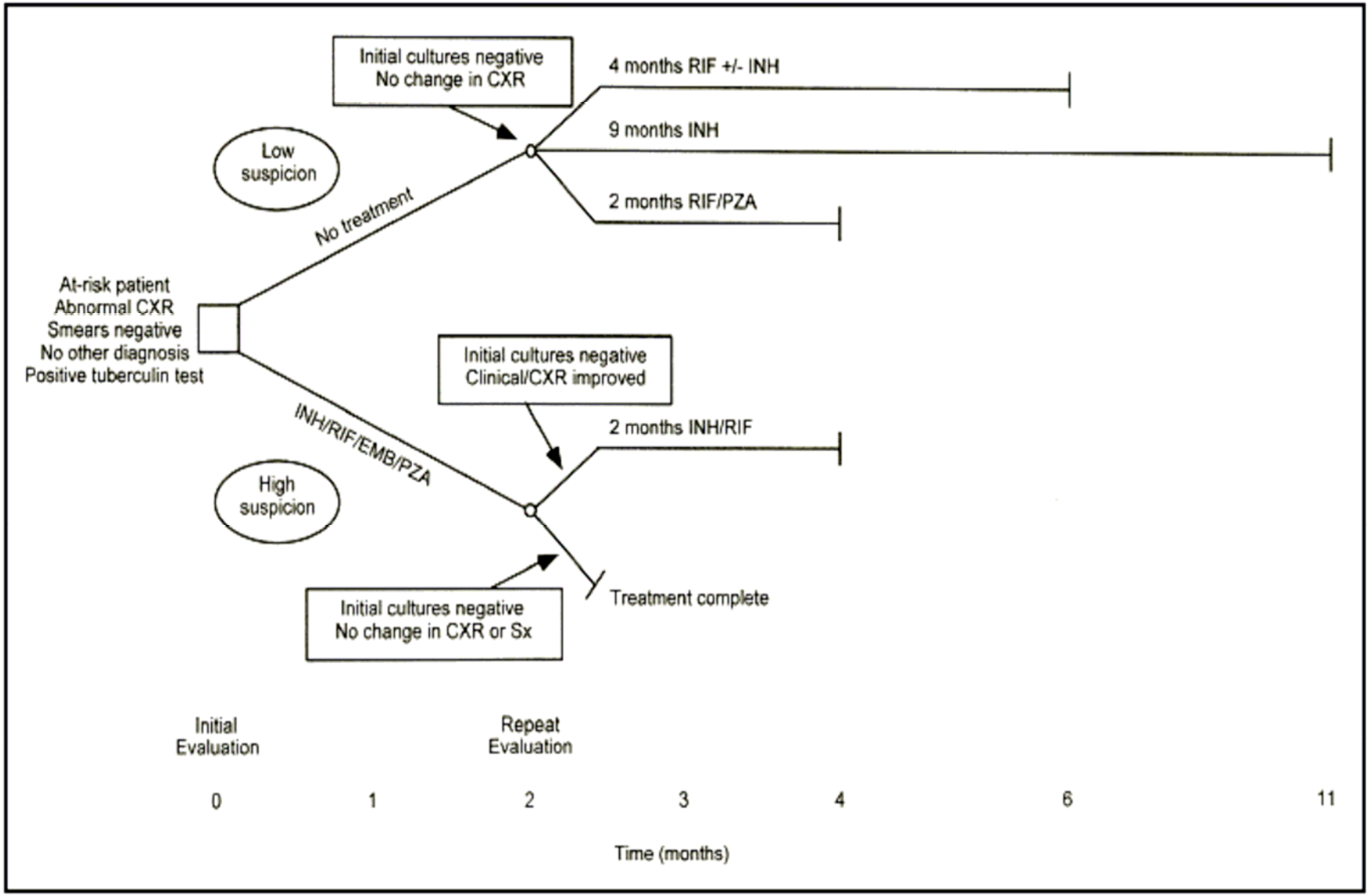


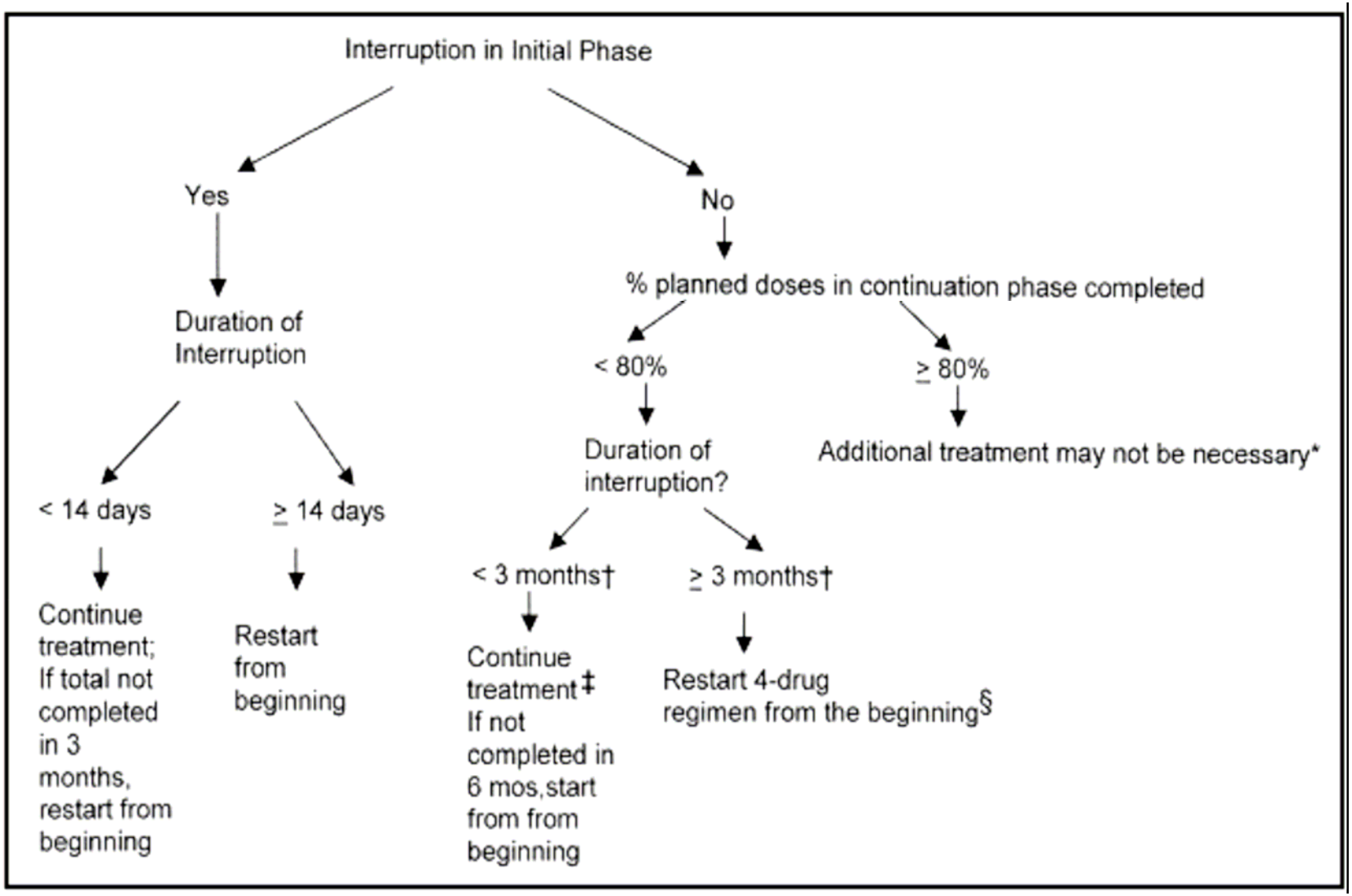
TABLE 14. Summary of evidence* for treatment of persons with radiographic evidence of prior tuberculosis and negative sputum cultures not treated previously

Treatment regimen	Rating/evidence	
	HIV negative	HIV positive
INH for 9 mo	AII	AII
RIF with or without INH for 4 mo	BII	BIII
RIF and PZA for 2 mo	CIII	BI

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

* For rating system, see Table 1.

Managment of treatment interuptions



Managment of treatment interuptions

* 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

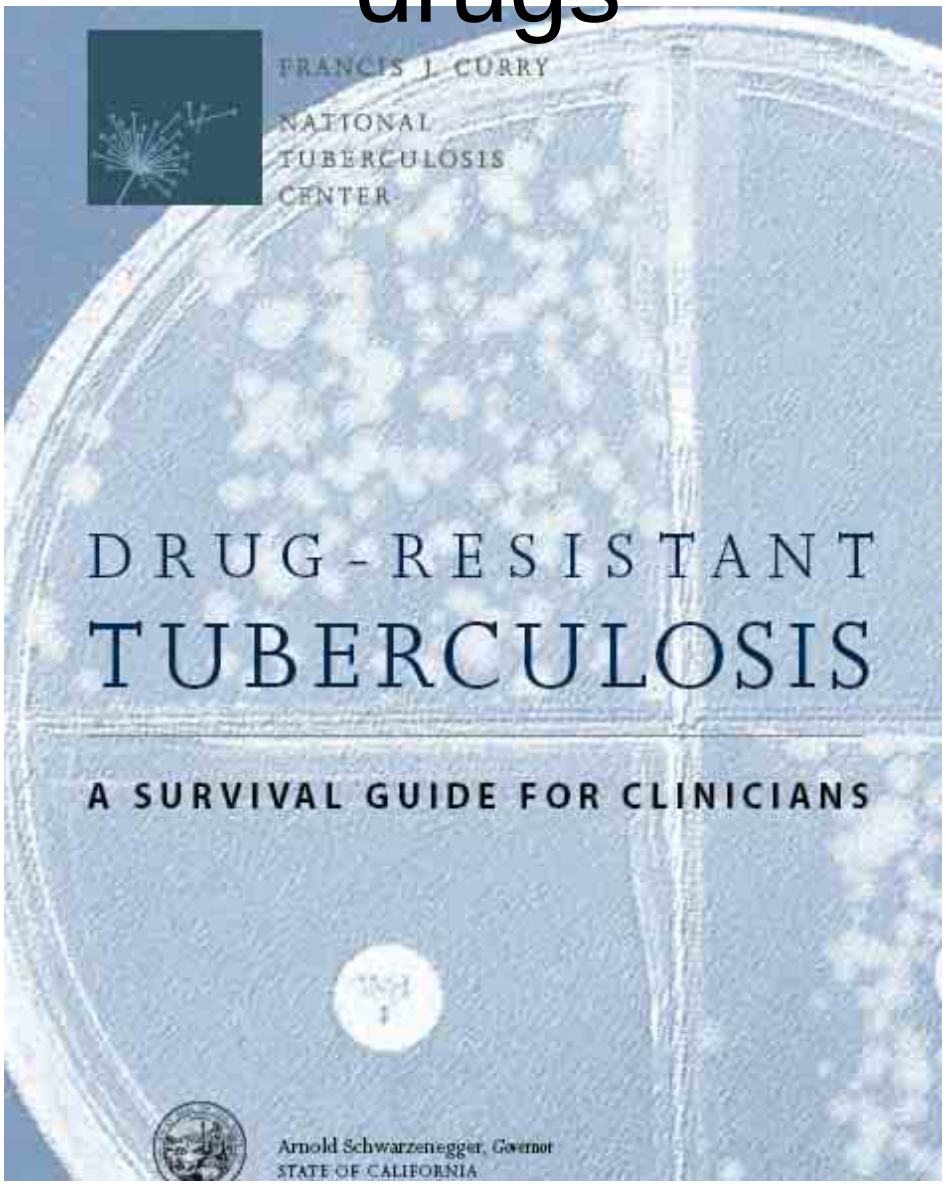


TABLE 10. Clinical hepatitis in persons taking isoniazid and rifampin*

Drug	Number of studies	Patients	Clinical Hepatitis (%)
INH	6	38,257	0.6
INH plus other drugs but *not* RIF	10	2,053	1.6
INH plus RIF	19	6,155	2.7
RIF plus other drugs but *not* INH	5	1,264	1.1

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

* **Source:** Steele MA, Burk RF, Des Prez RM. Toxic hepatitis with isoniazid and rifampin: a meta-analysis. Chest 1991;99:465–471. Reprinted with permission.

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 treatmnet
- 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

- **<u>EXPANDED REGIMEN:</u>**
- (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.

treatment regimen
IUTLD

- 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).