MAYO CLINIC

Mayo Clinic Center for Tuberculosis

Pulmonary Tuberculosis Therapy

Richard B. Kohler, MD
Indiana University School of Medicine (Emeritus)
Former Consultant, TB Control Division, Indiana State Department of Health

2016 Update

Indiana State Department of Health

 |

Disclosures

- None

Indiana State Department of Health

Learning Objectives

Learners should be able to:

- List three incentives and enablers to enhance compliance with TB therapy.
- Describe the drugs used to treat drug-sensitive pulmonary TB, including duration considerations in key situations.
- Name situations that require special considerations in treating pulmonary tuberculosis and describe what modifications are needed in these situations.

Organization and Supervision of Treatment

- Coordination of public and private care sectors
  - Public health case manager
  - Physician/physician surrogate
- Develop case management plan
  - Educate the patient (use medical interpreter if possible and if needed)
    - ✓TB treatment (drugs, side effects, expected duration of therapy)
    - ✓Expected outcomes
    - ✓Adherence support
    - ✓How response will be assessed
    - ✓Infectiousness and infection control interventions planned

Indiana State Department of Health

Potential Enablers and Incentives

- Enablers
  - Education and counselling about tuberculosis*
  - Transportation vouchers
  - Set convenient clinic hours and locations
  - Language services
  - Reminder system*
  - Social service assistance (substance abuse treatment, housing, others)
  - Demonstrate positive integration of public health and private caregivers
- Incentives
  - Food stamps, snacks, meals*
  - Coupons to restaurants, grocery stores
  - Direct housing assistance
  - Books
  - Stipends*
  - Care contracts

Indiana State Department of Health

Evidence on Programmatic Education and Counselling to Promote Adherence to TB Therapy

- There are no randomized controlled trials that assess the impact of programmatic education and counselling on completion of therapy for active tuberculosis.
- For treatment for latent tuberculosis:
  - A Spanish study showed improved therapy completion rates (by about 20%) for children whose parents were counselled either by home visits or telephones when compared to doctor's office counselling.
  - A US trial showed no benefit from peer counselling in adolescents (completion rates about 75% in both groups)
  - Another US trial showed improvement in completion rates from 12% to 24% (RR 1.94, 95% CI 1.03-3.68) in prisoners using an education program.

M'Imunya JM et al., Cochrane Database Syst Rev 2012; 5: CD006591

Evidence on Reminders in TB Care

- Pre-attendance reminders improved clinic attendance and TB therapy completion rates.
  - Clinic attendance rates improved from 50% to 66% (RR 1.32, 95% CI 1.10-1.59, 1 US trial.
  - Therapy completion rates improved from 88% to 100% (RR 1.14, 95% CI 1.02-1.27, 1 Thailand trial).
- Missed clinic calls improved both clinic attendance (10% vs 52%) (one trial, India) and therapy completion (17% improvement rate) (two trials, India, Iraq).

Liu Q et al., Cochrane Database Syst Rev 2014; 11: CD006594

Evidence For and Against the Use of Material Incentives in TB Care

- Latent TB
  - Two studies in drug users found that a $5-10 cash payment on induce return for tuberculin skin test read more than doubled the return rate.
  - Three studies in homeless persons and recently released prisoners showed a 60% improvement in return to clinic to initiate and/or continue treatment for latent TB using incentives worth $5-25.
  - Three studies showed that similar incentives failed to improve the completion rate for latent TB treatment in drug users and recently released prisoners.
  - Other trials also focused on latent TB therapy and showed small incremental effect of cash over non-cash material incentives and for more cash versus less cash.
- Active TB
  - One trial showed no benefit in a general TB population in Timor for completion of active TB therapy using clinic-based hot meals during intensive therapy and then food parcels during maintenance phase.

Lutge EE et al., Cochrane Database Syst Rev 2012; 1: CD007952

Potential Enablers and Incentives

- Enablers
  - Education and counselling about tuberculosis*
  - Transportation vouchers
  - Set convenient clinic hours and locations
  - Language services
  - Reminder system*
  - Social service assistance (substance abuse treatment, housing, others)
  - Demonstrate positive integration of public health and private caregivers
- Incentives
  - Food stamps, snacks, meals*
  - Coupons to restaurants, grocery stores
  - Direct housing assistance
  - Books
  - Stipends*
  - Care contracts

Indiana State Department of Health

TB Diagnosis

- Cough illness ≥2-3 weeks +
  - Fever, night sweats, weight loss, and/or hemoptysis
- Increased risk for TB, unexplained illness, including respiratory symptoms of ≥ 2-3 weeks duration
  - Recent exposure, known (+) TST, immigrant ≤5 years from high-risk region, HIV, drug use,, high-risk congregate setting, homeless, immunosuppressed, advanced CKD, silicosis, others
- HIV (+), unexplained cough, fever
- High risk and unresponsive community-acquired pneumonia after 7 days
- High risk and worrisome CXR
  - Details already covered by Dr. Kissner
- Perform appropriate diagnostic tests
  - Details already covered by Dr. Temesgen

Guidelines. MMWR 54:1 (2005)

Indiana State Department of Health

Treatment of Pulmonary TB

- When to start therapy?
- What drugs?
- How long?
- How often?
- DOT or SAT?
- Special situations

Indiana State Department of Health

Decide When to Initiate Therapy

- Balance waiting too long (intensification of illness, spread to others) versus starting too soon (treating incorrectly for a non-tuberculous infection, screwing up opportunity to obtain positive cultures).

Indiana State Department of Health

Findings That Favor Early Initiation of Therapy

- Child under 2 years old.
- Highly consistent clinical picture (symptoms and radiographic findings)
- Pretty consistent findings with positive AFB smears.
- Positive NAAT
- Life-threatening disease or situation (e.g., immunocompromised)
- High transmission risk (e.g., congregate setting)

Nahid P et al., ATS/CDC/IDSA Guidelines, Clinical Infectious Diseases 2016; advanced access 8/10/2016 pages 1-49

Indiana State Department of Health

Findings That May Temper Enthusiasm for Early Initiation of Therapy

- High risk for adverse medication effects (e.g., advanced liver disease)
- Clinical or radiographic picture not consistent with tuberculosis.
- Negative NAAT
- Clinical stability
- Alternative diagnosis seems more likely
- Low transmission risk (e.g., has already thoroughly exposed all/most likely contacts)

Nahid P et al., ATS/CDC/IDSA Guidelines. Clinical Infectious Diseases 2016; advanced access 8/10/2016 pages 1-49

Indiana State Department of Health

When to Initiate Therapy

- Integrate the pro's and con's already described.
- Judgement call – make it in concert with public/private partner.
- Seek advice from more experienced source if situation complex
  - Local physicians with TB management experience in areas with reasonable amounts of TB.
  - County health departments in areas with reasonable amounts of TB.
  - State health department TB control divisions
  - Regional TB consultants: Mayo Clinic Center for Tuberculosis
    - Phone: 855-360-1466 (toll-free)
    - Email: tbcenter@mayo.edu

Indiana State Department of Health

Treatment of Pulmonary TB

- When to start therapy?
- What drugs?
- How long?
- How often?
- DOT or SAT?
- Special situations

Indiana State Department of Health

Preferred Treatment Regimens for Pulmonary Tuberculosis

- 6 months (~70%)
  - RIPE* X 2 months (intensive phase), then RI X 4 months (continuation phase), for most cases.
- 9 months (~15%)
  - RIPE X 2 months, then RI X 7 months, if both the culture is still positive at 2 months and a cavity is present on the chest x-ray.
  - Pyrazinamide cannot be used
- 4 months (~15%)
  - RIPE X 2 months, then RI X 2 months, if the case seems highly likely to be TB (e.g., (+) IGRA or skin test) despite negative cultures and smears.

Indiana State Department of Health

RIPE

- R: rifampin
- I: isoniazid
- P: pyrazinamide
- E: ethambutol

- Brit/WHO-speak: HRZE
  - H: isoniazid (early brand names Hyzyd, Hydra). Drug is the hydrazide of isonicotinic acid)
  - R: rifampin
  - Z: pyrazinamide
  - E: ethambutol

Indiana State Department of Health

Ethambutol Is Not Necessary in RIP(E) To Treat Drug-Susceptible Tuberculosis

- Ethambutol is used until the susceptibility profile of the patient's Mycobacterium tuberculosis isolate is known.
- If the isolate is susceptible to RIP (rifampin, isoniazid, pyrazinamide), then the E (ethambutol) can be stopped. RIPE → RIP (during the intensive phase – first two months).
- Pyrazinamide is needed only for the intensive phase. It adds no significant benefit (only potential side effects) after that. RIP(E) → RI

Indiana State Department of Health

Effectiveness of Standard Regimen

Initiate	Mo.	Continue	Mo.	Relapse (%)	C (-) 2 mo.	n
RIP	2	RI	4	3.4	85	116
RIP	2	RI	4	4.1	--	330
RIP	2	RI	4	2.9	90	140
RIP	2	RI	4	3.5	80	206
RIP	2	RI	4	6.5	--	337
RIPE	2	RI	4	2.5	--	132

Poland, 1984, Am Rev Respir Dis 130:1091;US, 1990, Ann Int Med 112;397; Africa 1988, Am Rev Respir Dis 137:1147; Brazil 1989, Lancet 2:1174

Indiana State Department of Health

TB Relapses in 6-Month Regimen

- Twice weekly RI in continuation phase

Overall relapse rate (28/502)	5.6% (396)
Cavity, culture (+) at 2 months	21% (48)
Cavity, culture (-) at 2 months	5% (150)
No cavity, culture (+) at 2 months	6% (17)
No cavity, culture (-) at 2 months	2% (181)

Lancet 2002;360:528-534; MMWR 2003;52:35.
US/Canada multicenter rifampin vs rifapentine, HIV (-)

- Similar findings also in two prior studies

Indiana State Department of Health

Extend Treatment to 9 Months

- Combination of cavitary disease and positive culture at 2 months.

- But if not in combination, total duration of 6 months:
  - Cavitary disease, but cultures negative at 2 months: still 6 months of therapy
  - Cultures still positive at 2 months, but no cavity (assuming cultures negative at five months): 6 months of therapy still acceptable

Indiana State Department of Health

Smear-Negative Culture-Negative TB

- About 15% of all cases of TB in the US are smear- and culture-negative.
- Smear-negative culture-negative TB are cases of likely TB, but whose sputum AFB smears and cultures are consistently negative.
- Identifying smear-negative culture negative TB
  - Consistent clinical and radiologic picture.
  - There is usually also additional supportive evidence
    - History of known TB contact
    - History of residence in high incidence region
    - Positive tuberculin skin test or IGRA
  - No alternative diagnosis to explain the findings
- Reasons for negative culture: recent fluoroquinolone therapy, low infection burden, inadequate specimens (spit), overgrowth by other organisms in culture, processing errors. (Or, may not be TB)

Culture-Negative Smear-Negative Pulmonary Tuberculosis in Adults

- If TB seems reasonably likely despite negative smear and culture, treat with RIPE.
- Reassess at 2 months. If clinical and/or radiologic improvement, and all cultures negative, and no reasonable alternative explanation for clinical course, continue RI for 2 more months.
  - If no improvement, reassess for alternative diagnosis.
  - Decision whether or not to continue therapy is judgement call.
- If clinical and radiologic evaluation at 4 months are consistent with treatment success, therapy may be stopped.
- AFB smear-positive culture-negative cases (clinically highly suspicious for TB) should be treated with 6-month regimen.
- 4-month therapy is NOT RECOMMENDED FOR HIV-POSITIVE INDIVIDUALS.

Payam N et al., ATS/CDC/IDSA Guidelines. Clinical Infectious Diseases 2016; advanced access 8/10/2016

Indiana State Department of Health

4-Month Trial Data: Smear-Negative Culture-Negative Pulmonary TB

- 4-month RI regimen (Arkansas) → 1.2% relapse rate at ~44 months
  (Dutt et al., ARRD 1989;139:867-870)

- 3- versus 4-month RIPS regimens (Singapore) → 7% and 4% relapse rates at 5 years
  (British Medical Research Council, ARRD 1989;139:871-876)

Indiana State Department of Health

What if TB Treatment is Interrupted?

- Interruptions are common (e.g., 15% for adverse drug reactions in one 2006 UK study; ~50% overall in one 2009 Russian study)
- General principle: The earlier and/or longer the interruption, the more serious the effect and more likely the need to start over.
- Guidelines based on expert opinion -- not on trial data.

Breen RAM et al., Thorax 2006;61:791.
Jakubowiak W et al., International J Infect Dis 2009;13:362

Indiana State Department of Health

Guidelines for Dealing with Treatment Lapses

- These are not based on randomized trials.
- Start over if:
  - Sputum at time of reinstitution is still culture-positive
  - 14 days or more lapse during intensive phase
  - 3 months or more lapse during continuation phase if fewer than 80% of doses completed
  - Strongly consider if patient is significantly immunosuppressed
- Probably OK just to quit if:
  - 80+% of doses completed, were initially smear-negative, and completed the intensive phase appropriately
- Finish out planned number of doses if:
  - Less than 14 days during intensive phase or less than three months interruption during continuation phase
  - 3 months or more during continuation phase if 80+% of doses completed.

Bureau of Tuberculosis Control, New York City, Clinical Policies and Protocols, 4th edition, 2008

Indiana State Department of Health

Treatment of Pulmonary TB

- When to start therapy?
- What drugs?
- How long?
- How often?
- DOT or SAT?
- Special situations

Indiana State Department of Health

Frequency of Administration

- Preferred
  - Intensive phase: Daily
    - Five days per week is felt likely to be as good as seven days per week.
  - Continuation phase: Daily or three times per week

Indiana State Department of Health

Frequency of Administration

- Conditionally acceptable but not preferred
  - Three times weekly both phases if a) no cavity, b) not HIV-positive.
    - Evidence consistent with higher failure rates, higher relapse rates, and more drug resistance.
    - Non-HIV patients: increased failure rates from 2.7 to 5.2%, increased relapse rates from 1.9 to 3.2% (Evidence Profile 8, Appendix B)
    - HIV-positive patients: increased relapse rates from 6.2 to 24.7% (Evidence Profile 8, Appendix B)
  - Twice weekly throughout or continuation phase only
    - Limited data (no direct comparisons; n=211), but what's available suggests effectiveness equivalent to daily regimens.
    - ATS/IDSA guidelines: "not generally recommended". May be acceptable when more frequent dosing is simply not achievable for patients a) not HIV-positive and b) non-cavitary and/or smear-negative.
    - Still used by some US public health programs

Indiana State Department of Health

Treatment of Pulmonary TB

- When to start therapy?
- What drugs?
- How long?
- How often?
- DOT or SAT?
- Special situations

Indiana State Department of Health

Does Directly Observed Therapy Improve Outcomes?

Outcome	# Trials	SAT	DOT	RR	95% CI	Certainty
Mortality[1]	4	25/689 (3.6%)	42/914 (4.6%)	0.73	0.45-1.19	Very Low
Treatment Success [1]	5	566/775 (73.0%)	747/1001 (74.6%)	0.94	0.89-0.98	Moderate
Treatment Completion[1]	4	56/689 (8.1%)	76/914 (8.3%)	0.97	0.69-1.36	Moderate
Relapse by 24 months	1	15/290 (5.2%)	23/259 (8.9%)	0.58	0.31-1.09	Very Low
Adherence	1	78/86 (90.7%)	84/87 (96.6%)	0.94	0.87-1.02	Low
Smear (-) at 3 months	1	345/422 (81.8%)	366/414 (88.4%)	0.92	0.87-0.98	Low

[1]6-9 months

Supplementary Appendix B, Evidence Profile 4 from
Payam N et al., ATS/CDC/IDSA Guidelines. Clinical Infectious Diseases 2016; advanced access 8/10/2016

Indiana State Department of Health

Arguments For/Against DOT

- For
  - Randomized trial evidence suggests improved success [treatment completion + cures], smear conversion at 3 months.
  - Population trial evidence (a weaker type of evidence than randomized trials) suggests reduced acquisition of drug resistance (Texas), improved treatment success in HIV patients (New York), and higher treatment completion rates in released prisoners (Chicago).
  - Early recognition of adverse reactions
  - Early recognition of treatment irregularities
- Against
  - Randomized trial evidence to support better improved survival, treatment completion, relapse rates is negative
  - Time consuming
  - Expensive
  - Sometimes dangerous for public health employees
- Difficult to study, so existing evidence is of marginal reliability

Indiana State Department of Health

Bottom Line on DOT

- Still recommended by ATS/IDSA as a conditional recommendation despite low certainty in the evidence.
- Remains standard of practice in most US and European jurisdictions.

Indiana State Department of Health

Treatment of Pulmonary TB

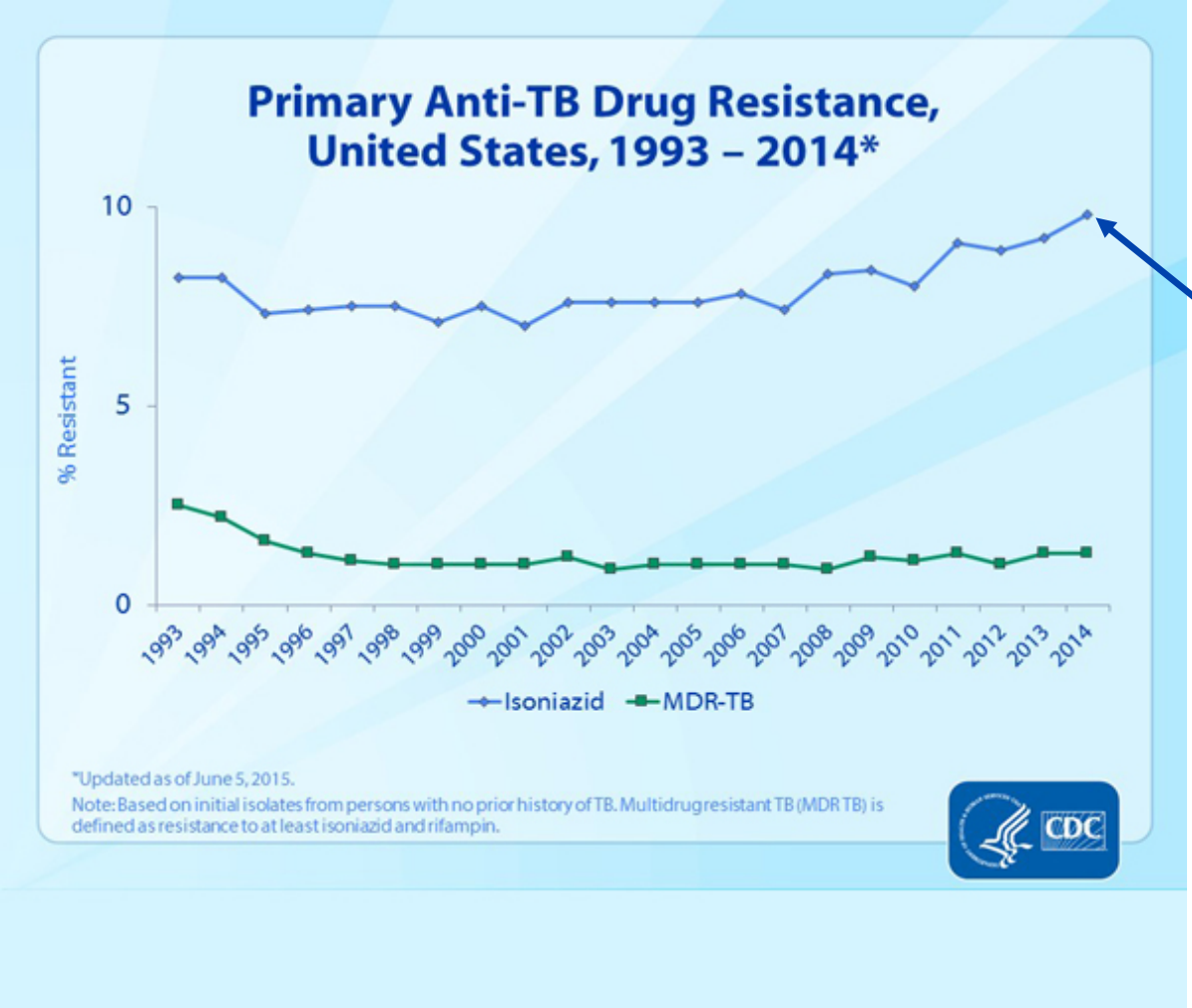
- When to start therapy?
- What drugs?
- How long?
- How often?
- DOT or SAT?
- Special situations

Indiana State Department of Health

Special Situations

- Drug resistance or intolerance
- HIV infection
- Pregnancy
- Kidney disease
- Liver disease
- Advanced age
- Recurrent disease
- Treatment failure

Isolated INH Resistance



- INH-resistance about 44% in eastern Europe
- Rest of world – about 14%
- About 10% of TB cases in US are caused by INH-resistant isolates.
    - About 2% are resistant to more than one drug.

US data from CDC web site.

World data from Jenkins HE et al., PLoS ONE 2011;6 (e22927

INH Mono-Resistant TB (or if INH Cannot Be Used): Can Still Use 6-Month Therapy

- As long as isolates remain susceptible to rifampin, pyrazinamide, and another drug, six month regimens are effective.
- With rifampin + 2 or more other active drugs, in 12 studies done in Africa, Hong Kong, and Singapore, success rate for 6-month regimens was over 95%. (n ~ 246 patients)
- (In 11 patients, rifampin resistance was present, and 5 failed treatment.)

Mitchison, DA, Nunn, AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. Am. Rev Respirator Dis 1986;133:423-430.

Treatment for INH-Resistant Pulmonary TB

- Rifampin + pyrazinamide + ethambutol (RPE) X 6 months.

If Pyrazinamide or Rifampin Cannot Be Used, 6-month Regimens Cannot Be Used

- Pyrazinamide resistance/intolerance
  - Use: RIE X 2 months, then RI X 7 months (9 months total)
- Rifampin resistance/intolerance
  - Use:
    - 12-18 months of INH + ethambutol + fluoroquinolone supplemented by pyrazinamide during first two months.
    - INH + PZA + streptomycin for 9 months can work but is difficult for patients to tolerate.

    (ATS/CDC/IDSA Guidelines. MMWR 2003;52:69) (also see Menzies D et al., PLoS Medicine 2009;6:e1000146 for impact of absence of rifampin in continuation phase)
- For INH and rifampin resistance, can use 18-24 months of pyrazinamide, ethambutol, fluoroquinolone, streptomycin.

Fluoroquinolones for Tuberculosis

- "The role of moxifloxacin or levofloxacin has not been established through clinical trials when INH or ethambutol cannot be used." "Experts on occasion use moxi or levo in place of ethambutol during intensive phase or INH throughout when INH cannot be used."
- Single trial of RMPE for two months, then moxifloxacin + rifapentine weekly X four months, was as effective as standard therapy. Participants were given a meal of two boiled eggs plus bread before each rifapentine dose.

Payam N et al., ATS/CDC/IDSA Guidelines. Clinical Infectious Diseases 2016; advanced access 8/10/2016

Special Situations

- Drug resistance or intolerance
- HIV infection
- Pregnancy
- Kidney disease
- Liver disease
- Advanced age
- Recurrent disease
- Treatment failure

Special Aspects of TB in HIV Patients

- Potential for drug interactions between TB and HIV drugs
- Paradoxical clinical reactions that mimic worsening of the TB due to immunologic reconstitution
- Tendency for development of rifampin/rifabutin/ rifapentine resistance during intermittent treatment regimens

Recommendations For Treating TB in HIV Patients

- Daily treatment regimens preferred (to minimize failures and relapses and development of rifamycin resistance) (4-fold risk of relapse with TIW vs daily during intensive phase in HIV non-HAART patients; Khan F et al., CID 2012;55:1154). In particular, avoid twice-weekly regimens.
- If not on HIV therapy: treat with 9-month regimen. If on HIV therapy: treat with standard 6-month regimen.
- Rifampin alters the metabolism of many HIV drugs. Check whether dose changes are needed. Monitor patients more closely than usual for disease exacerbations and drug toxicities. Consider using rifabutin instead of rifampin with some HIV drugs.
- Start HIV therapy within 2 weeks if CD4 count <50 and within 8 weeks otherwise. Exception: TB meningitis.
- Expect 5-10% of patients to develop IRIS (immune reconstitution inflammatory syndrome), especially if CD4 <50. Treatments: ibuprofen; drain abscesses/effusions; corticosteroids.

Special Situations

- Drug resistance or intolerance
- HIV infection
- Pregnancy
- Kidney disease
- Liver disease
- Advanced age
- Recurrent disease
- Treatment failure

Other Special TB Treatment Situations

- Pregnancy
  - RIPE drugs seem to be safe in pregnancy, but we just don't know for sure.
  - If the drugs are teratogenic, the frequency is apparently low.
  - Use either standard RIPE regimen or RIE X 9 months if patient wishes to avoid pyrazinamide
  - Breastfeeding is OK
- Kidney disease: Drug dose alterations and timing may be needed (particularly ethambutol and pyrazinamide). Consult literature and/or people resources for guidance.

Special Situations

- Drug resistance or intolerance
- HIV infection
- Pregnancy
- Kidney disease
- Liver disease
- Advanced age
- Recurrent disease
- Treatment failure

Treating TB in Face of Liver Disease

- Expect increased drug-induced hepatitis.
- Monitor closely.
- Alternative regimens suggested:
  1. RIE x 2 months, then RI X 7 months (9-month regimen)
  2. Rifampin + ethambutol + either fluoroquinolone (FQ) or injectable or cycloserine for 12-18 months
  3. RPE ± FQ for 6 months
  4. Ethambutol + FQ + cycloserine ± injectable for 18-24 months

Indiana State Department of Health

Special Situations

- Drug resistance or intolerance
- HIV infection
- Pregnancy
- Kidney disease
- Liver disease
- Advanced age
- Recurrent disease
- Treatment failure

Indiana State Department of Health

Other Special Situations

- Advanced age
  - Expect increased frequency of drug toxicity.
  - Consider 9-month no PZA regimen if >75 (RIE X 9 months)
  - Other considerations: Usual regimen for severe disease. Or add FQ to RIE regimen.
- Recurrent TB
  - If compliant prior DOT drug-susceptible isolate, standard regimen.
  - For others, assume resistance until proven otherwise: RIPE + FQ + injectable ± additional drug until testing done. Use DOT.
- Treatment failure
  - Culture still positive after 4 months (WHO uses 5 months)
  - Consider non-compliance, malabsorption, erroneous initial data, drug-drug interactions, laboratory cross-contamination, paradoxical reactions. Address if present.
  - Add 2-3 additional drugs while awaiting expanded drug susceptibility testing.
  - Seek expert help.

Indiana State Department of Health

TB Treatment: Future

- New drug regimens: high-dose rifapentine; higher doses of standard TB drugs; fluoroquinolones; new drugs (bedaquiline (FDA 2012), delamanid (Europe), pretomanid (ph III))
- Individualized regimens based on biomarkers, genetics
- Better data for pregnancy, children
- Substitutes for face-to-face DOT (e.g., cell-phone video) and new understanding of behavioral modification strategies

Indiana State Department of Health

Summary: Treatment of Pulmonary TB

- Coordination of public and private care, with public caregivers providing directly observed therapy and using enablers and incentives as needed.
- RIP(E)/RI usually X 6 months, sometimes 9 months, sometimes 4 months.
- Using daily regimens during intensive phase with daily or three-times weekly during continuation phase as preferred frequency.
- Being familiar with situations that require special regimens and/or monitoring: INH-resistance; other drug resistance or intolerance; HIV infection; pregnancy; kidney disease; liver disease; advanced age; recurrent disease; treatment failure

Indiana State Department of Health

Thank you for your attention

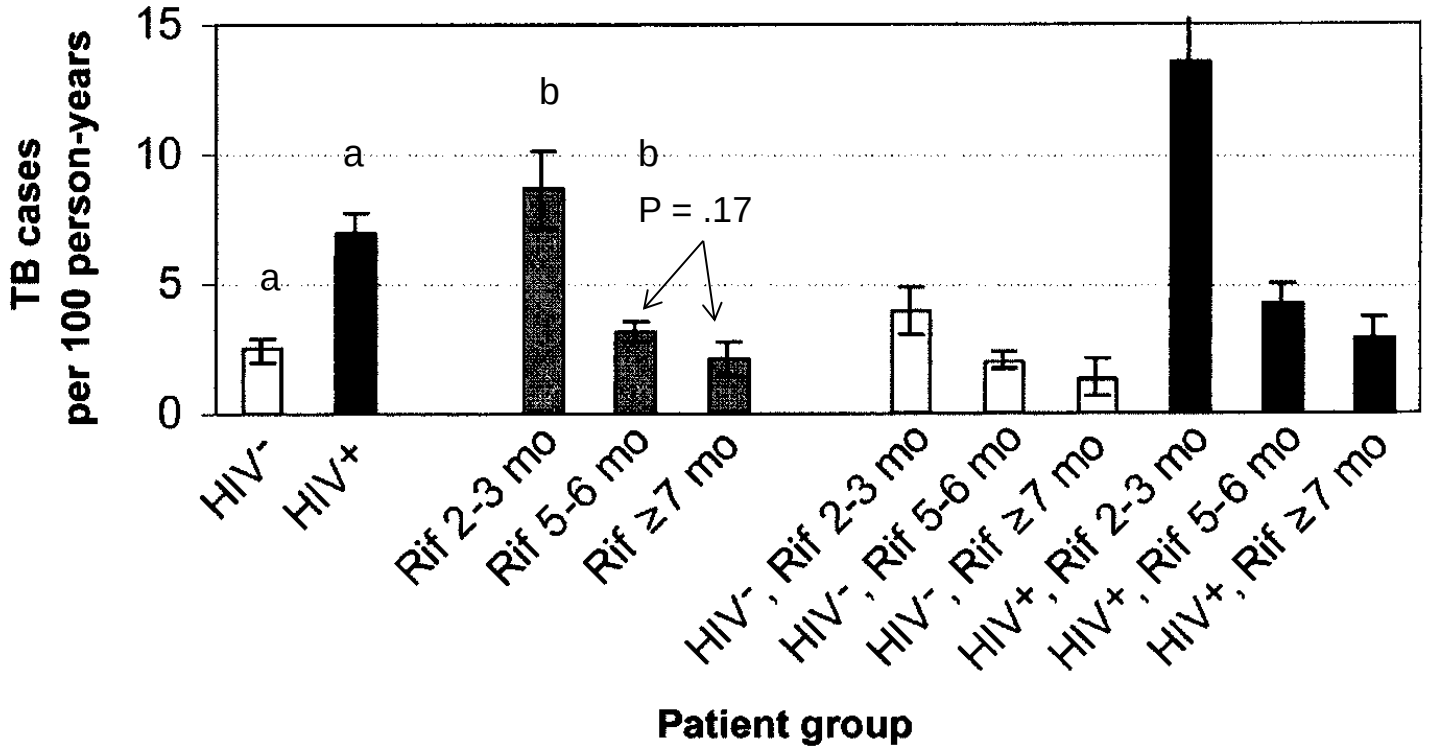
Objectives in Pulmonary Tuberculosis Therapy

- Overarching objectives: Cure the individual. Protect society.
- Specific objectives:
  - Rapidly reduce the number of actively growing bacilli.
  - Eradicate populations of persisting bacilli to achieve a durable cure.
  - Prevent resistance during therapy.

Nahid P et al., ATS/CDC/IDSA Guidelines. Clinical Infectious Diseases 2016; advanced access 8/10/2016 pages 1-49

Indiana State Department of Health

Rifampin Duration Impact on TB Recurrence Rates: Meta-Analysis



[a]P<.0001. [b]P=.0002

Korenromp EL et al; Clinical Infect Dis 2003;37:101

Indiana State Department of Health

