

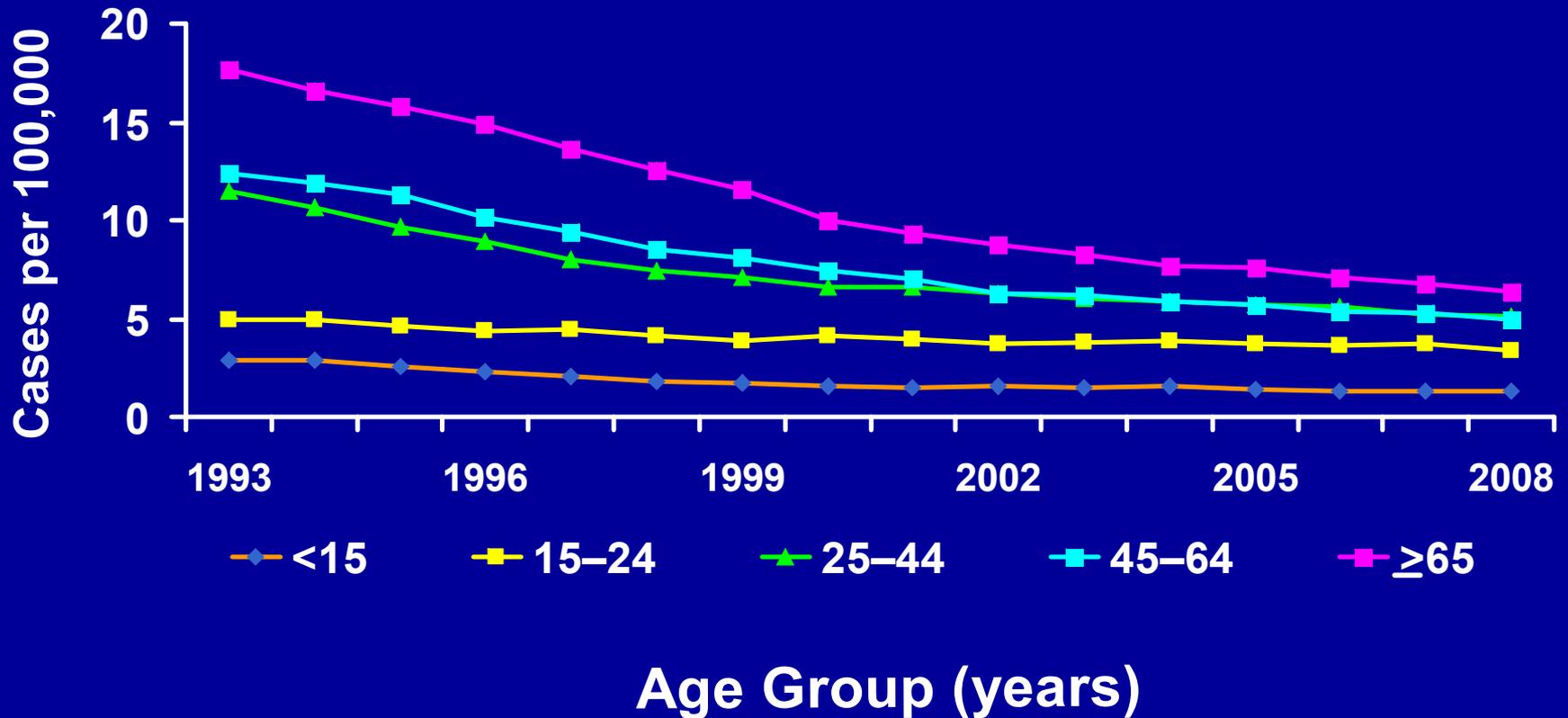
TB and the Elderly Patient

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TB in the United States

- Since 1993, case rates of TB have declined for all age groups
- In 2008, case rates declined or remained constant in all age groups
- The highest burden of disease continues to be among older adults
- 2008 case rate for all ages: 4.2/100,000
- 2008 case rates for age >65: 6.4/100,000

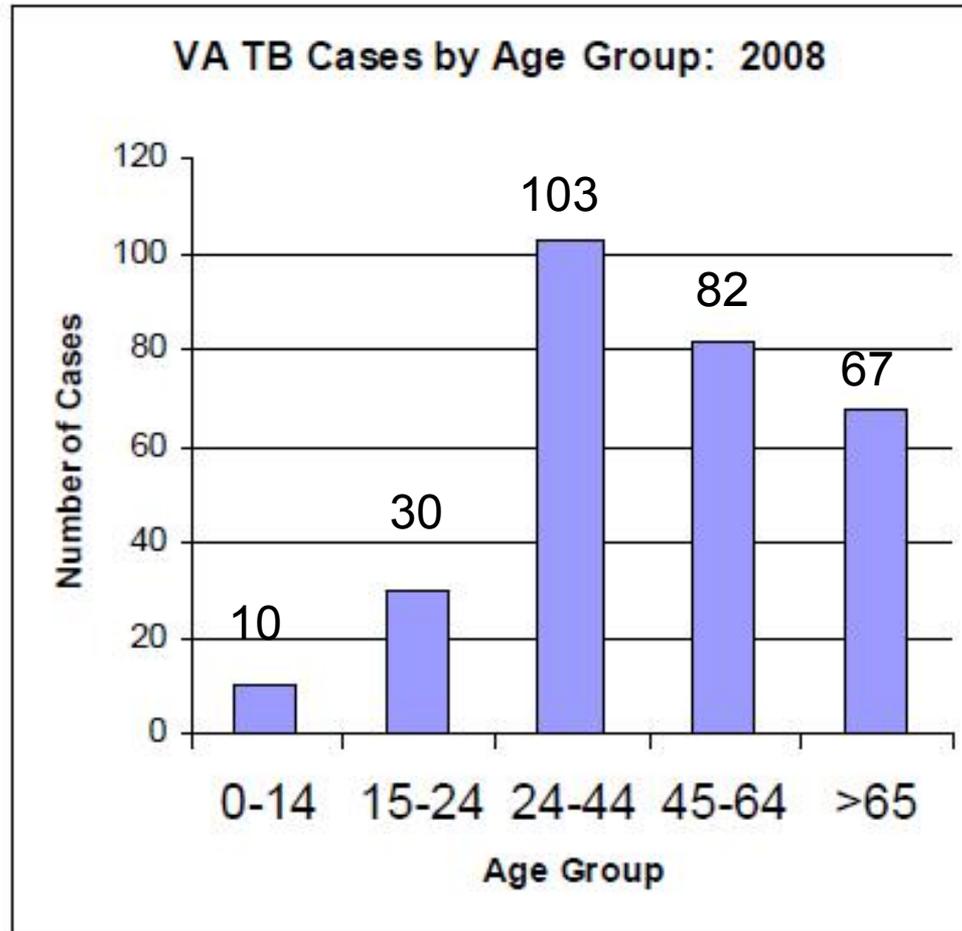
TB Case Rates* by Age Group United States, 1993–2008



*Updated as of May 20, 2009.

TB in Virginia: 2008

292 Total Cases



TB in Virginia

- The number of patients with TB increased in the following age groups:

	45-64	>65
2007	76 (24.6%)	46 (14.9%)
2008	82 (28.1%)	67 (22.9%)

Thomas T. Yoshikawa, Section Editor

Tuberculosis and Aging: A Global Health Problem

Shobita Rajagopalan

Department of Internal Medicine, Division of Infectious Disease, Charles R. Drew University of Medicine and Science,
Martin Luther King, Jr./Drew Medical Center, Los Angeles

“The geriatric population in developed countries, such as the United States, represents a large reservoir of tuberculosis infection across all ethnic and sex subsets.”

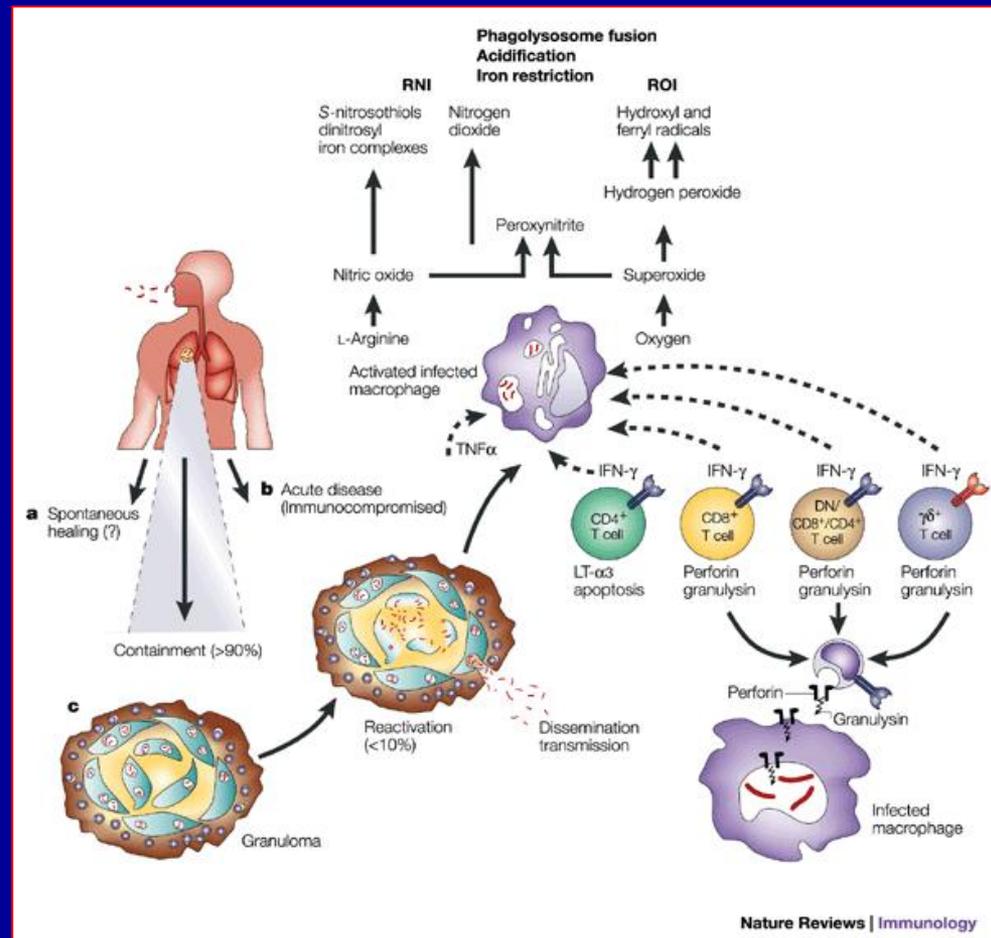
Which of the following events, all of which can happen at or around age 65, puts an individual at highest risk for developing active tuberculosis?

- A. Qualify for Medicare
- B. Retirement
- C. Age-related immune dysfunction



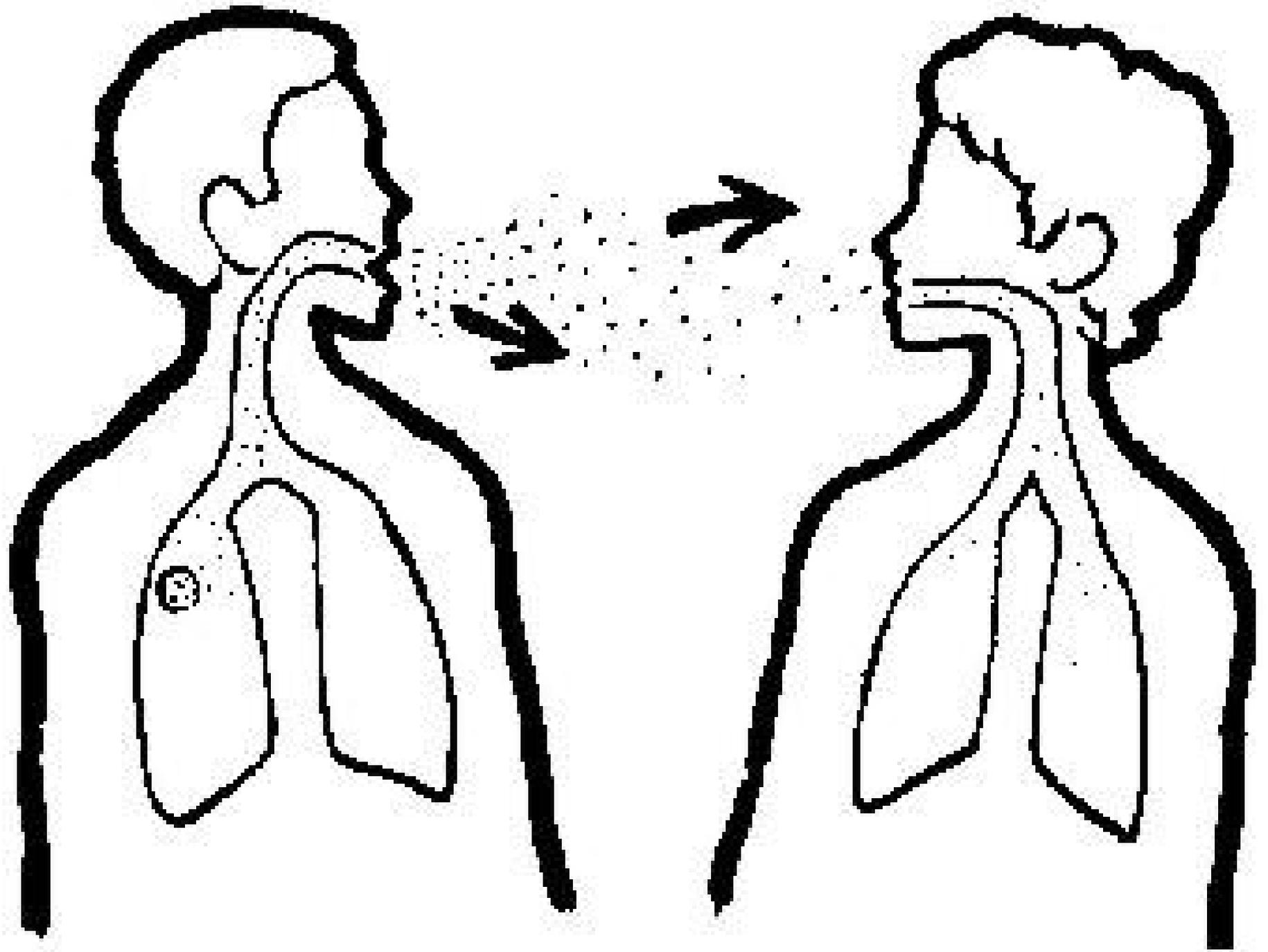
TB in the Elderly (1)

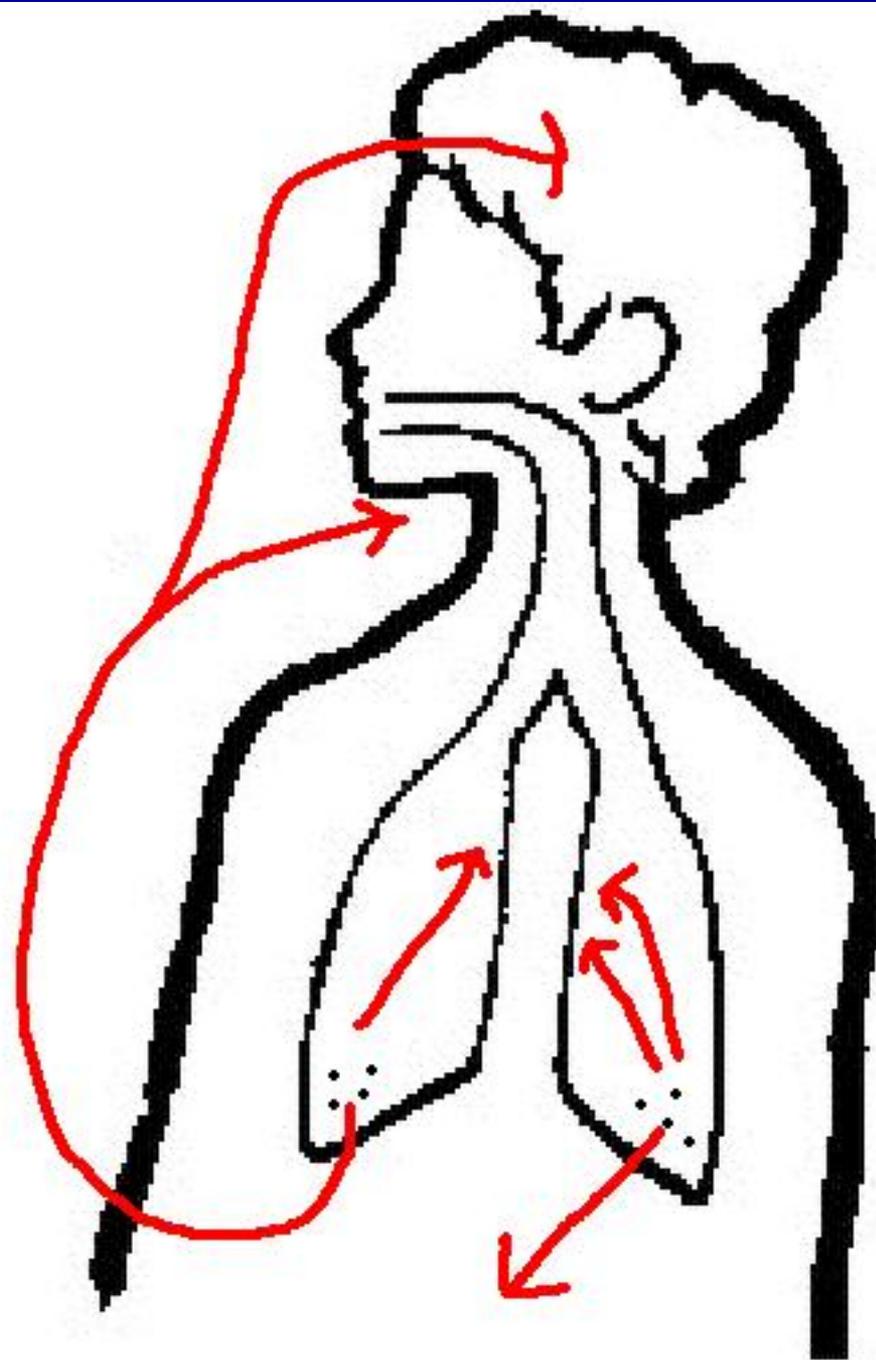
- The majority of TB in the elderly is secondary to reactivation of latent TB infection
- With age, the T-cell mediated immune response wanes allowing for latent TB to become active.



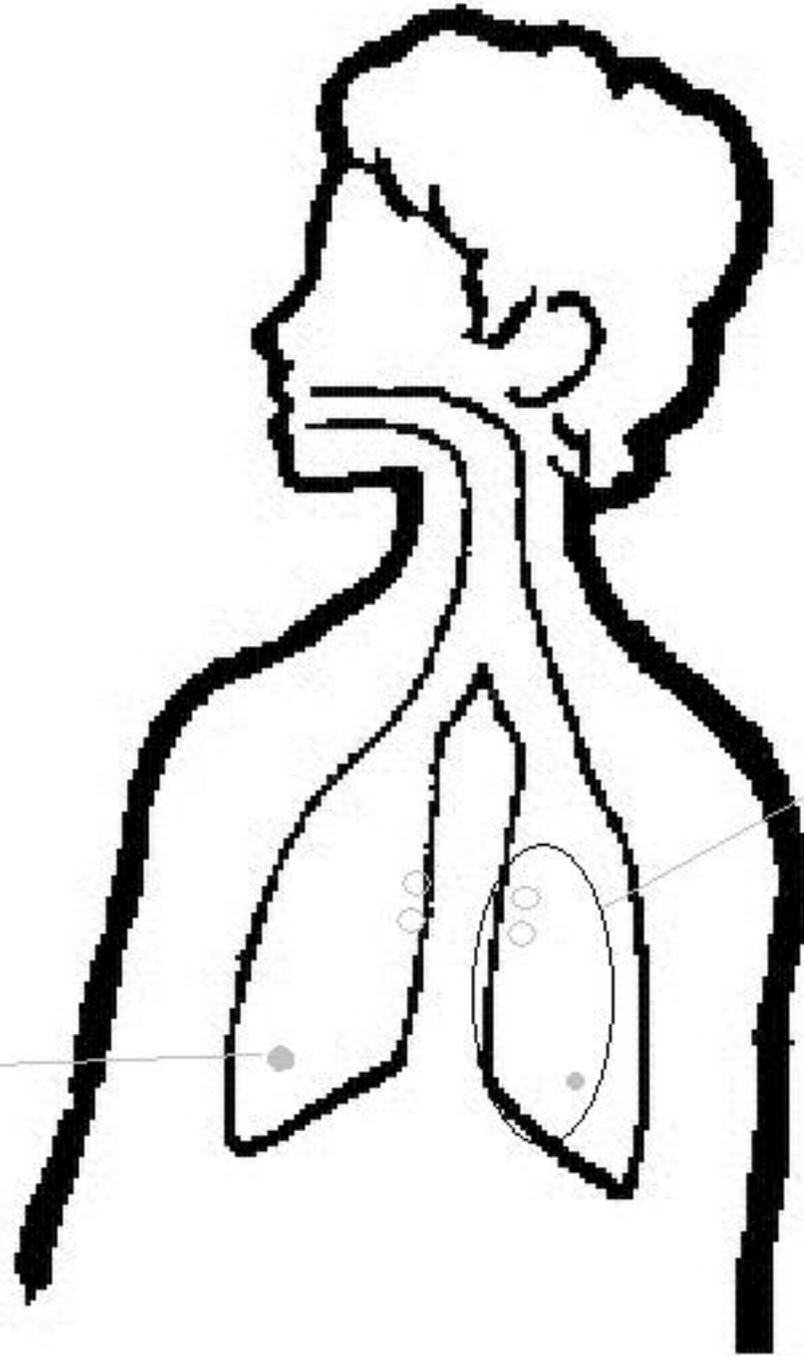
Nature Reviews | Immunology

Kaufmann SHE. Nature Reviews Immunology 2001;1:20-30.





**Ghon
Focus**



**Ranke
complex**

TB in the Elderly (2)

- Other factors contributing to reactivation of TB include:
 - Age-associated diseases:
cardiovascular disease, COPD
 - Poor nutrition
 - Chronic renal failure
 - Chronic institutionalization:
2-3 fold higher incidence of TB in nursing home residents

Presentation of TB in older adults (1)

- May be difficult to diagnose TB in older adults
- May not have classic presentation:
 - less likely to have hemoptysis, fever, night sweats than younger patients
- Nonspecific symptoms are common including:
 - Changes in activities of daily living
 - Chronic fatigue/weakness
 - Cognitive impairment
 - Anorexia/weight loss
 - Persistent low-grade fever
- Symptom duration may be greater in the elderly

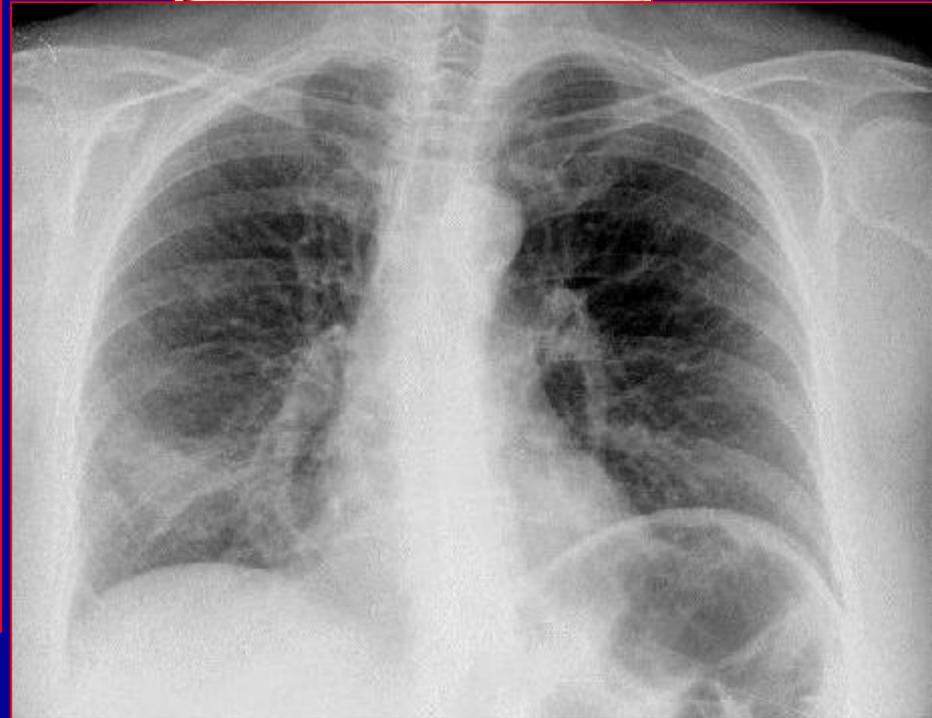
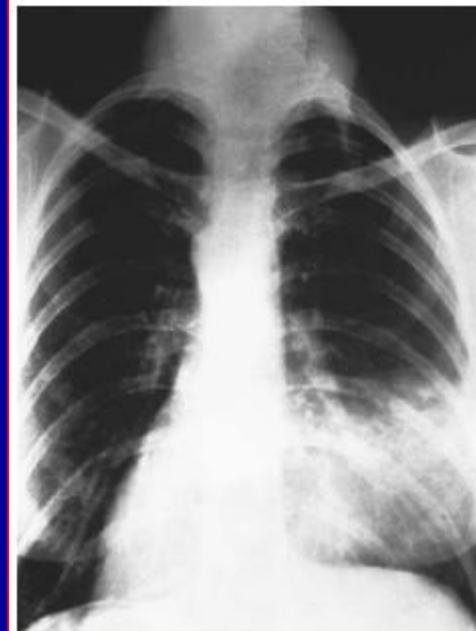
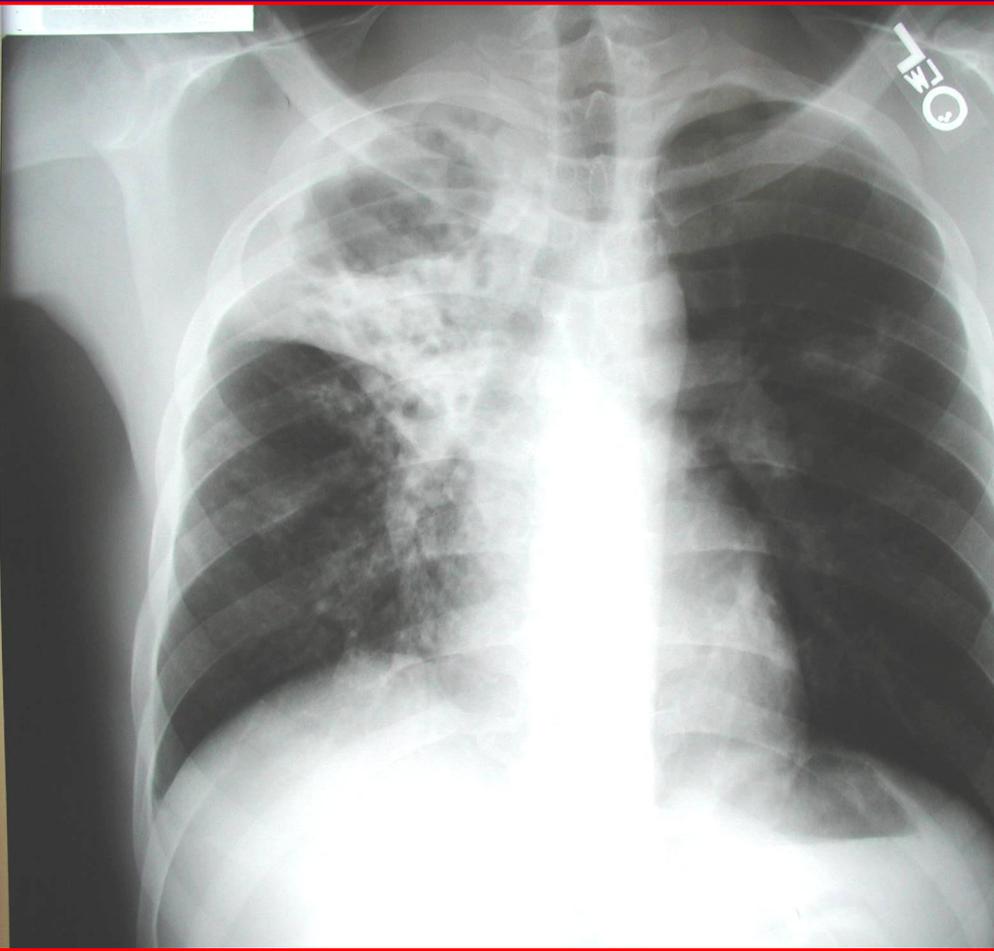
Korzeniewska-Kosela M et al. Chest 1994;106:28-32.

Van Den Brande P et . Journal of Gerontology 1991;46:204-9.

Presentation of TB in older adults (2)

- May be confused with age-related illnesses:
 - malignancy
 - diabetes mellitus
 - malnutrition
- Often only diagnosed postmortem
- *Lee et al.* found that in their study of young and elderly patients with pulmonary TB, initial diagnosis of TB was made correctly in 94.2% of younger patients, and only in 66.4% of elderly patients ($p < 0.0001$)
- Pneumonia and lung cancer were the other diagnosis considered

Typical TB Chest X-ray



Making the Diagnosis

- Two-step TST recommended due to waning immune response
- Sputum collection may be more difficult because older people may have trouble coughing
- Invasive procedure such as bronchoscopy may need to be performed to obtain sputum



Treatment

- Since most cases result from reactivation, drug resistance is less of a concern in elderly patients
- Resistance should be considered if patient is:
 - 1) From an area where there is a high prevalence of multi-drug resistance (MDR)
 - 2) A contact to a case with MDR
 - 3) Had previous inadequate treatment for active tuberculosis

Adverse Drug Effects (1)

TABLE 3. ADJUSTED HAZARD OF ALL, OR SPECIFIC, SIDE EFFECTS IN ASSOCIATION WITH CLINICAL CHARACTERISTICS

	Any Serious*		Rash/Fever†		Hepatitis‡		GI Upset§	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Female sex (versus male)	2.5	1.3 to 4.7	1.9	0.7 to 4.8	2.2	0.7 to 6.9	3.6	0.6 to 11.8
Age, yr								
35–59 (versus < 35)	1.7	0.8 to 3.8	1.0	0.3 to 3.1	4.8	0.9 to 25	2.1	0.3 to 14.9
60+ (versus < 35)	2.9	1.3 to 6.3	1.3	0.4 to 4.1	7.7	1.5 to 40	6.4	1.2 to 36
From Asia (versus all others)	2.5	1.3 to 5.0	2.8	1.1 to 7.5	2.2	0.7 to 6.9	3.6	0.8 to 15.2
Method of detection passive (versus active)	2.5	0.9 to 6.6	2.3	0.6 to 8.3	—	—	2.6	0.6 to 11.7
Smear positive (versus smear negative)	1.3	0.7 to 2.6	1.0	0.4 to 2.7	1.8	0.6 to 5.7	0.5	0.1 to 2.4
Drug resistant (versus pansensitive)	1.8	0.8 to 4.3	1.0	0.2 to 4.5	2.7	0.7 to 10.5	0.9	0.1 to 7.3
Abnormal baseline LFTs (versus normal) [¶]	1.6	0.6 to 4.2	2.3	0.6 to 8.0	—	—	3.9	0.8 to 19.5
HIV-positive (versus negative or NA)	3.8	1.05 to 13.4	5.1	1.02 to 27	4.3	0.5 to 38	—	—

Definition of abbreviations: CI = confidence interval; GI = gastrointestinal; HIV = human immunodeficiency virus; HR = hazard ratio; LFT = liver function test; NA = not available.

Boldface entries indicate statistically significant associations.

Hazard ratio and 95% confidence interval estimated from Cox multivariate proportional hazards modeling.

* Any serious side effects.

† Occurrence of rash or drug fever.

‡ Hepatitis defined as transaminases greater than three times the upper limit of normal with symptoms, or five times the upper limit of normal in the absence of symptoms.

§ Severe GI intolerance: sufficient to cause discontinuation of some or all medications and/or hospitalization.

|| Insufficient numbers, so estimates unstable.

¶ Before anti-TB therapy the liver transaminases were above the upper limit of normal.

Adverse Drug Effects (2)

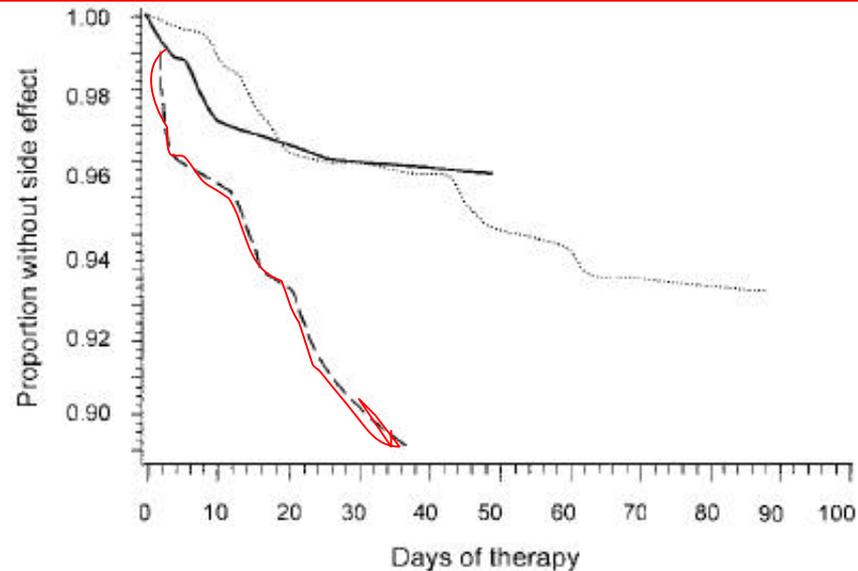


Figure 3. Association of age with interval from start of therapy until occurrence of any major side effect (using Cox proportional hazards regression). *Solid line*, age 17 to 34 years; *dotted line*, age 35 to 59 years; *dashed line*, age 60 years and older. *Lines* truncated at time after which no further events occurred.

Adverse Drug Effects (3)

- **Hepatotoxicity:**
 - incidence of INH-associated hepatotoxicity increases with age
 - risk of liver damage at age <35: 0.3%
 - risk of liver damage at age > 50: 2.3%
 - severity of hepatitis also increases with age, with a higher mortality in patients older than 50

Drug Interactions (1)

- Many elderly patients have multiple medical problems including:
 - Diabetes
 - Heart disease
 - Chronic lung disease
 - End-stage renal disease
- High potential for interaction with rifampin and other medications

Drug Interactions (1)

Table 1. Rifampin Drug Interactions of Major Clinical Significance*

Type of Drug	Comments
Oral anticoagulants	Monitor international normalized ratio; increased anticoagulant dose will likely be needed
Oral contraceptives	Use alternative form(s) of birth control; counsel patient and document in medical record
Cyclosporine	Monitor serum cyclosporine concentrations; increased dosage will likely be needed
Digitoxin	Monitor arrhythmia control, signs and symptoms of heart failure, and serum digitoxin concentrations
Glucocorticoids	Increase dose of glucocorticoid 2- to 3-fold
Itraconazole	Prefer to avoid use with rifampin; if must use, increase dose and monitor response
Ketoconazole	Avoid concomitant use if possible; if must use, increase dose and monitor response; space ketoconazole and rifampin doses by 12 h
Methadone hydrochloride	Increase methadone dose with concomitant rifampin therapy; monitor and control withdrawal symptoms
Midazolam or triazolam	Prefer to avoid use with rifampin; use another agent if possible
Phenytoin	Monitor serum phenytoin concentrations and seizure activity; increase dosage if needed
Quinidine	Monitor serum quinidine concentrations and arrhythmia control; increase dosage if needed
Theophylline	Monitor serum theophylline concentrations; increase dosage if needed
Verapamil	Use an alternative agent to verapamil because large oral verapamil doses may not be adequate; monitor patient for clinical response†

*Data adapted from Baciewicz and coworkers,^{1,2} Borchering et al.,³ and Strayhorn et al.⁴ Carefully adjust doses when rifampin use is discontinued. The enzyme induction effect is gradually reduced during a 1- to 2-week period or longer.

†See also data on diltiazem and nifedipine in Table 2.

http://www.drugs.com/drug_interactions.html

Drug Interactions (2)

Table 4. Updated Rifampin Drug Interactions*

Type of Drug	Comments
Controlled Drug Interaction Studies	
Selective serotonin receptor (5-HT ₂) antagonist ^{44,45}	Monitor clinical response; increase dose if needed; use another agent if needed
Buspirone hydrochloride ^{11,12}	Monitor clinical response; increased dose will likely be needed or use another agent if possible
3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors ^{17,18}	Monitor lipid panel; increased dose will likely be needed for simvastatin; further research needed for other agents in this class
Metronidazole ⁴⁵	Monitor for decreased clinical response; increase dose if needed or use another agent if possible
Opiates (morphine or codeine) ⁴⁶⁻⁴⁸	Monitor pain control and clinical response; increased dose may be needed in extensive metabolizers; use another agent if possible; may be associated with ethnic variability
Propafenone hydrochloride ^{20,21}	Monitor clinical response; increased dose may be needed or use another agent if possible
Tamoxifen citrate or toremifene citrate ⁴⁹	Monitor clinical response; increased dose likely needed
Zolpidem tartrate ¹⁴	Monitor clinical response; increased dose may be needed or use another agent if possible
Potential Interactions Based on Case Reports†	
Clozapine ¹³	Monitor clinical response; increase dose if needed or use another agent if possible
Levothyroxine sodium ⁵¹	Monitor thyrotropin level; increased dose likely needed
Sertraline hydrochloride ⁹	Monitor clinical response; increase dose if needed

*Carefully adjust dosage when rifampin use is initiated and discontinued. The enzyme induction effect is gradually reduced during a 1- to 2-week period or longer when rifampin therapy is discontinued. Based on the small number of reports, further studies are needed for most of these agents.

†Controlled study is needed to establish the importance and extent of the interaction.

http://www.drugs.com/drug_interactions.html

Finch et al. *Intern Med.* 2002;162:985-992.

HIV in the Elderly

- Individuals with HIV and a positive TST have a yearly risk for TB of 10%
- The number of people age 50 or older living with HIV/AIDS has been increasing in recent years
- In 2005, people age 50 or older:
 - accounted for 15% of new HIV/AIDS diagnoses
 - 24% of people living with HIV/AIDS

Outcomes

- Increased mortality due to TB noted in older populations
- *Wang et al.* reported a 26.5 % one-year mortality in patients >60 years old, versus 4.1% mortality in patient <60

Lee JH et al. J Korean Med Sci 2005; 20:784-9.

Wang CS et al. Infection 2008;36:335-40.

Leung et al. J Am Geriatr Soc 2002;50:1219-26.

Case: TB in the Elderly and the challenges of polypharmacy

- An 83 yo African-American gentleman presented to his local ER with complaints of extreme fatigue and severe weakness in both of his legs for one week.
- He did not have any cough, shortness of breath, no loss of appetite but had lost 30 lbs over the previous 6 months
- He was admitted to the hospital due to concern for malignancy or stroke

Case: Past Medical History

1. Diabetes mellitus
2. Hypertension
3. COPD
4. Peripheral vascular disease
5. Paroxysmal atrial fibrillation
6. History of Colon surgery for an unknown cause with chronic diarrhea as a result

Case: Medications

1. Coumadin
2. Actos
3. Sotalol
4. Omeprazole
5. Celebrex
6. Tylenol as needed
7. Combivent
8. Digoxin
9. Welchol
10. Lasix
11. Zocor
12. Hydralazine-
reserpine-HCTZ
13. Metoprolol

Which of the above medications interact with Rifampin and may require additional monitoring or dose adjustment?

Case: Events during hospitalization (1)

- Further discussion with patient and review of records revealed that he had been hospitalized at three different hospitals over the past 3-4 months for the same issues.
- A CT scan of his Chest/Abdomen/Pelvis showed: multiple liver lesions, splenic masses, pleural effusion and significant lymphadenopathy

Case: Events during hospitalization (2)

- A biopsy was performed due to concern for cancer
- The biopsy did not show cancer → it showed caseating granulomas
- A TST was placed—20 mm
- Patient was placed on 4 drug TB therapy and sent home

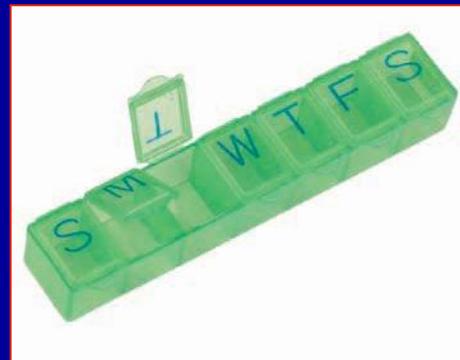
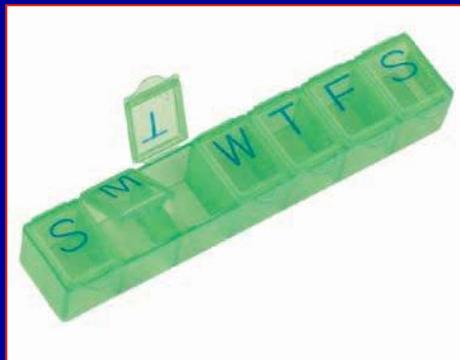
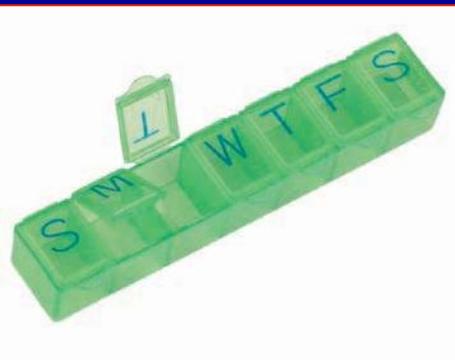
Case: Issues at home



- He complained of nausea when he took his medications.
- Anti-nausea medications were prescribed but they did not seem to work
- He was encouraged to eat with the medications but this did not seem to help
- He was becoming increasingly difficult to DOT

Case: Home visit (1)

- Lived with his elderly wife who was his main caregiver
- Very likely that she was unable to read
- Patient and his wife were very concerned about their friends knowing that the patient had TB
- A home health nurse helped the patient with his regular medications by filling pill boxes for him:



Case: Home Visit (2)

- Carefully reviewed all TB medications with patient to see which ones in particular made him feel ill:



- Discussed whether he was actually receiving nausea medication and if it helped when he did get it
- Discussed eating schedule, the foods that he enjoyed, encouraged him to try these foods prior to taking the medications

Case: Plan--Part 1

- Discussion with patient's primary care doctor's office:
 - limit other unnecessary medications
 - change medications if possible to cut down on pill burden and less frequent dosing
- Communication with patient's cardiologist as it seemed that some of the patient's issues were related to his atrial fibrillation and not to TB issues

Case: Plan--Part 2

- Scheduled anti-nausea medications to be taken at the same time as DOT
- TB nurse would extend her visits with patient to talk to him and sit with him before and after taking medications to help build rapport, and offer support and encouragement

Case: Outcome

- Scheduled anti-nausea medications helped
- Decreasing the amount of other medications the patient was taking was helpful
- TB nurse established terrific rapport with patient and his wife and he started to look forward to her visits
- Patient had a pacemaker placed which helped with his other symptoms and also decreased amount of medications he was taking
- He completed 9 months of therapy and is doing great

Lessons Learned

- Communication is key:
 - patient
 - caregiver
 - other providers
- Consider the whole patient
- Treating TB requires a team effort
- Be willing to be flexible
- Patience *is* a virtue

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Appendix A: Additional Rifampin Drug Reactions

Table 2. Rifampin Drug Interactions*

Type of Drug	Comments
β-Adrenergic blocking agents	Monitor patient for clinical response; increased propranolol hydrochloride or metoprolol dose may be needed
Chloramphenicol†	Monitor serum chloramphenicol concentrations; may need to increase dosage
Clarithromycin	Monitor signs and symptoms of infection; more study needed
Dapsone	Monitor clinical response; dosage increase may be necessary; additional study needed when used for <i>Pneumocystis carinii</i> prophylaxis; monitor for hematologic toxic effects
Diazepam†	Monitor clinical response; may need to increase diazepam dosage
Digoxin (oral)	Monitor arrhythmia control and signs and symptoms of heart failure; monitor digoxin serum concentrations
Diltiazem†	Use alternative agent if possible because intra oral doses of diltiazem may be ineffective; monitor clinical response‡
Disopyramide	Monitor arrhythmia control; increase dosage if needed
Doxycycline	Monitor clinical response; increase dosage if needed
Fluconazole	Monitor clinical response; may need to increase fluconazole dosage; less reduction in serum concentrations vs other azoles
Haloperidol†	Monitor clinical response; increase dosage if needed
Losartan potassium	Monitor patient for clinical response; may need to increase dosage
Nifedipine	Alternative class of agents should be considered; monitor clinical response; dosage increase may be needed†
Nortriptyline hydrochloride	Monitor clinical response and serum nortriptyline concentrations
Pefloxacin	Moderate rifampin induction effect; pending further research, no dosage adjustment recommended
Sulfonylureas	Monitor blood glucose levels; base any dosage adjustments on blood glucose control
Tacrolimus	Monitor serum tacrolimus concentrations and clinical response; increased dose may be needed or use another agent if possible
Tocainide	Monitor arrhythmia control; increase dosage if needed

*Data adapted from Baciewicz and coworkers,^{1,2} Borchering et al,³ and Strayhorn et al.⁴ Additional study is needed to clearly establish clinical significance. Carefully adjust doses when rifampin use is discontinued. The enzyme induction effect is gradually reduced during a 1- to 2-week period or longer.

†Probably of clinical significance.

‡See also data on verapamil in Table 1.