Tuberculosis remains the leading cause of death among HIV-infected patients living in Africa. This disease contributes significantly to the high mortality rates observed both before and after initiation of antiretroviral therapy. Improving HIV care will require increased detection and treatment of TB.

This book is targeted to those providing primary HIV care in Africa and other resource-limited settings: nurses, clinical officers, and medical officers without higher specialization. The manual aims to make the research about TB and HIV relevant to the daily practice of medicine.

Features include:

- An empirical approach consistent with World Health Organization guidelines
- Brief, bulleted text for quick review and ease of learning
- Case-based format
- Photographs of x-rays and clinical findings
- Helpful tables, charts, and diagrams
- Over 250 references for further study

This educational tool is made available free of charge. For information about obtaining additional copies, please write to the author at jonfielder6@gmail.com.

"The converging epidemics of TB and HIV are a perfect public health storm for sub-Saharan Africa and many other parts of the world. This straightforward but extremely well-referenced manual is a much-needed, practical reference for those on the clinical front lines of this battle. I highly recommend this text to anyone caring for those with TB or HIV in resource-limited settings."

***Dr. Nate Smith, former senior medical technical advisor, Institute of Human Virology, East Africa***

*Jon Fielder, MD, who trained in internal medicine at Johns Hopkins Hospital, was consultant physician at AIC Kijabe Hospital in Kijabe, Kenya from 2002-2006, where he directed a large HIV clinic and training program. He currently serves at the Partners in Hope Clinic in Lilongwe, Malawi.*

TUBERCULOSIS IN THE ERA OF HIV

A clinical manual for care providers working in Africa and other resource-limited settings

Jon Fielder, MD

# TUBERCULOSIS IN THE ERA OF HIV

## A clinical manual for care providers working in Africa and other resource-limited settings

**Jon Fielder, MD**

NOT FOR SALE

In Africa, tuberculosis is the leading cause of ...

## Mortality

**<u>Kenya:</u> Autopsy study (examination after death) of HIV-infected adults *(JAIDS 2000;24(1):23-29)***

- In HIV-infected patients, 1 out of every 2 deaths caused by TB
- TB was the most common cause of death in HIV-infected patients
  - Bacterial pneumonia was the second most common cause
  - In HIV-*negative* patients, TB was uncommon cause
- In 4 out of every 5 HIV-positive tuberculosis cases, TB had spread from the lungs to involve other organs (disseminated tuberculosis)
- Only 1 out of every 2 TB cases was diagnosed before death

**<u>Botswana:</u> Autopsy study *(Int J Tub Lung Dis 2002;6(1):55-63)***

- In HIV-infected patients, 2 out of every 5 deaths caused by TB
- TB was the most common cause of death in HIV-infected patients
  - Bacterial pneumonia was the second most common cause
  - In HIV-*negative* patients, TB was uncommon cause
- Tuberculosis disseminated in 9 out of every 10 HIV-positive cases

**<u>Ivory Coast:</u> Autopsy study *(AIDS 1993;7(12):1569-79)***

- In HIV-infected patients, 1 out of every 3 deaths caused by TB
- TB was the leading cause of death in HIV-infected patients
  - Bacteria in the blood was the second most common cause
  - In HIV-*negative* patients, TB was uncommon cause
- 9 out of every 10 HIV-infected patients with TB had dissemination

## "Slim disease"

Early in the epidemic, HIV was often referred to as "slim disease" because patients became so thin and wasted. Many people assumed that the wasting was caused mostly by malnutrition or by HIV itself.

However, in a study from the Ivory Coast, **TB was the leading cause of HIV-wasting syndrome** (*BMJ 1994;308(6943):1531-33*).

## Severe anemia

(*Trans R Soc Trop Med Hyg 2005;99(8):561-67*)

When HIV-positive patients presented to the hospital with hemoglobin values less than 7 g/dl, the most common causes were:

- **Tuberculosis (2 out of every 5 patients)**
- Bacteria, especially salmonella (1 out of 5 patients)
- Iron deficiency (only 1 out of 6 patients)
- Malaria and other parasites are rare causes in HIV-infected patients

In Africa, tuberculosis is the leading cause of ...

## Chronic cough

**<u>Zimbabwe:</u> Study of ambulatory (walking) adult outpatients with cough longer than 3 weeks *(Clin Infect Dis 2005;40(12):1818-27)***

- About 1 out of 2 patients had tuberculosis
- Bacterial pneumonia was second most common

## Blood infection in patients admitted to hospital with fever

**<u>Tanzania:</u> Patients with fever admitted to hospital (*Clin Infect Dis 1998;26(2):290-96*)**

- 1 out of every 5 HIV-infected patients with fever had TB in the blood
- Tuberculosis was the single most common blood infection
  - Salmonella and then other bacteria were next most common
  - Only 1 out of every 10 patients had malaria

**<u>Malawi:</u> All outpatient and hospitalized cases with fever *(J Infect Dis 2000;181(4):1414-20)***

- 1 out of every 8 HIV-infected patients with fever had TB in the blood
- Tuberculosis was the single most common blood infection
  - Salmonella and then other bacteria were next most common
  - Only 1 in 25 had malaria (during the dry season)

**<u>Uganda:</u> Patients with fever admitted to hospital (*JAIDS 1998; 19(5):484-89)***

- 1 out of every 8 HIV-infected patients with fever had TB in the blood
  - Salmonella and then other bacteria were next most common

## TB is also common in HIV-infected patients with a short duration of cough, but bacterial pneumonia is the #1 cause

**<u>Kenya:</u> Patients diagnosed with acute pneumonia and having cough for less than two weeks *(Lancet 200;355(9211):1225-30)***

- Most common cause in HIV-infected patients was bacterial pneumonia
- 1 out of every 8 HIV-infected patients had TB

**<u>Malawi:</u> HIV-positive and HIV-negative patients with cough less than three weeks, weight loss, and failure of antibiotics to improve symptoms *(Trans R Soc Trop Med Hyg 1998;92(2):161-63)***

- 1 out of every 3 patients had TB

# Tuberculosis in the Era of HIV

Dr. Jon F. Fielder

## Table of Contents

"The captain of all these men of death that came against him to take him away was the Consumption, for it was that that brought him down to the grave."

**— John Bunyan,**

***The Life and Death of Mr. Badman*,**

**referring to TB by its popular name of "consumption"**

## Introduction

The past five years have seen remarkable progress in the treatment of human immunodeficiency virus (HIV) infection in Africa. Yet, this progress is threatened by the epidemic of tuberculosis (TB). In North America and Europe, experience with the management of opportunistic infections preceded by years the availability of effective therapy for HIV itself. In Africa, the situation is reversed: the scale-up of antiretroviral access has come prior to the ability to manage complex opportunistic conditions. There is either no or limited access to bacterial blood cultures, sputum TB cultures, CT scans, cancer chemotherapy, or even simple serum cryptococcal antigen testing.

While working in Kenya from 2002 to 2006, where I directed a large HIV clinic, I was faced with many of these same difficulties. Our team used clinical clues to make empiric diagnoses of sputum smear-negative and extrapulmonary TB.

The material presented will, I hope, convince you that TB represents the single greatest threat to our patients. If we are to extend the lives of those we care for, we simply must be more aggressive concerning the diagnosis and treatment of TB in HIV-infected individuals.

I want to make several points about the approach of this book:

- **The manual is intended for front-line HIV care providers.**
  Nurses, clinical officers, and medical officers without higher specialization provide the bulk of care in Africa. But they often are unaware of the research which could help them care for patients. This book grew out of a curriculum I presented to primary HIV care providers in Kenya.

- **The approach is empirical.**
  "Empiric" means "best guess" based on the limited data available. In a perfect world, we would always obtain full and accurate information before making decisions. But we must do the best we can with history, physical exam, and basic lab tests. Working in an HIV clinic in the United States, I had to use empirical clinical reasoning to diagnose and treat infections such as cerebral toxoplasmosis and *Pneumocystis jirovecii (carinii)* (PCP) pneumonia. Even in the wealthy US, we did not always have access to the needed resources.

- **The approach is based on epidemiology.**
  Epidemiology means the study of disease patterns. There exists a large amount of very good and valuable research about HIV-related tuberculosis in Africa. We know TB is the leading cause of all of the following in patients infected with HIV: death, enlarged lymph nodes, severe anemia, chronic

cough, pleural effusion, pericardial effusion, "slim disease" (severe wasting) and fever in those hospitalized. We should use this information to make clinical decisions.

- **The approach is consistent with WHO guidelines.**

  The last chapter outlines the 2006 World Health Organization (WHO) guidelines on the diagnosis of smear-negative and extrapulmonary TB in resource-limited settings characterized by high HIV prevalence rates. If you read these guidelines or the summary I provide, you will see that the WHO approach also relies on basic lab tests and empirical clinical reasoning. This book is concerned primarily with diagnosis and the decision to initiate therapy for TB. National treatment guidelines should be followed.

- **The approach is case-based.**

  The cases presented are based on real patients and are meant to illustrate the relevance of important principles. The manual contains pictures, x-rays, tables, graphics, and highlighted text to help you understand the content. Over 250 references from the medical literature are cited.

I invite feedback about the manual. Please tell me what was useful, and what could be improved.

Jon Fielder, MD
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October 2009

### Acknowledgements

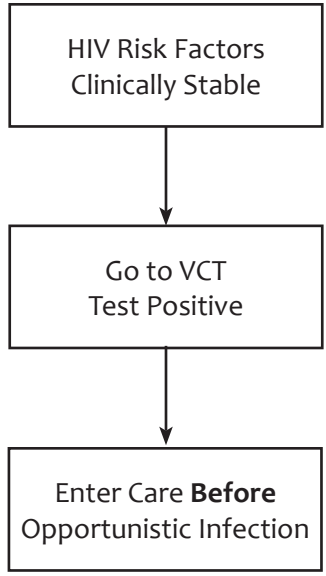
Lucky Sahualla of Performance Based Healthcare Solutions invested an enormous amount of uncompensated time into the layout of this book. Rebecca Thilo of Baylor College of Medicine and Adrienne Winston also contributed greatly. Angela Mutegi of the Ecumenical Pharmaceutical Network (Nairobi) and the staff of Kijabe Hospital facilitated publication. I am grateful to friends of the Fielder Medical Assistance Foundation for support of printing and distribution. Names and affiliations of reviewers are listed at the end of the References section.

This book is dedicated to my friend Kenneth Miriti, who has taught me much more than I have ever taught him.

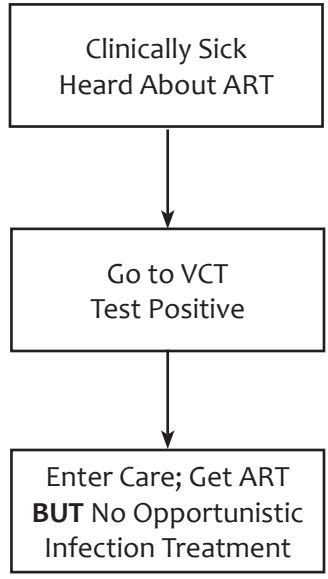
# Chapter 1

# Tuberculosis in the Era of HIV

## Voluntary counselling and testing (VCT): the ideal



## VCT: a common reality



## The limitations of "VCT"

- In Africa, "VCT" often comes too late in the course of HIV disease
- In reality, many clients get DTC (diagnostic testing and counseling) when they are ill and go to VCT
- Are patients ill because they have HIV only?
  - Or is something else making them come to hospital?
  - What opportunistic infections make them ill?

## TB rates are so high that even researchers are surprised

- Tanzania: Ambulatory (walking) HIV-infected outpatient volunteers were referred by VCT or by friends for a vaccine study[1]
- Of the 93 volunteers with CD4 counts higher than 200 cells/μl:
  - 10 had active tuberculosis by sputum TB culture (most of these were sputum AFB smear-negative)
  - 4 had early "subclinical" TB without symptoms of cough, fever or weight loss
  - In total, 15% (14 of 93) had active TB but were only diagnosed because they volunteered for a research study, not because they came to clinic!
- South Africa: One of every six patients (16%) who had no symptoms of tuberculosis at the time of screening actually had positive sputum cultures for TB
  - "Culture positive TB in the absence of symptoms is not uncommon, especially in participants initiating ART."[2]
  - Even adding chest x-ray screening will still miss many cases because the x-ray of HIV-infected TB patients can be normal (20-33% of the time), especially in cases of advanced AIDS[3-5]

## The surge in tuberculosis in the era of HIV

- Most of Africa is seeing out of control TB rates
- South Africa: 9% (1 of every 11) of randomly selected HIV-infected patients living in the community had TB[6]
  - More than half of these had not yet been diagnosed
  - "Lack of [typical] symptoms suggestive of pulmonary tuberculosis" may explain why so many patients are not diagnosed in clinic
- HIV is driving the tuberculosis epidemic[7, 8]
  - South Africa: As HIV infection rates increased from 6 to 22%, the number of TB cases more than doubled[9]

## Tuberculosis is the most common serious infection in HIV-positive patients in resource-limited settings

- Tuberculosis is a major cause of **slim disease**
- Slim disease was the name used in the early years of the HIV epidemic because the patients were so thin
- In West Africa, 2 out of every 5 patients with HIV-associated wasting (slim disease) had TB[10]
- In an African antiretroviral therapy clinic, **more than half** of the patients had a history of TB or developed TB after starting ART[11]

## Tuberculosis is the most common cause of death in HIV-infected patients living in Africa

- About 1 out of every 4 HIV-infected patients in the world dies of TB[12]
- Without antiretroviral therapy (ART), about 1 out of every 4 HIV-infected TB patients will die, even if they are treated for tuberculosis[13]
- In Africa, autopsy studies after death show tuberculosis is the leading cause of mortality (see table below)
  - TB had spread throughout the body in most cases
- South Africa: After starting ART, mycobacterial disease (TB and the related organism *Mycobacterium avium)* **remains a serious problem, accounting for 1 out of every 3 deaths in hospitalized patients[14]**
- South Africa: Among patients followed in an HIV clinic (on ART and not on ART), over half of deaths were due to TB[15]
- Burkina Faso: Among patients started on ART, "wasting syndrome" (1 of 4) and tuberculosis (1 of 5) were the leading causes of death[16]
  - Recall that in Africa, TB is the leading cause of HIV-related wasting, or "slim disease"[10]

**Table 1-1: Proportion of HIV-related deaths caused by tuberculosis in autopsy studies of patients not using antiretroviral therapy**

| Country | HIV-infected patients who died of TB | Comment |
|---|---|---|
| **Kenya[17]** | 1 out of 2 | Only half of TB cases diagnosed before death |
| **Botswana[18]** | 2 out of 5 | |
| **Ivory Coast[19]** | 1 out of 3 | |
| **Democratic Republic of Congo[20]** | 2 out of 5 | |

## Why is tuberculosis so common in HIV-infected patients?

- Many Africans and others living in resource-limited settings are already infected with tuberculosis, but TB infection may be quiet and not active
  - This stage is called **latent ("sleeping") tuberculosis**
  - Without ART, 30% (about 1 out of every 3) of those with latent tuberculosis will go on to develop active TB disease at some point during their lives[13]
  - This means that we can expect millions of new HIV-related TB cases in coming years[21]
  - In 2007, there were 1.4 million new HIV-related TB cases in the world, and about 80% of these were in Africa[12]
    - There were 450,000 HIV-related TB deaths
- As the CD4 count declines, tuberculosis wakes up, called **reactivation,** and now TB can cause disease and symptoms
  - HIV-infected patients are 10 times as likely to reactivate latent tuberculosis[22]
  - In resource-limited countries with HIV epidemics, HIV-infected people are 20 times as likely to develop TB[12]
- Sometimes, patients with low CD4 counts can contract a new TB infection which spreads through the body very quickly to cause disease and symptoms[23, 24]
  - This form is called **primary tuberculosis**, and the spread throughout the body is called **disseminated TB**
- It is possible for HIV-infected patients who are treated for TB to get it again[25]; this is called **recurrence**
  - **Relapse** occurs when tuberculosis was not treated completely or effectively the first time
  - **Re-infection** occurs when the weak immune system allows a new TB infection (strain) to enter the body for a second time

## Primary vs. re-activation tuberculosis[23]

- **Primary tuberculosis** is the first time the infection enters the body through the lungs
  - HIV-negative patients and HIV-positive patients with high CD4 counts have strong immune systems and contain TB in the lung
  - HIV-positive patients with low CD4 counts (< 200/μl) and children may develop pneumonia and disseminated *primary* tuberculosis because the weak immune system fails
- **Reactivation tuberculosis** occurs when "sleeping" tuberculosis awakes and causes disease
  - In HIV-negative patients, upper lobe cavitary disease (holes in the lung) is the classic example of reactivation tuberculosis
  - In HIV-positive patients, there is a higher chance that TB will wake up and spread throughout the entire body

## Active tuberculosis may increase the amount of HIV in the body and weaken the immune system

- The **viral load** is the amount of HIV in blood
- Higher viral loads cause faster disease progression, meaning patients develop opportunistic infections and AIDS more quickly[26]
- Tuberculosis may increase the HIV viral load[27-29]
  - So TB can accelerate the decline in the immune system which leads to other opportunistic infections[30]
  - Treating TB leads to increases in CD4 counts, but the viral load does not improve[31]

## TB rates are even higher than most people realize

- Uganda: Many more TB cases diagnosed in poor areas of Kampala city than public health system officially estimated[32]
  - Twice the rates officially reported for Kampala city
  - **Most of these cases were acid-fast bacilli (AFB) smear-negative**
- There is often underreporting because of failure to diagnose smear-negative and extrapulmonary TB in patients with HIV[6]

## Sputum smear-negative pulmonary tuberculosis: a reason for missed diagnoses

- Older studies show that anywhere from 33% to 50% of pulmonary TB cases in HIV-positive patients will be AFB smear-negative[33-38]
- Newer studies show that **most pulmonary TB cases in HIV-infected subjects are AFB sputum smear-negative**
  - South Africa: Active screening of all HIV-infected patients coming to an antiretroviral therapy (ART) clinic found that even with the best microscopes **87% of the culture-proven pulmonary TB cases were AFB smear-negative!**[5]
    - 1 out of every 4 patients had TB on joining the clinic
    - 2 out of 5 (38%) patients with CD4 < 100 cells/μl had TB
  - South Africa: Aggressive screening using induced sputum (nebulized saline) found that **64% of confirmed and possible TB cases were AFB sputum smear-negative**[39]
  - Kenya: Using standard microscopes, 2 out of every 3 (64%) HIV-infected patients with culture-confirmed TB were AFB smear-negative[40]
- Zimbabwe: Using standard clinical protocols for evaluating AFB smear-negative TB suspects, less than 1 out of every 3 cases (29%) of culture-proven tuberculosis were actually diagnosed and treated[41]
- Other studies show that HIV-infected patients with TB are less likely to have positive sputum smears than HIV-negative TB patients[33-38]
- The overburdened health system does not have the resources[42] or personnel[43] to screen sputum samples appropriately

## Tuberculosis threatens the successful scale-up of HIV care programs and antiretroviral therapy

- Death rates on ART are much higher in Africa than in the West[44-47]
  - Opportunistic infections, like TB, are still common on ART[48]
- Many patients waiting for antiretroviral therapy die[49]
  - Since TB is the most common cause of death in HIV patients, we can assume tuberculosis kills many patients still waiting for ART
  - If we are looking carefully for TB, we should be able to treat it while patients are waiting to start ART
- Since many cases of tuberculosis are not diagnosed,[17] patients starting ART have a high risk of the immune reconstitution inflammatory syndrome[50] (see Chapter 5)

## TB in a South African ART clinic: a case study[11]

- Before starting ART,
  - 1 of every 2 patients had a history of TB
- At the time of starting ART,
  - 1 out of every 4 patients was on TB treatment
- After starting ART,
  - Another 1 out of every 10 patients developed new TB
- **By the end of three years of follow-up, 70% (7 out of every 10) had experienced at least one episode of TB**

Your clinic should examine its patients' records and ask: "How many of our patients have been treated for TB?" If the number is very low, are you missing cases? Are you rushing people on to ART before diagnosis?

## "Textbook" tuberculosis in HIV-negative patients[23]

- Ill for a few weeks or months
- Night sweats, fever, weight loss
- Severe cough, sometimes with hemoptysis
- Upper lobe cavitary disease on chest x-ray

Theclassic symptoms which care providers remember from their medical training are still very important, but we need to add some new ideas.

In the era of HIV, care providers need a new textbook to diagnose and treat TB.

Tuberculosis comes in entirely new forms.

## Standard protocols fail to identify many cases of pulmonary tuberculosis

- Based on traditional understandings of HIV-negative tuberculosis, standard screening approaches rely on symptoms of cough for more than 2-3 weeks in order to identify pulmonary TB suspects[51]
- In an HIV clinic in South Africa, relying only on cough missed half of the cases of pulmonary TB[52]
  - Of all patients entering the ART clinic who were not already on TB treatment, 1 out of every 5 (19%) were found to have confirmed, culture-positive pulmonary tuberculosis
  - 1 out of every 5 (22%) patients with TB had **no symptoms at all**
  - **Only 9% of proven TB cases were sputum AFB smear-positive**

## Fundamental characteristics of TB in the era of HIV

- Duration of symptoms
  - Traditional teaching is to screen patients for TB when they have more than three weeks of cough
  - In one study, patients had tuberculosis for **more than a year** before diagnosis[6]
  - And TB is also common in those patients **with less than three weeks** of cough[53, 54]
  - **A very short or a very long course does not rule out TB**
- Symptoms can be "**atypical**," or not what you expect
  - Severe anemia (hemoglobin < 7 mg/dl)[55]
  - Mild cough without blood[23] or sputum[56]
- Pulmonary TB in HIV-infected patients shows a different pattern on chest x-ray[3-5, 57]
  - Disease occurs **anywhere** in lung
  - Cavities are rare when the CD4 count is low (< 200/µl)
  - CXR **may be negative** in as many as 1 of every 3 HIV-infected patients with TB
- Extrapulmonary tuberculosis
  - Spread from lung to other organs is common: brain, heart, bone, blood, liver, spleen and lymph nodes[57, 58]
  - Studies show most patients who die with TB have infection spread outside the lung and throughout the body[17, 18]

## The body's immune response to TB: effect on signs and symptoms

- The "fight" between TB and the normal body with a strong immune system leads to:[23]
  - Tissue destruction
  - Classic symptoms
    - High fevers
    - Severe cough and bloody sputum
    - Severe headache with tuberculous meningitis
- When the immune system is weak, there is not a big fight between TB and the body:
  - Atypical (unusual) symptoms (slow, mild at first)[1]
  - Less tissue destruction (lung cavities are rare)[23]
  - Patients sometimes become sick over a long period of time, and the absence of the usual symptoms delays diagnosis[6]

## Comparison of the presentation of pulmonary TB: HIV-negative and HIV-positive patients[23]

| Sign or Symptom | Strong Immune System (HIV-negative or HIV-positive with high CD4 count) | Weak Immune System (HIV-positive with low CD4 count) |
|---|---|---|
| **Primary or re-activation** | Re-activation | Re-activation or primary |
| **Time between infection and symptoms** | Years of delay between first infection and actual symptoms | Years of delay between first infection and actual symptoms, **OR** rapid progression from first infection to symptoms |
| **Severity of cough** | Severe | Mild (at first) |
| **Hemoptysis** | Common | Uncommon |
| **X-ray pattern**[3-5, 59, 60] | Destructive<br>Upper lobe<br>Cavities | Interstitial (like PCP)<br>Miliary<br>Lymph nodes common<br>Lobar (like bacterial pneumonia)<br>**May be normal** |

## TB in the era of HIV is a multi-system disease[17, 18, 57, 58, 61, 62]

- Tuberculosis very often spreads to:
  - Brain
  - Heart
  - Bone and bone marrow
  - Lymph nodes
  - Liver and gastrointestinal system
- So, if a patient is weak and confused and there is evidence for TB in the lung, then one can assume there is also tuberculosis in the brain[63]

## Antiretroviral therapy can decrease tuberculosis rates and improve treatment outcomes

- Directly-observed therapy short-course (DOTS) has not been able to contain the exploding TB epidemic in Africa[9]
- By restoring immunity, ART can help prevent new cases of TB[64, 65]
- ART reduced new TB cases by 70% over five years in a South African ART clinic[66]
- ART can also reduce rates of TB in the surrounding community[67]
- But failure to diagnose and treat tuberculosis before ART is started can also have a negative impact on ART programs[11, 50, 68-71]
- ART given during TB treatment can lower mortality[72-75] but can also cause the immune reconstitution inflammatory syndrome, or IRIS (see Chapter 5)[50, 68, 69, 71, 76-78]

## Summary: tuberculosis in the era of HIV

- Tuberculosis is surging in much of Africa because of the HIV epidemic
  - The TB rates are usually higher than what is reported in the public health system
- Tuberculosis is the number one cause of death in HIV-infected patients in Africa
  - TB has usually spread throughout the body by the time of death
  - In many cases, the lung is not even involved[79, 80]
  - Only half of these TB cases are diagnosed while the patient is alive
- The patterns of tuberculosis disease are changing
  - TB can cause chronic cough for weeks to months
  - TB can even go on for **more than one year**
  - TB can sometimes be an acute disease causing illness with a cough of less than three weeks, much like bacterial pneumonia
- Tuberculosis is a multi-system disease
  - The weak immune system allows TB to spread
  - TB can cause disease in many organs, such as the brain, heart, bone, blood, liver and lymph nodes
- This surge of tuberculosis places a great strain on ART clinics
  - Many patients present to clinic with TB and must be treated for it before starting ART
  - The death rates in African ART clinics are higher than in the West, and tuberculosis is a major cause
  - Immune reconstitution inflammatory syndrome due to TB complicates ART scale-up
  - ART can decrease new cases of tuberculosis and death rates

# Chapter 2

# Pulmonary Tuberculosis in the Era of HIV

## Case 1: presentation

- 41-year-old HIV-infected male; CD4 count unknown
- History of present illness: 5 week history of cough. Seen elsewhere and given antibiotics without improvement.
- Medications: The patient was not using antiretroviral therapy or cotrimoxazole prophylaxis
- Examination: Temperature 37.9 degrees Celsius, pulse 111 beats per minute and respiratory rate 26 breaths per minute. Thin but not in distress. Palpable enlarged (2 centimeter) cervical and axillary lymph nodes. Chest clear to auscultation.
- Laboratory: Two AFB sputum examinations negative

---

The clinician wanted to treat this person for PCP.

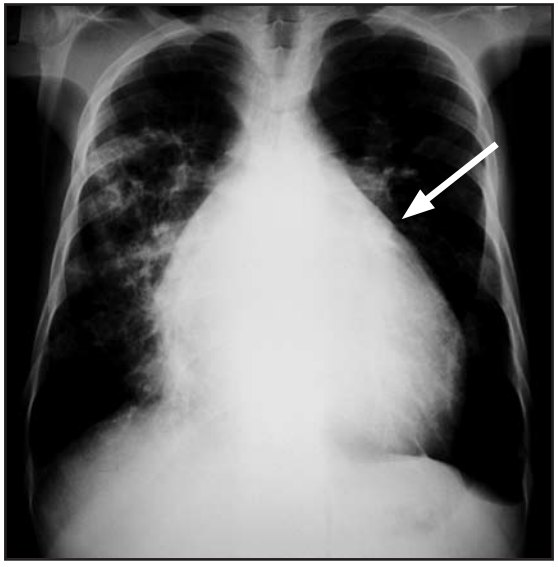
Is this the right choice?

---

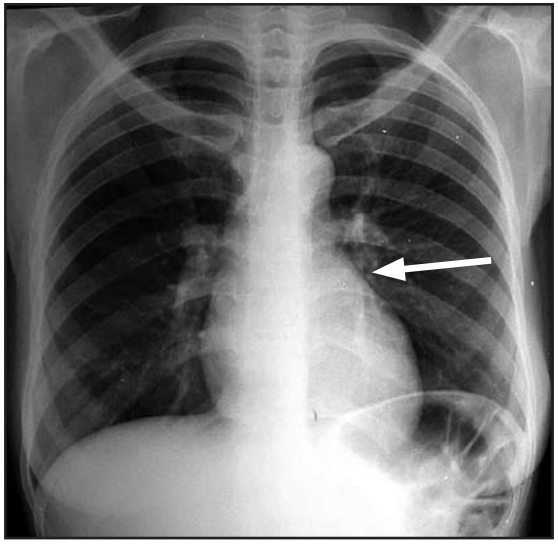
## Case 1: discussion

- What does the presence of large lymph nodes mean?
  - *Pneumocystis* pneumonia (PCP) causes cough
  - But PCP does **not** cause large lymph nodes
  - Tuberculosis causes cough **AND** large lymph nodes[81]
- Later, the patient brought a chest x-ray from the other hospital which showed a pneumonia and a large heart (see next page)
  - PCP does not cause a pericardial effusion
  - Tuberculosis can cause a pericardial effusion

## Case 1: large heart due to a pericardial effusion



Large heart with straight left heart border (arrow)
due to pericardial effusion; infiltrate also present



Normal heart size
The arrow shows that the normal heart border is curved, not straight

## Case 1: clinical reasoning

- The patient's vital signs and symptoms are already showing a significant problem, and he is at risk of becoming very ill soon:
  - Fever and fast pulse
  - Fast breathing
- He has already failed to improve on one course of antibiotics
- Tuberculosis is the disease which can cause all of these symptoms:
  - Chronic cough
  - Large lymph nodes
  - Pneumonia and large heart on the chest x-ray
- PCP can cause cough **but not** large lymph nodes or large heart
  - Ultrasound examination showed fluid around the heart
- Diagnosis: Smear-negative pulmonary and extrapulmonary TB involving the pericardium (space around the heart)
  - Patient treated for tuberculosis and improved

---

He does not need another course of antibiotics. The high suspicion for tuberculosis in a sick HIV-infected patient means you should treat for TB even though the sputum smear is negative. This approach is consistent with World Health Organization guidelines.[82]

---

## Case 1: clinical reasoning—chronic cough, lymph nodes, and pericardial effusion in HIV-infected African

| Infection | Chronic cough > 3 weeks | Large lymph Nodes | Large heart/ pericardial effusion |
|---|---|---|---|
| **Bacterial pneumonia** | Less common | Rare | Rare |
| **PCP** | Common | No | No |
| **Tuberculosis** | Common | Common | Common |

We see that in this case, tuberculosis is the best explanation.

Basic history, physical examination, and knowledge of disease patterns (called epidemiology) can help us make a diagnosis even when the sputum AFB smear is negative.

In Africa, we must often use **clinical reasoning** because we do not have the necessary laboratory information.

## TB of the respiratory tract in HIV-infected patients

- Laryngeal (voice box)
- Pulmonary
  - Like pneumonia
  - Cavitary/destructive
  - Miliary
  - Bilateral (both sides of lung) infiltrates
- Pleural
  - Pleural TB is usually classified as extrapulmonary, but for ease of organization the condition will be discussed in this chapter

## Respiratory tuberculosis in the era of HIV

- **Before** era of HIV, most TB occurred only in the lungs[62, 83, 84]
  - Lungs (pulmonary): 85%
  - Outside lungs (extrapulmonary): 15%
- Now, **in the era of HIV**, more than half of tuberculosis is extrapulmonary, with many patients having infection both in and outside the lung at the same time[57, 58, 62]
  - Pulmonary alone
  - Pulmonary + extrapulmonary
  - Extrapulmonary alone

  } More than half of the cases in the era of HIV
- Clinicians can use this change in epidemiology (disease pattern) to help diagnose pulmonary TB by recognizing its signs and symptoms outside of the lung
- Your old tuberculosis textbook is out of date!
  - In the age of HIV, tuberculosis is an entirely different disease
  - The weakened immune system causes TB to present in new ways
- Pulmonary tuberculosis in HIV-infected patients often involves the lungs and spreads to other parts of the body at the same time

## Pulmonary and extrapulmonary TB in the same patient

- Most HIV-positive patients with pulmonary tuberculosis also have evidence of extrapulmonary disease[17, 18]
- By the time of death, almost all HIV-positive pulmonary tuberculosis patients have TB throughout the body
- The presence of extrapulmonary tuberculosis can help diagnose TB in the lung
  - Example: In an AFB smear-negative patient, aspiration of a swollen lymph node may show tuberculosis[81]

Extrapulmonary TB will be covered in more detail in the next chapter.

## Pulmonary tuberculosis in the era of HIV: an overview of diagnostic approach

**We will explore these principles in this chapter**

- History
  - Cough of any duration should raise suspicion, but chronic cough (more than 3 weeks) is most common[6, 53, 85]
    - Even in culture-proven cases of pulmonary tuberculosis, cough can be absent,[1, 2, 5, 52] so the clinician must look for other signs and symptoms to suggest the diagnosis of TB
  - Shortness of breath and fatigue[56]
  - Fever and weight loss are common and can be very severe but are not present in every case[6]
  - **Key Concept:** Symptoms of tuberculosis **outside the lung** can help to suggest the presence of TB **inside the lung**
- Physical examination
  - Lung exam may reveal crepitations or rhonchi but these findings can also occur in pneumonia and PCP
  - Lung exam is **normal** in about one-half of all HIV-infected patients with pulmonary tuberculosis[86, 87]
    - So, a normal lung exam does not rule out TB
  - Lymph nodes (neck and armpit) are commonly enlarged and may be filled with tuberculosis[81, 88-90]
  - A very high respiratory rate (> 40 breaths per minute) or extreme fatigue **when walking** suggests PCP rather than TB[86, 87]
  - The clinician must look for signs of TB elsewhere in the body
    - Central nervous system: Difficulty thinking, talking or walking; headache
    - Heart: Lower extremity edema
    - Abdomen: Ascites (fluid in the belly)
    - Blood and bone marrow: Severe anemia[55]

## Pulmonary tuberculosis in the era of HIV: an overview of diagnostic approach

**We will explore these principles in this chapter**

- Laboratory
  - Sputum smears for AFB
    - 3 smears collected on at least two separate days[51]
    - Collect the first sample in the clinic
    - Send patient home with a sample cup and have him collect a morning sample on the day he will return to the clinic
    - The third sample can be collected on return to the clinic
    - The first two samples are the most important[23, 51]
    - As mentioned in Chapter 1, many cases of pulmonary TB in HIV-infected patients will be AFB smear-negative
  - Evidence of extrapulmonary tuberculosis
    - Lumbar puncture (Chapter 4)
    - Aspiration or biopsy of lymph node for AFB (Chapter 3)
    - Cardiac ultrasound to look for effusion or stranding (Chapter 3)
    - Abdominal ultrasound to identify enlarged lymph nodes (Chapter 3)
    - Aspiration of pleural fluid (Chapter 2)
    - Severe anemia (Chapter 3)
- Chest x-ray
  - "Atypical" and often different than those without HIV
    - Miliary and interstitial pattern, lower lung disease, and pleural effusions common
    - Cavities less common
  - A normal x-ray is actually common (as many as 1/3 of patients) and, like a negative AFB smear, does not rule out HIV-related TB[3-5]

## TB is the most common cause of chronic cough in Africa

- "Chronic cough" means coughing for more than 3 weeks
- Zimbabwe: Among HIV-infected clinic patients with chronic cough, almost half (or 1 of every 2) had TB[85]
  - Almost 1 out of every 3 (29%) patients with pulmonary tuberculosis in this study had negative AFB sputum smears
  - The study used fluorescence microscopy to detect AFB, which is much better than sputum examinations done in most African labs
- Malawi: Among HIV-positive and HIV-negative patients with cough for more than three weeks, weight loss, and no response to antibiotics, one-half (53%) had tuberculosis

## Obtaining an accurate history is very important

It is necessary to find out exactly when the cough began.

| Disease | Usual Duration of Symptoms Before Coming to Hospital |
|---|---|
| Bacterial Pneumonia | Hours, days, or a few weeks |
| *Pneumocystis jiroveci* Pneumonia (PCP) | Several days to weeks |
| Pulmonary Tuberculosis | Weeks to months to more than one year |

These are the three main causes of chest complaints in HIV-infected patients. Of course, there are other less common causes, like asthma, heart failure, and cancer, but these conditions do not cause fever.

## How long do HIV-infected patients with tuberculosis have symptoms before presenting for care?

### Tuberculosis can have a very slow course

- World Health Organization protocols (WHO) call for evaluating patients for TB when the duration of symptoms is longer than 2-3 weeks[51]
  - But few clinicians think of tuberculosis lasting more than one year
- In HIV-infected patients pulmonary TB can occur **more slowly** than most clinicians expect
  - In a South African study, the time before patients came to medical attention was **very long**[6]
  - Average duration between symptoms and diagnosis was **more than one year**!

### Tuberculosis can also have a fast course

- Malawi: 1 out of 3 patients with cough for less than 3 weeks had TB[53]
  - Most of these patients were AFB smear-negative
  - And most had **other symptoms (weight loss, fever) for longer than three weeks**
- Kenya: 1 out of every 8 HIV-infected patients with cough for less than 2 weeks had pulmonary TB[54]
  - Tuberculosis was the second most common cause of acute (rapid) pneumonia after bacterial pneumonia (*Streptococcus pneumoniae)*

## Considerations in ill HIV-infected patients

- These research studies show the importance of **considering the diagnosis of tuberculosis in ALL ill HIV-positive patients with cough and weight loss** which does not respond to antibiotics
- Both **short** (less than 3 weeks) and **very long** (more than one year) durations of cough should still raise clinical suspicion for tuberculosis, especially if there is evidence of TB elsewhere in the body or if the patient is very ill and has a low CD4 count
- But it remains the case that most HIV-infected patients with pulmonary TB will be coughing for weeks or months before presenting for care
- It is very important to get a good history from patients
  - Many patients tend to minimize their symptoms
  - You must find out **exactly when** the patient began to cough.
- Remember: **Coughing is not normal.** Any cough in an HIV-infected patient must be investigated to learn the cause.

## Pulmonary tuberculosis: comparison between HIV(+) and HIV(-) patients[23]

**Clinical presentation depends on the strength of the immune system**

| Sign or Symptom | Strong Immune System (HIV-negative or HIV-positive with high CD4 count) | Weak Immune System (HIV-positive with low CD4 count) |
|---|---|---|
| **Area of lung** | Upper lobe | Anywhere in lung |
| **Cavities** | Common | Uncommon |
| **Severity of cough** | Severe | Mild (at first) |
| **Hemoptysis** | Common | Uncommon |
| **X-ray pattern**[3-5, 59, 60] | Destructive<br>Upper lobe<br>Cavities | Interstitial (like PCP)<br>Miliary<br>Lymph nodes common<br>Lobar (like bacterial pneumonia)<br>**May be normal** |

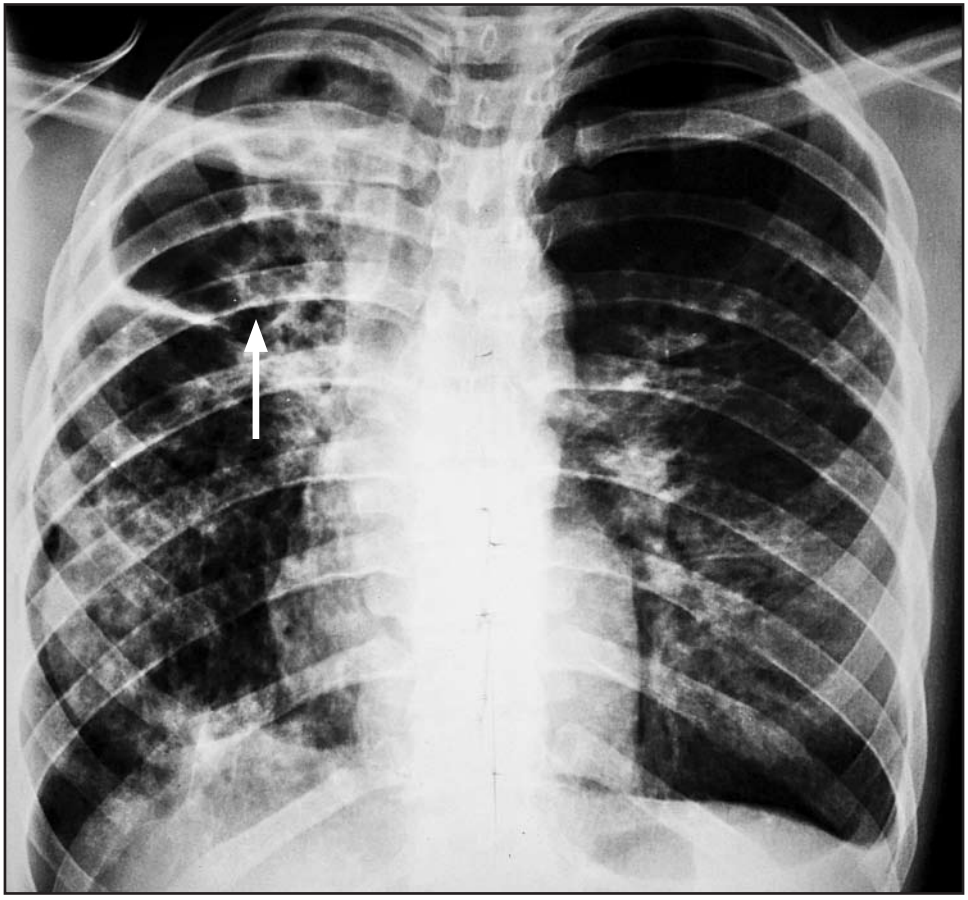
See the picture examples to understand the x-ray patterns of TB.

## Tuberculosis can occur at any CD4 Count

### The immune system's strength affects how TB damages the body

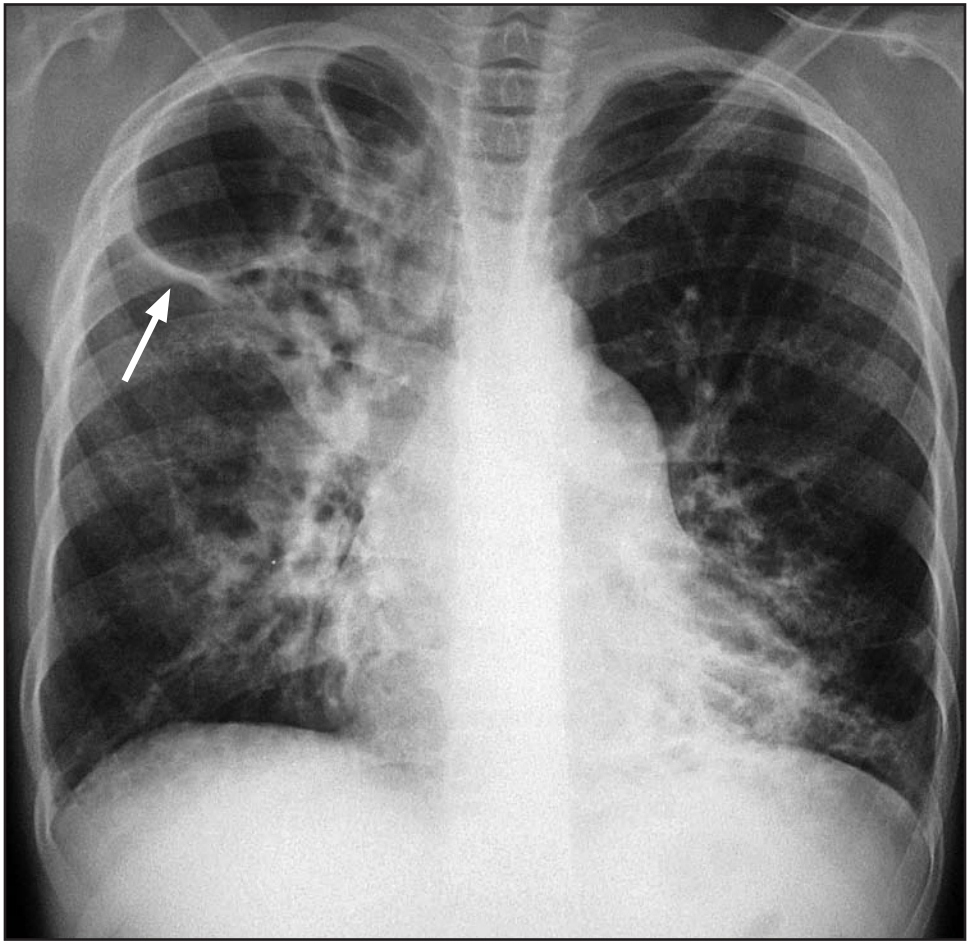
- In central Africa, HIV-positive patients with tuberculosis had a range of CD4 counts[91]
  - Less than 200 cells/µl: 1 out of 3
  - 200-500 cells/µl: 1 out of 3
  - More than 500 cells/µl: 1 out of 3
- The risk of getting TB doubles in the very first year after being infected with HIV[92]
- When the CD4 count is low (less than 200 cells/µl), tuberculosis rarely causes cavities and looks more like the right side of table on the previous page
- When the CD4 count is higher (more than 200 cells/µl), TB may look more like the disease in HIV-negative patients (left side of table on the previous page)
- South Africa: Even after the CD4 count rises with successful ART, the risk for TB remains,[93] although the risk is less than before ART[66]
  - CD4 200-500 cells/µl on ART: 5 -10 times the normal risk
  - CD4 > 500 cell/µl on ART: 2 times the normal risk

## HIV-negative tuberculosis chest x-ray



Classic upper lobe destructive, cavitary TB (arrow)

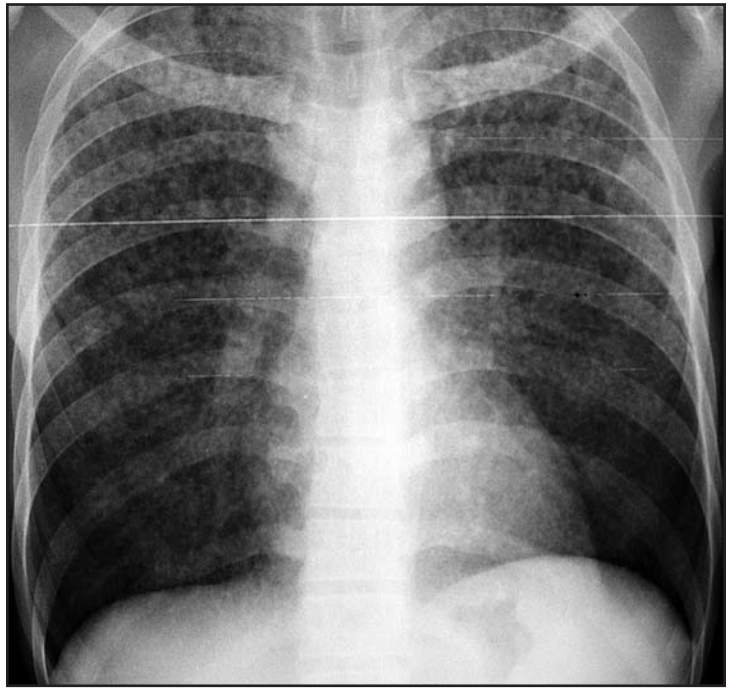
## Another example of “textbook” upper lobe cavitary TB

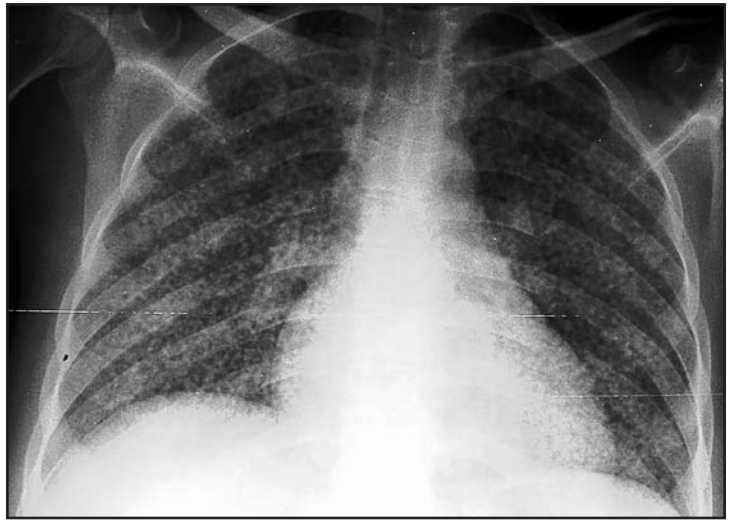


Upper lobe cavities (arrow)

Cavities can also occur in HIV-infected patients with high CD4 counts.

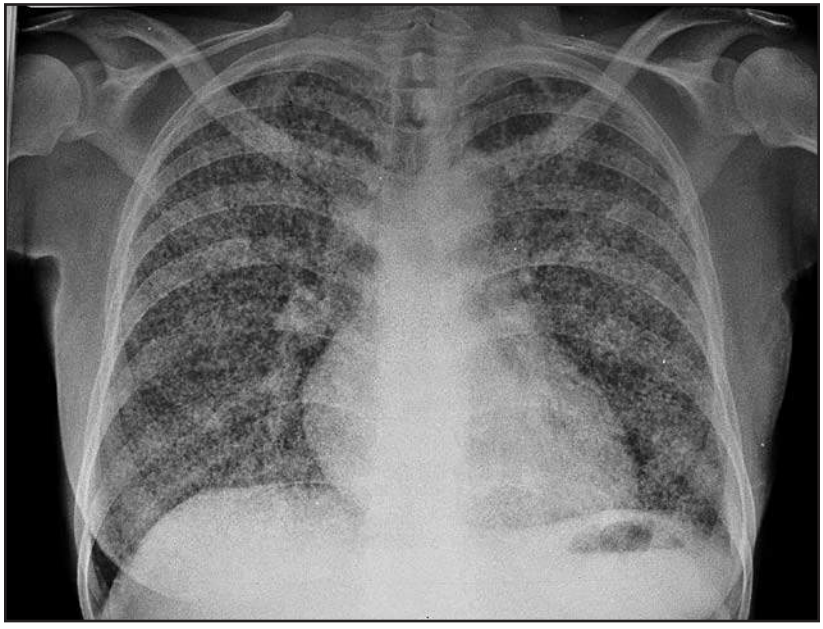
## Miliary tuberculosis chest x-ray in HIV-infected patients

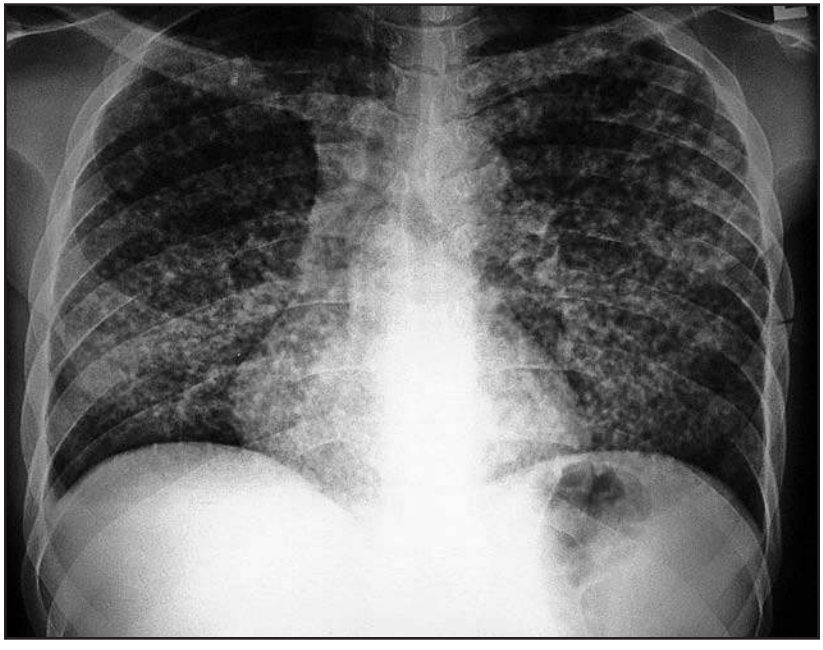




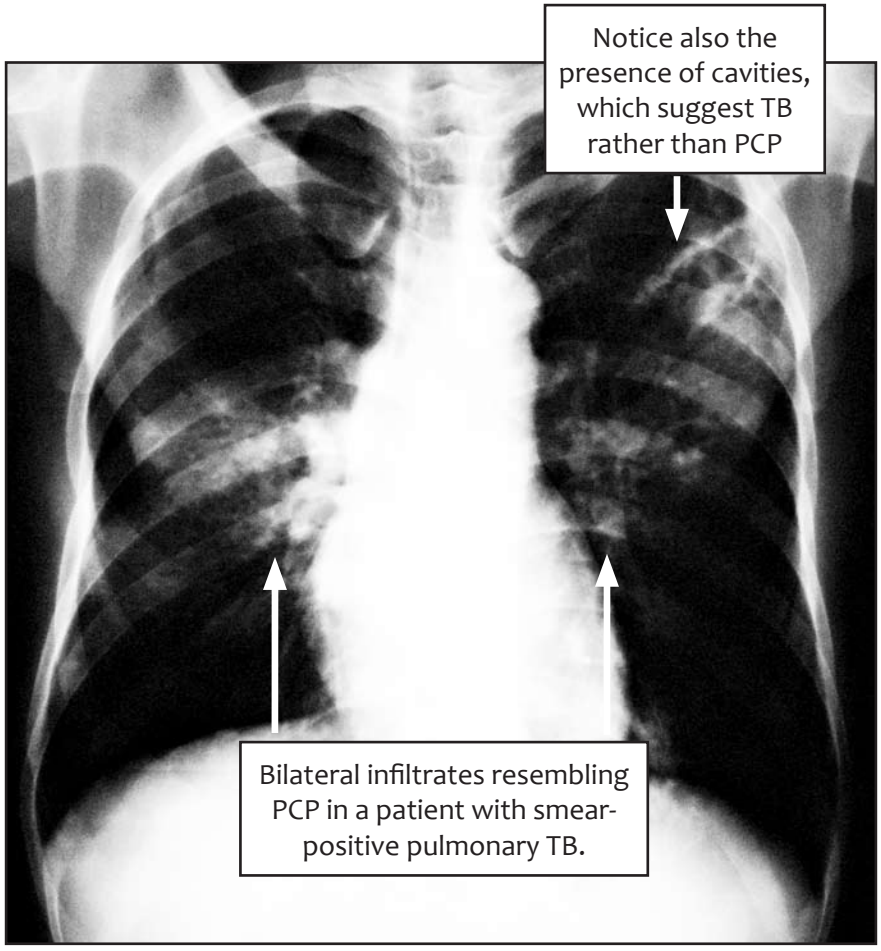
In both cases, the entire lung is filled with small nodules resembling millet seeds. You should learn to recognize this pattern.

## More miliary tuberculosis in HIV-infected patients





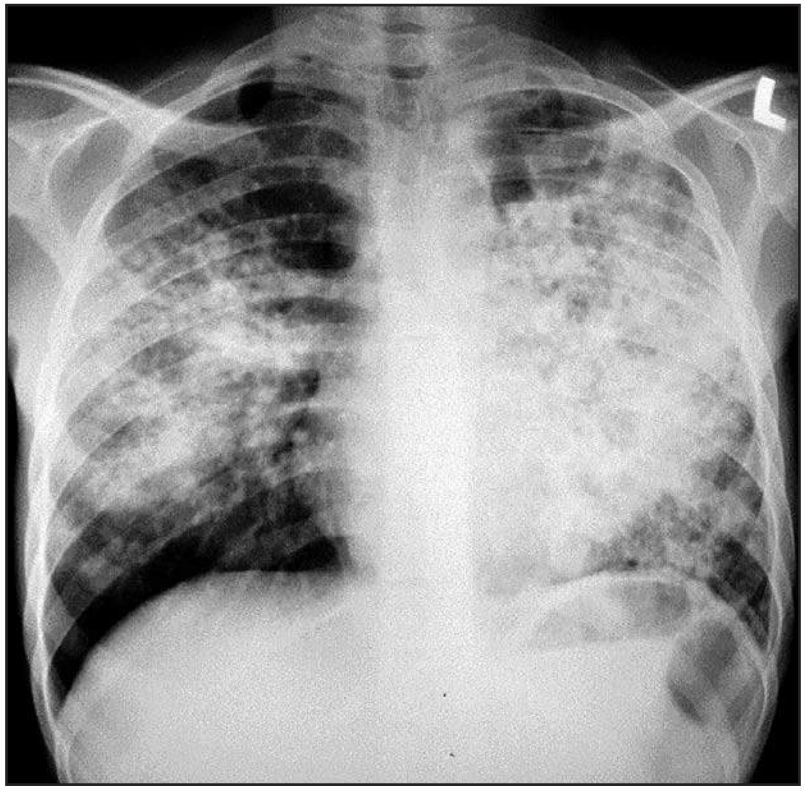
## HIV-related tuberculosis with bilateral infiltrates




A bilateral mid- or lower-lung zone distribution is common in HIV-positive patients but uncommon in HIV-negative patients.

This pattern is not specific and resembles PCP, bacterial pneumonia, and even heart failure. Telling the difference between PCP and TB can be very difficult, although the presence of cavities in this case strongly suggests TB (and the sputum AFB smear was positive). In addition to performing sputum AFB smears, you need to look for evidence of TB outside of the lung.

## Bilateral opacifications (cloudy infiltrates) in a patient with HIV and TB




Very severe pneumonia or PCP can also look like this on chest x-ray, so you must learn other information:

How long has the patient been sick and coughing?

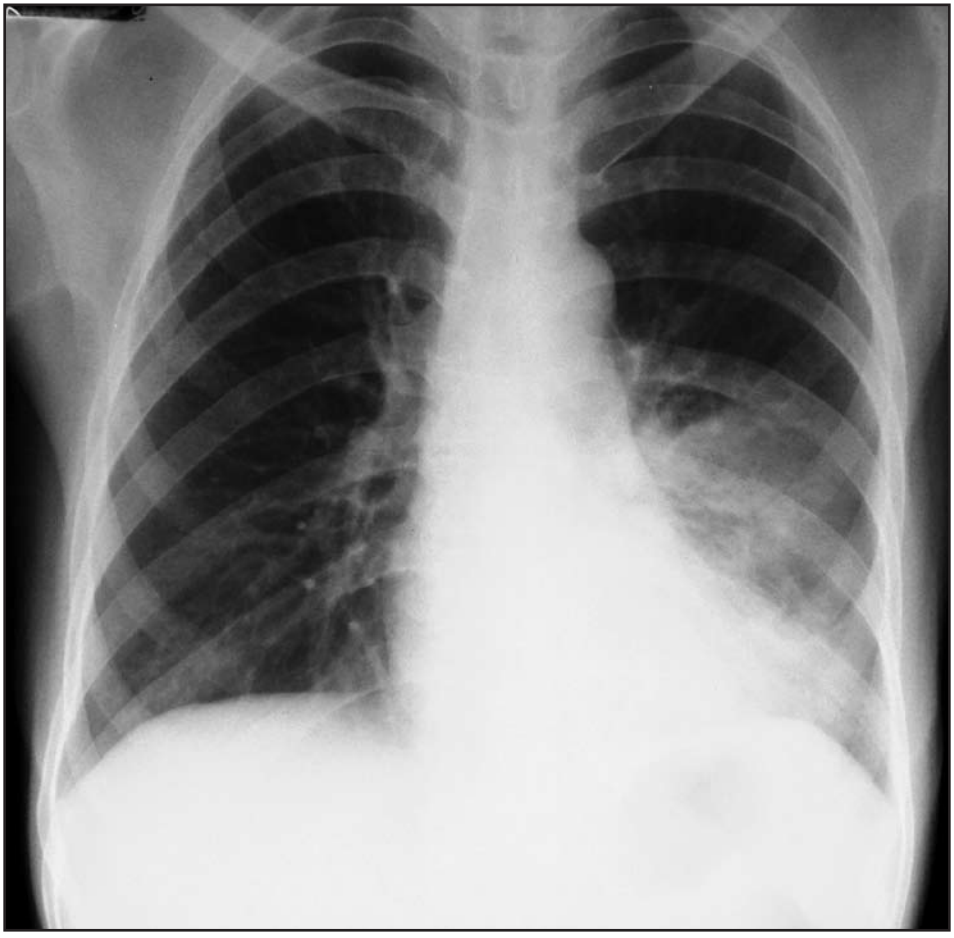
Cough for months suggests TB.

Cough for days suggests bacterial pneumonia.

Has the patient been using cotrimoxazole prophylaxis?

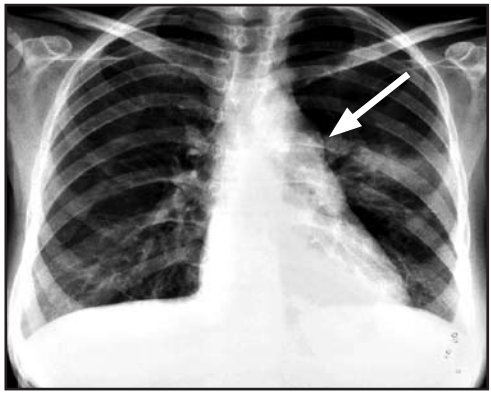
Using cotrimoxazole prophylaxis means PCP is not likely.

## Pulmonary TB presenting like bacterial pneumonia

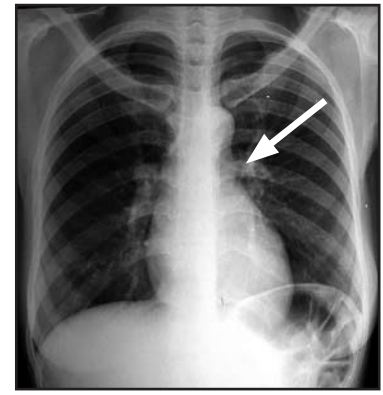


This example of TB looks like a simple case of bacterial pneumonia.

## Intrathoracic (inside the chest) lymph nodes in an HIV-positive patient with tuberculosis



HIV-Positive with TB



Normal Chest X-Ray

The "bulge" (arrow, left picture) in the HIV-positive patient is a **lymph node**. Compare this with the **absence** of a "bulge" (arrow, right picture) in the normal chest x-ray.

## "The sputum smear is negative. How can there be TB?"

- Many patients with proven pulmonary TB by culture have negative sputum smears, even in the best laboratories and research studies[42, 94]
- "Real world" studies from the 1980-90s show that 1/3 to 1/2 of HIV-positive pulmonary TB patients are actually smear-negative[33-38]
- Newer studies show even higher rates of smear-negative TB
  - Kenya (2003): 64% of HIV-infected patients with proven TB were AFB sputum smear-negative using conventional microscopes[40]
  - South Africa (2008): screening of all patients entering the ART clinic found that **26% (one of every 4) had active pulmonary TB, and of these 87% were AFB smear-negative even with fluorescence microscopy**[5]
- HIV-infected patients rarely have cavities
  - Half of all TB patients without cavities are smear-negative even in a fully-equipped laboratory[36, 59]
- HIV-positive patients may have less tuberculosis in the sputum[95-97] even with low CD4 counts[76]
- The number of reported smear-negative cases in African countries is increasing and in some places are more than the smear-positive cases[23]
- Patients diagnosed with smear-negative tuberculosis have a high mortality rate, even with TB treatment[98]
  - This fact may be due the presence of other diseases, like Kaposi's sarcoma, in the lung
- Because of the limited numbers of lab technicians and high sample load, positive AFB smears may be missed in a real world setting
  - Research from Kenya and South Africa shows that many positive smears are missed in routine practice[43, 99]
  - Many hospitals do not process specimens appropriately, which also leads to missing AFB in the sputum[100]
- HIV-positive patients with TB are more likely to have negative sputum smears than are HIV-negative TB patients (see next page)

## Negative AFB sputum smears in pulmonary tuberculosis

This table shows *rates of **negative** AFB sputum smears* even when the culture grows tuberculosis (culture-proven TB).

| Country | HIV-Positive with TB | | HIV-Negative with TB | |
|---|---|---|---|---|
| **Zambia**[33] | 43% | 2/5 | 24% | 1/4 |
| **Zambia**[35] | 37% | 1/3 | 18% | 1/5 |
| **Senegal**[36] | 35% | 1/3 | 17% | 1/5 |
| **Haiti**[37] | 34% | 1/3 | 21% | 1/5 |
| **New York**[38] | 55% | 1/2 | 19% | 1/5 |
| **Zimbabwe**[85†] | 30% | 3/10 | 26% | 1/4 |
| **Kenya**[40†] | 64% | 2/3 | 43% | 2/5 |
| **Cambodia**[101] | 54% | 1/2 | | |
| **South Africa**[102†] | 59% | 3/5 | | |
| **South Africa**[5†] | 87% | 9/10 | | |
| **South Africa**[52†] | 91% | 9/10 | | |

From the table we see that HIV-positive patients are more likely to have negative AFB sputum smears even though they have active tuberculosis in the lung. And more recent studies show that **most pulmonary TB cases in HIV-infected adults are AFB smear-negative.**

† Even with induced sputum and/or fluorescence microscopy, most of these culture-proven TB cases were AFB smear-negative. The differing results of these studies are likely due to diverse populations (baseline screening vs. symptomatic), varying lab quality, and other factors. For example, in the study from Zimbabwe, half of the patients had been coughing for 2 or more months, and the smears were more likely to be positive. In the studies from South Africa, which had low smear-positive rates, patients were screened regardless of symptoms, and many were not even coughing despite having culture-proven TB.

## A negative AFB sputum smear does not rule out TB

- We have seen that HIV-positive patients with tuberculosis are more likely to have negative sputum smears even though TB is in the lung
- The laboratory staff in most hospitals do not have the money, supplies and time available like those working in research studies
  - **Ask yourself, "Could the busy laboratory staff in my hospital be missing AFB on the sputum smears?"**
- So a significant number of your HIV-infected patients with TB will have negative AFB smears
  - You must look for other evidence of TB in the body
  - You must avoid repeated courses of antibiotics just because the smear is negative
- Tuberculosis is actually the **number one cause of disease** in patients empirically diagnosed with "smear-negative" TB[87, 103-106]
  - Sputum culture is better than a sputum smear when looking for TB
  - Research studies show that when clinicians diagnose "smear-negative TB" in patients with chronic cough, at least 2 out of every 5 of these cases really do have TB found on sputum culture
  - Others may have sputum-negative and culture-negative TB but the disease does not become obvious until later, because not even a sputum culture is perfect[107]
  - In sputum smear-negative patients with chronic cough, actual TB is still much more common than other causes, like PCP
- Even though TB is the actual #1 cause of smear-negative chronic cough, over-diagnosis (treating for tuberculosis when it is really not the cause) is a concern in resource-limited settings
  - Overuse of TB drugs can lead to side effects and increased cost
  - The table on the next page lists some other causes of chronic cough besides "smear-negative" tuberculosis; consider these conditions before making a diagnosis of smear-negative TB

## Differential diagnosis of AFB sputum smear-negative chronic cough

| Disease | Features to differentiate from tuberculosis |
|---|---|
| Bacterial pneumonia | Usually does not go on for many weeks or months; should respond to antibiotics |
| PCP | Usually does not go on for months; cotrimoxazole daily prevents PCP |
| Bacterial empyema | Infection in sac around the lung; should be obvious on x-ray and by testing pleural fluid |
| Lymphocytic interstitial pneumonitis (LIP)[108] | Similar clinical features to tuberculosis and PCP: cough, weight loss, shortness of breath; nodules on chest x-ray; consider this diagnosis if patient does not respond to TB or PCP therapy |
| Kaposi's sarcoma | Skin or mouth lesions obvious; mass lesions or pleural effusion may be present on chest x-ray |
| Cryptococcus | Rarely involves lung; headache may be present; serum cryptococcal antigen (CRAG) positive |
| Asthma | Wheezing on exam; no fever or enlarged lymph nodes; symptoms come and go |
| Heart failure | Leg swelling; large heart on x-ray; no fever unless TB is the cause |
| Environmental toxins | Example: Cooking fire in the home; does not cause fever or enlarged lymph nodes |

Always consider the possibility that two problems may be present in the lung at the same time. Patients can have both tuberculosis and pneumonia. If a patient does not completely recover from pneumonia, look carefully for TB that might have been missed.

## Severe anemia is strongly correlated with tuberculosis in HIV-infected patients

- Severe anemia (**hemoglobin < 7 g/dl**) is strongly suggestive of TB in African HIV-infected patients[55]
- Moderate anemia (< 10 g/dl) is also commonly present[56]

| *Clinical Clues* |
| --- |
| Severe anemia + cough—consider TB |
| Severe anemia + fever—consider TB |
| Severe anemia + neurological findings/headache—consider TB |
| Severe anemia + lymph nodes—consider TB |
| Also consider salmonella in cases of severe anemia with fever, abdominal pain, or diarrhea |

## Lymphadenopathy can help diagnose smear-negative pulmonary tuberculosis

- Remember that TB is a multisystem disease in HIV-positive patients
- Lymph nodes of the neck and armpits are often also infected with TB
- The presence of enlarged, hard or tender lymph nodes should make the clinician think of tuberculosis, especially if cough is present[56]
- Most enlarged, hard and tender lymph nodes in sick HIV-infected patients in Africa are caused by TB[89, 109]
- If the sputum smear is negative, aspiration of these lymph nodes (Chapter 3) can help confirm the diagnose of TB in the lung or elsewhere in the body[81, 110]

## Anemia and lymphadenopathy help predict TB in patients with chronic cough and negative sputum smears

- In an East African study[56] of patients evaluated for smear-negative tuberculosis:
  - Hematocrit < 30% (similar to a hemoglobin less than 10 g/dl) was twice as common among patients with TB
  - Lymphadenopathy was 3½ times as common among patients with tuberculosis compared to patients without TB

These data do not mean that all patients with anemia and lymphadenopathy have TB, but when these findings exist with chronic cough the clinician should even more strongly suspect and carefully investigate for tuberculosis.

## The erythrocyte sedimentation rate is not very useful in the diagnosis of tuberculosis

- Many clinicians order an ESR when investigating possible TB
- The ESR can be normal even in cases of active tuberculosis,[111] so a **normal ESR does not rule out TB**
- A high level (above 50 mm/hr) may occur with tuberculosis,[112, 113] but the ESR cannot tell TB apart from other infections[94]

A high ESR only tells you that something might be wrong with the patient, but it cannot tell you if the problem is tuberculosis, salmonella, another infection, or even cancer.

## Smear-negative tuberculosis is too confusing! How do I understand it?

- Look for these factors in an HIV-infected patient with cough and negative AFB sputum smears:[56, 94, 114]
  - Cough for more than 21 days
  - Chest pain for more than 15 days
  - Weight loss > 10%
  - Failure to gain weight despite ART
  - Minimal or no sputum production
  - Lymphadenopathy (on exam or x-ray)
  - Severe anemia
  - Signs of extrapulmonary TB
  - Miliary pattern on chest x-ray
  - If severe shortness of breath, consider PCP first

The more of these findings that a patient has, the more likely that the cough is caused by tuberculosis.

## Is a trial of antibiotics helpful in diagnosing smear-negative pulmonary tuberculosis?

- Older guidelines required a trial of antibiotics before diagnosing smear-negative pulmonary tuberculosis
- The 2006 World Health Organization guidelines do not recommend a trial of antibiotics for diagnosis of smear-negative pulmonary TB in HIV-positive persons[82]
  - But your country guidelines may still require antibiotics
- HIV-infected TB patients often have both tuberculosis **and** bacterial pneumonia
  - Many patients who respond to a trial of antibiotics for routine bacterial pneumonia actually turn out to have TB also[103, 115]
- Antibiotics are indicated when the patient is coughing and the clinician expects:
  - Acute bacterial pneumonia
  - *Pneumocystis* (PCP) pneumonia (cotrimoxazole indicated)

***Summary***

A trial of antibiotics is not very helpful in diagnosing TB.

Still, antibiotics may be needed to treat pneumonia or PCP.

Follow the appropriate national guidelines.

## World Health Organization (WHO) guidelines on use of antibiotics in HIV-infected tuberculosis suspects with negative sputum smears

- "There is **limited evidence for the use of empiric antibiotic treatment to rule out tuberculosis** in HIV-infected persons"[82] (emphasis added)
- "The **primary role of antibiotics should not be as a diagnostic aid**; they should be used to treat bacterial infections in people living with HIV/AIDS with cough or serious illness." (emphasis added)
  - Patients who are acutely ill can be given antibiotics while a decision is being made whether to treat for TB
- **However, if the patient is dangerously ill and tuberculosis is strongly suspected, TB diagnosis and treatment should not be delayed just to give a course of empiric antibiotics**
- What are "**danger signs**"?[82]
  - Respiratory rate > 30 breaths per minute
  - Fever > 39 degrees Celsius
  - Pulse > 120 beats per minute
  - Unable to walk alone

***Summary***

These vital signs are evidence that a patient is dangerously ill.

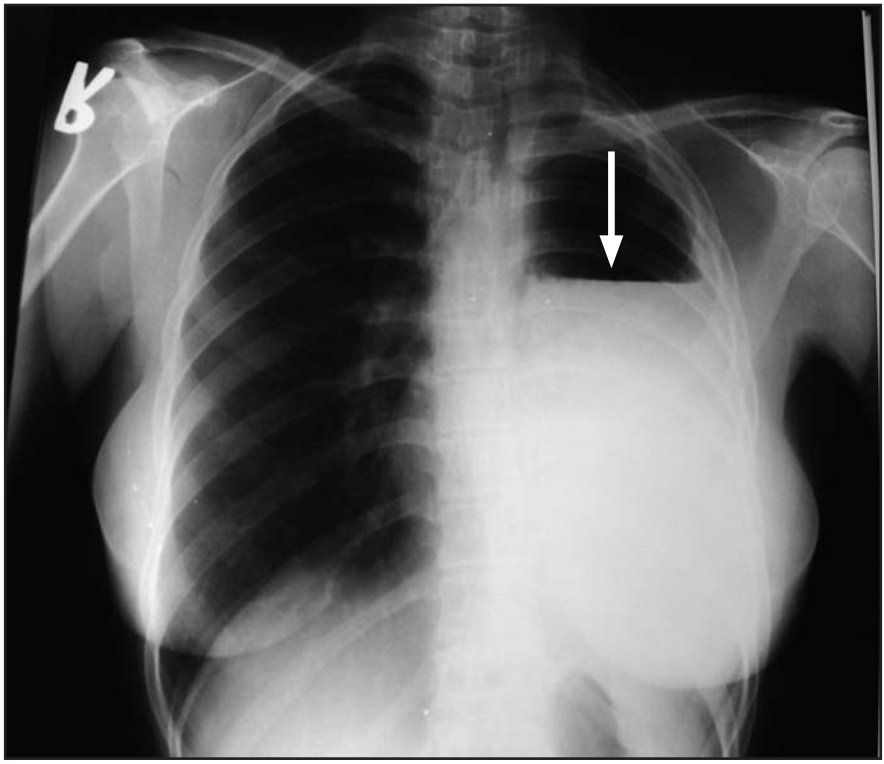
If tuberculosis is suspected, anti-TB treatment should not be delayed.

Antibiotics are also reasonable if the onset is acute (days to a few weeks) and a bacterial infection (like bacterial pneumonia or salmonella sepsis) is expected.

You can treat with antibiotics and TB drugs if the patient is very ill and you think both infections may be present.

## Pleural tuberculosis

- TB infects the sac around the lung
  - The sac fills with fluid
- Usually one-sided (unilateral)
- Pleural tuberculosis is often called "extrapulmonary" disease
  - For ease of organization, discussion of pleural TB is included here
- Pleural tuberculosis can occur when:
  - TB spreads through the blood to the sac around the lung, **OR**
  - TB spreads directly from the lung to the sac



Fluid level (arrow) at the top of a tuberculous pleural effusion

## Presentation of pleural tuberculosis

- TB is the most common cause of pleural effusion in HIV-infected Africans[116-118]
  - Almost all cases of pleural effusion are caused by tuberculosis
- Look for typical TB symptoms
  - Fever, cough, shortness of breath, weight loss
- Dullness to percussion and decreased breath sounds on physical exam
- Always look for other evidence of tuberculosis
  - Lymph nodes
  - Severe anemia
  - Central nervous system symptoms
- High mortality reported, so do not delay diagnosis and treatment[119]

## Diagnosing pleural tuberculosis

**If a higher level laboratory is available and costs allow**

- Sputum smear for AFB: Active pulmonary TB may also be present
- Diagnostic thoracentesis (remove 10 cc of fluid)
  - Cell count/differential: Mostly lymphocytes[117]
  - AFB stain: Usually negative; does not rule out TB[116]
  - Gram stain: Rule out bacteria causing pneumonia
  - Protein: Almost always higher than 30 g/l[116]
    - The high protein may cause the fluid to clot[82]
  - Cytopathology (if possible): Rule out cancer
- Pleural biopsy: technically difficult and usually not necessary

### "But I do not know how to do a pleural aspiration."

### "My lab does not do all of those tests."

**In a setting with limited laboratory and technical expertise**

- You can still diagnose TB empirically!
- Yield from pleural fluid smears is low
- If you can do a thoracentesis, then consider the following:
  - If there is pus, empyema is likely present; send for gram stain and culture to identify the organism; a chest tube is necessary
  - If there is blood, consider cancer
  - If the fluid is clear, treat for TB
- But if you cannot do thoracentesis, follow the guidelines from WHO:

> **"If thoracentesis is not available, tuberculosis treatment should be started immediately,** particularly if the patient is HIV-infected**,** unless there are clinical or radiographic features suggestive of a diagnosis other than tuberculosis**."** (emphasis added)
>
> World Health Organization[82]

## Case 2: presentation

- A 41-year-old HIV-positive man (CD4 count unknown) had been treated for pneumonia and a pleural effusion with antibiotics
  - He returned three months later with severe shortness of breath and wasting
- Aspiration of the fluid revealed gross pus
  - Microscopy: No AFB seen, but gram stain showed streptococcus bacteria
  - Diagnosis: Bacterial empyema
    - In this case, tuberculosis was not the cause
- The patient was too ill to undergo chest surgery and had a permanent chest tube placed

---

This case shows the importance of performing a pleural aspiration, if possible. **If it is not possible** to do a thoracentesis, then TB treatment should still be strongly considered, according to the WHO.[82]

---

## Clues that something <u>besides</u> tuberculosis is causing a pleural effusion[82]

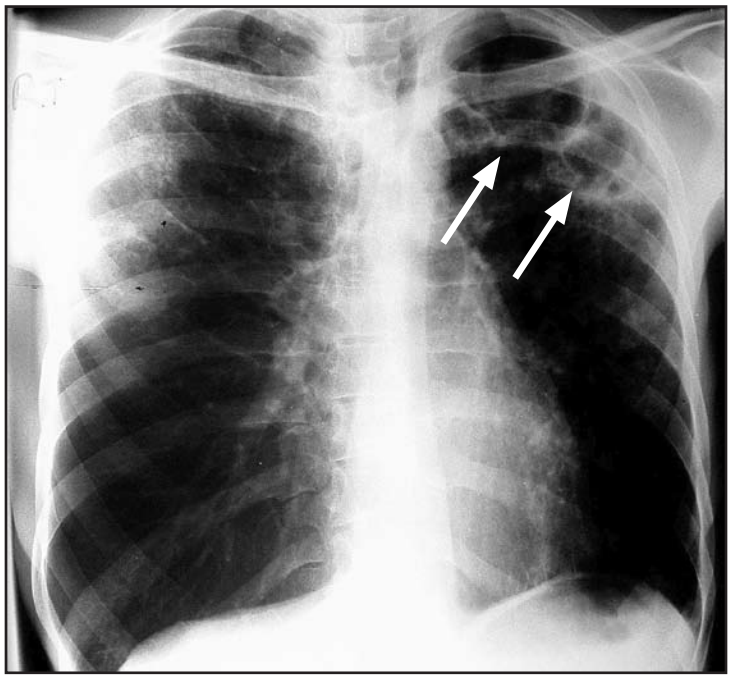
- Bilateral pleural effusion (both sides of the lung)
  - Heart failure
  - Kidney failure
  - Cancer
- **Bloody** pleural effusion
  - Cancer
  - Lymphoma
  - Kaposi's sarcoma
  - Primary lung cancer in a smoker
- Gross pus
  - Bacterial empyema

## Treatment of pleural tuberculosis

- Use standard national regimens
- **Therapy is reasonable in any patient with undiagnosed pleural effusion**, but avoid treatment trials which are shorter than the standard full course
  - "The **aim should be to start tuberculosis treatment in seven days** unless another diagnosis has been made."[82]
  - Very sick patients may need to start TB treatment before one week
- Therapeutic drainage (by thoracentesis or chest tube) is usually not necessary unless the patient is very sick and needs immediate relief
- Corticosteroids are no longer recommended[119]
  - Corticosteroids help effusion resolve faster
  - But in HIV-infected patients steroid use for pleural TB leads to **higher risk of Kaposi's sarcoma**[119] and higher HIV viral loads[120]

## Case 3: presentation

- 44-year-old HIV-negative male
- History: Weight loss, fever, and cough for six months
  - The patient has become so hoarse that he can barely speak
- Exam: T 38.2 degrees Celsius, pulse 93 beats per minute and respiratory rate 26 breaths per minute. Wasted. Hoarse with weak voice. No enlarged lymph nodes. Crackles left upper lung field.



Multiple left upper lobe cavities (arrows) in an HIV-negative patient

## Case 3: course

- Chest x-ray: Multiple left upper lobe cavities
- Sputum: 4+ positive for AFB
- Diagnosis: Pulmonary and laryngeal TB
- Treatment: Standard national protocol
- Follow-up: Improvement in voice and other symptoms

## Laryngeal tuberculosis: presentation

- Tuberculosis infects the vocal cords
- Chronic hoarseness is the classic sign
- Often occurs with pulmonary TB at the same time
- Very infectious form of TB[121]
  - Family should be screened for disease

## Laryngeal tuberculosis: diagnosis

- Usually AFB smear-positive
- Chest x-ray may show pulmonary TB
- Any patient with chronic laryngitis/hoarseness in Africa should be investigated for TB
- Anti-TB therapy may be warranted if there is no other explanation for the hoarseness

## Laryngeal tuberculosis: treatment

- Standard national tuberculosis guidelines
- Given the lack of effective ventilation and isolation in many resource-limited facilities, consider discharging the patient home on TB therapy
  - He should wear a mask in the home; most likely his family members and other people in close contact were exposed prior to the TB diagnosis
- If the patient is very sick and must be hospitalized, be sure to isolate the patient and have him wear a mask at all times
  - Do not allow the patient to sit without a mask next to others
- It may require weeks for the sputum smear to become negative[122]
- Patients may remain with permanent hoarseness

## Summary of pulmonary TB in the HIV-infected patient

- TB should be suspected and investigated in all HIV-positive patients with cough for more than **2-3 weeks**
  - Those with short (less than 2 weeks) period of cough should also be considered for TB evaluation if they do not improve with antibiotics
- Be alert if other signs of TB, such as weight loss and wasting, lymph nodes, or severe anemia are also present
- HIV-infected patients with pulmonary tuberculosis often have **TB elsewhere in the body**, and this fact can be used to help in diagnosis of sputum smear-negative cases
  - Example: lymph node aspiration for AFB staining
- Many cases of pulmonary TB in HIV-infected patients will be sputum AFB **smear-negative**
- Chest x-ray patterns are "**atypical**" and may resemble PCP or bacterial pneumonia
- Some patients with HIV and pulmonary TB will even have normal chest x-rays
- **Severe anemia** suggests TB or salmonella in HIV-infected patients
- The WHO no longer recommends a trial of antibiotics to "rule out" TB, but antibiotics are suggested for ill HIV-infected patients with possible acute bacterial pneumonia or sepsis (bacteria in the blood)
- **When the clinician suspects TB in a very ill HIV-infected patient with danger signs, treatment should be started quickly and should not be delayed by a trial of antibiotics**
  - Since patients can have TB **and** bacterial pneumonia, antibiotics may also be needed
- Pleural TB is the **most common cause of pleural effusions** in HIV-infected patients
  - Ideally, a pleural aspirate should be obtained for analysis, but when this is not possible TB treatment should be started unless another cause (such as heart failure or cancer) is obvious
- Any patient with chronic hoarseness (more than three weeks) should be investigated for TB with sputum smears and a chest x-ray

# Chapter 3

# Disseminated and Extrapulmonary Tuberculosis (Other Than Tuberculous Meningitis) In the Era of HIV

## Overview of chapter

- We will spend more time on the common forms of extrapulmonary tuberculosis
- At the end of the chapter, we will briefly survey the less common types of extrapulmonary disease
- Central nervous system tuberculosis (TB meningitis) will be discussed in the next chapter

## Case 1: presentation

- 35-year-old HIV-positive man; CD4 count 60 cells/µl
- History of present illness: 2 weeks of fever, weight loss, and jaundice
- Medications: None
- Physical exam: Pulse 110 beats per minute, temperature 38.1 degrees Celsius. Severely wasted. Yellow eyes. Lung exam normal. Right upper quadrant abdominal tenderness.
- Investigations
  - Chest x-ray normal
  - Elevated bilirubin
  - Hemoglobin 9 g/dl
- Initial treatment: Broad-spectrum oral antibiotics (azithromycin, ciprofloxacin) given
  - Mild improvement after one week, then worse again in two weeks

***Questions***

Could this patient have tuberculosis?

What are the other possibilities?

Can he have TB even if he is not coughing?

Can he be treated for tuberculosis even though we lack the laboratory equipment to prove the diagnosis?

## Definitions

- **Extrapulmonary tuberculosis**
  - TB occurring at a site in the body outside of the lungs
- **Disseminated tuberculosis**
  - TB that has spread widely throughout the body to involve multiple locations, such as:
    - Blood
    - Liver
    - Brain
    - Heart
    - Bone

## Reminder: definition of "empiric"

- **Empiric** means that a clinician decides to diagnose and treat an infection even though he does not have complete evidence that the infection is present
  - Example: A patient with a two-day history of cough and chest pain is treated for bacterial pneumonia even though there is no chest x-ray or sputum culture available
- The **empiric** diagnosis is a **"best guess"** based on a careful history and physical examination, basic laboratory tests, and the reasoning and judgment of the clinician
  - The 2006 WHO guidelines[82] provide more flexibility in making an empiric diagnosis of TB in HIV-infected patients

## Extrapulmonary tuberculosis: causes

- Most of the time, people with normal immune systems contain TB in the lung
- The weak immune system of HIV-infected patients allows TB to spread throughout the body
- Because most patients in resource-limited settings have AIDS and low CD4 counts before seeking care, extrapulmonary TB is very common in the era of HIV

## Extrapulmonary tuberculosis in the era of HIV

- Before the era of HIV, most TB occurred only in the lungs[62, 83]
  - Lungs (pulmonary): 85%
  - Outside lungs (extrapulmonary): 15%
- In HIV-infected patients, more than half of TB cases are extrapulmonary, with many patients having infection both in and outside the lung at the same time[10, 17, 18, 20, 57, 58, 62]
  - Pulmonary alone
  - Pulmonary + extrapulmonary
  - Extrapulmonary alone

  } More than half of the cases in the era of HIV
- Clinicians can use this change in **epidemiology** (disease pattern) to help diagnose pulmonary TB by recognizing its signs and symptoms outside of the lung

## Epidemiology of extrapulmonary tuberculosis

- 20% (1 out of 5) to 33% (1 out of 3) of *all* TB cases (HIV-positive and HIV-negative combined) in Africa are registered as extrapulmonary disease[35, 123, 124]
- These registration figures are likely underestimates because:
  - **TB is only recognized in half of African HIV-positive patients before death**[17]
  - TB in the blood is a common cause of death and is often missed[61]
  - Many HIV-infected TB patients with low CD4 counts (< 200/μl) will have some form of extrapulmonary disease, often combined with pulmonary TB at the same time[57]
- In one study of HIV-infected patients with TB, almost all participants had CD4 counts less than 200 cells/μl, **and over half had extrapulmonary tuberculosis**[125]

## Overview of blood infections

- Bacteria in the blood is called "**bacteremia**"
  - A well-known example of bacteremia in resource-limited settings is typhoid fever
  - When the bacteremia is caused by TB we call it **"mycobacteremia"**
- Bacteremia can occur when infection spreads from the lung or another body part
  - But bacteremia can also occur "on its own" without obvious pneumonia or intestinal infection
- Signs and symptoms of bacteremia include:
  - Very sick
  - High fever
  - May have signs of infection somewhere else in the body
  - Headache and confusion
  - Remember the WHO **danger signs** (see page 52)

## Tuberculosis in the blood

- Many HIV-infected patients with advanced AIDS and low CD4 counts have tuberculosis in the blood (mycobacteremia)
- Research studies show that 10% (1 out of 10) to 25% (1 out of 4) of advanced AIDS patients admitted to African hospitals with fever have mycobacteremia[79, 80, 126-129]
- **Tuberculosis is the most common blood infection** in HIV-infected patients with fever admitted to the hospital
  - **TB is more common than salmonella** (the bacteria that causes typhoid fever)
  - **TB is even more common than malaria** (in dry season)
- Many patients with mycobacteremia have no signs or symptoms of pulmonary TB[61, 79, 80]

## Tuberculosis in the blood: how to diagnose?

- Most laboratories in resource-limited settings cannot detect tuberculosis in the blood
- The clinician must look for other evidence of TB[55, 79, 80, 128, 130]
  - Sputum AFB smear
  - Chest x-ray changes
  - Cough
  - Severe anemia
  - Clinician assesses advanced AIDS at admission
  - Many large lymph nodes
  - Altered mental status
- Most cases of tuberculosis in the blood can be detected by diagnosing TB somewhere else in the body[128]
- However, sometimes a blood culture is the only certain way to diagnose mycobacteremia[126]
- About half of the patients (1 of every 2) with tuberculosis in the blood will have **no evidence of TB in the lungs**[61, 79, 80]
  - So you must also look for tuberculosis elsewhere in the body (such as brain, heart, or lymph nodes)

## Disseminated tuberculosis:

### The importance of severe anemia

- In disseminated TB, infection often spreads to the bone marrow, causing a low hemoglobin level
- But there are other causes of anemia, including bacteria and malaria
- When the hemoglobin is < 7 g/dl in HIV-infected patients, the following causes are most frequent[55]
  - **Tuberculosis:** 1 out of every 3
  - Bacteria in the blood: 1 out of every 5
    - Most common cause is salmonella
  - Other (iron, B12 deficiency, etc.)

Note that in a patient with fever, vitamin deficiency alone cannot be the explanation.

## Using anemia to help diagnose TB

- In HIV-infected patients with severe anemia (hemoglobin < 7 g/dl) other symptoms can be used to support a diagnosis of tuberculosis:
  - Severe anemia + chronic cough (> 3 weeks)
  - Severe anemia + headache
  - Severe anemia + lymph nodes
    - TB is the most common cause of enlarged and tender lymph nodes in ill HIV-infected patients in resource-limited settings[89]
  - Severe anemia + pleural effusion
    - TB is also the most common cause of pleural effusion in HIV-infected patients in resource-limited settings[116-118]
  - Severe anemia + fever
    - Consider TB and salmonella in addition to malaria

## Tuberculosis in the blood: when do you treat if you do not have the necessary laboratory tests?

- Patients with the following characteristics should be considered for empiric tuberculosis therapy:[82, 131]
  - HIV-positive with fever and/or unexplained rapid weight loss for more than 2 weeks
  - Cough for longer than two weeks with WHO **danger signs**[82]
    - Respiratory rate > 30 breaths per minute
    - Fever > 39 degrees Celsius
    - Pulse > 120 beats per minute
    - Unable to walk alone
    - Note the importance of the physical exam and of confirming the vital signs
  - Failure to respond to a course of broad-spectrum antibiotics
  - Evidence for tuberculosis elsewhere in the body
- A patient does not need to meet all of these criteria before TB therapy can be started
  - **Very sick, advanced HIV-infected patients should be treated before it is too late**
  - **Empiric (best guess based on clinical judgment) treatment of TB is often correct**[103]

***Vital signs are vital!***

Good clinicians pay attention to the vital signs.

If the patient appears ill, confirm the vital signs yourself.

## What does the World Health Organization recommend about empiric treatment of tuberculosis?[82]

- Sick HIV-infected patients can be treated empirically for TB if they:
  - Have cough for more than two weeks
  - **Danger signs** are present
  - Even if sputum smears for AFB are negative
  - No response to parenteral antibiotics after 3-5 days
    - Also consider PCP therapy
- Healthcare providers working in clinics and health centers which lack complete diagnostic testing **"should initiate empirical tuberculosis therapy early in serious illness in patients thought to be due to extrapulmonary tuberculosis"** (emphasis added)
- Referral should be made to a higher level health center as soon as possible

## Kenya's example: What does an African Ministry of Health recommend?

> "Advanced TB and HIV can be clinically indistinguishable—the clinician should ALWAYS consider if there is active TB and this should be excluded as far as possible.
>
> [Treatment] with TB drugs should be considered, **even in the absence of definite radiological or microbiological evidence.**" (emphasis added)
>
> —Kenyan National Clinical Manual for ARV Providers, 1st ed., 2004[132]

## Return to case 1: follow-up

- Patient did not respond to good antibiotics
  - Failure to respond to these antibiotics makes pneumonia and salmonella unlikely
- No evidence of another infection like malaria
  - The several week course also argues against pneumonia
- Patient remained persistently febrile (temperature 38.5 degrees Celsius) and became unable to walk alone
  - Presence of **danger signs**

Would you treat for tuberculosis? Would you do other tests?

## Case 1: clinical reasoning

- Blood culture for bacteria is expensive and not always available
  - Blood culture for tuberculosis is almost never available in resource-limited clinics
- This patient is very ill and becoming more sick over time
- He did not respond to good antibiotics
- Chest x-ray was done but was normal
- He has the following predictors of TB in the blood
  - Low CD4 count
  - Persistent fever and weight loss
  - Moderate anemia
  - Danger signs: unable to walk alone

## Case 1: treatment

- The patient was started on empiric treatment for disseminated tuberculosis, including TB in the blood
  - The jaundice probably means he also has TB in the liver
- He improved significantly on TB treatment and began walking again

## Case 1: summary

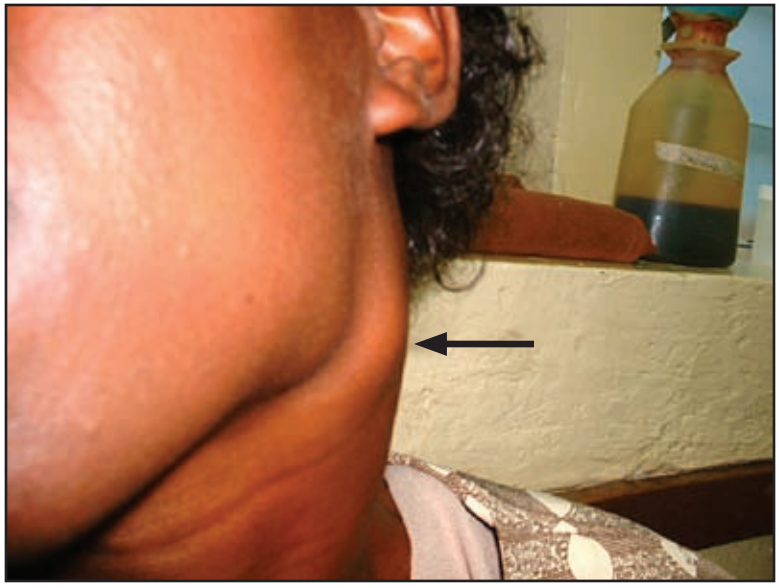
- Sometimes, treatment of tuberculosis in the sick HIV-infected patient is necessary even though all the information is not available
  - Delaying therapy for too long could lead to death
  - In this case, we do not know for 100% certain that TB was present
- However, we do know that:
  - The clinicians did everything possible to find an answer using the limited diagnostic tests available
  - Research shows that many HIV-infected patients like this one in resource-limited settings do actually have TB
  - The patient responded to anti-tuberculosis treatment
  - The patient would probably have died if anti-tuberculosis treatment had been delayed any longer

## Cautions about case 1

- Why did the patient initially improve on antibiotics?
  - The ciprofloxacin (chosen to treat possible salmonella) may have partially treated the TB,[133] followed by a worsening condition
  - Tuberculosis can develop resistance to ciprofloxacin
  - Consider using a different antibiotic (ceftriaxone, cotrimoxazole, chloramphenicol, or azithromycin) for salmonella when TB may be present, and avoid ciprofloxacin when the patient is coughing
    - WHO guidelines recommend against using ciprofloxacin when TB may be present[51]
- One could argue, based on WHO guidelines, to treat this patient for tuberculosis after only 3-5 days of antibiotics
- When deciding to start empiric treatment for TB, **treat for the entire course** per national protocol
  - The WHO recommends against short "treatment trials"[82]

## Case 2: presentation

- 35-year-old HIV-positive female; CD4 count unknown
- History of present illness: Weight loss and fever for more than one month
- Past medical history: Daughter has pulmonary tuberculosis
- Physical examination: Temperature 37.8 degrees Celsius, pulse 92 beats per minute. Wasted. Multiple hard and tender nodules left and right neck (see picture). Lung exam normal.



Enlarged and firm cervical lymph node

What are the possible causes of her illness?

What is your differential diagnosis?

What would you do next?

## Case 2: diagnostic approach

- Patient not coughing or producing sputum for AFB analysis
- Chest x-ray normal
- Fine needle aspirate of enlarged cervical lymph node positive for AFB
  - Diagnosis: tuberculous lymphadenitis

## Case 2: treatment

- Patient improved and gained weight on tuberculosis treatment
- Lymph node became smaller

## Tuberculous lymphadenitis: definitions

- **Lymphadenopathy** means:
  - Lymph nodes which are **not** normal size, shape or form
  - Increased size
  - Firm or hard
  - Painful or full of pus
- When two or more locations are involved the term is **generalized lymphadenopathy**
- Tuberculous lymphadenitis means lymph nodes which have been infected and swollen with TB

## Persistent generalized lymphadenopathy in HIV disease

- Persistent generalized lymphadenopathy **(PGL)** is common in HIV-infected adults[134]
- PGL itself is not a disease
  - PGL occurs as the body tries to fight HIV
  - Patients with PGL have large lymph nodes but may not be sick
- PGL can occur by itself, without another disease, or it can occur with TB, another infection, or cancer
- Persistent generalized lymphadenopathy is also very common in HIV-infected children at all stages of HIV infection[135]
  - It is more difficult to tell in children if enlarged lymph nodes are due to another problem (like TB or cancer) or to HIV itself
- The clinician should look elsewhere for evidence of TB, another infection, or cancer to determine the cause of lymphadenopathy
  - Lungs
  - Brain
  - Blood
- When in doubt, aspiration or biopsy of a lymph node should be done, if possible

## Tuberculous lymphadenitis: epidemiology

- In **sick HIV-infected patients** in African settings who present to the clinic, TB is the most common cause of lymphadenopathy[89, 110, 136]
- In patients who are **clinically stable** and without complaints, generalized lymphadenopathy is more likely to be PGL[137]
- Lymphadenitis is the most common form of extrapulmonary TB[18, 138]
- The number of cases of tuberculous lymphadenitis has increased because of the HIV epidemic[109, 139]
  - Clinicians practicing HIV medicine in a resource-limited setting will see many cases of TB in the lymph nodes
- Tuberculous lymphadenitis often exists with pulmonary and extrapulmonary TB
- Clinicians can use the presence of lymph nodes to help diagnose tuberculosis elsewhere in the body[63, 81, 110, 140]
  - Lymph nodes + chronic cough = think pulmonary TB even if the sputum AFB smears are negative
  - Lymph nodes + severe anemia = think disseminated TB
  - Lymph nodes + confusion = think TB meningitis

## Tuberculous lymphadenitis: size and location

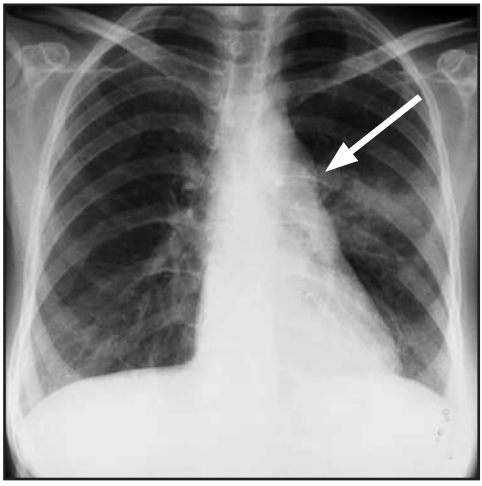
- Tuberculosis infection of the lymph nodes[88]
  - Cervical (neck)
  - Axillary (armpit)

  } Most common
  - Supraclavicular (above collarbone)
  - Epitrochlear (elbow)
  - Inguinal (groin)
  - Intrathoracic (chest)
  - Intra-abdominal

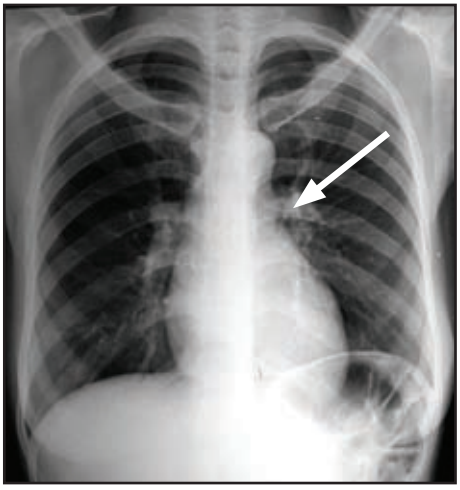
  } Seen only on chest x-ray or abdominal ultrasound
- Enlarged lymph nodes are:
  - ≥ 2 cm in the inguinal region, or
  - ≥ 1 cm anywhere else in the body

## Intrathoracic (inside the chest) lymph nodes in an HIV-infected patient with tuberculosis

- Intrathoracic (hilar or mediastinal) lymphadenopathy is a common finding in HIV-infected patients with tuberculosis
  - In one study, 2 out of every 5 HIV-infected TB patients had lymphadenopathy on the chest x-ray[57]
  - South Africa: the combination of lymph nodes in the chest with either fever or sweats meant TB was present 94% of the time[39]
  - **In sick HIV-infected Africans with lymphadenopathy on the chest x-ray, think TB!**



HIV-infected with TB and lymph node



Normal chest x-ray

The "bulge" (arrow, left picture) in the HIV-infected patient is a **lymph node** inside the chest. Compare this with the **absence** of a "bulge" (arrow, right picture) in the normal chest x-ray.

## Tuberculous lymphadenitis: patterns of disease

- **Focal (one location in the body)**[88, 141]
  - More common in **HIV-negative** patients
  - Classic example is scrofula: tuberculosis of the cervical (neck) lymph nodes in HIV-negative children
  - May or may not occur at the same time as TB elsewhere in the body
- **Generalized (two or more locations)**[142]
  - Common in HIV-positive patients[88]
  - Lymph nodes may occur on one or both sides of the body
  - Accompanied by fever and weight loss
  - Represents **dissemination of TB** throughout the blood and body
  - Multiple organs (lung, brain, heart, liver, etc.) usually also affected, so look for other evidence of tuberculosis in these organs

## Tuberculous lymphadenitis: clinical presentation

- Nodes are usually "**firm**" or "**hard**"[88]
  - Normal lymph nodes are soft
  - Normal lymph nodes may not be felt
    - One exception is the inguinal area, where lymph nodes are easily felt in most individuals, so the nodes must be larger (> 2 cm) to draw clinical attention
- Nodes with TB may drain purulent material (pus)
- Consistency, or how the nodes "feel" when TB is present: **smooth, irregular, or "matted" (stuck) together**
- Other signs and symptoms of TB lymphadenitis often reflect disseminated infection with tuberculosis[142]
  - Fever and weight loss
  - TB somewhere else in the body, such as the brain, lungs, or heart[15]
- In patients with suspected TB lymphadenitis, look for tuberculosis in the lung also
  - Chest x-rays will often show evidence of TB[88, 139]
  - If coughing, examine sputum for AFB
- In patients with **generalized lymphadenopathy** who have the following signs and symptoms, suspect **disseminated tuberculosis**:[136]
  - WHO danger signs (refer back to page 52)
  - Shortness of breath
  - Neurological dysfunction (headache, problems with thinking, weakness, paralysis)
  - Large liver or spleen

Sometimes enlarged lymph nodes may be the only evidence of tuberculosis in a very sick HIV-infected patient.

## Tuberculous lymphadenitis: differential diagnosis

- **HIV itself (PGL)**
  - After TB, next most common cause of enlarged lymph nodes in HIV-positive Africans
  - **Persistent generalized lymphadenopathy** of HIV disease (PGL) can cause soft, "rubbery" lymph nodes
  - Usually occurs at higher CD4 counts
- Cancer (third most common cause of large lymph nodes)
  - Kaposi's sarcoma and lymphoma
  - Can also be detected with fine needle aspirate of the lymph node if pathology services are available
- Other infections (uncommonly found in lymph node biopsy studies)
  - Disseminated cryptococcal disease
  - Bacteria such as staphylococcus
    - Focal disease in one location and not generalized
  - Salmonella can sometimes cause generalized lymphadenopathy

## Very ill HIV-infected patients with generalized lymphadenopathy

- In acutely ill AIDS patients with lymphadenopathy, fever and WHO **danger signs**, consider the following:
  - Tuberculosis
  - Cryptococcus
  - Salmonella
  - Lymphoma
- How can you differentiate these infections?
  - Look for other evidence of TB
    - Brain, heart, lungs, blood and bone marrow
  - Cryptococcal antigen in serum or cerebrospinal fluid or India ink in cerebrospinal fluid
  - Aspirate or biopsy of lymph node
- South African HIV-infected patients with the following characteristics had a 94% chance of having extrapulmonary TB:[39]
  - Palpable lymphadenopathy (> 3 cm in length)
  - And one of the following:
    - Fever > 38.0 degrees Celsius on two occasions
    - Drenching night sweats for 2 weeks
- Cambodia: the presence of enlarged intra-abdominal lymph nodes (two or more lymph nodes > 1.2 cm in diameter) was highly predictive of tuberculosis as confirmed by culture of other body sites[143]

***Key Concept***

Remember that TB is the most common cause of generalized lymphadenopathy and severe illness in HIV-infected Africans.

## Tuberculous lymphadenitis vs. PGL

Remember that PGL stands for "persistent generalized lymphadenopathy" of HIV disease.

| | Tuberculosis | PGL |
|---|---|---|
| **Frequency** | Most common in ill, symptomatic patients | More common in stable patients without symptoms |
| **CD4 count** | Any, but more common when CD4 < 200 | Any |
| **Signs and symptoms** | WHO **danger signs**, weight loss, fever, cough, shortness of breath, headache, anemia | PGL does not cause symptoms by itself |
| **Node character** | Firm, hard, lumpy, tender, or draining | Soft, "rubbery," not lumpy or tender |
| **Location** | Focal (one place) or generalized; cervical & axillary most common | Generalized |
| **Size** | 66%: 1-3 cm<br>33%: 3-5 cm | 1–3 cm;<br>never larger than 3 cm |

## Important note about interpreting lymphadenopathy

- The presence of lymphadenopathy by itself, without other symptoms or signs of infection, does not always mean that tuberculosis or another infection is present
- The presence of lymphadenopathy must be interpreted in the setting of the patient's complaints and the rest of the physical exam
  - Is the patient acutely or chronically ill? Is the patient wasted?
  - Are the vital signs normal? Is there fever?
  - Are there WHO **danger signs**?
- Does the patient have new symptoms? Did he come to the clinic seeking care for a specific complaint?
  - Patients with tuberculous lymphadenitis will often have fever and weight loss
  - Or is he a stable HIV-positive patient who only came to the clinic to enroll in chronic care?
    - If this is the case, PGL may be the cause of the large lymph nodes in this otherwise well patient

## Tuberculous lymphadenitis: diagnosis

### If a higher level laboratory is available and costs allow

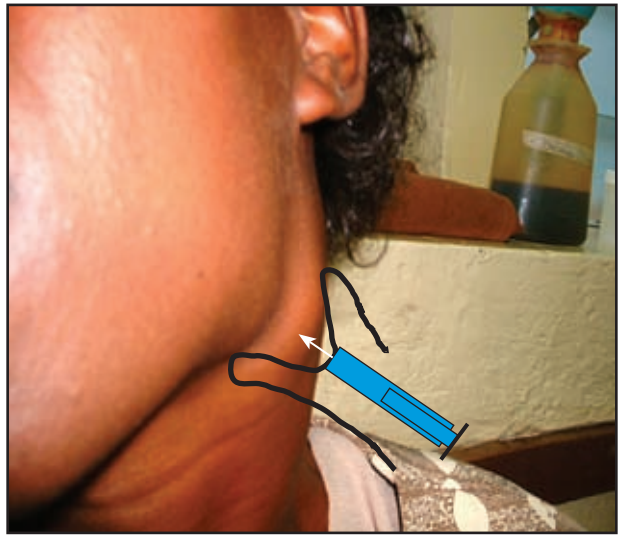
- Fine needle aspirate (FNA) and stain for AFB
  - See procedure example on next page
  - FNA is particularly useful when a diagnosis other than tuberculosis is suspected
    - Example: A patient is treated for TB but fails to respond
    - Example: A patient has lymph nodes but also has Kaposi's sarcoma lesions on the skin
- If the fine needle aspirate fails to give a diagnosis, an *excisional* biopsy (complete removal of the lymph node) can be done, if the diagnosis is in doubt
  - But *incisional* biopsy (partial removal) is not recommended as tuberculosis prevents the wound from healing well
  - The diagnosis can usually be made on clinical grounds (see below) instead of undertaking the risks and expense of surgery
- If the lymph node is draining pus, press a glass slide to the material and send to the lab for staining for AFB
- Remember the study previously mentioned from Cambodia: the presence of enlarged intra-abdominal lymph nodes detected on ultrasound is highly suggestive of tuberculosis[143]

### In a setting with limited laboratory and technical expertise

- According to the WHO,[82] an **empiric diagnosis** can be made if lymphadenopathy is present and:
  - The patient is very ill (fever, rapid weight loss, suspected TB in other body sites)
  - **A lymph node aspiration or biopsy cannot be done**
- Recall from above that if an HIV-infected patient has lymphadenopathy which is > 3 cm and either persistent fever or night sweats, he has a 94% chance of having extrapulmonary TB[39]

## Tuberculous lymphadenitis: fine needle aspiration (FNA)

- This procedure can be useful in diagnosing TB[81, 90, 140]
  - However, the test is not perfect; a negative aspirate and stain for AFB does **not** rule out TB in every patient[110, 144]
- **Caution:** In the neck, people sometimes mistake the bulb of the carotid artery for a lymph node
  - You should receive training from an experienced person before attempting this procedure on your own; if in doubt, refer to an experienced clinician to do the procedure
- FNA can diagnose other diseases like cancer and bacterial infections
- If the clinician suspects TB somewhere else in the body (lung, brain), FNA of a lymph node can prove TB as cause of those symptoms[63, 81]



1. Explain the procedure[82] to the patient. Obtain her consent.
2. Clean the site with alcohol or iodine. Use gloves.
3. Pinch and raise the node with your thumb and finger.
4. Using a 19 gauge needle, insert slowly into the center of the node.
5. Pull back until a small amount of fluid is visible in the syringe.
6. Place this aspirate onto a slide and dry in the air.
7. Send to the lab for AFB smear and gram stain.

## Tuberculous lymphadenitis: treatment

- Standard national anti-tuberculosis regimen
- Look carefully for signs of TB elsewhere in the body
- Be aware that "**paradoxical worsening**" may occur with treatment and the lymph node may enlarge before healing
  - The lymph node may become more tender and even drain pus before it starts healing
  - This is a form of **immune reconstitution inflammatory syndrome** (**IRIS**) which can occur with or without HIV or ART
    - Paradoxical worsening of TB lymphadenitis is a known problem in *HIV-negative* patients
- Paradoxical worsening means patients get worse even though they are getting the correct TB treatment
- The presence of IRIS or tuberculosis in the brain or heart may require corticosteroids to calm the inflammation
  - See Chapter 6 for guidance on the use of corticosteroids

## Tuberculous lymphadenitis and IRIS

- TB lymphadenitis may only reveal itself **after** a patient starts ART[145]
- Patients who start ART while having active, undiagnosed and untreated TB become clinically ill
  - Lymph nodes infected with tuberculosis may become large and tender because the immune system is now stronger on ART
  - The stronger immune system starts attacking TB
  - This may occur within days, weeks or months after starting ART
- Be careful to rule out active tuberculosis before starting ART
  - **All HIV-infected patients should undergo a thorough lymph node examination**
- Management of IRIS due to TB following initiation of ART[145]
  - Continue ART, if possible
  - Start tuberculosis therapy
- Use non-steroidal anti-inflammatory drugs (NSAIDs), like aspirin, ibuprofen or diclofenac, to control pain and swelling
  - Some patients with very severe lymph node swelling and inflammation may benefit from a short course of oral corticosteroids[146]

A thorough HIV clinician will routinely place his fingers in the axillae (armpits) of patients to feel for lymphadenopathy.

There is no substitute for a thorough clinical examination.

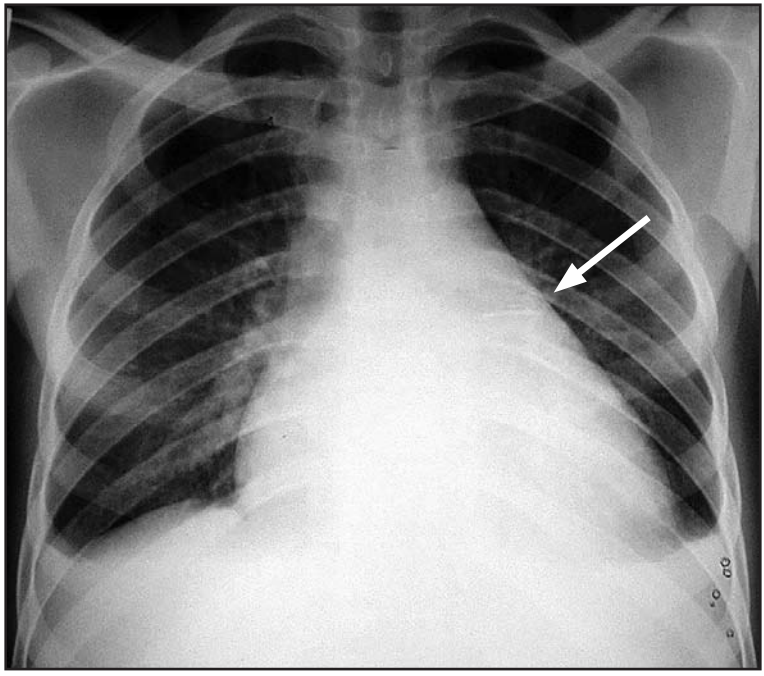
## Case 3: presentation

- 36-year-old female, CD4 count unknown
- Medical history:
  - After experiencing an episode of *Pneumocystis* pneumonia (PCP), patient started inadequate two-drug ART in 2001 because that was all she could afford
  - Initially improved and later switched to three-drug ART, but experienced weight loss
  - Started second-line ART with protease inhibitor and two weeks later developed a hard, tender 2 cm lymph node in the left supraclavicular region (above the left collarbone)
  - The patient was also coughing
- Chest x-ray: Infiltrate in left middle lung
- Sputum smear: Positive for AFB
- Diagnosis: Pulmonary and extrapulmonary (lymph nodal) tuberculosis with immune reconstitution inflammatory syndrome (IRIS) following start of second-line ART
- Treatment:
  - Patient started TB treatment according to national guidelines
  - She had to stop ART because protease inhibitors cannot be given with rifampicin
  - Given ibuprofen for pain and swelling but two weeks later the lymph node was larger and more tender
  - Then given prednisolone 10 mg daily for two weeks with resolution of symptoms
  - Later completed TB treatment and re-started second-line ART

Notice how extrapulmonary TB (lymph node swelling) came together with pulmonary TB (infiltrate and positive AFB sputum smear).

## Case 4: presentation

- 28-year-old HIV-positive man
  - CD4 count 166 cells/µl
- History of the present illness: Fever and racing heart for three weeks
- Physical examination: Temperature 38.6 degrees Celsius, pulse 126 beats per minute. Otherwise normal.
- Initial treatment: Given ciprofloxacin for presumed salmonella but no improvement
- Further investigation done
  - Chest x-ray: Enlarged heart

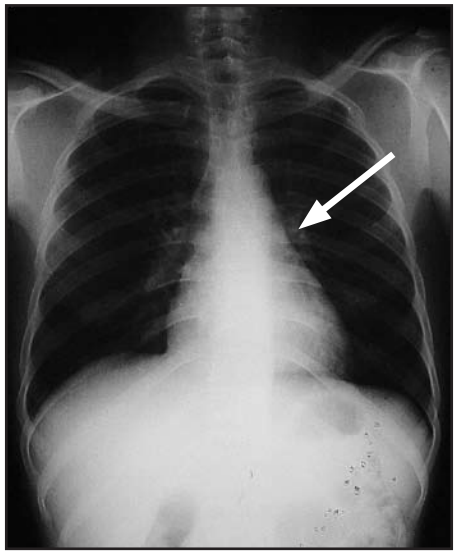


Note the enlarged heart and straight left heart border (arrow)

This change can occur when the pericardial sac around the heart has too much fluid. An enlarged heart can also be seen with heart failure due to other causes (like high blood pressure).

## Case 4: diagnosis and treatment

- Diagnosis: TB pericarditis (infection of the sac around the heart)
- Treatment:
  - Standard 4 drug therapy according to national guidelines for severe extrapulmonary tuberculosis (RHZE, or RIPE)
  - Oral prednisolone 30 mg twice per day
- Follow-up: Improved greatly in 2 weeks
  - Finished TB treatment and started ART
  - Pericardial effusion resolved
  - Repeat chest x-ray after completion of TB therapy was normal:



Notice that the heart is much smaller and that the left heart border is now curved inward (arrow) and not straight.

***Caution***

The use of ciprofloxacin for presumed salmonella infection could have led to resistance because cipro and other quinolone antibiotics have some anti-TB activity.[147] Every attempt should be made to rule out TB before starting treatment with ciprofloxacin.

## Tuberculous pericarditis: epidemiology

- Represents approximately 1 out of every 20 cases of TB in Africa[35, 148]
- Almost all cases of pericardial disease in patients with HIV is due to tuberculosis[148-150]
  - If a patient with HIV has a pericardial effusion seen on chest x-ray or ultrasound, there is at least a 90% chance he has TB
  - Knowing this fact can help clinicians diagnose TB pericarditis based on clinical grounds in resource-limited settings
- Any patient with a pericardial effusion should be tested for HIV

***Key Concept***

This is another example of **empiric diagnosis**: the use of the medical history, physical exam, basic tests and known epidemiology to make a diagnosis and start treatment. There has been much research about HIV and TB in Africa using sophisticated technology. We should apply this research even when we do not have access to the same technology.

## Tuberculous pericarditis: presentation

- Tuberculosis spreads from lung, lymph nodes, or blood to the sac around the heart called the **pericardium**[151]
- 1 out of 3 patients with pericardial tuberculosis will also show pulmonary TB on chest x-ray
- Presenting symptoms usually occur over weeks to months and are not specific for tuberculosis[152, 153]
  - Night sweats and weight loss
  - Chest pain and shortness of breath
- HIV-infected patients with tuberculous pericarditis may not have other signs of AIDS[148]
- Generalized lymphadenopathy does occur in 4 out of 5 patients[154]

Notice again how important it is to look for TB in more than one place!

- Physical examination may include:[148, 151, 153, 155]
  - Fever
  - Tachycardia (pulse greater than 100)
  - Low blood pressure
  - Elevated neck veins
  - Shortness of breath and high respiratory rate
  - Chest dullness to percussion
  - Friction rub (scratching sound) over heart
  - Distant (hard to hear) heart sounds
  - Signs of heart failure:
    - Large, tender liver (hepatomegaly)
    - Ascites (fluid in the abdomen)
    - Ankle edema

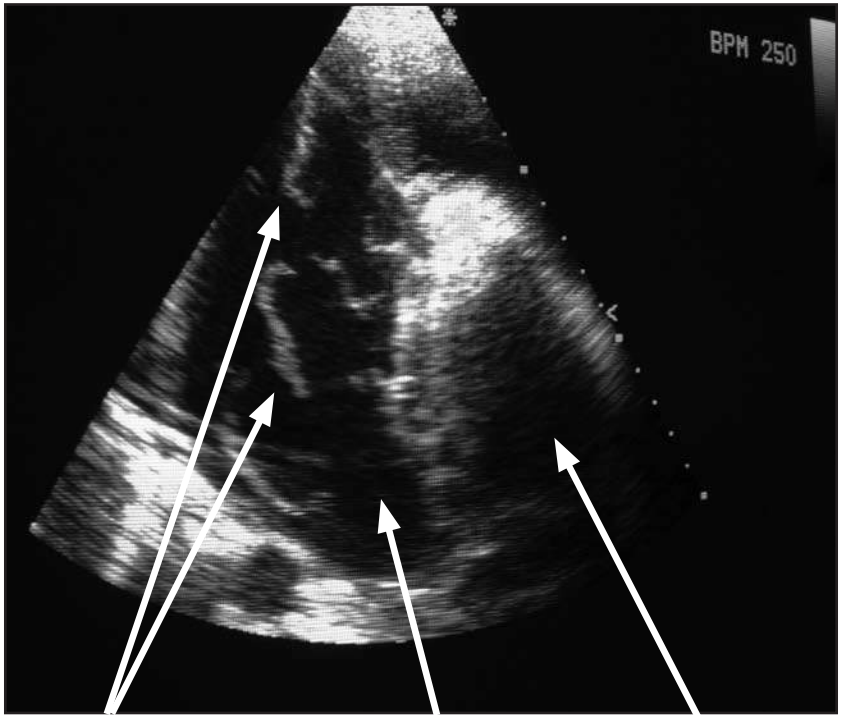
Vital signs are vital!
Pay attention to the vital signs.

Heart failure must always be explained and should have a reason, such as high blood pressure or tuberculosis.

## Tuberculous pericarditis: diagnosis

- Compatible clinical history
  - Knowledge of HIV status is extremely important because, as we have seen, **at least 90% of the time pericardial effusion is caused by tuberculosis in HIV-infected Africans**
- Chest x-ray:
  - Large heart often seen,[156] as in Case 4 above
  - Straight left heart border[157]
  - Other evidence of TB (miliary pattern, cavity, lymphadenopathy)
- Heart ultrasound, if available
  - Pericardial effusion (fluid around the heart)
  - May show fibrous "strands" of TB (see picture next page)
- Pericardiocentesis (removal of fluid from around the heart using a needle); **should be done only by an experienced physician**
  - Look for TB (AFB stain and culture, if available)
  - Rule out other causes (such as bacteria and cancer)
  - Pericardiocentesis is usually not necessary
    - Technically difficult and usually not an option in most resource-limited settings
    - **The diagnosis of pericardial TB can almost always be made based on clinical presentation and chest x-ray alone**
  - Pericardiocentesis is indicated in cases of tamponade (to relieve pressure around the heart and raise blood pressure)
- Electrocardiogram
  - Low voltage; the usual waves are not seen well[158]
  - Raised ST-segments[151] (see EKG on page 97)
- Look for TB elsewhere: sputum for AFB, chest x-ray, fine needle aspirate and/or biopsy of enlarged lymph node, severe anemia, evidence of meningitis

## Pericardial tuberculosis: cardiac ultrasound

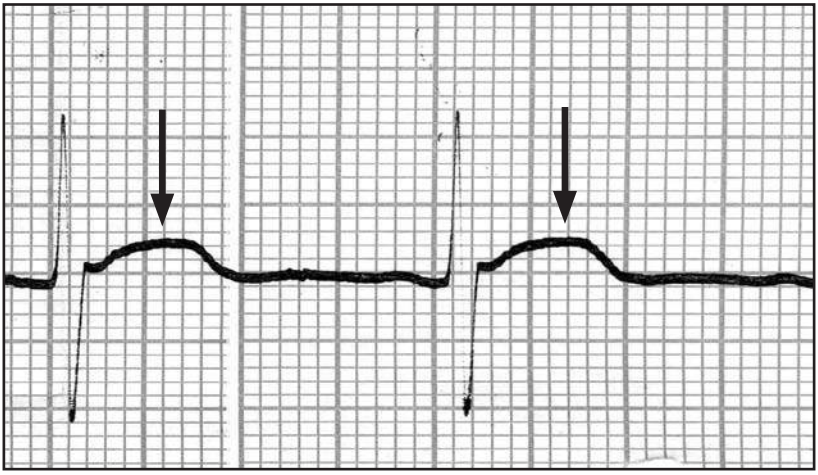



Strands of fibrinous TB and inflammation in the pericardial sac

Fluid in the sac around heart (this patient has a lot of fluid)

Left ventricle

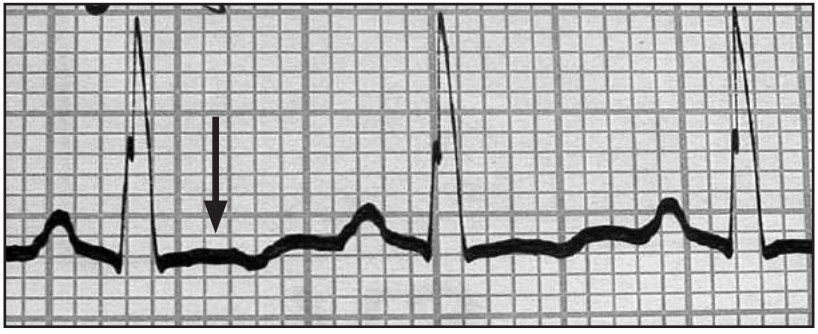
## EKG changes in tuberculous pericarditis



ST segment elevated (raised)

A patient with HIV and TB pericarditis presented with low blood pressure and **elevated ST segments** on his EKG (arrows).

These elevated ST segments indicate damage to the heart muscle. This patient later went into heart block, causing his heart rate and blood pressure to drop. His condition improved with TB therapy and corticosteroids.



ST segment not elevated

A different patient **without** ST segment elevation (arrow)

## Tuberculous pericarditis: treatment

- Follow national guidelines for severe extrapulmonary TB
- Corticosteroids decrease risk of death and complications like chronic heart failure[154, 159, 160]
  - Very sick: Admit to the hospital and start dexamethasone 8 mg intravenously or intramuscularly three times per day
  - Less sick: May treat as outpatient and start prednisolone 30 mg orally twice per day[154]
- Taper slowly over approximately 3-4 weeks
- Drainage of fluid around the heart can also improve outcome,[159] but pericardiocentesis is difficult and not needed unless the patient is very sick with low blood pressure; only experienced clinicians should attempt this procedure
  - If tamponade with low blood pressure is present, and pericardiocentesis cannot be done, start TB therapy and corticosteroids immediately

---

**Empiric** diagnosis and treatment is usually necessary:

**"The diagnosis of tuberculous pericardial effusion is therefore often presumptive [empiric; best guess],** based on consistent clinical and investigative findings and the exclusion of other possible diagnoses."[148] (emphasis and comment added)

---

- Survival is likely with timely diagnosis[148, 159]
- Watch for later development of heart failure
  - Long term risk of constrictive pericarditis (heart failure)
  - Sometimes "pericardial stripping," removal of the damaged sac around the heart, is required, if expertise is available
  - **Patients who receive corticosteroids for three to four weeks are less likely to develop these complications**[159]

---

Again, the importance of rapid diagnosis and treatment is obvious. If you wait for 100 percent confirmation of TB, the patient may die during this period.

---

## Case 5: presentation

- 48-year-old Somali female; HIV status unknown
- Medical History: Weight loss, fever, abdominal pain and swelling
  - No history of alcohol abuse
- Examination: T 38.3 degrees Celsius. Pulse 110 beats per minute. Abdominal ascites and diffuse tenderness.
- Investigations:
  - Chest x-ray: normal
  - Abdominal paracentesis: 280 cells (90% lymphocytes), AFB smear negative
  - Hepatitis B surface antigen negative

## Case 5: treatment

- Diagnosis: Without a clear reason for the ascites, empiric diagnosis of tuberculous peritonitis made in a patient from an area with a high rate of TB
- Treatment: Standard 4-drug therapy (RHZE) according to national guidelines for severe extrapulmonary disease
- Follow-up: The patient improved significantly with resolution of ascites
  - Successfully completed therapy

## Intestinal or abdominal tuberculosis

- Tuberculosis can spread from the lung through the blood to the gastrointestinal system, or TB may be swallowed in sputum
- In HIV-infected patients who die from disseminated tuberculosis, infection is often found in the intestinal system[19]
- TB can infect the entire gastrointestinal tract[161]
  - Esophagus
  - Stomach
  - **Peritonitis** (infection of sac containing abdominal contents)
  - Intestinal
    - Duodenum
    - **Ileocaecal**
    - Colon and rectum
  - Abdominal lymph nodes
  - Liver

---

Ileocaecal and peritoneal tuberculosis are the most common clinical sites and usually occur together.

The liver and abdominal lymph nodes are also often involved in disseminated TB.[18, 162]

---

## Abdominal tuberculosis: presentation[163, 164]

- Usually chronic illness (lasting weeks to months)
- HIV-positive patients can present with an **"acute abdomen"**
  - Surgical emergency due to ileocaecal TB causing intestinal rupture and/or blockage[165]
- Common symptoms
  - Weight loss
  - Abdominal pain (mid-abdomen and right lower quadrant)
  - Change in stool habits (constipation or diarrhea)
    - In Kenya, 1 out of every 8 HIV-infected patients with chronic diarrhea had TB in the stool, and half also had pulmonary TB[166]
  - Other possible symptoms
    - Nausea, vomiting, and night sweats
    - Bloody stools (red or black)
- Exam
  - Fever and wasting
  - Palpable right lower quadrant mass
  - **Ascites** (fluid in the abdomen)
    - TB should be considered in patients with ascites
  - Lung involvement in 1 of 5 patients with abdominal TB[163]
- Because abdominal tuberculosis is a presentation of disseminated disease, other organs may show evidence of TB
- Hepatic tuberculosis may present with jaundice (yellow eyes and skin), along with fever, weight loss, and abdominal pain[167]
  - Liver function tests may be abnormal (high bilirubin and alkaline phosphatase)
  - Recall the patient from Case 1 of this chapter, who presented with jaundice and elevated bilirubin and responded to anti-tuberculosis treatment

## Differential diagnosis of ascites in HIV infection

- Infections
  - Abdominal tuberculosis
- Liver failure from any cause, such as:
  - Hepatitis B or C
  - Alcohol
- Kidney failure from any cause
- Heart failure from any cause, such as:
  - Tuberculous pericarditis
  - Other causes such as high blood pressure
- Cancer
  - Lymphoma (can occur with large abdominal lymph nodes and can be hard to tell from tuberculosis)
  - Kaposi's sarcoma

## Abdominal tuberculosis: diagnosis

- Paracentesis (needle aspiration of ascites)[164]
  - Mostly lymphocytes
  - **AFB are rarely seen in peritoneal fluid**
- **As in pulmonary TB, a negative smear does <u>not</u> rule out abdominal tuberculosis**[163]
- Exploratory surgery and biopsy, if available, may be necessary to confirm the diagnosis (as in Case 5 above)
- Abdominal ultrasound may identify abdominal lymph nodes or lesions in the liver and spleen[162]
- If available, colonoscopy and biopsy may identify TB[161]
- Look for TB elsewhere (lung, lymph nodes, brain) since abdominal TB is often a sign of widespread infection
- In a sick HIV-infected patient, empiric therapy is acceptable if you suspect TB and these tests are not available[82, 163]
- In one study, all six HIV-infected patients with lymphocytes in the ascites fluid and persistent fever or night sweats had TB[39]
- If referral to another facility is not possible, consider starting tuberculosis treatment because delay can lead to death[168]

## Abdominal tuberculosis: treatment

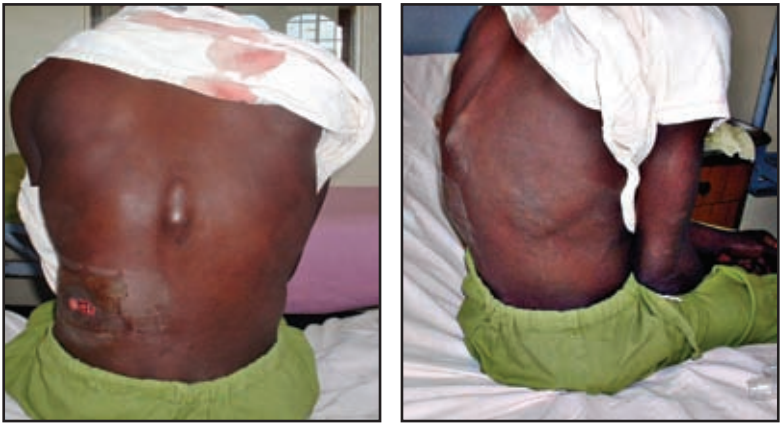
- Standard national regimens for extrapulmonary tuberculosis
- Sometimes patients cannot absorb the drugs because TB has damaged the intestine; in these cases, consult an expert
- Attention must be paid to the patient's nutritional status
- Occasionally, surgery is needed to relieve a bowel obstruction or to drain an abscess.

> You must think of abdominal TB in HIV-infected patients with these signs and symptoms because "in areas of the world where the disease is endemic, correct clinical diagnoses are made only 50% of the time. Without a high index of suspicion, [abdominal TB] is rarely diagnosed correctly."[163, 169]

## Case 6: presentation

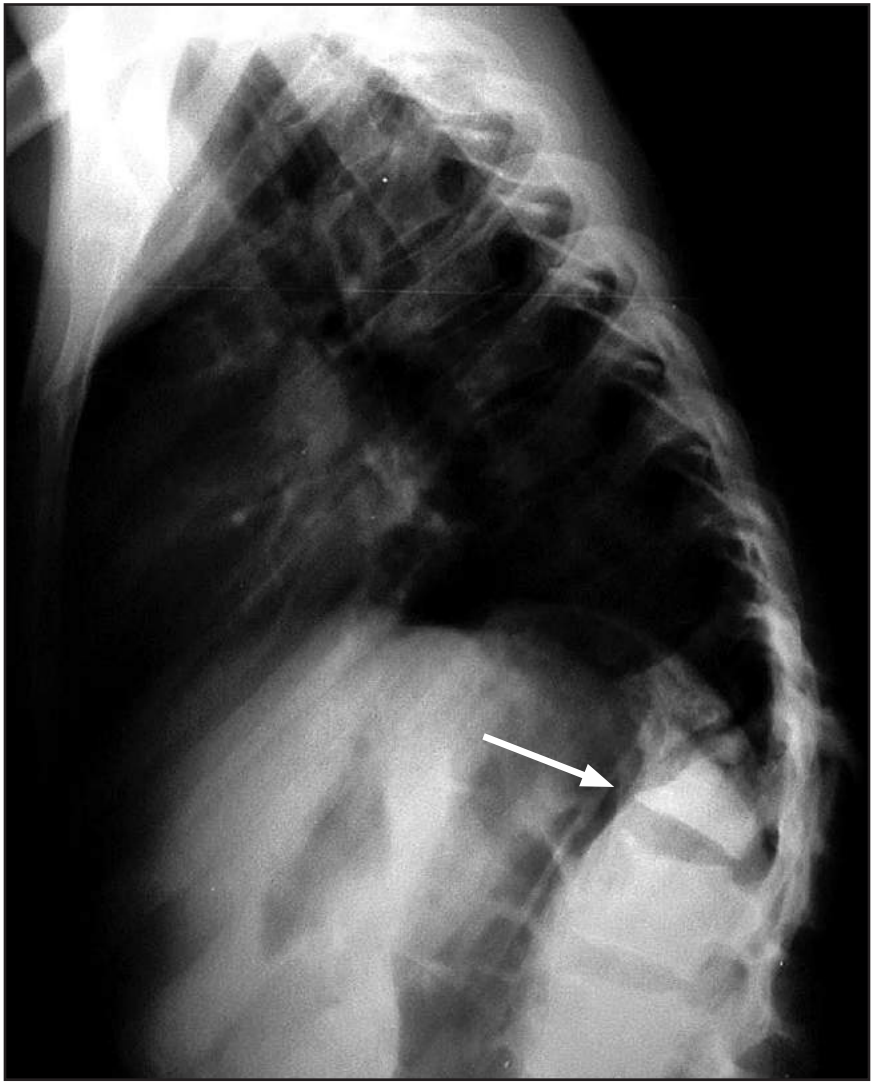
- 28-year-old male; refused HIV testing
- Medical history: Six months of back pain progressing to the point that he could not work. Developed draining wound on back (see pictures below). No cough or fever.
- Physical examination: Kyphosis (a curve in the spinal column) with a hard lump of bone and a draining wound
- Chest x-ray: Normal

Paraspinal abscess



He has the classic **Gibbus deformity** on his back.

## Case 6: spine x-ray



There is a severe angulation (bending) of the spine because the infected vertebra is collapsing (arrow).

He had the classic Gibbus deformity, showing as a "hump" on the back.

## Case 6: diagnosis and treatment

- Underwent drainage of abscess near the spine (epidural abscess)
- Sample of pus positive for AFB
- Diagnosis: Pott's disease (TB of the spine) with spinal abscess
- Received anti-tuberculosis treatment according to national protocol for severe extra-pulmonary disease
- Continued to refuse HIV testing

## Skeletal tuberculosis: overview

- Skeletal system affected in about 1 of 50 patients with TB[62, 170]
- TB gets to bone by spreading from the lung through the blood
- So, like in disseminated TB, HIV-infected patients are at risk for tuberculosis in the blood spreading to the bones
- Forms of skeletal TB
  - Spinal TB (Pott's disease): most common
    - With or without an abscess
  - TB arthritis (infection of a joint)
    - Usually just one large joint affected
  - Osteomyelitis: TB infection of other bones

## Spinal tuberculosis

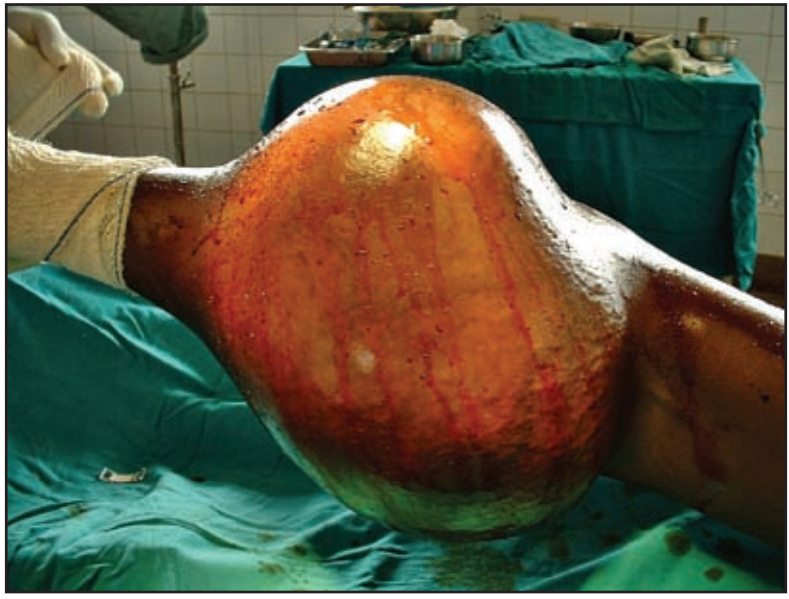
- Usually young patients less than 30 years of age[62, 170]
- Most common symptom is back pain getting worse over months
- Lumbar and lower thoracic (middle and lower) spine most common
  - Classic Gibbus deformity is a bony hump in the spine (see picture from case 6)
- Greatest danger is development of spinal cord compression:
  - Lower extremity weakness and inability to walk
  - Loss of bowel and bladder control
  - Spastic lower extremities and increased deep tendon reflexes
- Fever and weight loss occur in less than half of the patients[136]
- The chest x-ray may be normal
- Be aware of the possibility of disseminated TB in HIV-infected patients, although spinal TB may be less common in HIV-infected populations[171]

## Other forms of skeletal tuberculosis

**These conditions are less common**

- Joint (arthritis)
  - Usually one large joint (such as the hip) is involved without other signs of TB
- Osteomyelitis is an infection of bone[137]
  - Tuberculosis can infect almost any bone
  - Hand, foot, pelvis, elbow, knee (see picture below)
  - The primary symptom is pain

## Skeletal TB can involve almost any part of the body



Tuberculosis of the knee

The diagnosis was proven by biopsy of the synovium, the tissue which lines the knee joint.

## Skeletal tuberculosis: diagnosis

- Since other signs and symptoms of TB are not always present, a surgical biopsy may be necessary to diagnose skeletal disease
- Arthrocentesis of an affected joint (removal of fluid) for AFB analysis, but smears of the fluid are often negative[170]
  - A surgeon can also biopsy the synovial tissue lining the joint to look for AFB
- If there is drainage from the wound, press a glass slide to the material and send to the lab for AFB staining
- X-rays may show nonspecific evidence of infection, such as lytic lesions (which appear like holes in the bone)

## Skeletal tuberculosis: management

- Follow national treatment protocols
- Some experts would recommend treating spinal tuberculosis for 12 to 18 months if ethambutol and isoniazid are used in the continuation phase of TB treatment[172]
- If rifampicin and isoniazid are used in the continuation phase, standard six month short course therapy is usually adequate[96]
- Surgery is usually only required for:[122]
  - Spinal instability
  - Progression of weakness despite drug therapy, or
  - Drainage of abscess
- Corticosteroids are not indicated in spinal TB

---

If the patient has neurological dysfunction, such as weakness or urinary incontinence, and TB is suspected, treatment should be started **immediately** and referral made to a surgical specialist.[82]

Delay may result in disability and death.

HIV-infected patients may have disseminated infection.

---

## Major differential diagnoses of bony lesions in HIV-infected patients in resource-limited settings

- Infections
  - Tuberculosis
  - Bacteria, especially *Staphylococcus aureus* or salmonella
- Cancer
  - Lymphoma
  - Metastatic cancer from breast or lung

## Differential diagnosis of spinal cord disease in HIV-infected patients

Spinal cord disease may present as lower extremity weakness, increased reflexes, loss of bowl and bladder control, and back pain.

- Tuberculosis (either Pott's disease or meningitis)
- Epidural abscess from bacteria, such as *Staphylococcus aureus* or salmonella
- Transverse myelitis (viral infection of spinal cord)
- Vacuolar myelopathy caused by HIV itself[173]
  - About 1 of every 10 patients with advanced AIDS will have evidence of this condition, but they will not have back pain
  - Before this diagnosis is made, other infections should be investigated and ruled out
- Cancer
  - Lymphoma
  - Metastatic cancer from breast or lung

## Case 7: presentation

- 24-year-old HIV-infected female with a baseline CD4 count of 147 cells/μl
- Medical history: Three months of cough and fever treated as pneumonia and salmonella without improvement.
  - Sputum smear-positive for AFB and chest x-ray showed interstitial infiltrate in right upper lobe
  - Developed hepatitis from TB drugs but recovered
    - Placed back on regimen which she could tolerate
  - Started antiretroviral therapy with efavirenz, stavudine and lamivudine
  - Despite anti-TB therapy and antiretroviral therapy, patient continued to lose weight and could not walk. She also had a fast heart rate (130 beats per minute) and low systolic blood pressure (below 80 mm Hg)
- Repeat chest x-ray: Now normal; infiltrate resolved
- Repeat sputum smears for AFB: negative four times
- Repeat CD4 count six months after starting antiretroviral therapy: 387 cells/μl
- Viral load measurement: undetectable viral load (< 400 copies/ml)

Why did this patient become more ill even though she received effective therapy for tuberculosis and HIV?

## Case 7: clinical course

The clinicians had several ideas about the patient's decline:

- *Resistant tuberculosis and treatment failure*
  - But the x-ray was normal, the cough had resolved, and the sputum smears were repeatedly negative
- *Lactic acidosis from stavudine*
  - Tenofovir (Viread, TDF) was substituted for stavudine, without improvement
- *Adrenal (steroid) insufficiency resulting from severe TB*
  - Treated with prednisolone 60 mg once daily and began walking in one week
  - Prednisolone tapered down to 5 mg every day and patient remained clinically well

## Adrenal insufficiency

- The adrenal glands sit on top of the kidneys and are responsible for making the body's own corticosteroids (like prednisolone)
- These corticosteroids help to increase:
  - Glucose
  - Salt
  - Blood pressure
- "Insufficiency" means "not enough"
  - Not enough sugar and salt, so the patient becomes weak and loses weight
  - Blood pressure falls to low levels

## Adrenal insufficiency: symptoms and signs[174]

- Symptoms
  - Weakness
  - Weight loss and loss of appetite
  - Nausea, vomiting, diarrhea or constipation
  - Muscle aches
  - Slow thinking
- Physical examination
  - Low blood pressure and high pulse
  - Dark skin (hyperpigmentation)
- Laboratory
  - Low glucose
  - Low sodium and high potassium
  - Tests not usually available in resource-limited settings
    - Cortisol measurement is low
    - Adrenocorticotropin hormone (ACTH) level is high

## Adrenal insufficiency: severity

- Adrenal crisis
  - The patient has very low blood pressure and is near death because of lack of steroid hormones (as in this case)
- Chronic adrenal insufficiency
  - The patient will have less severe symptoms but still needs long-term oral steroid replacement

## Tuberculous adrenal insufficiency

- As we have learned in this chapter, TB frequently disseminates (spreads) throughout the body in HIV-infected patients
- TB spreads through the blood to the adrenal glands[175]
  - The damage can cause adrenal insufficiency and low corticosteroid levels
- In African patients who die of tuberculosis, about one out of four have TB in the adrenal gland[17]
- Tuberculosis has spread from the lungs through the blood
- Not all of these will have clinical symptoms of adrenal insufficiency, but some will

## How common is adrenal damage from TB?

- Kenya: 1 out of 2 patients with pulmonary TB had decreased adrenal function[176]
  - Adrenal dysfunction was more common in cases of extrapulmonary tuberculosis
  - But not all cases were severe
- Tanzania: 1 out of 3 patients with pulmonary TB had decreased adrenal function[177]
  - Patients with poor adrenal function had lower blood pressure
  - Clinicians must be able to recognize the rarer cases of adrenal crisis, as in the case presentation
- Uganda: Among critically ill HIV-infected patients admitted to hospital, 1 out of every 5 had low cortisol levels[178]
  - The most common cause of illness was tuberculosis
  - About 1 out of every 6 TB patients had adrenal insufficiency

## What are the causes of adrenal insufficiency in HIV-infected patients?[179]

- Tuberculosis
- HIV itself
  - But severe symptoms are rare
- Bacterial sepsis
  - Salmonella can cause adrenal insufficiency in HIV-infected patients by destroying the glands
- Other infections (like cryptococcus) are less common
- Drugs
  - Ketoconazole
  - Rifampicin can decrease steroid levels in the blood and make a patient with adrenal insufficiency more ill, but rifampicin is essential for the treatment of TB

## Adrenal insufficiency: diagnosis

- Usually, cortisol levels in the blood are measured, but these tests are not available in most resource-limited laboratories
- Clinicians must use a series of clues instead:
  - Is there evidence of pulmonary or disseminated tuberculosis or another infection?
  - Is this patient weak and losing weight?
  - Does the patient have low blood sugar or blood pressure?
  - Is the sodium low and potassium high?
  - Is the patient using any drugs like ketoconazole?
  - Does the patient improve with a trial of prednisolone?
- Eosinophilia on the complete blood count can suggest the diagnosis; half of patients with adrenal insufficiency will have a high eosinophil count (> 3% of white cells) in the blood[178]

## Adrenal insufficiency: differential diagnosis

- Before diagnosing adrenal insufficiency due to tuberculosis, consider whether the patient has evidence of:
  - A new or untreated infection such as:
    - Salmonella
    - Cryptococcus
  - Failure of anti-tuberculosis therapy
  - Lactic acidosis from stavudine (Zerit, D4T)
  - Liver disease

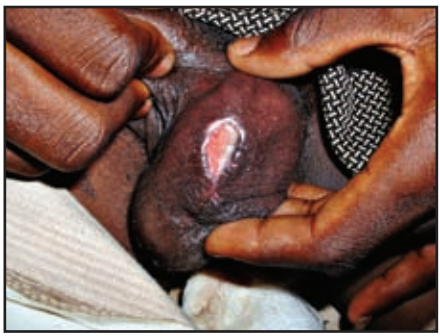
## Adrenal Insufficiency: management[180]

- If the patient is near death, the treatment is:
  - 2 liters of intravenous saline to raise blood pressure
  - Dexamethasone (4 mg daily) or hydrocortisone (100 mg every 6 hours) by vein (IV) or muscle (IM), until vital signs are stable
  - If IV or IM corticosteroids are not available, give at least prednisolone 30 mg orally twice daily
  - If the patient is also on rifampicin therapy for TB, consider increasing these steroid doses
- Once the patient is stabilized (blood pressure and pulse have improved), the patient will need long-term oral corticosteroids
  - Start with prednisolone 7.5 mg nightly
  - This dose may be decreased later to 5 or 2.5 mg
    - Most patients will need lifelong oral therapy
    - Rarely, patients can stop corticosteroids if the adrenal gland recovers
    - Watch for recurrent problems such as weight loss, weakness, high pulse or low blood pressure
- Patients will benefit from another hormone called fludrocortisone 0.1 mg daily, but it is not widely available
  - Fludrocortisone helps to keep salt in the body
  - If fludrocortisone is unavailable, patient can add salt to food
- Be very careful about using corticosteroids
  - Tuberculosis is a common (maybe the most common) cause of adrenal insufficiency in resource-limited settings
  - Remember that if corticosteroids are given to patients with TB but anti-tuberculosis treatment is not given, then the patient will become very sick and will likely die[181]
  - Any patient with suspected adrenal insufficiency should be considered for anti-tuberculosis treatment, especially if corticosteroids will be given

## Other forms of extrapulmonary tuberculosis

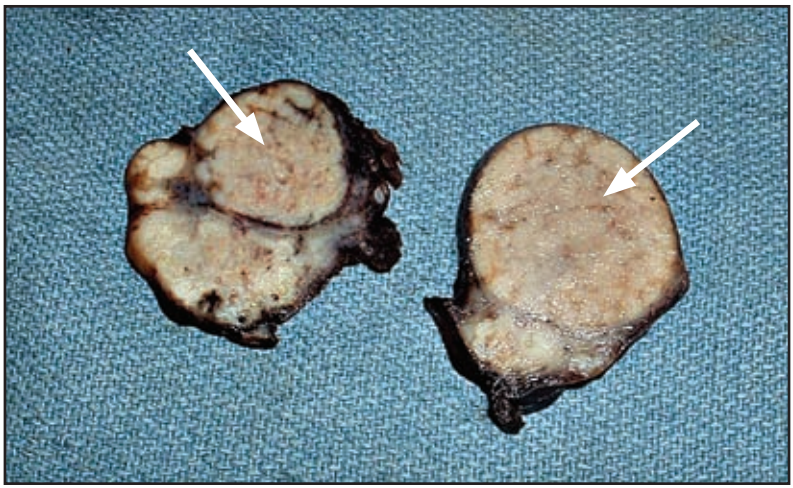
Tuberculosis can infect almost any part of the body

## Scrotal tuberculosis (TB orchitis)



Before treatment

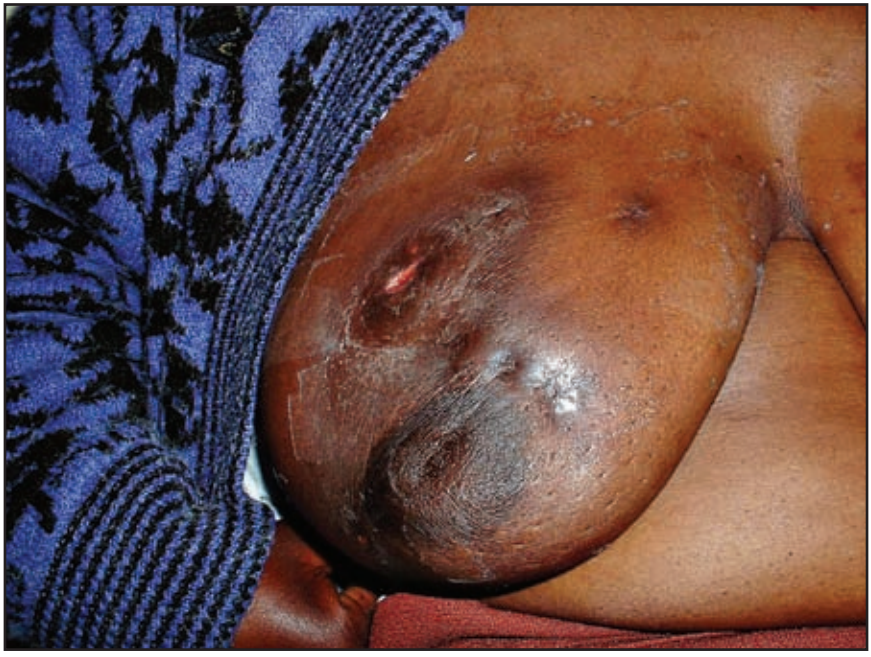
After treatment



Pathological specimen, different case

TB replaced almost the whole testicle (arrows), which was removed.

## Tuberculous mastitis



Both breasts were affected in this 23-year-old HIV-negative woman.

The lesions completely healed with TB therapy.

## Summary of extrapulmonary tuberculosis

- In the HIV-infected patient, TB is a disease which easily spreads throughout the body
- When the CD4 count is low, about half of TB patients have the infection throughout the body
- Mycobacteremia (TB in the blood) is the most common infection in African HIV-positive patients admitted to hospital with fever
- Predictors of mycobacteremia include:
  - Low CD4 count
  - Clinical diagnosis of AIDS on admission to hospital
  - Severe anemia
  - WHO **danger signs**
  - Other signs of TB (chronic cough, large lymph nodes)
- Pericardial tuberculosis is a dangerous form of extrapulmonary infection which should be suspected when:
  - The patient has heart failure
  - Other signs of disseminated TB
  - Large heart on chest x-ray
- Pericardial tuberculosis is by far the most common cause of a pericardial effusion in HIV-infected patients in Africa

## Summary of extrapulmonary tuberculosis

- The most common type of extrapulmonary TB is lymphadenitis
  - TB is the most common cause of large lymph nodes in sick HIV-infected Africans
  - One or more lymph nodes can be affected
  - The lymph nodes are usually larger than 2 centimeters, firm or hard, tender and may drain pus
  - Other signs of tuberculosis (cough, wasting, anemia, headache or confusion) may be present because TB lymphadenitis is usually a sign of disseminated infection
  - Large lymph nodes can help in the diagnosis of tuberculosis because they are accessible to fine needle aspiration, biopsy, or sampling of draining material
- Two other common and dangerous forms of extrapulmonary tuberculosis are pleural TB (Chapter 2) and tuberculous meningitis (Chapter 4)
- Less common clinical forms of TB include:
  - Skeletal tuberculosis
  - Adrenal tuberculosis
  - Tuberculosis of the sexual organs

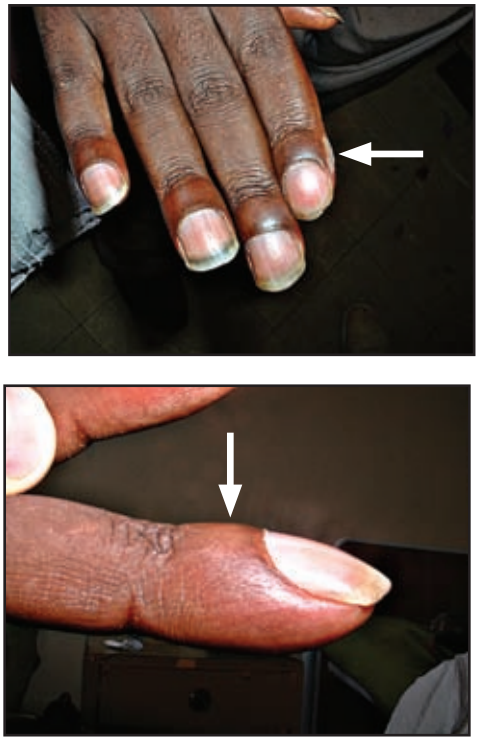
# Chapter 4

# Tuberculous Meningitis in the Era of HIV

## Case 1: presentation

- 45-year-old man; HIV status unknown
- History: Seizures for 8 months; diagnosed with epilepsy
  - CT scan of the head (see page 126) done by another hospital showed lesion in base of the brain
  - Denied chest symptoms and cough
- Medications: Phenobarbital
- Physical exam: Normal except finger clubbing (see below)
- Chest x-ray: Bilateral infiltrates with cavity (following page)
- Laboratory: Sputum AFB smear negative three times

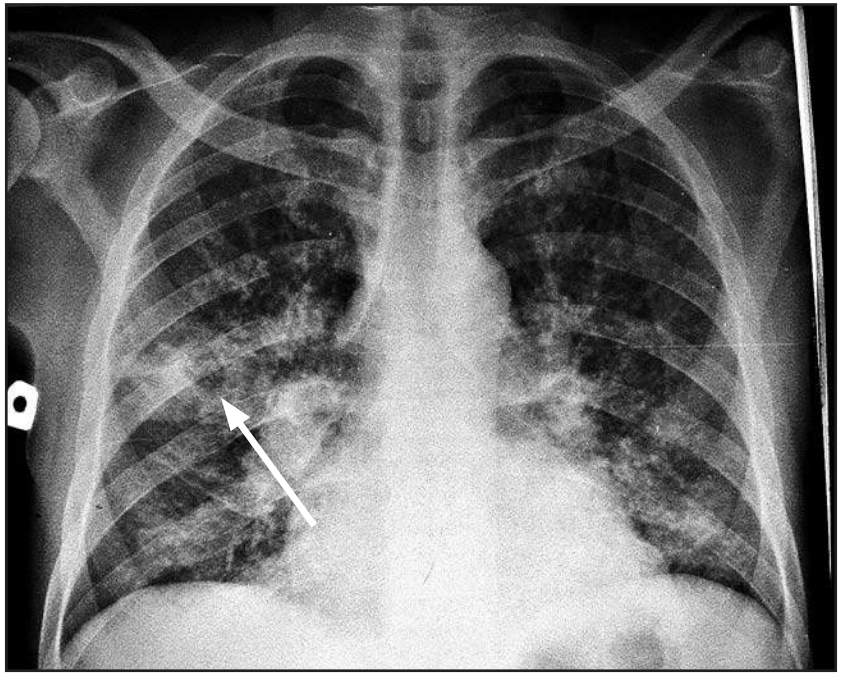
## Case 1: finger clubbing



Finger clubbing (arrows) is enlargement of the nail bed.

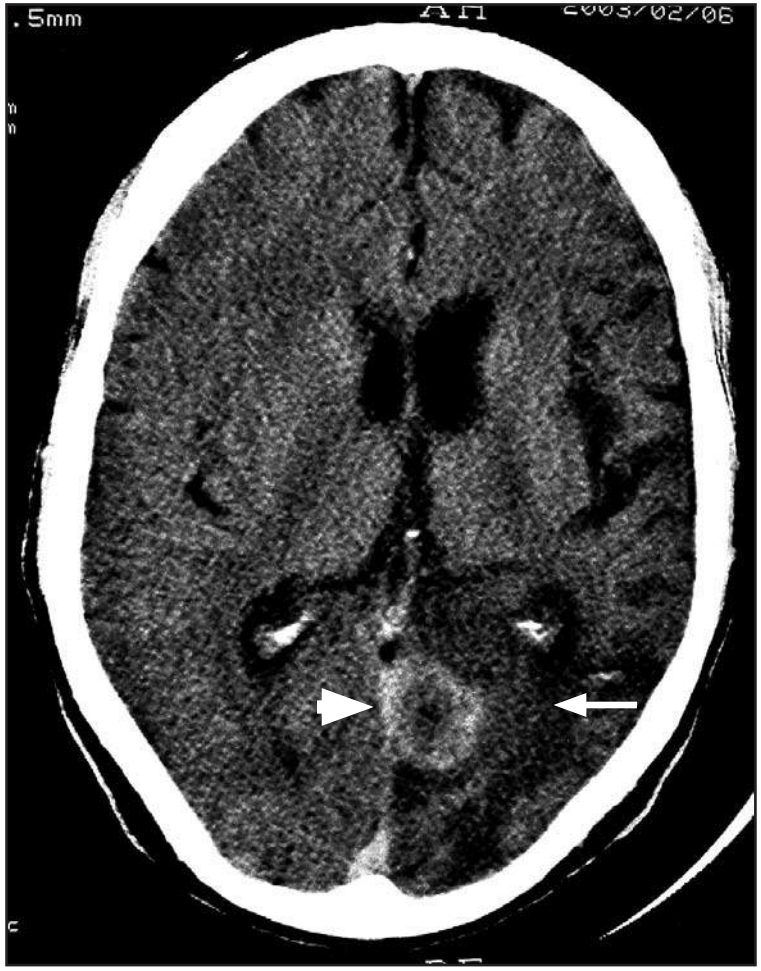
Clubbing can be evidence of chronic lung disease and may occur in 1 out of every 3 African patients with tuberculosis.[182]

## Case 1: chest x-ray with bilateral infiltrates



The arrow points to a cavitary lung lesion

## Case 1: CT scan of the brain




Ring-enhancing mass (arrowhead) near base of brain (bright contrast material around lesion) alongside edema (arrow)

"Ring enhancement" suggests active inflammation and breakdown of the barrier between the brain and blood.

It is usually difficult to tell the difference between a tuberculoma, lymphoma, and toxoplasmoma.

## Case 1: course

- Diagnosis: Pulmonary and central nervous system tuberculosis
- Treatment: No further seizures on RHZE and corticosteroids
- Follow-up: Transferred to another clinic
  - Continued to refuse HIV testing

## Case 1: clinical reasoning

- Several diseases can cause this kind of brain lesion in populations with a high prevalence of HIV infection:
  - **Tuberculosis**
  - Toxoplasmosis
  - Bacteria
  - Cancer (like lymphoma)

| Disease | Brain lesion | Lung disease | Lung cavity | Chronic illness in brain and lung for 8 months |
|---|---|---|---|---|
| **Tuberculosis** | **Yes** | **Yes** | **Yes** | **Yes** |
| **Toxoplasmosis** | Yes | Rare | No | No |
| **Bacteria** | Yes | Yes | Yes | No; death would occur earlier |
| **Cancer** | Yes | Yes | Uncommon | Rare; death would usually occur earlier |

Note that TB shares every one of this case's features.

## Case 1: empiric diagnosis and treatment based on clinical reasoning

- Objections to this approach
  - "You have not proven for certain that the cause is TB. How can you start anti-tuberculosis treatment?"
  - "You do not know for sure that this patient is HIV-infected."
    - The same clinical reasoning applies: TB should be strongly considered in any patient with lung disease and a brain infection

---

Note that the diagnosis in this case was **empiric** (best guess).

The diagnosis was made on the basis of epidemiology, disseminated disease, characteristic findings, and response to treatment.

It is not always possible in resource-limited settings to prove 100% that TB is the cause of the illness.

But if you wait and wait for complete proof, the proof may never come, and the patient may die waiting.

Delay is associated with higher death rates.[57]

---

## Case 1: summary

- Tuberculosis is often a multi-system disease
  - Many parts of the body can be affected
  - The brain and the lung were involved in this case
- The diagnosis of extrapulmonary tuberculosis is often **"empiric"** (a best guess) based upon facts of the case
- We do not know for certain that this case represented TB because we could not do a culture or biopsy
- We must accept uncertainty and instead rely on the research which shows that most of these cases in Africa are in fact TB
- Tuberculosis, even meningitis, can have a slow course
  - The usual duration of symptoms is 2-4 weeks, but symptoms can go on for months[183-189]
- Careful history and exam often provide clues to the diagnosis
  - New onset epilepsy is rare in a 46-year-old person
  - Finger clubbing suggested lung involvement
- Remember that disseminated TB is the most common cause of death in HIV-infected Africans,[17-19] but only half of these cases are detected before death
  - We must detect more of these cases earlier

---

The World Health Organization says the following:

"[T]uberculosis treatment should be started **immediately** if the patient is HIV-infected and has clinical features of disseminated tuberculosis (such as … multiple sites of infection)."

"For a patient with suspected extrapulmonary tuberculosis who is started on anti-tuberculosis treatment without bacteriological or histological confirmation, response to treatment should be assessed after one month."[82] (emphasis added)

---

## Tuberculous meningitis: epidemiology

- Tuberculosis is a common cause of meningitis in HIV-infected patients in resource-limited settings[190]
- The HIV epidemic accounts for most cases of TB meningitis (TBM)[191-193]
- Some research studies show TB meningitis is at least as common as cryptococcal meningitis in HIV-infected patients living in Africa and other resource-limited settings[190, 191, 194]
  - Other studies say cryptococcal meningitis is more common[192,195 196]
- Tuberculosis meningitis is more likely to occur when the CD4 count is low (less than 200 cells/μl)[85, 185, 187, 192, 197]

## Tuberculosis meningitis: overview

- The course of TB meningitis is usually long
  - Symptoms can last weeks to months before the patient presents to the hospital for care[183-189]
  - Tuberculosis may be present somewhere else in the body (like the lungs) for one year before spreading to the brain[183]
  - Cryptococcal meningitis can also go on for weeks to months[198, 199]
  - Bacterial meningitis and cerebral malaria usually make a patient very sick quickly, over hours to days[200, 201]
- TB in the brain often comes together with TB elsewhere in the body (such as in the lung or lymph nodes)[63, 183, 185, 202-205]
- Tuberculosis in the brain has two major forms
  - Meningitis
  - Tuberculoma

## Tuberculosis meningitis: classification[189]

| Stage | Signs and Symptoms | Neurological damage | Mortality Rate (HIV-negative) | Mortality Rate (HIV-positive)[186]* |
|---|---|---|---|---|
| **One** | Headache, stiff neck | None | 0 | 23% |
| **Two** | Confused | Partial one-sided paralysis cranial nerve dysfunction | 10% | 36% |
| **Three** | Very drowsy | Coma, complete one-sided paralysis | 46% | 57% |

***** Including patients who received placebo or corticosteroids in a clinical trial

Rapid diagnosis and treatment is crucial because delayed treatment can lead to death. The higher the stage at the time treatment is started, the higher the risk of death.[184, 186, 189]

## Tuberculosis in the brain: meningitis

- **Meningitis** is infection of the lining of the brain
  - Tuberculosis often causes a "basilar" meningitis[202]
  - "Basilar" means the bottom of the brain where the nerves to the muscles and ears pass through
- Because the meninges cover the whole brain, weakness can be on both sides of the body
  - Sometimes, tuberculous meningitis causes a stroke and **only one side of the body** is paralyzed[186, 187, 196]

## Tuberculous meningitis: presentation[185, 186, 202, 204, 205]

- Headache and confusion
- Typical signs and symptoms are sometimes present:
  - Neck stiffness
  - Nausea and vomiting
  - Photophobia (light hurts the eyes)
- Affects nerves to the muscles
  - Weakness (one or both sides of the body)
  - Increased reflexes (one or both sides of the body)
- Poor hearing (the nerves to the ears are affected)
- Eyes
  - Poor vision
  - Increased pressure can also stretch the 6th cranial nerve controlling eye movement
    - The patient is then unable to look to the side

## Tuberculosis in the brain: tuberculoma

- A **tuberculoma** is a mass of TB bacteria in the brain, like a tumour
- Recall the CT scan from Case 1 at the beginning of this chapter
- HIV-infected patients may be more likely to develop tuberculomata,[197] which can be confused with toxoplasmosis or lymphoma
- Presentation[188, 202]
  - Headache
  - Seizures
  - One-sided stroke and weakness
  - Tuberculosis elsewhere in the body

## Tuberculosis in the brain often means TB somewhere else also

- When you suspect TB in the brain, do not forget to look for disseminated TB elsewhere in the body[63, 183, 185, 188, 204, 205]
- About 10-20% (1 out of every 5 to 10) of HIV-infected patients who die of pulmonary TB also have it in the brain[17, 18]
- In one study from South Africa, 3 out of every 4 HIV-infected patients with TB meningitis had tuberculosis somewhere else in the body[203]

> In cases of TB meningitis, infection may only be in the brain, or it may be in the brain and somewhere else.

## Tuberculosis: lung and brain

**Remember, TB can infect more than one organ**

- When suspecting TB meningitis, look for TB elsewhere
  - Lungs
    - Chest x-ray
    - Sputum smear for AFB
  - Lymph nodes
    - Examination (neck and armpits)
    - Aspirate or biopsy (perform AFB stain)
  - Heart
    - Chest x-ray
    - Ultrasound
  - Bone marrow
    - Low hemoglobin (< 7 g/dl)
    - Bone marrow biopsy and AFB stain

---

If you suspect TB meningitis and find TB elsewhere, the patient probably also has TB in the brain, just like in Case 1.

Tuberculosis is the most common opportunistic infection which regularly attacks both the **lungs** and the **brain.**[17]

Tuberculosis is the most common opportunistic infection which regularly affects both the **brain** and the **lymph nodes.**[18]

So when the **lungs** or the **lymph nodes** are affected in a patient with **central nervous system** symptoms, think **tuberculosis**!!!

---

## Summary of diagnosis of tuberculous meningitis

- History: You must speak with the patient carefully
  - HIV-infected with headache and/or confusion
  - Usual duration of weeks to months
  - Symptoms of pulmonary or extrapulmonary TB
- Physical exam: Be sure to examine the lung for signs of TB
  - Fever and lymph nodes
  - Weakness and increased reflexes
  - Confusion and slow speech
  - Hearing or visual problems
- Laboratory:
  - Low hemoglobin (evidence of disseminated TB)[55]
  - Chest x-ray or sputum: look for TB in the lung
  - Aspiration of lymph node: stain for AFB
  - Lumbar puncture (LP) for cerebrospinal fluid (CSF analysis)
    - However, this test is not always available and can be expensive
    - A serum cryptococcal antigen (CRAG) and a serum VDRL (for syphilis) can help rule out cryptococcal meningitis and syphilis
    - **In cases of significant unilateral weakness or coma, a lumbar puncture should be avoided**; a sudden drop in pressure can cause herniation (movement of the brain) and possibly death

A lumbar puncture can help make the diagnosis of tuberculosis meningitis, but it is not always necessary; the history and physical exam, especially evidence for TB elsewhere in the body, are the most important tools available in the resource-limited setting.

## TB meningitis: lumbar puncture[183, 185, 186, 202, 204, 205]

The table summarizes the CSF findings in TB meningitis.

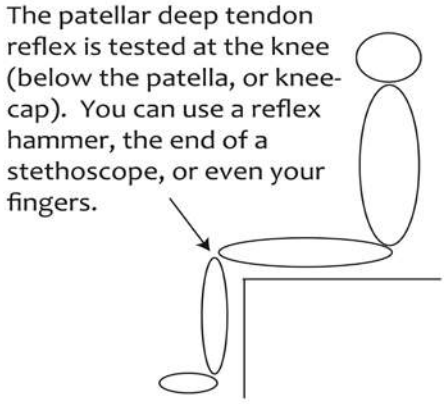
| Test | Value | Range | Comment |
|---|---|---|---|
| **White blood cells** | Usually high, lymphocytes | 0-1000 | Absent WBC in the CSF can occur with TBM[183, 203] |
| **RBC** | normal | Zero | Presence of red blood cells indicates a traumatic procedure or another disease |
| **Protein** | High | Usually > 100 mg/dl | Very high protein levels can be seen in severe TBM |
| **Glucose** | Low | < 2.2 mmol/l, or < 40 mg/dl | When the glucose is low, also consider bacterial meningitis |
| **Smear** | If AFB seen, diagnosis is certain | | AFB usually not seen, even in the best labs; negative smear does not rule out TB |
| **Culture** | Usually, but not always, positive | Not widely available in resource-limited settings; takes weeks to perform, and treatment should not be delayed if TB meningitis suspected | |

If a lumbar puncture is done, perform a test for cryptococcal antigen or India ink to rule out the other major cause of meningitis in HIV-infected Africans (cryptococcal meningitis). Also do a CSF VDRL, if possible.

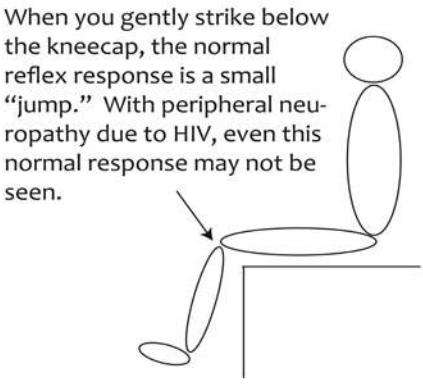
> Sometimes the CSF is normal in early TBM, in patients with very low CD4 counts, or when there is a tuberculoma. A tuberculoma does not always touch the meninges, so the lumbar puncture may be normal even when TB is present.

## Increased reflexes

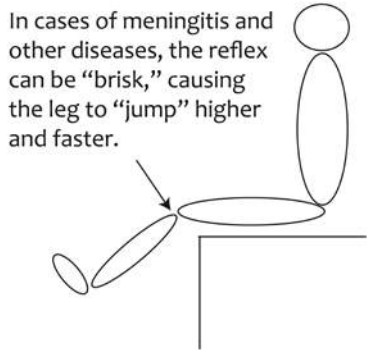
- Important physical exam sign; can occur with meningitis
- When increased **bilaterally** (both sides), consider:
  - Tuberculosis
  - Cryptococcus
- When increased **unilaterally** (one side), consider:
  - Tuberculosis
  - Toxoplasmosis




Deep tendon reflex at rest




Normal deep tendon reflex




Hyper-reflexia, or increased deep tendon reflexes

## Tuberculous meningitis: differential diagnosis

- Cryptococcal meningitis
  - A serum or CSF cryptococcal antigen (CRAG) can help you tell the difference from TB
- Toxoplasmosis
  - Common (about 1 out of every 10 deaths) in West[19] and Central[20] African autopsy studies
  - Rare in Eastern[17] and Southern[18] African studies
- Syphilis
  - A serum or CSF VDRL can help make this diagnosis
- Central nervous system lymphoma
  - There is usually no good treatment available for this condition in resource-limited settings

Bacterial meningitis and cerebral malaria occur more quickly and make the patient very ill in a short period of time (over hours or days, not weeks or months).

If a patient presents with headache for several weeks, do not just assume bacterial meningitis and treat with only antibiotics. This author has seen this incorrect approach on more than one occasion.

## Cryptococcal meningitis

- Presentation:[192, 206, 207]
  - CD4 < 200 cells/μl
  - Severe headache
  - Confusion
  - Fever
  - Stiff neck or pain on movement of neck
  - Weakness and increased reflexes **bilateral**, meaning both sides (not just one side)
  - Duration: about 2 weeks, but can last for months[199]
  - Enlarged lymph nodes possible
  - Severe anemia not common
- Diagnosis
  - Lumbar puncture: 1 out of every 4 are normal
    - Very high opening pressure compared to cases of TB meningitis[195]
    - Normal or slightly high protein
    - WBC < 50 cells/μl, mostly lymphocytes
      - Often < 20 cells/μl in advanced HIV disease
    - Glucose: slightly low (< 2.4 mmol/l or 43 mg/dl)
    - India Ink may be positive
  - Cryptococcal antigen **(CRAG)** positive
    - The serum CRAG is actually a better test than the CSF CRAG for detecting cryptococcus in the brain
    - CRAG testing is more sensitive than CSF India Ink
    - In order of sensitivity for detecting cryptococcus in the CSF: serum CRAG > CSF CRAG > India Ink

## Cryptococcal meningitis[206]

- Treatment
  - Most resource-limited settings: Fluconazole
    - 400 mg orally once daily for 12 weeks
      - Some countries start with 800 mg daily
    - Then 200 mg once daily for life, or until CD4 > 200 cells/μl for six months on ART
    - When the patient worsens or does not fully respond to fluconazole, the dose should be doubled
    - If the patient is also receiving rifampicin for TB treatment, also strongly consider doubling the dose because rifampicin can lower levels of fluconazole
  - Intravenous amphotericin B may be an initial option in some resource-limited settings, or may be considered in severe cases or those that do not respond to fluconazole
    - 0.7-0.8 mg/kg once daily for two weeks
    - Requires adequate hydration: 1 liter normal saline before amphotericin B
    - Monitor kidney function and potassium levels
    - After discharge continue fluconazole as above
  - Repeated lumbar punctures are often necessary to reduce intracranial pressure and relieve symptoms
    - Perform lumbar punctures daily when there are severe symptoms, removing 15-20 milliliters (cc), until the symptoms improve significantly

## Toxoplasmosis[208, 209]

- Brain infection
  - Like a tuberculoma or a tumor
  - **Not a meningitis**, so cerebral spinal fluid is often normal
- Presentation
  - Occurs when CD4 count < 100 cells/μl
  - Patients at risk if not using cotrimoxazole prophylaxis
    - If patients are using cotrimoxazole prophylaxis, consider another infection as cause of symptoms
  - Duration: weeks
  - Fever, confusion, headache
  - Weakness and increased reflexes **unilateral** (one side)
  - **Seizures common**
- Diagnosis
  - Consider toxoplasmosis when the above clinical presentation occurs in a patient with advanced AIDS
  - CT scan may show one or more ring-enhancing lesions
    - Lesions can look like the tuberculoma in Case 1
    - But CT scan is expensive and not necessary in resource-limited settings
  - Cerebral spinal fluid analysis helpful to rule out evidence of cryptococcus or TB
- Treatment: high-dose cotrimoxazole
  - Below 50 kg: 3 single strength tablets twice per day
  - Above 50 kg: 4 single strength tablets twice per day
  - A regimen of sulfadiazine, pyrimethamine, and folinic acid is used in the West, but these drugs are not widely available in Africa, and it is not clear that this regimen is better than high-dose cotrimoxazole

## Summary of common HIV-related brain infections

| Finding | Tuberculosis | Cryptococcus | Toxoplasmosis |
|---|---|---|---|
| **Headache, fever, confusion** | Yes | Yes (often severe headache) | Yes |
| **Seizures** | Uncommon | Uncommon | Common |
| **Duration** | Weeks to months | Weeks, sometimes > 1 month | Weeks |
| **Hearing & vision problems** | Yes | Yes | No |
| **Weakness and increased reflexes** | Unilateral or bilateral | Bilateral | Unilateral |
| **Lung complaints** | Frequent | Uncommon | Rare |
| **Severe anemia** | Yes | No | No |
| **Lymph nodes** | Common | Sometimes | No |
| **Lumbar puncture** | Lymphocytes; very high protein; AFB smear usually negative | Lymphocytes; CRAG or India Ink positive; protein mildly elevated; high pressure | Often normal; mild elevation in lymphocytes and protein may occur |
| **CD4 count** | Any, usually < 200 | < 200 | < 200 |
| **Other methods** | Chest x-ray, sputum smear, lymph node aspirate | Serum CRAG | CT scan |
| **Cotrimoxazole prevents** | No | No | Yes |

## Neurosyphilis[210]

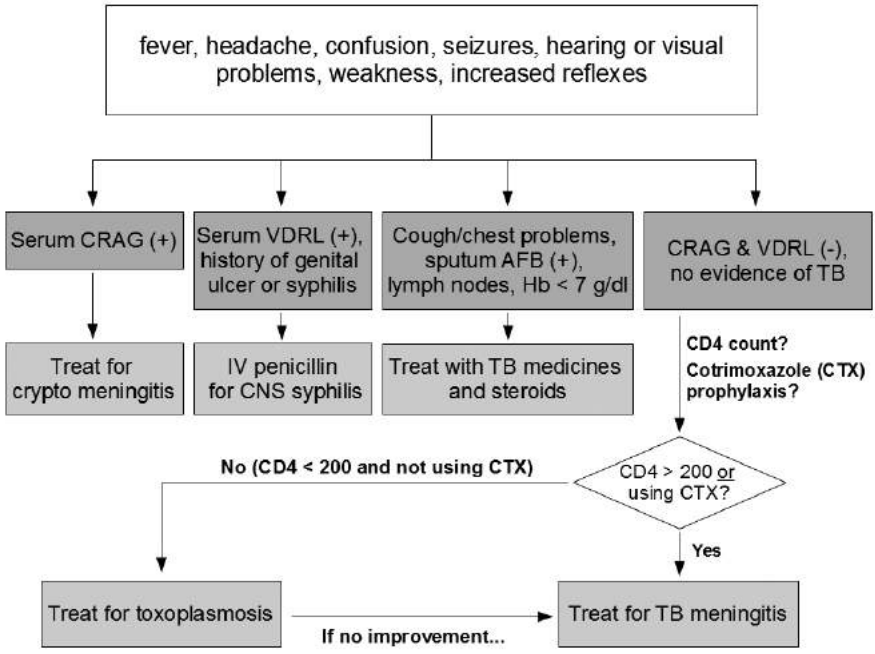
- May present in different ways
  - Stroke with weakness on one side
  - Bacterial meningitis
  - Dementia
- History of primary syphilis (genital ulcer)
  - Can spread quickly to the brain in HIV-infected patients with low CD4 counts
- Laboratory tests
  - Positive VDRL in CSF confirms the diagnosis
    - But CSF VDRL is usually negative (is not sensitive)
  - Positive RPR or VDRL in serum
    - Most patients will have a positive serum RPR or VDRL, although even this test can be negative late in the disease[211]
- Treatment: IV aqueous penicillin G 3-4 million units every 4 hours for 10-14 days
  - Alternatives include:
    - Penicillin G procaine 2.4 million units daily with probenicid 500 mg every 6 hours, for 10-14 days
    - Ceftriaxone 2 grams IV daily

## Central nervous system lymphoma[212]

- A mass lesion occurring at low CD4 counts (< 50 cells/μl)
- Signs and symptoms
  - Can present like toxoplasmosis or tuberculoma
  - Fever, headache, confusion
  - **Unilateral** weakness
  - Seizures
- Lumbar puncture usually normal
  - No sign of infection
- CT scan of the brain may show a well-defined mass lesion which can resemble toxoplasmosis and a tuberculoma
  - In general, a CT scan cannot differentiate between the major causes of central nervous system lesions in HIV-infected patients; given cost considerations, I do not recommend routine CT scans in resource-limited settings
- Fatal within weeks to months without therapy
  - Usual treatment includes radiation and corticosteroids; chemotherapy may provide some additional benefit
    - Remember that, if you want to use corticosteroids, you should strongly consider treating for tuberculosis also; untreated TB will worsen quickly in the setting of corticosteroids
  - Usually limited treatment options in Africa
  - Patient may improve with antiretroviral therapy, which should be started if CNS lymphoma is suspected

## Algorithm for empiric diagnosis of chronic brain infections in HIV-infected Africans

- This algorithm uses basic physical exam and lab findings to make an empiric diagnosis of common brain infections
  - This algorithm represents a more realistic approach than performing a lumbar puncture and CT scan on every patient
  - **But if the patient has been sick for only a few hours or days**, a lumbar puncture should be performed to rule out bacterial meningitis
    - And cerebral malaria must also be considered




*RHZE = standard 4 drug therapy for severe extrapulmonary tuberculosis (rifampicin, isoniazid, pyrazinamide, ethambutol)

## Clues to the diagnosis of brain infections in HIV-infected patients

- Lung problems (cough, shortness of breath)
  - Tuberculosis
- Vision and hearing problems
  - Tuberculosis
  - Cryptococcus
- Seizures
  - Toxoplasmosis
- Very severe headache
  - Cryptococcus
- Weakness or increased reflexes **unilateral** (one side)
  - Toxoplasmosis
  - Tuberculosis (tuberculoma)
- Weakness or increased reflexes **bilateral** (both sides)
  - Tuberculosis (meningitis)
  - Cryptococcus

## Treatment of tuberculous meningitis

- Follow national guidelines
  - Some countries use different regimens for cases of meningitis than those used for pulmonary disease alone
- Patients previously treated for tuberculosis or those currently on treatment for pulmonary TB can still develop tuberculous meningitis[191]
- Corticosteroids indicated for all cases of TB meningitis[186]
  - Corticosteroids lower death from TB meningitis by 30%
    - Inpatient: Dexamethasone 8 mg intravenously or intramuscularly three times per day
    - Outpatient: Prednisolone 30 mg orally twice daily

---

As one expert has written:

"Early recognition of TB meningitis is of paramount importance because the clinical outcome depends greatly upon the stage at which therapy is initiated. **Empiric antituberculous therapy should be started immediately** in any patient with meningitis syndrome and cerebrospinal fluid (CSF) findings of low glucose concentration, elevated protein, and lymphocytic pleocytosis, if there is evidence of TB elsewhere in the body or if prompt evaluation fails to establish an alternative diagnosis." (emphasis added)

And also this:

"We recommend specific antituberculous chemotherapy should be initiated on the basis of **strong clinical suspicion of CNS tuberculosis and should not be delayed until proof of infection has been obtained.**" (emphasis added)[202]

---

## The dangers of corticosteroids

- Corticosteroids are also useful in severe cases of toxoplasmosis
- However, if you treat for toxoplasmosis with high-dose cotrimoxazole and corticosteroids and it turns out the patient actually had tuberculosis, the TB will get much worse
- Do not give corticosteroids unless:
  - You are certain tuberculosis is **not** the diagnosis, **or**
  - You also are giving anti-TB treatment
  - Sometimes you do not know the diagnosis for certain and it is necessary to treat for toxoplasmosis **and** tuberculosis
- Corticosteroids can make cryptococcal meningitis worse

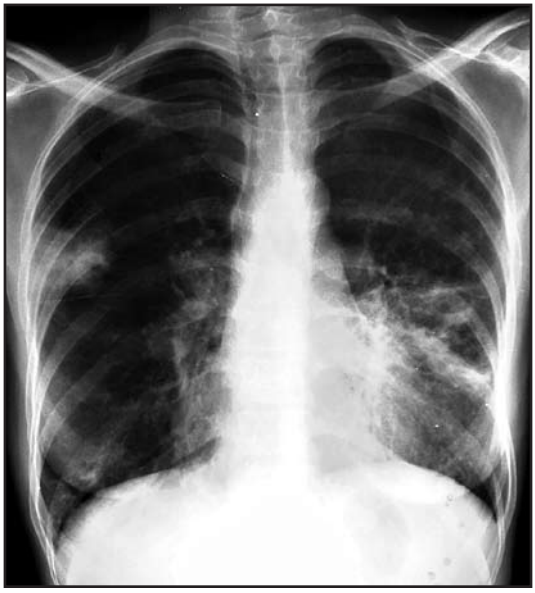
> Only use corticosteroids after careful consideration of the diagnosis, benefits, and risks.

## Tuberculosis meningitis: prognosis

- High death rates in HIV-positive and HIV-negative patients
  - Approximately 1-2 of every 3 HIV-positive patients (33-67%) with TB meningitis will die[183, 184, 186, 192, 203]
- Delayed treatment leads to higher death rates[185]
  - Even a one day delay in therapy can lead to a higher risk of death[203]
- Disability is common, occurring in ~15% of survivors[183, 185, 186]
  - Weakness, paralysis
  - Hearing or visual loss
- Relapse rates are high
  - 1 of 6 patients improve but then have the TB return later[186]
  - Watch for high relapse rates if ethambutol (as part of the fixed-dose combination EH containing ethambutol and isoniazid) is used in the continuation phase
  - Ethambutol does not cross the blood brain barrier fully and is not as potent as rifampicin and isoniazid[213]

## Case 2: presentation

- 42-year-old HIV-infected female; CD4 = 62 cells/μl
- History of present illness: 3 week history of cough and fever, treated with antibiotics without improvement
  - Later developed difficulty hearing
- Past medical history: pulmonary TB one year ago; salmonella
- Medications: (1) cotrimoxazole, (2) multivitamin, (3) previously on ARVs but stopped due to social difficulties
- Exam: Wasted, T 38.4 degrees Celsius, pulse 110 per minute
  - Poor hearing; examiner must come close for patient to hear
  - Lungs clear to auscultation
  - Bilateral increased reflexes in both legs
- Laboratory and other investigations:
  - Hemoglobin 7.0 g/dl
  - First sputum negative for AFB
  - Cerebrospinal fluid normal; CRAG negative
  - Chest x-ray: right middle lung and left lower lung infiltrates



## Case 2: differential diagnosis & clinical reasoning

- ↓ hearing, ↑ deep tendon reflexes bilaterally (both sides)
  - **Tuberculous meningitis**
  - Cryptococcal meningitis
- Anemia (hemoglobin < 7 g/dl)
  - **Tuberculosis**
  - Salmonella
- Cough for three weeks
  - **Tuberculosis**
  - *Pneumocystis* pneumonia

## Case 2: clinical reasoning

- Tuberculosis is on every list
- TB is the only disease which explains decreased hearing, increased reflexes, chronic cough, and severe anemia
- The normal lumbar puncture helps rule out cryptococcal meningitis, **but it does not rule out TB in the brain**[183, 191, 203]

Your history and exam are as important as the lab tests!

## Case 2: Diagnosis and treatment

- Diagnosis: Tuberculosis of the lungs and central nervous system (probably basilar meningitis)
- Treatment: Standard four drug anti-TB therapy (RHZE) and oral corticosteroids
- Follow-up: Much stronger after 2 weeks
  - Hearing improved

## Case 2: summary

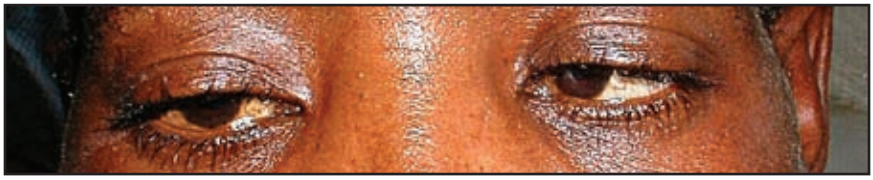
- Previous tuberculosis is a risk factor for future TB
- The combination of lung and central nervous system findings in an HIV-positive patient strongly suggests tuberculosis
- Deafness and increased reflexes are common with TB meningitis
  - But these problems are not present every time
- Tuberculosis is a multi-system disease affecting different organs in the body

## Case 3: presentation

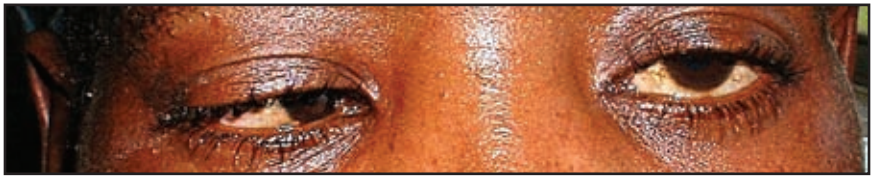
- 34-year-old HIV-negative African female
- History of present illness: Transferred from another hospital after 3 weeks in a coma
  - Ill with headache for several weeks prior to admission to other hospital
- Exam: No fever
  - Comatose and not opening eyes or responding to commands.
  - Possible right-sided facial droop (7th cranial nerve palsy)
- Lumbar puncture:
  - White blood cells = 0
  - Protein = 121 mg/dl (normal < 45)
  - Glucose = 2.7 mmol/l, or 49 mg/dl (low)
  - Red blood cells = 0
  - India Ink stain negative for cryptococcus
  - Note that performing a lumbar puncture in this patient carried a risk of herniation, but the clinicians believed it was necessary to assist with a diagnosis

## Case 3: presumptive diagnosis and clinical course

- Slowly progressive headache in HIV-negative female and high protein in CSF suggested tuberculous meningitis
  - Cryptococcal meningitis rare in HIV-negative patients and the India Ink was negative
- Treatment
  - Four drug anti-TB therapy (RHZE) through nasogastric tube
  - Corticosteroids (dexamethasone 8 mg intramuscularly three times per day)
- Patient awoke after 2 days and had eye problems (see figure)



She is trying to look right but her right eye cannot.



She is trying to look left but her left eye cannot.

This is a case of tuberculous meningitis causing headache and eye muscle paralysis (of the 6th cranial nerve). Cryptococcus can also cause this problem, but this patient was HIV-negative and the India ink stain was negative.

The patient completely recovered with treatment.

## Case 3: course

- The patient spent 3 weeks in the hospital
  - Multiple attempts to taper (decrease the dose of) corticosteroids resulted in severe headache
  - After 3 months corticosteroids were finally stopped
- The patient's eye movements returned to normal
  - She could look completely in both directions with both eyes

## Case 3: manifestations of tuberculous meningitis

- Vision problems are common
  - These problems result from meningitis blocking cerebral spinal fluid drainage and increasing pressure in the brain
  - Eye muscle paralysis and blindness can occur
  - These problems can also occur with cryptococcal meningitis
- High CSF protein is common
  - Mild protein elevation can also occur with cryptococcal meningitis and toxoplasmosis
  - The cerebrospinal fluid white blood cell count can be normal,[183, 191, 203] as in this case

## Summary of tuberculous meningitis

**A very common brain infection in HIV-infected patients**

- Tuberculosis is a multi-system disease
  - Brain
  - Lung
  - Lymph nodes
  - Heart
- Signs and symptoms
  - Headache, fever, confusion
  - Weakness (one or both sides)
  - Hearing and eye problems
  - Increased reflexes common
  - Can present after starting ART as part of the immune reconstitution inflammatory syndrome (IRIS; see Chapter 5)
- Differential diagnosis
  - Cryptococcus
  - Toxoplasmosis
  - Syphilis
  - CNS lymphoma
  - Bacterial meningitis
  - Cerebral malaria
- Treatment
  - Standard national TB therapy
  - Corticosteroids
- Prognosis
  - At least 1 out of 3 die
  - Many are left with disabilities
  - AIDS-defining illness; candidates for ART

# Chapter 5

# Immune Reconstitution Inflammatory Syndrome (IRIS) After ART Initiation: The Role of Tuberculosis

## Case 1: presentation

- 33-year-old HIV-infected African female; CD4 count 26 cells/µl
- Medical history: Significant weight loss; no other symptoms
  - Started ART with nevirapine, zidovudine, and lamivudine
  - Two weeks after starting ART developed cough
  - Given doxycycline but no improvement
  - Two weeks later cough persisted and she developed mild headache and difficulty hearing
- Physical exam: T 37.6 degrees Celsius; pulse 102 beats per minute
  - Decreased ability to hear in the right ear
  - Speech and thinking are obviously slow
- Differential diagnosis:
  - Tuberculosis (pulmonary and meningitis)
  - Cryptococcal meningitis
  - Immune reconstitution inflammatory syndrome (IRIS) due to one of above infections after starting ART
- Investigations:
  - Hemoglobin 9.6 g/dl
  - Sputum for AFB: negative
  - Chest x-ray: machine broken
  - Lumbar puncture:
    - White blood cells = 0; red blood cells = 0
    - glucose 3.1 mg/dl
    - protein 58 mg/dl (normal < 45)
    - cryptococcal antigen (CRAG) negative

What is your differential diagnosis? What do you do?

## Case 1: treatment and follow-up

- Empiric diagnoses:
  - Pulmonary and central nervous system tuberculosis
    - Advanced AIDS; CD4 < 100 cells/µl; high risk of baseline TB[5]
    - Cough > 2 weeks and unresponsive to antibiotics
    - Evidence of TB elsewhere in body (headache, decreased hearing, slow thinking)
    - **Empirical clinic reasoning used to diagnose TB in a deteriorating AIDS patient,** even when laboratory investigations do not prove the diagnosis
  - IRIS secondary to tuberculosis
- Treatment:
  - Standard four drug therapy (RHZE) for tuberculosis
  - Corticosteroids: dexamethasone 8 mg IM three times per day, then later prednisolone 30 mg by mouth twice per day
  - ART changed to efavirenz, zidovudine, and lamivudine
- Clinical course:
  - Improved after 2 days on TB therapy and corticosteroids
  - No hearing complaints or cough after 3 months follow-up

**The Immune Reconstitution Inflammatory Syndrome**

# IRIS

Also, sometimes called:

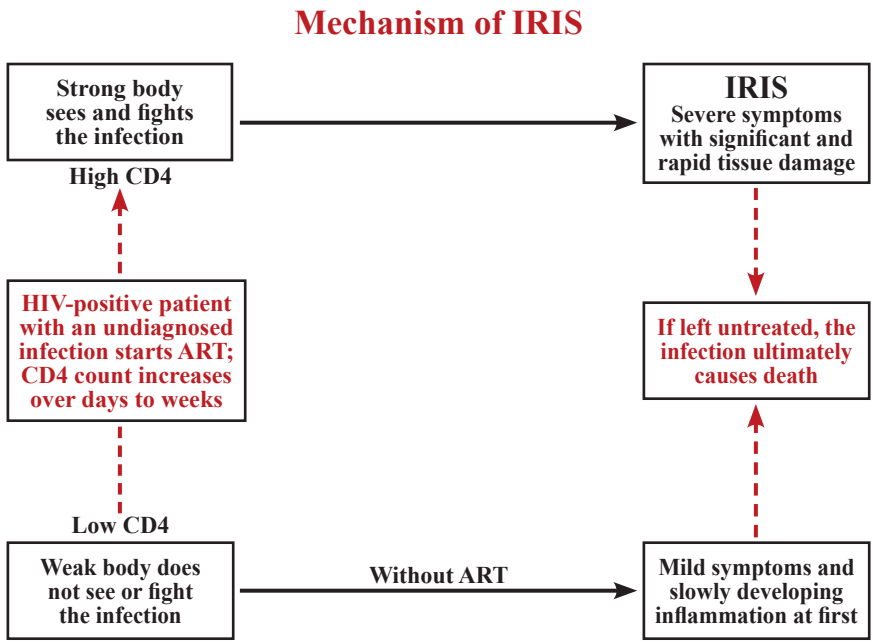
**Immune restoration disease**

**Paradoxical worsening**

**"Awakening Syndrome"**[214]

## What is IRIS?

- Inflammation occurs when the body's immune system attacks an invader, like an infection, cancer or foreign body. So, in a way, the body damages itself when it attacks infections.
- When the CD4 count is low, the immune system is too weak to attack invaders. So there is very little inflammation **even if tuberculosis is present in the body**.
- Once a patient starts ART, the CD4 count rises and the immune system is "switch[ed] on,"[68] leading to **"immune re-constitution," or return of a strong immune system.**
- After immune reconstitution, the strong immune system starts to attack invaders again.
- If there is an infection that was not recognized before starting ART, now the immune system fights it. This fight leads to inflammation.
- Inflammation causes tissue damage and other symptoms, such as fever, tachycardia, cough, enlarged and tender lymph nodes, headache, and hearing and vision loss.



## What infections cause IRIS?[70, 215, 216]

### Conditions common in resource-limited settings

- Tuberculosis
  - Common cause of IRIS in resource-limited settings[50, 69, 78]
  - Most common cause of IRIS-related death in Africa[70]
- Cryptococcal meningitis
  - Often presents as severe headache
  - A potentially deadly cause of IRIS[217]
- Toxoplasmosis
- Cytomegalovirus retinitis
  - Blindness
- *Pneumocystis* pneumonia (PCP)
- Others
  - Kaposi's sarcoma[218, 219]
  - Skin and mucous membranes: most common sites of IRIS reactions[70, 220]
    - Folliculitis, zoster, molluscum contagiosum
    - Genital lesions: Genital herpes simplex virus (HSV) and warts (human papilloma virus, HPV)

## Is IRIS a reaction to ARVs?

- "Yes" and "No"
- IRIS occurs because a patient starts ART and becomes stronger
- **IRIS is the reaction of a stronger immune system to another infection like TB**
- But IRIS is not a side effect (like hepatitis or skin rash from nevirapine)

Some antiretroviral drugs (like nevirapine and abacavir) can cause a hypersensitivity reaction. These hypersensitivity reactions can lead to hepatitis, fever, enlarged lymph nodes, and skin rash. A hypersensitivity reaction can be difficult to tell apart from IRIS.

## IRIS definition[68, 221, 222]

- Association in time between start of ART and onset of new or worsening symptoms
  - Usually within 3 months
- Evidence of inflammation
  - Fever, tachycardia, pain, disability, or other symptoms related to inflammation
- Absence of another cause
  - Look for other new infections, like malaria or salmonella
- Consider possibility of drug side-effect or resistance
  - Drug reaction, non-compliance, drug resistance, or poor drug absorption
- Good CD4 and viral load response to ART

## Why is IRIS important?

- Studies in Africa show high death rates after starting ART; the early death rate is not so high in the West[44-47, 223]
  - But why should this happen?
  - Why should so many patients die **after** starting ART?
- One cause of early death on ART is IRIS and new cases of TB diagnosed after starting ART[11, 50, 69-71, 217, 224]
  - IRIS can also lead to hospitalization and procedures[70, 225]
- Infections such as TB are often not recognized in HIV-infected patients before starting ART[41, 102]
  - Symptoms may be mild because of a weak immune system[23]
  - The infection may be disseminated and hard to diagnose
- South Africa: Almost 1 out of every 4 patients developed an IRIS reaction after starting ART[70]
  - Tuberculosis was the most common cause

> "Managing IRIS is becoming a nightmare. The first reaction of a patient who develops an immune reconstitution reaction after being told he will be better is to stop treatment."
>
> —Dr. Ely Katabira, Makerere University, Kampala Uganda[226]

## TB-IRIS in an African ART Clinic[50]

- South Africa: patients **who were already diagnosed with TB** started ART:
  - 1 out of 8 patients developed IRIS
  - 1 out of 3 developed IRIS if they started ART within two months of beginning TB medicines
  - Risk factors for IRIS:
    - CD4 count < 50 cells/μl
    - Starting ART within 2 months of TB diagnosis

## What is the role of tuberculosis in IRIS?

- TB is a common cause of IRIS in Africa and other resource-limited settings[50, 69-71, 78, 227]
  - Patients may already be on anti-tuberculosis treatment when starting ART, and then IRIS develops (**"paradoxical" tuberculosis-associated IRIS**)[228]
    - In Thailand, 1 out of 5 HIV-infected TB patients starting ART developed "paradoxical" IRIS[229]
  - Patients may develop symptoms of tuberculosis **after** starting ART, a process referred to as **"unmasking" TB**[230]
- IRIS (paradoxical worsening) was described in **HIV-negative** TB patients even **before the era of HIV and ART**[231, 232]
- TB is very smart; even in HIV-negative patients, it causes parts of the immune system to go to sleep[68]
  - When TB therapy is started, the immune system wakes up
- The traditional TB symptoms (severe cough, hemoptysis, high fevers) are a result of the immune system attacking TB
  - Review the chart below[23] from Chapter 1

| Sign or Symptom | Strong Immune System (HIV-negative or -positive with high CD4 count) | Weak Immune System (HIV-positive with low CD4 count) |
|---|---|---|
| **Severity of cough** | Severe | Mild (at first) |
| **Hemoptysis** | Common | Uncommon |
| **X-ray pattern**[3-5, 59, 60] | Destructive<br>Upper lobe<br>Cavities | Interstitial (like PCP)<br>Miliary<br>Lymph nodes common<br>Lobar (like bacterial pneumonia)<br>**May be normal** |

## Manifestations of TB-IRIS in HIV-infected patients after starting ART[68]

- Pulmonary
  - Worsening cough
  - Shortness of breath
  - Laryngitis
  - Pleural effusion
- Pericardial
  - Heart failure
  - Tachycardia
  - Pericardial effusion
- Meningitis
  - Headache
  - Hearing loss
  - Visual loss
  - Eye muscle paralysis
  - Weakness/stroke
  - Increased reflexes
- Systemic
  - Fever
  - Enlarged and tender lymph nodes
  - Anemia
  - Large liver and spleen
- Bone and joint
  - Septic arthritis
  - Osteomyelitis
  - Pott's disease (TB of spine)

## Risk factors (predictors) for IRIS

- Low CD4 count before starting ART
  - CD4 < 100 cells/μl in adults[76, 77]
  - CD4% < 15% in children[233]
- Patients with evidence of undiagnosed and/or untreated opportunistic infections[227]
  - Wasted patients (at high risk for TB and other infections)
  - Chronic cough
  - Lymphadenopathy
  - Fever
  - Headache
  - WHO **danger signs**
- Failure to screen patients for TB before ART
  - On-site tuberculosis clinic improves detection of cases[234]
- Initiating ART soon after starting therapy for an opportunistic infection (e.g. TB or cryptococcus)[50, 77]

All patients should have a through history and exam looking for opportunistic infections **before** starting ART. But patients with the above risk factors should receive extra attention. Any suspicion for tuberculosis should prompt thorough investigation before ART is started.

## When does IRIS happen?

- Usually occurs within 2-3 months of starting ART[68, 77, 232]
  - But IRIS can occur within days of starting ART[235, 236]
- The World Health Organization recommends (see chart) several approaches to starting ART in known TB patients[237]
  - Refer to the chart on page 193 to compare the advantages and disadvantages of starting ART early in TB patients

| CD4 count | ART recommendations | Timing of ART after starting TB treatment |
|---|---|---|
| < 200 | Recommend ART | Within 2-8 weeks |
| 200-350 | Recommend ART | After 8 weeks |
| > 350 | Defer ART* | Re-evaluate patient at 8 weeks and at end of TB treatment |
| Not available | Recommend ART | Within 2-8 weeks |

Adapted from reference 237

* Comment: Patients with HIV who have experienced an episode of TB are considered to have AIDS, even if the CD4 count is above 350. Starting ART in patients with AIDS is not wrong. Clinicians should follow national guidelines, which sometimes recommend ART in patients with WHO stage III or IV disease in the setting of recent TB.

For many patients, the diagnosis of tuberculosis leads to a diagnosis of HIV **at the same time**. These individuals need time to accept and understand their conditions. And some patients may have cognitive dysfunction from TB meningitis.

Also remember the risk of IRIS if ART is started too soon after antituberculosis therapy. The decision to start ART when the patient is on TB medicines requires the judgment of the clinician.

## Management of TB-IRIS

- Best treatment is prevention
- Do not ignore cough, shortness of breath, headache, fever, enlarged lymph nodes, and other evidence of tuberculosis before starting ART
  - **Suspected TB needs to be aggressively evaluated prior to start of ART**
- Part of ART preparation is ruling out opportunistic infections

> "Advanced TB and HIV can be clinically indistinguishable—the clinician should **always** consider if there is active TB and this should be excluded as far as possible.
>
> [Treatment with] TB drugs should be considered, **even in the absence of definite radiological or microbiological evidence.**" (emphasis added)
>
> —Kenyan National Clinical Manual for ARV Providers, 2004[132]

- After diagnosing TB-IRIS
  - Continue ART, if possible[145]
    - Use efavirenz-based regimens with rifampicin-containing TB therapy, if possible, but follow national guidelines
    - Very ill patients may have to stop ART temporarily until TB is more completely treated
    - The pill burden of ART and TB therapy is high
      - Some patients may have to stop ART if they cannot tolerate so many pills because of nausea and adherence problems
  - Start anti-tuberculosis therapy
    - Use standard national regimens

## Role of corticosteroids in management of TB-IRIS

- Some patients have very severe symptoms of inflammation, such as large, tender lymph nodes, so corticosteroids may be necessary to calm the IRIS response[68, 236]
  - Start prednisolone 1-2 mg/kg every day
  - Example: 50 kg patient with severe IRIS and TB pericarditis may require prednisolone 50 mg orally twice per day
  - Taper (lower) the dose of prednisolone over several weeks as symptoms improve
- A clinical trial from South Africa demonstrated that corticosteroids for TB-IRIS help prevent long hospital stays and the need for invasive procedures[225]
- If a decision is made to start corticosteroids, tuberculosis treatment must also be started
  - Patients with TB who receive corticosteroids but do not receive anti-TB treatment will become very ill and likely die because corticosteroids can allow the infection to spread
- Corticosteroids are indicated in the presence of certain types of extrapulmonary tuberculosis
  - Tuberculous meningitis (Chapter 4)
  - Pericardial tuberculosis (Chapter 3)
- If you are worried about giving corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and aspirin may be used instead[78]

## Prognosis of TB-IRIS[50, 78]

- Most patients with TB-IRIS will recover if:
  - IRIS is recognized
  - The responsible infection is diagnosed and treated
  - ART is continued in those patients who can still tolerate it without nausea, vomiting or side effects
- IRIS can be a cause of early death after starting ART[70, 71, 225] but careful management can keep the mortality rate low[216]

## Summary of IRIS and TB

- The body needs a strong immune system and high CD4 count to cause inflammation
- Inflammation leads to symptoms and tissue damage
- Tuberculosis causes a lot of inflammation and tissue damage when the immune system is normal
- When the immune system is weak, recognizing TB can be difficult because the infection presents in "atypical" fashion
  - Review earlier chapters regarding presentation of TB in patients with low CD4 counts
- The predictors of TB-IRIS are:
  - Low CD4 count before starting ART
  - Wasting, symptoms of infection, and **danger signs**
  - Initiating ART soon after TB diagnosis and treatment
  - Failure to screen for tuberculosis prior to ART
- Any patient who develops symptoms or worsens after starting ART should be investigated for IRIS
- It is usually possible to continue ART after diagnosis of TB-IRIS
  - Efavirenz-based regimens are preferred, if available, because rifampicin TB therapy may lower nevirapine levels
- Corticosteroids may be needed, depending upon the type of tuberculosis (meningitis, pericardial) and the severity of the IRIS symptoms
- Most patients will recover if managed appropriately

## Differential diagnosis of worsening condition after initiation of ART[145]

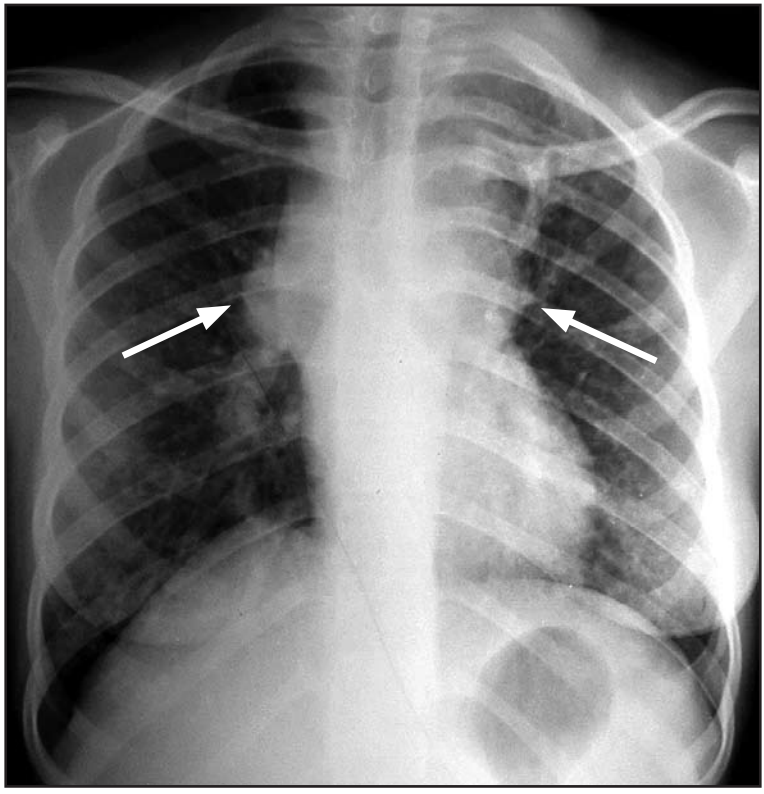
- IRIS
  - Tuberculosis
  - Cryptococcus
  - Kaposi's sarcoma
  - Other underlying condition
- New infection (such as malaria, pneumonia, or salmonella)
- Malabsorption
  - Vomiting
  - Diarrhea
- Poor adherence
- Malnutrition
  - Food insecurity
- Side-effects
- Resistance
  - Baseline resistance (such as mothers who received single-dose nevirapine)
  - Re-infection with resistant virus

Patients should get better after starting ART!

If they do not improve—or if they become more ill—we must ask, "Why?"

## Case 2: presentation

- 15-year-old Kenyan female
- Medical history:
  - Diagnosed with smear-positive pulmonary tuberculosis
  - Began standard four drug therapy (RHZE) and improved initially
  - Three months later developed worsening cough, weight loss, and enlarging mass in the right neck
- Examination:
  - No fever
  - Mildly wasted
  - Large (6 cm) draining, tender lymph node in right supraclavicular fossa (above the collarbone)
- Chest x-ray: Massive intrathoracic lymphadenopathy (arrows)



## Case 2: diagnosis and treatment

- Underwent drainage of abscess in right neck and removal of supraclavicular lymph node
  - Lymph node positive for AFB
  - These TB organisms may have been dead
- Diagnosis: IRIS after starting TB therapy
  - HIV antibody test **negative**
- Treatment:
  - Continued ethambutol and isoniazid
  - Started prednisolone 30 mg per day
  - Improved dramatically
  - Corticosteroids tapered slowly and finished TB therapy

IRIS isn't just for HIV/ART patients.

HIV-negative patients can also suffer "paradoxical worsening" after starting TB therapy.

# Chapter 6

# Tuberculosis Therapy in the Era of HIV

## Overview of this chapter

- When to treat for tuberculosis
- When to start antiretroviral therapy in patients with TB
- Interactions between TB drugs and antiretroviral drugs
- Case challenges:  common TB drug side-effects
- Use of corticosteroids and cotrimoxazole in patients with TB
- Chronic complications of tuberculosis

## The Importance of national and WHO guidelines[51]

- This book is aimed at clinicians working in different resource-limited countries and regions
- Different countries use different tuberculosis treatment regimens, which should be followed strictly
- This book focuses on diagnosis and the decision to treat
  - Treatment regimens should follow national TB program protocols

## When should tuberculosis be treated?

- The easy answer is: as soon as TB is diagnosed
  - For example: a patient with chronic cough produces sputum positive for AFB by microscopy
- However, as we have seen in this book, diagnosing TB in HIV-infected patients is often difficult
  - Many HIV-infected patients with TB are AFB smear-negative
  - Extrapulmonary TB is often an empiric (best guess) diagnosis
  - Access to TB cultures is limited
- The 2006 WHO guidelines[82] attempt to address the issue of when to treat for TB when the diagnosis is not certain (see Chapter 8)

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The World Health Organization states:

"Sound clinical judgment is needed to put seriously ill patients with negative sputum smear results on anti-tuberculosis treatment using only suggestive radiographical findings. In such circumstances, the clinical response of the patient has to be monitored and tuberculosis diagnoses should be confirmed at least by clinical response to anti-tuberculosis treatment and preferably by culture."[82]

---

## Treatment of pulmonary TB: when to start therapy

- Positive AFB sputum smear
- If repeat sputum-smears are negative, then perform a chest x-ray, if possible, and recall the patterns of HIV-related TB (Chapter 2)
  - Look for another way to make the diagnosis:
    - Aspiration and AFB staining of lymph node material
    - Classic miliary pattern on chest x-ray
  - When the patient is very ill, WHO recommends treatment be started if the clinician thinks TB is the most likely cause (Chapter 8)[82]
    - Evidence of TB meningitis
    - Presence of WHO **danger signs** (reminder on next page)
    - Evidence of disseminated TB (Chapter 3), such as severe wasting syndrome and hemoglobin less than 7 g/dl
- For stable patients, repeat your evaluation and if, in your clinical judgment, TB is the most likely cause of the respiratory symptoms, start treatment
  - Always consider if another condition could be present (Chapter 2)
  - Once treatment is started, commit to a **full course** of therapy (either 6 or 8 months according to national guidelines)
  - **Avoid short "treatment trials"** because of the danger of resistance
- Initiation of therapy should **not be delayed** when TB is suspected in very ill HIV-infected patients
  - Remember that TB is the leading cause of death in HIV-infected patients around the world (Chapter 1)
  - The current problem is **under-diagnosis** and **under-treatment** of TB; the problem is not over-treatment
    - Zimbabwe: Only 29% (less than 1 out of every 3) patients with smear-negative pulmonary TB were diagnosed and treated in the clinic following standard protocols[41]
    - South Africa: 1 of every 5 routine ART clinic attendees found to have TB but had not previously been diagnosed[102]

## Approach to the HIV-infected pulmonary TB suspect

- If you suspect TB, you must then collect AFB smears and assess the clinical status:
  - Is the patient seriously ill and in danger of death in the near future?
  - Is the patient clinically stable and able to return for multiple visits over several weeks?
  - Is there evidence of extrapulmonary TB?
  - Are **danger signs** present?[82]
- WHO **danger signs** include:
  - Respiratory rate > 30 breaths per minute
  - Fever > 39 degrees Celsius
  - Pulse > 120 beats per minute
  - Unable to walk alone

---

Your answers to these clinical questions will determine how quickly the decision to treat for tuberculosis must be made.

These "danger signs" have been listed by the WHO to help you decide which patients are very sick. But these danger signs can occur in many different diseases. You must also use other evidence to decide if TB is present.

When no danger signs are present, you can safely spend more time investigating the illness. Patients who are clinically stable can undergo a full evaluation over 3 to 4 visits (2-3 weeks).

When danger signs are present and TB is strongly suspected, treatment should be started **without a significant delay**. Patients who are severely ill with danger signs and evidence of disseminated tuberculosis will require initiation of TB therapy very soon in order to prevent death.

---

## WHO guidelines: treatment decisions for ambulatory (stable) HIV-positive pulmonary tuberculosis suspects

**No danger signs**

| Visit | Sputum AFB smear | |
|---|---|---|
| | Negative | Positive |
| 1st | Perform HIV test<br>Start collection of AFB smears<br>[Comment: consider antibiotics for pneumonia] | Treat<br>HIV testing |
| 2nd | Repeat AFB smears (total of 3)<br>Chest x-ray<br>Sputum TB culture, if available<br>[Comment: consider antibiotics for pneumonia] | Treat |
| 3rd | Treat for bacterial pneumonia<br>Consider PCP treatment* | Treat |
| 4th | **Response to antibiotics:** Follow-up HIV care<br>**No response:** Re-assess for tuberculosis | |

Adapted from reference 82.

* Standard therapy for PCP includes four tablets of single-strength cotrimoxazole (400-80 mg) every eight hours for 21 days. In cases of severe disease (if pulse oximetry is available and measures less than 90%) add prednisolone according to this schedule: 40 mg twice per day for 5 days, 20 mg twice per day for 5 days, and prednisone 20 mg once daily for 11 days. Again, if the suspicion for TB is high, consider deferring corticosteroids as untreated TB may worsen rapidly if corticosteroids are given.

> If patients are suspected of having acute bacterial pneumonia or PCP, treatment may be given immediately, even before the 3rd visit. Response should be expected within 5 days.

## WHO guidelines: treatment decisions for seriously ill HIV-infected pulmonary tuberculosis suspects

**Danger signs present**

| Referral possible | Referral not possible |
|---|---|
| Parenteral antibiotics<br>AFB sputum smears<br>Chest x-ray<br>AFB culture, if available | Parenteral antibiotics<br>Consider cotrimoxazole for PCP treatment<br>Sputum AFB smear |
| **Evidence of TB:** Treat<br>**No evidence:** Follow up | **Smear (+):** Treat TB<br>**Smear (-):** Continue antibiotics |
| **After 3-5 days**<br>If there is a response to antibiotics, continue and re-assess for TB.<br>If there is no response to antibiotics, start anti-tuberculosis treatment immediately and refer, if these things have not already been done. | |

Adapted from reference 82.

Parenteral means through the vein (intravenous, IV) or intramuscular (IM).

***Comment***

The "referral not possible" column applies to patients presenting to lower-level health facilities with limited laboratory capabilities and no physician consultation. However, if you find evidence of TB (such as generalized lymphadenopathy or severe anemia), it is acceptable to treat a very sick patient for tuberculosis without delay. Remember that (1) TB is the most common cause of death in HIV-infected Africans, and (2) A delay in therapy will increase the risk of death.

## When should treatment be started for disseminated or extrapulmonary tuberculosis?

- Smear or culture positive for AFB
- However, we know from earlier chapters that:
  - Smears of body fluids (CSF, ascites, and pleural) are usually negative; although these tests are recommended by international guidelines,[82] they are probably not cost-effective in resource-limited settings and can be difficult to perform
  - Facilities for biopsy and culture are often not available or the tests are expensive
  - Many patients with disseminated or extrapulmonary TB do not have cough[61]
- According to the WHO, healthcare providers working in clinics and health centers which lack diagnostic testing **"should initiate empirical tuberculosis therapy early in serious illness thought to be due to extrapulmonary tuberculosis"**[82]

***Comment***

Note the importance of your clinical judgment. Even if TB cultures are available, a result usually takes weeks. Yields from smears of body fluids are low. So, you must be willing to empirically diagnose disseminated tuberculosis based on your history and exam.

## Case 1: presentation

- 43-year-old HIV-infected male; lowest (nadir) CD4 count 80 cells/µl
- Past medical history:
  - Cryptococcal meningitis diagnosed two years earlier
    - Continued fluconazole maintenance 200 mg daily
  - History of alcohol abuse
- HIV treatment: Did not tolerate ART with nevirapine, stavudine, and lamivudine or nevirapine, zidovudine, and lamivudine because of pancreatitis
  - Finally started on efavirenz, tenofovir, and lamivudine
- Because of chest pain and a pericardial effusion on ultrasound, he was diagnosed with pericardial TB and started standard therapy (RHZE; rifampicin, isoniazid, pyrazinamide, ethambutol) and corticosteroids
- Returned 1 month later with headache and poor vision

What happened? What explains the new symptoms?

## Case 1: discussion

- The rifampicin used in the TB treatment regimen (RHZE) caused the level of fluconazole in the blood to drop to low levels
  - The fluconazole dose had not been increased to prevent low blood levels of the drug
  - Corticosteroids allow cryptococcus to multiply
- The cryptococcal meningitis relapsed (came back), causing headache and poor vision
- Patient admitted for intravenous amphotericin for 2 weeks
  - Discharged on fluconazole **800** mg daily
  - The higher fluconazole dose will help make up for the fact that the patient is using rifampicin
  - The patient improved and his vision returned to normal

## Drug interactions: rifampicin and drugs commonly used in HIV-infected patients[238]

Rifampicin acts in the liver to lower the blood levels of some drugs

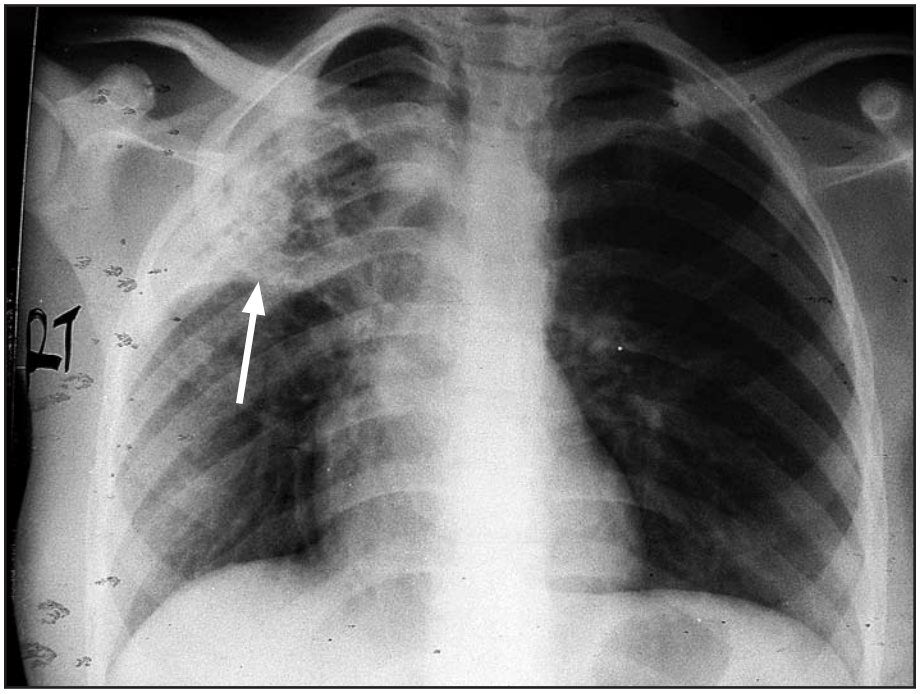
| Always avoid use with rifampicin | May be used with rifampicin, if necessary | Can use with rifampicin |
|---|---|---|
| estrogen-containing oral contraceptives<br>**Protease inhibitors**, such as:<br>Kaletra or Alluvia (lopinavir/ritonavir)<br>nelfinavir<br>indinavir<br>atazanavir<br>fosamprenavir | nevirapine: if possible, switch to efavirenz; follow national guidelines<br>Some research indicates rifampicin and nevirapine can be used together effectively,[239, 240] but other research suggests a higher risk of HIV treatment failure because rifampicin lowers the levels of nevirapine in the blood[241] | efavirenz*<br>fluconazole: adjustment is necessary; increase the dose of fluconazole<br>**Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)**, such as:<br>stavudine (d4T)<br>zidovudine (AZT)<br>lamivudine (3TC)<br>tenofovir (TDF)<br>didanosine (ddI)<br>abacavir (ABC) |

* For patients weighing over 60 kg, some experts recommend increasing the efavirenz dose from 600 to 800 mg, but this increase is probably not necessary[242-245] and no standards have been established.

## Case 2: presentation

- A 23-year-old HIV-negative female presented in coma with jaundice
  - Bilirubin 10 mg/dl (normal value range 0.1-0.4 mg/dl)
  - SGOT (AST) = 400 international units/liter (normal < 37 IU/l)
  - Patient's weight = 45 kg
- Diagnosed 3 weeks prior with tuberculosis and started on RHZE
  - See chest x-ray below

## Case 2: chest x-ray



Upper lobe disease (arrow) in an HIV-negative patient

What is happening?

How do you manage this patient?

## Case 2: course

- Anti-tuberculosis drugs were stopped and patient woke up in 4 days
- She started **"liver-friendly"** anti-tuberculosis therapy[122]
  - Ciprofloxacin 750 mg twice daily
  - Streptomycin 750 mg IM daily (17 mg/kg)
  - Ethambutol 1000 mg daily (22 mg/kg)
- After the liver recovered, isoniazid plain 300 mg daily was introduced and the current regimen (ethambutol, streptomycin, and ciprofloxacin) was continued
  - One week later, SGOT rose back to 120 IU/l (3 times baseline level)
  - Isoniazid stopped again
- Liver-friendly drugs (ethambutol, streptomycin, and ciprofloxacin) were continued
- After the liver recovered and the SGOT returned to normal again, rifampicin was introduced without problems
  - SGOT measured after 1 week and was normal
  - Ciprofloxacin was then stopped
- Next pyrazinamide was introduced without problems
  - Streptomycin was then stopped.
- Continued to measure SGOT every 2 weeks
- RZE continued for 2 months, then RE for one year
  - The patient completely recovered

## TB drug-induced hepatitis: fundamental principles

- Stop offending drug(s)
  - Isoniazid, rifampicin, and pyrazinamide are most likely causes
- Start a liver-friendly regimen
  - Ciprofloxacin **750** mg twice per day
  - Streptomycin 15 mg/kg IM daily
  - Ethambutol 15-20 mg/kg daily
  - This regimen should only be started in consultation with the national TB program or after referral to an experienced center
- Re-introduce the standard **plain** drugs, **ONE AT A TIME**, measuring the SGOT every 1-2 weeks

## Tuberculosis drugs and existing liver disease

- If a patient has baseline liver disease which is not severe, standard TB drugs may be used with close monitoring
- Consider frequent liver function tests to assess for worsening liver disease
  - But clinical monitoring is acceptable if chemistry measurements are not available
- If the liver disease is severe (for example, end-stage cirrhosis) consult an expert
  - A liver-friendly TB drug regimen may be needed

***Consult a specialist to help manage these cases!***

If the first-line drugs isoniazid, rifampicin, or pyrazinamide are not given for the first two months, then the course of therapy may have to be extended or the continuation phase may have to include a different regimen.

## Hepatitis from isoniazid[246]

- Several TB drugs can cause hepatitis, but isoniazid is the most likely
  - Isoniazid > Rifampicin > Pyrazinamide
- **Mild** form of hepatitis
  - Occurs in as many as 1 out of 5 cases
  - Usually the patient has no symptoms, but the liver function tests are mildly elevated
- **Severe** form of hepatitis
  - Occurs in less than 1 out of every 300 patients treated with INH[247]
  - Can be fatal, so it is very important to recognize severe hepatitis and stop isoniazid and other TB drugs until the cause is discovered
- Risk factors
  - Older age, female, or pregnant
  - Diabetes or alcoholism
  - Baseline liver disease (such as hepatitis B virus infection)
  - Use of other drugs which can cause hepatitis
    - Nevirapine
    - Protease inhibitors, e.g. Alluvia (lopinavir/ritonavir)
    - Other TB drugs (rifampicin, pyrazinamide)
- Clinical features of severe hepatitis
  - Half of cases occur in the first two months, but drug-induced hepatitis can occur any time during TB treatment
  - Nausea, fatigue, abdominal pain, loss of appetite
  - Jaundice, right upper quadrant tenderness
  - May progress to hepatic coma and encephalopathy in severe cases
- Treatment
  - Stop isoniazid and other drugs which may be causing hepatitis (such as other TB drugs and ARVs)
- Supportive care (nutrition, fluids)

## Case 3: presentation

- 34-year-old HIV-infected female with a CD4 count of 238 cells/µl was diagnosed with pulmonary tuberculosis
  - She began standard TB therapy (RHZE) and pyridoxine 25 mg daily
  - Two months later she started ART with nevirapine, stavudine and lamivudine
- During a nurse's visit to the home, the patient complained of numbness and tingling in the feet

---

What is happening? Why?

How do you manage the case?

---

## Case 3: course

- In this patient, neuropathy can be caused by one or more of the following:
  - HIV
  - Isoniazid (the H in RHZE and the I in RIPE)
  - Stavudine (D4T)
- Neuropathy occurred despite daily preventive therapy with pyridoxine 25 mg
- The stavudine was changed to a drug which does not cause neuropathy (AZT, zidovudine)
- High-dose pyridoxine (150 mg daily) was given
- The peripheral neuropathy resolved

## Case 3: discussion[248]

- Peripheral neuropathy is pain, burning and numbness beginning in fingers and toes; the symptoms can spread up the arms and legs
- INH blocks the actions of vitamin B6 (pyridoxine)
- All patients living in resource-limited settings who are using INH should be given vitamin B6 (25-50 mg daily)
- Risk factors for INH-induced peripheral neuropathy
  - HIV
    - The HIV virus itself can be a cause of neuropathy, especially when the CD4 count is low
    - The drugs stavudine (D4T) and didanosine (DDI) are also common causes of neuropathy
  - Diabetes
  - Malnutrition
  - Chronic alcoholism
- Neuropathy can have more than one cause (see previous point)
- It is usually necessary to continue isoniazid so that TB can be treated appropriately
  - In cases of peripheral neuropathy caused by INH, high doses of pyridoxine (100-200 mg per day) may reverse the symptoms
  - High-dose pyridoxine does **not** help for peripheral neuropathy caused by stavudine or by HIV itself
    - Stavudine is unlikely to be the cause of neuropathy if the patient has been taking it for less than six months
- If the patient with neuropathy is using stavudine as part of an ART regimen, switch to zidovudine (AZT) or tenofovir (TDF), if possible
- Although some clinicians use amitriptyline to treat neuropathy, there is no convincing evidence that this drug is helpful[249, 250]

## Summary of anti-TB drug side effects[213, 238, 248, 251-253]

| Drug | Major | Other | Comments |
|---|---|---|---|
| **Rifampicin** | hepatitis, rare cases of severe hypersensitivity reaction (fever, muscle aches) | red-orange urine, rash, anemia, low platelets | be aware of interactions with other drugs as outlined previously |
| **Isoniazid** | hepatitis, peripheral neuropathy | rash | treat peripheral neuropathy with higher doses of pyridoxine |
| **Pyrazinamide** | hepatitis | gout, joint pains | |
| **Ethambutol** | visual disturbance (optic neuritis) | | use in children only if truly necessary |
| **Streptomycin** | kidney dysfunction, balance problems, decreased hearing, ringing in ears (tinnitus) | | Measure creatinine and calculate creatinine clearance |

## Tuberculosis and quinolone antibiotics[147]

- Ciprofloxacin has some activity against TB
  - The same is true of other "respiratory" fluoroquinolone antibiotics (sparfloxacin, ofloxacin, levofloxacin, moxifloxacin)
- **Do <u>NOT</u> use ciprofloxacin or other fluoroquinolones to treat pneumonia in Africa**
- Remember that it is often very difficult to tell the difference between pneumonia and tuberculosis
  - Ciprofloxacin is a poor pneumonia drug; it does not treat the major cause of bacterial pneumonia (*Streptococcus pneumoniae*)
  - If tuberculosis is present ciprofloxacin will partially treat it and diagnosis will be delayed[133]
  - TB can develop resistance to ciprofloxacin when it is given alone
- Ciprofloxacin may have a role with other TB drugs in special situations, but should be used at a high dose (750 mg twice per day)
  - Steven-Johnson (severe, blistering rash which may be caused by anti-TB drugs)
  - Drug-induced hepatitis (as part of **"liver-friendly" regimen**)
  - Multi-drug resistant (MDR)-TB under the care of a specialist

## Death rates are high even with anti-tuberculosis treatment

- About 1 out of every 4 HIV-infected patients with TB may die despite being started on the correct anti-TB treatment[13]
- Most of the deaths due to TB occur in the first month, but many patients with TB actually die of other diseases (such as PCP)[254, 255]
- Patients with lower CD4 counts have a higher risk of death[256]
  - Patients with low CD4 counts should be quickly prepared for ART
- Evidence suggests that ART given either at the **same time** as TB diagnosis and treatment[73] or **later during** TB treatment[72, 74] lowers mortality; other studies are still being done[257]
  - See chart on the next page for a comparison of early and late ART

## When should ART be started in HIV-infected TB patients?

- The exact answer is not yet known
- The benefits and risk of starting ART quickly or waiting are summarized in the table below
- WHO recommendations are summarized in the table on the next page
- Even if patients medically qualify for ART, HIV treatment should only be started if the patient:
  - Has accepted his or her HIV status
  - Has been prepared and counseled for lifelong ART
  - Is able to handle the burden of HIV and TB drugs

| **Early Initiation of ART** *During intensive phase (first 2 months) of TB therapy* | **Late Initiation of ART** *During continuation phase (after 2 months) of TB therapy* |
|---|---|
| Likely lower overall mortality[72, 73] | Likely higher overall mortality |
| Raise CD4 counts earlier to fight TB and avoid other infections | |
| Drug interactions (rifampicin and nevirapine or protease inhibitors) | No drug interactions in countries which use ethambutol/isoniazid in the continuation phase |
| Higher risk of IRIS[68] | Lower risk of IRIS |
| Higher pill burden; risk of poor adherence and resistance to ART | Lower pill burden; already demonstrated adherence to TB drugs |

## World Health Organization recommendations for starting ART in patients with tuberculosis[237]

| CD4 count | ART recommendations | Timing of ART after starting TB treatment |
|---|---|---|
| < 200 | Recommend ART | Within 2-8 weeks |
| 200-350 | Recommend ART | After 8 weeks |
| > 350 | Defer ART* | Re-evaluate patient at 8 weeks and at end of TB treatment |
| Not available | Recommend ART | Within 2-8 weeks |

Adapted from reference 237

* Patients with HIV who have experienced an episode of TB are considered to have AIDS, even if the CD4 count is above 350. Starting ART in patients with AIDS is not wrong. Clinicians should follow national guidelines, which sometimes recommend ART in patients with WHO stage III or IV disease in the setting of recent TB.

## The importance of daily cotrimoxazole prophylaxis in HIV-infected TB patients

- **All** HIV-infected TB patients, regardless of CD4 count, should use cotrimoxazole preventive therapy to prevent opportunistic infections
  - Cotrimoxazole prophylaxis reduces death and hospitalization rates by almost half[258]

## Case 6: presentation

- 34-year-old HIV-infected Ugandan male
  - CD4 count unknown
- History: Admitted with inability to speak or stand
  - Note the presence of WHO **danger signs** (cannot stand)
- Physical examination:
  - Vital signs: Temperature 38.7° Celsius.
  - Right-sided gaze preference (staring to the right)
  - Multiple palpable enlarged cervical and axillary lymph nodes.
  - Pericardial rub
- Chest x-ray: bilateral infiltrates
- Sputum samples: could not be obtained because of poor mental status
- Diagnosis: disseminated tuberculosis with lung, brain, lymph node and pericardial involvement
- Treatment: started RHZE and intramuscular dexamethasone 8 mg every 8 hours
- Course: The next day the patient was able to speak and to walk without assistance

Why did he improve so quickly?

## Case 6: discussion

- The corticosteroids rapidly treated the inflammation in the brain
- Anti-tuberculosis drugs would not produce such a dramatic improvement after just one day
- The patient returned home but died about six months later
- Remember that:
  - Tuberculosis causes almost all cases of pericardial disease in HIV-infected Africans[148-150] (Chapter 3)
    - The "rub" suggested pericardial disease
  - Tuberculosis is the leading cause of lymphadenopathy in sick, HIV-infected Africans[89, 110, 136] (Chapter 3)
  - Consider TB in any ill HIV-infected patient with signs and symptoms in multiple body locations

## The role of corticosteroids in the treatment of TB

- Tuberculous meningitis[186]
  - Significant (31 percent) reduction in mortality
  - Patients with both mild and severe TB meningitis benefit
  - Disability levels remain high even with corticosteroids
- Tuberculous pericarditis[159]
  - Significant (36 percent) reduction in long-term mortality
  - Chronic heart failure may still result from the damage caused to the pericardium
- Immune reconstitution after ART initiation[225]
  - Corticosteroids decrease days in hospital
- Hospitalized patients who are very ill with the above forms of TB
  - Dexamethasone 8 mg three times daily is appropriate for most patients (approximately 0.4 mg/kg per day[186])
  - May give via intramuscular (IM) or intravenous (IV) route
  - After improvement, taper slowly
    - After 2 days, dexamethasone 8 mg twice daily
    - Discharge on prednisolone 40-60 mg orally twice daily
- Outpatients; less ill
  - Start prednisolone 30 mg orally twice daily
  - After improvement, taper by 10-20 mg every 1-2 weeks

---

Corticosteroids can be used for these three forms of tuberculosis (meningitis, pericarditis, TB-IRIS). There is not enough evidence to suggest routine corticosteroids for other types.

If corticosteroids are tapered too rapidly:

Rebound inflammation may occur and the patient will worsen

Adrenal insufficiency can develop

---

## Case 7: presentation

- A 34-year-old HIV-infected male presented with chest pain and cough
- Blood pressure low (80/40 mm Hg) and pulse 127 beats per minute
- The chest x-ray showed a very large heart (review case 4 in Chapter 3)
- Ultrasound confirmed a large pericardial effusion with "stranding"

How would you manage this patient?

## Case 7: management

- A diagnosis of pericardial tuberculosis was made (review Chapter 3)
  - Standard 4-drug TB therapy (RHZE) was started the same day
- Because the blood pressure was low, the patient was admitted to the hospital
  - Dexamethasone 8 mg three times per day IM
  - The next day the blood pressure was 100/70 mm Hg and the pulse was 107 beats per minute

How would you taper his corticosteroids?

## Case 7: steroid taper in hospital

| Hospital day | Blood pressure (mmHg) | Pulse (per minute) | Steroid dose |
|---|---|---|---|
| 1 | 80/40 | 127 | Dexamethasone 8 mg intramuscular route every 8 hours |
| 2 | 100/70 | 101 | |
| 3 | 110/80 | 91 | Dexamethasone 8 mg intramuscular route every 12 hours |
| 4 (discharge) | 110/80 | 85 | Prednisone 40 mg twice per day by mouth |

Some clinicians would recommend keeping the patient in the hospital for longer, but a long stay is not always possible because of social and financial barriers.

## Case 7: steroid taper in clinic

- The patient was discharged and seen in clinic 2 weeks later
  - Prednisolone dose was decreased from 40 mg twice daily to 30 mg twice daily
- The dose was reduced over 3 months' time

| Weeks from discharge | Prednisolone dose |
|---|---|
| 2 | 30 mg twice per day |
| 4 | 20 mg twice per day |
| 6 | 10 mg twice per day |
| 8 | 10 mg once per day |
| 10 | 5 mg once per day |
| 12 | Stop |

It is acceptable to taper the corticosteroids a little faster than this (over 8 weeks rather than 12), but it is difficult to see patients frequently enough to evaluate their condition.

## What about the use of corticosteroids in pleural tuberculosis?

- Pleural tuberculosis is infection of the sac around the lung (review Chapter 2)
- Older teaching recommended using corticosteroids for pleural TB
  - Faster resolution of symptoms
  - But corticosteroids do not change the death rate[119]
- Some new research suggests the use of corticosteroids for pleural TB increases the risk of Kaposi's sarcoma in the future[119]
  - Given that corticosteroids do not reduce the death rate in these cases, this author suggests avoiding corticosteroids for pleural TB unless the patient is in respiratory distress

## When are corticosteroids contraindicated?

- If corticosteroids are given without anti-TB therapy but tuberculosis is actually present, then the patient will become more ill and likely die[181]
  - Patients might get better for a day or two after receiving corticosteroids, because of reduction in the inflammation caused by tuberculosis, but then they will become very sick if anti-TB treatment is not given
- Remember that corticosteroids weaken the immune system, which can allow tuberculosis to spread in the body, so corticosteroids are only safe to use if TB is also being treated
  - Example: A patient is mistakenly treated for PCP with high-dose cotrimoxazole and corticosteroids, but the real diagnosis is TB
  - Remember that TB and PCP can be difficult to tell apart in HIV-infected patients
- If you cannot rule out TB, then do not give corticosteroids, OR give corticosteroids and also treat for TB
- There may be other reasons not to give corticosteroids (see below)

## Steroid side effects[259]

- Short term:
  - Infections: thrush and esophageal candidiasis
  - Metabolic: hyperglycemia (high blood sugar)
  - Neurologic: psychosis
- Long term:
  - Body deformity: Cushing's syndrome
  - Gastritis, ulceration, bleeding: antacids or omeprazole might help
  - Dermatologic: acne
  - Osteoporosis: HIV-infected patients are already at risk for weak bones
  - Metabolic: diabetes, especially if obese patient
  - Cardiovascular: hypertension
- If a patient develops severe side effects from corticosteroids, try to taper the dose quickly

## Case 8: presentation

- A 40-year-old HIV-negative male presents with cough for two years
- Two years earlier he had received treatment for smear-positive pulmonary tuberculosis at another clinic
- His weight has been stable at 64 kg since that time
- He has no fever
- A chest x-ray shows scarring and a cavity in the right upper lobe

---

How do you manage this case?

Is this recurrence of TB, or something else?

---

## Case 8: management

- The patient was observed over one month
  - **Four** negative sputum smears for AFB
  - Weight stable
  - No fever
  - Not becoming more ill
- Diagnosis: Bronchiectasis caused by the earlier episode of TB
- Management:
  - Inhaled corticosteroids (beclamethasone 2 puffs daily)
  - Erythromycin given for the first week of every month for three months
  - After every three months, the antibiotic was changed (amoxicillin, then cotrimoxazole, etc.)
- The patient's cough reduced considerably

## Complications of pulmonary tuberculosis

- Bronchiectasis[260-262]
  - A frequent effect of chronic, destructive tuberculosis
  - Lung damage sometimes remains even after successful TB treatment
  - Tuberculosis damages airways
  - Chest x-ray may show scarring or shifted mediastinum/heart
  - Patients are at risk for frequent episodes of pneumonia even though TB is no longer present
- Treatment options[263]
  - Inhaled corticosteroids (such as beclamethasone)
  - **Rotating** antibiotics
    - For example, erythromycin for one week of every month for three months, then amoxicillin for one week of every month for three months, etc.
  - Another approach is to use antibiotics every day, such as erythromycin 500 mg twice daily
  - Bronchodilators, such as salbutamol (albuterol), may provide relief
  - In certain cases, surgery to remove the damaged part of the lung may be an option

## Heart failure as a complication of tuberculosis

- Two mechanisms
  - **#1: Pericardial TB** (see Chapter 3) causes the sac around the heart to "tighten"
    - The heart cannot fill with blood and pump normally
  - **#2: Bronchiectasis** increases the pressure in the blood vessels to the lung
    - The heart strains to pump blood to the lung
- Both of these processes can take place months or years **after** tuberculosis has been successfully treated and cured
- Presentation
  - Lower extremity edema and ascites
  - Fatigue
  - Shortness of breath
- Management
  - Diuretics (furosemide) to remove excess fluid
  - "Pericardial stripping," in cases of healed pericardial tuberculosis, if the surgical expertise is available

# Chapter 7

# Tuberculosis Case Challenges

## Case 1: presentation

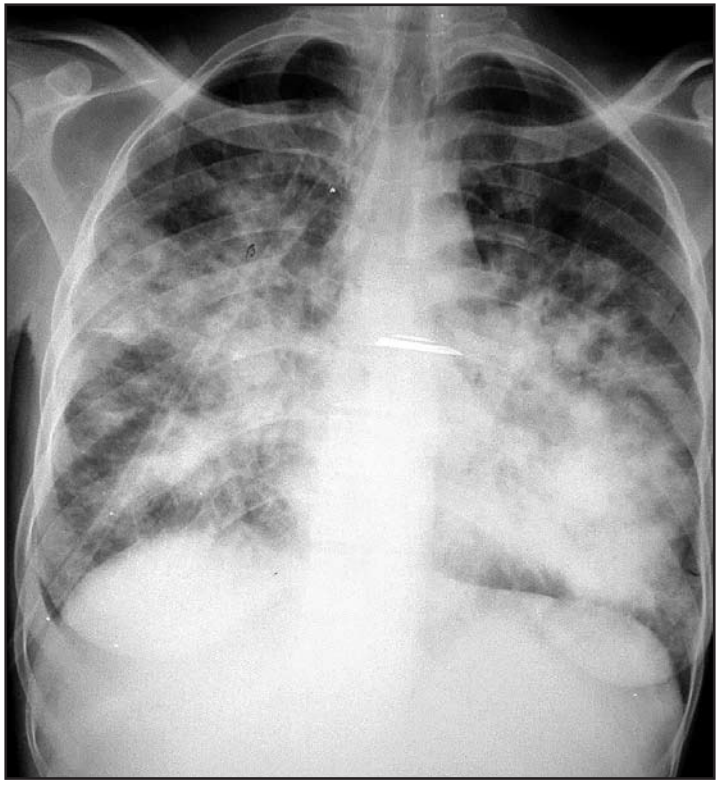
- 29-year-old HIV-infected female; baseline CD4 10 cells/μl
- Medical history:
  - Cerebral toxoplasmosis in past (empirically diagnosed and treated)
  - Kaposi's sarcoma of right leg requiring local injection of vincristine chemotherapy
  - Began ART 15 months prior
    - Viral load undetectable (< 400 copies/ml) and CD4 now 170 cells/μl
    - Kaposi's lesions temporarily disappeared
- Medications: ART (efavirenz, stavudine, lamivudine); cotrimoxazole prophylaxis
- Present illness: Two week history of cough, shortness of breath, and hemoptysis
- Examination:
  - Vital signs: T 38.1 degrees Celsius, respiratory rate 28 breaths per minute
  - Hard lymph nodes in the neck
  - Crackles both lungs
  - Kaposi's sarcoma returning in right leg

What is your differential diagnosis? What would you do next?

## Case 1: course

- Clinician suspected tuberculosis because of the presence of enlarged lymph nodes and hemoptysis
  - Initial chest x-ray showed bilateral fluffy infiltrates
  - Sputum negative for AFB
  - Started anti-tuberculosis treatment because patient very sick and TB strongly suspected
- Initial mild improvement but then patient became more ill with worsening cough and hemoptysis
  - Given antibiotics for pneumonia but no improvement
  - Follow-up chest x-ray shown below

## Case 1: chest x-ray



## Case 1: conclusion

- Repeat chest x-ray showed bilateral, dense, mass-like infiltrates consistent with tumor
- Presumptive diagnosis: Metastatic Kaposi's sarcoma
- Treatment: Palliative care
- Follow-up: Patient expired 2 days after x-ray

## Case 1: summary

- Not all hemoptysis is caused by tuberculosis
  - Remember that hemoptysis caused by TB is less common in HIV-positive compared with HIV-negative patients[23]
  - Kaposi's lesions often spread to the lung and cause bleeding[264]
- Not all enlarged lymph nodes come from TB
  - Recall that Kaposi's sarcoma is the 3rd most common cause of enlarged lymph nodes in African HIV-infected patients[89]
    - TB is the most common cause, and persistent generalized lymphadenopathy is the 2nd most common reason
  - A lymph node biopsy or fine needle aspirate before starting TB treatment would have been a good diagnostic approach in this case, especially given the history of Kaposi's sarcoma in the leg
    - But pathology services are required
- Not all bad chest x-rays represent tuberculosis
- Advanced Kaposi's sarcoma is usually not curable in the resource-limited setting

## Case 2: presentation

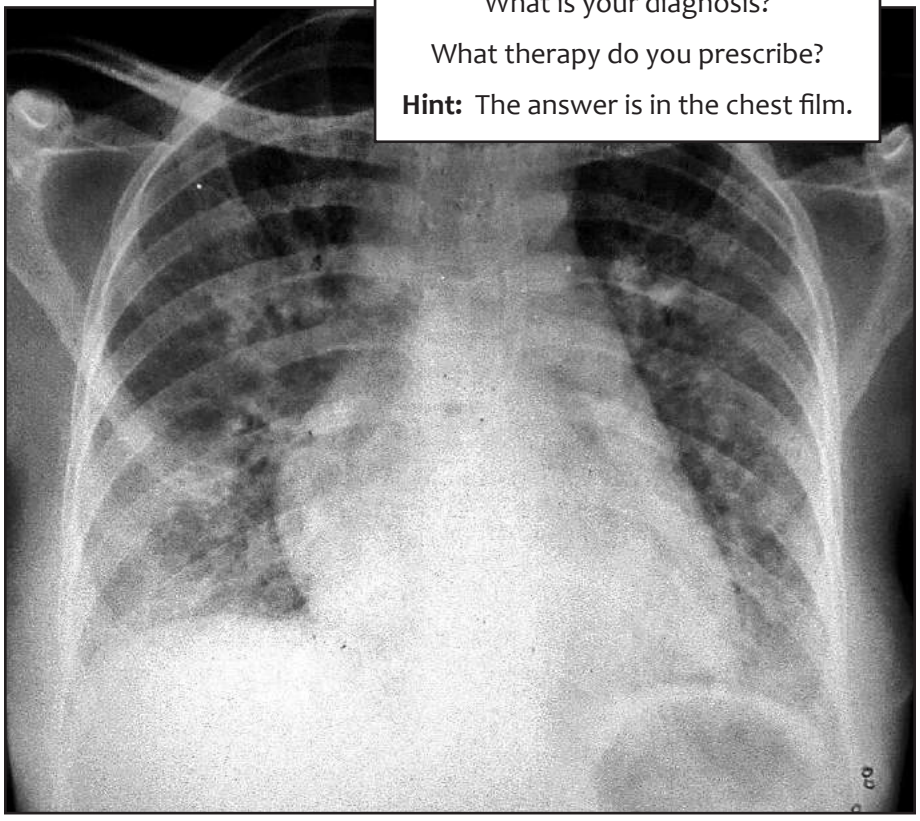
- 34-year-old pregnant female newly diagnosed with HIV; CD4 count unknown
- Medical History: 3 weeks of cough and shortness of breath
- Medications: None; not using cotrimoxazole prophylaxis
- Exam:
  - Vital signs: T 38.6° Celsius. P 121 beats per minute. Respiratory rate 42 breaths per minute. Oxygen saturation 79% on room air.
  - Acutely ill in respiratory distress
  - Lung exam revealed bilateral crepitations
  - No enlarged lymph nodes
- Chest x-ray done (see figure on following page)

## Case 2: chest x-ray

What is your diagnosis?

What therapy do you prescribe?

**Hint:** The answer is in the chest film.

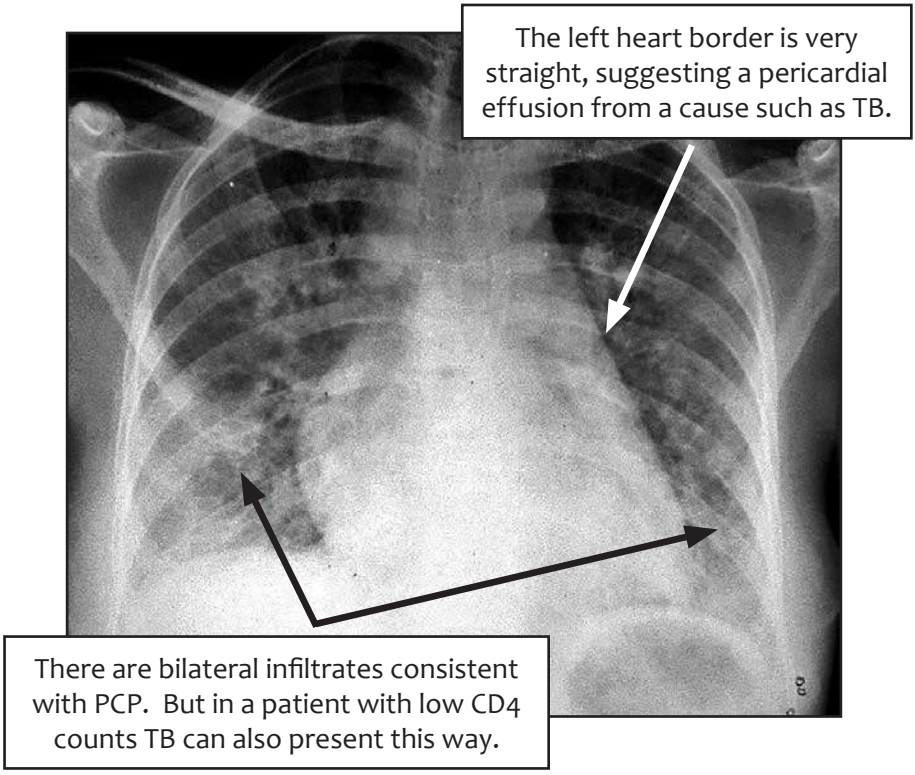


## Case 2: hospital course

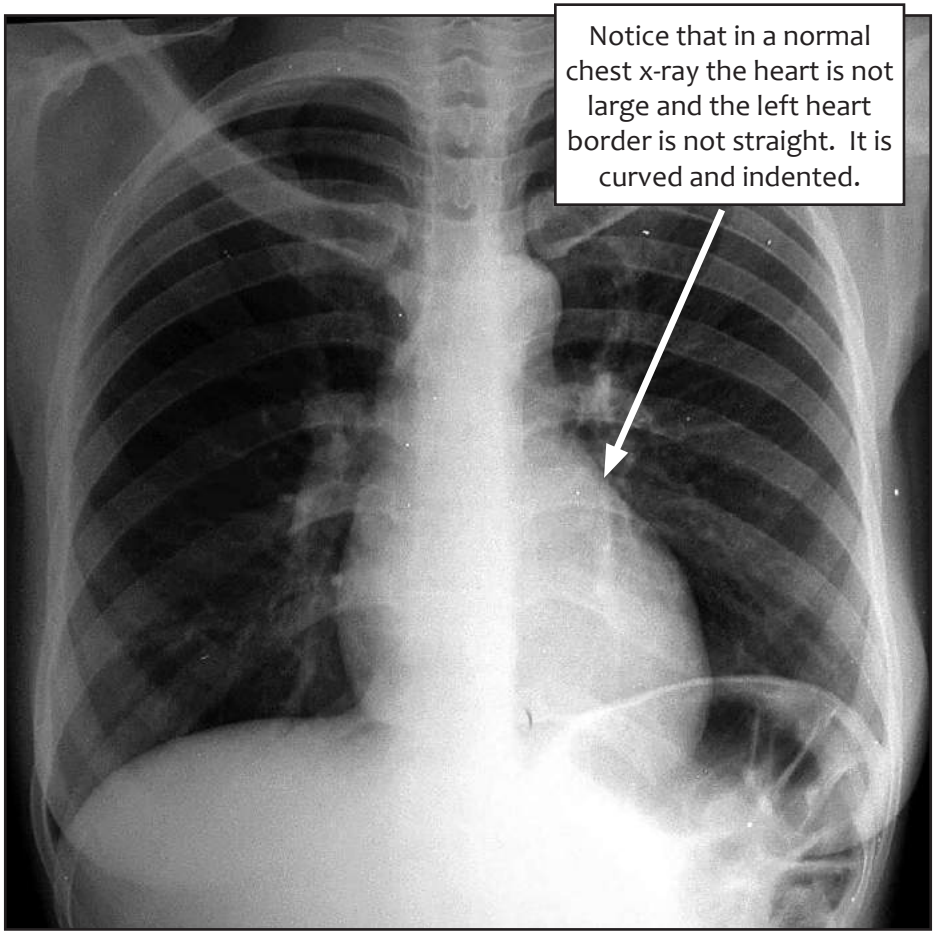
- Preliminary diagnosis: *Pneumocystis* (PCP) pneumonia
- Initial treatment:
  - Cotrimoxazole 4 tabs three times per day
  - Prednisolone 40 mg orally twice per day
- Course:
  - Patient worsened over next three days
  - Transferred to intensive care unit

What is the explanation for her worsening condition? What would you do next? How would you change therapy?

## Case 2: chest x-ray review



## Case 2: normal chest x-ray




## Case 2: follow-up

- The chest x-ray showed an enlarged heart shadow with a straight left heart border
- An ultrasound showed a significant pericardial effusion (fluid in the sac around the heart)
- Tuberculosis therapy was started
  - The patient died three days later

## Case 2: summary

- In advanced HIV disease with low CD4 counts, TB can look like PCP on chest x-ray[3]
  - Bilateral infiltrates
- In advanced HIV, TB spreads frequently from organ to organ, so look in more than one place
  - Remember that TB causes **almost all** cases of pericardial effusion in African HIV-infected patients[148-150]
  - PCP does not cause a pericardial effusion
  - Pericardial effusion can present as a straight left heart border[157]
- If you are planning to give corticosteroids, then TB **must** be ruled out, or TB therapy should also be given
  - Corticosteroids can weaken the immune system, so the TB can spread easily unless treated with anti-tuberculosis drugs[181]

## Case 3: presentation

- 38-year-old HIV-infected female; CD4 40 cells/μl
- Medical history: Cryptococcal meningitis on maintenance therapy
- Medications: Fluconazole, ART (nevirapine, zidovudine, lamivudine)
- History: Three days after starting ART developed cough, headache and fatigue
- Exam:
  - Vital signs: T 38.2 degrees Celsius. Pulse 104 beats per minute. Respiratory rate 28 breaths per minute.
  - Wasted, with difficulty sitting up.
  - Mild weakness left hand and leg. Right-sided strength normal.
  - Increased deep tendon reflexes at the knees, left side more than right

What is your differential diagnosis?

What treatment will you give?

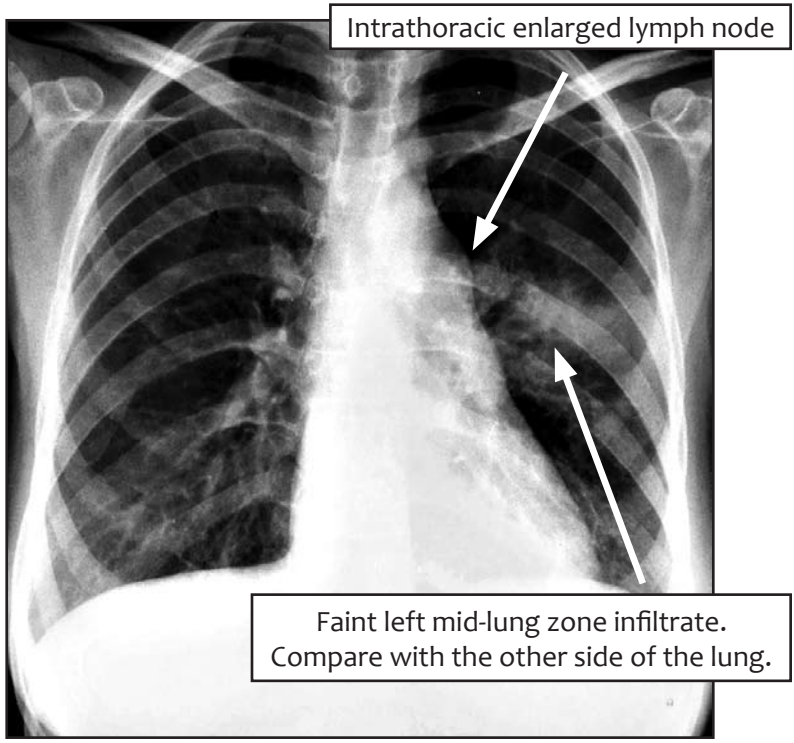
## Case 3: course

- Initial diagnosis: Initiation of ART leading to the immune reconstitution inflammatory syndrome (IRIS) in the presence of cryptococcal meningitis
- Treatment: Admitted and given intravenous amphotericin for cryptococcal disease
- Clinical course: Headache, fever, and weakness worsened over 5 days

Why is the patient not improving?

Now what should be done?

## Case 3: chest x-ray



## Case 3: conclusion

- Chest x-ray: Faint left mid-lung zone infiltrate and lymphadenopathy
- Sputum smear examination: Positive for AFB
- Diagnosis: IRIS caused by pulmonary and meningeal TB
- Treatment: 4-drug tuberculosis therapy (RHZE) and corticosteroids
  - Initially dexamethasone 8 mg IM three times per day
  - 4 days later discharged on prednisolone 40 mg orally twice per day
  - ART changed: nevirapine switched to efavirenz
    - Remember that there is some concern that rifampicin will significantly lower nevirapine levels in the blood;[241] you should follow national guidelines regarding this issue
- Follow-Up: Improved quickly and weakness gone by second day
  - Discharged home after four days

## Case 3: summary

- Both cryptococcal meningitis and TB can lead to IRIS following initiation of ART[215]
- IRIS can occur **within days** of ART initiation[235]
- Clinical clues suggesting TB in this case
  - Cough: In an African setting cryptococcus is a rare cause of cough[85]
  - One side of the body weaker than the other
    - TB can affect both sides **or** localize to one side only
    - Cryptococcus is usually symmetrical and bilateral (affects both sides)[198, 206]
- When your first treatment is not working, then re-evaluate, collect new information, and change your approach

Notice in this case how important the physical exam was to making the diagnosis. The weakness on one side of the body was mild, but one-sided findings suggest TB instead of cryptococcal meningitis.

## Reminder: risk factors for IRIS

Recall from Chapter 5

- Low CD4 count before starting ART
  - CD4 < 100 cells/μl in adults[76, 77]
  - CD4% < 15% in children[233]
- Patients with evidence of undiagnosed, untreated opportunistic infection
  - Wasted patients
  - Chronic cough
  - Lymphadenopathy
  - Fever
  - Headache
  - WHO **danger signs**
- Failure to screen patients for tuberculosis before starting ART
- Initiating ART soon after starting therapy for an opportunistic infection (such as TB or cryptococcus)[50, 77]

## Case 4: presentation

- 26-year-old HIV-infected female with unknown CD4 count
- Medical History: One month of weight loss, cough, and shortness of breath
- Medications: None; new HIV diagnosis
- Exam:
  - Vital signs: Temperature 38.6 degrees Celsius. Pulse 117 beats per minute. Respiratory rate 30 breaths per minute.
  - Pale
  - Lung examination revealed bilateral crepitations (rales)
  - No enlarged lymph nodes but hepatomegaly (large liver) felt in the right upper quadrant of the abdomen
- Labs: Hemoglobin 6.5 g/dl, WBC 2.7/ml, Platelets 37,000/ml
- Sputum smear: Negative for AFB

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What is the differential diagnosis?

What tests do you order?

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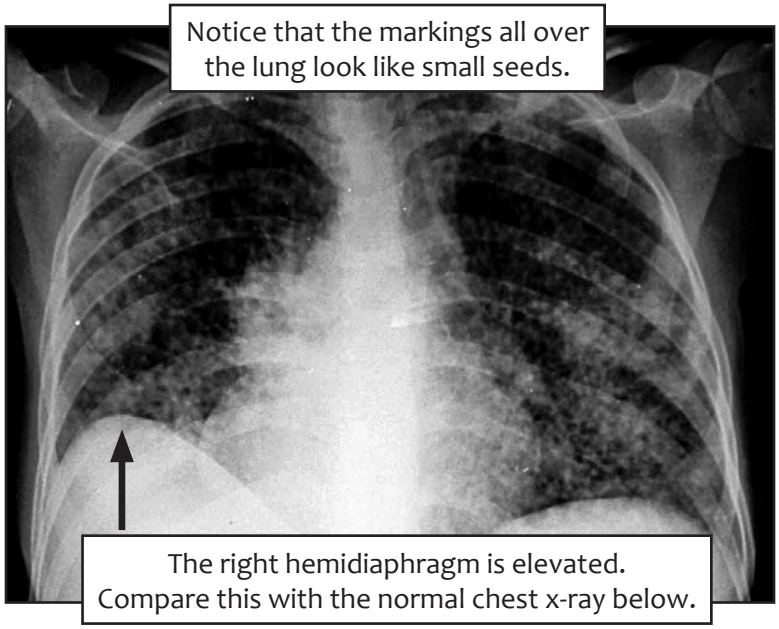
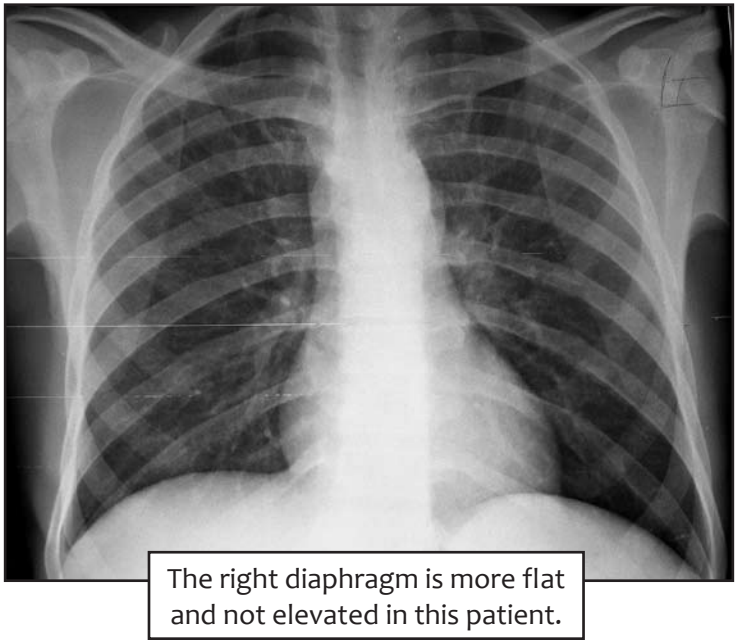
## Case 4: chest x-ray




## Normal chest x-ray



## Case 4: course

- Initial clinical diagnosis: *Pneumocystis* pneumonia (PCP)
- Treatment:
  - Cotrimoxazole 4 tabs orally three times per day
  - Prednisolone 40 mg orally twice per day
- Clinical course: Initial mild improvement

Is this the correct diagnosis?

## Case 4: summary

- PCP is not the correct diagnosis
  - The **miliary** pattern (like millet seeds) on x-ray is classic for TB
    - PCP does not produce a miliary pattern
  - The hepatomegaly may represent TB in the liver
- The anemia and pancytopenia (low hemoglobin, white cells and platelets) along with lung disease strongly suggest tuberculosis
  - **Lung disease + severe anemia → think TB!**
- Follow-up
  - Patient expired the day after starting anti-tuberculosis drugs
- An **interstitial** pattern (fine lines) on x-ray can represent TB or PCP[57]
  - But a **miliary** (millet seeds) pattern is classic for tuberculosis
- Tuberculosis can spread to the bone marrow and cause severe anemia
  - In Africa, when the hemoglobin is **less than 7 g/dl** in a sick HIV-positive patient, consider TB or salmonella[55]
- Prompt recognition and treatment are essential
  - If TB is on the differential diagnosis but corticosteroids must also be used for possible PCP, then you should also start anti-TB drugs
  - The use of corticosteroids without TB drugs in this case may have contributed to the patient's death[181]

## Case 5: presentation

- 42-year-old HIV-infected African female; baseline CD4 141 cells/μl
- Past medical history: Locally advanced right-sided breast cancer
  - Underwent mastectomy and radiation therapy
- Medications: tamoxifen (breast cancer drug), cotrimoxazole prophylaxis, and multivitamins
- Present illness:
  - Started ART with nevirapine, zidovudine, and lamivudine
  - Two weeks later developed cough
  - Given antibiotics without improvement
  - Another two weeks later the cough became worse and she also developed low back pain

---

What is the differential diagnosis?

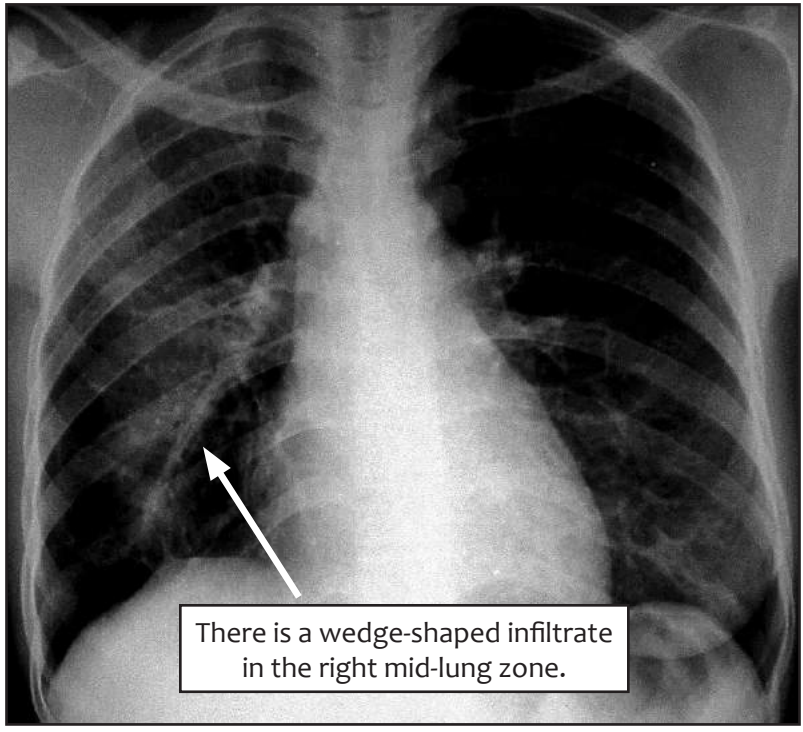
What tests would you order?

---

## Case 5: evaluation

- Differential diagnosis:
  - Pneumonia: Given antibiotics already without improvement
  - *Pneumocystis* pneumonia (PCP): Already on cotrimoxazole prophylaxis, so PCP is less likely to develop
  - IRIS due to undiagnosed tuberculosis at time of ART initiation
  - Radiation pneumonitis (lung damage from radiation therapy)
- Chest x-ray: Wedge-shaped faint infiltrate in the right mid-lung (see below). No previous x-ray available.
- Sputum for AFB: Three samples negative
- Lumbar puncture: Normal

## Case 5: chest x-ray



## Case 5: clinical course

- Because of the cough following ART initiation, lack of response to antibiotics, and infiltrate on chest x-ray, the patient was started on anti-tuberculosis treatment
  - Nevirapine was changed to efavirenz
- The patient's condition worsened after 2 weeks on anti-TB therapy
  - Progressive shortness of breath and low oxygen levels
  - Oxygen saturation 85% on room air; the normal value is above 95%
  - Chest x-ray remained unchanged
- In addition to low back (spine) pain, now has new bone complaints:
  - Point tenderness left scapula
  - Point tenderness left iliac crest

---

Given the lack of response to TB therapy and the new symptoms, now what do you do?

What is your new diagnosis?

What new treatment do you give?

---

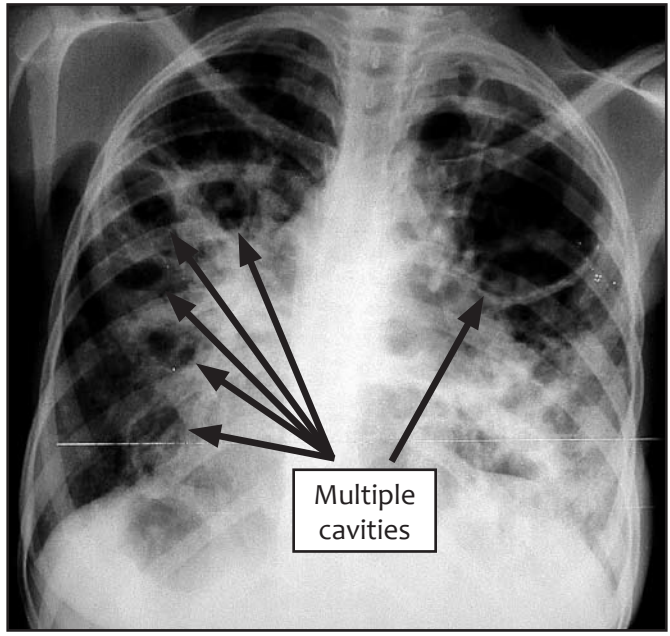
## Case 5: diagnosis and treatment

- Given the history of advanced breast cancer, the new lung findings, and the pinpoint bony tenderness, a new diagnosis of **metastatic breast cancer** was made
- The patient was admitted for pain control and IM dexamethasone (8 mg three times per day)
  - Significant improvement in two days; pain nearly resolved
- Referred back to her oncologist
  - Given radiation therapy, which caused anemia
  - Continued ART but died of breast cancer
  - The wedge-shaped infiltrate on x-ray probably represented metastatic lung cancer or radiation-induced damage

## Case 5: summary

- Not all lung complaints are due to tuberculosis
- When you are not sure of a diagnosis, it is acceptable to try an **empiric therapy** (best guess)
  - If the first treatment does not work, re-evaluate, re-investigate and try a different therapy
- With difficult cases, it is hard to know the answer quickly
  - But it is **not acceptable** to allow a patient to become sicker and sicker without any attempt at treatment
  - In this case, the change to a new therapy (corticosteroids) produced significant pain relief for the patient
  - If necessary, start a treatment and refer to another center for additional diagnosis and management[82]

## Case 6: Is this TB patient also HIV-positive?




- This 24-year-old African female presented in respiratory distress
- She had been sick for 4 months but unable to travel to the hospital
- Exam:
  - Vital signs: Temperature 38.3 degrees Celsius. Pulse 140 beats per minute. Respiratory rate 64 breaths per minute. Oxygen saturation 53% on room air (normal value above 95%).
  - The patient was in respiratory distress with severe crepitations (rales) in both lungs
- Sputum smear examination positive for AFB
- Started TB treatment and improved slowly over two weeks
  - Eventually successfully completed therapy

The HIV test was negative. You probably could have predicted this result from the many cavities and tremendous destruction in her lung, which are evidence of a strong immune system.

## Case 6: summary

- HIV-negative patients are much more likely to have upper lobe tuberculosis and cavities[23]
  - Cavities are uncommon in sick, advanced HIV-infected patients who have low CD4 counts[3, 57]
- Still, every patient who is a TB suspect should be offered HIV testing[51]

## Summary: tuberculosis case challenges

- TB and HIV present a complicated spectrum of diseases to the clinician
- Learning to manage complicated cases is necessary for high quality patient care
  - "Complicated" does not mean "rare"
- Knowledge and skill come with experience and hard work

# Chapter 8

# Overview of World Health Organization Guidelines

## About this chapter

- This chapter provides a summary of the World Health Organization (WHO) guidelines for the diagnosis and treatment of tuberculosis in areas of high HIV prevalence
- The referenced document[82] is available at the following website: http://www.who.int/publications/tb/2006/tbhiv_recommendations.pdf
- These guidelines were released in November 2006
- I encourage you to review this excellent and helpful document

This book presents an approach consistent with the WHO guidelines.

Unless otherwise indicated, my personal thoughts and suggestions are contained in the ***"Comment"*** boxes.

## The problem

- The WHO recognizes that smear-negative pulmonary and extrapulmonary tuberculosis are major causes of mortality among HIV-infected patients living in resource-limited regions
- Older clinical protocols may delay the diagnosis of TB and contribute to higher death rates
- Advanced diagnostic methods (such as culture) are rarely available in resource-limited settings

## New WHO overall approach

- Provide more flexibility to clinicians when diagnosing TB in HIV-infected patients
- Recommend faster diagnostic work-up of suspected tuberculosis
- Allow more rapid initiation of therapy for tuberculosis
  - Remember from earlier chapters that the word **"empirical"** means **"best clinical guess"** based on the available evidence

## New case definition: smear-negative pulmonary tuberculosis in the HIV-infected patient

- At least **two** negative sputum smears for AFB
- X-ray showing evidence of tuberculosis
- Evidence of HIV (blood test or clinical)
- Decision to treat with **full course** of TB therapy

***Comment***

Chest x-rays are not always available. Remember that chest x-rays are sometimes normal even in HIV-infected patients with TB.[3-5, 57]

Also recall from Chapter 2 that in real-world clinical settings, sputum smears are often negative in HIV-infected patients with active tuberculosis.[4, 5, 33-38, 40, 42, 52, 101, 102]

Because of the high risk of death, very sick HIV-infected patients with clinical evidence of TB should be strongly considered for treatment even when the sputum smears are negative.[132]

The WHO includes in the case definition **the clinician's decision to treat**. Make the best decision you can based on the evidence, then stand by that decision by committing to a **full course** of anti-tuberculosis therapy. Because of the risk of resistance, the WHO does not recommend short trials of therapy.

## Decision to treat for tuberculosis

- The WHO wants clinicians who strongly suspect TB to commit to treat the patient for the **full course** of tuberculosis therapy
- Short "trials" of TB therapy which last less than the full 6 or 8 month course should not be used
  - Anti-tuberculosis therapy should be stopped **only** if another diagnosis becomes obvious (for example, lung cancer) and explains all of the patient's symptoms
  - If the clinician believes strongly that tuberculosis is present, he should prescribe a full course of treatment

---

"Advanced TB and HIV can be clinically indistinguishable—the clinician should **always** consider if there is active TB and this should be excluded as far as possible.

TB drugs should be considered, **even in the absence of definite radiological or microbiological evidence.**" (emphasis added)

—*Kenyan National Clinical Manual for ARV Providers*, 1st ed., 2004[132]

---

***Comment***

Review Cases 1 and 5 in Chapter 8 for examples of lung cancer presenting like tuberculosis in HIV-infected patients.

The guidelines should not lead to overuse or abuse of TB medicines. Use the principles of careful history and physical examination described in this book and in the WHO guidelines to determine the most likely TB cases.

Overuse of TB therapy can cause:

Resistance due to inappropriate short "trials" of therapy

High cost

Drug toxicity

---

## Role of "antibiotic trial"

- Old approach: Response to antibiotics can be used to "rule out" TB
- New approach: Trial of antibiotics **not** useful in ruling out the diagnosis of TB
  - Antibiotics should be used if the clinician suspects bacterial pneumonia or *Pneumocystis* pneumonia (PCP)
- Do not use ciprofloxacin or other fluoroquinolones for pneumonia
  - Cipro might partially treat TB, causing delays in diagnosis and creating resistance[133, 147]
  - Cipro is not a good bacterial pneumonia drug, anyway

***Comment***

The common practice or repeated courses of antibiotics should be avoided as it often leads to delay in diagnosis of tuberculosis. I have seen patients receiving three or four courses of antibiotics over the period of many months. **We must move more quickly to consider the diagnosis and treatment of tuberculosis.**

However, it is possible for two infections (such as TB and bacterial pneumonia) to be present at the same time, so a course of antibiotics is reasonable if you suspect bacterial pneumonia in a sick patient.

If you decide to use a course of antibiotics but the patient does not respond, you should consider another approach instead of just repeating another trial of a different antibiotic.

If a patient presents with cough for two months, the cause is not likely to be bacterial pneumonia (review Chapter 2). Giving antibiotics to this patient may not be helpful.

If the patient presents with one month of cough and fever but is taking cotrimoxazole prophylaxis, PCP is not likely to be the cause since cotrimoxazole prevents this infection. Giving high-dose cotrimoxazole to such a patient will probably not be helpful.

## Role of chest x-rays in diagnosing smear-negative pulmonary TB in HIV-infected patients

- Chest x-ray is very important to prevent delays in diagnosis
  - Recommended for **all** patients with possible tuberculosis
- Old thinking: HIV-infected patients with TB have "atypical" (unusual) x-rays
  - May look like regular bacterial "pneumonia"
  - Lymph nodes
  - Interstitial markings (like PCP)
- New thinking: These x-ray patterns should now be considered **"typical"** (common) for HIV-infected patients with low CD4 counts
- When sputum smears are negative and the chest x-ray is suggestive, clinical judgment is necessary to start therapy for tuberculosis
- Response to anti-TB therapy should help make the final diagnosis

***Comment***

Review the chest x-rays included in this book.

Remember: X-rays can even be normal in HIV/TB co-infected patients.[3-5, 59, 60]

In patients with advanced HIV infection, you should not expect to see cavities and upper lobe disease (review Chapter 2).

Apply the clinical principles presented in this book to look for other signs of tuberculosis in the body (review Chapters 3 and 4). These signs of extrapulmonary TB can include:

Enlarged lymph nodes

Severe anemia

Central nervous system: increased reflexes, confusion, headache, weakness on one or both sides of the body

Heart: enlarged heart shadow on x-ray, effusion on ultrasound

## Role of sputum culture in diagnosis of smear-negative pulmonary tuberculosis

- When available, sputum samples should be sent for TB culture
  - Culture is the "gold standard" (best) test for diagnosing TB, and it is more sensitive than sputum smears
  - Culture is better than sputum smears and empiric therapy
- But this test is rarely available in resource-limited settings

## Immune reconstitution inflammatory syndrome: the interaction between tuberculosis and ART

- Occurs when ART is started in a patient with unrecognized TB
  - Example: Mild cough due to TB is not investigated or diagnosed properly. The patient starts ART and the chest problems become worse two weeks later.
- Also can occur in an HIV-infected patient who is already on anti-tuberculosis treatment and then starts ART
- WHO recommendations regarding IRIS caused by tuberculosis
  - Diagnose TB and start treatment before initiating ART
  - IRIS does **not** mean failure of ART
  - If IRIS occurs, continue first-line ART
  - The ART regimen may need to be adjusted; if efavirenz is available, it can be substituted for nevirapine, but follow national guidelines
- If IRIS occurs, continue TB treatment **and** ART

***Comment***

Review Chapter 5 of this book on IRIS and tuberculosis.

IRIS means the ART is working to make the body stronger.

Some patients with TB-IRIS may need to stop ART if the pill burden is too high for them to handle.

Remember that rifampicin may affect the levels of nevirapine.[241]

## Extrapulmonary tuberculosis

- Extrapulmonary tuberculosis is common in HIV-infected patients
  - Presence of extrapulmonary TB should raise suspicion of HIV infection (if not already diagnosed)
- Tuberculosis can disseminate (spread) throughout the body of an HIV-infected patient
- The diagnosis of extrapulmonary TB is difficult because of:
  - Lack of tuberculosis culture capabilities
  - Lack of biopsy services

## Case definition: extrapulmonary tuberculosis in HIV-infected patients

- One positive AFB specimen (smear or culture) from a location outside of the lungs
- Biopsy suggesting TB
- **Strong clinical evidence** suggesting TB
- Evidence of HIV infection (blood or clinical)
- Decision to treat for **full course** of tuberculosis treatment

***Comment***

Notice the flexibility allowed in diagnosing a case of tuberculosis on the basis of **strong clinical suspicion.** Remember that we call this "empiric," or "best guess," when we lack all the necessary tests, such as tuberculosis culture facilities.

## Diagnosis and treatment of extrapulmonary tuberculosis in HIV-infected patients

- The WHO says that healthcare providers working in clinics and health centers which lack diagnostic testing **"should initiate empirical tuberculosis therapy early in serious illness in patients thought to be due to extrapulmonary tuberculosis"**
  - Referral should be made to a higher level health center as soon as possible
- Use first-line TB drugs according to national protocols
- Do not stop therapy until the full course is completed
  - **Short treatment trials with TB drugs should not be done**
  - **If you decide to treat for TB, complete the full course**

***Comment***

If you think a very sick patient has TB then treatment should not be delayed for many days because of the high risk of death.

Using less than a full course of anti-TB therapy can lead to resistance.

## Approach to the diagnosis of tuberculosis in the ambulatory HIV-infected patient

- **Ambulatory** = walking
  - Not very sick
  - No danger signs
- What are WHO "**danger signs**"?
  - Respiratory rate > 30 breaths per minute
  - Fever > 39 degrees Celsius
  - Pulse > 120 beats per minute
  - Unable to walk alone

---

***Comment***

Vital signs are vital!

Measure vital signs yourself in sick patients!

---

## Diagnosis of pulmonary tuberculosis in ambulatory (stable) HIV-infected patients

| Visit | Sputum AFB smear | |
|---|---|---|
| | Negative | Positive |
| 1st | Perform HIV test<br>Collect AFB smears<br>[Comment: consider antibiotics for pneumonia] | Treat<br>HIV testing |
| 2nd | Repeat sputum AFB smears<br>Chest x-ray<br>Sputum TB culture, if available<br>[Comment: consider antibiotics for pneumonia] | Treat |
| 3rd | Treat for pneumonia<br>Consider PCP treatment | Treat |
| 4th | **Response to antibiotics:** Follow-up HIV care<br>**No response:** Re-assess for tuberculosis | |

Adapted from Reference 82

***Comment***

If patients are suspected of having acute bacterial pneumonia or PCP, antibiotics or high-dose cotrimoxazole may be given immediately, even before the third visit.

## Diagnosis of TB in seriously ill HIV-infected patients

### Use "danger signs" to help identify seriously ill patients

| Referral possible | Referral not possible |
|---|---|
| Parenteral antibiotics<br>AFB sputum smears<br>Chest x-ray<br>AFB culture, if available | Parenteral antibiotics<br>Consider cotrimoxazole for PCP treatment<br>Sputum AFB smear |
| **Evidence of TB:** Treat<br>**No evidence of TB:** Follow-up, monitor closely | **Smear (+):** Treat for TB<br>**Smear (-):** Continue antibiotics |
| **After 3-5 days …**<br>If there is a response to antibiotics, continue and re-assess for TB.<br>If there is no response to antibiotics, start anti-tuberculosis treatment immediately and refer, if these things have not already been done. | |

Adapted from Reference 82

***Comment***

The "referral not possible" column applies to patients presenting to lower-level health facilities with limited laboratory capabilities and no physician consultation. However, if you find evidence of TB (such as generalized lymphadenopathy or severe anemia), it is acceptable to treat a very sick patient for tuberculosis without delay. Remember that (1) TB is the most common cause of death in HIV-infected Africans, and (2) A delay in therapy will increase the risk of death.

## Characteristics of extrapulmonary tuberculosis in HIV-infected patients

| History and symptoms | Physical examinations and investigations |
|---|---|
| Weight loss, night sweats, fever | WHO danger signs, enlarged or tender lymph nodes in neck or armpit |
| Difficulty breathing | Reduced breath sounds, dullness to chest percussion |
| | Swollen legs, distant heart sounds, swollen neck veins |
| | X-ray: miliary or interstitial pattern, bilateral infiltrates, pleural effusion, large heart shadow, large lymph nodes in chest |
| Headache, altered mental status | Stiff neck, confusion, vision or eye movements not normal |

Adapted from reference 82

> "Suspect disseminated tuberculosis in all people living with HIV who experience rapid or marked weight loss, fever and night sweats."
>
> —World Health Organization[82]

## Additional characteristics to consider in the diagnosis of extrapulmonary tuberculosis in HIV-infected patients

**Suggestions by the author**

- Severe anemia (hemoglobin < 7 g/dl)[55]
  - Strongly suggests TB or bacteria in the blood (such as salmonella)
  - Look for signs and symptoms of tuberculosis elsewhere in the body
- Cough
  - Extrapulmonary and pulmonary TB often occur together
  - Chest x-ray and sputum for AFB
- Lymph nodes
  - Needle aspiration and smear for AFB
- Consider a brain infection in patients with:
  - Headache, fever, or confusion:
    - Perform a lumbar puncture
    - Look for bacterial meningitis if symptoms develop quickly
  - Symmetric (both sides) increased reflexes:
    - Consider tuberculosis or cryptococcal meningitis
  - Unilateral (one side) increased reflexes:
    - Consider tuberculoma or toxoplasmosis
  - Review Chapter 4 (tuberculous meningitis)

## Tuberculous lymphadenitis

- Diagnosis
  - Suspect tuberculosis if you can feel lymph nodes
    - 2 centimeters or larger
    - Firm, fluctuant (filled with pus), or draining pus
    - Most common site in the neck
  - Needle aspiration for AFB staining
  - If needle aspiration negative or unavailable, then excisional biopsy of lymph node
- Treatment
  - If aspiration or biopsy specimen is AFB smear positive, may begin therapy for tuberculosis
  - May also begin TB treatment **immediately** without aspiration or biopsy if:
    - Patient is very ill
      - Remember **danger signs**
    - Evidence of disseminated tuberculosis
    - If biopsy will not be available for two weeks and TB is the most likely diagnosis

***Comment***

Remember to feel for lymph nodes in the neck and armpits of all ill HIV-positive patients.

If the lymph node is draining, press a slide to the pus and send to the lab for AFB smear microscopy.

Remember from Chapter 3 that tuberculosis is the most common cause of lymphadenopathy in sick HIV–infected Africans.[89, 110]

Tuberculous lymphadenitis may present as part of IRIS after ART.

## Pleural tuberculosis in the HIV-infected patient

- Diagnosis
  - Pleural TB is the most common cause of **unilateral (one-sided)** pleural effusion in HIV-infected patients
    - Tuberculosis caused 95 out of 100 cases of unilateral pleural effusion in two African research studies[116, 117]
    - **WHO says that "Tuberculosis is the likely cause of unilateral pleural effusion in countries with a high tuberculosis burden."**
  - Confirm the effusion with a chest x-ray (see Chapter 2 for example)
- If possible, aspirate fluid:
  - Plain tube: If the fluid clots after a few minutes, then the fluid contains high amounts of protein and TB is the likely cause
  - Send fluid to lab for protein and cell count
    - Protein > 30 mg/dl
    - Lymphocytes > 50% of cell count
  - If fluid is on both sides of chest or is bloody or cloudy, consider other causes:
    - Severe pneumonia with pus (empyema)
    - Heart or kidney failure
    - Cancer
- Pleural biopsy is **not** necessary to confirm TB
- If aspiration is not available, start TB treatment immediately in HIV-infected patients with pleural effusions
  - Treatment with antibiotics is **not required** prior to starting tuberculosis therapy.
  - Mortality rate is high early in disease course
- Treatment is first-line therapy according to national guidelines

## Pleural tuberculosis in the HIV-infected patient

***Comment***

Avoid using corticosteroids in patients with pleural tuberculosis because of an increased risk of Kaposi's sarcoma[119] and temporarily higher HIV viral loads.[120] Recall that corticosteroids do not improve death rates in cases of pleural TB.[119]

Generally, large volume drainage of fluid is not necessary for treatment purposes, although patients presenting in respiratory distress may require it.

As with other forms of TB, delay in therapy can lead to death.

## Other forms of extrapulmonary tuberculosis in the HIV-infected patient

The WHO states the following[82] regarding other forms of extrapulmonary tuberculosis, such as pericarditis and meningitis:

"Most patients with other forms of tuberculosis present in a sufficiently characteristic way to allow tuberculosis treatment to be started **without attempting to confirm the diagnosis bacteriologically or histologically.**" (emphasis added)

Multiple cultures and invasive biopsy procedures "are expensive and may result in lengthy diagnostic delays that can reduce the chances of a good treatment response."

***Comment***

In other words, some cases of TB are so obvious (such as pericardial disease, which is almost always caused by TB in HIV-infected Africans) that treatment can be started without further special tests.

## Pericardial tuberculosis

- Chest x-ray or ultrasound may show evidence of fluid around the heart (pericardial effusion)
- In HIV-positive Africans, more than 90% (almost all) of pericardial effusions are due to tuberculosis[148-150]
- If no other cause is present, WHO recommends to **start TB treatment immediately**

***Comment***

Review the clinical presentation, diagnosis, and management of pericardial tuberculosis in Chapter 3.

## Tuberculosis meningitis

- Suspect tuberculosis if:
  - Slow onset of symptoms (headache, weakness)
  - Cerebrospinal fluid
    - High protein
    - Mostly lymphocytes
    - Cryptococcal antigen test is negative
    - Evidence of tuberculosis elsewhere (lung, lymph node)
- Start tuberculosis treatment immediately if no other cause is found

***Comment***

Review the features of TB meningitis in Chapter 4.

## Suspected disseminated disease: tuberculosis in the blood and throughout the body

- Common in very ill HIV-infected patients in the hospital
  - Lack of tuberculosis blood culture facilities means many of these cases are missed
  - High mortality
- Rapid and profound weight loss
- Tuberculosis may be present in multiple locations
  - Large liver or spleen
  - Miliary tuberculosis on chest x-ray
  - Anemia
- Reasons to suspect a cause **other than TB**
  - Rigors (shaking fever and chills)
  - Severe diarrhea
  - Blood in stool
- Other infections to consider
  - Pneumonia (rigors, very fast breathing)
  - Salmonella (rigors, diarrhea, blood in stool)
  - Malaria (rigors)
- **If there is evidence of tuberculosis only:**
  - **Start TB therapy immediately**
- Evidence of another diagnosis; investigations before starting TB drugs
  - Blood culture, if available
  - Malaria smear
  - Chest x-ray
  - Cryptococcal antigen (CRAG) test

## Suspected disseminated disease: tuberculosis in the blood and throughout the body

***Comment***

Review the features of disseminated tuberculosis and mycobacteremia in Chapter 3.

Remember, the importance of severe anemia (hemoglobin < 7 g/dl)[55] and large lymph nodes in HIV-infected patients with fever.

Careful history and physical examination with other basic lab tests should help to tell the difference between tuberculosis and other infections.

Do not delay therapy if the patient is critically ill and near death. It is acceptable to start both antibiotics and TB therapy.

## Summary: smear-negative pulmonary tuberculosis in HIV-infected patients

- Investigations
  - **At least two** negative AFB sputum smears
  - Chest x-ray evidence of tuberculosis
  - Culture, if available
  - Clinical assessment:
    - Monitor vital signs for **danger signs**
  - Antibiotic trial has no place in the WHO **diagnostic** algorithm for HIV-related TB, but follow national guidelines regarding antibiotics
    - Use antibiotics for treatment if you suspect bacterial pneumonia or PCP
  - Goal: Diagnosis or improvement in symptoms within 4 clinic visits
- For **stable** ambulatory clinic patients without danger signs
  - Treat for TB only after repeated clinical and sputum evaluations on 3 or 4 separate days
  - If tuberculosis is likely based upon results of chest x-ray and clinical assessment, then treat for TB **even if repeated sputum examinations for AFB are negative**
  - Commit to **full course** of anti-tuberculosis treatment
  - Assess clinical response to therapy
- For **critically ill** patients who have been sick for 2 weeks or more with cough and **danger signs**:
  - Refer to higher level facility, if available
  - Start intravenous or intramuscular antibiotics and consider high-dose cotrimoxazole for PCP
  - If no improvement after 3 to 5 days, start anti-tuberculosis drugs **even if AFB smears are negative**
  - **If critically ill and there is other evidence of TB, start treatment immediately**

## Summary: extrapulmonary TB in HIV-infected patients

- Investigations
  - Lymph node: Aspiration or biopsy
  - Pleural: Chest x-ray or aspiration
  - Pericardial: Chest x-ray or ultrasound
  - Meningitis: Lumbar puncture; look for bacterial meningitis if symptoms develop rapidly
  - Disseminated: Look for evidence of tuberculosis in organ systems
    - Liver (large liver, jaundice)
    - Lungs (cough, difficulty breathing)
    - Blood (severe anemia)
    - Brain (headache, confusion)
- Treatment
  - If TB is the **most likely** cause, start therapy as soon as possible
  - If the patient is **clinically stable** and another diagnosis is likely (such as pneumonia or salmonella), then:
    - Delay TB therapy until other investigations are conducted
    - Give 3-5 days of parenteral antibiotics
  - If patient is **critically ill,** consider starting tuberculosis treatment **and** antibiotics without waiting for definite diagnosis

***Comment***

The World Health Organization guidelines and the recommendations of this book are very similar.

Clinicians should follow the protocols of their national tuberculosis control programs and should discuss difficult cases with program officers and consultants.

## References


1. Mtei L, Matee M, Herfort O, et al. High rates of clinical and subclinical tuberculosis among HIV-infected ambulatory subjects in Tanzania. Clin Infect Dis 2005;40(10):1500-7.

2. Rangaka M, du Toit E, van Cutsem G, et al. Tuberculosis screening and intensified case finding at an integrated HIV/TB clinic in Khayelitsha, Cape Town. In: 5th International AIDS Conference on HIV Pathogenesis, Treatment and Prevention, abstract TUPEB153. Capetown; 2009.

3. Greenberg SD, Frager D, Suster B, Walker S, Stavropoulos C, Rothpearl A. Active pulmonary tuberculosis in patients with AIDS: spectrum of radiographic findings (including a normal appearance). Radiology 1994;193(1):115-9.

4. Chamie G, Luetkemeyer A, Walusimbi-Nanteza M, et al. Significant variation in radiographic presentation of pulmonary tuberculosis across a high resolution of CD4 strata and by HIV infection status in Uganda. In: 5th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention, abstract TUPEB133 Capetown; 2009.

5. Edwards D, Vogt M, Bangani N, et al. Baseline screening for TB among patients enrolling in an ART service in South Africa. In: 16th Conference on Retroviruses and Opportunistic Infections, abstract 780. Montreal; 2009.

6. Wood R, Middelkoop K, Myer L, et al. Undiagnosed tuberculosis in a community with high HIV prevalence: implications for tuberculosis control. Am J Respir Crit Care Med 2007;175(1):87-93.

7. Corbett EL, Marston B, Churchyard GJ, De Cock KM. Tuberculosis in sub-Saharan Africa: opportunities, challenges, and change in the era of antiretroviral treatment. Lancet 2006;367(9514):926-37.

8. Lienhardt C, Rodrigues LC. Estimation of the impact of the human immunodeficiency virus infection on tuberculosis: tuberculosis risks re-visited? Int J Tuberc Lung Dis 1997;1(3):196-204.

9. Lawn SD, Bekker LG, Middelkoop K, Myer L, Wood R. Impact of HIV infection on the epidemiology of tuberculosis in a peri-urban community in South Africa: the need for age-specific interventions. Clin Infect Dis 2006;42(7):1040-7.

10. Lucas SB, De Cock KM, Hounnou A, et al. Contribution of tuberculosis to slim disease in Africa. BMJ 1994;308(6943):1531-3.

11. Lawn SD, Myer L, Bekker LG, Wood R. Burden of tuberculosis in an antiretroviral treatment programme in sub-Saharan Africa: impact on treatment outcomes and implications for tuberculosis control. AIDS 2006;20(12):1605-12.

12. World Health Organization. Global tuberculosis control - epidemiology, strategy, financing. Geneva: World Health Organization; 2009.

13. Mukadi YD, Maher D, Harries A. Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. AIDS 2001;15(2):143-52.

14. Karstaedt A. Causes of death in patients on ART in a Soweto Clinic, 2004-2009. In: 5th International Conference on HIV Pathogenesis, Treatment and Prevention, abstract TUPDB101. Capetown; 2009.

15. Behroozi F, Meintjes G, Crede T, Burch V, Rebe K. Causes of mortality in relation to HIV status and antiretroviral access at a referral hospital in Cape Town, South Africa. In: 5th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, abstract TUPEB104. Capetown; 2009.

16. Meda IB, Kouanda S, Tiendrebeogo S, Ouedraogo HG, Doulougou B, Sondo B. Risk factors and causes of death of PLWH in Ouagadougou. In: 5th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, abstract TUPEB107. Capetown; 2009.

17. Rana FS, Hawken MP, Mwachari C, et al. Autopsy study of HIV-1-positive and HIV-1-negative adult medical patients in Nairobi, Kenya. J Acquir Immune Defic Syndr 2000;24(1):23-9.

18. Ansari NA, Kombe AH, Kenyon TA, et al. Pathology and causes of death in a group of 128 predominantly HIV-positive patients in Botswana, 1997-1998. Int J Tuberc Lung Dis 2002;6(1):55-63.

19. Lucas SB, Hounnou A, Peacock C, et al. The mortality and pathology of HIV infection in a west African city. AIDS 1993;7(12):1569-79.

20. Nelson AM, Perriens JH, Kapita B, et al. A clinical and pathological comparison of the WHO and CDC case definitions for AIDS in Kinshasa, Zaire: is passive surveillance valid? AIDS 1993;7(9):1241-5.

21. Maher D, Floyd K, Raviglione M. Strategic Framework to Decrease the Burden of TB/HIV. Geneva: World Health Organization; 2002.

22. Horsburgh CR, Jr. Priorities for the treatment of latent tuberculosis infection in the United States. N Engl J Med 2004;350(20):2060-7.

23. Harries AD, Maher D, Nunn P. An approach to the problems of diagnosing and treating adult smear-negative pulmonary tuberculosis in high-HIV-prevalence settings in sub-Saharan Africa. Bull World Health Organ 1998;76(6):651-62.

24. Di Perri G, Cruciani M, Danzi MC, et al. Nosocomial epidemic of active tuberculosis among HIV-infected patients. Lancet 1989;2(8678-8679):1502-4.

25. Daley CL. Tuberculosis recurrence in Africa: true relapse or re-infection? Lancet 1993;342(8874):756-7.

26. Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med 1997;126(12):946-54.

27. Goletti D, Weissman D, Jackson RW, et al. Effect of Mycobacterium tuberculosis on HIV replication. Role of immune activation. J Immunol 1996;157(3):1271-8.

28. Day JH, Grant AD, Fielding KL, et al. Does tuberculosis increase HIV load? J Infect Dis 2004;190(9):1677-84.

29. Masur H, Komati S, Shaw PA, et al. History of recent tuberculosis is associated with poor prognosis in South African-HIV therapy trial. In: 5th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention, abstract TUPEB143. Capetown; 2009.

30. Whalen C, Horsburgh CR, Hom D, Lahart C, Simberkoff M, Ellner J. Accelerated course of human immunodeficiency virus infection after tuberculosis. Am J Respir Crit Care Med 1995;151(1):129-35.

31. Morris L, Martin DJ, Bredell H, et al. Human immunodeficiency virus-1 RNA levels and CD4 lymphocyte counts, during treatment for active tuberculosis, in South African patients. J Infect Dis 2003;187(12):1967-71.

32. Guwatudde D, Zalwango S, Kamya MR, et al. Burden of tuberculosis in Kampala, Uganda. Bull World Health Organ 2003;81(11):799-805.

33. Elliott AM, Namaambo K, Allen BW, et al. Negative sputum smear results in HIV-positive patients with pulmonary tuberculosis in Lusaka, Zambia. Tuber Lung Dis 1993;74(3):191-4.

34. Wilkinson D, Sturm AW. Diagnosing tuberculosis in a resource-poor setting: the value of sputum concentration. Trans R Soc Trop Med Hyg 1997;91(4):420-1.

35. Elliott AM, Luo N, Tembo G, et al. Impact of HIV on tuberculosis in Zambia: a cross sectional study. BMJ 1990;301(6749):412-5.

36. Samb B, Sow PS, Kony S, et al. Risk factors for negative sputum acid-fast bacilli smears in pulmonary tuberculosis: results from Dakar, Senegal, a city with low HIV seroprevalence. Int J Tuberc Lung Dis 1999;3(4):330-6.

37. Long R, Scalcini M, Manfreda J, Jean-Baptiste M, Hershfield E. The impact of HIV on the usefulness of sputum smears for the diagnosis of tuberculosis. Am J Public Health 1991;81(10):1326-8.

38. Klein NC, Duncanson FP, Lenox TH, 3rd, Pitta A, Cohen SC, Wormser GP. Use of mycobacterial smears in the diagnosis of pulmonary tuberculosis in AIDS/ARC patients. Chest 1989;95(6):1190-2.

39. Wilson D, Nachega J, Morroni C, Chaisson R, Maartens G. Diagnosing smear-negative tuberculosis using case definitions and treatment response in HIV-infected adults. International Journal of Tuberculosis and Lung Disease 2006;10(1):31-8.

40. Kivihya-Ndugga L, van Cleeff M, Githui W. A comprehensive comparison of Ziehl-Neelsen and fluorescence microscopy for the diagnosis of tuberculosis in a resource-poor urban setting. International Journal of Tuberculosis and Lung Disease 2003;7(12):1163-71.

41. Dimairo M, Mativenga S, Dauya E, et al. The fate of sputum-smear negative TB suspects managed by routine clinical services in Harare, Zimbabwe. In: 16th Conference on Retroviruses and Opportunistic Infections, abstract 778. Montreal; 2009.

42. Steingart KR, Henry M, Ng V, et al. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. Lancet Infect Dis 2006;6(9):570-81.

43. Hawken MP, Muhindi DW, Chakaya JM, Bhatt SM, Ng'ang'a LW, Porter JD. Under-diagnosis of smear-positive pulmonary tuberculosis in Nairobi, Kenya. Int J Tuberc Lung Dis 2001;5(4):360-3.

44. Braitstein P, Brinkhof MW, Dabis F, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet 2006;367(9513):817-24.

45. Ferradini L, Jeannin A, Pinoges L, et al. Scaling up of highly active antiretroviral therapy in a rural district of Malawi: an effectiveness assessment. Lancet 2006;367(9519):1335-42.

46. Wools-Kaloustian K, Kimaiyo S, Diero L, et al. Viability and effectiveness of large-scale HIV treatment initiatives in sub-Saharan Africa: experience from western Kenya. AIDS 2006;20(1):41-8.

47. Rosen S, Fox MP, Gill CJ. Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review. PLoS Med 2007;4(10):e298.

48. Seyler C, Toure S, Messou E, Bonard D, Gabillard D, Anglaret X. Risk factors for active tuberculosis after antiretroviral treatment initiation in Abidjan. Am J Respir Crit Care Med 2005;172(1):123-7.

49. Lawn SD, Myer L, Orrell C, Bekker LG, Wood R. Early mortality among adults accessing a community-based antiretroviral service in South Africa: implications for programme design. AIDS 2005;19(18):2141-8.

50. Lawn SD, Myer L, Bekker LG, Wood R. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. AIDS 2007;21(3):335-41.

51. Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC). The Hague: Tuberculosis Coalition for Technical Assistance; 2006.

52. Bassett I, Chetty S, Wang B, et al. Intensive TB screening for HIV-infected patients ready to start ART in Durban, South Africa: limitations of WHO guidelines. In: 16th Conference on Retroviruses and Opportunistic Infections, abstract 779. Montreal; 2009.

53. Banda HT, Harries AD, Welby S, et al. Prevalence of tuberculosis in TB suspects with short duration of cough. Trans R Soc Trop Med Hyg 1998;92(2):161-3.

54. Scott JA, Hall AJ, Muyodi C, et al. Aetiology, outcome, and risk factors for mortality among adults with acute pneumonia in Kenya. Lancet 2000;355(9211):1225-30.

55. Lewis DK, Whitty CJ, Walsh AL, et al. Treatable factors associated with severe anaemia in adults admitted to medical wards in Blantyre, Malawi, an area of high HIV seroprevalence. Trans R Soc Trop Med Hyg 2005;99(8):561-7.

56. Samb B, Henzel D, Daley CL, et al. Methods for diagnosing tuberculosis among in-patients in eastern Africa whose sputum smears are negative. Int J Tuberc Lung Dis 1997;1(1):25-30.

57. Alpert PL, Munsiff SS, Gourevitch MN, Greenberg B, Klein RS. A prospective study of tuberculosis and human immunodeficiency virus infection: clinical manifestations and factors associated with survival. Clin Infect Dis 1997;24(4):661-8.

58. Atomiya AN, Uip DE, Leite OH. Evaluation of disease patterns, treatment and prognosis of tuberculosis in AIDS patient. Braz J Infect Dis 2002;6(1):29-39.

59. Keiper MD, Beumont M, Elshami A, Langlotz CP, Miller WT. CD4 T lymphocyte count and the radiographic presentation of pulmonary tuberculosis. A study of the relationship between these factors in patients with human immunodeficiency virus infection. Chest 1995;107(1):74-80.

60. Post FA, Wood R, Pillay GP. Pulmonary tuberculosis in HIV infection: radiographic appearance is related to CD4+ T-lymphocyte count. Tuber Lung Dis 1995;76(6):518-21.

61. von Reyn CF, Waddell R, Pallanygo K. Extrapulmonary tuberculosis. Lancet 2001;358(9286):1010-1.

62. Sharma SK, Mohan A. Extrapulmonary tuberculosis. Indian J Med Res 2004;120(4):316-53.

63. Schutte CM, Van der Meyden CH, Labuscagne JH, Otto D. Lymph node biopsy as an aid in the diagnosis of intracranial tuberculosis. Tuber Lung Dis 1996;77(3):285-6.

64. Kirk O, Gatell JM, Mocroft A, et al. Infections with Mycobacterium tuberculosis and Mycobacterium avium among HIV-infected patients after the introduction of highly active antiretroviral therapy. EuroSIDA Study Group JD. Am J Respir Crit Care Med 2000;162(3 Pt 1):865-72.

65. Girardi E, Antonucci G, Vanacore P, et al. Impact of combination antiretroviral therapy on the risk of tuberculosis among persons with HIV infection. AIDS 2000;14(13):1985-91.

66. Lawn SD, Badri M, Wood R. Tuberculosis among HIV-infected patients receiving HAART: long term incidence and risk factors in a South African cohort. AIDS 2005;19(18):2109-16.

67. Middelkoop K, Wood R, Myer L, Sebastian E, Bekker L-G. Can antiretroviral therapy contain a previously escalating TB epidemic in a high HIV prevalence community? In: 5th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, abstract WELBB105. Capetown; 2009.

68. Lawn SD, Bekker LG, Miller RF. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. Lancet Infect Dis 2005;5(6):361-73.

69. Bonnet MM, Pinoges LL, Varaine FF, et al. Tuberculosis after HAART initiation in HIV-positive patients from five countries with a high tuberculosis burden. AIDS 2006;20(9):1275-9.

70. Haddow L, Moosa Y, Mosam A, Khanyile N, Easterbrook P. Immune reconstitution inflammatory syndrome is an important contributor to HIV-related morbidity and mortality in an ART program in South Africa. In: 16th Conference on Retroviruses and Opportunistic Infections, abstract 602. Montreal; 2009.

71. Eshun-Wilson I, Havers F, Nachega J, et al. Evaluating TB-associated immune reconstitution inflammatory syndrome using standardized case definitions. In: 16th Conference on Retroviruses and Opportunistic Infections, abstract 768. Montreal; 2009.

72. Velasco M, Castilla V, Sanz J, et al. Effect of simultaneous use of highly active antiretroviral therapy on survival of HIV patients with tuberculosis. J Acquir Immune Defic Syndr 2009;50(2):148-52.

73. Karim S, Naidoo K, Grobler A, et al. Initiating ART during TB treatment significantly increases survival: results of a randomized controlled clinical trial in TB/HIV co-infected patients in South Africa. In: 16 Conference on Retroviruses and Opportunistic Infections, abstract 36A. Montreal; 2009.

74. Fatti G, Grimwood A, Bock P. Improved TB treatment outcomes at facilities enhanced by a non-governmental organization-assisted ART program: Western Cape, South Africa. In: 16th Conference on Retroviruses and Opportunistic Infections, abstract 591. Montreal; 2009.

75. Girardi E, Vanacore P, Palmieri F, Angeletti C, Carbonara S, Ippolito G. Impact of previous ART and of ART initiation on outcome of HIV-associated TB. In: 5th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, abstract CDB040. Capetown; 2009.

76. Breton G, Duval X, Estellat C, et al. Determinants of immune reconstitution inflammatory syndrome in HIV type 1-infected patients with tuberculosis after initiation of antiretroviral therapy. Clin Infect Dis 2004;39(11):1709-12.

77. Shelburne SA, Visnegarwala F, Darcourt J, et al. Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. AIDS 2005;19(4):399-406.

78. Kumarasamy N, Chaguturu S, Mayer KH, et al. Incidence of immune reconstitution syndrome in HIV/tuberculosis-coinfected patients after initiation of generic antiretroviral therapy in India. J Acquir Immune Defic Syndr 2004;37(5):1574-6.

79. Archibald LK, McDonald LC, Nwanyanwu O, et al. A hospital-based prevalence survey of bloodstream infections in febrile patients in Malawi: implications for diagnosis and therapy. J Infect Dis 2000;181(4):1414-20.

80. McDonald LC, Archibald LK, Rheanpumikankit S, et al. Unrecognised Mycobacterium tuberculosis bacteraemia among hospital inpatients in less developed countries. Lancet 1999;354(9185):1159-63.

81. Pithie AD, Chicksen B. Fine-needle extrathoracic lymph-node aspiration in HIV-associated sputum-negative tuberculosis. Lancet 1992;340(8834-8835):1504-5.

82. World Health Organization. Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adolescents and adults: Recommendations for HIV-prevalent and resource constrained settings. Geneva: World Health Organization; 2006 November 2006.

83. Farer LS, Lowell AM, Meador MP. Extrapulmonary tuberculosis in the United States. Am J Epidemiol 1979;109(2):205-17.

84. Tuberculosis in Kenya 1984: a third national survey and a comparison with earlier surveys in 1964 and 1974. A Kenyan/British Medical Research Council Co-operative Investigation. Tubercle 1989;70(1):5-20.

85. Munyati SS, Dhoba T, Makanza ED, et al. Chronic cough in primary health care attendees, Harare, Zimbabwe: diagnosis and impact of HIV infection. Clin Infect Dis 2005;40(12):1818-27.

86. Selwyn PA, Pumerantz AS, Durante A, et al. Clinical predictors of Pneumocystis carinii pneumonia, bacterial pneumonia and tuberculosis in HIV-infected patients. AIDS 1998;12(8):885-93.

87. Malin AS, Gwanzura LK, Klein S, Robertson VJ, Musvaire P, Mason PR. Pneumocystis carinii pneumonia in Zimbabwe. Lancet 1995;346(8985):1258-61.

88. Bem C. Human immunodeficiency virus-positive tuberculous lymphadenitis in Central Africa: clinical presentation of 157 cases. Int J Tuberc Lung Dis 1997;1(3):215-9.

89. Bem C, Patil PS, Bharucha H, Namaambo K, Luo N. Importance of human immunodeficiency virus-associated lymphadenopathy and tuberculous lymphadenitis in patients undergoing lymph node biopsy in Zambia. Br J Surg 1996;83(1):75-8.

90. Bem C, Patil PS, Elliott AM, Namaambo KM, Bharucha H, Porter JD. The value of wide-needle aspiration in the diagnosis of tuberculous lymphadenitis in Africa. AIDS 1993;7(9):1221-5.

91. Mukadi Y, Perriens JH, St Louis ME, et al. Spectrum of immunodeficiency in HIV-1-infected patients with pulmonary tuberculosis in Zaire. Lancet 1993;342(8864):143-6.

92. Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Faussett P, Shearer S. How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. J Infect Dis 2005;191(2):150-8.

93. Lawn S, Myer L, D Edwards D, Wood R. Short- and long-term risks of TB associated with CD4 cell response to ART in South Africa. In: 16th Conference on Retroviruses and Opportunistic Infections, Abstract 788. Montreal; 2009.

94. Siddiqi K, Lambert ML, Walley J. Clinical diagnosis of smear-negative pulmonary tuberculosis in low-income countries: the current evidence. Lancet Infect Dis 2003;3(5):288-96.

95. Brindle RJ, Nunn PP, Githui W, Allen BW, Gathua S, Waiyaki P. Quantitative bacillary response to treatment in HIV-associated pulmonary tuberculosis. Am Rev Respir Dis 1993;147(4):958-61.

96. Johnson JL, Vjecha MJ, Okwera A, et al. Impact of human immunodeficiency virus type-1 infection on the initial bacteriologic and radiographic manifestations of pulmonary tuberculosis in Uganda. Makerere University-Case Western Reserve University Research Collaboration. Int J Tuberc Lung Dis 1998;2(5):397-404.

97. Mugusi F, Villamor E, Urassa W, Saathoff E, Bosch RJ, Fawzi WW. HIV co-infection, CD4 cell counts and clinical correlates of bacillary density in pulmonary tuberculosis. Int J Tuberc Lung Dis 2006;10(6):663-9.

98. Hargreaves NJ, Kadzakumanja O, Whitty CJ, Salaniponi FM, Harries AD, Squire SB. 'Smear-negative' pulmonary tuberculosis in a DOTS programme: poor outcomes in an area of high HIV seroprevalence. Int J Tuberc Lung Dis 2001;5(9):847-54.

99. Sahid F, Samuel E, Moosa M-Y. High rate of false negative TB smear microscopy in a busy urban clinic: a need to revisit the process. In: 5th International AIDS Society Conference on Pathogenesis, Treatment and Prevention, abstract WEPED229. Capetown; 2009.

100. Steingart KR, Ng V, Henry M, et al. Sputum processing methods to improve the sensitivity of smear microscopy for tuberculosis: a systematic review. Lancet Infect Dis 2006;6(10):664-74.

101. Pe R, Koole O, Thai S, Choun K, Lynen L. Diagnostic evaluation of smear microscopy of different samples as screening tool for tuberculosis in HIV patients at Sihanouk Hospital Center of Hope, Phnom Penh, Cambodia. In: 5th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, abstract CDA102. Capetown; 2009.

102. Babaria P, Shah S, Moll A, Gandhi N, Friedland G. High rate of unrecognized TB and drug-resistant TB among ART clinic patients in rural South Africa. In: 16th Conference on Retroviruses and Opportunistic Infections, abstract 782. Montreal; 2009.

103. Hargreaves NJ, Kadzakumanja O, Phiri S, et al. What causes smear-negative pulmonary tuberculosis in Malawi, an area of high HIV seroprevalence? Int J Tuberc Lung Dis 2001;5(2):113-22.

104. Parry CM, Kamoto O, Harries AD, et al. The use of sputum induction for establishing a diagnosis in patients with suspected pulmonary tuberculosis in Malawi. Tuber Lung Dis 1995;76(1):72-6.

105. Elvin KM, Lumbwe CM, Luo NP, Bjorkman A, Kallenius G, Linder E. Pneumocystis carinii is not a major cause of pneumonia in HIV infected patients in Lusaka, Zambia. Trans R Soc Trop Med Hyg 1989;83(4):553-5.

106. McLeod DT, Neill P, Robertson VJ, et al. Pulmonary diseases in patients infected with the human immunodeficiency virus in Zimbabwe, Central Africa. Trans R Soc Trop Med Hyg 1989;83(5):694-7.

107. Harries AD, Banda HT, Boeree MJ, et al. Management of pulmonary tuberculosis suspects with negative sputum smears and normal or minimally abnormal chest radiographs in resource-poor settings. Int J Tuberc Lung Dis 1998;2(12):999-1004.

108. Fagan K, King T. Lymphocytic interstitial pneumonitis. In: Rose B, ed. UpToDate. Waltham, MA: UpToDate; 2008.

109. Bem C, Patil PS, Luo N. The increased burden of tuberculous lymphadenitis in central Africa: lymph node biopsies in Lusaka, Zambia, 1981 and 1990. Trop Doct 1996;26(2):58-61.

110. Voetberg A, Lucas SB. Tuberculosis or persistent generalised lymphadenopathy in HIV disease? Lancet 1991;337(8732):56-7.

111. Al-Marri MR, Kirkpatrick MB. Erythrocyte sedimentation rate in childhood tuberculosis: is it still worthwhile? Int J Tuberc Lung Dis 2000;4(3):237-9.

112. Venkatesh PA, Bosch RJ, McIntosh K, Mugusi F, Msamanga G, Fawzi WW. Predictors of incident tuberculosis among HIV-1-infected women in Tanzania. Int J Tuberc Lung Dis 2005;9(10):1105-11.

113. Wood R, Maartens G, Lombard CJ. Risk factors for developing tuberculosis in HIV-1-infected adults from communities with a low or very high incidence of tuberculosis. J Acquir Immune Defic Syndr 2000;23(1):75-80.

114. Bedell R, Chan AK, Bourgeois J, Kanyerere H, Schouten E, van Lettow M. Clinical features amongst ART patients who develop suspected TB early after initiation in a district in Southern Malawi. In: 5th International AIDS Conference on Pathogenesis, Treatment, and Prevention, abstract TUPEB137. Capetown; 2009.

115. Wilkinson D, De Cock KM, Sturm AW. Diagnosing tuberculosis in a resource-poor setting: the value of a trial of antibiotics. Trans R Soc Trop Med Hyg 1997;91(4):422-4.

116. Heyderman RS, Makunike R, Muza T, et al. Pleural tuberculosis in Harare, Zimbabwe: the relationship between human immunodeficiency virus, CD4 lymphocyte count, granuloma formation and disseminated disease. Trop Med Int Health 1998;3(1):14-20.

117. Luzze H, Elliott AM, Joloba ML, et al. Evaluation of suspected tuberculous pleurisy: clinical and diagnostic findings in HIV-1-positive and HIV-negative adults in Uganda. Int J Tuberc Lung Dis 2001;5(8):746-53.

118. Richter C, Perenboom R, Swai AB, et al. Diagnosis of tuberculosis in patients with pleural effusion in an area of HIV infection and limited diagnostic facilities. Trop Geogr Med 1994;46(5):293-7.

119. Elliott AM, Luzze H, Quigley MA, et al. A randomized, double-blind, placebo-controlled trial of the use of prednisolone as an adjunct to treatment in HIV-1-associated pleural tuberculosis. J Infect Dis 2004;190(5):869-78.

120. Mayanja-Kizza H, Jones-Lopez E, Okwera A, et al. Immunoadjuvant prednisolone therapy for HIV-associated tuberculosis: a phase 2 clinical trial in Uganda. J Infect Dis 2005;191(6):856-65.

121. Centers for Disease Control and Prevention. Guidelines for the investigation of contacts of persons with infectious tuberculosis. Recommendations from the National Tuberculosis Controllers Association and CDC. Morb Mortal Wkly Rep 2005;54:1-47.

122. Blumberg HM, Burman WJ, Chaisson RE, et al. American Thoracic Society/ Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med 2003;167(4):603-62.

123. Harries AD, Nyangulu DS, Kangombe C, et al. The scourge of HIV-related tuberculosis: a cohort study in a district general hospital in Malawi. Ann Trop Med Parasitol 1997;91(7):771-6.

124. Harries AD, Parry C, Nyongonya Mbewe L, et al. The pattern of tuberculosis in Queen Elizabeth Central Hospital, Blantyre, Malawi: 1986-1995. Int J Tuberc Lung Dis 1997;1(4):346-51.

125. Lee MP, Chan JW, Ng KK, Li PC. Clinical manifestations of tuberculosis in HIV-infected patients. Respirology 2000;5(4):423-6.

126. Archibald LK, den Dulk MO, Pallangyo KJ, Reller LB. Fatal Mycobacterium tuberculosis bloodstream infections in febrile hospitalized adults in Dar es Salaam, Tanzania. Clin Infect Dis 1998;26(2):290-6.

127. Ssali FN, Kamya MR, Wabwire-Mangen F, et al. A prospective study of community-acquired bloodstream infections among febrile adults admitted to Mulago Hospital in Kampala, Uganda. J Acquir Immune Defic Syndr Hum Retrovirol 1998;19(5):484-9.

128. Peters RP, Zijlstra EE, Schijffelen MJ, et al. A prospective study of bloodstream infections as cause of fever in Malawi: clinical predictors and implications for management. Trop Med Int Health 2004;9(8):928-34.

129. Gilks CF, Brindle RJ, Mwachari C, et al. Disseminated Mycobacterium avium infection among HIV-infected patients in Kenya. J Acquir Immune Defic Syndr Hum Retrovirol 1995;8(2):195-8.

130. Lewis DK, Peters RP, Schijffelen MJ, et al. Clinical indicators of mycobacteraemia in adults admitted to hospital in Blantyre, Malawi. Int J Tuberc Lung Dis 2002;6(12):1067-74.

131. Harries AD, Hargreaves NJ, Kumwenda J, Kwanjana JH, Salaniponi FM. Trials of anti-tuberculosis treatment in areas of high human immunodeficiency virus prevalence in sub-Saharan Africa. Int J Tuberc Lung Dis 2000;4(11):998-1001.

132. Ministry of Health. Kenyan National Clinical Manual for ARV Providers. 1st ed. Nairobi: NASCOP; 2004.

133. Dooley KE, Golub J, Goes FS, Merz WG, Sterling TR. Empiric treatment of community-acquired pneumonia with fluoroquinolones, and delays in the treatment of tuberculosis. Clin Infect Dis 2002;34(12):1607-12.

134. Kaslow RA, Phair JP, Friedman HB, et al. Infection with the human immunodeficiency virus: clinical manifestations and their relationship to immune deficiency. A report from the Multicenter AIDS Cohort Study. Ann Intern Med 1987;107(4):474-80.

135. World Health Organization. Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access. Geneva: World Health Organization; 2006.

136. Perenboom RM, Richter C, Swai AB, et al. Clinical features of HIV seropositive and HIV seronegative patients with tuberculous lymphadenitis in Dar es Salaam. Tuber Lung Dis 1995;76(5):401-6.

137. Katzenstein DA, Latif AS, Grace SA, et al. Clinical and laboratory characteristics of HIV-1 infection in Zimbabwe. J Acquir Immune Defic Syndr 1990;3(7):701-7.

138. Rieder HL, Snider DE, Jr., Cauthen GM. Extrapulmonary tuberculosis in the United States. Am Rev Respir Dis 1990;141(2):347-51.

139. Nambuya A, Sewankambo N, Mugerwa J, Goodgame R, Lucas S. Tuberculous lymphadenitis associated with human immunodeficiency virus (HIV) in Uganda. J Clin Pathol 1988;41(1):93-6.

140. Wilson D, Nachega JB, Chaisson RE, Maartens G. Diagnostic yield of peripheral lymph node needle-core biopsies in HIV-infected adults with suspected smear-negative tuberculosis. Int J Tuberc Lung Dis 2005;9(2):220-2.

141. Artenstein AW, Kim JH, Williams WJ, Chung RC. Isolated peripheral tuberculous lymphadenitis in adults: current clinical and diagnostic issues. Clin Infect Dis 1995;20(4):876-82.

142. Shriner KA, Mathisen GE, Goetz MB. Comparison of mycobacterial lymphadenitis among persons infected with human immunodeficiency virus and seronegative controls. Clin Infect Dis 1992;15(4):601-5.

143. Chea V, D. S, Pe R, Sar B, Thai S, Lynen L. Performance of abdominal ultrasound for diagnosis of tuberculosis in HIV-infected persons living in Cambodia. In: 5th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention, abstract TUPEB138 Cape Town; 2009.

144. Bekedam HJ, Boeree M, Kamenya A, et al. Tuberculous lymphadenitis, a diagnostic problem in areas of high prevalence of HIV and tuberculosis. Trans R Soc Trop Med Hyg 1997;91(3):294-7.

145. Orlovic D, Smego RA, Jr. Paradoxical tuberculous reactions in HIV-infected patients. Int J Tuberc Lung Dis 2001;5(4):370-5.

146. Meintjes G, Wilkinson R, Morron C, et al. Randomized placebo-controlled trial of prednisone for the TB immune reconstitution inflammatory syndrome. In: 16th Conference on Retroviruses and Opportunistic Infections, abstract 34. Montreal; 2009.

147. Sterling TR. The WHO/IUATLD diagnostic algorithm for tuberculosis and empiric fluoroquinolone use: potential pitfalls. Int J Tuberc Lung Dis 2004;8(12):1396-400.

148. Maher D, Harries AD. Tuberculous pericardial effusion: a prospective clinical study in a low-resource setting--Blantyre, Malawi. Int J Tuberc Lung Dis 1997;1(4):358-64.

149. Cegielski JP, Lwakatare J, Dukes CS, et al. Tuberculous pericarditis in Tanzanian patients with and without HIV infection. Tuber Lung Dis 1994;75(6):429-34.

150. Reuter H, Burgess LJ, Doubell AF. Epidemiology of pericardial effusions at a large academic hospital in South Africa. Epidemiol Infect 2005;133(3):393-9.

151. Mayosi BM, Burgess LJ, Doubell AF. Tuberculous pericarditis. Circulation 2005;112(23):3608-16.

152. Corey G, Sexton D. Tuberculous pericarditis. In: Rose B, ed. UpToDate. Waltham, MA: UpToDate; 2006.

153. Mayosi BM, Wiysonge CS, Ntsekhe M, et al. Clinical characteristics and initial management of patients with tuberculous pericarditis in the HIV era: the Investigation of the Management of Pericarditis in Africa (IMPI Africa) registry. BMC Infect Dis 2006;6:2.

154. Hakim JG, Ternouth I, Mushangi E, Siziya S, Robertson V, Malin A. Double blind randomised placebo controlled trial of adjunctive prednisolone in the treatment of effusive tuberculous pericarditis in HIV seropositive patients. Heart 2000;84(2):183-8.

155. Corey GR SD. Tuberculous pericarditis. In: BD R, ed. UpToDate. Waltham, MA: UpToDate; 2006.

156. Reuter H, Burgess LJ, Doubell AF. Role of chest radiography in diagnosing patients with tuberculous pericarditis. Cardiovasc J S Afr 2005;16(2):108-11.

157. Spodick DH. The Pericardium: A Comprehensive Textbook. New York: Marcel Dekker; 1997.

158. Smedema JP, Katjitae I, Reuter H, et al. Twelve-lead electrocardiography in tuberculous pericarditis. Cardiovasc J S Afr 2001;12(1):31-4.

159. Strang JI, Nunn AJ, Johnson DA, Casbard A, Gibson DG, Girling DJ. Management of tuberculous constrictive pericarditis and tuberculous pericardial effusion in Transkei: results at 10 years follow-up. QJM 2004;97(8):525-35.

160. Strang JI, Kakaza HH, Gibson DG, Girling DJ, Nunn AJ, Fox W. Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. Lancet 1987;2(8573):1418-22.

161. Sharma MP, Bhatia V. Abdominal tuberculosis. Indian J Med Res 2004;120(4):305-15.

162. Tarantino L, Giorgio A, de Stefano G, Farella N, Perrotta A, Esposito F. Disseminated mycobacterial infection in AIDS patients: abdominal US features and value of fine-needle aspiration biopsy of lymph nodes and spleen. Abdom Imaging 2003;28(5):602-8.

163. Horvath KD, Whelan RL. Intestinal tuberculosis: return of an old disease. Am J Gastroenterol 1998;93(5):692-6.

164. Song L, Wong K, Marcon N. Tuberculous enteritis. In: Rose B, ed. UpToDate. Waltham, MA: UpToDate; 2007.

165. Smit SJ, Du Toit RS. The acute AIDS abdomen--a prospective clinical and pathological study. S Afr J Surg 2005;43(3):88.

166. Mwachari C, Batchelor BI, Paul J, Waiyaki PG, Gilks CF. Chronic diarrhoea among HIV-infected adult patients in Nairobi, Kenya. J Infect 1998;37(1):48-53.

167. Vilaichone RK, Vilaichone W, Tumwasorn S, Suwanagool P, Wilde H, Mahachai V. Clinical spectrum of hepatic tuberculosis: comparison between immunocompetent and immunocompromised hosts. J Med Assoc Thai 2003;86 Suppl 2:S432-8.

168. Chow KM, Chow VC, Hung LC, Wong SM, Szeto CC. Tuberculous peritonitis-associated mortality is high among patients waiting for the results of mycobacterial cultures of ascitic fluid samples. Clin Infect Dis 2002;35(4):409-13.

169. Das P, Shukla HS. Clinical diagnosis of abdominal tuberculosis. Br J Surg 1976;63(12):941-6.

170. McDonald M SD. Skeletal tuberculosis. In: Rose B, ed. UpToDate. Waltham, MA: UpToDate; 2006.

171. Godlwana L, Gounden P, Ngubo P, Nsibande T, Nyawo K, Puckree T. Incidence and profile of spinal tuberculosis in patients at the only public hospital admitting such patients in KwaZulu-Natal. Spinal Cord 2008;46(5):372-4.

172. Five-year assessment of controlled trials of short-course chemotherapy regimens of 6, 9 or 18 months' duration for spinal tuberculosis in patients ambulatory from the start or undergoing radical surgery. Fourteenth report of the Medical Research Council Working Party on Tuberculosis of the Spine. Int Orthop 1999;23(2):73-81.

173. Di Rocco A, Simpson DM. AIDS-associated vacuolar myelopathy. AIDS Patient Care STDS 1998;12(6):457-61.

174. Nieman L. Clinical manifestations of adrenal insufficiency. In: Rose B, ed. UpToDate. Waltham, MA: UpToDate; 2006.

175. Guttman P. Addison's disease. A statistical analysis of five hundred and sixty-six cases and a study of the pathology. Archives of Pathology 1930;10:742-85.

176. Hawken MP, Ojoo JC, Morris JS, et al. No increased prevalence of adrenocortical insufficiency in human immunodeficiency virus-associated tuberculosis. Tuber Lung Dis 1996;77(5):444-8.

177. Mugusi F, Swai AB, Turner SJ, Alberti KG, McLarty DG. Hypoadrenalism in patients with pulmonary tuberculosis in Tanzania: an undiagnosed complication? Trans R Soc Trop Med Hyg 1990;84(6):849-51.

178. Meya DB, Katabira E, Otim M, et al. Functional adrenal insufficiency among critically ill patients with human immunodeficiency virus in a resource-limited setting. Afr Health Sci 2007;7(2):101-7.

179. Nieman L. Causes of primary adrenal insufficiency (Addison's disease). In: Rose B, ed. UpToDate. Waltham, MA: UpToDate; 2006.

180. Nieman L. Treatment of adrenal insufficiency. In: Rose B, ed. UpToDate. Waltham, MA: UpToDate; 2006.

181. Clark TM, Burman WJ, Cohn DL, Mehler PS. Septic shock from Mycobacterium tuberculosis after therapy for Pneumocystis carinii. Arch Intern Med 1998;158(9):1033-5.

182. Ddungu H, Johnson JL, Smieja M, Mayanja-Kizza H. Digital clubbing in tuberculosis--relationship to HIV infection, extent of disease and hypoalbuminemia. BMC Infect Dis 2006;6:45.

183. Yechoor VK, Shandera WX, Rodriguez P, Cate TR. Tuberculous meningitis among adults with and without HIV infection. Experience in an urban public hospital. Arch Intern Med 1996;156(15):1710-6.

184. Katrak SM, Shembalkar PK, Bijwe SR, Bhandarkar LD. The clinical, radiological and pathological profile of tuberculous meningitis in patients with and without human immunodeficiency virus infection. J Neurol Sci 2000;181(1-2):118-26.

185. Berenguer J, Moreno S, Laguna F, et al. Tuberculous meningitis in patients infected with the human immunodeficiency virus. N Engl J Med 1992;326(10): 668-72.

186. Thwaites GE, Nguyen DB, Nguyen HD, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med 2004;351(17):1741-51.

187. Schutte CM. Clinical, cerebrospinal fluid and pathological findings and outcomes in HIV-positive and HIV-negative patients with tuberculous meningitis. Infection 2001;29(4):213-7.

188. Mwang'ombe NJ, Mwago JK. Intracranial tuberculomas at the Kenyatta National Hospital, Nairobi. East Afr Med J 2000;77(6):333-5.

189. Kennedy DH, Fallon RJ. Tuberculous meningitis. JAMA 1979;241(3):264-8.

190. Bergemann A, Karstaedt AS. The spectrum of meningitis in a population with high prevalence of HIV disease. QJM 1996;89(7):499-504.

191. Silber E, Sonnenberg P, Ho KC, et al. Meningitis in a community with a high prevalence of tuberculosis and HIV infection. J Neurol Sci 1999;162(1):20-6.

192. Hakim JG, Gangaidzo IT, Heyderman RS, et al. Impact of HIV infection on meningitis in Harare, Zimbabwe: a prospective study of 406 predominantly adult patients. AIDS 2000;14(10):1401-7.

193. Schutte CM, Van der Meyden CH, Magazi DS. The impact of HIV on meningitis as seen at a South African Academic Hospital (1994 to 1998). Infection 2000;28(1):3-7.

194. Rizal A, Wisaksana R, Parwati I, van Crevel R. Adult meningitis in HIV-positive and -negative patients in Indonesia: a cohort study. In: 5th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention, abstract CDB061. Capetown; 2009.

195. Cohen D, Zijlstra E, Mukaka M, et al. Distinguishing features of cryptococcal and tuberculous meningitis in adults in Malawi. In: 16th Conference on Retroviruses and Opportunistic Infections, abstract 791. Montreal; 2009.

196. Helbok R, Pongpakdee S, Yenjun S, et al. Chronic meningitis in Thailand. Clinical characteristics, laboratory data and outcome in patients with specific reference to tuberculosis and cryptococcosis. Neuroepidemiology 2006;26(1):37-44.

197. Dube MP, Holtom PD, Larsen RA. Tuberculous meningitis in patients with and without human immunodeficiency virus infection. Am J Med 1992;93(5):520-4.

198. Heyderman RS, Gangaidzo IT, Hakim JG, et al. Cryptococcal meningitis in human immunodeficiency virus-infected patients in Harare, Zimbabwe. Clin Infect Dis 1998;26(2):284-9.

199. Maher D, Mwandumba H. Cryptococcal meningitis in Lilongwe and Blantyre, Malawi. J Infect 1994;28(1):59-64.

200. Mohapatra MK. The natural history of complicated falciparum malaria--a prospective study. J Assoc Physicians India 2006;54:848-53.

201. Scarborough M, Gordon SB, Whitty CJ, et al. Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa. N Engl J Med 2007;357(24):2441-50.

202. Leonard J. Central nervous system tuberculosis. In: Rose B, ed. UpToDate. Waltham, MA: UpToDate; 2006.

203. Karstaedt AS, Valtchanova S, Barriere R, Crewe-Brown HH. Tuberculous meningitis in South African urban adults. QJM 1998;91(11):743-7.

204. Porkert MT, Sotir M, Parrott-Moore P, Blumberg HM. Tuberculous meningitis at a large inner-city medical center. Am J Med Sci 1997;313(6):325-31.

205. Sanchez-Portocarrero J, Perez-Cecilia E, Jimenez-Escrig A, et al. Tuberculous meningitis. Clinical characteristics and comparison with cryptococcal meningitis in patients with human immunodeficiency virus infection. Arch Neurol 1996;53(7):671-6.

206. Cox GM PJ. AIDS-associated cryptococcal meningoencephalitis. In: Rose B, ed. UpToDate. Waltham, MA: UpToDate; 2006.

207. Mwaba P, Mwansa J, Chintu C, et al. Clinical presentation, natural history, and cumulative death rates of 230 adults with primary cryptococcal meningitis in Zambian AIDS patients treated under local conditions. Postgrad Med J 2001;77(914):769-73.

208. Heller H. Toxoplasmosis in HIV-infected patients. In: Rose B, ed. UpToDate. Waltham, MA: UpToDate; 2007.

209. Porter SB, Sande MA. Toxoplasmosis of the central nervous system in the acquired immunodeficiency syndrome. N Engl J Med 1992;327(23):1643-8.

210. Sparling PF HC. Clinical manifestations of neurosyphilis. In: BD R, ed. UpToDate. Waltham, MA: UpToDate; 2006.

211. Hicks C. Serologic testing for syphilis. In: Rose B, ed. UpToDate. Waltham, MA: UpToDate; 2008.

212. Doweiko J, Groopman J. AIDS-related lymphomas: primary central nervous system lymphoma. In: Rose B, ed. UpToDate. Waltham, MA: UpToDate; 2006.

213. Drew R. Ethambutol: an overview. In: Rose B, ed. UpToDate. Waltham, MA: UpToDate; 2007.

214. Attributed to Mamlin J. Academic Model for the Prevention and Treatment of HIV/AIDS, Moi Teaching and Referral Center, Eldoret, Kenya.

215. Shelburne SA, Hamill RJ. The immune reconstitution inflammatory syndrome. AIDS Rev 2003;5(2):67-79.

216. Murdoch DM, Venter WD, Feldman C, Van Rie A. Incidence and risk factors for the immune reconstitution inflammatory syndrome in HIV patients in South Africa: a prospective study. AIDS 2008;22(5):601-10.

217. Lawn SD, Bekker LG, Myer L, Orrell C, Wood R. Cryptococcal immune reconstitution disease: a major cause of early mortality in a South African antiretroviral programme. AIDS 2005;19(17):2050-2.

218. Connick E, Kane MA, White IE, Ryder J, Campbell TB. Immune reconstitution inflammatory syndrome associated with Kaposi sarcoma during potent antiretroviral therapy. Clin Infect Dis 2004;39(12):1852-5.

219. Martin J, Laker M, Clutter D, et al. Kaposi's sarcoma-associated immune reconstitution inflammatory syndrome in Africa: initial findings from a prospective evaluation. In: 16th Conference on Retroviruses and Opportunistic Infections, abstract 31. Montreal; 2009.

220. Ratnam I, Chiu C, Kandala NB, Easterbrook PJ. Incidence and risk factors for immune reconstitution inflammatory syndrome in an ethnically diverse HIV type 1-infected cohort. Clin Infect Dis 2006;42(3):418-27.

221. Robertson J, Meier M, Wall J, Ying J, Fichtenbaum CJ. Immune reconstitution syndrome in HIV: validating a case definition and identifying clinical predictors in persons initiating antiretroviral therapy. Clin Infect Dis 2006;42(11):1639-46.

222. Shelburne SA, Montes M, Hamill RJ. Immune reconstitution inflammatory syndrome: more answers, more questions. J Antimicrob Chemother 2006;57(2): 167-70.

223. Stringer JS, Zulu I, Levy J, et al. Rapid scale-up of antiretroviral therapy at primary care sites in Zambia: feasibility and early outcomes. JAMA 2006; 296(7):782-93.

224. Zampoli M, Kilborn T, Eley B. Tuberculosis during early antiretroviral-induced immune reconstitution in HIV-infected children. Int J Tuberc Lung Dis 2007;11(4):417-23.

225. Meintjes G. WR, Morron C., Pepper D., Rebe K., Rangaka M., Oni T., and Maartens G. Randomized placebo-controlled trial of prednisone for the TB immune reconstitution inflammatory syndrome. In: 16th Conference on Retroviruses and Opportunistic Infections, Abstract 34. Montreal; 2009.

226. Drug side-effects place treatment scale-up at risk, says Ugandan HIV expert. www.aidsmap.com, 2004. (Accessed at http://aidsmap.com/en/news/C303AF5E-8CDA-431D-9D67-866C1217BCEA.asp.)

227. Haddow L, Moosa Y, Moodley P, et al. Using TB screening and pre-ART serology to predict immune reconstitution inflammatory syndrome in a resource-limited setting with high TB and HIV prevalence. In: 16th Conference on Retroviruses and Opportunistic Infections, abstract 767. Montreal; 2009.

228. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. Lancet Infect Dis 2008;8(8):516-23.

229. Manosuthi W, Van Tieu H, Mankatitham W, et al. Clinical case definition and manifestations of paradoxical tuberculosis (TB) immune reconstitution inflammatory syndrome (IRIS). In: 5th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention, abstract TUPEB158. Capetown; 2009.

230. Lawn SD, Wilkinson RJ, Lipman MC, Wood R. Immune reconstitution and "unmasking" of tuberculosis during antiretroviral therapy. Am J Respir Crit Care Med 2008;177(7):680-5.

231. Cheng VC, Ho PL, Lee RA, et al. Clinical spectrum of paradoxical deterioration during antituberculosis therapy in non-HIV-infected patients. Eur J Clin Microbiol Infect Dis 2002;21(11):803-9.

232. Breen RA, Smith CJ, Bettinson H, et al. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. Thorax 2004;59(8):704-7.

233. Puthanakit T, Oberdorfer P, Akarathum N, Wannarit P, Sirisanthana T, Sirisanthana V. Immune reconstitution syndrome after highly active antiretroviral therapy in human immunodeficiency virus-infected Thai children. Pediatr Infect Dis J 2006;25(1):53-8.

234. Howard A, Saito S, Nash D, et al. On-site location of TB services is associated with TB screening of HIV-infected patients at enrollment in HIV care programs: 6 Sub-Saharan African countries. In: 16th Conference on Retroviruses and Opportunistic Infections, abstract 590. Montreal; 2009.

235. Narita M, Ashkin D, Hollender ES, Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. Am J Respir Crit Care Med 1998;158(1):157-61.

236. John L, Baalwa J, Kalimugogo P, et al. Response to 'Does immune reconstitution promote active tuberculosis in patients receiving highly active antiretroviral therapy?' AIDS, 22 July 2005. AIDS 2005;19(17):2049-50.

237. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents in resource-limited settings: towards universal access. Recommendations for a public health approach. 2006 ed. Geneva: World Health Organization; 2006.

238. Drew R. Rifampicin: an overview. In: Rose B, ed. UpToDate. Waltham, MA: UpToDate; 2006.

239. Manosuthi W, Tantanathip P, Prasithisirikul W, Likanonsakul S, Sungkanuparph S. Durability of stavudine, lamivudine and nevirapine among advanced HIV-1 infected patients with/without prior co-administration of rifampicin: a 144-week prospective study. BMC Infect Dis 2008;8:136.

240. Bonnet M, Bhatt NB, Jani IV, et al. Pharmacokinetic (pk) parameters of nevirapine (NVP) when initiated without 2-weeks leading dose in tuberculosis (TB)-HIV co-infected patients receiving rifampicin (RMP): substudy of the CARINEMO- ANRS 12146 trial in Maputo (Mozambique). In: 5th International AIDS Society Conference on Pathogenesis, Treatment and Prevention, abstract WEPEB253. Capetown; 2009.

241. Boulle A, Van Cutsem G, Cohen K, et al. Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. JAMA 2008;300(5):530-9.

242. Patel A, Patel K, Patel J, Shah N, Patel B, Rani S. Safety and antiretroviral effectiveness of concomitant use of rifampicin and efavirenz for antiretroviral-naive patients in India who are coinfected with tuberculosis and HIV-1. J Acquir Immune Defic Syndr 2004;37(1):1166-9.

243. Manosuthi W, Kiertiburanakul S, Sungkanuparph S, et al. Efavirenz 600 mg/day versus efavirenz 800 mg/day in HIV-infected patients with tuberculosis receiving rifampicin: 48 weeks results. AIDS 2006;20(1):131-2.

244. Lartey V, Sagoe K, Kenu E, et al. Early responses to efavirenz-based HAART in HIV/TB co-infected patients on concurrent TB therapy is not different from that in HIV-infected patients. In: 5th International AIDS Society Conference on Pathogenesis, Treatment and Prevention, TUPEB126. Capetown; 2009.

245. Ello NF, Moutomé K, Tanon A, Adjé C, Eholié S, Bissagnene E. A randomized clinical trial of efavirenz 600 mg/day versus 800 mg/day in HIV-infected patients with tuberculosis receiving rifampicin in Abidjan (Cote d'Ivoire). In: 5th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, abstract TUPEB142. Capetown; 2009.

246. Larson AM, Graziani AL. Isoniazid hepatotoxicity. In: Rose B, ed. UpToDate. Waltham, MA: UpToDate; 2006.

247. LoBue PA, Moser KS. Use of isoniazid for latent tuberculosis infection in a public health clinic. Am J Respir Crit Care Med 2003;168(4):443-7.

248. Drew R. Isoniazid: an overview. In: Rose B, ed. UpToDate. Waltham, MA: UpToDate; 2006.

249. Shlay JC, Chaloner K, Max MB, et al. Acupuncture and amitriptyline for pain due to HIV-related peripheral neuropathy: a randomized controlled trial. Terry Beirn Community Programs for Clinical Research on AIDS. JAMA 1998;280(18):1590-5.

250. Kieburtz K, Simpson D, Yiannoutsos C, et al. A randomized trial of amitriptyline and mexiletine for painful neuropathy in HIV infection. AIDS Clinical Trial Group 242 Protocol Team. Neurology 1998;51(6):1682-8.

251. Drew R. Pyrazinamide: an overview. In: Rose B, ed. UpToDate. Waltham, MA: UpToDate; 2007.

252. Drew R. Second-line antituberculous therapy. In: Rose B, ed. UpToDate. Waltham, MA: UpToDate; 2008.

253. World Health Organization. Treatment of tuberculosis: guidelines for national programmes. Geneva: World Health Organization; 2004.

254. Greenberg AE, Lucas S, Tossou O, et al. Autopsy-proven causes of death in HIV-infected patients treated for tuberculosis in Abidjan, Cote d'Ivoire. AIDS 1995;9(11):1251-4.

255. Martinson N, Variava E, Chaudhary M, et al. Early mortality in a prospective cohort of hospitalized adults with a presumptive diagnosis of TB. In: 16th Conference on Retroviruses and Opportunistic Infections, abstract 789. Montreal; 2009.

256. Ackah AN, Coulibaly D, Digbeu H, et al. Response to treatment, mortality, and CD4 lymphocyte counts in HIV-infected persons with tuberculosis in Abidjan, Cote d'Ivoire. Lancet 1995;345(8950):607-10.

257. Blanc FX, Havlir DV, Onyebujoh PC, Thim S, Goldfeld AE, Delfraissy JF. Treatment strategies for HIV-infected patients with tuberculosis: ongoing and planned clinical trials. J Infect Dis 2007;196 Suppl 1:S46-51.

258. Wiktor SZ, Sassan-Morokro M, Grant AD, et al. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Cote d'Ivoire: a randomised controlled trial. Lancet 1999;353(9163):1469-75.

259. Saag KG FD. Major side effects of systemic glucocorticoids. In: Rose B, ed. UpToDate. Waltham, MA: UpToDate; 2007.

260. Corpe RF, Hwa EC. A correlated bronchographic and histopathologic study of bronchial disease in 216 tuberculous patients. Am Rev Tuberc 1956;73(5):681-9.

261. Olson DE, Jones FS, Angevine DM. Bronchial disease in lungs resected for pulmonary tuberculosis. Am Rev Tuberc 1953;68(5):657-77.

262. Dheda K, Booth H, Huggett JF, Johnson MA, Zumla A, Rook GA. Lung remodeling in pulmonary tuberculosis. J Infect Dis 2005;192(7):1201-9.

263. Barker A. Treatment of bronchiectasis. In: Rose B, ed. UpToDate. Waltham, MA: UpToDate; 2007.

264. Meduri GU, Stover DE, Lee M, Myskowski PL, Caravelli JF, Zaman MB. Pulmonary Kaposi's sarcoma in the acquired immune deficiency syndrome. Clinical, radiographic, and pathologic manifestations. Am J Med 1986;81(1):11-8.

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