Screening and diagnosis of TB in HIV positive patients

TB/HIV

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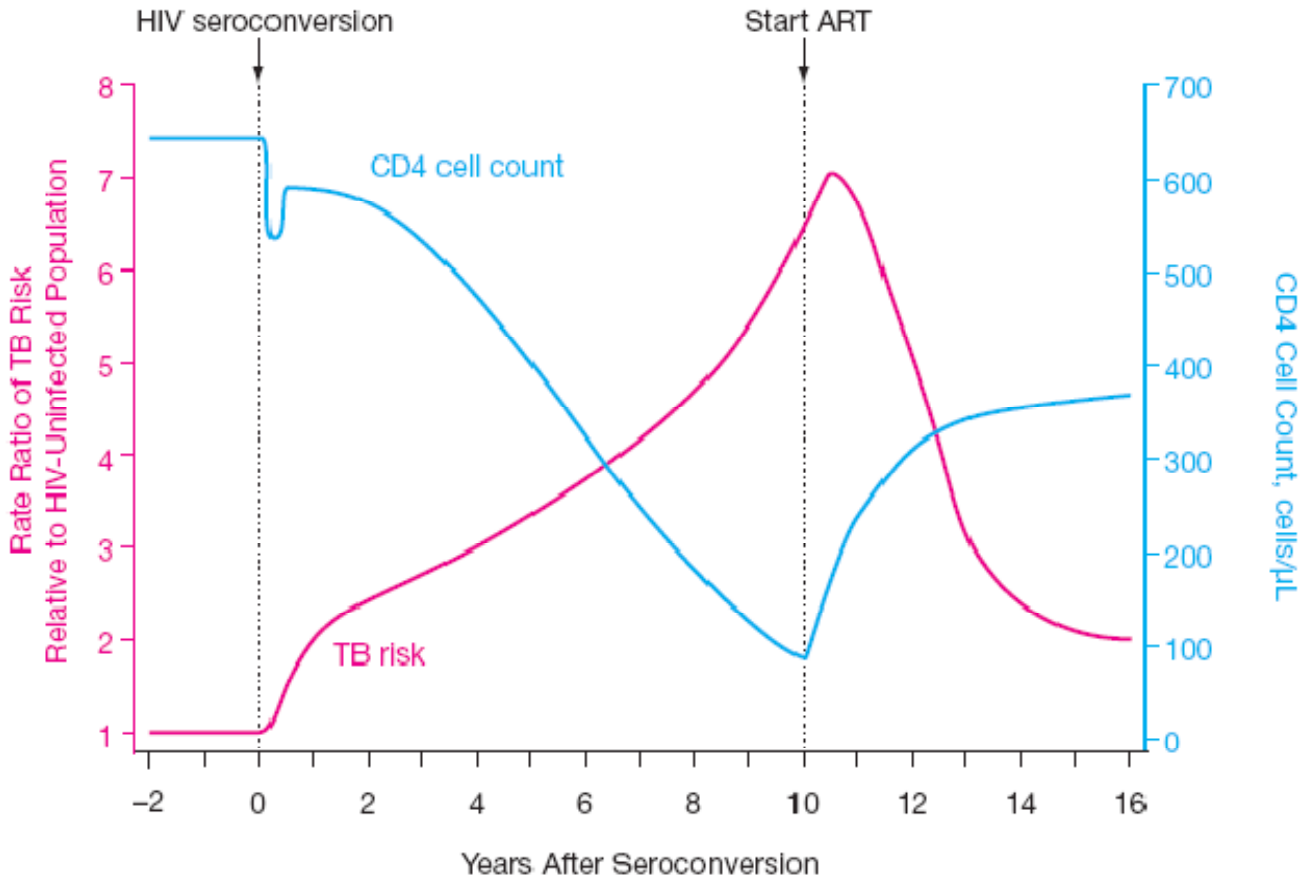
TB- HIV

- Two thirds of the world population, or nearly two billion people, is infected with the tuberculosis bacillus
- About 33 million people were living with HIV by the end of 2007
- The convergence of the two epidemics affects about 11 million people

Journal of the International AIDS Society 2008, **11**:6

HIV influences TB

- Increasing the risk of reactivation of latent TB infection
- Rapid progression of new TB infection to disease
- Recurrent disease from both re-infection and relapse


HIV seroconversion
Start ART
CD4 cell count
TB risk
Rate Ratio of TB Risk
Relative to HIV-Uninfected Population
CD4 Cell Count, cells/μL
Years After Seroconversion
1
2
3
4
5
6
7
8
0
100
200
300
400
500
600
700
−2
0
2
4
6
8
10
12
14
16

Clinical manifestation

Pulmonary Disease

- Although HIV-infected persons with TB may have the classic symptoms of TB, many such patients have few symptoms or have symptoms that are even less specific than those mentioned.
- Small proportion of HIV infected patient with TB are minimally symptomatic or asymptomatic.
- UP to 22% have normal X-RAY

Clinical Infectious Diseases 2010; 50(S3):S223–S230

Clinical manifestation

Smear Negative pulmonary disease

- Smear negative pulmonary TB is more common
- Mortality is higher among this group

Clinical Infectious Diseases 2010; 50(S3):S223–S230

Clinical manifestation

Sub clinical TB

- Often the manifestation of TB do not become apparent until the patient has initiated ART.
- Sub clinical TB represent early stage of TB that will inevitably progress to overt disease

Clinical Infectious Diseases 2010; 50(S3):S223–S230

Clinical manifestation

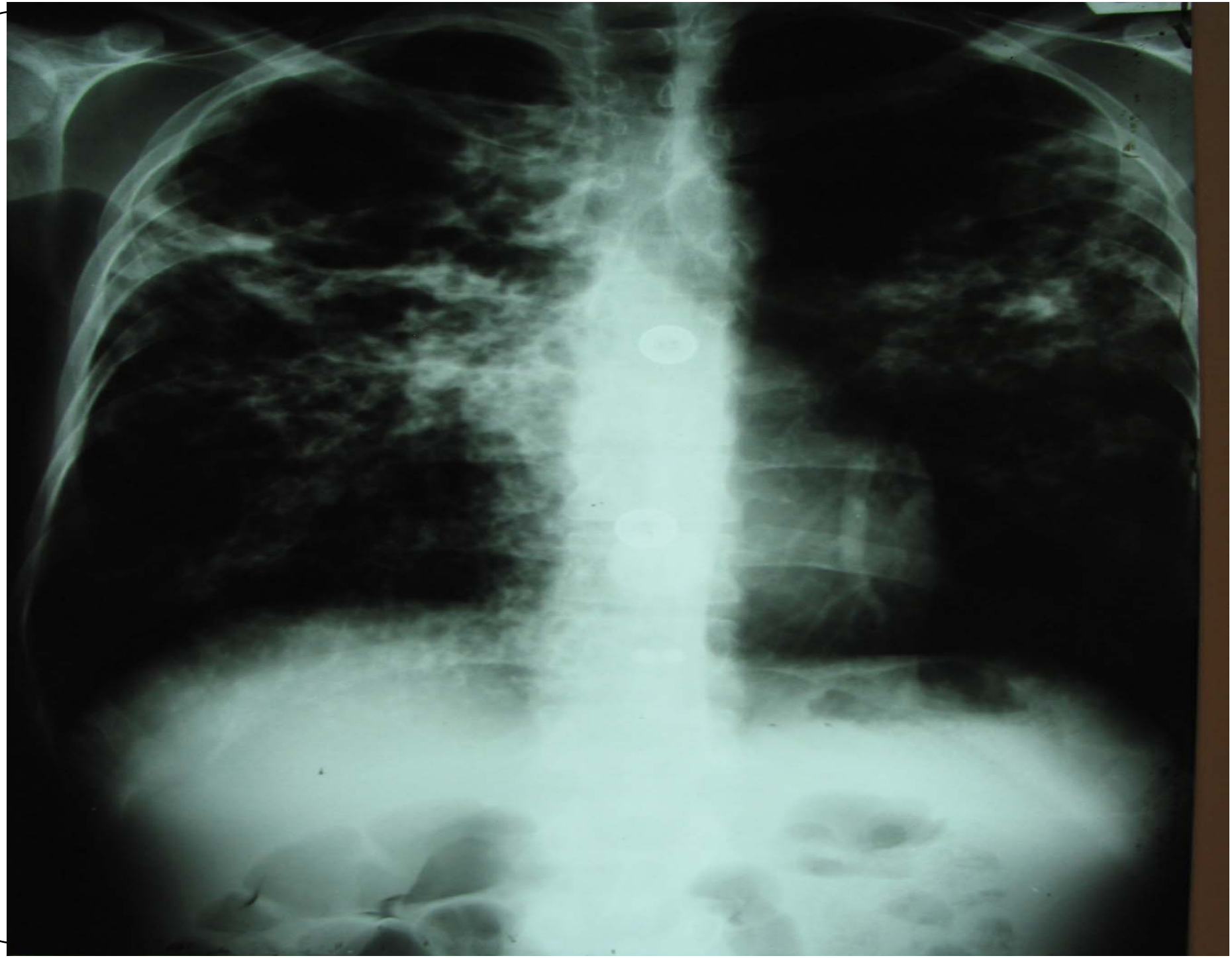
Extra-pulmonary Disease

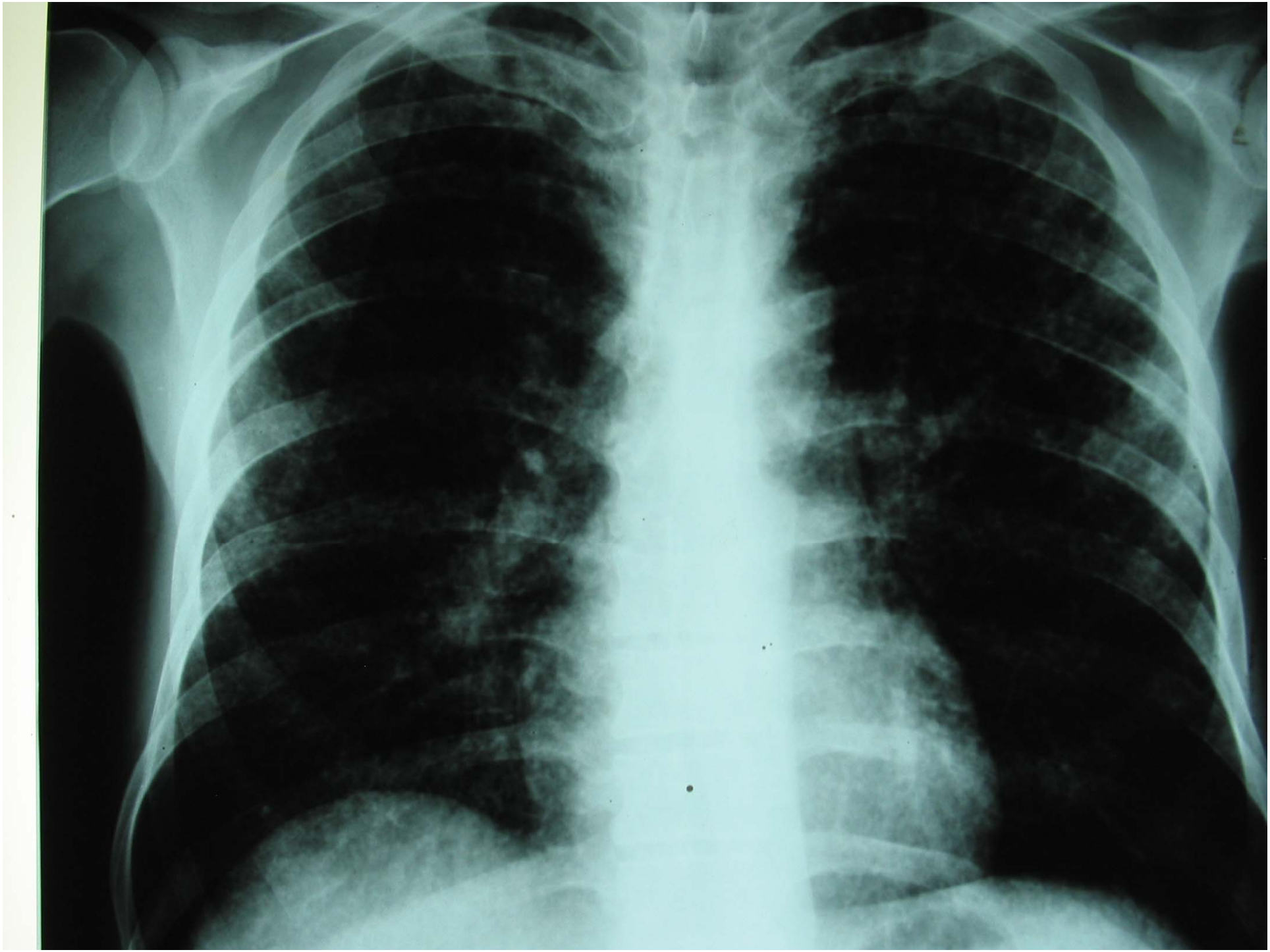
- 40-80%of HIV infected person with TB have extra pulmonary disease

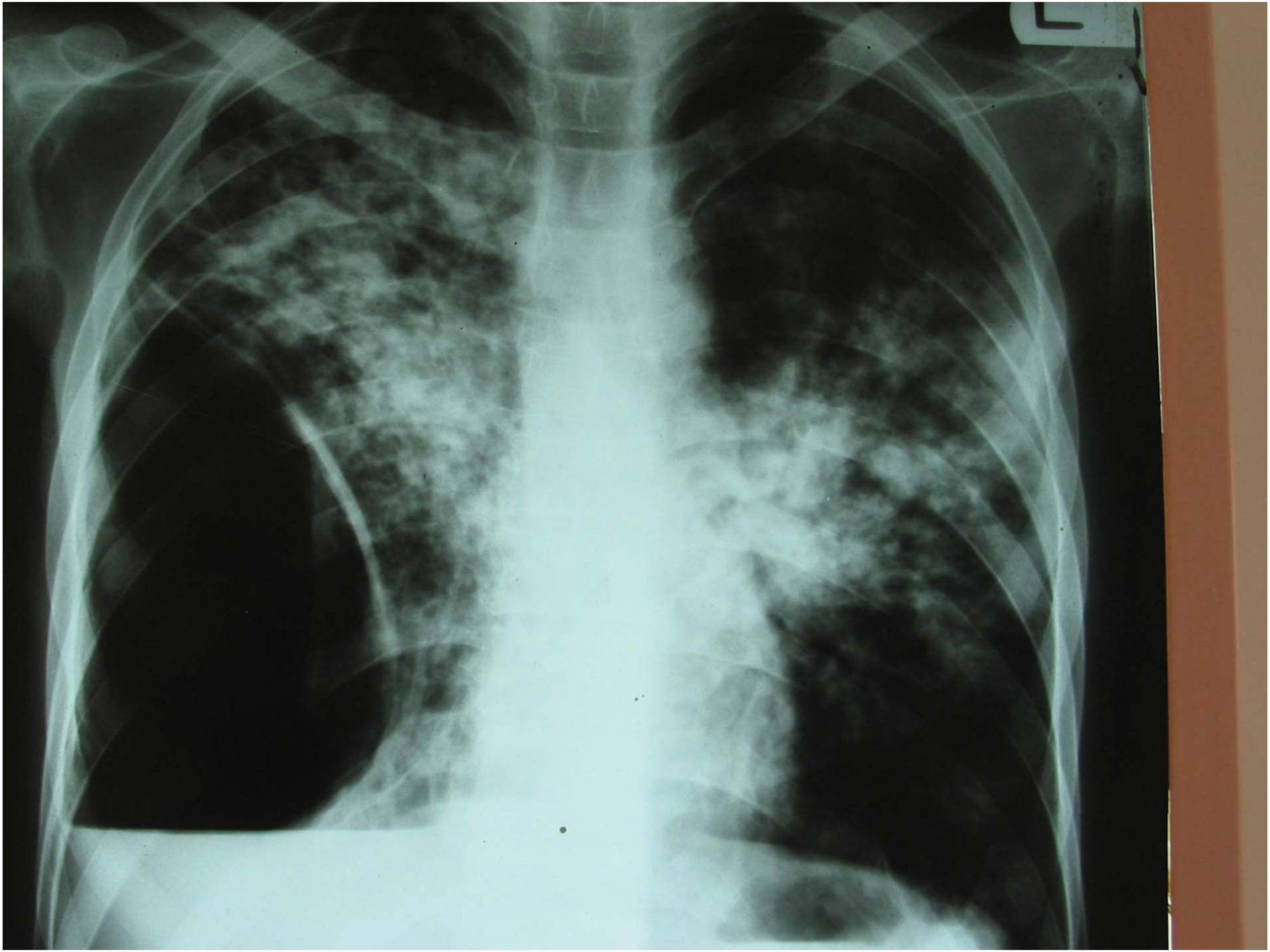
- The risk of extra pulmonary disease increases with lower CD4 count

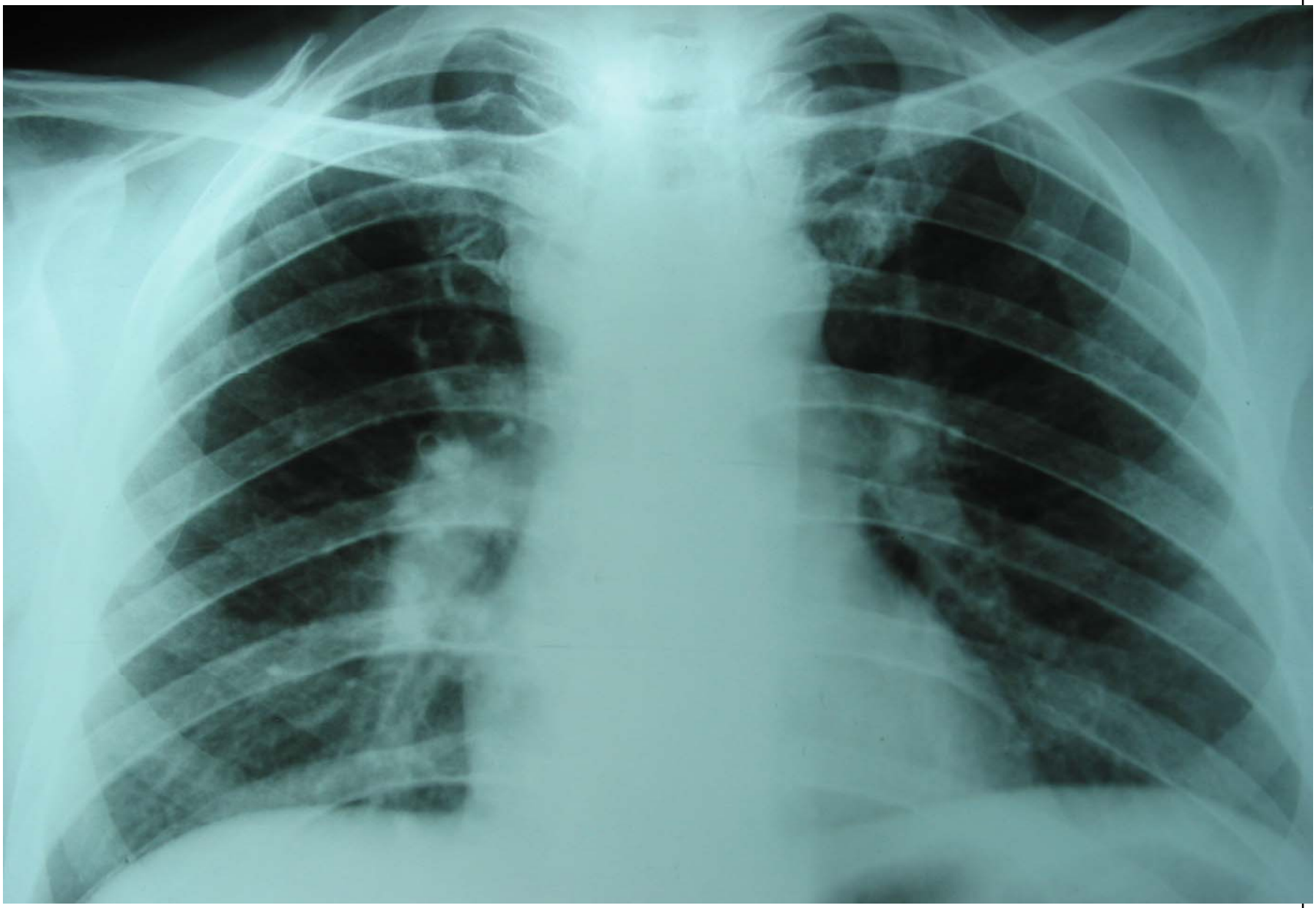
Clinical Infectious Diseases 2010; 50(S3):S223–S230

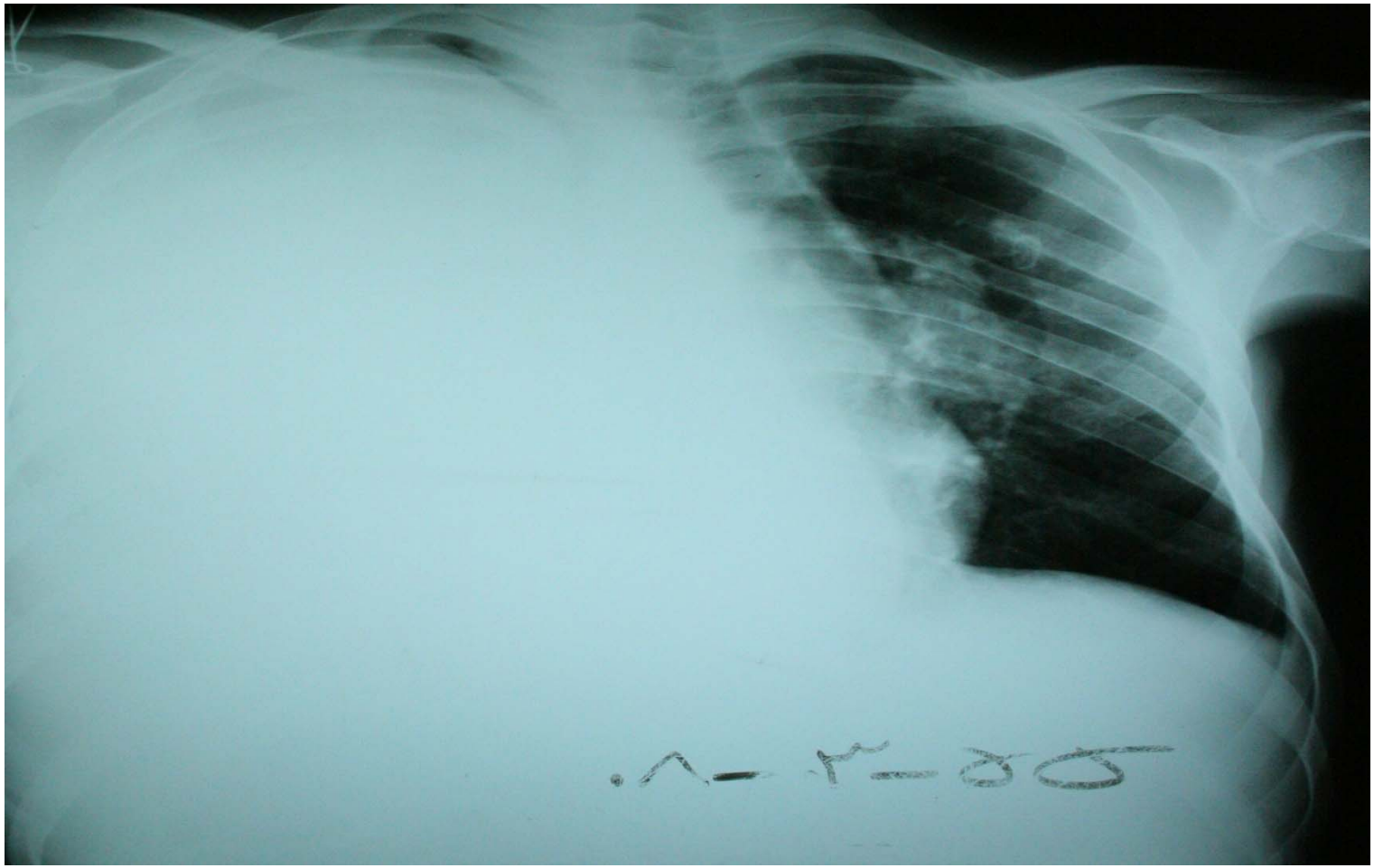
- The most common forms are lymphatic and pleural







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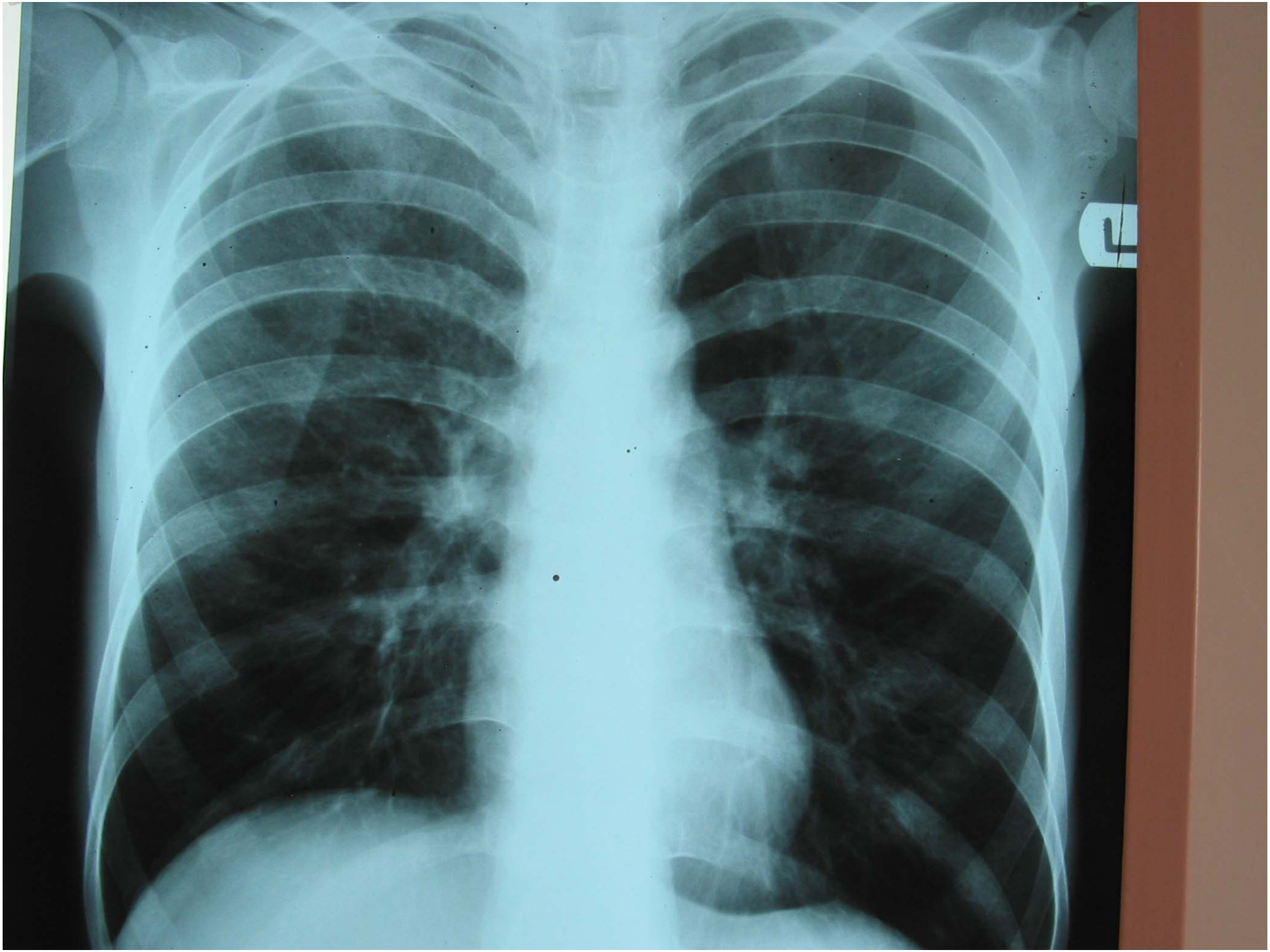


- A 29-year-old single man presented with 2 months history of fever and chills accompanied by intermittent productive cough and abdominal pain

- He was an intravenous drug abuser and a heavy smoker.
- He had spent 3 months in jail.
- His HIV and HCV serology tests had been reported positive since 4 years earlier.
- He gave no history of contact with a tuberculosis patient and did not mention further medical problems

- His chest x-ray was normal and he had a CD4 count of 45 one month ago.

- He was not on any medication or prophylaxis.

- On clinical examination, the patient was febrile.
- All physical findings were normal except for fever and hepatosplenomegaly.
- Laboratory studies revealed a microcytic anemia (Hgb: 6.2) and elevated erythrocyte sedimentation rate (1 hour: 120), highly elevated alkaline phosphatase and absolute CD4 count of 23.
- PPD and sputum smear were negative for Mycobacterium tuberculosis (MTB).

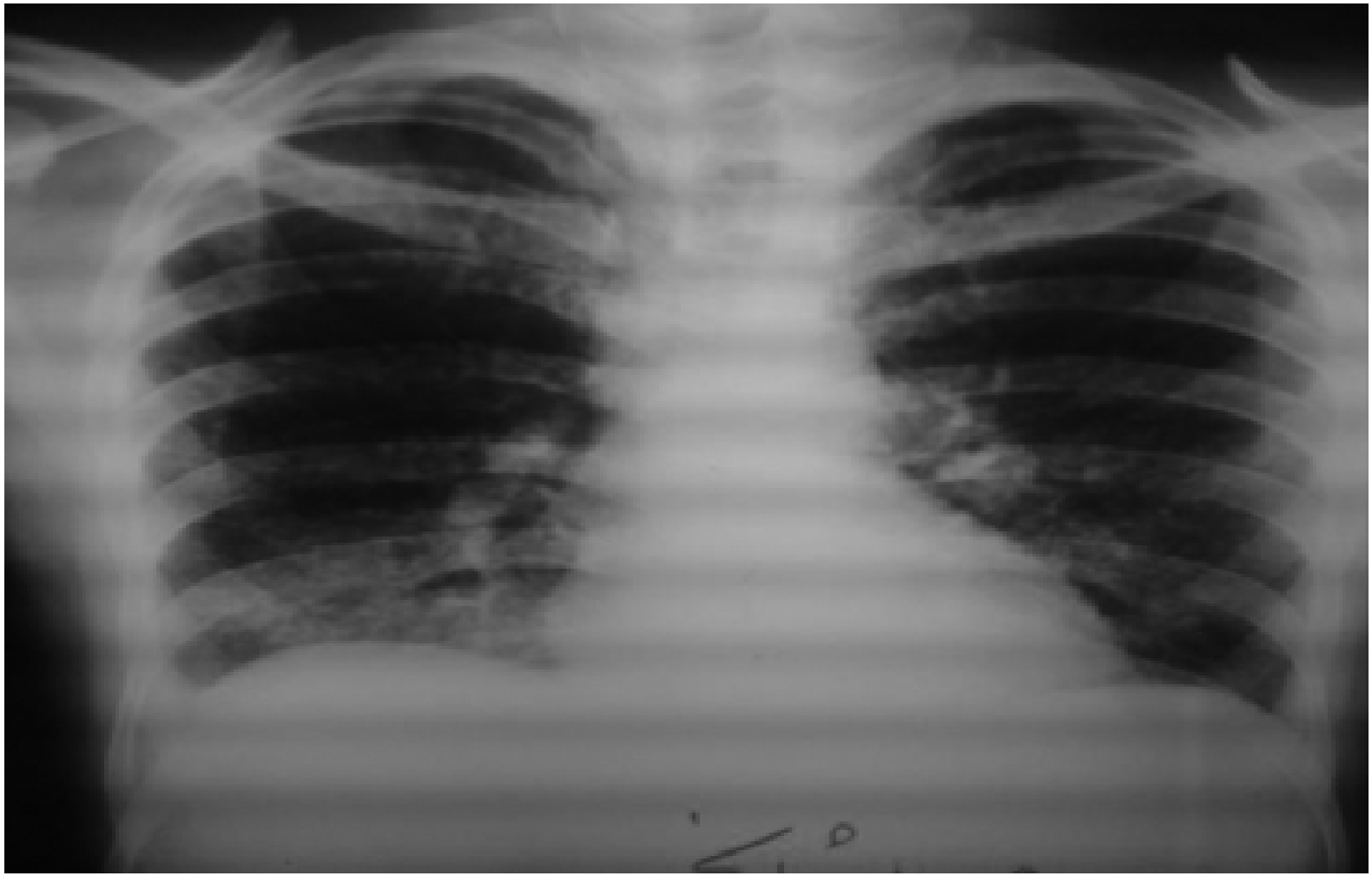


Figure 1. CXR of the patient.

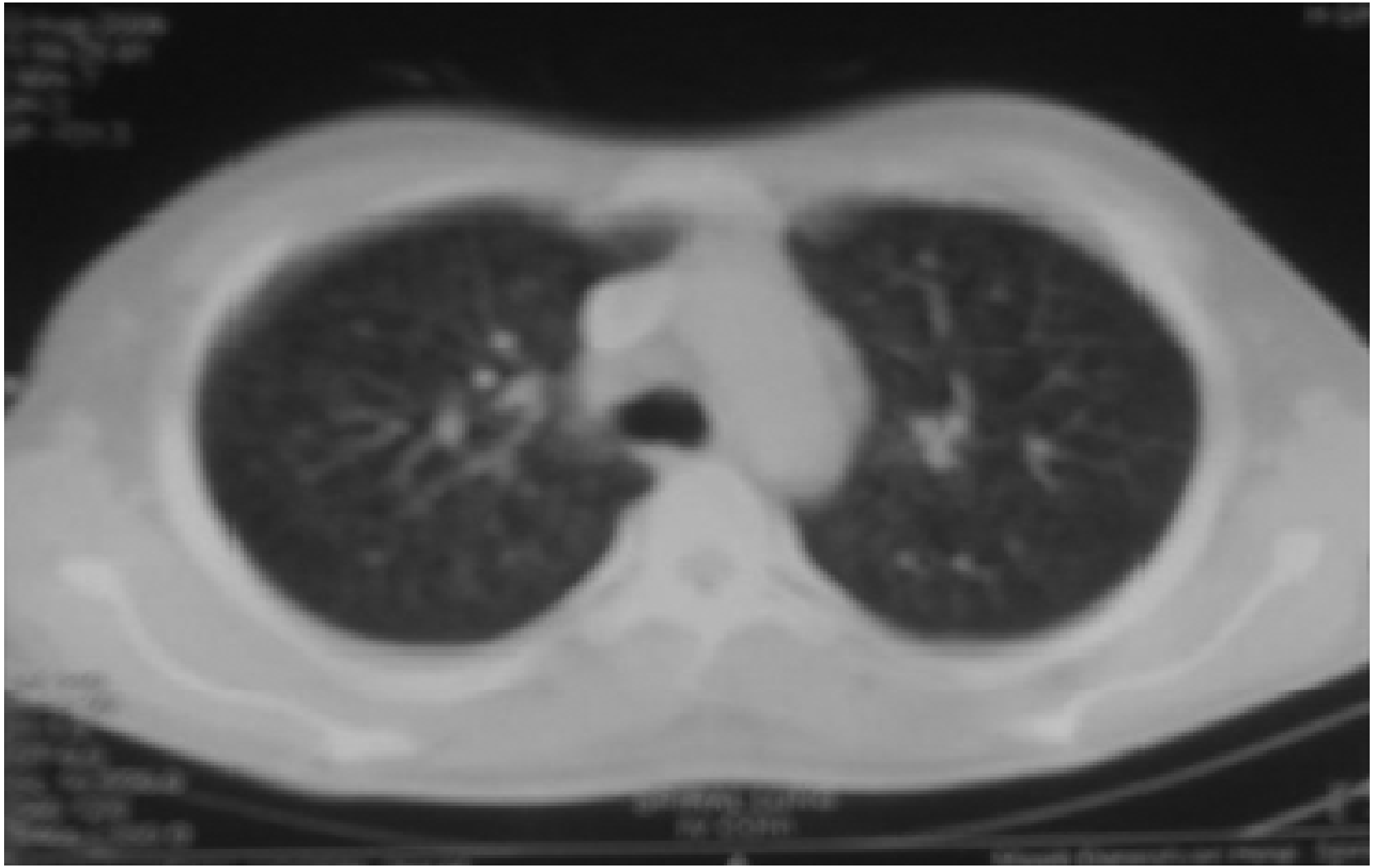


Figure 2. Spiral CT-scan of the patient.

Diagnosis

Diagnosis of TB

- Microscopic detection
- Growth-based detection
- Antigen detection(TAUNS,ESAT-6,LIPOARABINOMANAN)
- Molecular detection
- Antibody detection
- IGRA

Bacteriology

Sputum microscopy

Simplest, quickest, most reliable and most economical

- Available
- Cheap
- Rapid

- High predictive value (>90%) the prevalence of tuberculosis in the population tested is > 10%
- Specificity of 98%
- Correlate with infectiousness

Identification of 70% of bacteriologically positive TB pulmonary cases

Culture

- The only definitive diagnosis of tuberculosis– 99% specificity
- Detect lower numbers of AFB/ml (10 -100/ml)
- Makes possible the identification of mycobacterial species
- Essential role in case classification – non viable bacillus may remain microscopically visible even 5 months or more after treatment
- Adds 20-30% to the total number of bacteriologically confirmed cases

Disadvantages of culture

- Specially trained and skilled staff
- Long interval before results are available
- Special facilities - permanent supply of water and electricity
- Costly equipment
- Reliable thermoregulation of hot room
- Biosafety measures

Radiology

- No radiographic pattern is diagnostic of TB!
- The chest radiography is unrealiable as unique tool in the diagnosis or follow up of TB cases!
- Unreliable: observers errors (inter and intra observer variation), over and under-reading, influence of experience.
- Atypical radiographic pattern seen in patients with TB/HIV

- The second and third smears and PCR of the sputum for MTB complex turned positive for acid fast bacteria (AFB).

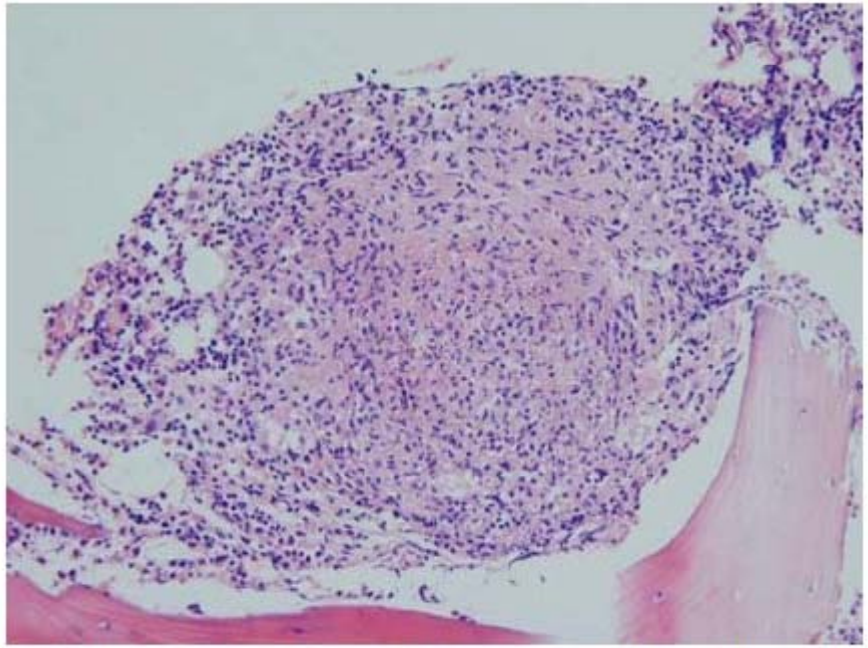


Figure 3. Bone marrow biopsy: Chronic granulomatous inflammation (H&E, LP)

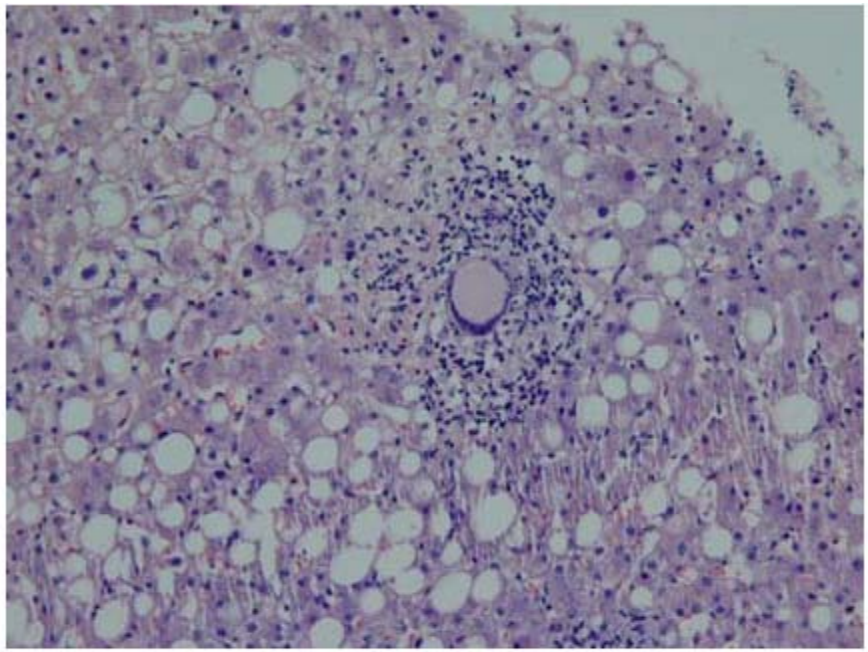


Figure 4. Liver biopsy: well formed granuloma, composed of epithelioid histiocytes, multinucleated giant cell and rim of small lymphosytes(H&E, HP)

- A regimen of isoniazid, ethambutol, pyrazinamide and rifampin accompanied by efavirenz, lamivudine, zidovudine and co-trimoxazole (prophylactic dose) was started for the patient.
- After two months of treatment, the patient is doing well and is supposed to complete six months of anti-TB medication and lifelong antiretroviral therapy (ART).

- Sputum at 2,5and 6 month was negative.
- Treatment of TB was stopped and patient was recorded as cure.
- At the end of 3 month patient discontinued ART.

- 20 days after stopping treatment patient readmitted to hospital due to fever,cough,night sweat and lung infiltration.

- Sputum smear :positive
- PCR for MTB:Positive
- DST:Resistance to RIF

GENOTYPIC (Molecular) TESTS

A. Line Probe Assay (LPA)

1. Inno-Lipa

- Tested and validated in Culture

2. GenoType MDR-TB Assay (Hain Test)

- Tested and validated in Culture
- Good Reproducibility in Direct Sputum (1 day)

B. GeneXpert System (Cepheid)

- Real Time PCR
- Tested and validate in Direct Sputum (2 hours)

Cepheid

MTB / Rif-resistance test

Workflow
- sputum
- simple 1-step external sample prep. procedure
- time-to-result < 2 h
- throughput: ≥ 16 tests / day / module
- no need for biosafety cabinet
- integrated controls
- true random access

Performance
- specific for MTB
- sensitivity better than smear, similar to culture
- detection of R resistance via *rpoB* gene

Product and system design
- test cartridges for GeneXpert System
- several GeneXpert modules can be combined in 1 workstation
- swap replacement of detection unit
- ~1 day technician training for non-mycobacteriologists

FIND
FOUNDATION FOR INNOVATIVE NEW DIAGNOSTICS

Intensified TB case finding

- When screened for TB up to 25% of people living with HIV will have prevalent TB and an additional 11% will have incident TB.

- Persons initiating ART who develop TB have an increased risk of death which may reach 15–20%.

AIDS 2006,**20:**1605-1612

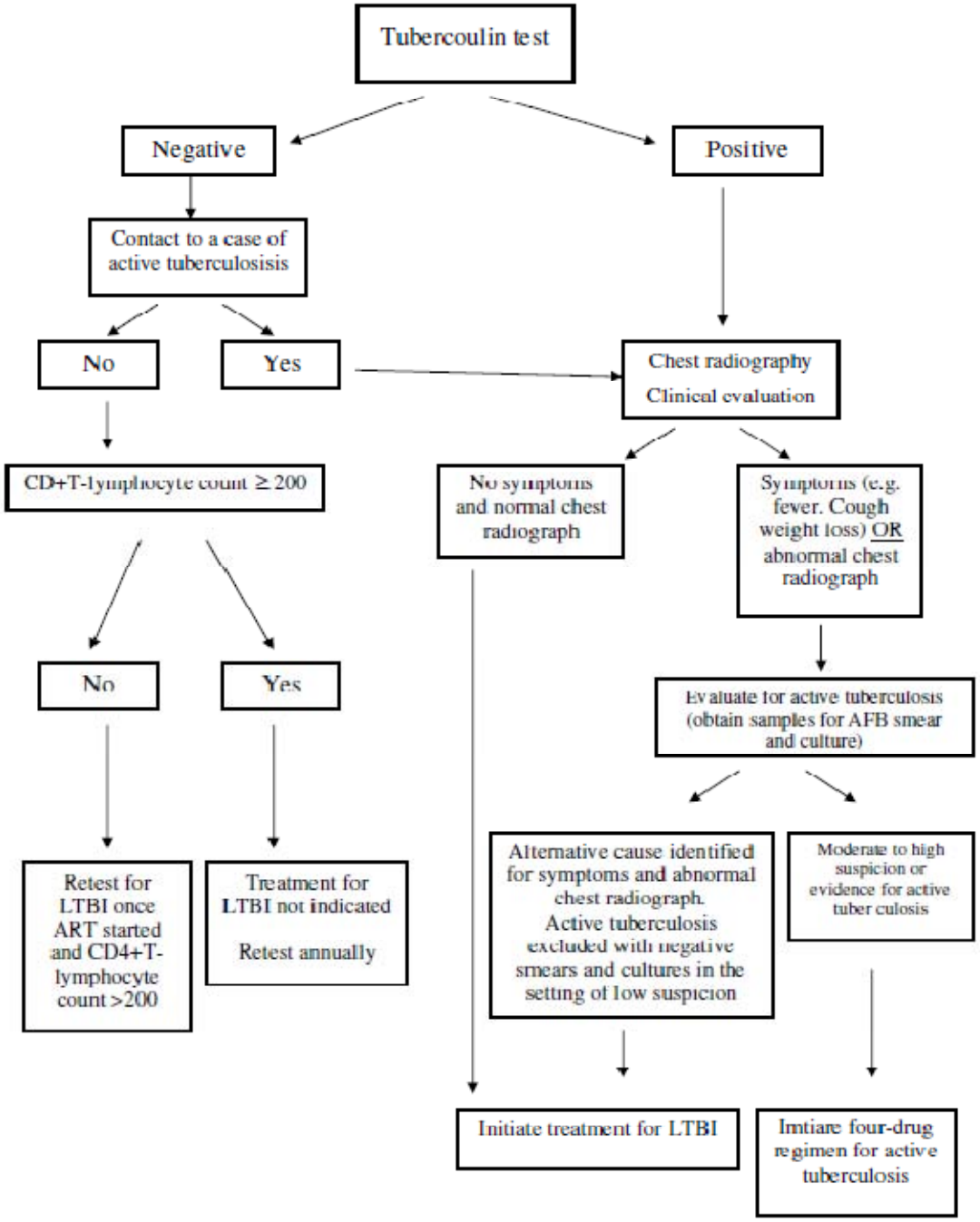
Activity	Purpose	Frequency/Indication
Intensified case finding	Early identification and treatment of TB; rapid identification of multidrug-resistant and extensively drug-resistant TB	Entry to HIV care; routine clinic visits; household contacts of TB cases
Treatment of TB cases	Successfully treat TB, deliver antiretroviral therapy and TB compatible regimens as indicated, provide cotrimoxazole and manage immune reconstitution events	For each TB episode
Isoniazid preventive treatment	Prevent TB	Isoniazid preventive therapy for every patient after excluding active TB
Antiretroviral therapy	Prevent TB	According to national guidelines
Infection control	Reduce TB transmission	Continuous
TB reporting	Contribute to national and global TB monitoring efforts	Report isoniazid preventive therapy, TB cases, and drug resistance to TB control programs on annual basis
Joint HIV/TB planning	Coordinate HIV/TB action at all levels	HIV/TB coordinating body with at least bi-annual meetings

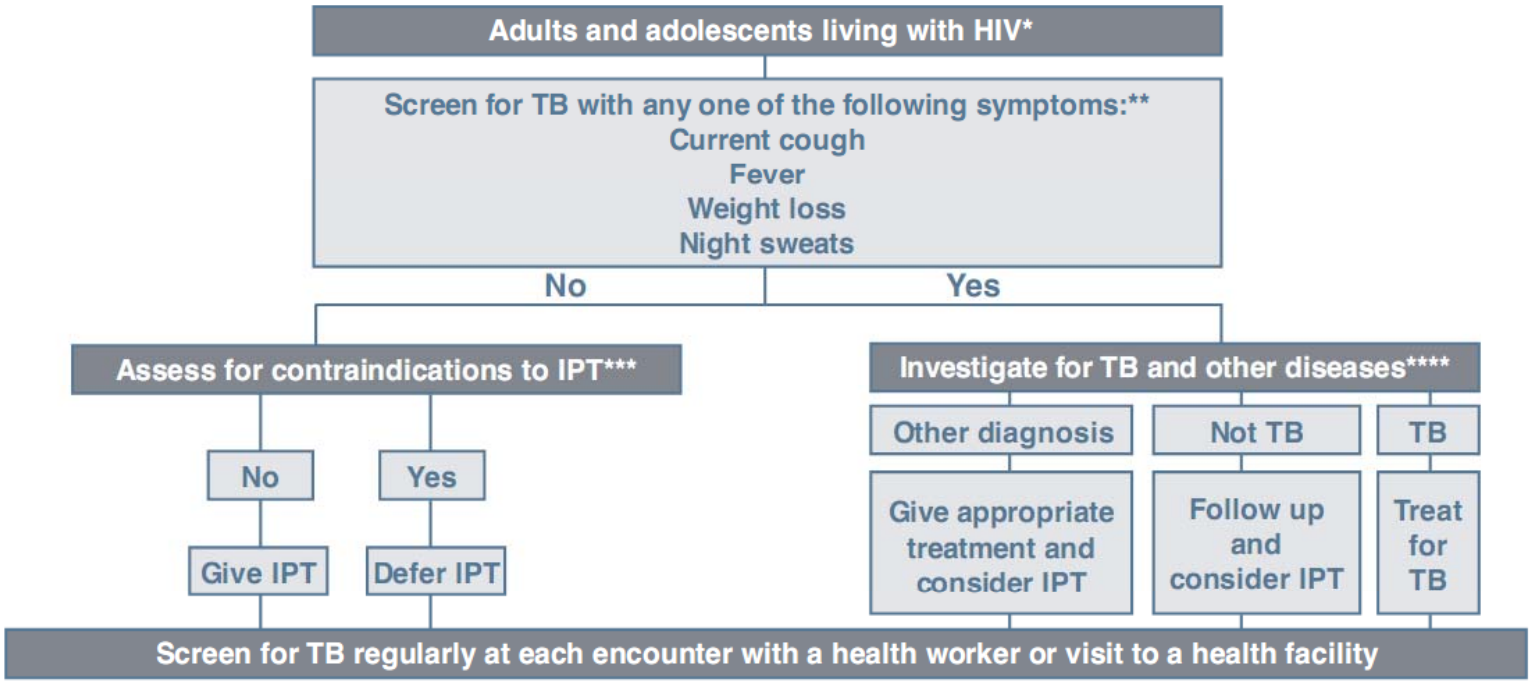
TABLE 10.1 **WHO-recommended collaborative TB/HIV activities**[a]

A. ESTABLISH THE MECHANISMS FOR COLLABORATION
A.1 Set up a coordinating body for TB/HIV activities effective at all levels
A.2 Conduct surveillance of HIV prevalence among TB patients
A.3 Carry out joint TB/HIV planning
A.4 Conduct monitoring and evaluation
B. DECREASE THE BURDEN OF TB IN PEOPLE LIVING WITH HIV/AIDS
B.1 Establish intensified TB case-finding and contact tracing
B.2 Introduce isoniazid preventive therapy
B.3 Ensure TB infection control in health-care and congregate settings
C. DECREASE THE BURDEN OF HIV IN TB PATIENTS
C.1 Provide HIV testing and counselling
C.2 Introduce HIV prevention methods
C.3 Introduce co-trimoxazole preventive therapy
C.4 Ensure HIV/AIDS care and support
C.5 Introduce antiretroviral therapy

[a] A detailed description of each of the activities listed in Table 10.1 can be found in the WHO document *Interim policy on collaborative TB/HIV activities* (*10*).

Figure1.Schema for the Diagnosis of LTBI




Adults and adolescents living with HIV*
Screen for TB with any one of the following symptoms:**
Current cough
Fever
Weight loss
Night sweats
No
Yes
Assess for contraindications to IPT***
Investigate for TB and other diseases****
No
Yes
Other diagnosis
Not TB
TB
Give IPT
Defer IPT
Give appropriate treatment and consider IPT
Follow up and consider IPT
Treat for TB
Screen for TB regularly at each encounter with a health worker or visit to a health facility

Isoniazid preventive therapy

- The incidence of HIV associated TB could be effectively reduced but IPT had no impact on all cause mortality.
- The protective effect diminishes with time and lasts one to three years on average.
- In the short term expansion of Isoniazid resistance may not be a major outcome of IPT

Cochrane Database of Systematic Reviews 2004

Anti-retroviral therapy and IPT

- A recent retrospective study carried out in Rio D Janeiro, Brazil, suggests that the combination of ART and IPT has the greatest impact on TB incidence when compared to IPT or ART alone

AIDS 2007, **21:**1441-144

Source	Setting	No. of Patients in the Cohort	TB Incidence Rates per 100 Person-Years		Comment
			With Antiretroviral Therapy	Without Antiretroviral Therapy	
Seyler et al,[17] 2005	Abidjan, Côte d'Ivoire	129	4.8	NA	TB incidence 11.3 per 100 person-years with prior TB; 3.0 per 100 person-years with no prior TB
Badri et al,[8] 2002	Cape Town, South Africa	1034	2.4	9.7	Adjusted relative risk, 0.19; 95% CI, 0.09-0.38 for antiretroviral therapy vs no antiretroviral therapy
Brinkhof et al,[18] 2007	Africa Latin America Asia	4540	10.7 (1-3 mo) 7.5 (4-6 mo) 5.2 (7-12 mo)	NA	
Lawn et al,[11] 2005	Cape Town, South Africa	346	3.35 (year 1) 1.56 (year 2) 1.36 (year 3) 0.90 (year 4) 1.01 (year 5)	NA	
Bonnet et al,[19] 2006	Cambodia Kenya Malawi Cameroon	3151	4.8-17.6 (pulmonary TB) 0-12.7 (extrapulmonary TB)	NA	
Golub et al,[9] 2007	Rio de Janeiro, Brazil	11 026	1.90	4.01	Rates with isoniazid preventive therapy plus antiretroviral therapy, 0.80 per 100 person-years
Moore et al,[20] 2007	Tororo, Uganda	1044	3.9	NA	
Lawn et al,[10] 2006	Gugulethu Community Healthcenter, South Africa	1002	23.0 (1-3 mo) 10.7 (3-6 mo) 7.0 (6-12 mo) 3.7 (12-24 mo) 7.4 (> 2 y)	NA	67% of patients with previous or prevalent TB at start of antiretroviral therapy
Walters et al,[21] 2008	Cape Town, South Africa	290	6.4	53.3	Pediatric cohort study