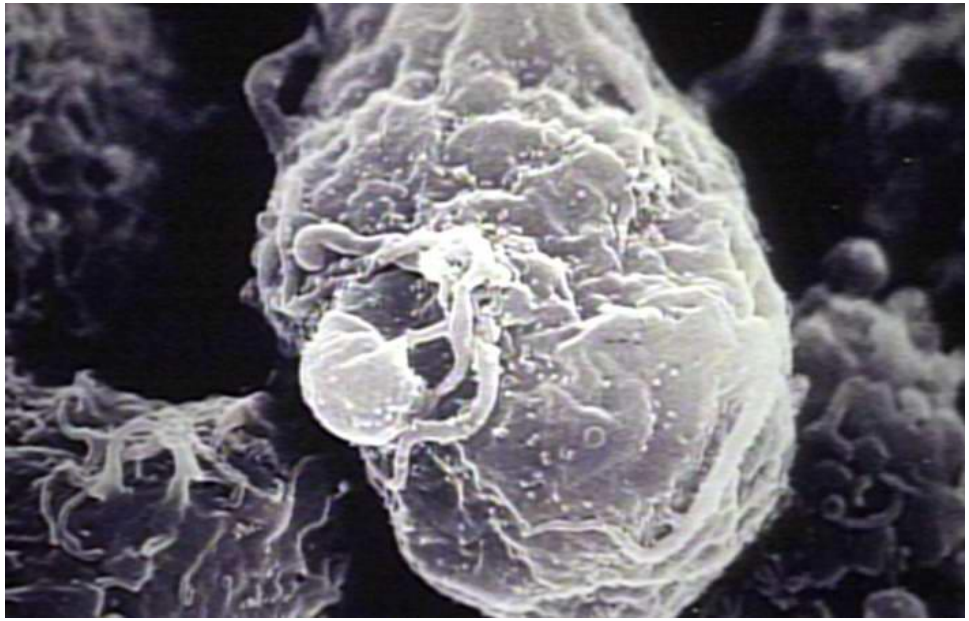
HIV and TB Co-infection

HIV Basics: A Course for Physicians

Management of HIV-TB Co-infection



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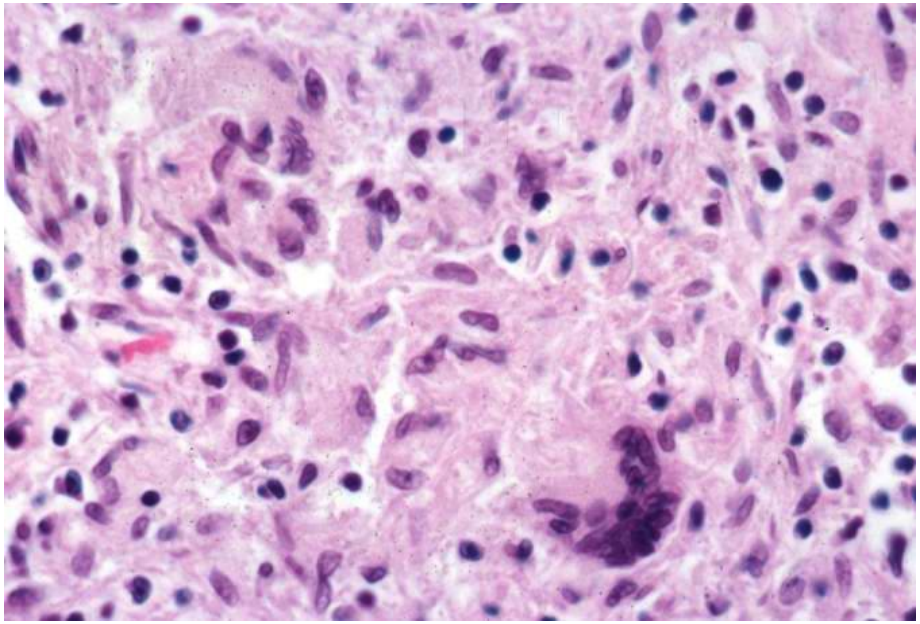

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Learning Objectives

- Describe the epidemiology of TB-HIV co-infection
- Characterize the impact of HIV on TB infection
- Recognize the effect of TB on the progression of HIV infection
- List the recommended treatment of TB
- List the challenges of combining TB treatment with ART
- Recognize the use of INH preventive therapy

Global Epidemiology

- HIV has contributed to a substantial increase in the incidence of TB worldwide
- 15 million people are co-infected with TB and HIV
- 90% of these infected people live in developing nations
- 8% of global tuberculosis is attributable to HIV infection
- TB is the most common opportunistic infection in some area
- At least 1/3 of all TB cases occur in HIV patients
- HIV associated TB is most common in IDUs

potential forExposure of TB

- HCW s
- Prisons
- Homeless
- IVDUs
- Poor economic condition
- Malneutrition

Physical exam in HIV cases for pul inf

- Skin testing
- Fundoscopy
- LN may be enlarged
- Organomegaly
- Chest exam
- CNS exam

- Specific infections is closely related to degree of altered immune system
- Stage of HIV are defined by CD4 count
- Early = CD4 count >500
- Intermediate CD4 200-500
- Advanced 100-200
- Late stage CD4<100

CXRay in HIV

- Focal or diffused opacity
- Nodules with or without cavitation
- Pleural eff
- Interathoracic adenopathy

CXRay

- Often atypical
- May be like as post primary(upper lobe opacification, cavitation,
- Like as primary infectin (adenopathy, lower lobe opacities, pleural eff)
- In CD4 count >200 more commonly as post primary pattern
- In CD4 count < 200 like as normal or primary infection

- Sputum smear and culture is the best technic to diagnosis
- Smear is positive in 30-89%
- Culture is positive in 85-100%
- Induced sputum is not superior to good sample
- Is useful in who is unable to produce sputum
- May be equivalent to fibroptic broncoscopy
- 2 sufficient specimen one morning at least

- CT scan
- Pleural tap
- Pleural biopsy
- PCR (sensi low and speci high)
- ABG
- Trans bronchial lung biopsy
- Trans thoracic lung biopsy
- Bronchoscopy and BAL
- FNA

TB treatment

- Appropriate multidrug treatment
- Early Empiric treatment
- Subsequently consider drug resistance pattern
- Need for ART ? Since TB is an AIDS-defining illness
- Close monitoring for treatment response
- Monitoring for IRIS
- DOTS
- Monitoring for sputum conversion

- Empiric treatment in probable MDR (4 drugs+ a fluoroquinolon and an aminoglycoside
- Standard course treatment? 6 or 9 MO
- Sometimes intermittent therapy but not in CD4 count< 100 and receive daily
- Risk factors for drug resistance?
- RMP has interaction with PI and some NNRT
- in RMP based regimen EFV + 2 NT rather than NVP +2NT
- Rifabutin lower than RMP
- EFV decrease rifabutin level

Timing of ART treatment

- In CD4 count < 50 ART after 2 W that decrease aids related mortality despite IRIS risk
- In CD4> 50 ART after 8-12 W
-

Risk factors for progression to active TB

- Abnormal CXR (fibrotic…)
- Contact with an active TB case
- Positive skin test for LTBI
- High incidence rate origin
- Detectable HIV RNA
- CD4 <200

Whom to treat in LTBI

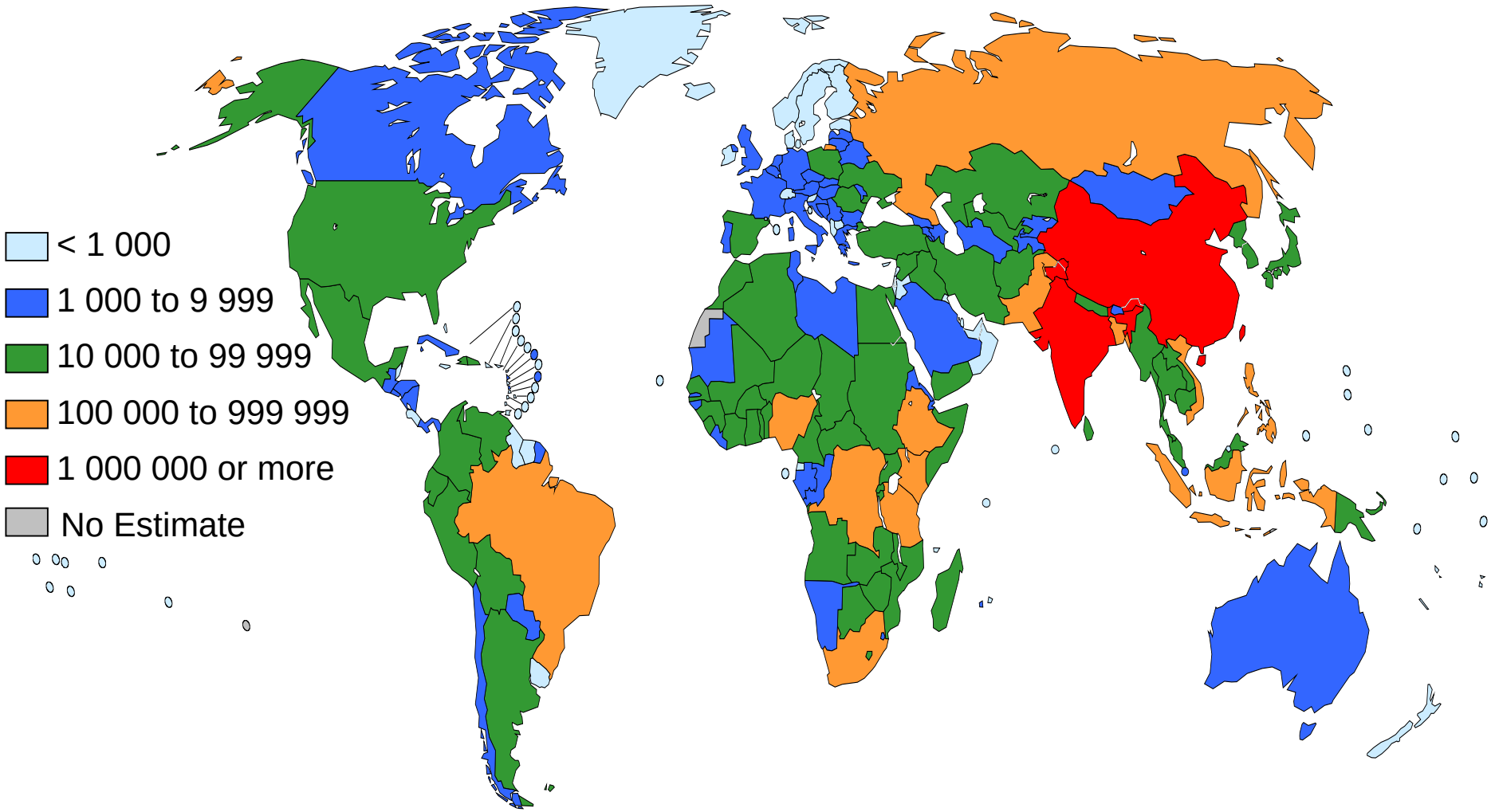
- Recent contact with active TB
- History of inadequate treated healed TB
- Positive skin test or gamma INF
- Not available skin test in high incidence area

- Firstly evaluation for active TB
- Monotherapy but not in active infection
- LFT is necessary before therapy
- INH toxicity is comparable non-HIV cases
- INH for 9 MO
- INH and RMP for 3MO
- RMP for 4 MO

Global Epidemiology (2)

- In Africa, as high as 2/3 of TB cases are HIV co-infected
- TB is the most common cause of death among AIDS patients worldwide
  - Kills 1 of every 3 AIDS patients
- MDR-tuberculosis among HIV patients can be transmitted in nosocomial settings
- Rifampin resistance is also found among HIV-infected patients with tuberculosis

Number of New TB Cases



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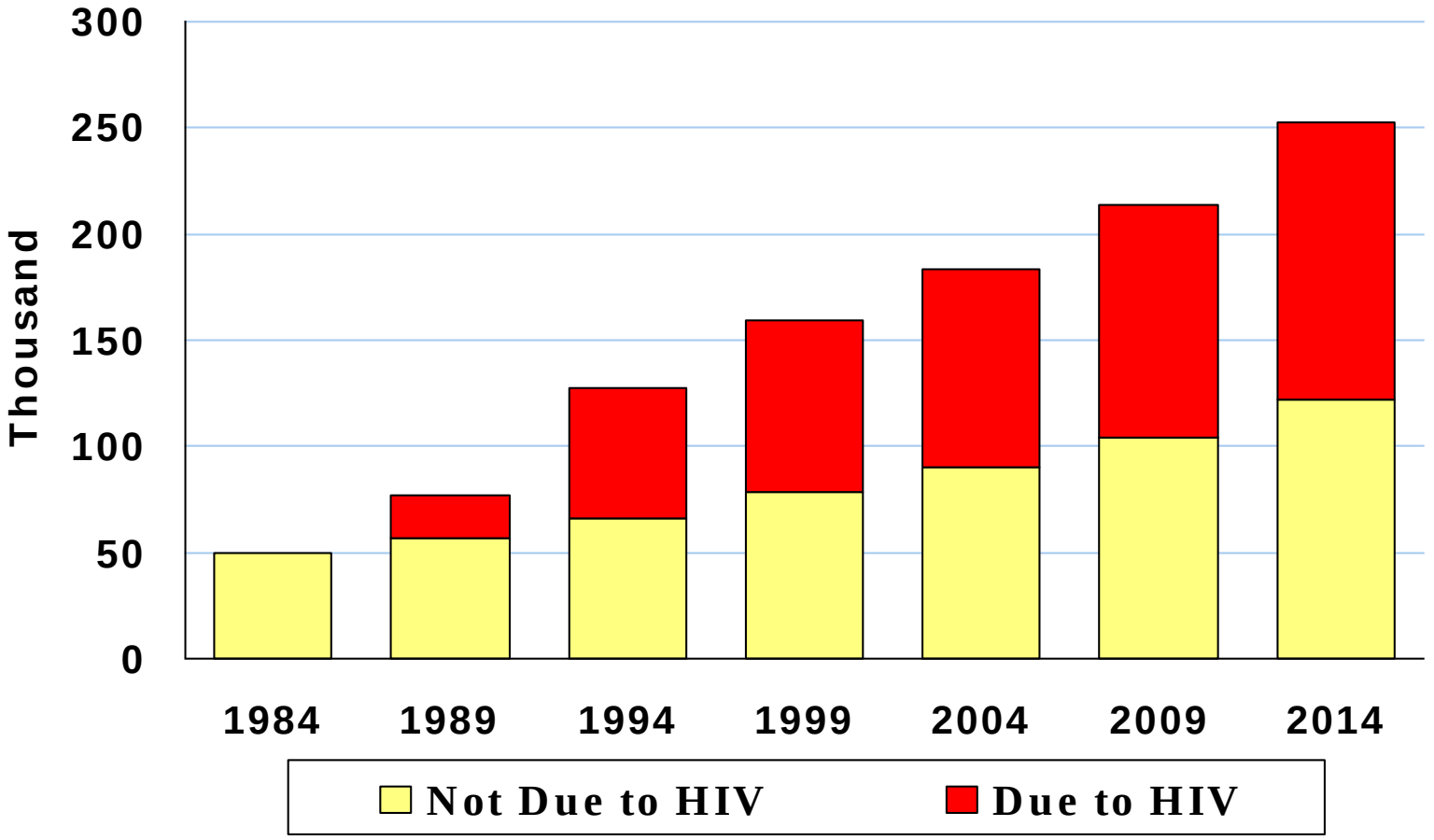
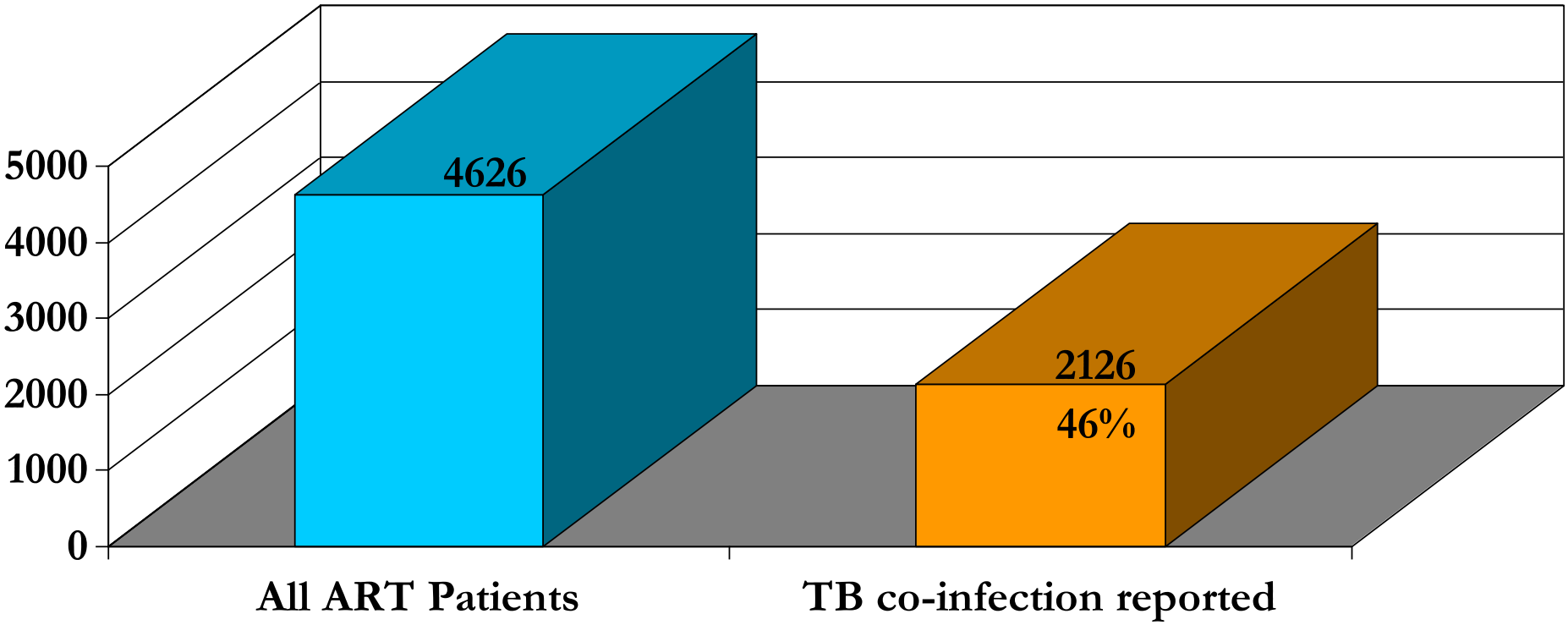
Estimated New Adult Cases of TB



Source: Dr. Asegid Woldu, Ethiopian Ministry of Health

HIV/TB Co-Infection



Of 4626 Ever Started ART

Implications of TB-HIV Co-infection

- Need to screen all HIV patients for TB
  - Thorough history and physical to identify “TB suspects”
  - CXR and sputum AFB for all “TB suspects”
- Need to screen all TB patients for HIV
  - Active promotion and routine offering of Voluntary Cancelling and Testing

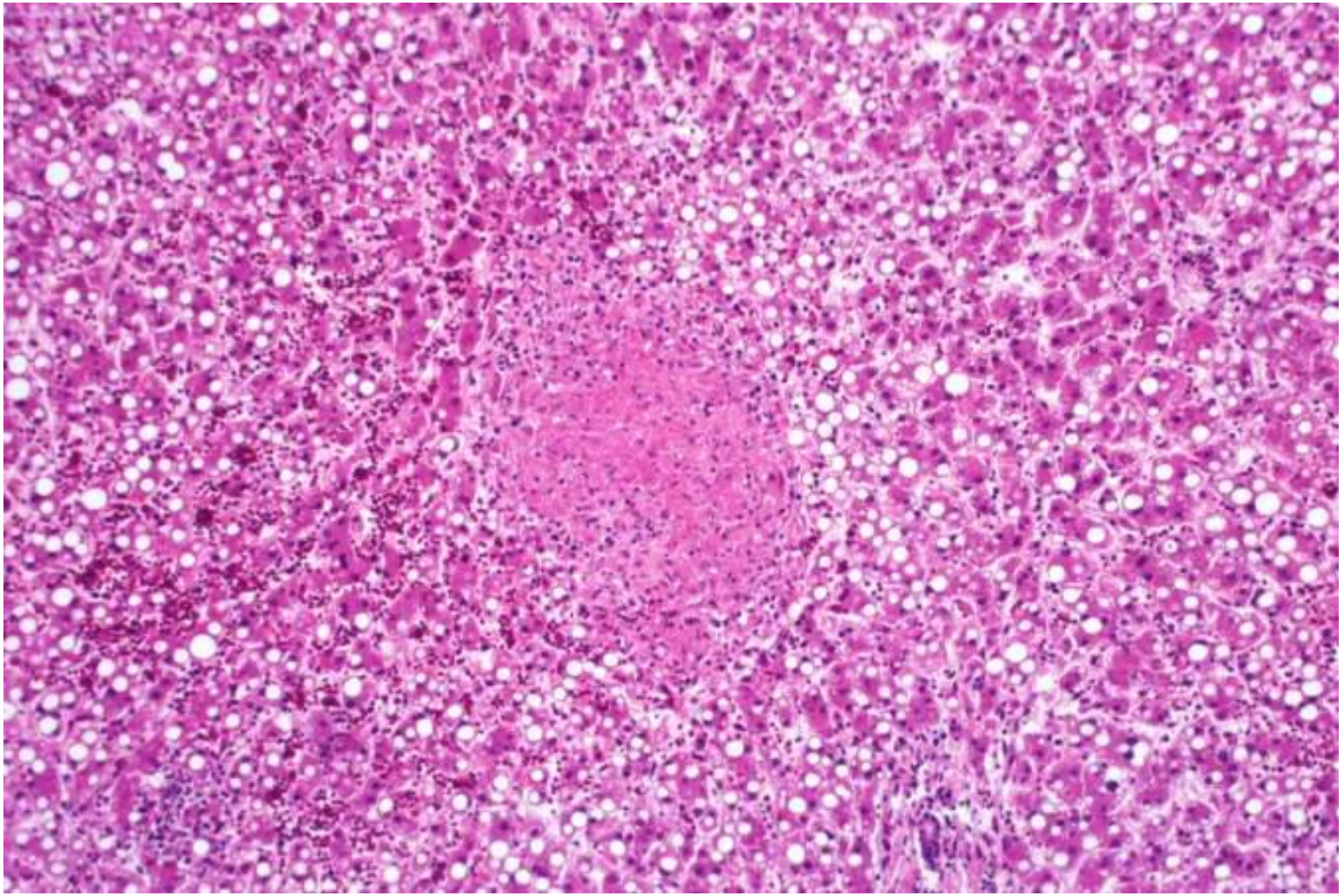
Impact of HIV on TB

- Increases rate of TB re-activation and progression
- Increases TB morbidity
- Increases TB mortality (5-14 fold)
- Alters clinical manifestations of TB
- Creates diagnostic challenges
- Complicates treatment

Impact of HIV on TB (2)

- HIV increases risk of developing active tuberculosis
  - 5 -10% chance per year of re-activation
  - 9 times greater risk compared to HIV negative people
  - 50% chance per lifetime of re-activation

Granuloma Formation for TB Control



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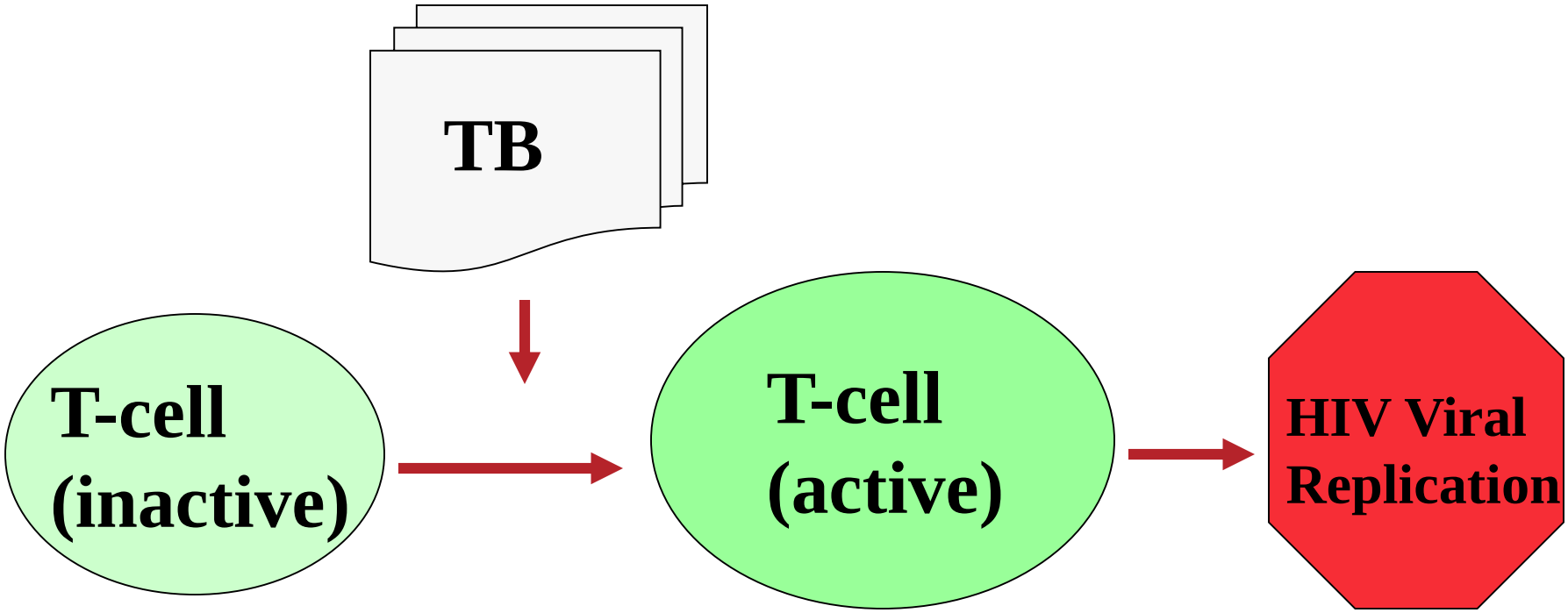
Impact of TB on HIV

- TB infection activates T-cells, indirectly supporting HIV replication
- Active TB is associated with
  - Increased HIV-1 viral load
  - Rate of progression to AIDS
  - Mortality
- HIV viral load decreases with successful TB therapy
- TB therapy when combined with ARV has potential for drug-drug interactions and side effects

Impact of TB on HIV replication



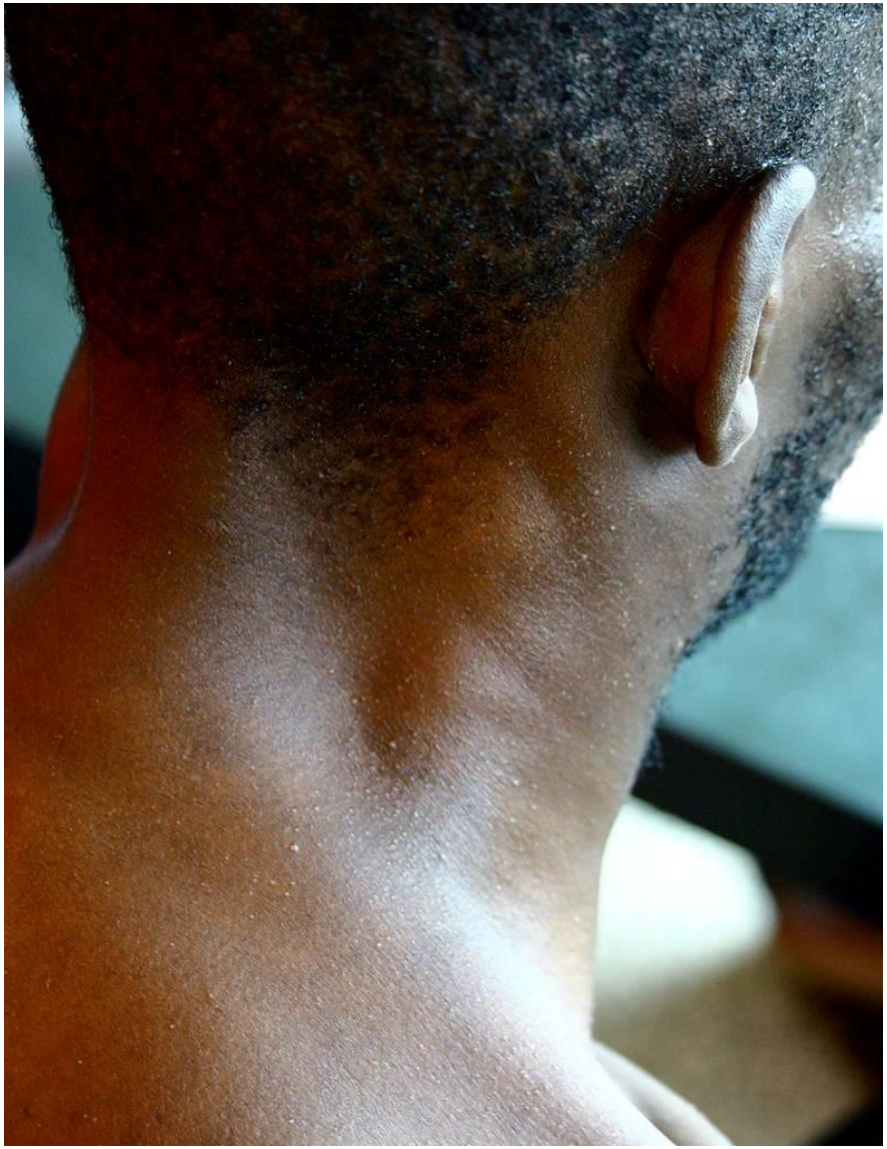
Clinical Manifestations

- Clinical presentation of TB in HIV patients is variable, depending on CD4
- Extra-pulmonary disease is more likely as CD4 count declines
  - Reported in up to 70% when CD4 <200
  - Atypical clinical and radiographic manifestations

Common Sites of Extra-pulmonary Disease

- Lymphatic System
- Pleura
- Pericardium
- CNS
- GI
- Kidney
- Bone

Posterior Cervical Adenopathy



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Atypical CXR in Advanced HIV

- Lower/middle lobe opacity
- Interstitial or miliary pattern
- Adenopathy (hilar, paratracheal)
- Pleural effusion
- Pericardial effusion
- MAY BE NORMAL

National TB Control Program

- Identifying “TB suspects” is critical
- “TB suspect” is defined by one or more of following:
  - Cough > 2 weeks
  - Constitutional symptoms (fever, weight loss, night sweats, etc)
  - CXR suggestive of pulmonary TB

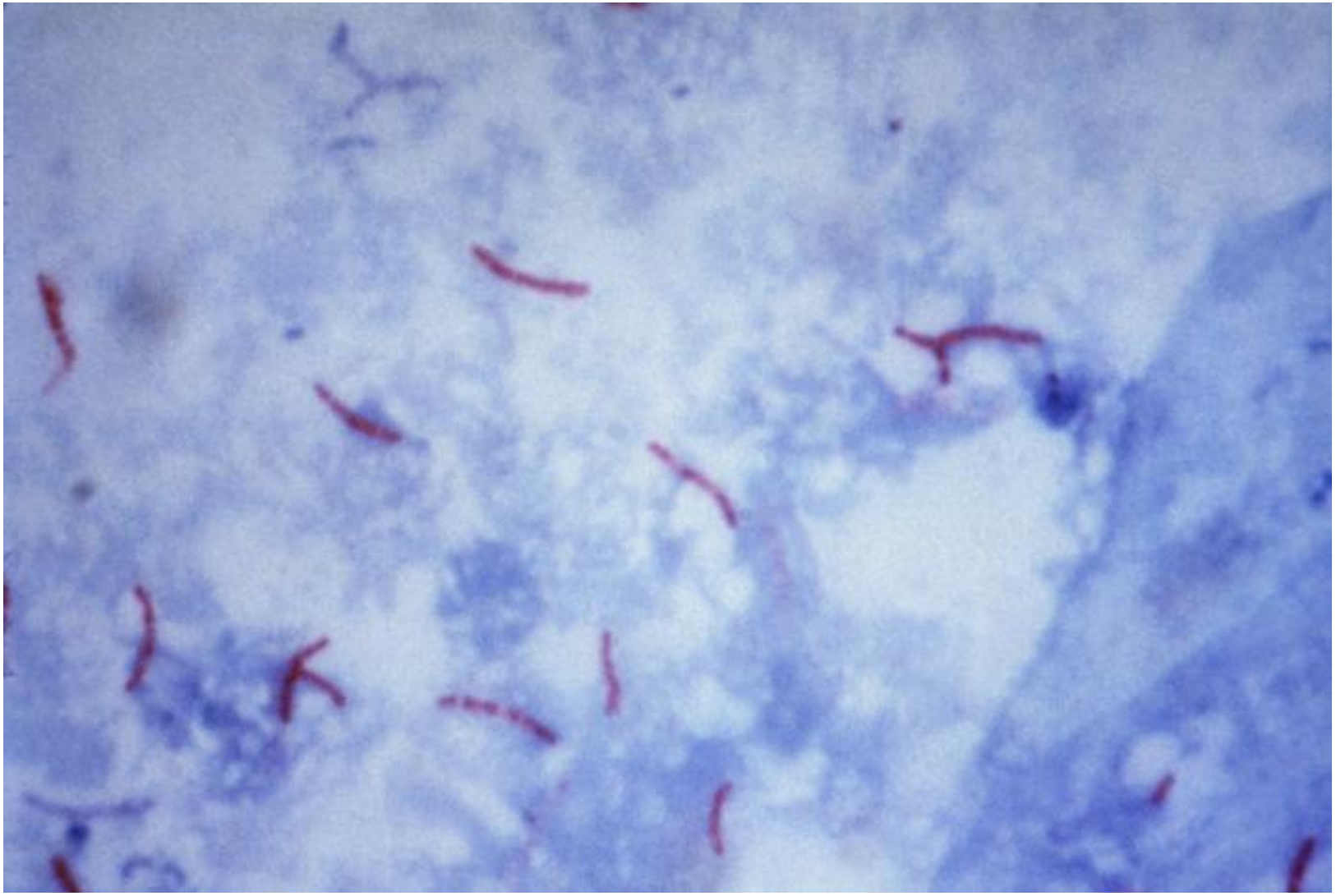
Diagnostic Methods

- Microscopic examination of sputum smears
  - Specific, readily available, and most important test
  - 3 specimens collected in 2 consecutive days (spot, early morning, and spot)
  - Positive if ≥ 3 AFB are seen 100-oil immersion field
- Radiologic examination (CXR)
  - Non-specific, but may be helpful; available
- Histo-pathological examination
  - Specific, but not routinely available in poor income area
- Culture
  - Specific, but not routinely available in poor income area

Diagnosis

- Sensitivity of sputum smear for AFB is reduced in HIV-related TB
- A negative smear does not exclude diagnosis of TB

AFB Stain



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Diagnosis Key Points

- TB diagnosis in HIV infected patients is difficult
  - Clinical manifestations become more atypical as immune function deteriorates
  - Negative AFB does not rule out PTB
- Empiric anti-TB treatment may be warranted in many circumstances

Standardized Treatment of TB

Duration	Drugs	20-29 kg	30-37 kg	38-54 kg	>55 kg
Intensive phase (8 weeks)	ERHZ (275/150/ 75/400)	1 ½ tablets	2 tablets	3 tablets	4 tablets
Continuation phase (6 months)	RH (400/ 150)	1 tablet	1 ½ tablets	2 tablets	3 tablets

Treatment Side Effects

Rifampin	Orange body fluids Drug interactions Hepatotoxicity
INH	Neuropathy Hepatotoxicity GI intolerance
PZA	Hepatotoxicity Joint pains GI intolerance
Ethambutol	Ocular toxicity (dose related) GI intolerance

Overlapping Side Effect Profiles of ARV and Anti-TB drugs

Side Effect	Anti-TB drugs	ARV drugs
Skin rash	PZA, rifampicin, rifabutin, INAH	NVP, DLV, EFV, ABC
Nausea, vomiting	PZA, rifampicin, rifabutin, INAH	AZT, RTV, AMP, IDV
Hepatitis	PZA, rifampicin, rifabutin, INAH	NVP, PI
Leucopenia, anaemia	Rifampicin, rifabutin	AZT

Immune Reconstitution Inflammatory Syndrome

- Development of clinical manifestations of a previously sub-clinical opportunistic infection and/or paradoxical worsening of active infection despite appropriate treatment
- Occurs usually within 3 months of starting ART
- Reflects a restored, protective, pathogen-specific immune response
- Not ART treatment failure

TB-related IRIS

- Symptoms and signs
  - High fevers
  - Lymphadenopathy
  - Worsening cough
  - Worsening of chest radiographic findings
- Management
  - TB treatment
  - Corticosteroids may be indicated for severe CNS and pericardial disease, hypoxemia, and airway obstruction

Cotrimoxazole Preventive Therapy (CPT)

- Background
  - Reduced morbidity and mortality in TB-HIV co-infected patients
- Indications
  - ALL HIV patients with active TB, regardless of WHO stage or CD4 count
- Dose
  - One double strength tablet daily (or 2 single strength)

Isoniazid Preventive Therapy (IPT)

- Background
  - 10% risk per year of developing active TB
  - IPT reduces active TB in HIV patients
- Indications
  - ALL HIV infected patients without active TB
  - MUST exclude active TB prior to initiating IPT
    - Sputum specimens for patient with cough > 2 weeks and
    - CXR where available
- Dose
  - INH 300 mg/day (150mg/day if wt <30kg) x 6 months
  - Addition: Pyridoxine 25mg qd

Case Study:

- 34 year-old male, was treated for EPTB 1 year ago. He has been on NVP/ZDV/3TC for 2.5 months, and presents with gradual onset pleuritic chest pain and fatigue

A. What additional information is needed for accurate diagnosis and treatment?

Case Study: Kebede (2)

B. What is Your Diagnosis?

a) Viral pericarditis
b) Toxoplasma myopericarditis
c) IRIS with underlying TB pericarditis
d) ZDV related myocarditis

Principles of combining ART and TB treatment

Rifamycin and HAART

- Rifamycin induces CYP450
  - May substantially decrease blood levels of the antiretroviral drugs (NNRTIs and PIs)
  - May lead to drug resistance and treatment failure

- Decrease in ARVs when combined with Rifampicin

- NVP ↓ 37-58%
- EFV ↓ 13-26%
- NLF ↓ 82%
- LPV/r ↓ 75%

HAART and Rifamycin

- PIs and NNRTIs may inhibit or induce cytochrome P-450 (CYP450)
  - May alter the concentration of the rifampicin
    - Delay sputum conversion
    - Prolong the duration of therapy
    - Possibly result in worse outcome

Combining HIV and TB Therapy

- Always look-up drug drug interactions when using rifampicin and ARV
  - Bidirectional: may require dose adjustment of both the antiviral and rifampicin
- Avoid combining rifampicin with
  - Nevirapine (unless no alternative is available)
  - PIs: exception of saquinavir/ritonavir combination
- Use Efavirenz or triple nucleoside combinations (eg. ABC containing)

Rifamycin and Efavirenz (EFV)

- Rifampicin decreases EFV levels
  - Increase dose of EFV from 600mg/day to 800mg/day
  - May use 600mg/day if 800mg not tolerated

- Patients developing TB while on ARV therapy:
  - A change to EFV is recommended for patient on NVP whenever possible
  - If EFV not possible (eg intolerance of EFV, pregnancy) NVP “may be continued in selected cases, with close clinical and laboratory monitoring”

- Patients presenting with TB before commencing ARVs:
  - EFV containing regimen preferred
  - If EFV not available or not possible, NVP may be given with caution, “monitoring ALT every month”

Case Study:

- 34 year-old woman on Efavirenz/Combivir and Rifampin containing anti-TB therapy for pulmonary TB. She missed her menstrual period 12 days ago and pregnancy test in clinic today is positive

A. What further information is necessary for the management of this patient?

Case Study: Nigist (2)

B. Which option would be best for managing this patient?

a) Change EFV to NVP (200mg bid)

b) Change EFV to NVP (400mg bid)

c) Change ZDV to d4T

d) Continue present regimen

e) Stop all ART; resume after completion of initial phase (rifampicin-containing) TB treatment

Coordinating TB Treatment and ART

- WHO TB guideline:
  - Complete TB therapy prior to starting ART
  - Start ART and TB therapy together for patients at high risk of death during treatment period:
    - CD4 < 200cell/mm3 and/or
    - Disseminated TB

Coordinating Treatment

- Potential advantages of delaying ART:
  - Reduced pill burden and better drug adherence
  - Less chance of drug interactions and toxicity
  - Reduced chance of IRIS
- Potential disadvantages of delaying ART:
  - Patient may die from a different OI that could have been prevented by improving immune status with ART
  - TB disease may progress faster without ART

Coordinating Treatment (2)

- Recommended options (WHO):
- Defer ART until completion of TB therapy
- Defer ART until completion of intensive phase, then use RMP and INH for continuation phase
- Start EFV containing ART regimen in conjunction with intensive phase TB therapy
  - ART generally starts two weeks after starting TB therapy, to ensure that the patient is tolerating the TB drugs

Case Study:

A 24 year-old male is referred from TB clinic for initiation of HIV care. The patient started standard initial phase therapy for pulmonary TB 2 weeks ago. He has thrush on examination. CD4 count is 300.

A. What further information is needed to help manage this patient?

Special Situations

- Patient becomes pregnant while on ART and TB therapy
  - Problem:
    - EFV contraindicated (possible exception: 3rd trimester)
    - NVP levels are substantially reduced in presence of Rifampicin
  - Management:
    - Continue NVP-containing regimen with careful monitoring for clinical treatment failure or
    - Stop entire regimen during initial (Rifampicin-containing) TB treatment phase and
    - Refer for PMTCT

Special Situations (2)

- EFV not available (e.g. pharmacy out of stock)
  - Problem:
    - NVP level substantially reduced in presence of Rifampicin
  - Management options:
    - Continue NVP with careful monitoring for clinical failure
    - Stop entire ART regimen until initial phase (Rifampin-containing) TB therapy is complete
    - Consider switching to triple NNRTI regimen or SGV/r based regimen

Combining Treatment Key Points

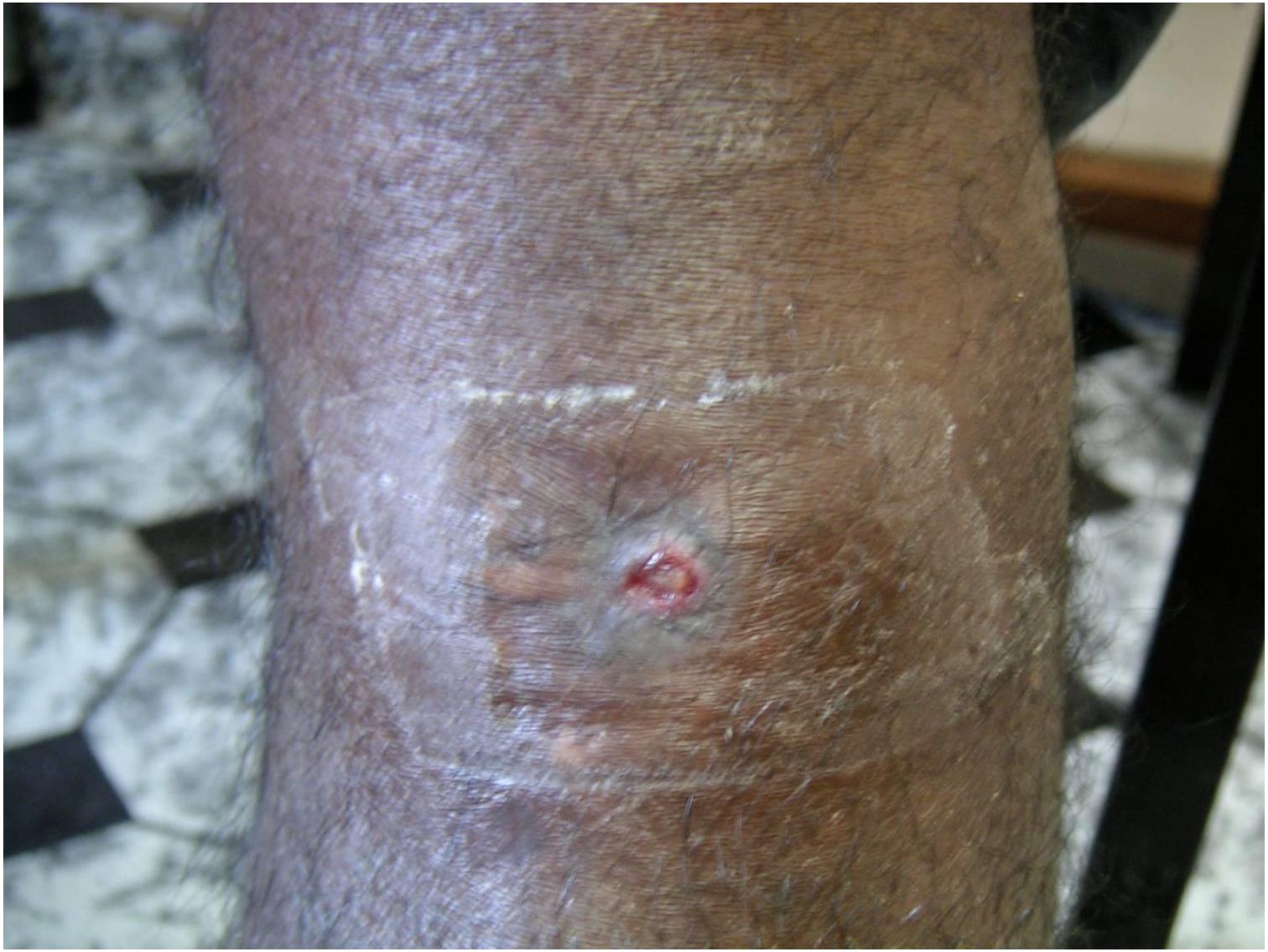
- TB treatment takes priority over ART
- Rifampicin reduces NVP level by 37-58%
- Use of NVP with Rifampicin may lead to ARV treatment failure
- ART and TB treatment have overlapping toxicities
- Watch for immune reconstitution inflammatory syndrome

Case Study: Tamarat

- Tamarat, a 36 year-old male, with history of Pulmonary TB, is referred to clinic for evaluation of a left tibial wound that has continued for three years. He has been on NVP/Combivir for one year, purchased on the "black market." Current CD4 is 140

A. What additional information is needed for appropriate management?

Case Study: (2)



Courtesy of Samuel Anderson, MD

Case Study: (3)

B. What is Your Next Step?

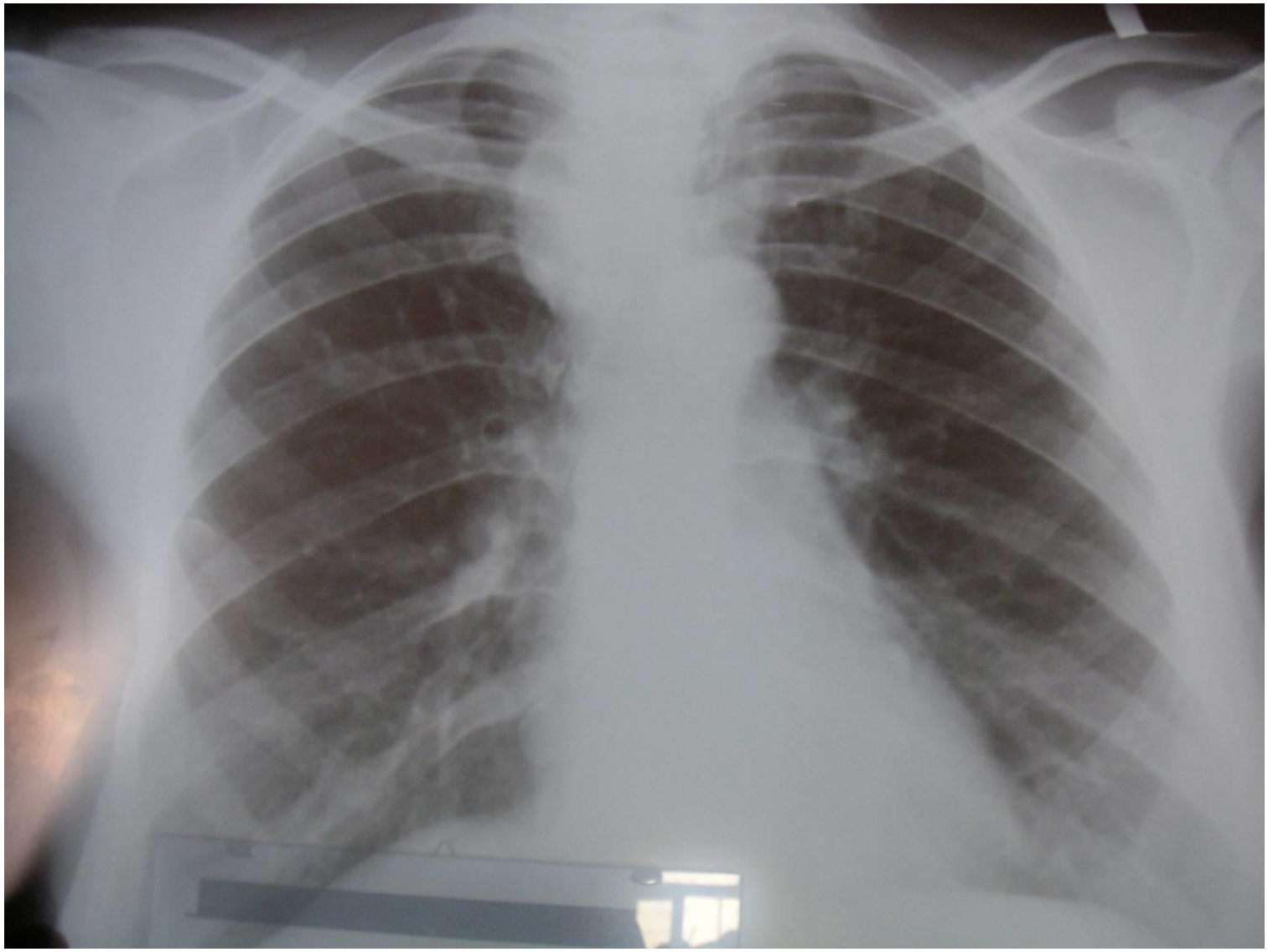
a) Ciprofloxacin plus rifampin
b) Fluconazole
c) Tibial biopsy
d) Anti-TB therapy
e) Tibial X-Ray

Case Study:

- 44 year-old HIV+ female, TLC 600, presents with one month cough, fever, and night sweats. Review of systems also reveals 3 months abdominal cramping and chronic diarrhea. Sputum AFB smear is negative

A. What additional information is needed for appropriate management?

Case Study: (2)



Courtesy of Samuel Anderson, MD

Case Study: (3)

B. What is Your Next Step?

a) Anti-TB therapy
b) Ciprofloxacin x7 days
c) FNA cervical adenopathy, if present
d) Stool studies
e) Abdominal ultrasound

Case Study:

- A 25 year-old male with HIV is referred for initiation of ART. He has never been treated for TB. Exam is normal.

A. What is the current standard of care in regarding LPT?

Case Study: Lemma (2)

B. Which option would be best for managing this patient?

a) Tuberculin skin testing
b) CXR
c) CXR if patient reports cough (>2wks)
d) CXR if patient reports constitutional symptoms
e) Sputum AFB smear if patient reports either cough or fever (>2wks)

Case Study:

- 24 year-old male student on NVP and Combivir for one year develops pulmonary TB. Last CD4 count was 200 at time of initiation. The pharmacy does not have EFV this month.

A. What additional information is needed for appropriate management?

Case Study: Zema

- Zema, a 34 year-old female with CNS TB, CD4 24. Initial phase anti-TB therapy is begun.

A. When should she start ART?

Case Study: Zema (2)

B. Which option would be best for managing this patient?

a) Start NVP/combivir when tolerating anti-TB meds

b) Start EFV/combivir when tolerating anti-TB meds

c) Start EFV/d4T/3TC when tolerating anti-TB meds

d) Delay ART; start NVP/combivir after completion of initial phase anti-Tb therapy

e) Delay ART; start EFV/combivir after completion of continuation phase anti-TB therapy

Key Points

- Tuberculosis is a major cause of morbidity and mortality in HIV-infected people
- All HIV-infected patients should be carefully evaluated for TB
- All TB-infected patients should be offered VCT
- HIV impacts the presentation of TB and makes the diagnosis of TB difficult
- Active TB increases the rate of HIV disease progression

Key Points (2)

- Treating TB takes priority over initiating ART
- Rifampicins have significant drug-drug interactions with ARV
- Use of Rifampicin with NVP may lead to NVP resistance and ARV treatment failure