

# Clinical manifestations and opportunistic infections in HIV infection

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# Clinical manifestations

1. Acute HIV-1 infection
2. General manifestations
3. HIV-associated Skin and Mucocutaneous diseases
4. Oral manifestations of HIV
5. HIV and Tuberculosis co-infection
6. PCP

- 29 year old man, no medical history
- 2 weeks of malaise, myalgia and since a couple days a rash
- Four weeks ago unprotected sex
- Complaints of severe fatigue, no weight loss or mouth sores
- 1week ago his GP gave him amoxicilline with no effect
- Physical exam: temperature of 38.3 C, diffuse adenopathy, maculopapular rash

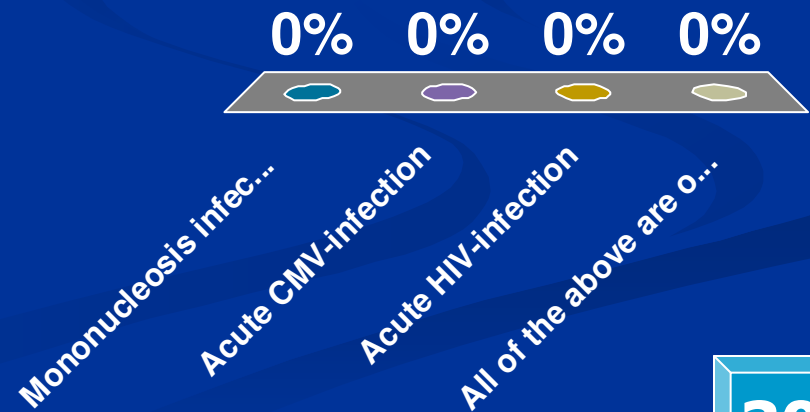
# Rash

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# What is your diagnosis?

1. Mononucleosis infectiosa
2. Acute CMV-infection
3. Acute HIV-infection
4. All of the above are optional



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# Test results

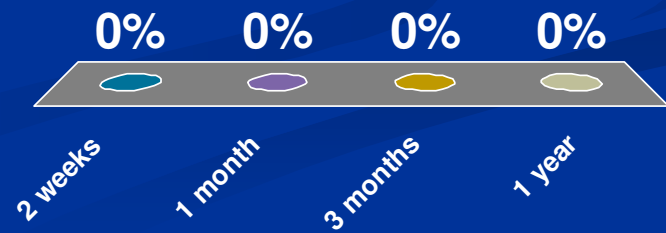
- HIV RNA: 63.700 copies/ml
- HIV antibody: negative
- What is your diagnosis?
  - Acute HIV-infection

# How long is your diagnostic window?

The current HIV-antibody screening tests are able to recognise almost 99.5 % of HIV– infections.....

- A. 2 weeks
- B. 1 month
- C. 3 months
- D. 1 year

....after primary HIV infection





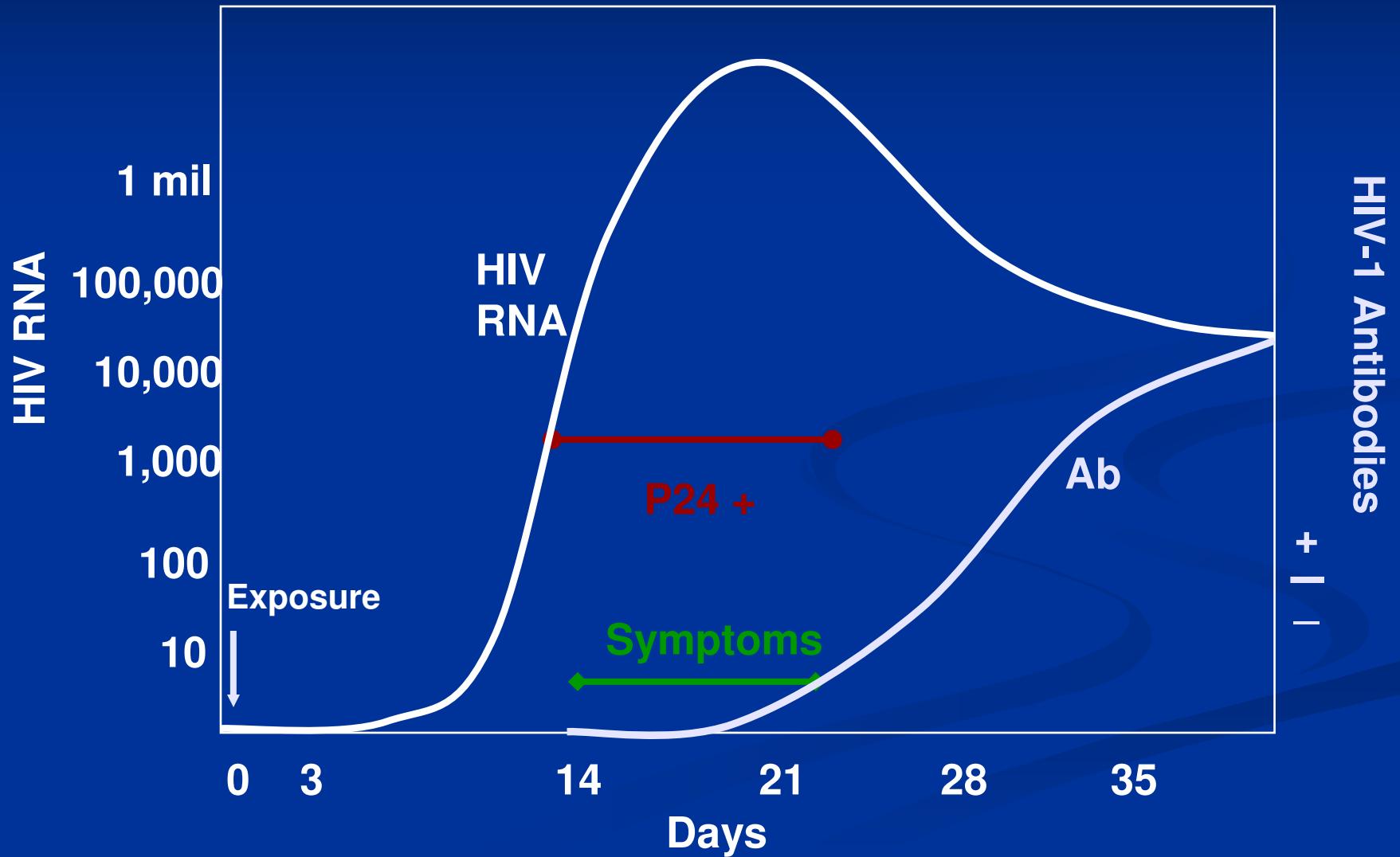
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.....after primary infection with HIV

# Typical Course of Primary HIV



# Typical Risk of Unprotected Exposures

## Estimated Average Per Contact Transmission Risk (%)

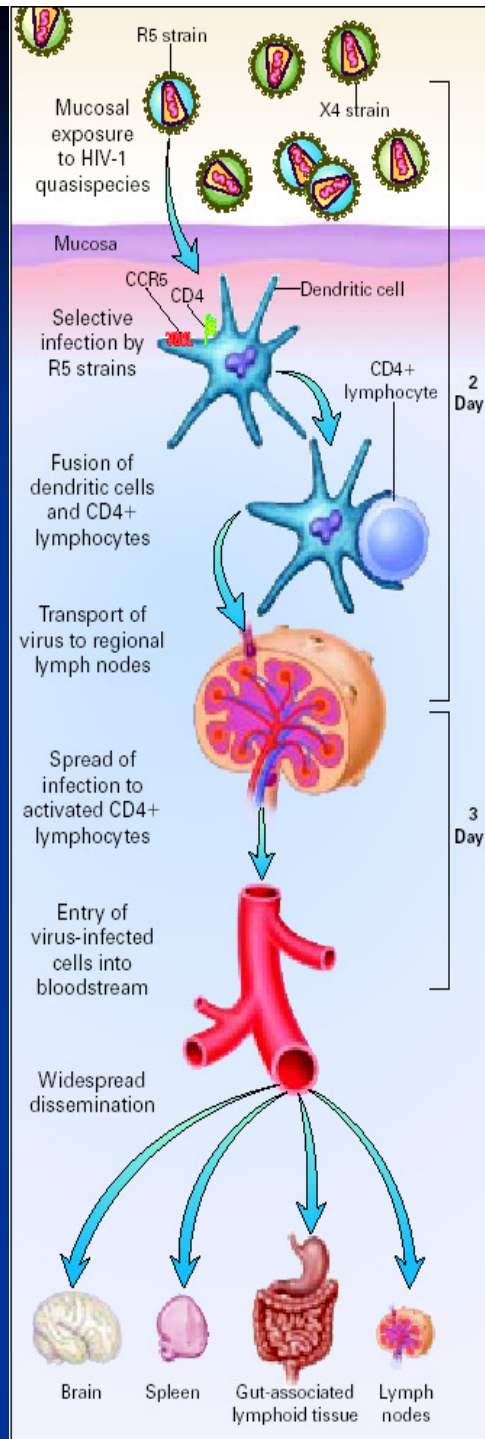
Shared Needles	0.7%
Occupational Needlestick	0.3 %
Male to female, vaginal sex	0.2%
Female to male, vaginal sex	0.1%
Insertive anal sex	0.1%
Receptive oral sex with male	0.03%

Day 0

Day 0-2

Day 3-11

Day 11 on



Exposure to HIV at mucosal surface (sex)

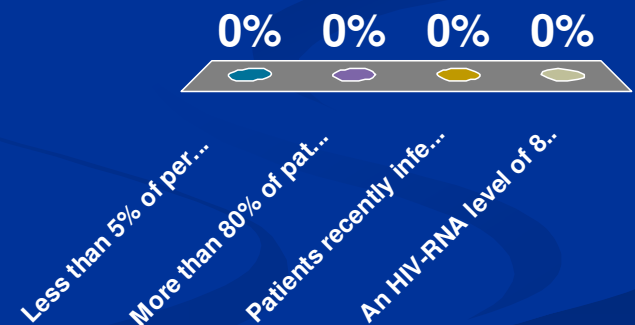
Virus collected by dendritic cells, carried to lymph node

HIV replicates in CD4 cells, released into blood

Virus spreads to other organs

# Which one of the following statement is true regarding acute HIV infection?

- A. Less than 5% of persons who acquire HIV develop an acute illness
- B. More than 80% of patients with acute HIV present with an aseptic meningitis
- C. Patients recently infected with HIV typically have plasma HIV RNA levels greater than 50.000 copies/ml within 4 weeks of acquiring HIV
- D. An HIV-RNA level of 800 copies/ml and a negative HIV-antibody test would be diagnostic for an acute HIV infection



## Which one of the following statement is true regarding acute HIV infection?

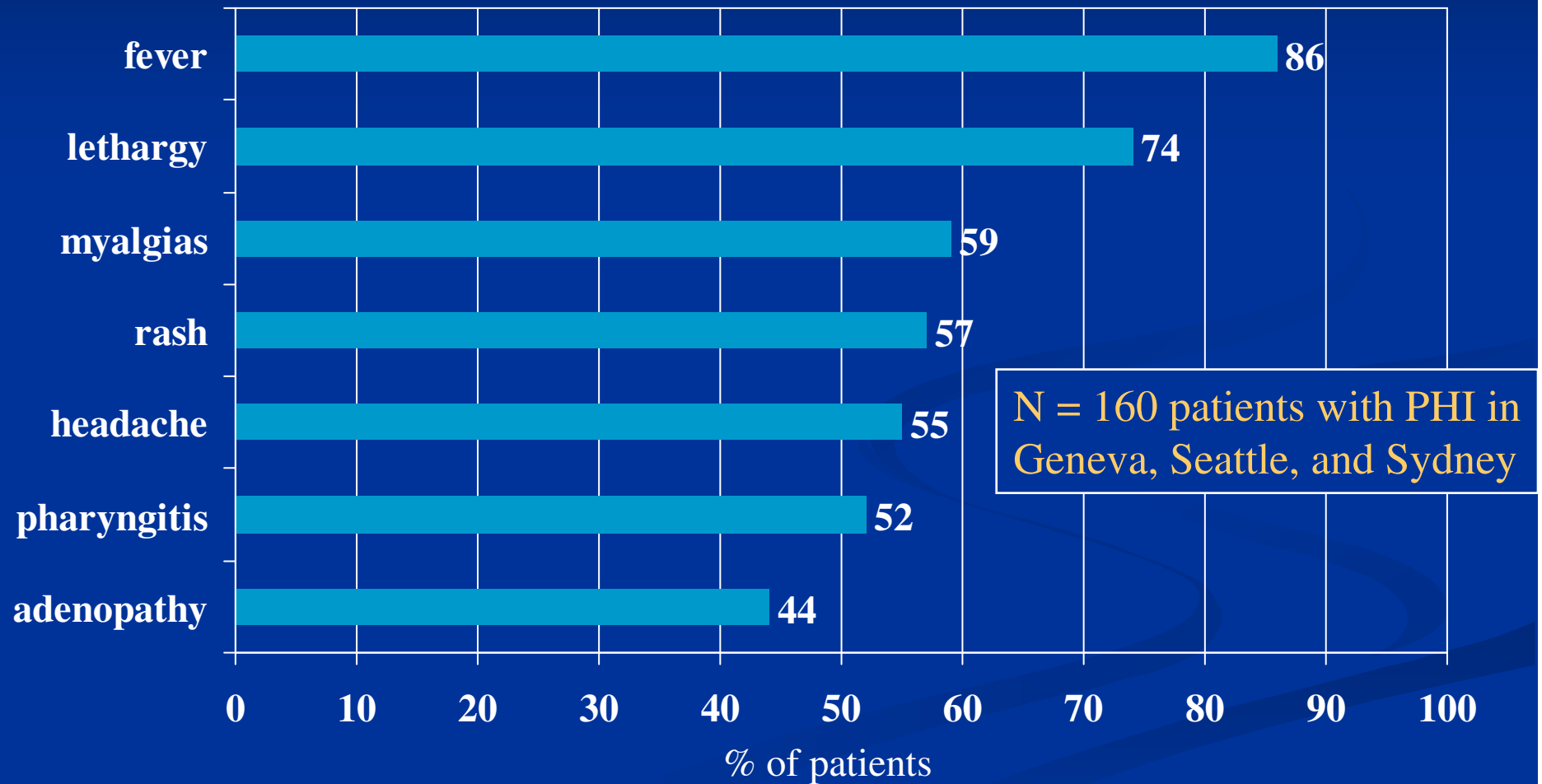
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# Primary HIV Infection: Signs & Symptoms

- 80-90% of patients will be symptomatic
- A mononucleosis-like illness of non-specific signs and symptoms
- Signs and symptoms typically begin 1-4 weeks post-exposure
- High index of suspicion is critical

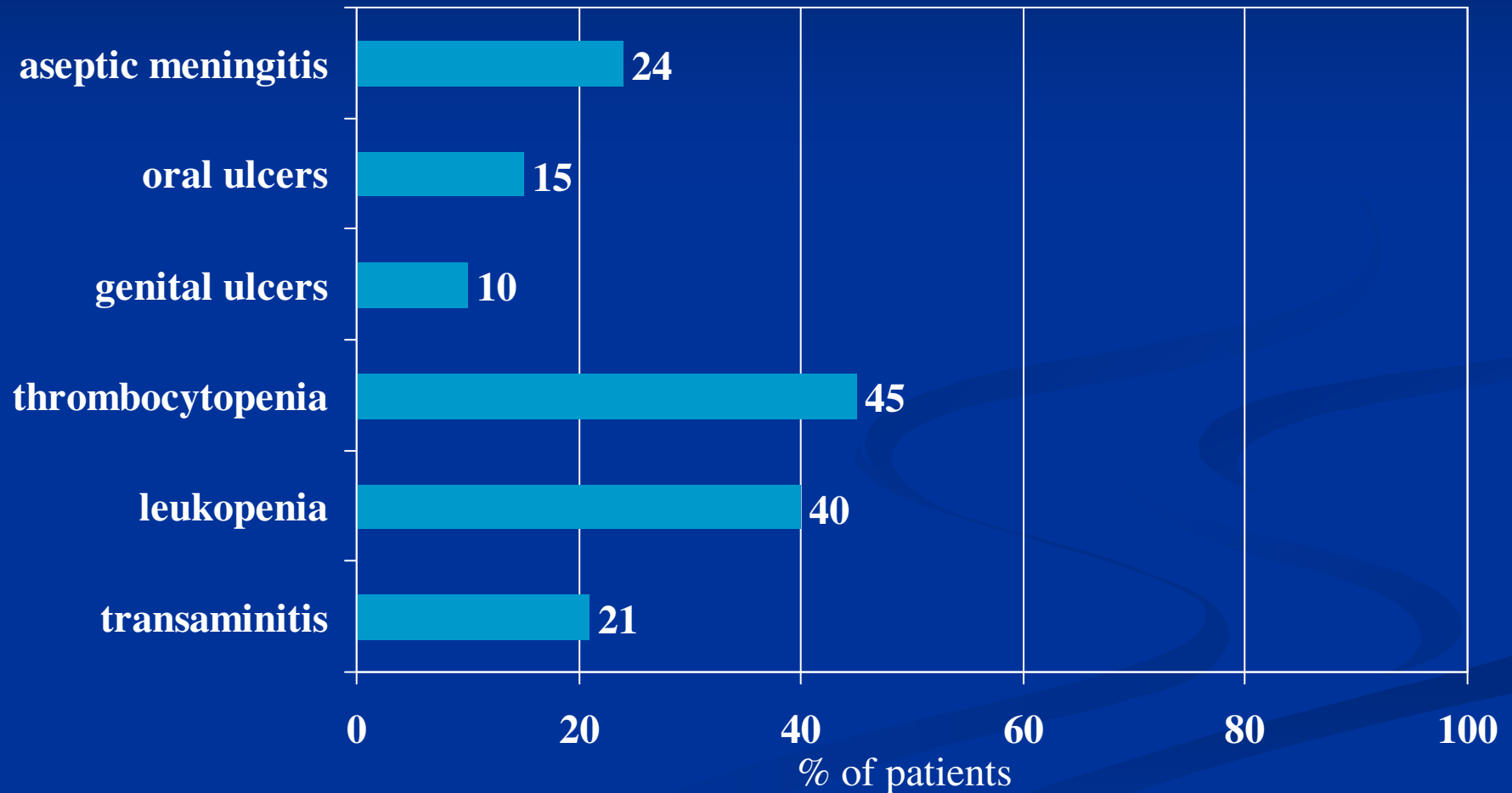
Kahn JO, Walker BD. N Engl J Med. 1998;339:33-39.  
Schacker T, et al. Ann Intern Med. 1996;125:257-264.

# Primary HIV Infection: Common Signs & Symptoms





# Primary HIV Infection: Other Signs & Symptoms



Kahn JO, Walker BD. N Engl J Med. 1998;339:33-39.

# Oral Ulcers in Acute HIV Infection



From: Walker, B. 40<sup>th</sup> IDSA, Chicago 2002.

# Genital Ulcer in Acute HIV Infection



From: Walker, B. 40<sup>th</sup> IDSA, Chicago 2002.

# Diagnostic Testing: Viral Load

- More sensitive than HIV antibody<sup>3</sup>
- Positive one to three weeks before antibody test<sup>1</sup>
- Typically high level, e.g. greater than 50,000-100,000 copies/mL in acute infection<sup>2,3</sup>
- False positives can occur
  - Most false positives are low level (<10,000 copies/mL)
  - HIV VL <10,000 copies/mL should probably be considered “indeterminate”

1. Busch MP, Satten GA. *Am J Med* 1997;102:Suppl 5B:117-24.

2. Kahn JO, Walker BD. *N Engl J Med*. 1998;339:33-39.

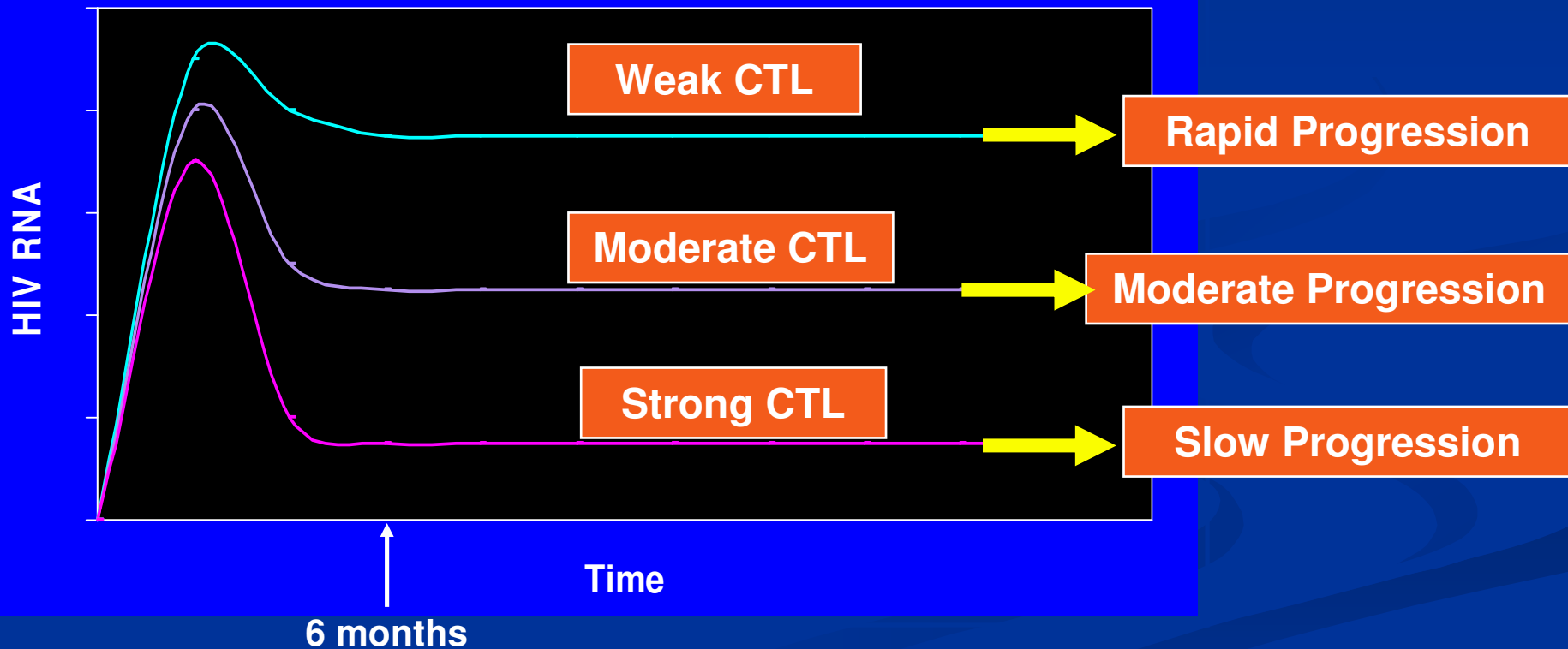
3. Daar ES et al. *Ann Intern Med*. 2001;134:25-29.

# Why do we Care about Diagnosing PHI?

- Public Health:
  - Patients with PHI are likely to be highly infectious
  - Diagnosis of HIV infection may lead to safer sex
- Personal Health
  - 40% of patients with HIV not diagnosed until they have AIDS

# Cellular Immune Response to Acute HIV Infection

Acute HIV



From: Walker BD. Nature 2000;407:313-4.

Slide courtesy David Spach, MD

# Primary HIV Infection: Conclusions

- PHI is under-diagnosed
- A high index of suspicion, recognition of key signs & symptoms, and lab testing are required for the diagnosis

# Clinical manifestations

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# Common Clinical Manifestations of Chronic HIV Infection

- Constitutional Symptoms
  - fever
  - weight loss/wasting
  - fatigue
- Organ/System Specific
  - virtually all organ systems can be affected
- Consider HIV testing for unexplained syndromes

# Wasting



Before HAART



After HAART

# Wasting syndrome

- Involuntary weight loss of at least 10%
  - Accompanied by persistent diarrhea  
(at least two bowel movements daily for more than 30 days)
  - Or extreme fatigue
  - And/or fever without infectious focus

Exclude other infections like: TB, MAC, cryptosporidiosis and microsporidiosis

# Clinical manifestations

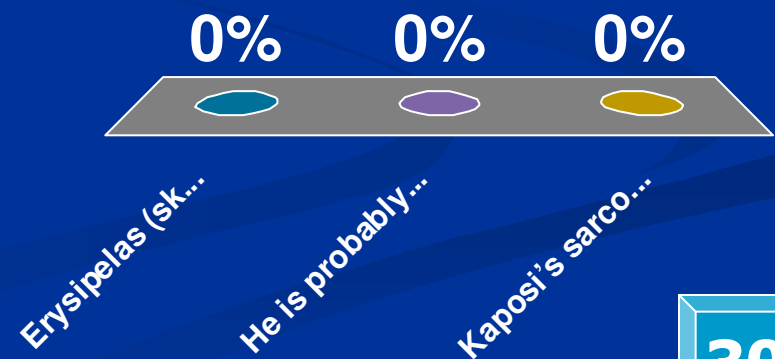
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- A 32-year-old HIV-infected man presents to your clinic having noticed his nose is reddish to purple. He is HIV-positive, his CD4 count is 230 cells/mm<sup>3</sup>, and he has never taken antiretroviral agents.



# What is your diagnosis?

- A. Erysipelas (skin infection)
- B. He is probably drinking too much alcohol
- C. Kaposi's sarcoma





# What is your diagnosis?

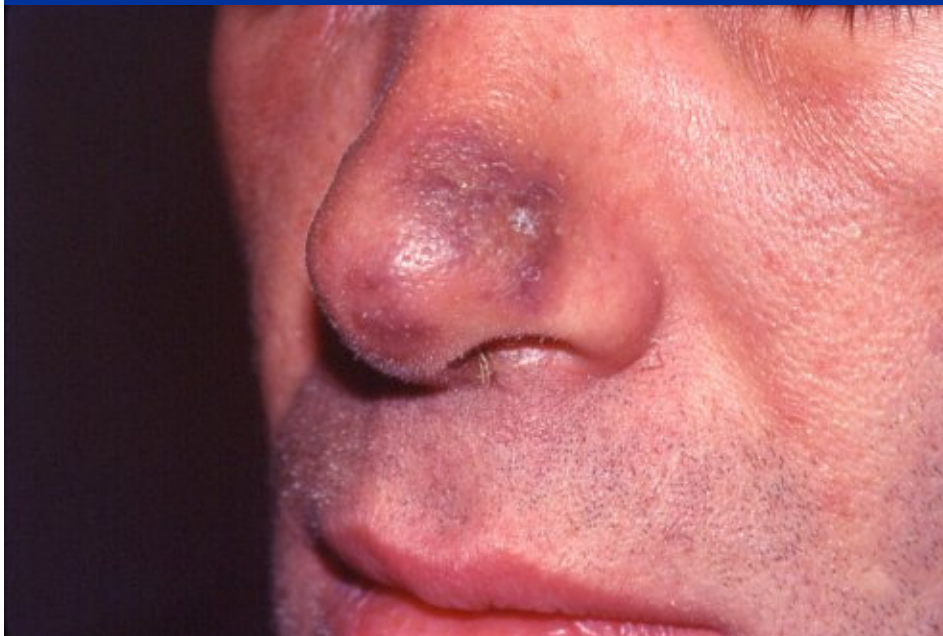
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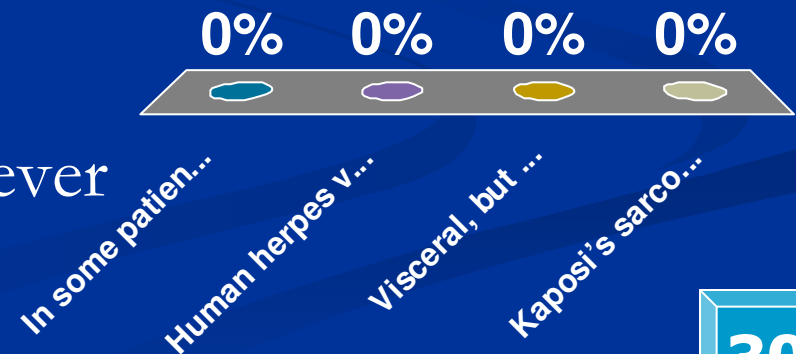
Kaposi's sarcoma





# Which of the following is true?

- A. In some patients HAART alone causes significant improvement of Kaposi's sarcoma lesions
- B. Human herpes virus type 6 is the causative agent of Kaposi's sarcoma
- C. Visceral, but not isolated cutaneous Kaposi's sarcoma, is an AIDS-defining illness
- D. Kaposi's sarcoma lesions will never involve external genitalia



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# Kaposi's sarcoma

- Vascular malignant tumour → nodular lesions
  - Mostly skin lesions;
  - oral/genital/GI-tract/lungs can be involved
- Due to infection HHV-8
- KS is an AIDS-defining illness
- Since HAART: frequency of KS decreased 90%
- HAART= first line treatment
- Local therapy/chemotherapy

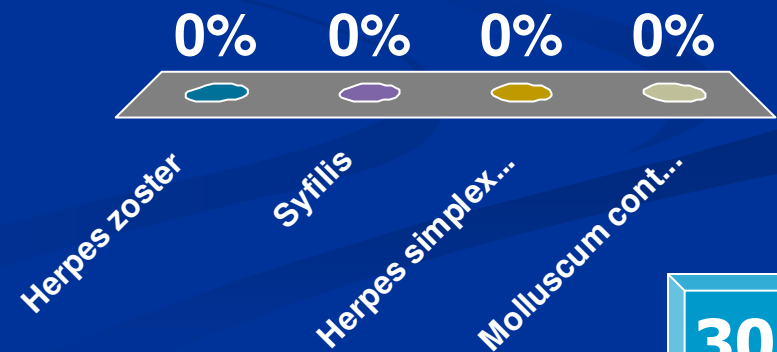
- A 28-year-old HIV-infected man with at presentation a CD4 count of 26 cells/mm<sup>3</sup>, and a 4 week history of genital lesions. At first there were vesicles and for the past week, the lesions have become more painful.

- What is your diagnosis?



# What is your diagnosis?

- A. Herpes zoster
- B. Syphilis
- C. Herpes simplex virus
- D. Molluscum contagiosum



# What is your diagnosis?

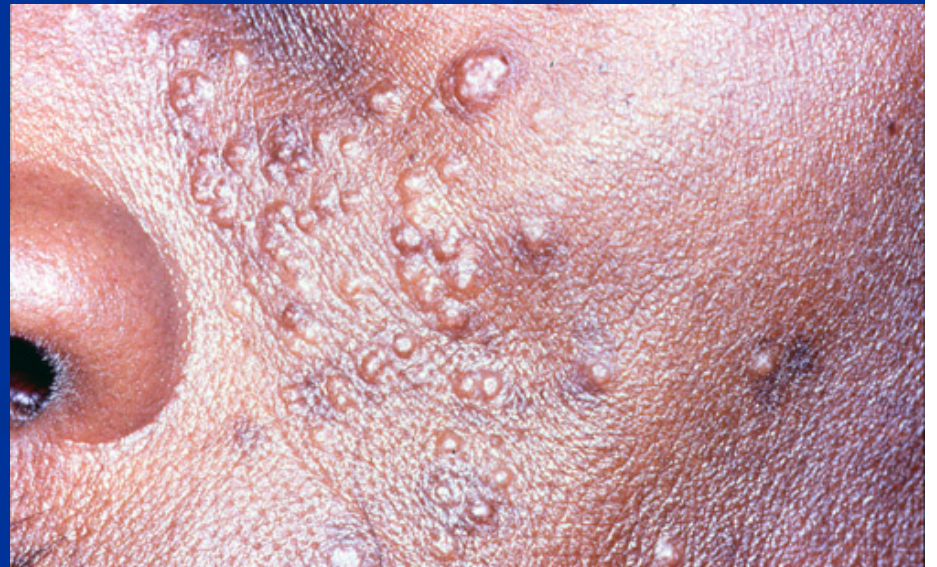
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# HSV

- 80% seropositive for HSV-1 and/or -2
- Normal cell-mediated function:
  - Grouped vesicles; heal spontaneously
  - Cold blister lip (mostly HSV-1)
  - Genital lesions (mostly HSV-2)
  - Genital HSV → asymptomatic shedding
- Advanced HIV (CD4 cell < 100/μl)
  - After grouped vesicles → painful deep ulcerations mostly anogenital and face



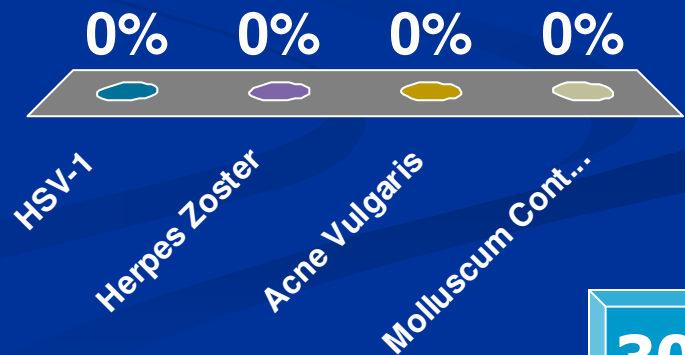
- 48-year-old HIV-infected man comes in for routine care and evaluation of skin lesions on his face. His most recent labs showed a CD4 count of 38 cells/mm<sup>3</sup> and HIV RNA of 87,000 copies/ml. He is an active intravenous heroin user and has not been able to stay on antiretroviral therapy. The patient describes a 2-3 month history of persistent papules on his face that have gradually increased in number and size.





# What is your diagnosis?

- A. HSV-1
- B. Herpes Zoster
- C. Acne Vulgaris
- D. Molluscum Contagiosum



# What is your diagnosis?

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- B. Herpes Zoster
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# Molluscum contagiosum

- Benign viral infection of the skin
- Pox virus
- Diagnosis made on clinical grounds
- HIV-patients high number of lesions, typically face and neck, otherwise rare location
- Presence of multiple mollusca on face; indicating CD4 cell  $< 100/\mu\text{l}$

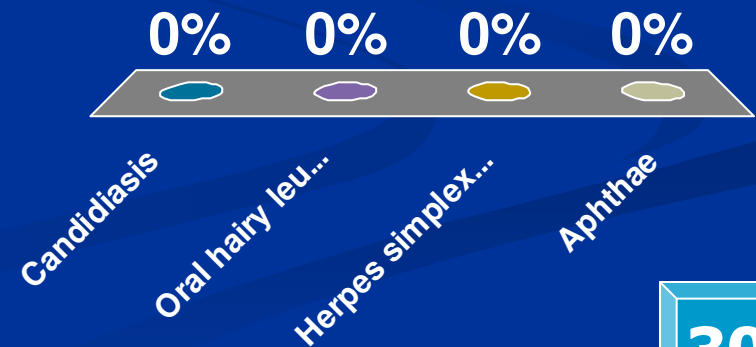
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5. PCP-infection

A 33-year-old HIV-infected man with a CD4 count of 120 cells/mm<sup>3</sup> visits the clinic for a routine appointment. On examination, white papular lesions are seen bilaterally on the lateral side of his tongue, which do not rub off



# What is your diagnosis?

- A. Candidiasis
- B. Oral hairy leukoplakia
- C. Herpes simplex
- D. Aphthae



# Oral manifestations

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# Oral hairy leukoplakia





# Oral hairy leukoplakia

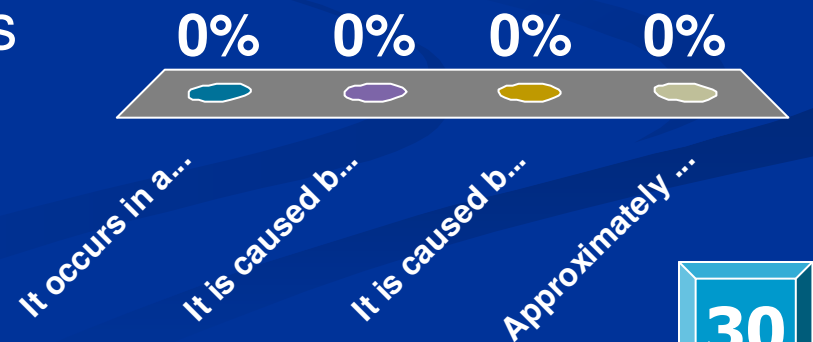


# Oral hairy leukoplakia



# Which of the following statements is true regarding oral hairy leukoplakia?

- A. It occurs in approximately 5% of persons infected with hepatitis C, who are not co-infected with HIV
- B. It is caused by an infection with human herpes virus type 8
- C. It is caused by an infection with Epstein-Barr virus
- D. Approximately 15% of lesions develop into premalignant lesions that require surgical removal



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# Oral hairy leucoplakia

- Clinical manifestation of EBV
- Exclusively in patients with untreated advanced HIV (median CD4 cell of  $230/\mu\text{l}$ )
- White verrucous plaques, especially lateral parts of tongue, do not rub off
- Treatment: antiviral drugs: aciclovir, ganciclovir
- No respond on antifungal

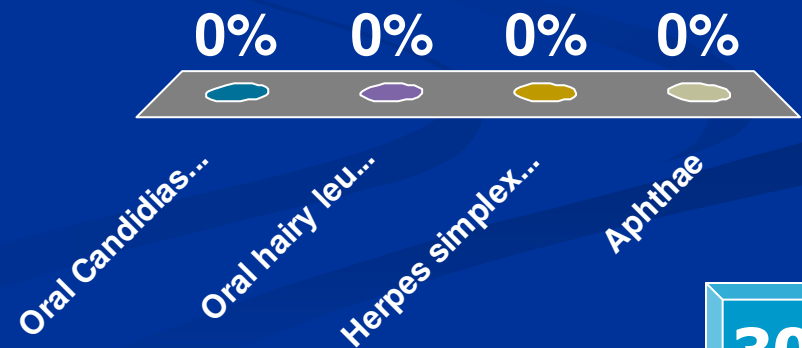
A 39-year-old HIV-infected male presents to the clinic with a 14-day history of a mild burning sensation in his mouth. He was diagnosed with HIV infection in 2001, but has remained asymptomatic up until now. Most recent laboratory studies performed 2 months earlier showed a CD4 count of 250 cells/mm<sup>3</sup>.

By inspection of the mouth you see creamy white plaques or patches on oral tissues that can be scraped off



# What is your diagnosis?

- A. Oral Candidiasis
- B. Oral hairy leukoplakia
- C. Herpes simplex virus
- D. Aphthae





# What is your diagnosis?

- A. Oral Candidiasis
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# Oral candidiasis



# Oral candidiasis

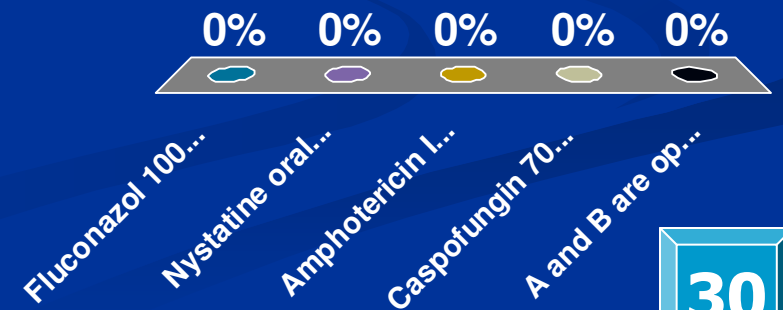


# Oral candidiasis

- Commensal microbe in oral cavity and female genital tract
- Vaginal candidiasis also in immunocompetent female
- Candida oesophagitis usually CD4-count  $< 100/\mu\text{l}$
- KOH: prep showing yeast, however usually clinical diagnosis

# What kind of treatment will you start?

- A. Fluconazol 100 mg/d PO x 14 days
- B. Nystatine oral suspension 4 a 6 mg qid
- C. Amphotericin IV 03-05 mg/kg/d x 1-2 wks
- D. Caspofungin 70 mg day 1, then 50 mg/d IV x 1-2 wks
- E. A and B are optional



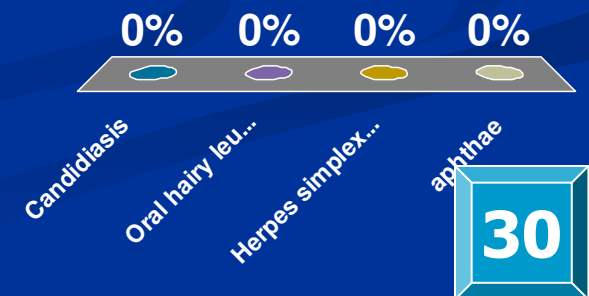
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## What is your diagnosis?

A 36-year-old HIV-infected man with at presentation a CD4 count of 350 cells/mm<sup>3</sup>

- A. Candidiasis
- B. Oral hairy leukoplakia
- C. Herpes simplex virus
- D. aphthae





# What is your diagnosis?

A 36-year-old HIV-infected man with at presentation a CD4 count of 350 cells/mm<sup>3</sup>

- A. Candidiasis
- B. Oral hairy leukoplakia
- C. Herpes simplex virus
- D. aphthae

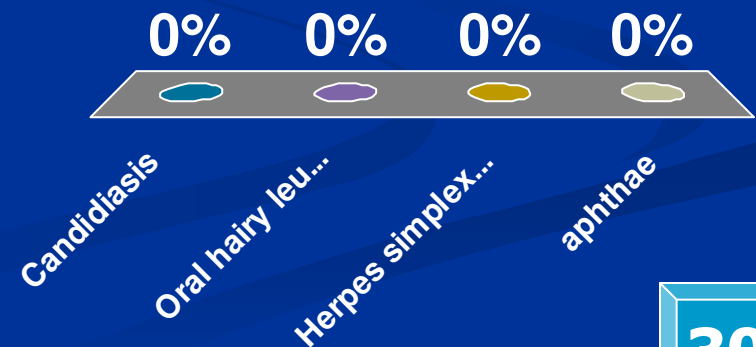






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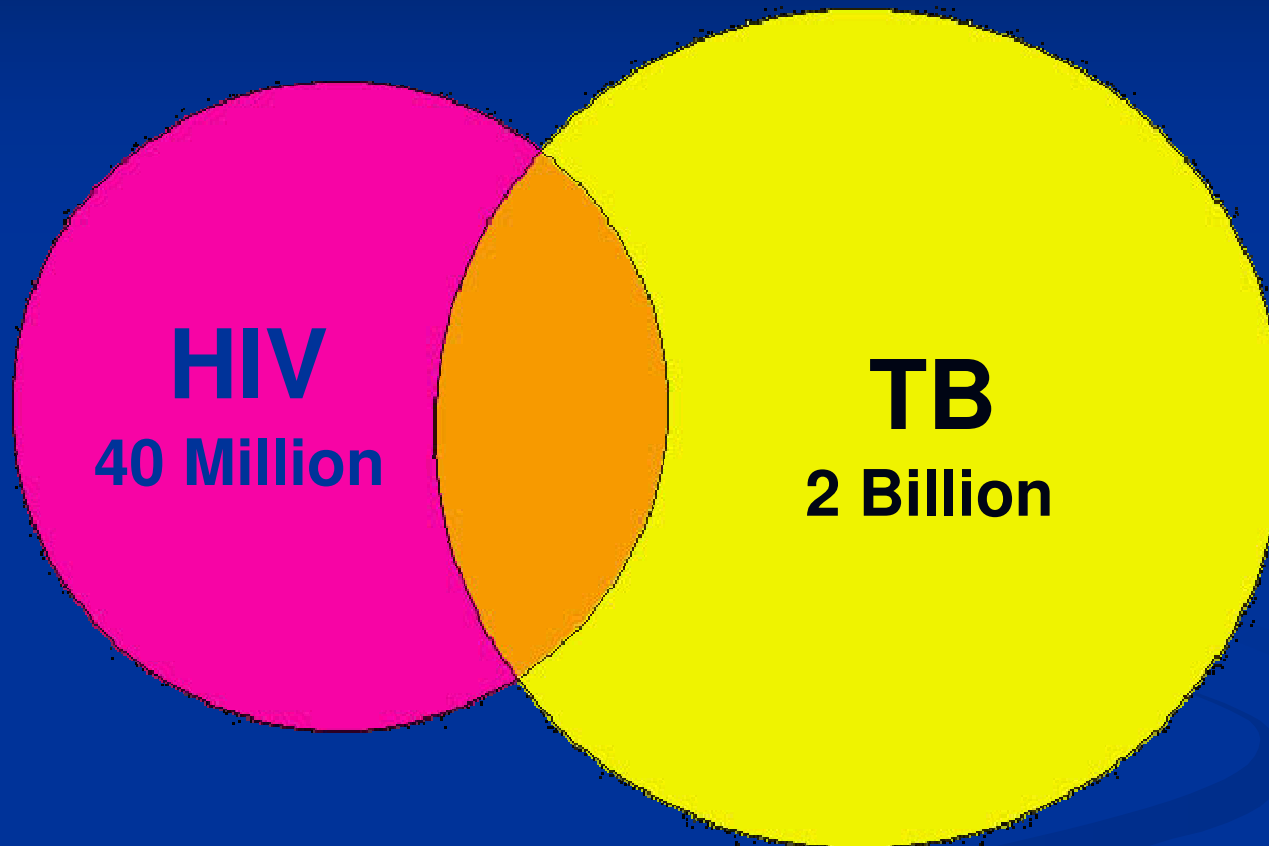
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# The Dual Epidemic



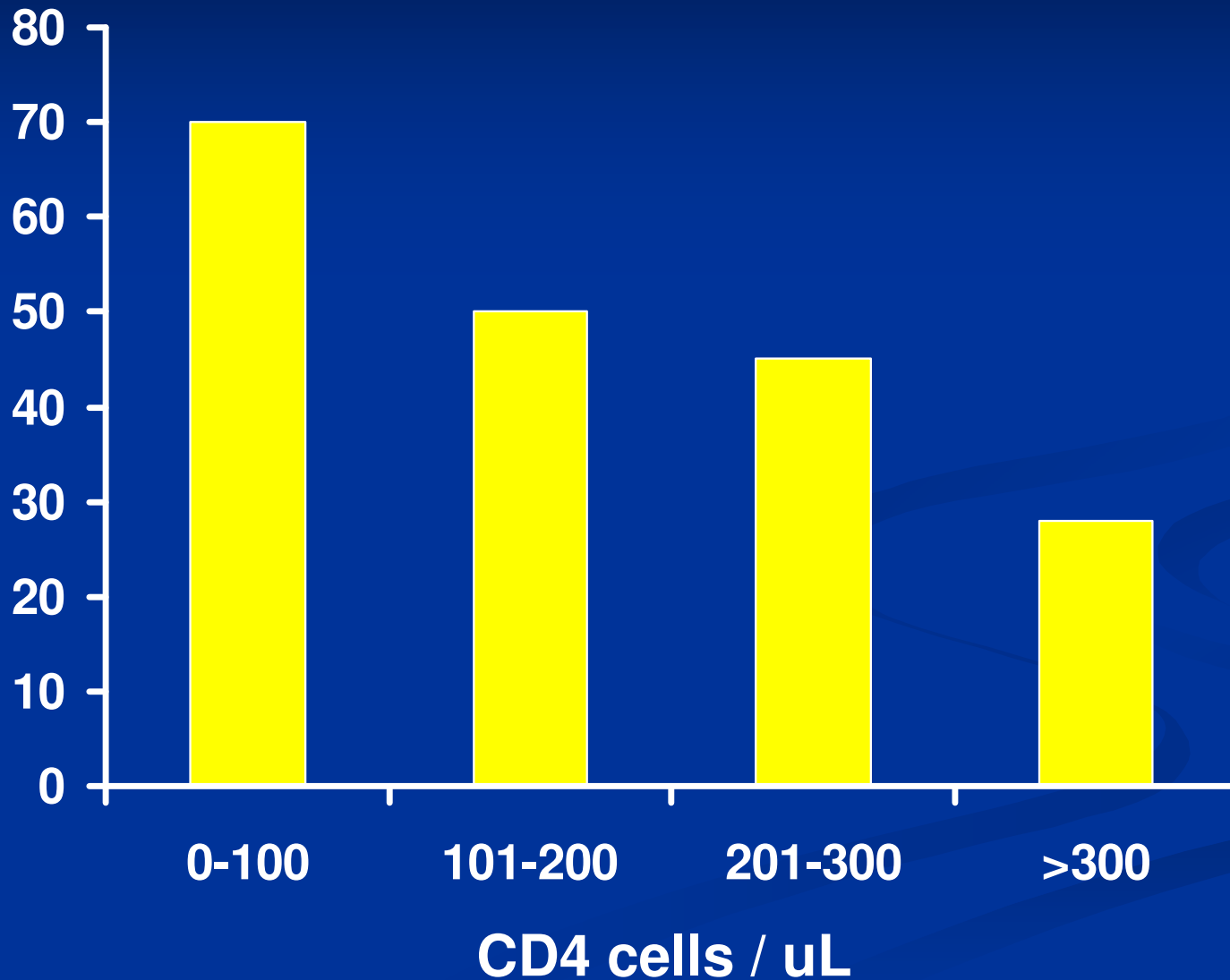
# HIV and TB: Global Epidemiology

- Proportion of TB cases with HIV infection increased dramatically in 1990s
- Burden per capita highest in sub-Saharan Africa
- >50% of TB cases HIV infected

# HIV-Infected Patients Are at Increased Risk

- To acquire TB
- To develop active TB once infected with TB
- To become re-infected with a second strain of TB

# Extrapulmonary Tuberculosis





# MTB Pulmonary Disease in AIDS Patients

- 75 % of patients have pulmonary disease
- 20 – 59 % have hilar or mediastinal adenopathy
- 12 – 28 % have pleural effusions
- 7 – 18 % have miliary pattern
- 12 % have normal CXR, positive sputum culture
- Other diseases masquerade as TB

# TB Treatment

- Treat HIV+ same as HIV-
- INH, RIF, PZA x 2 months, INH, RIF x 4 months
- Use EMB initially while sensitivities pending if INH resistance  $> 4\%$

# TB Treatment in HIV Co-infected Patients

- Response rates similar between HIV+ and HIV– patients
- Components of successful therapy:
  - Resistance testing
  - DOT
- Multiple-drug-resistant TB will emerge and spread with inadequate treatment programs

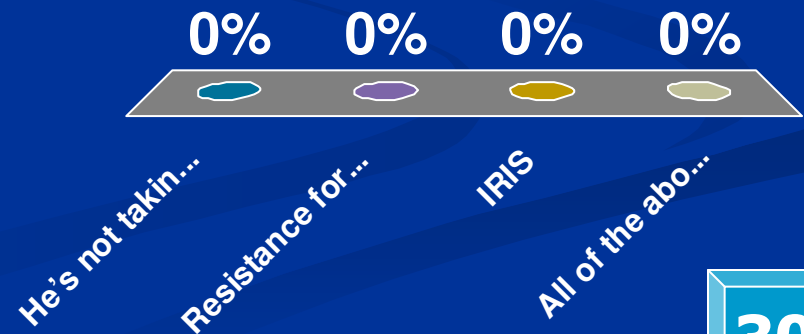
- A 32-year-old man with pulmonary TB is treated with INH, PZA, EMB, RIF

At first there is a good response, however two weeks after starting treatment he's getting fever of 38.3C, cervical lymphadenopathy and shortness of breath



# What is your diagnosis?

- A. He's not taking his medicine
- B. Resistance for the prescribed medicine
- C. IRIS
- D. All of the above are optional



- What is your diagnosis?
  - A. He's not taking his medicine
  - B. Resistance for the prescribed medicine
  - C. IRIS
  - D. All of the above are optional



# “Paradoxical Reactions” in Tuberculosis (IRIS)

Transient worsening of clinical signs  
and symptoms after initial response to  
anti-tuberculosis therapy



# “IRIS” in Tuberculosis

- First recognized in 1950s
- Lymphadenitis (12 – 25 %), pulmonary disease, central nervous system, tuberculomas
- 1 – 6 months post initiation of therapy
- May require steroids

# “IRIS” in Tuberculosis and HIV Co-infection

- Can happen with any antiretroviral regimen
- Mean onset of symptoms is 2 weeks
- Mean duration of symptoms is 3 weeks
- Most common symptoms include fever, cervical lymphadenopathy, intrathoracic lymphadenopathy
- Associated with restoration of immune responses to *M. tuberculosis*

# TB and HIV: Immediate vs. Delayed HAART

- TB treatment must be given urgently.
- The urgency of HIV treatment depends on predictors of HIV disease progression especially the CD4 cell count.
  - $<100$  cells/mm<sup>3</sup> - **HAART ASAP**
  - 100-200 cells/mm<sup>3</sup> - **HAART after 2 months**
  - $>200$  cells/mm<sup>3</sup> - **HAART after TB RX finished**

# Antiretroviral Therapy Options

- Triple NRTI with Rifampin
- NNRTI (EFV) 800 mg\* with Rifampin
- Ritonavir + saquinavir with rifampin
- Protease inhibitor (IDV, NFV, APV)\* with Rifabutin

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A 23 year old male presents with dry cough since three weeks and dyspnoea. He was tested HIV-positive three years ago. Then with a CD4 count of 300. He stopped taking his medicine in 2007 because of side effects

What is your most likely diagnosis?

- A. Pneumococcal pneumonia
- B. PCP-infection
- C. VZV-pneumonia



# *Pneumocystis jiroveci*

## Pneumonia: Epidemiology

- Caused by *P jiroveci* (formerly *P carinii*)
- Before widespread use of PCP prophylaxis and effective ART, PCP seen in 70-80% of AIDS patients
- Risk factor: CD4 count  $<200$  cells/ $\mu$ L



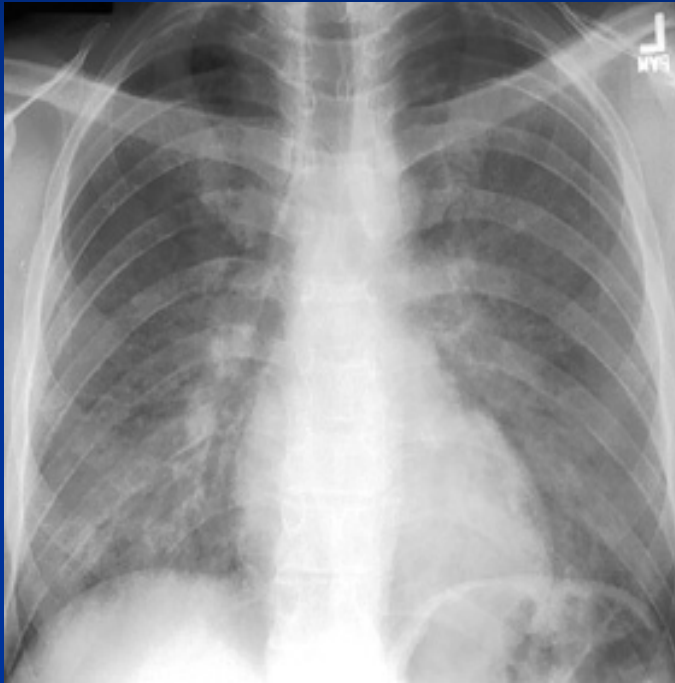
# PCP: Clinical Manifestations

- dyspnea, fever, nonproductive cough, chest discomfort
- Subacute onset, worsens over days-weeks
- Chest exam may be normal, or diffuse dry rales, tachypnea
- CXR: Typical: diffuse bilateral, symmetrical interstitial infiltrates

# PCP: Diagnosis

- Clinical presentation, blood tests, radiographs suggestive but not diagnostic
  - Organism cannot be cultured
- Hypoxemia: characteristic, may be mild or severe ( $PO_2 < 70$  mmHg)
- LDH  $> 500$  mg/dL is common

# PCP: Diagnosis (Imaging)



Chest X ray: PCP with bilateral, diffuse granular opacities



Chest X ray: PCP with bilateral perihilar opacities, interstitial prominence, hyperlucent cystic lesions

# PCP: Diagnosis

- Definitive diagnosis requires demonstrating organism:
  - Induced sputum (sensitivity <56%)
    - Spontaneously expectorated sputum: low sensitivity
  - Bronchoscopy with bronchoalveolar lavage (sensitivity 90-99%)

# PCP: Diagnosis (Histopathology)



silver stain: *P jiroveci* organisms in tissue

# PCP: Primary Prophylaxis

- Initiate:
  - CD4 <200 cells/ $\mu$ L
- Discontinue:
  - On ART with CD4 >200 cells/ $\mu$ L for >3 months
- Reinitiate:
  - CD4 decreases to <200 cells/ $\mu$ L

# PCP: Primary Prophylaxis (2)

- First choice:
  - Trimethoprim-sulfamethoxazole 480 mg QD



# PCP: Primary Prophylaxis (3)

## ■ Alternative

- TMP-SMX DS 1 tablet PO 3 times Q week
- Dapsone 100 mg PO QD or 50 mg BID
- Aerosolized pentamidine 300 mg Q month
- Atovaquone 1,500 mg PO QD\*

\* Effective as toxoplasmosis prophylaxis (for CD4 count <100 cells/ $\mu$ L + positive serology)

# PCP: Treatment

- Duration: 21 days for all treatment regimens
- Preferred: TMP-SMX 1980 mg tid
  - Adjust dosage for renal insufficiency

# PCP: Treatment

- Adjunctive:
  - Corticosteroids
    - For moderate-to-severe disease (room air  $PO_2 < 70$  mmHg)
    - Give as early as possible (within 72 hours)
    - ❖ Prednisone 40 mg BID days 1-5
    - ❖ 40 mg QD days 6-10
    - ❖ 20 mg QD days 11-21

Questions?