

# HIV and Related Infections

**Kaya Sürer, MD**

Near East University Faculty of Medicine  
Infectious Diseases and Clinical Microbiology

# HIV

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- Human immunodeficiency virus (HIV) infection results
  - from asymptomatic carriage
  - life threatening opportunistic disease.
- In persons infected with HIV, ongoing viral replication produces a sequential decline in and ablation of cell-mediated immunity, giving rise to diverse manifestations of opportunistic disease.

# History

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- Disease caused by HIV-induced immunosuppression was first described in 1981,
  - Los Angeles,
  - New York,
  - San Francisco observed opportunistic infections in homosexual men.
- Simultaneously, an outbreak of Kaposi's sarcoma was reported in young homosexual men from the same three cities.
- These patients had a
  - selective defect in cell-mediated immunity
  - low numbers of CD4+ T lymphocytes
  - development of opportunistic infections.

# History 1983-84

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- Pasteur institute :
  - Lymphadenopathy associated virus LAV
- National Institute Health (USA) :
  - Human T lymphotropic virus HTLV-III
- Levy et al :
  - AIDS associated virus ARV
- International Virus Taxonomy Comitee :
  - Human immunodeficiency virus HIV

# History

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- Retrospective studies of serum and tissue indicated that the virus was present in Africa as early as 1959 and that disease associated with HIV occurred in the United States in 1968
- Clavel, Montagnier at 1986:
  - isolated different virus in Africa
  - called HIV-2

# Correlation of complications with CD4 cell counts

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CD <sub>4</sub> Cell Count	Infectious Complications	Non-Infectious Complications
> 500 / mm <sup>3</sup>	Acute Retroviral Syndrome  Candidal Vaginitis	Persistent Generalized Lymphadenopathy (PGL)  Guillain Barre Syndrome  Myopathy  Aseptic Meningitis

# Correlation of complications with CD4 cell counts

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CD <sub>4</sub> Cell Count	Infectious Complications	Non-Infectious Complications
200-499 mm <sup>3</sup>	<ul style="list-style-type: none"><li>Pneumococcal and other bacterial pneumonias</li><li>Pulmonary tuberculosis</li><li>Herpes zoster</li><li>Oropharyngeal candidiasis (thrush)</li><li>Kaposi's sarcoma</li><li>Oral hairy leukoplakia</li></ul>	<ul style="list-style-type: none"><li>Cervical intraepithelial neoplasia</li><li>Cervical cancer</li><li>B-cell Lymphoma</li><li>Anemia</li><li>Mononeuritis multiplex</li><li>Idiopathic thrombocytopenic purpura</li><li>Hodgkin's lymphoma</li><li>Lymphocytic interstitial pneumonitis</li></ul>

# Correlation of complications with CD4 cell counts

CD <sub>4</sub> Cell Count	Infectious Complications	Non-Infectious Complications
< 200 / mm <sup>3</sup>	<ul style="list-style-type: none"><li>Pneumocystis carinii pneumoniae</li><li>Disseminated Histoplasmosis and Coccidioidomycosis</li><li>Miliary / Extrapulmonary tuberculosis</li><li>Disseminated CMV</li><li>Disseminated Mycobacterium avium complex</li></ul>	<ul style="list-style-type: none"><li>Wasting syndrome</li><li>Peripheral neuropathy</li><li>HIV associated dementia</li><li>Cardiomyopathy</li><li>Vacuolar myelopathy</li><li>Progressive polyradiculopathy</li><li>Non-Hodgkin's lymphoma</li><li>CNS lymphoma</li><li>Progressive multifocal leukoencephalopathy</li></ul>



# HIV Infections Staging System (2008)

## CDC

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STAGE	LABORATORY EVIDENCE	CLINICAL EVIDENCE
STAGE 1	Laboratory confirmation of HIV infection and CD <sub>4</sub> cell > 500 mm <sup>3</sup>	No AIDS defining conditions
STAGE 2	Laboratory confirmation of HIV infection and CD <sub>4</sub> cell 200-499 mm <sup>3</sup>	No AIDS defining conditions
STAGE 3 (AIDS)	Laboratory confirmation of HIV infection and CD <sub>4</sub> cell < 200 mm <sup>3</sup>	Or documentation of an AIDS defining condition with laboratory confirmation of HIV infection
STAGE UNKNOWN	Laboratory confirmation of HIV infection and CD <sub>4</sub> cell unknown	And no information on presence of AIDS defining conditions

# Asymptomatic Disease

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- Is the longest period in the course of HIV
- Here the patient is asymptomatic & apparently healthy
- High CD4 count (often  $> 500$  cells/mm<sup>3</sup>)
- Slow progressive decline in CD4+ count
- Typically lasts for 7-12 years

# THE ACUTE HIV SYNDROME (Acute Retroviral Syndrome)

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- 50 to 70% with HIV infection experience acute clinical syndrome approximately 3 to 6 weeks after primary infection
- The syndrome is typical of an acute viral syndrome and produces an acute infectious mononucleosis like picture .

# THE ACUTE HIV SYNDROME

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- May present with :
  - Fever
  - Pharyngitis
  - Lymphadenopathy
  - Headache/ retroorbital pain
  - Arthralgia/myalgia
  - Lethargy/malaise
  - Anorexia/weight loss
  - Nausea/vomiting/diarrhea

# THE ACUTE HIV SYNDROME

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- The Maculopapular Rash of Acute Seroconversion Illness



# THE ACUTE HIV SYNDROME

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- High levels circulating virus
- Often greater than one million copies/ml
- Acute symptoms may or may not occur
- Symptoms are often vague
- High chance that patients seeking care may not be tested

# AIDS / Neurological manifestations

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- Headache & lethargy
- Dementia, ataxia, altered personality,
- Convulsions, incontinence
- Meningism
- Visual impairment
- Focal seizures, hemiplegia, other focal neurologic deficits.

# AIDS / Opportunistic infections

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- Toxoplasmosis
- Cryptococcosis
- Progressive multifocal leukoencephalopathy
- Cytomegalovirus disease
- Syphilis
- Tuberculosis
- HTLV-1 infection



# AIDS / Neoplasms

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- Primary CNS lymphoma
- Kaposi's sarcoma

# AIDS / Result of HIV Infections

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- Aseptic meningitis
- HIV encephalopathy (AIDS dementia complex)
- Myelopathy-vacuolar myelopathy
  - Pure sensory ataxia
  - paresthesia/dysaesthesia
  - Peripheral neuropathy
- Myopathy

# Respiratuar manifestations

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- Persistent cough
- Dyspnea, cyanosis, tachypnea
- Fever, haemoptysis, pleural effusion
  
- PCP
- TB

# Cardiac Manifestations

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- HIV associated cardiomyopathy :
  - Late complication
  - Clinical features like CCF, edema, shortness of breath.
  - May be a side effect of IFN- $\alpha$  or nucleoside analogue therapy

# Cardiac Manifestations

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- Other diseases of myocardium :
  - Kaposi sarcoma
  - Cryptococcosis
  - Chagas disease
  - Toxoplasmosis

# Cardiac Manifestations

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- Pericardial Efusion :
- Predisposing factors include
  - Mycobacterial infection
  - Cryptococcal infection
  - Pulmonary infection
  - Lymphoma
  - Kaposi Sarcoma

# Cardiac Manifestations

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- Pericarditis :
  - Rare 5%
  - Tamponade and death can occur

# Other Cardiac Manifestations

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- Nonbacterial thrombotic endocarditis –this may explain the embolic phenomena
- Hypotension and Collapse
- High % of patients has hypertriglyceredemia and elevations of serum cholesterol , this problem appears to be a side effect of HAART.



# Oropharyngeal and Gastrointestinal system

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- Clinical manifestations most frequently due to
  - Secondary infection
  - Kaposi Sarcoma
  - Lymphoma

# Oropharyngeal and Gastrointestinal system

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- Oral lesions :
  - Thrush –candida
  - Oral hairy Leukoplakia
  - Aphthous ulcers

# Oropharyngeal and Gastrointestinal system

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- THRUSH :
- Due to candida
- Occur in patients with CD4 count less than 300
- Characterized by White cheesy exudate often on an erythematous mucosa
- Commonly seen on soft palate
- Early lesions found on gingival border
- Diagnosis by scrapping-pseudo hyphal elements
- Culture no diagnostic value

# Oropharyngeal and Gastrointestinal system

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- ORAL HAIRY LEUKOPLAKIA :
- Is one of the early manifestation.
- Along the lateral borders of the tongue and adjacent buccal mucosa
- Not considered premalignant
- Serial cases respond to topical podofylline / systemic therapy with anti herpesvirus agents

# Oropharyngeal and Gastrointestinal system

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- ESOPHAGITIS :
- Candida infection
- CMV - associated with single large ulcer
- HSV - Multiple small ulcers
- KS
- Lymphoma

# Oropharyngeal and Gastrointestinal system

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- APHTHOUS ULCERS :
- Posterior oropharageal
- Unknown etiology
- Painful and interfering with swallowing
- Palatal, glossal, gingival ulcers may be due to Cryptococcus diseases or histoplasmosis

# Oropharyngeal and Gastrointestinal system

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- INFECTIONS OF SMALL AND LARGE INESTINE :
- May cause diarrhea, abdominal pain and fever due to
  - Bacterial
  - Protozoa
  - Viral diseases

# Oropharyngeal and Gastrointestinal system

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- Bacterial Agents :
  - Salmonella
  - Shigella
  - Campylobacter
  - *S. typhimurium*



# Oropharyngeal and Gastrointestinal system

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- *Salmonella typhimurium* :
  - Presents with non specific symptoms including fever, anorexia, fatigue & malaise diarrhea common diagnosis made by blood and stool culture
  - Treatment is long term Ciprofloxacin
  - HIV infected increases incidence of *S.typhi* infection

# Oropharyngeal and Gastrointestinal system

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- Campylobacter :
  - Campylobacter jejuni
  - Presents with crampy abdominal pain, fever & bloody diarrhea
  - Systemic infection can occur
  - Sensitive to Erythromycin

# Oropharyngeal and Gastrointestinal system

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- Fungal Infections :
  - Histoplasmosis
  - Coccidioidomycosis
  - Penicilliosis
  - Peritonitis is seen with *C.immitis*

# Oropharyngeal and Gastrointestinal system

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- Opportunistic infections of the bowel
  - Cryptosporidia
  - Microsporidia
  - Isospora belli

# Oropharyngeal and Gastrointestinal system

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- Cryptosporidium infection :
- EARLY STAGES OF HIV INFECTION.
- Most common opportunistic protozoa infecting GIT, 1 % per year & produces a life threatening diarrhea 75 % cases diarrhea and pain abdomen is the symptom 25% nausea and vomiting
- May also cause biliary tract disease-cholecystitis with or without cholangitis
- Diagnosed by stool examination
- Treated with Nitaoxanide 2000 mf per day

# Oropharyngeal and Gastrointestinal system

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- Microsporidia :
- Small unicellular, obligate intracellular parasite.
- Clinical picture similar to cryptosporidial infection and include abdominal pain & diarrhea
- Diagnosed by exam of the stool ,intestinal aspirate ,or intestinal biopsy specimen.
- Microsporidia are located in variety of extra intestinal locations including eye, muscle, liver -- conjunctivitis and hepatitis
- Treated by Albendazole 400mg twice daily

# Oropharyngeal and Gastrointestinal system

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- *Isospora belli* :
  - Clinical syndrome identical to cryptosporidia
  - Treated with TMP/SMX

# Oropharyngeal and Gastrointestinal system

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- CMV colitis :
- 5 to 10 %of patients with AIDS
- Less common with the advent of HAART
- Presents as diarrhea, abdominal pain, weight loss and anorexia
- Non bloody diarrheas
- Endoscopy shows multiple mucosal ulceration and characteristic inclusion bodies
- Treatment with Ganciclovir or Foscarnat for three to six weeks relapse common
- CMV retinitis should be looked for...



# Hepatobiliary Diseases

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- 95% have evidence of infection with HBV
- 5 To 40 % are co-infected with HCV
- Co-infection with D, E and G viruses common
- Interferon- $\alpha$  is less successful in the treatment of HBV / HIV
- The treatment of choice is lamivudine, adefovir, tenofovir
- HCV infection is more severe in patients with HIV infection
- Increased chance of developing cirrhosis
- Treatment for HCV infection consists of pegylated IFN- $\alpha$  and Ribavirin.

# Hepatobiliary Diseases

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- Hepatitis A virus infection IS NOT SEEN FREQUENTLY in patients with HIV infection
- Infection with hepatitis G virus , also known as GB virus , is seen in 50 % of patients with HIV infection
- Granulomatous hepatitis
- Mycobacterial
- fungal infections

# Hepatic masses

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- Fungal infection *C. immitis* and *Histoplasma capsulatum* are those most likely to involve the liver.
- Biliary tract disease in the form of papillary stenosis or sclerosing cholangitis has been reported in the context of
  - Cryptosporidiosis
  - CMV
  - KS

# Hepatic failure

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- Fatal hepatic reactions have been reported with antiretrovirals including :
  - nucleoside analogues,
  - nonnucleoside analogues,
  - protease inhibitors,

# Drug Toxicity

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- Hepatic steatosis
- Lactic acidosis
- Fulminant liver failure.
- Nevirapine-fatal fulminant and cholestatic hepatitis, hepatic necrosis, hepatic failure
- Indinavir, atazanvir —moderate elevations of SGOT/SGPT
- Pentamidine, dideoxynucleosides may cause pancreatic injury

# Diseases of the Kidney and Genitourinary tract

- Direct consequence of HIV infection,
- Opportunistic infection or neoplasm,
- Related to drug toxicity

# HIV-Associated Nephropathy

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- HIV-ASSOCIATED NEPHROPATHY CAN BE AN EARLY MANIFESTATION
- HIV patients typically present with a nephrotic syndrome
- Nephrotic- range proteinuria (>3.5 g/d),
- Azotemia, hypoalbuminemia, edema and hyperlipidemia.

# HIV-Associated Nephropathy

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- The CD4 count in these patients is usually depressed below 200 cells/ mm<sup>3</sup>
- The prognosis for renal survival is worse CD4 <50 cells/ mm<sup>3</sup>
- Hypertension are rare.
- Ultrasound examination reveals enlarged, hyperechogenic kidneys.
- A definitive diagnosis is obtained through renal biopsy.



# HIV-Associated Nephropathy

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- Histologically focal segmental glomerulosclerosis and mesangial proliferation in 10 to 15% of cases.
- Prior to effective antiretroviral therapy, this disease was characterized by relatively rapid progression to end-stage renal disease.
- Treatment with prednisone. 60 mg/d has been reported to be of benefit in some cases

# Lipodystrophy Syndrome

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- Seen in 33 to 75% of patients with HIV infection receiving HAART
- Elevations in plasma triglycerides, total cholesterol, apo-lipoprotein B, as well as hyperinsulinemia and hyperglycemia
- Clinical consists of truncal obesity coupled with peripheral wasting
- In Patients receiving thymidine analogues...this is severe

# Metabolic problems

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- Patients with HIV on HAART have an increased incidence of osteonecrosis or avascular necrosis the hip and shoulders.
- Advanced HIV disease may develop hyponatremia due to the Syndrome of InappropriateADH secretion.
- Lactic acidosis

# Adrenal Insufficiency

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- Mycobacterial infections,
- CMV
- Cryptococcal disease,
- Histoplasmosis,

# Thyroid Gland

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- Elevated TSH in 2-3%
- Advanced HIV infection of the thyroid gland may occur with opportunistic infections including
  - *P. carinii*,
  - CMV,
  - Mycobacteria,
  - *Toxoplasma gondii*,
  - *Cryptococcus neoformans*

# Rheumatologic Diseases

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- 50% have arthralgias
- 5-10% have some form of reactive arthritis
- Increased incidence of reactive arthritis
- Variant of Sjogrens syndrome ...now referred as DIFFUSE INFILTRATIVE LYMPHOCYTOSIS SYNDROME(DILS)

# Painful Articular Syndrome.

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- The cause of this arthropathy is unclear
- This condition, found in as many as 10% of AIDS patients- presents as an acute, severe, sharp pain in the affected joint.
- It affects primarily the knees & shoulders
- Lasts 2 to 24 h; and pain may be severe enough to require narcotic analgesics.

# Diseases of the Hematopoietic System

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- Lymphadenopathy,
- Anemia
- Leucopenia,
- Thrombocytopenia



# Generalized Lymphadenopathy

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- EARLY CLINICAL MANIFESTATION OF HIV
- This condition is defined as the presence of enlarged lymph nodes (>1 cm) in two or more extralingual sites for >3 months without an obvious cause.
- In more advanced disease, lymphadenopathy may also be due to
  - atypical mycobacterial infection,
  - toxoplasmosis,
  - systemic fungal infection,
  - bacillary angiomatosis.

# Anemia

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- Drug toxicity- zydovudine, dapsone
- Systemic fungal
- Mycobacterial infections,
- Nutritional deficiencies,
- Parvovirus B19 infections.

# Neutrophenia

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- Seen in advanced HIV
- Neutropenia may be seen in approximately half of patients.

# Thrombocytopenia

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- An early consequence of HIV
- For platelet counts  $<20,000$  intravenous Ig or anti- Rh Ig for an immediate response
- Splenectomy rarely needed

# Ophthalmologic disease

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- OCCUR IN 50% OF PATIENTS WITH ADVANCED HIV—MOSTLY CMV INFECTION
- MAJORITY OF CMV CASES OCCUR WHEN THE CD4 COUNT IS <50
- CMV retinitis causes painless progressive loss of vision
- Acute retinal necrosis syndrome-is a bilateal necrotising retinitis due to HSV or VZV

# CMV INFECTIONS

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- Reactivation disease with low CD4 counts (counts often below 50-100).
- Most frequent end-organ disease of GI tract, central nervous system and eyes.
- CMV pneumonia less frequent than in other groups of compromised hosts
- Ganciclovir, Foscarnet and Cidofovir are available therapeutic agents.

# **Mycobacterium avium complex infection**

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- Most often characterized by fever, weightloss , night sweats
- Anemia, thrombocytopenia, elevated alkaline phosphatase in highly advanced AIDS (CD4 < 50).
- It may be seen as an immune reactivation disease (lung, LNs, diarrhea) with HAART initiation.
- Diagnosis often established by blood culture.

# Some Clinical Features

## Suspicious/suggestive of HIV infection

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- Sexually Transmitted infections
- Multiple sex partners
- Sex partner with known HIV infection
- Sex with commercial sex workers
- Present or past injecting drug use
- Recipient of blood products
- Injections, tattooing or body piercing
- Using non sterile instruments
- Recurrent Herpes Zoster (shingles)
- Recurrent Pneumonia
- Bacteraemia (especially *Salmonella typhimurium*)



# Some Clinical Features

## Suspicious/suggestive of HIV infection

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- **Symptoms Weight Loss (>10 kg or >20% of original weight)**
  - Diarrhea (>1 month)
  - Pain on Swallowing (suggests oesophageal candidiasis)
  - Burning sensation in the feet (peripheral sensory neuropathy)
- **Signs**
  - Herpes zoster scar (shingles)
  - Pruritic papular rash
  - Kaposi's sarcoma
  - Persistent Generalized Lymphadenopathy
  - Oral Candidiasis
  - Oral Hairy Leukoplakia
  - Persistent painful genital ulceration

