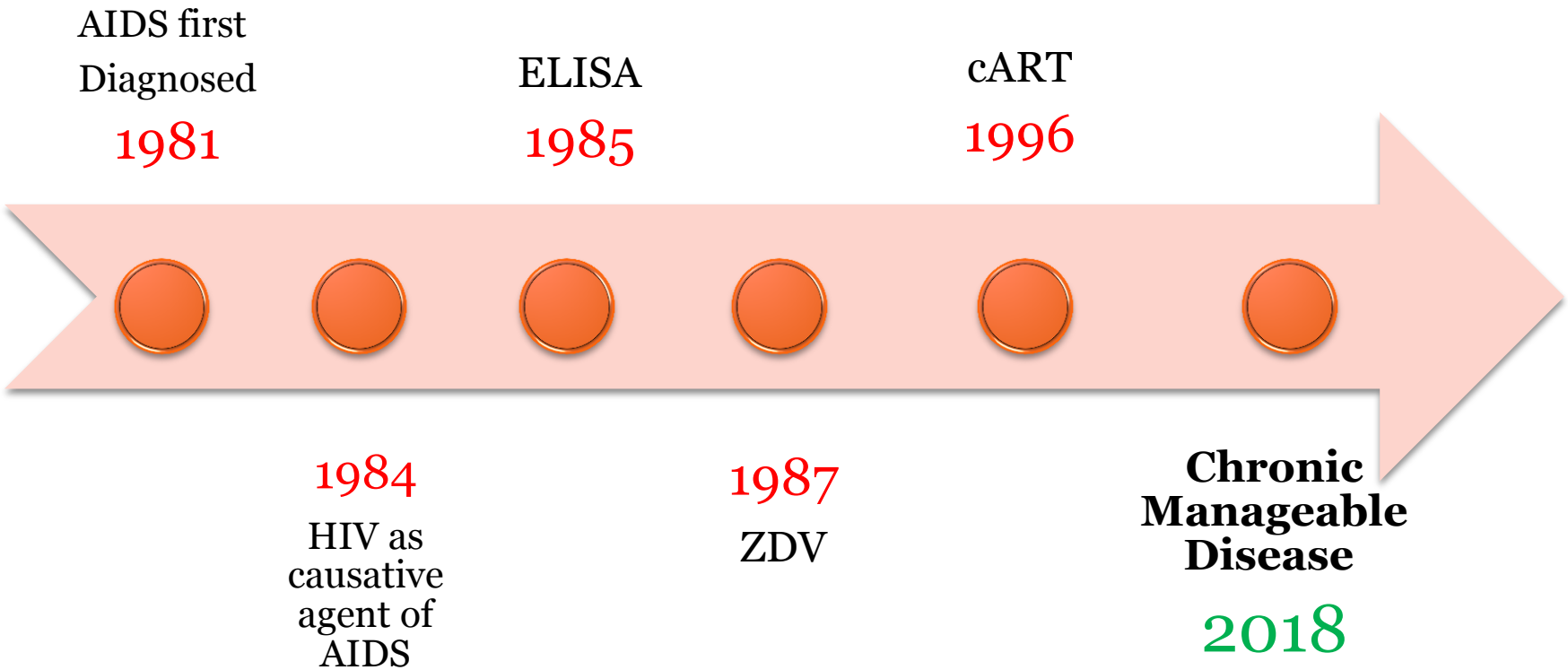
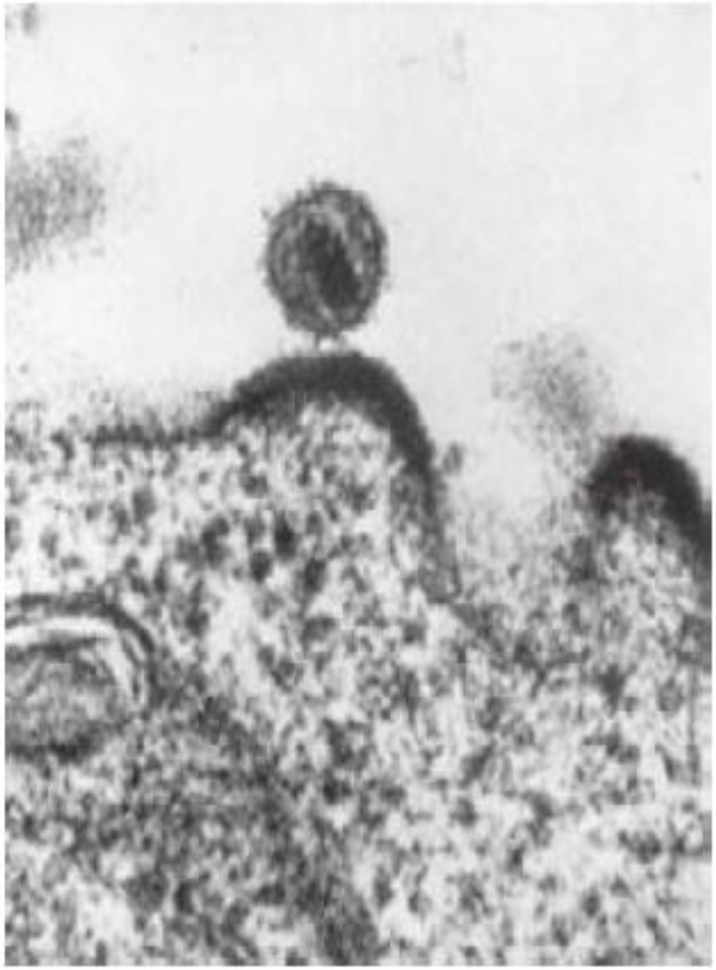
HIV/AIDS

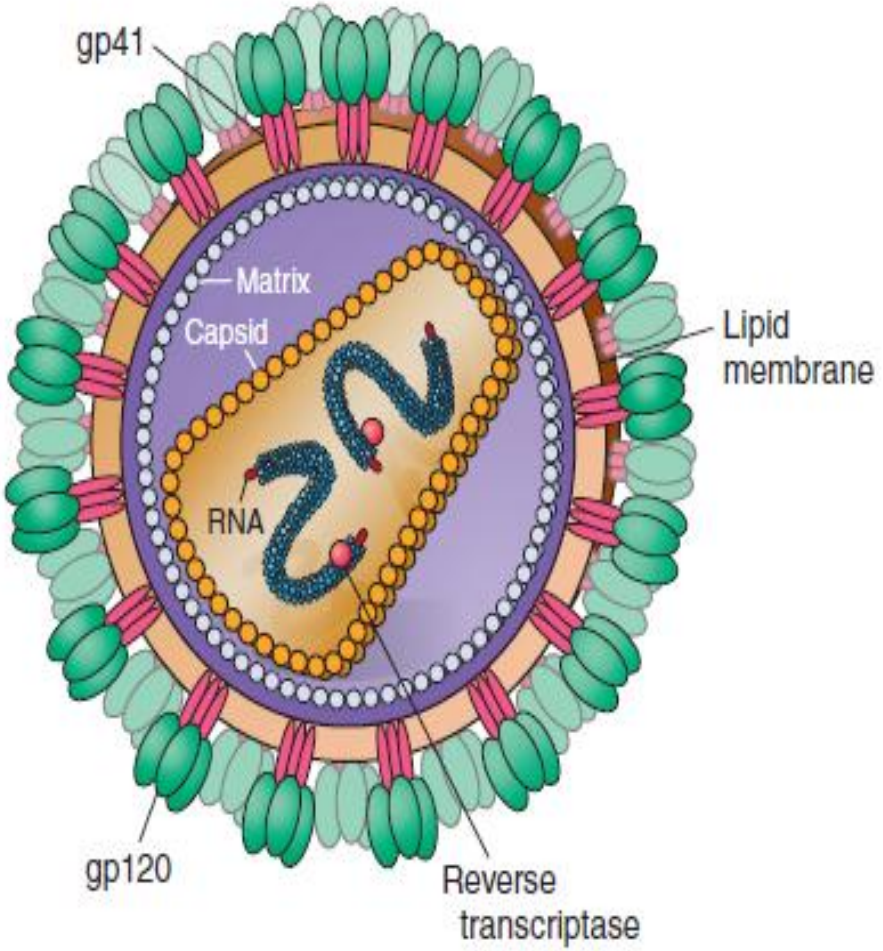
By: Saeed reza jamali mogadam


AIDS first Diagnosed
1981
1984
HIV as causative agent of AIDS
ELISA
1985
1987
ZDV
cART
1996
Chronic Manageable Disease
2018

ETIOLOGIC AGENT

- HIV
  - Retroviridae
    - Lentiviruses
  - HIV-1
    - The most common cause of HIV disease throughout the world
  - HIV-2
    - West Africa




gp41
Matrix
Capsid
Lipid membrane
RNA
gp120
Reverse transcriptase

OCCUPATIONAL TRANSMISSION

- Small but definite
- Percutaneous injuries or contact of mucous membrane or non-intact skin with blood, tissue, or other potentially infectious body fluids
- Risk of HIV transmission
  - Skin puncture from a needle or a sharp object : **0.3%**
  - Mucous membrane exposure: **0.09%**
  - Non-intact skin exposure: **not precisely determined**

OCCUPATIONAL TRANSMISSION

- Potentially infectious
  - Blood
  - Visibly bloody body fluids
  - CSF; Synovial, pleural, peritoneal, pericardial and amniotic fluid
  - Semen and vaginal secretions (Non-occupational)
  - Breast milk (Non-occupational)

- **Not** potentially infectious
  - Feces, nasal secretions, saliva, sputum, sweat, tears, urine, and vomitus

Universal Precautions **PEP**

MOTHER-TO-CHILD TRANSMISSION

- <u>During pregnancy and delivery</u>
  - Mostly perinatal

- Probability of transmission
  - Without prophylactic ART: 15% - 35%
  - With cART: **<1%**

- Related Factors
  - Mother's level of plasma viremia
    - <1000 copies of HIV RNA/mL of blood → very unlikely
  - HLA match
  - Prolonged interval between membrane rupture and delivery

MOTHER-TO-CHILD TRANSMISSION

- Breast-feeding
- Risk factors
  - Detectable levels of HIV in breast milk
  - Mastitis
  - Low maternal CD4+ T cell counts
  - Maternal vitamin A deficiency

PATHOPHYSIOLOGY AND PATHOGENESIS

- Hallmark of HIV disease
  - Profound immunodeficiency resulting primarily from progressive quantitative and qualitative deficiency of helper T cells (CD4+)

- Patients with CD4+ T cell levels below certain thresholds are at high risk of developing a variety of opportunistic diseases
  - Infections
  - Neoplasms

- Aberrant immune activation and inflammation, play a critical role in the pathogenesis of HIV disease and other chronic conditions associated with HIV disease

  - Accelerated aging syndrome
  - Bone fragility
  - Cancers
  - Cardiovascular disease
  - Diabetes
  - Kidney disease
  - Liver disease
  - Neurocognitive dysfunction

Autoimmune Phenomena

- Psoriasis
- Idiopathic thrombocytopenic purpura
- Graves' disease
- Antiphospholipid syndrome
- Primary biliary cirrhosis

DIAGNOSIS OF HIV INFECTION

- Diagnosis of HIV infection depends on
  - Demonstration of antibodies to HIV
    - Generally appear in the circulation 3–12 weeks following infection
  - Direct detection of HIV or one of its components

- The standard blood screening tests for HIV infection are based on the detection of antibodies to HIV

Enzyme Immunoassay (EIA)

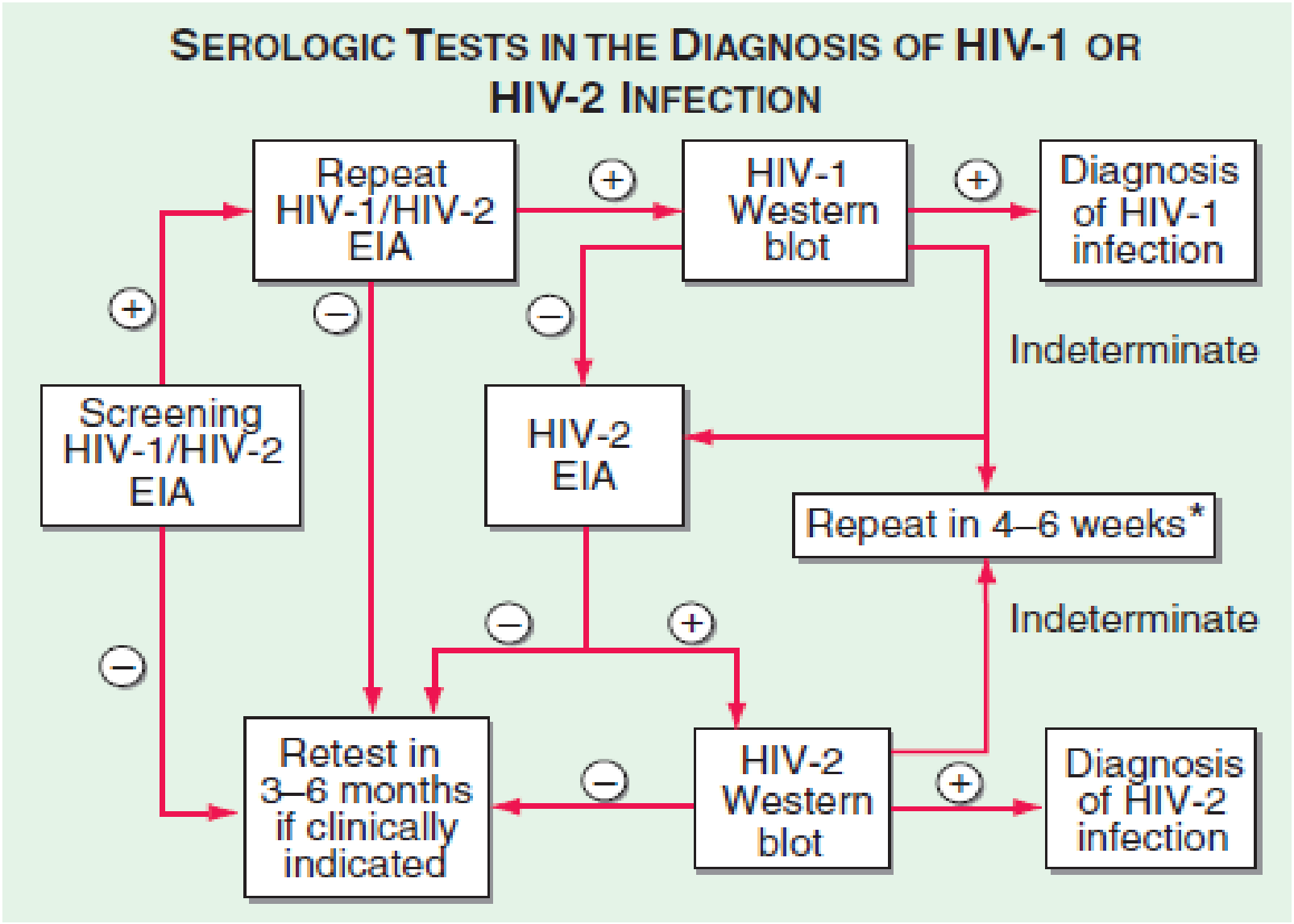
- Extremely good screening test with a sensitivity of >99.5%
- Antigens from both HIV-1 and HIV-2
- The fourth-generation
  - Antibodies to HIV + p24 antigen

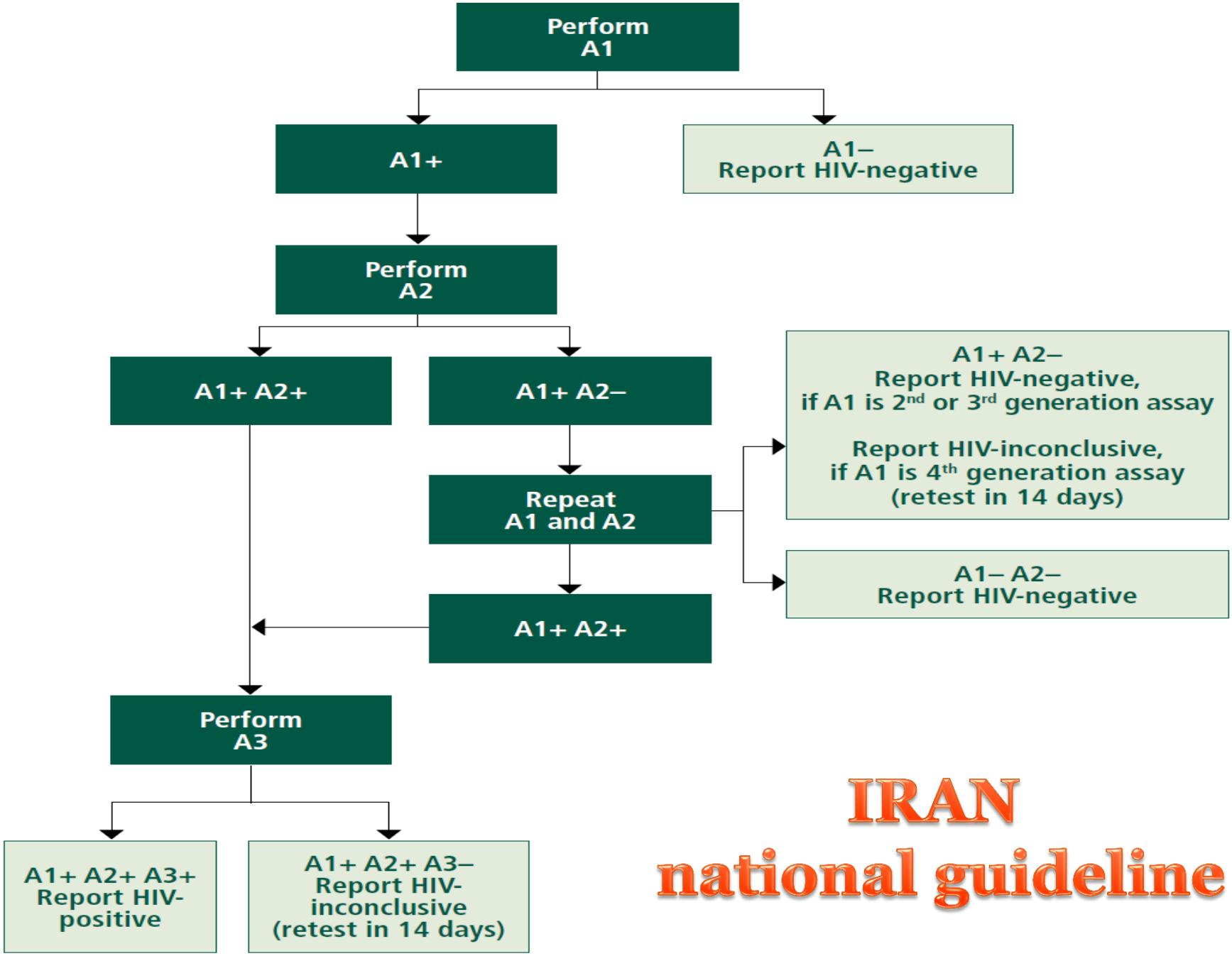
Enzyme Immunoassay (EIA)

- Not specific
- False-positive
  - Antibodies to class II antigens
    - Pregnancy
    - Blood transfusion
    - Transplantation
  - Autoantibodies
  - Hepatic disease
  - Recent influenza vaccination
  - Acute viral infections

Western blot

- Most commonly used confirmatory test
- Results
  - Positive
  - Negative
  - Indeterminate


SEROLOGIC TESTS IN THE DIAGNOSIS OF HIV-1 OR HIV-2 INFECTION
Repeat HIV-1/HIV-2 EIA
HIV-1 Western blot
Diagnosis of HIV-1 infection
Indeterminate
Screening HIV-1/HIV-2 EIA
HIV-2 EIA
Repeat in 4–6 weeks*
Indeterminate
Retest in 3–6 months if clinically indicated
HIV-2 Western blot
Diagnosis of HIV-2 infection



IRAN national guideline

HIV RNA or DNA

- Making a diagnosis when the Western blot results are indeterminate

- False-positive results have been reported
- Should be used for diagnosis only when standard serologic testing has failed to provide a definitive result

TREATMENT

TABLE 226-19 INITIAL EVALUATION OF THE PATIENT WITH HIV INFECTION

History and physical examination
Routine chemistry and hematology
AST, ALT, direct and indirect bilirubin
Lipid profile and fasting glucose
CD4+ T lymphocyte count
Two plasma HIV RNA levels
HIV resistance testing
HLA-B5701 screening
RPR or VDRL test
Anti-*Toxoplasma* antibody titer
PPD skin test or IFN-γ release assay
Mini-Mental Status Examination
Serologies for hepatitis A, hepatitis B, and hepatitis C
Immunization with pneumococcal polysaccharide; influenza as indicated
Immunization with hepatitis A and hepatitis B if seronegative
Counseling regarding natural history and transmission
Help contacting others who might be infected

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPD, purified protein derivative; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory.

- More than 25 ARV drugs in 6 mechanistic classes are approved for treatment of HIV infection:
  - Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)
  - Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
  - Protease inhibitors (PIs)
  - Integrase strand transfer inhibitors (INSTIs)
  - A fusion inhibitor (FI): Enfuvirtide
  - A CCR5 antagonist: Maraviroc

- Pharmacokinetic enhancers or boosters
  - Ritonavir
  - Cobicistat

ARVs

NRTI	NNRTI	PI	INSTI
Tenofovir (TDF)	Efavirenz (EFV)	Lopinavir (LPV)	Raltegravir (RAL)
Emtricitabine (FTC)	Nevirapine (NVP)	Atazanavir (AZV)	Dolutegravir (DTG)
Lamivudine (3TC)	Rilpivirine (RPV)	Darunavir (DRV)	Elvitegravir (EVG)
Abacavir (ABC)	Etravirine (ETR)	Fosampernavir (FPV)	Bictegravir (BIC)
Zidovudine (ZDV)	Delavirdine (DLV)	Tipranavir (TPV)	
	Doravirine (DOR)	Ritonavir (RTV)	
		Saquinavir (SQV)	
		Indinavir (IDV)	
		Nelfinavir (NFV)	

Iran 2017

Initial Regimens

NNRTI + 2 NRTI regimen

Efavirenz + Tenofovir + Emtricitabine

Efavirenz + Tenofovir + Lamivudine

INSTI + 2 NRTI regimen

Dolutegravir + Tenofovir + Emtricitabine

Dolutegravir + Tenofovir + Lamivudine

IRI National Guideline

- Everyone with HIV infection should be treated with cART regardless of CD4

- Patients initiating antiretroviral therapy must be willing to commit to life-long treatment and understand the importance of adherence to their prescribed regimen

- Follow up
  - Clinical
  - CD4: every 3-6 months
  - HIV RNA viral load: every 3-6 months
  - Other: LFT, CBC, Kidney function, ...

Vaccination

Pathogen	Indications	First Choice
Hepatitis B	All susceptible (anti-HBc- and anti-HBs-negative) patients	Hepatitis B vaccine: 3 doses
Hepatitis A	All susceptible (anti-HAV-negative) patients	Hepatitis A vaccine: 2 doses
Influenza	All patients annually	Inactivated trivalent influenza virus vaccine 1 dose yearly
Streptococcus pneumoniae	All patients, preferably before CD4≤200	PCV13 × 1 followed in 8 weeks or more by PPSV23 if CD4>200/μL
	Reimmunize patients initially immunized at a CD4<100 whose CD4+ >200/μL	
Human papillomavirus	All patients 13–26 years of age	HPV vaccine; 3 doses

CLINICAL MANIFESTATIONS

ACUTE HIV INFECTION

- Acute clinical syndrome ~3–6 weeks after primary infection
- 50-70%
- Acute infectious mononucleosis

General	Neurologic
Fever	Meningitis
Pharyngitis	Encephalitis
Lymphadenopathy	Peripheral neuropathy
Headache/retroorbital pain	Myelopathy
Arthralgias/myalgias	Dermatologic
Lethargy/malaise	Erythematous maculopapular rash
Anorexia/weight loss	Mucocutaneous ulceration
Nausea/vomiting/diarrhea	

ACUTE HIV INFECTION

- Most patients
  - Recover spontaneously
  - Followed by a prolonged period of clinical latency or smoldering low disease activity

- 10% of patients
  - Fulminant course of immunologic and clinical deterioration

ASYMPTOMATIC STAGE (CLINICAL LATENCY)

- Time from initial infection to clinical disease
  - Varies greatly
  - Median time ~10 years
- Disease progression is directly correlated with HIV RNA levels
- Average rate of CD4+ T cell decline is ~50/μL per year
- CD4+ <200/μL → clinically apparent disease
  - Infection
  - Cancer

SYMPTOMATIC DISEASE

- Any time during the course of HIV infection
- Spectrum of illnesses related to CD4+ T cell count

AIDS

- Anyone with HIV infection
  - CD4+ T cell count <200/μL in age 6 years and older
  - Who develops one of the HIV-associated diseases

6

AIDS

TABLE 226-2 CDC HIV INFECTION STAGES 1–3 BASED ON AGE-SPECIFIC CD4+ T LYMPHOCYTE COUNT OR CD4+ T LYMPHOCYTE PERCENTAGE OF TOTAL LYMPHOCYTES[a]

	Age on Date of CD4 T+ Lymphocyte Test					
	<1 Year		1–5 Years		6 Years through Adult	
Stage[a]	Cells/μL	%	Cells/μL	%	Cells/μL	%
1	≥1,500	≥34	≥1,000	≥30	≥500	≥26
2	750–1,499	26–33	500–999	22–29	200–499	14–25
3	<750	<26	<500	<22	<200	<14

SYMPTOMATIC DISEASE

- Respiratory
- Cardiovascular
- Oropharynx and Gastrointestinal
- Hepatobiliary
- Kidney and Genitourinary Tract
- Endocrine and Metabolic
- Immunologic and Rheumatologic
- Hematopoietic
- Dermatologic
- Neurologic
- Ophthalmologic
- Additional Disseminated Infections and Wasting Syndrome
- Neoplastic Diseases
- Immune Reconstitution Inflammatory Syndrome (IRIS)

Pulmonary disease

- Pneumonia
  - Recurrent bacterial pneumonia
  - Tuberculosis
  - Pneumocustis jiroveci pneumonia (PCP)

- Other major causes of pulmonary infiltrates
  - Other mycobacterial and fungal infections
  - Nonspecific interstitial pneumonitis
  - KS
  - Lymphoma

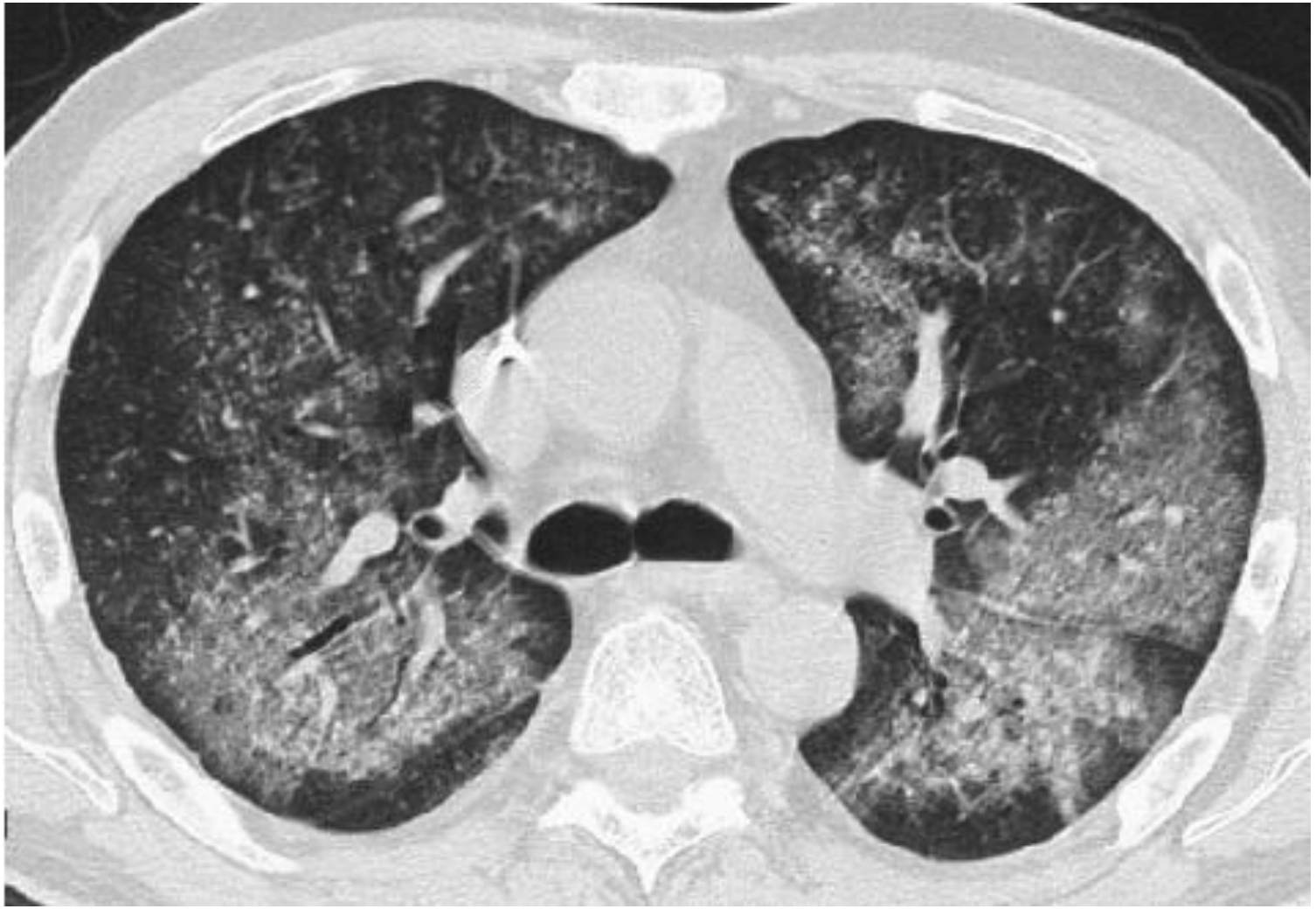
Pneumocystis pneumonia (PCP)

- 95% of patients have CD4+ T cell counts <200/μL

Pneumocystis pneumonia (PCP)

- Clinical findings
  - Fever
  - Nonproductive cough
  - Sharp or burning retrosternal chest worse on inspiration
  - Unexplained weight loss
- Indolent course

- Radiologic findings
  - CXR → normal film or faint bilateral interstitial infiltrate
  - Chest CT scan → patchy **ground-glass** appearance



Pneumocystis pneumonia (PCP)

- Prophylaxis
  - Who
    - Prior bout of PCP
    - CD4+ <200/µL or a CD4 percentage <15
    - Unexplained fever for >2 weeks
    - Recent history of oropharyngeal candidiasis
  - TMP/SMX, one DS or SS tablet daily
  - Toxoplasmosis and some bacterial respiratory pathogens
  - Until CD4+ T >200/µL for at least 3 months

Tuberculosis

- Reactivation TB in PPD+ is **7–10% per year**
- Can occur in any CD4 but clinical manifestation varied based on CD4 level
  - High CD4+
    - Typical pattern + cavitary apical lung involvement
  - Lower CD4+
    - Disseminated disease
    - Diffuse or lower-lobe bilateral reticulonodular infiltrates
    - Hilar and/or mediastinal adenopathy

Diseases of the Oropharynx and Gastrointestinal System

Oral lesions

- Thrush
  - White, cheesy exudate, often on an erythematous mucosa
  - Treatment: Nystatin / Fluconazole
- Oral hairy leukoplakia
  - White frondlike lesions along the lateral borders
  - EBV
  - Treatment: topical podophyllin or anti-herpesvirus agents
- Aphthous ulcers
  - Painful / Posterior pharynx / Unknown etiology
  - Treatment: Topical anesthetics / Thalidomide

A

Thrush

OHL

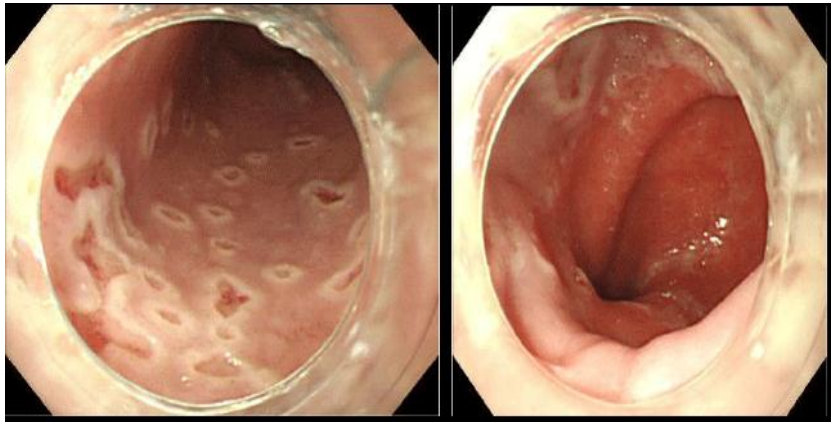
C

Aphthous Ulcer

Esophageal Disease

- Esophagitis
  - Candida
  - CMV
  - HSV

- Aphthous ulcers
- KS
- Lymphoma



Diseases of the Hematopoietic System

TABLE 226-13 CAUSES OF BONE MARROW SUPPRESSION IN PATIENTS WITH HIV INFECTION

HIV infection

Mycobacterial infections

Fungal infections

B19 parvovirus infection

Lymphoma

Medications

- Zidovudine
- Dapsone
- Trimethoprim/sulfamethoxazole
- Pyrimethamine
- 5-Flucytosine
- Ganciclovir
- Interferon α
- Trimetrexate
- Foscarnet

Lymphadenopathy

- Persistent generalized lymphadenopathy (PGL)
  - An early clinical manifestation of HIV infection
  - Presence of enlarged lymph nodes (>1 cm) in two or more extrainguinal sites for >3 months without an obvious cause
  - Marked follicular hyperplasia in the node in response to HIV
  - Discrete and freely movable nodes

- KS
- TB
- lymphoma
- Atypical mycobacterial infection
- Toxoplasmosis

Dermatologic Diseases

- Dermatologic problems
  - Can be seen throughout the course of HIV infection

- Seborrheic dermatitis
  - Up to 50% of patients

- Eosinophilic pustular folliculitis
  - Multiple, urticarial perifollicular papules
  - Eosinophilic infiltrate of the hair follicle in skin biopsy
  - Elevated serum IgE

- Norwegian scabies
- Reactivation herpes zoster (shingles)
- Herpes simplex virus

- Molluscum contagiosum

- Condyloma acuminatum

- Drug reactions

Neurologic Diseases

TABLE 226-14 NEUROLOGIC DISEASES IN PATIENTS WITH HIV INFECTION

- Opportunistic infections
  - Toxoplasmosis
  - Cryptococcosis
  - Progressive multifocal leukoencephalopathy
  - Cytomegalovirus
  - Syphilis
  - *Mycobacterium tuberculosis*
  - HTLV-1 infection
  - Amebiasis
- Neoplasms
  - Primary CNS lymphoma
  - Kaposi's sarcoma
- HIV-1 infection
  - Aseptic meningitis
  - HIV-associated neurocognitive disorders (HAND), including HIV encephalopathy/AIDS dementia complex
  - Myelopathy
    - Vacuolar myelopathy
    - Pure sensory ataxia
    - Paresthesia/dysesthesia
  - Peripheral neuropathy
    - Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome)
    - Chronic inflammatory demyelinating polyneuropathy (CIDP)
    - Mononeuritis multiplex
    - Distal symmetric polyneuropathy
  - Myopathy

Cryptococcal Meningitis

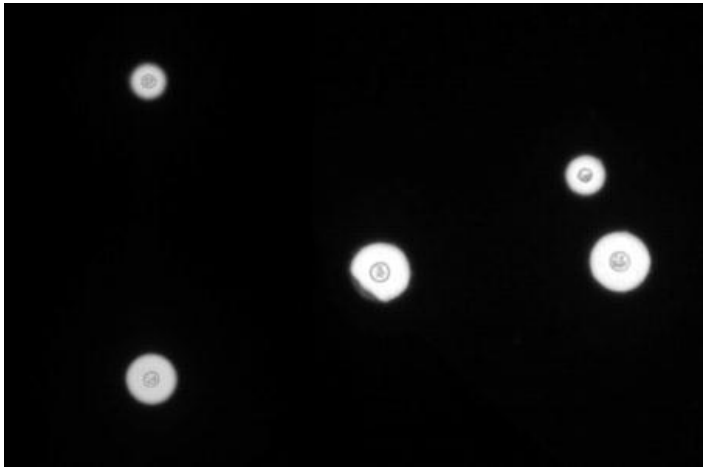
- CD4+ T cell counts <100/μL

- Subacute meningoencephalitis
  - Fever
  - Nausea
  - Vomiting
  - Altered mental status
  - Headache
  - Meningeal signs

Cryptococcal Meningitis *(Cont'd)*

- CSF
  - Normal
  - Modest elevations in WBC or protein levels and decreases in glucose
  - Opening pressure is usually elevated

- Diagnosis is made by identification of organism in CSF
  - Indian ink examination
  - Detection of cryptococcal antigen
  - Culture



Cryptococcal Meningitis *(Cont'd)*

- Treatment
  - Drug
    - Induction: Amphotericin B + flucytosine for at least 2 weeks
    - Fluconazole 400 mg/d PO for 8 weeks
    - Fluconazole 200 mg/d until the CD4+ >200 cells/µL for 6 months in response to ART
  - Repeated lumbar puncture

HIV-associated dementia

- Generally a late complication of HIV
- Major feature is the development of dementia, defined as a decline in cognitive ability from a previous level
  - Impaired ability to concentrate
  - Increased forgetfulness
  - Difficulty reading
  - Increased difficulty performing complex tasks

HIV-associated dementia *(Cont'd)*

- Diagnosis
  - Exclusion of other CNS diseases
  - MRI
    - Cerebral atrophy + bilateral ill-defined hyperintense signal in the periventricular white matter
  - CSF
    - Ruling out other
- Treatment
  - ART

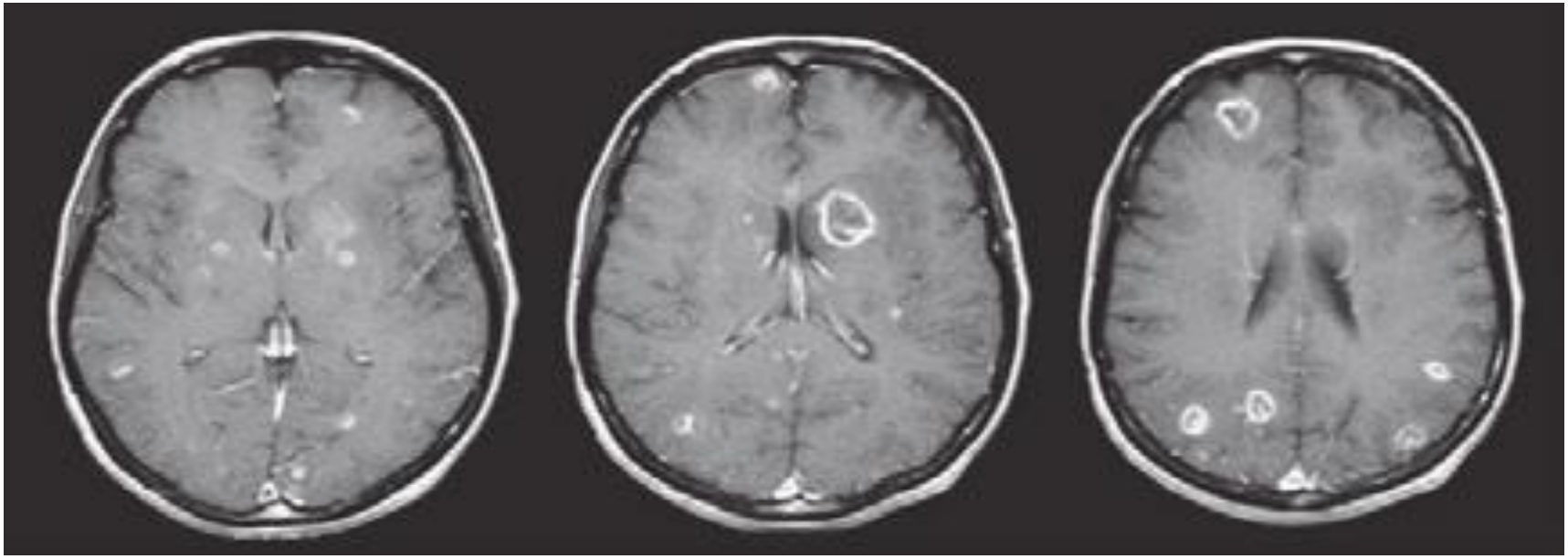
Toxoplasmosis

- Usually in patients with CD4+ <200
- Reactivation of latent tissue cysts

- Clinical presentation
  - Fever
  - Headache
  - Focal neurologic deficits: hemiparesis or aphasia
  - Seizure

Toxoplasmosis *(Cont'd)*

- MRI
  - Multiple lesions with ring-enhancement in multiple locations
  - Surrounding edema
  - Eccentric target sign



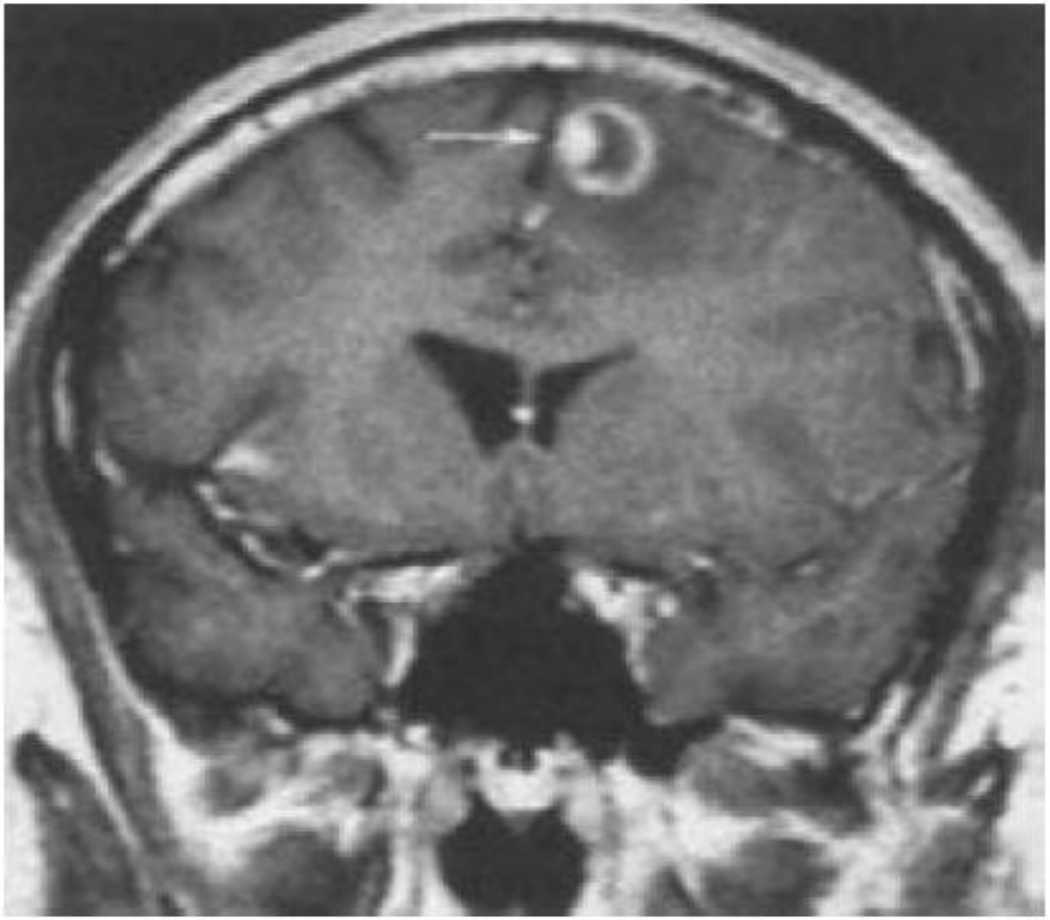


FIGURE 226-40 Central nervous system toxoplasmosis. A coronal postcontrast T1-weighted MRI scan demonstrates a peripheral enhancing lesion in the left frontal lobe, associated with an eccentric nodular area of enhancement (*arrow*); this so-called eccentric target sign is typical of toxoplasmosis.

Toxoplasmosis *(Cont'd)*

- Standard treatment
  - Sulfadiazine + pyrimethamine + leucovorin for a minimum of 4–6 weeks
- Maintenance therapy as long as CD4+ <200
- Patients with CD4+ T cell counts <100/µL and IgG antibody to Toxoplasma should receive primary prophylaxis for toxoplasmosis

Progressive multifocal leukoencephalopathy (PML)

- Late manifestation of AIDS (1-4%)
- JC virus
- Demyelination in subcortical white matter

- Protracted course with multifocal neurologic deficits, with or without changes in mental status
  - Seizures
  - Ataxia
  - Hemiparesis
  - Visual field defects
  - Aphasia
  - Sensory defects

PML *(cont'd)*

- MRI
  - Multiple nonenhancing white matter lesions
- Diagnosis
  - JC virus DNA levels in CSF
  - Biopsy
- Treatment
  - ART

Neoplastic Diseases

- AIDS-defining
  - Kaposi's sarcoma
  - Non-Hodgkin's lymphoma
  - Invasive cervical carcinoma

- Non-AIDS-defining
  - Hodgkin's disease
  - Multiple myeloma
  - Leukemia
  - Melanoma
  - Cervical, brain, testicular, oral, lung, gastric, liver, renal, and anal cancers

Kaposi's sarcoma (KS)

- HHV-8 (KSHV) has been strongly implicated as a viral cofactor in the pathogenesis of KS
- Any stage of HIV infection

KS *(Cont'd)*

- Clinical Manifestations
  - Skin
    - Raised reddish-purple nodule on or a discoloration on the oral mucosa
  - Lymph nodes
  - GI tract
  - Lung


Thank you