Common opportunistic infections and other co-morbidities in HIV

HIV Clinical Overview for Southeast Providers
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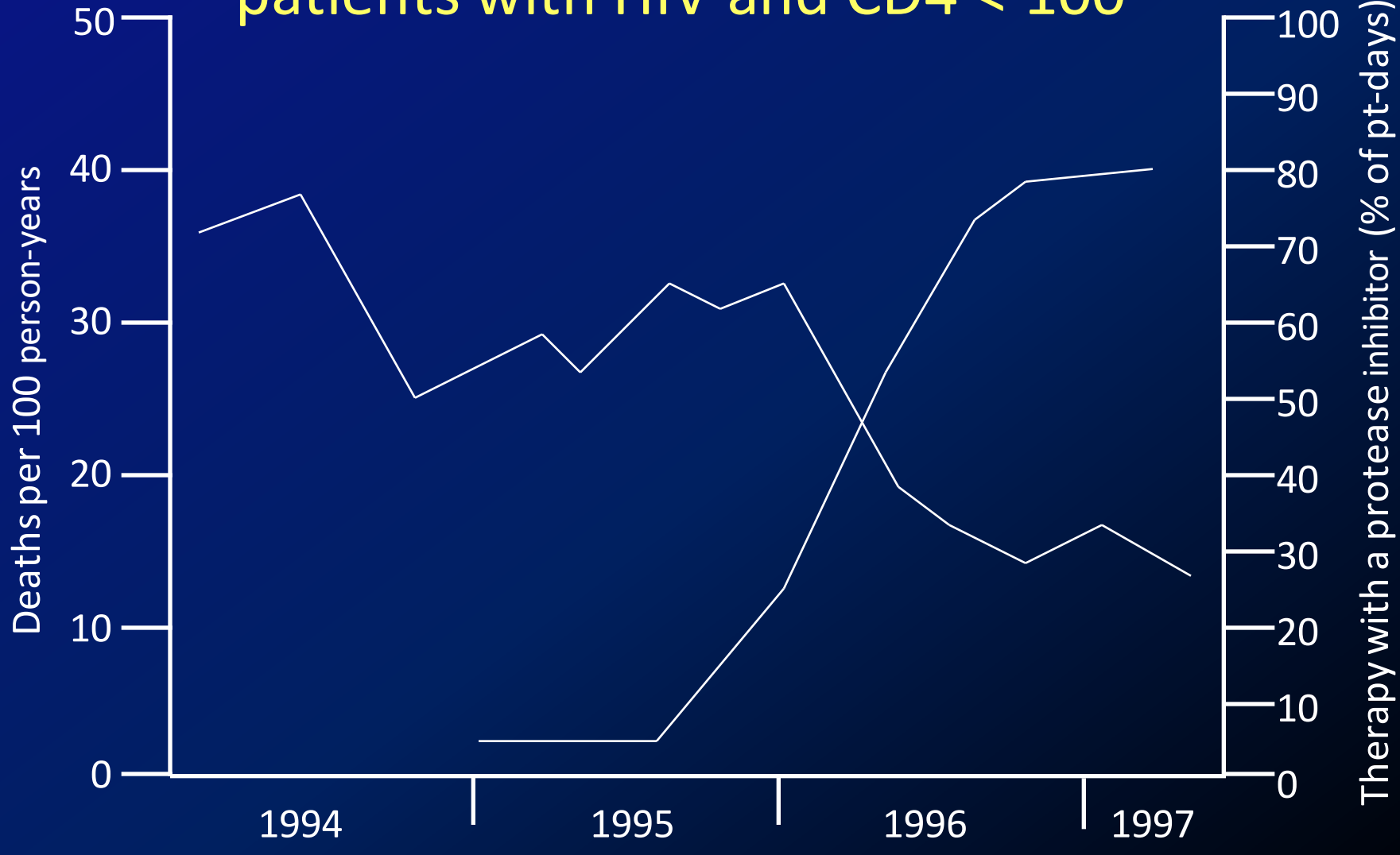
Outline

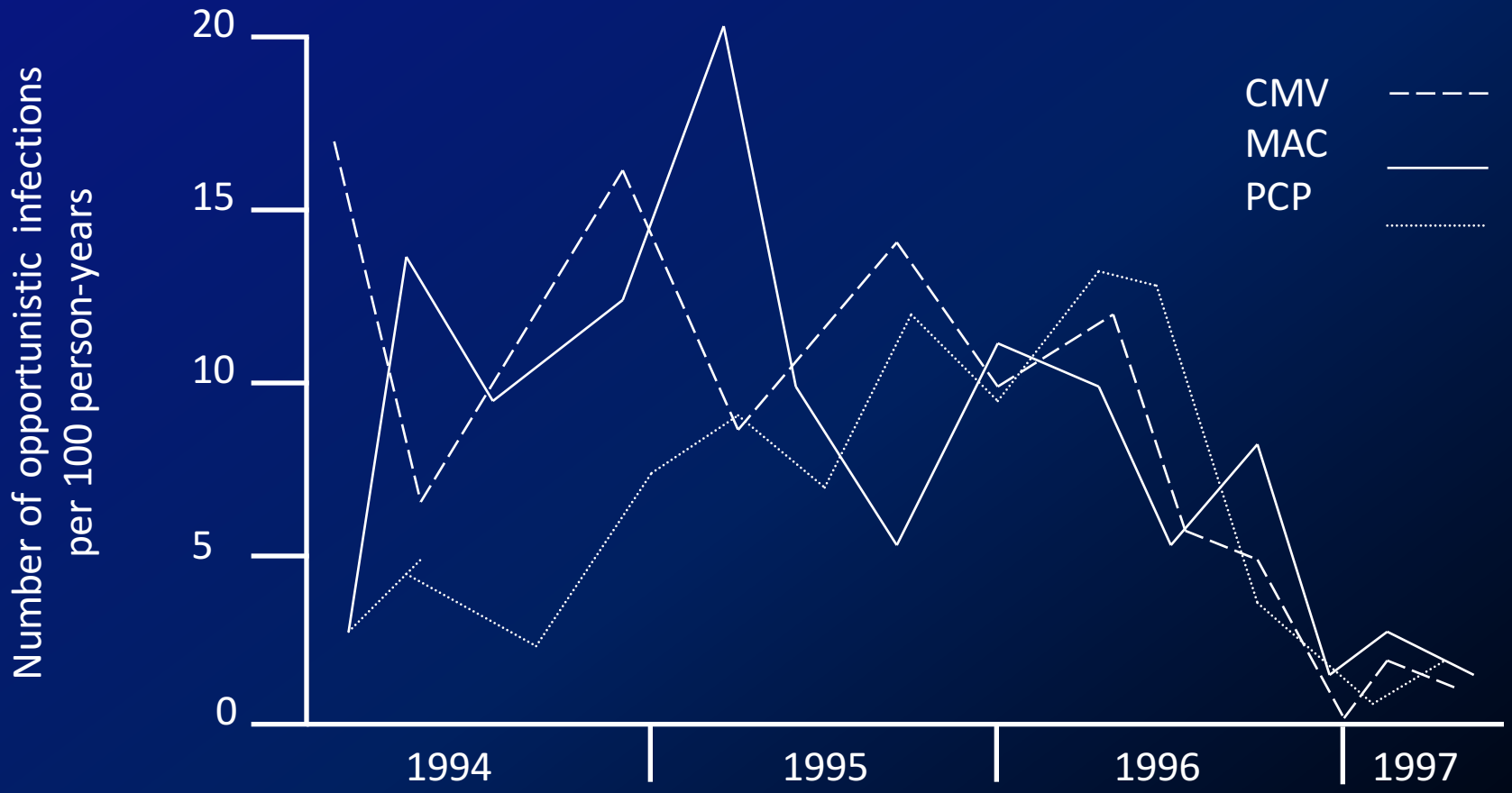
- Changing epidemiology of co-morbid conditions in persons living with HIV
- Recognition, treatment, and prevention of opportunistic infections
- Clinical challenges in an aging population with HIV

Mortality and frequency of use of protease-inhibitor based antiretroviral therapy among patients with HIV and CD4 < 100



Palella et al. New Engl J Med 1998;338:853-60

Rates of opportunistic infections among HIV-infected patients with CD4 < 100



Palella et al. New Engl J Med 1998;338:853-60

Swiss Cohort Study
Incidence of clinical events 2008-2010

Endpoint	Total (%)	Rate (95% CI)/1000PY
Bacterial Pneumonia	201 (20)	9.03 (7.87-10.4)
Fracture	123 (12.4)	5.48 (4.60-6.540
Non-AIDS malignancy	115 (12)	5.12 (4.27-6.15)
CDC Stage B event	100 (8)	4.52 (3.72-5.510
CDC Stage C event	95 (8)	4.32 (3.53-5.28)
Coronary Angioplasty	76 (7)	3.38 (2.70-4.23)
Diabetes	70 (7)	3.12 (2.46-3.94)
Osteoporosis	61 (6)	2.71 (2.11-3.48)
Myocardial Infarction	55 (5.5)	2.44 (1.88-3.18)
Kidney events	31 (3)	1.37 (0.96-1.95)

Hasse B et al. Clin Infect Dis 2011;53:1130-1139

Cardiovascular disease in SMART trial of immediate vs deferred ART

Endpoint*	Drug Conservation Group (N = 2720)		Viral Suppression Group (N = 2752)		HR for Conservation Group vs Viral Suppression Group (95% CI)	*P* Value
	Participants With Event, n	Event Rate (per 100 Person-Yr)	Participants With Event, n	Event Rate (per 100 Person-Yr)		
Primary endpoint	120	3.3	47	1.3	2.6 (1.9-3.7)	< .001
▪ Death from any cause	55	1.5	30	0.8	1.8 (1.2-2.9)	.007
Opportunistic disease						
▪ Serious	13	0.4	2	0.1	6.6 (1.5-29.1)	.01
▪ Nonserious	63	1.7	18	0.5	3.6 (2.1-6.1)	< .001
Major CV, renal, or hepatic disease	65	1.8	39	1.1	1.7 (1.1-2.5)	.009
▪ Fatal or nonfatal CVD	48	1.3	31	0.8	1.6 (1.0-2.5)	.05
▪ Fatal or nonfatal renal disease	9	0.2	2	0.1	4.5 (1.0-20.9)	.05
▪ Fatal or nonfatal liver disease	10	0.3	7	0.2	1.4 (0.6-3.8)	.46
Grade 4 event	173	5.0	148	4.2	1.2 (1.0-1.5)	.13
Grade 4 event or death from any cause	205	5.9	164	4.7	1.3 (1.0-1.6)	.03

El Sadr W, et al. N Engl J Med. 2006;355:2283-2296

START Study: Randomized Comparison of Immediate vs Delayed ART

Treatment-naive pts with CD4+ cell count > 500 cells/mm³

(N = 4685)

Immediate treatment

Defer treatment until CD4+ cell count ≤ 350 cells/mm³

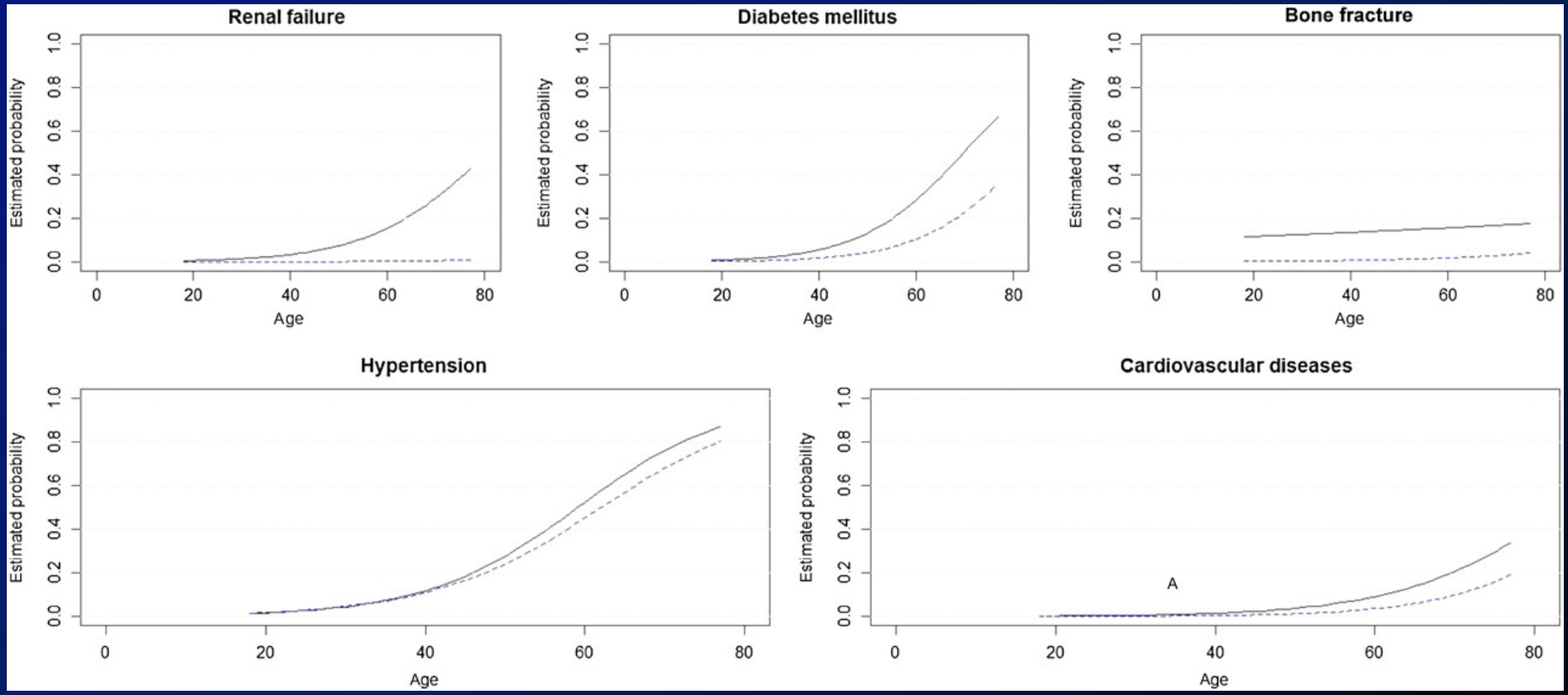
Study endpoints (over 6 yrs)

- Fatal AIDS or nonfatal serious AIDS events (CV, liver, renal, and cancer)
- Non-AIDS–related death

- Study stopped in May 2015 due to excess of events (86 vs 41) in the deferred treatment arm
- Most common AIDS-related illnesses among study participants were pulmonary TB, Kaposi's sarcoma, and non-Hodgkin's lymphoma; the most common serious non-AIDS–related illnesses were cancer, heart attack, and deaths due to various causes

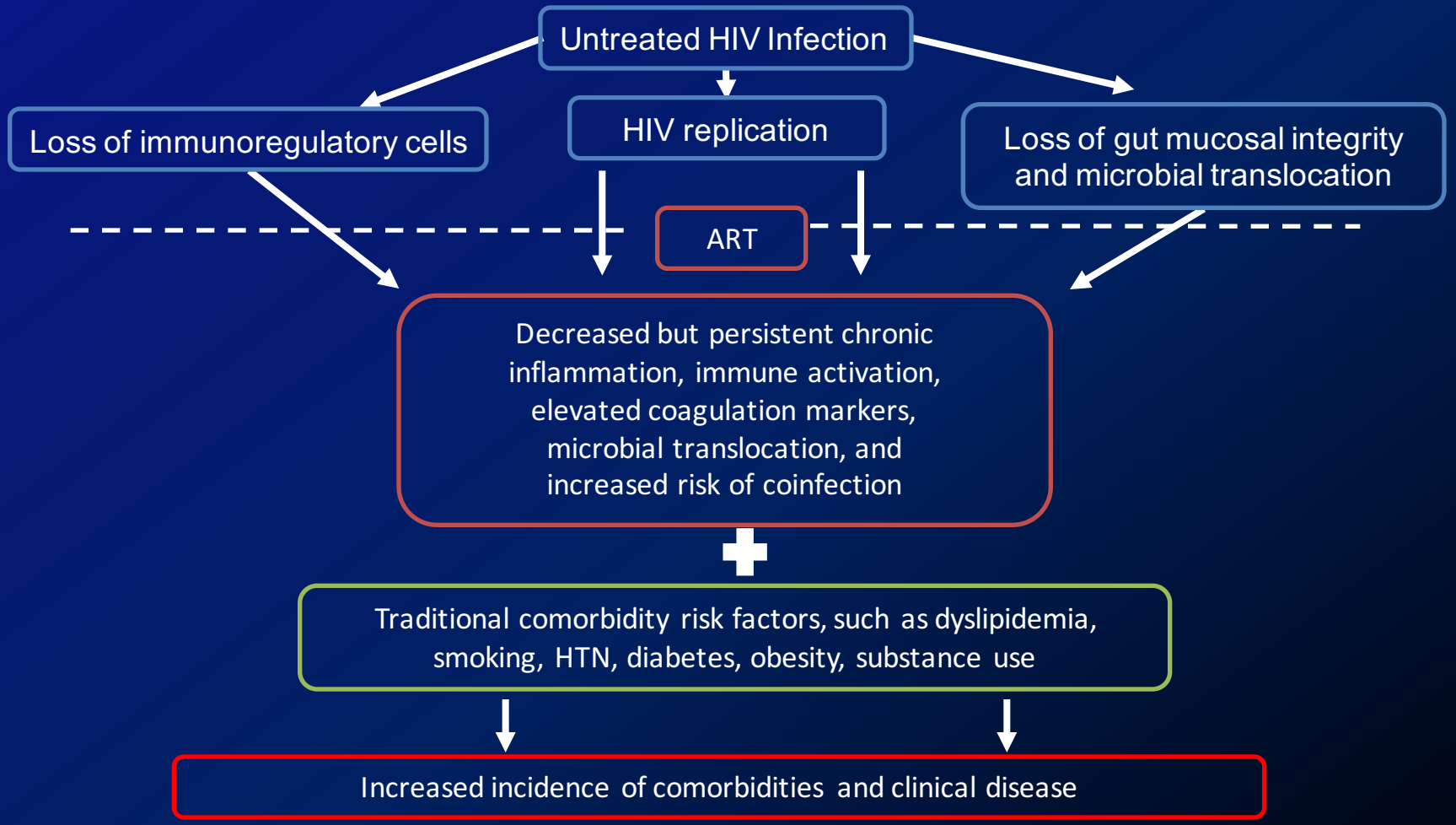
NIH. Press release. May 27, 2015.

Comparative risk of hypertension, diabetes mellitus, renal failure, cardiovascular disease, and fracture, by age, among HIV patients versus control subjects



Giovanni Guaraldi et al. Clin Infect Dis. 2011;53:1120-1126

Chronic inflammation and increased risk of comorbidities in HIV infection



Deeks SG. Annu Rev Med. 2011;62:141-155

“Aging” of the HIV epidemic

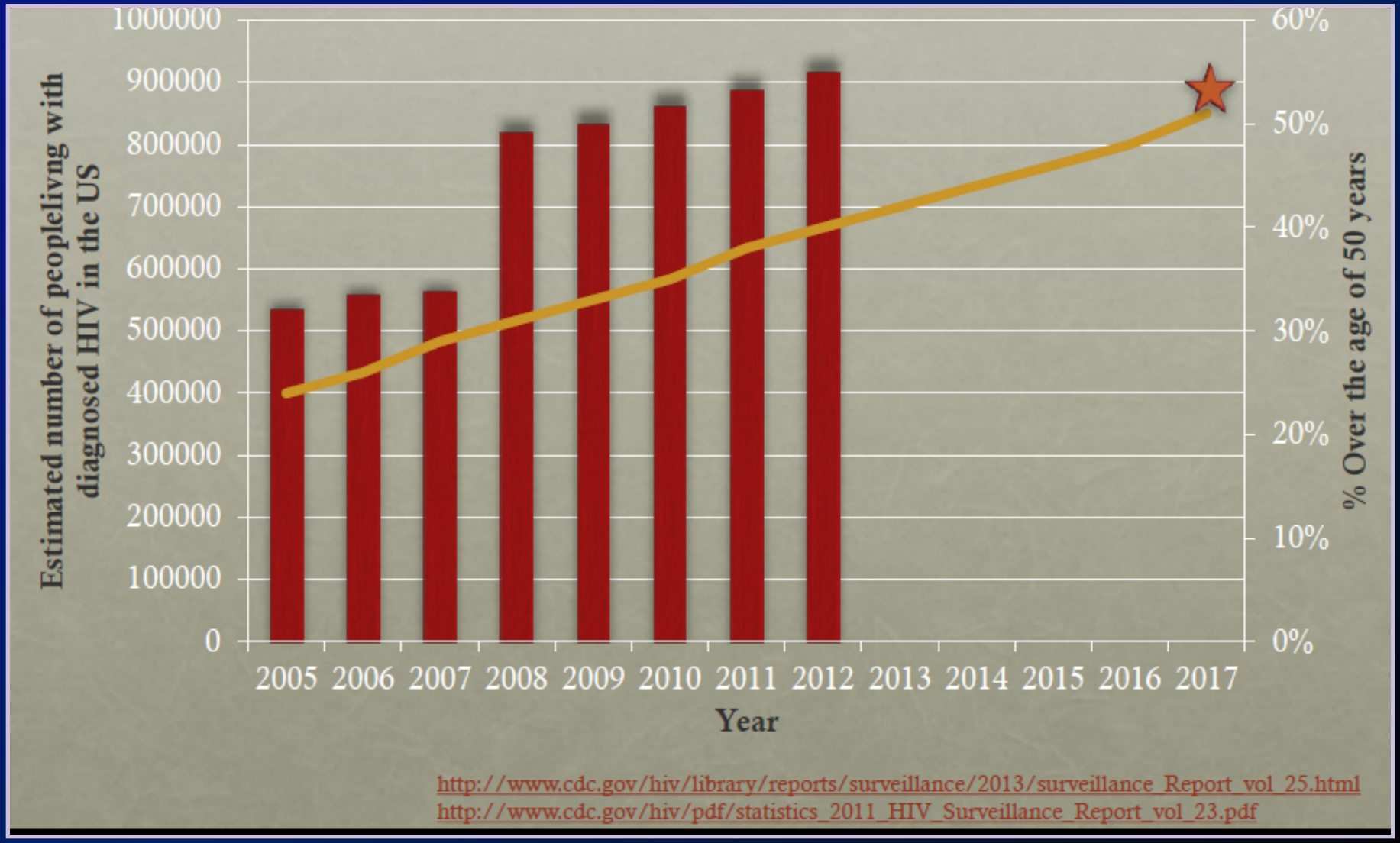
- Success of ART in prolonging the lives of people living with HIV
- Decreasing HIV incidence among younger adults shifting the disease burden to older ages
- People aged 50 years and older exhibit many of the risk behaviors also found among younger people

UNAIDS, 2013

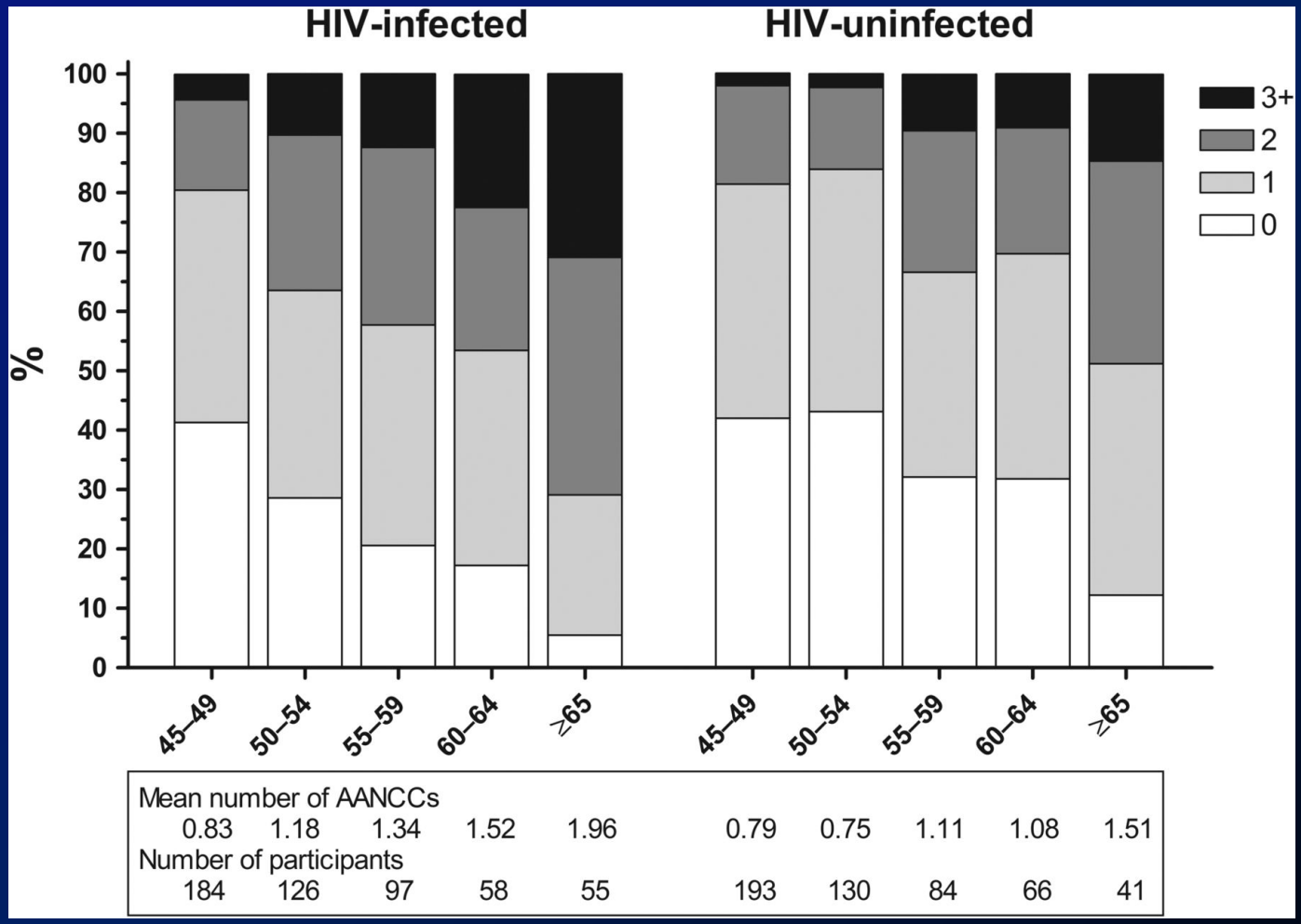
Estimated percentage of the adult population living with HIV which is aged 50 years or over, by region, 2012

UNAIDS, HIV and Aging, 2013

Aging of the US HIV epidemic

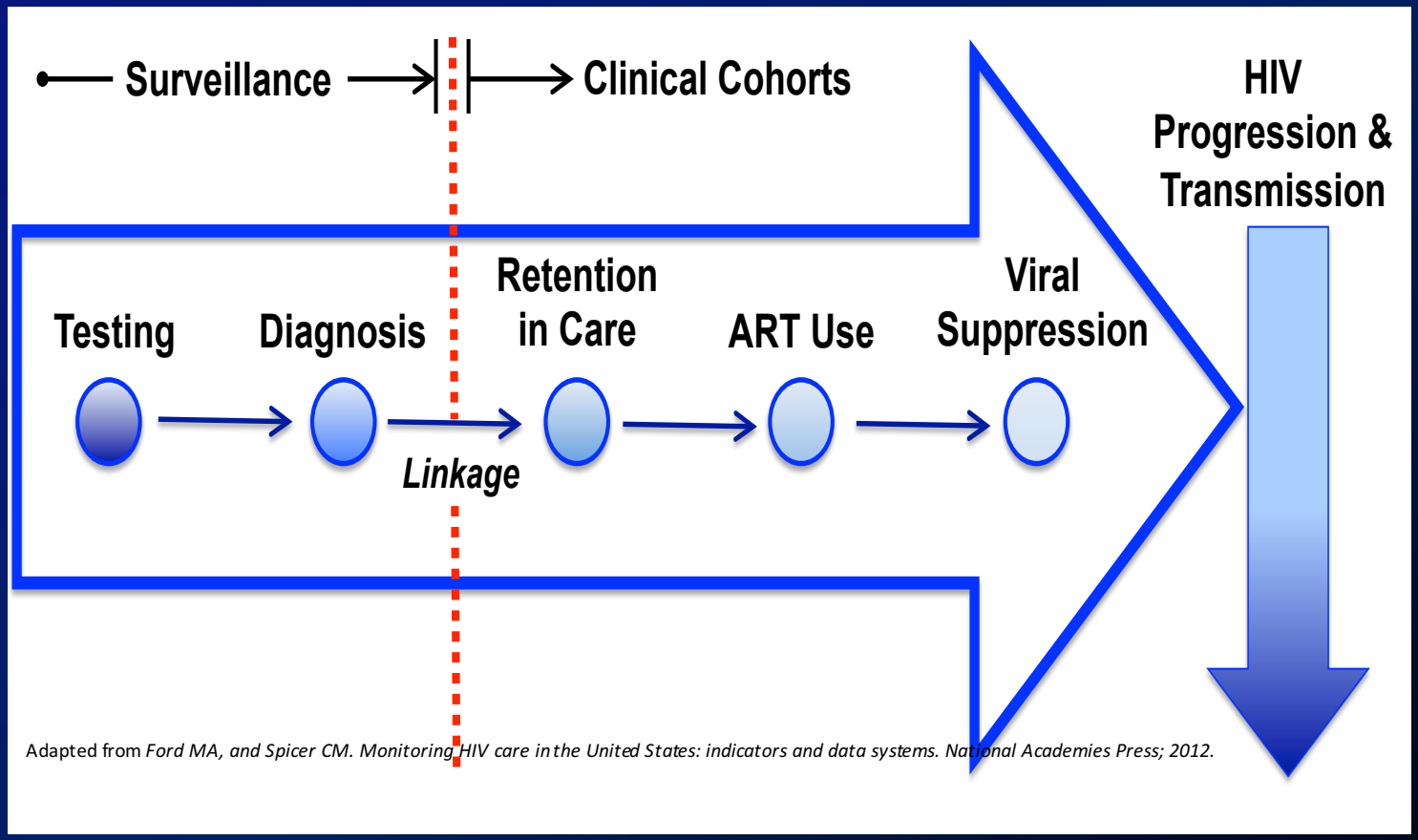


Distribution of the number of age-associated noncommunicable comorbidities stratified by age

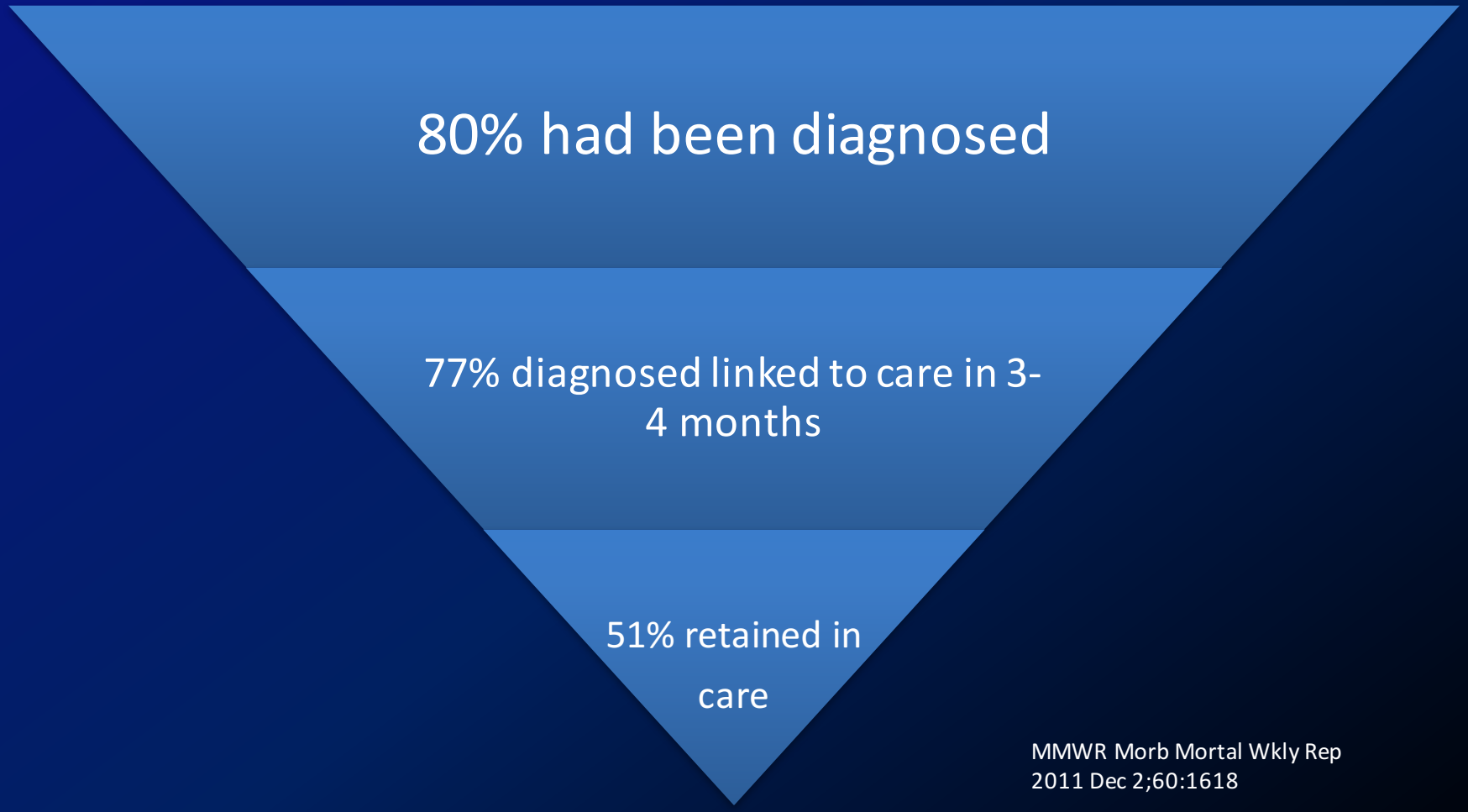


Schouten et al. Clin Infect Dis. 2014;59:1787-1797

HIV Continuum of Care Conceptual framework



The Cascade of Linkage-to-Care: the US reality



MMWR Morb Mortal Wkly Rep 2011 Dec 2;60:1618

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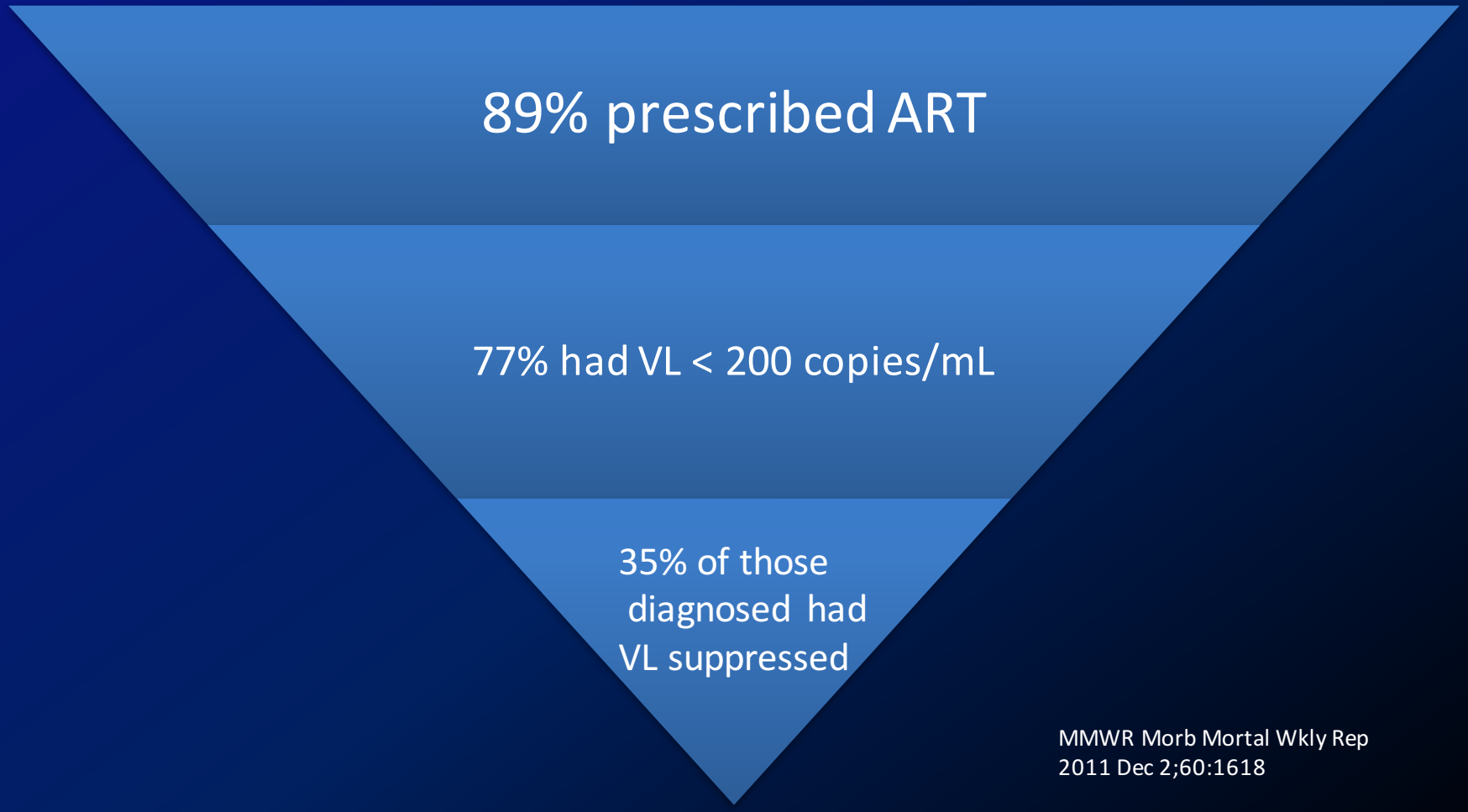
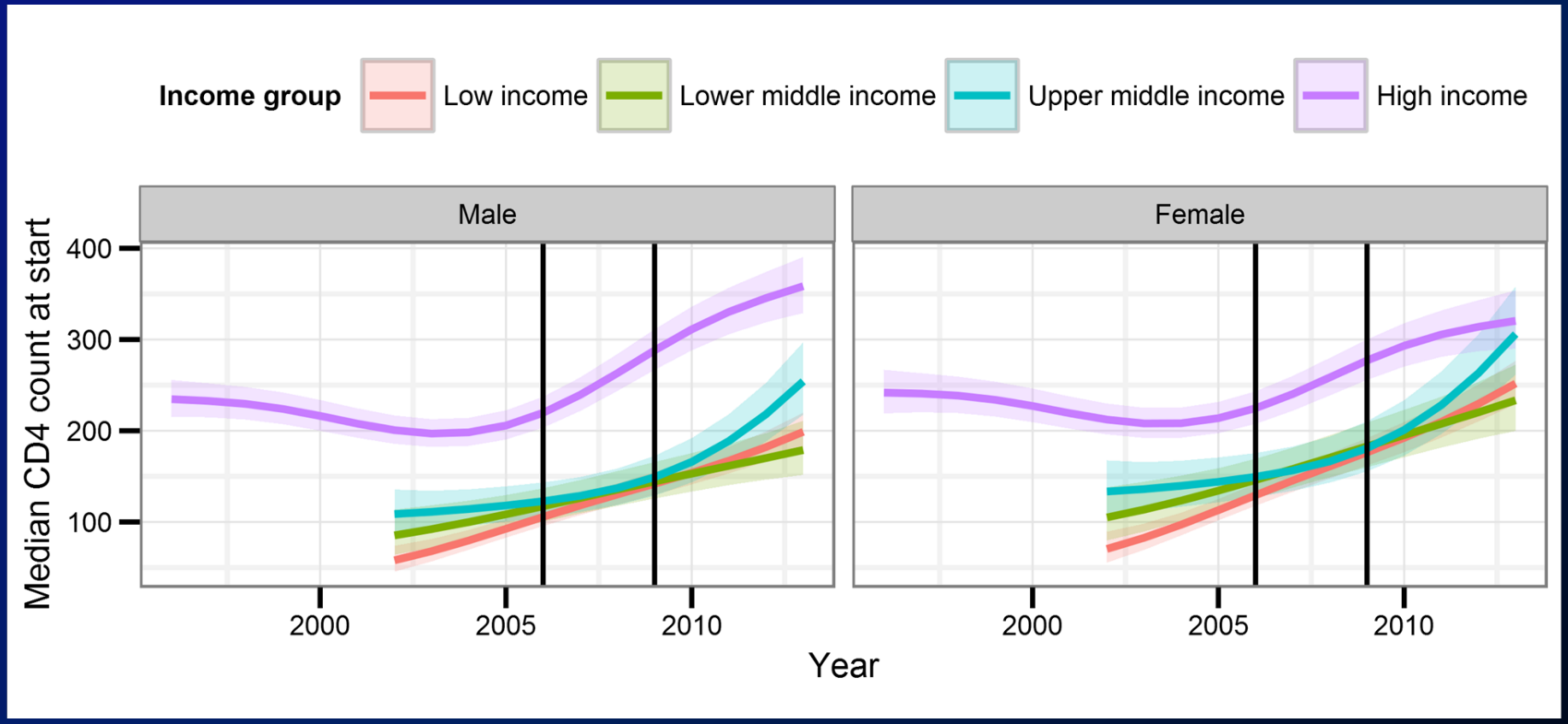


MMWR Morb Mortal Wkly Rep
2011 Dec 2;60:1618

Immunodeficiency at the start of ART: a global view

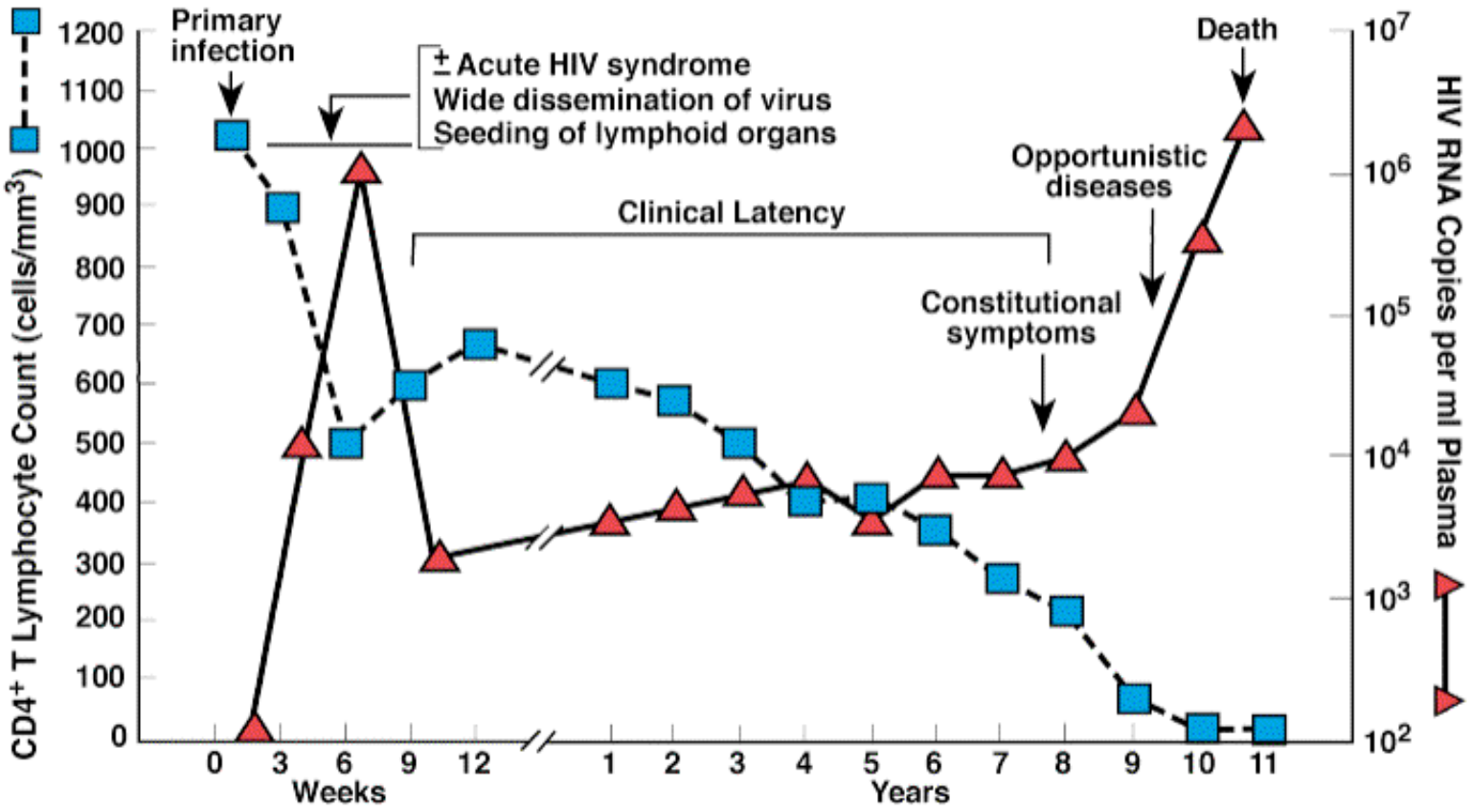


Panayidou et al., CROI 2015

HIV care in 2016

- **Chronic lifelong treatment with all the associated issues**
  - medication tolerability
  - medication adverse events
  - resistance
  - drug-drug interactions
  - polypharmacy
  - adherence
  - pharmacy costs and formularies
- **General Medicine in the "Fast Lane"**
  - Chronic inflammatory state
  - Accelerated cardiovascular disease
  - Metabolic disorders (obesity, DM, dyslipidemia)
  - Accelerated fragility
  - Cognitive issues I aging patients

Typical Course of HIV Infection



Modified From: Fauci, A.S., et al, *Ann. Intern. Med.*, 124:654, 1996

CDC classification system for HIV-infected adults and adolescents

CD4 Cell Count Categories	Clinical Categories		
	A Asymptomatic, Acute HIV, or PGL	B* Symptomatic Conditions, not A or C	C# AIDS-Indicator Conditions
(1) ≥500 cells/µL	A1	B1	C1
(2) 200-499 cells/µL	A2	B2	C2
(3) <200 cells/µL	A3	B3	C3

Abbreviations: PGL = persistent generalized lymphadenopathy

MMWR 1994;43[No. RR-12]

Early Symptomatic Infection ("B conditions)

- Fever, constitutional symptoms or diarrhea for more than one month
- Thrush or persistent vaginal candidiasis
- Oral hairy leukoplakia
- Herpes zoster (multidermatomal or multiepisodic)
- Cervical dysplasia or carcinoma in situ
- Peripheral neuropathy
- Bacillary angiomatosis (*Bartonella henselae*)
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Complicated pelvic inflammatory disease

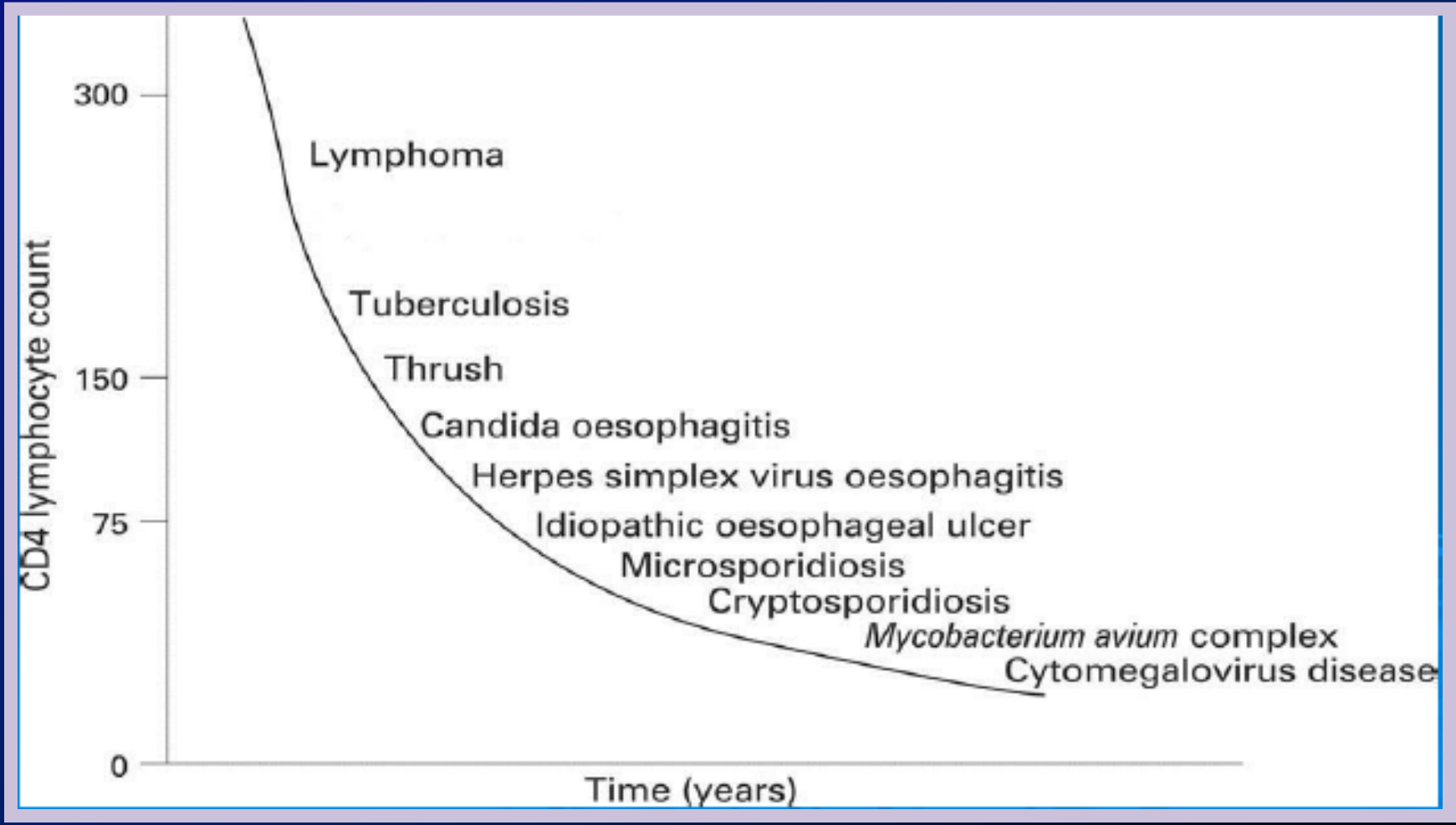
MMWR 1994;43[No. RR-12]

AIDS-defining Conditions

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi sarcoma
- Lymphoma, Burkitt
- Lymphoma, immunoblastic
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii,* disseminated or extrapulmonary
- *Mycobacterium tuberculosis* of any site, pulmonary, disseminated, or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jirovecii* pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome attributed to HIV

MMWR 1994;43[No. RR-12]

Natural history of HIV-1 infection



Opportunistic infections (OIs)
General concepts

- Occur in late presenters to diagnosis/care and others who are untreated
- Should not occur in an adherent patient engaged in care
- Many OIs may be prevented with specific prophylaxis, but immune reconstitution due to cART is the ultimate prophylaxis
- Secondary prophylaxis can be discontinued with immune recovery

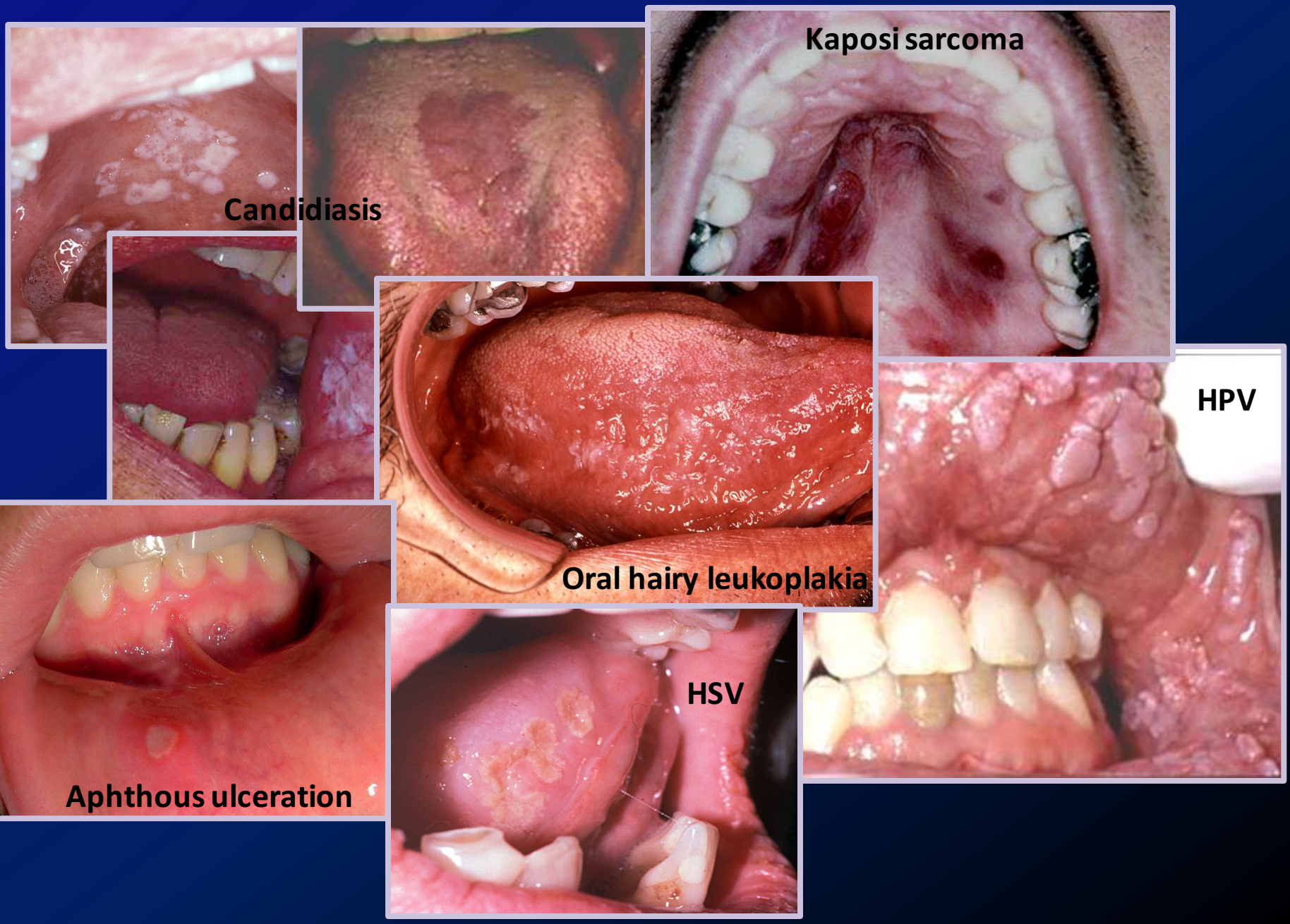
Opportunistic infections
General concepts

- Diagnostic considerations are broad but most OIs will present as distinct clinical scenarios
  - Respiratory symptoms/distress
  - Headache or CNS signs/symptoms
  - Fever, night sweats, weight loss
  - Dysphagia/odynophagia
  - Diarrhea/abdominal pain
- Profoundly immunosuppressed patients may have multiple co-existing OIs

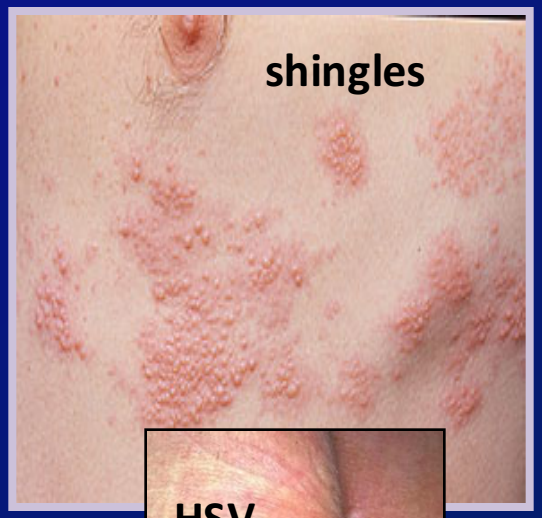
Immune reconstitution inflammatory syndrome (IRIS)

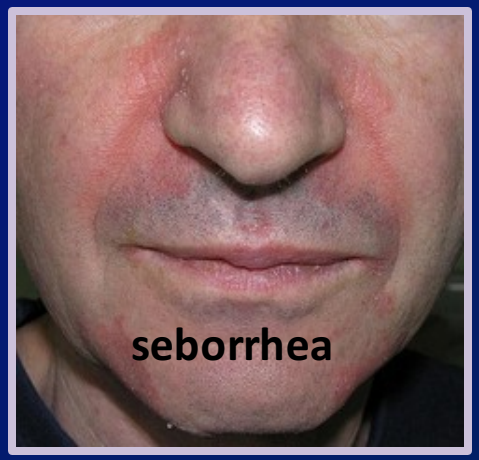
- Parodoxical worsening in setting of appropriate OI therapy due to rapid restoration of pathogen-specific immune response
- May be due to unmasking of undiagnosed OI
- Low CD4 and rapid viral decline places at highest risk
- Most common
  - Mycobacterial
  - Cryptococcosis
  - Histoplasmosis
  - CMV
  - PML
  - Kaposi sarcoma
  - HBV

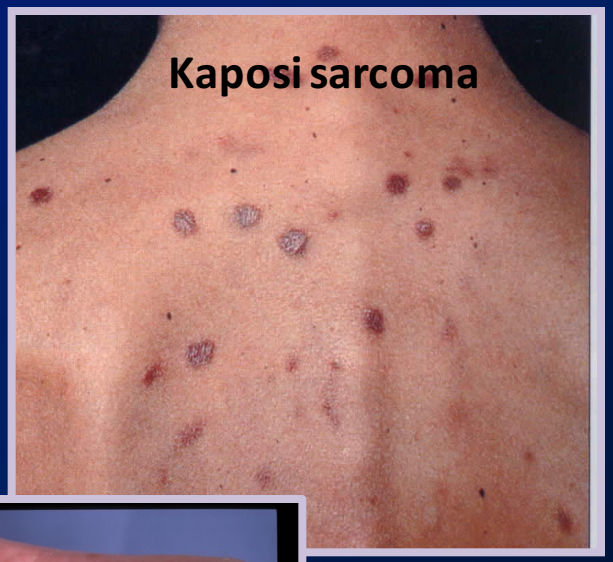
Mucocutaneous manifestations: to name a few

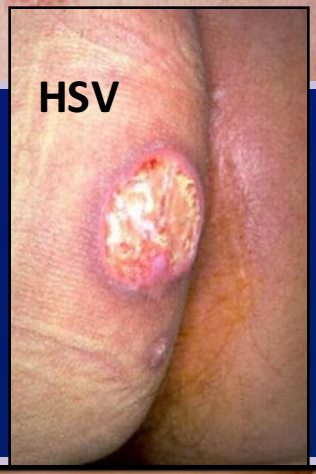


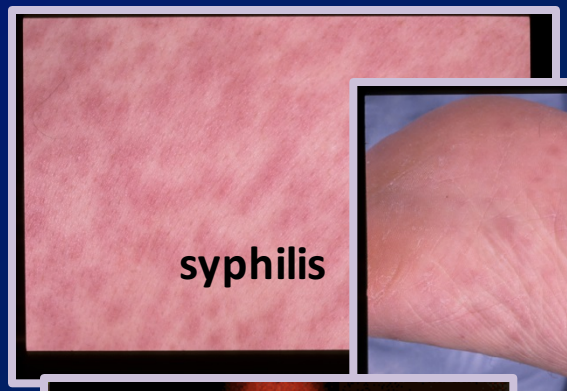
Cutaneous manifestations: to name a few

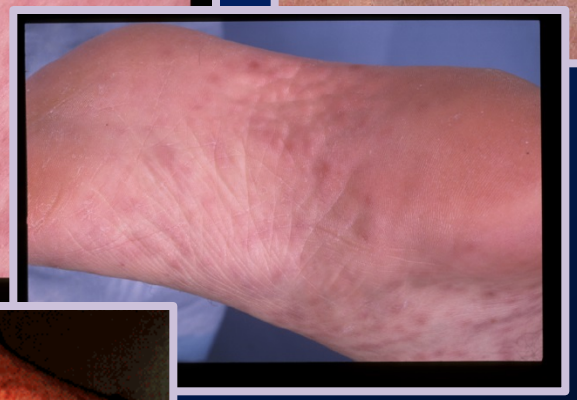


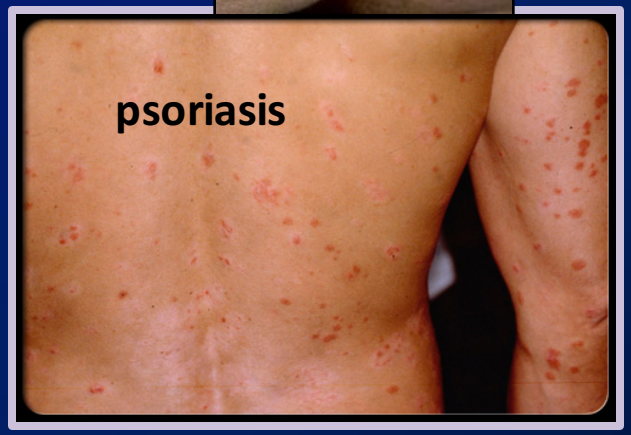


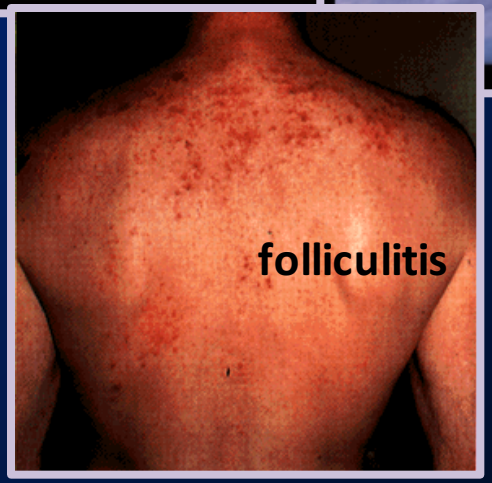


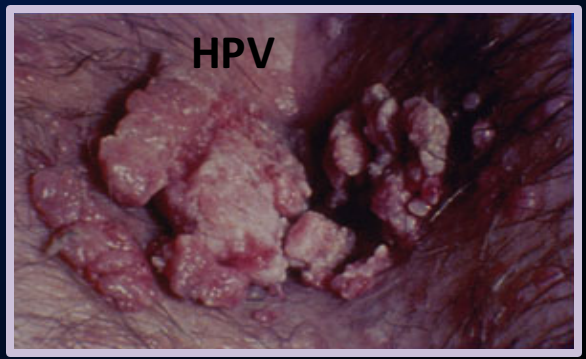






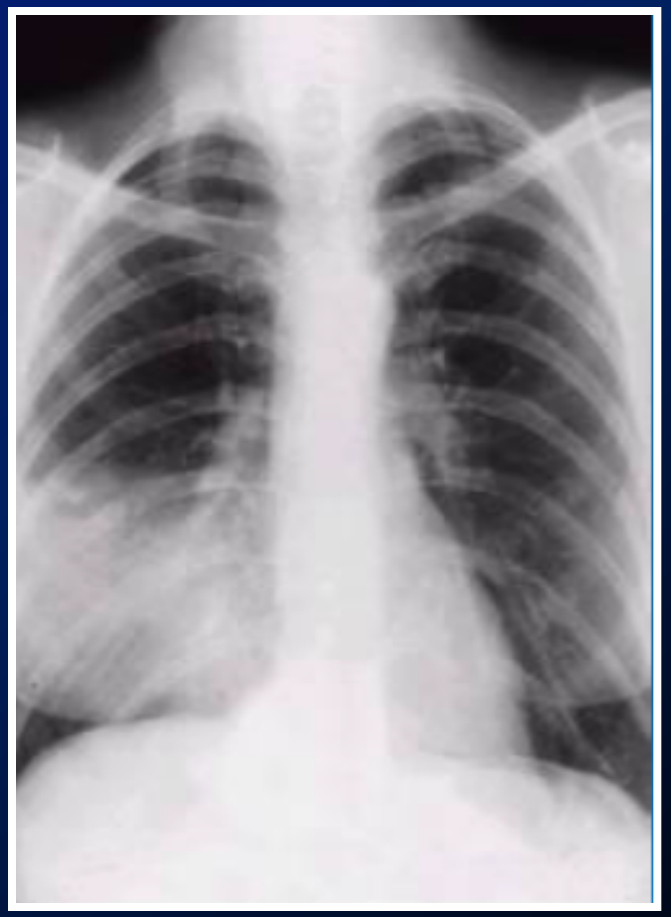






Case 1

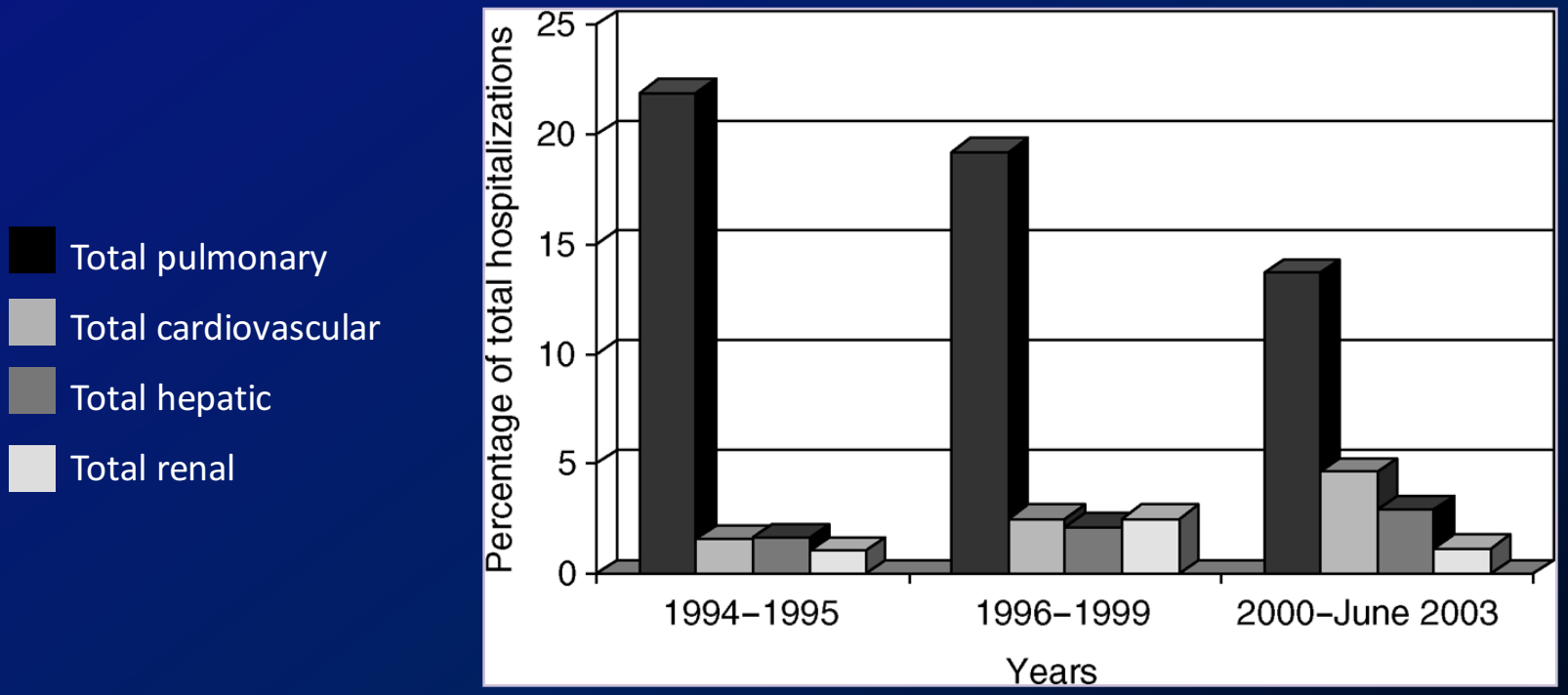
- CD4 = 450 cells/mm^3
- 5 days duration of fevers, chills, chest pain, productive cough and dyspnea
- Physical exam has egophony and decreased breath sounds on right



Differential diagnosis for focal infiltrates in HIV infection with CD4 >250 cells/mm^3

- Bacterial pneumonia
- Tuberculosis
- Endemic fungi
- Non-Hodgkin lymphoma
- Malignancy with post-obstructive pneumonia
- Non-HIV related causes (hemorrhage, fluid, rheumatologic)

Pulmonary, cardiovascular and hepatic hospitalizations as percentage of total hospitalization: HOPS in 2003



AIDS 2006;20:1095

Pulmonary complications

- Infectious etiologies are the most common
  - Bacterial (pneumococcus)
  - Opportunistic (PCP, TB, fungal)
  - Viral
- COPD
  - May be accelerated process in HIV-positive smokers
- Malignancy
- Pulmonary hypertension
  - prevalence higher in HIV compared to general population
- Venous thromboembolism

Effects of HIV in the lung

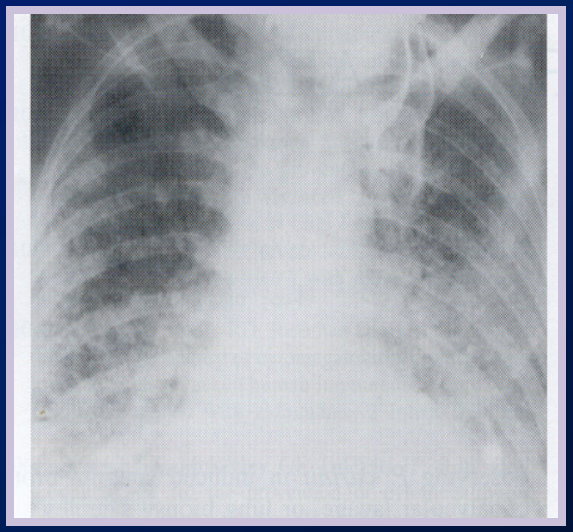
- Direct infection of pulmonary macrophages and lymphocytes
- Progression of HIV infection decreases lung CD4+ T cells
- Intense infiltration of CD8+ T cells may occur within the lung with up-regulation of cytokines
- Defects in humoral immunity lead to impaired antigen-specific responses
- Viral compartmentalization may occur in lung

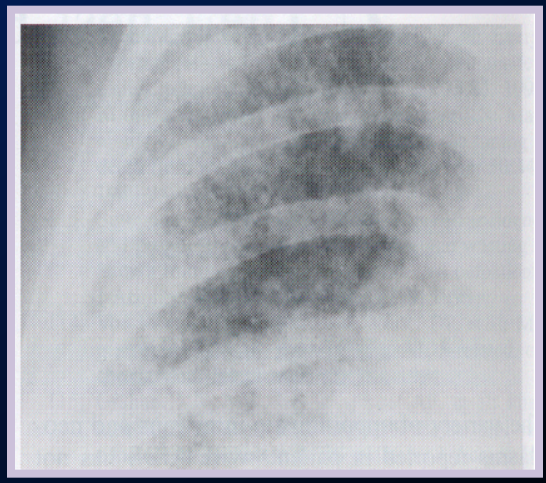
Features of bacterial pneumonia in HIV-infected patients

- Rate of development is inversely related to CD4 count
- Risk is significantly increased in injection drug users
- Two major differences compared with HIV-negative controls
  - higher frequency of bacteremia
  - higher recurrence rate 🎭 relapse, recrudescence, re-infection
- Most common etiologic agents are *S. pneumoniae* and Gram-negative organisms (haemophilus, pseudomonas)

Case 2

- Out of care for 6 years
- Current CD4 unknown (350 cells/mm^3 in 2010)
- 5 days duration of fevers, chills, chest pain, ~ 1 month duration of dry cough, exertional dyspnea, and low grade fever
- Mild temporal wasting, thrush on exam and lungs clear to auscultation





Diffuse pulmonary infiltrates in HIV infection

Interstitial	Reticulonodular
Pneumocystis jiroveci	*Pneumocystis jiroveci*
CMV pneumonia	Tuberculosis
Viral pathogens	Histoplasmosis
	Coccidioidomycosis

Epidemiology and transmission of *Pneumocystis jiroveci*

- Serologic studies demonstrate that infection occurs early in life
- Dormancy with reactivation of infection is unlikely
- Asymptomatic colonization may occur in immunocompetent and some immunocompromised individuals
- Person-to-person transmission is possible based on limited data and one clustered outbreak

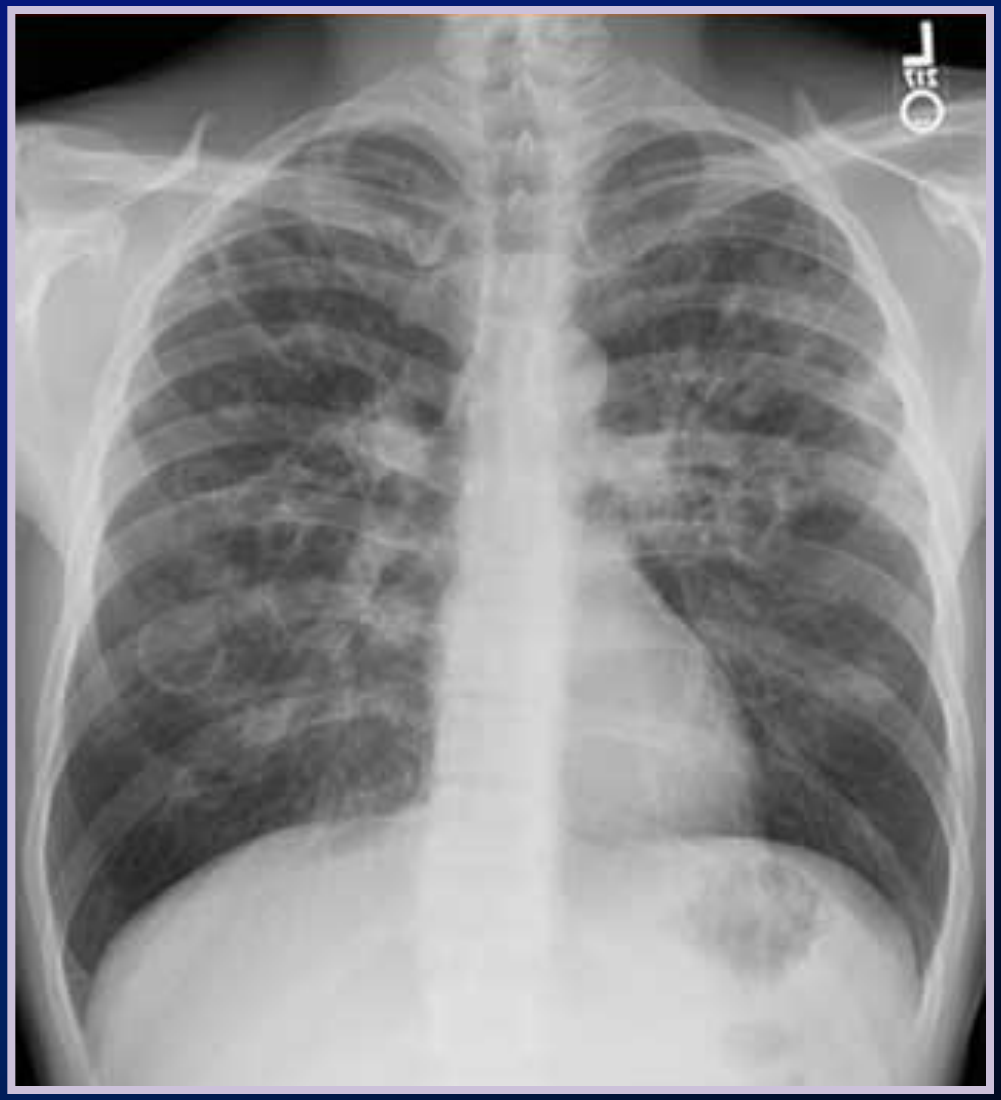
Pneumocystis jiroveci

- Incidence
  - 70-80% of AIDS patients prior to prophylaxis
  - Now most common new ADE or in untreated patients
- Prognosis
  - Lethal if untreated
  - Advanced HIV and severe PCP carry 20-40% mortality
- Risk factors
  - CD4<200 cells/mm^3 or CD4% <14%
  - Thrush
  - Wasting
  - Recurrent bacterial pneumonia
  - Elevated HIV-1 RNA

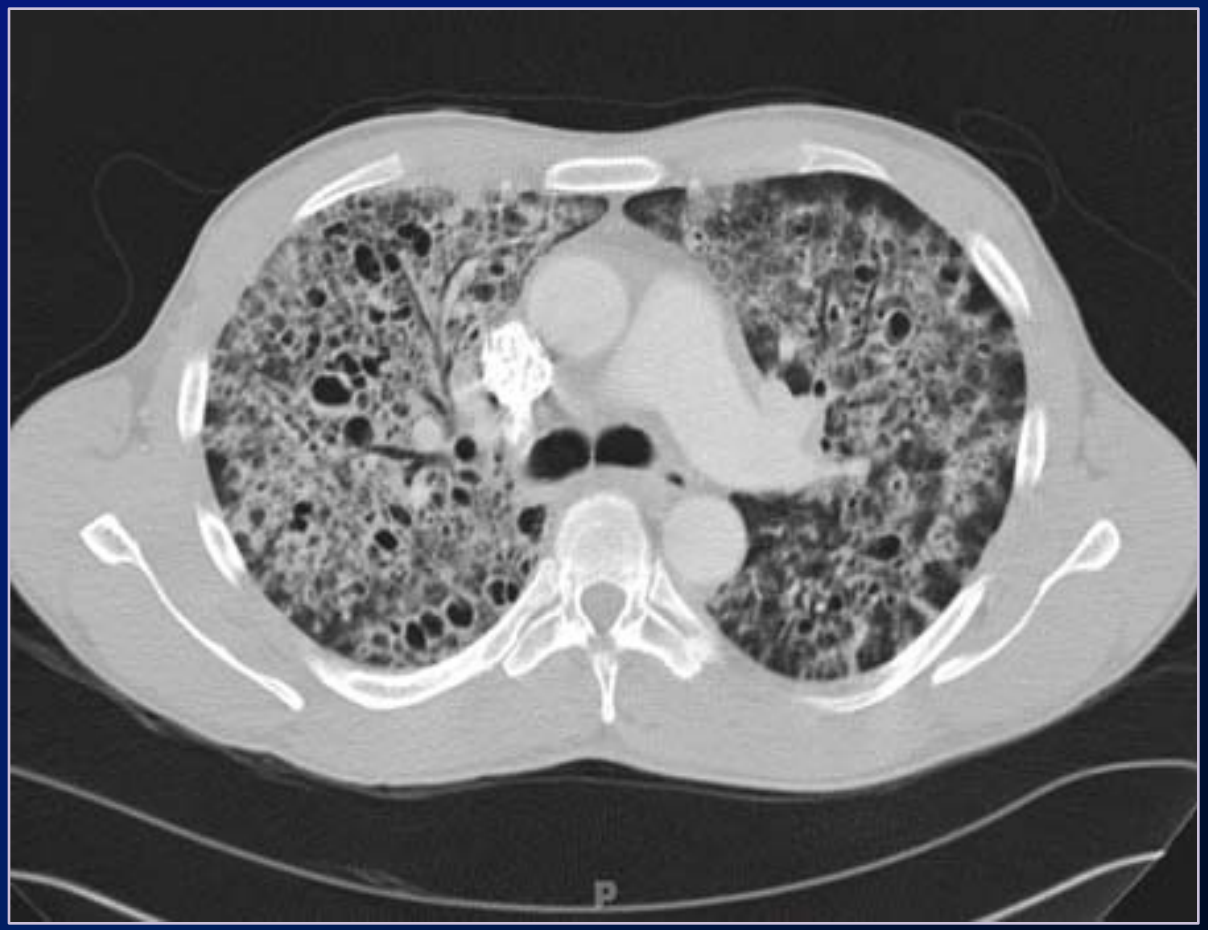
Pneumocystis

- Clinical presentation depends on duration of illness, concurrent morbidities and patient's activity level
- Early disease
  - fever, dry cough, dyspnea on exertion
  - normal CXR and pO2
  - O2 % sat is not ideal marker *(RA ABG is critical!)*
- Moderate to severe disease
  - progressive dyspnea, chest discomfort, headache and associated advanced HIV disease symptoms
- Pneumothorax in a patient at risk should be considered PCP until proven otherwise
- Imaging
  - early disease may have normal CXR
  - "classic" findings are butterfly-interstitial pattern
  - high resolution CT can help determine appropriate course

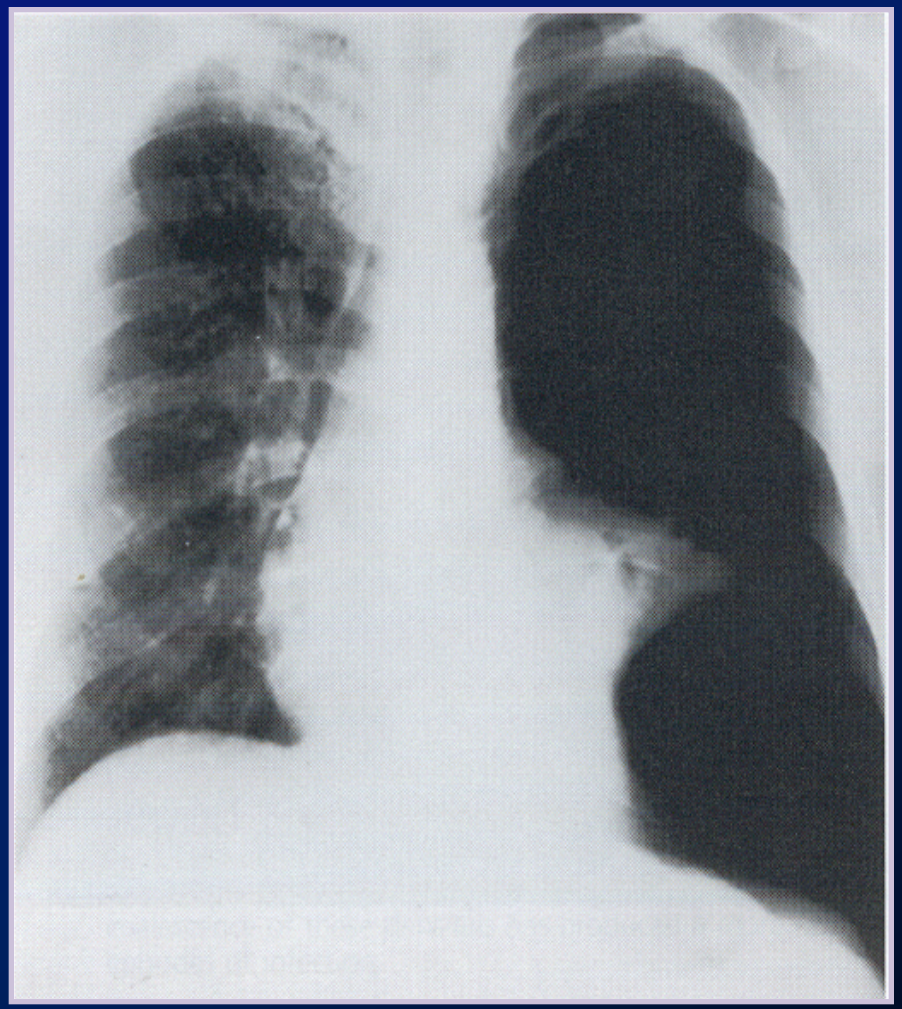
P. jiroveci pneumonia with reticular infiltrates and pneumatoceles



P. jiroveci pneumonia with ground glass opacifications, infiltrates and pneumatoceles



P. jiroveci pneumonia and pneumothorax



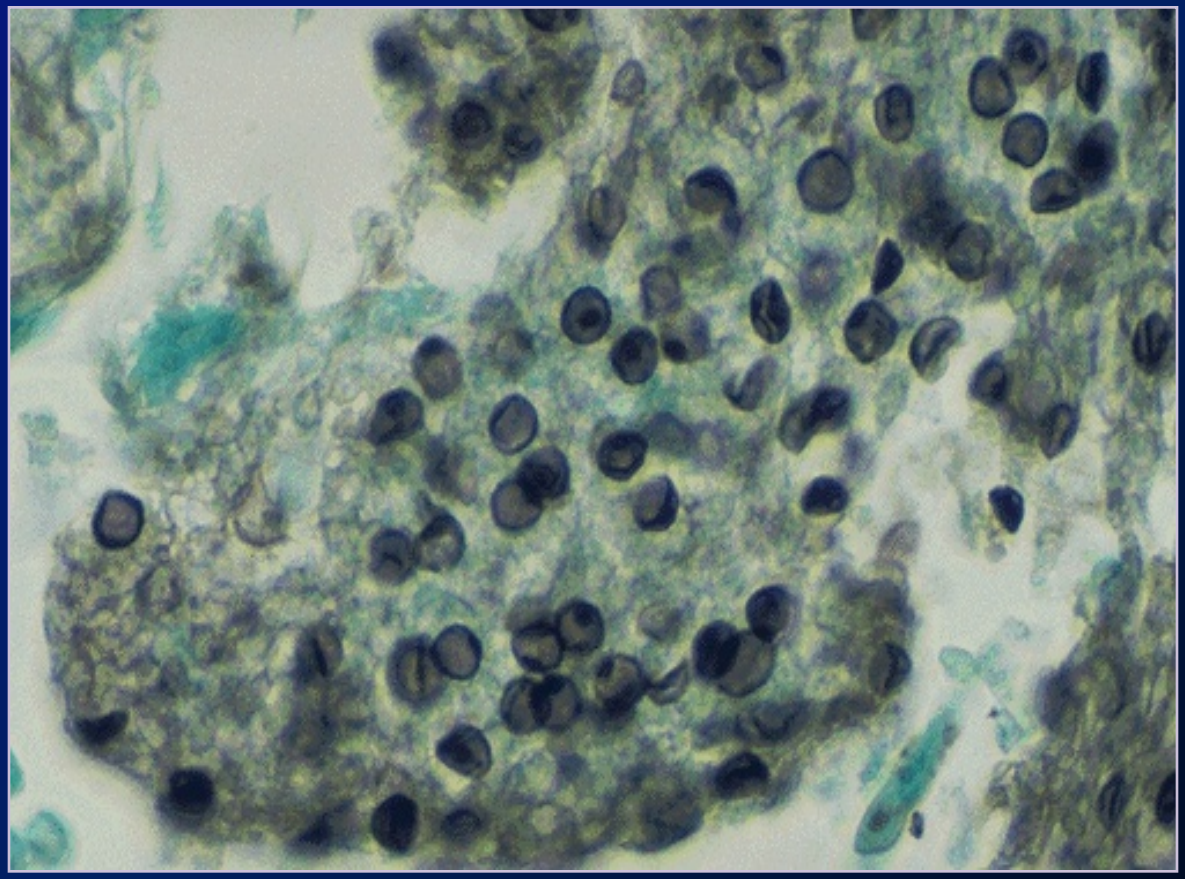
Pneumocystis: diagnosis

- Diagnosis made in setting of appropriate clinical presentation *(prove the patient doesn't have PCP)*
- Organism cannot be cultured, serology is not helpful
- Demonstration of organism in tissue required for definitive diagnosis
  - GMS in BAL (90-99%)
  - Bronch biopsy (95-99%)
  - Spontaneous sputum (50%)
  - Cysts remain present after treatment
- Presumptive diagnosis of PCP may be considered in certain cases

Criteria for empiric *Pneumocystis jiroveci* pneumonia therapy

- At risk for *P. jiroveci* pneumonia
- Not receiving PCP prophylaxis
- Clinical presentation suggestive of PCP
- Mild disease
- Reliable, adherent, tolerate PO intake
- Sputum induction unavailable or low yield

Gomori methenamine silver stain at high magnification demonstrates cysts of *Pneumocystis jiroveci* in lung



Treatment of Pneumocystis Pneumonia

Table 2. Treatment of Pneumocystis Pneumonia.

Drug	Dose	Route	Comments
Trimethoprim–sulfamethoxazole	15–20 mg/kg 75–100 mg/kg daily in divided doses	Oral or intravenous	First choice
Primaquine plus clindamycin	30 mg daily 600 mg three times daily	Oral	Alternate choice
Atovaquone	750 mg two times daily	Oral	Alternate choice
Pentamidine	4 mg/kg daily 600 mg daily	Intravenous Aerosol	Alternate choice

Thomas C and Limper A. N Engl J Med 2004;350:2487

Use of adjuvant corticosteroid therapy in treatment of *P. jiroveci* pneumonia

- Worsening often occurs 3-5 days after start of anti-PCP therapy
- Corticosteroids significantly improve gas exchange
- Use if P_{O2} < 70 mm Hg or alveolar-arterial gradient > 35 mm Hg
- Start early
- Establish diagnosis (many things improve with steroids)

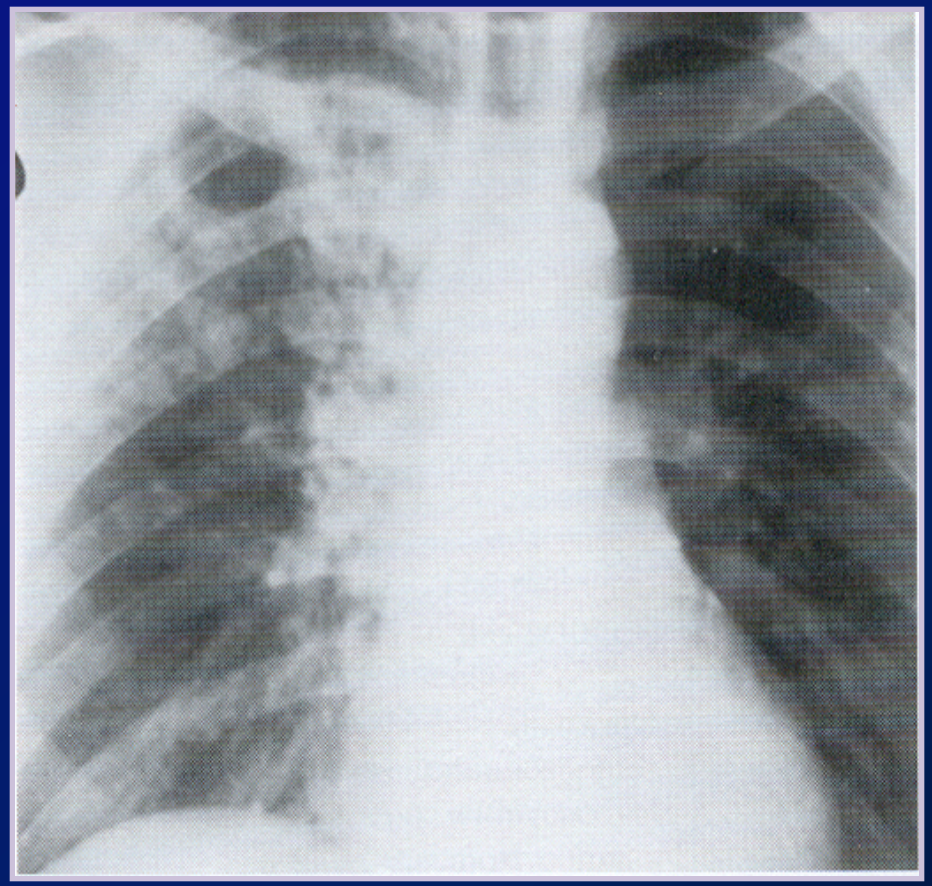
Prophylaxis against Pneumocystis

Table 1. Drugs for Prophylaxis against Pneumocystis Pneumonia.

Drug	Dose	Route	Comments
Trimethoprim–sulfamethoxazole	1 double-strength tablet daily or 1 single-strength tablet daily	Oral	First choice
	1 double-strength tablet 3 times per week		Alternate choice
Dapsone	50 mg twice daily or 100 mg daily	Oral	Ensure patient does not have glucose-6-phosphate dehydrogenase deficiency
Dapsone plus pyrimethamine plus leucovorin	50 mg daily 50 mg weekly 25 mg weekly	Oral	
Dapsone plus pyrimethamine plus leucovorin	200 mg weekly 75 mg weekly 25 mg weekly	Oral	
Pentamidine	300 mg monthly	Aerosol	
Atovaquone	1500 mg daily	Oral	Give with high-fat meals, for maximal absorption

Thomas C and Limper A. N Engl J Med 2004;350:2487

Case 3



- Living in homeless shelter
- CD4 150 cells/mm^3
- 3-months, productive cough, night sweats, 20# weight loss

Differential diagnosis of cavitary pulmonary lesions in patients infected with HIV/AIDS

Mycobacterial infections	Bacterial infections
Mycobacterium tuberculosis	*Pseudomonas aeruginosa*
Mycobacterium kansasii	*Staphylococcus aureus*
Mycobacterium avium complex	*Nocardia asteroides*
	Rhodococcus equi

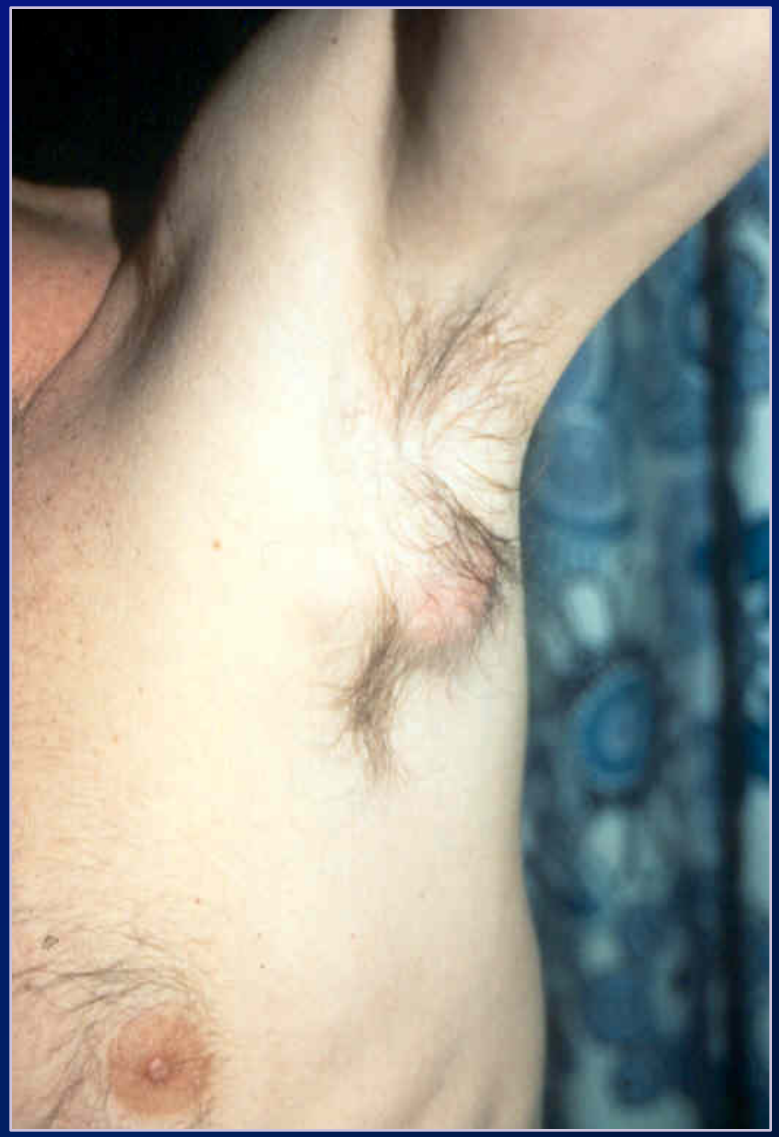
Differential diagnosis of cavitary pulmonary lesions in patients infected with HIV/AIDS

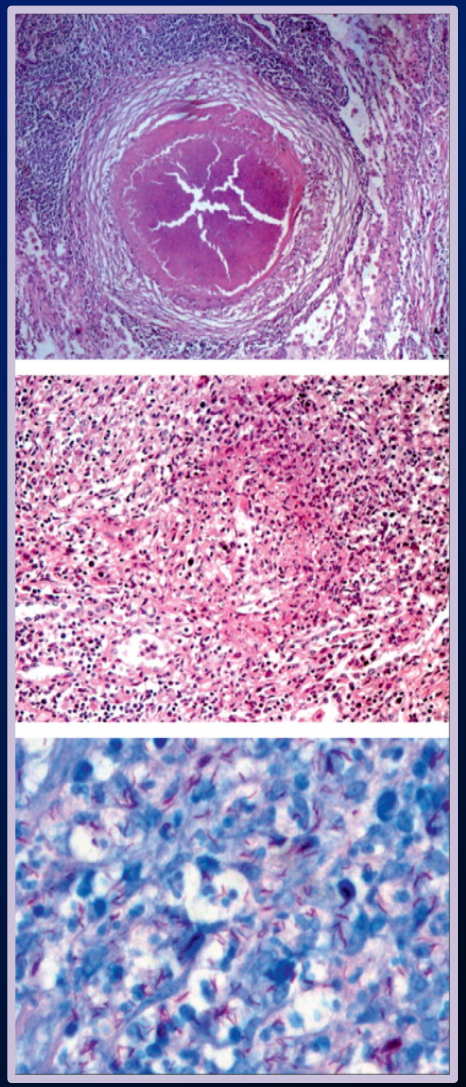
Protozoal infections	Fungal infections
Toxoplasma gondii	*Cryptococcus neoformans*
	Histoplasma capsulatum
	Pneumocystis jiroveci
	Coccidioides immitis
	Aspergillus species
	Blastomycosis

Tuberculosis and HIV

- Persons with HIV have a greatly increased susceptibility to TB infection, primary progressive disease, reactivation, and recurrence
- Highest risk groups in US include those with history of incarceration, homelessness, group living, active drug use, and reside in, or travel to TB endemic region
- Extrapulmonary disease more likely compared to persons without HIV
- Radiographic presentation depends on underlying immune status

Lymphadenopathy due to TB





Tuberculosis and HIV: diagnosis

- Paucibacillary disease is common (smear negative, culture positive)
- Mycobacterial PCR of culture facilitates differentiation from nontuberculous strains
- NAAT (nucleic acid amplification tests) permit rapid identification of TB and rifampin resistance
- Multi-drug resistance TB should be considered in foreign-born individuals

Tuberculosis and HIV: treatment

- Major drug interactions between antiretrovirals and rifamycins may require dose adjustment of either HIV or TB medications
- Treatment regimen (HRZE) and duration is same as for HIV-uninfected persons
- IRIS may occur in persons with low CD4 but survival benefit of early ART initiation (within 2-8 weeks) outweighs risk

Screening for latent TB infection

- Tuberculin skin test (≥5 mm)
- Interferon-gamma release assays (IGRA)
  - Tspot
  - Quantiferon-gold
- Positive results should trigger CXR, sputum analysis, and careful review of signs/symptoms

MMWR Recommendations and Reports. June 25, 2010 / 59(RR05);1-25

Evaluation of pulmonary disease in setting of low CD4

- Bacterial blood and sputum cultures
- Fungal blood cultures
- Cryptococcal serum antigen
- Histoplasma urine antigen
- (1→3)-β-D-glucan
- AFB blood and sputum cultures
- PCP sputum immunofluorescence
- Rapid viral panel
- IGRA
- Bronchoscopy!
- Respiratory isolation

Cryptococcal meningitis

- C. *neoformans*
  - Encapsulated yeast
  - Inhalation initial route of infection
  - Pulmonary disease often subclinical
  - Disseminates to blood and CNS
  - Produces no toxins
  - Minimal inflammatory response
  - Polysaccharide capsule is main virulence factor

Cryptococcal meningitis: clinical aspects

- Subacute onset
- Common
  - headache
  - fever
  - malaise
- Infrequent
  - stiff neck (*true meningismus is rare)*
  - photophobia
  - seizures (5-10%)
  - nausea
- Poor prognosis
  - altered mental status
  - increased opening pressure
  - CSF CRAG >1:1024
  - lack of CSF pleocytosis

Cryptococcal meningitis: diagnosis and treatment

- Diagnosis made by CSF examination
  - India ink (74-88%)
  - cryptococcal Ag serum/CSF (99%)
  - CSF and blood culture
  - cryptococcal Ag is not marker for severity of disease nor for response to therapy
- Treatment

  Acute:
  - Amphotericin B (0.7-0.8 mg/kg/d) for 14 days with or without 5-FC 25 mg/kg QID then Fluconazole 400 mg/d for 8-10 weeks. Using 5-FC with ampho is better than ampho alone; Lipid preparations of ampho at 4-6 mg/kg may be adequate
  - Alternatives: fluconazole 400-800 mg/d + 5 FC for 6-10 weeks then maintenance

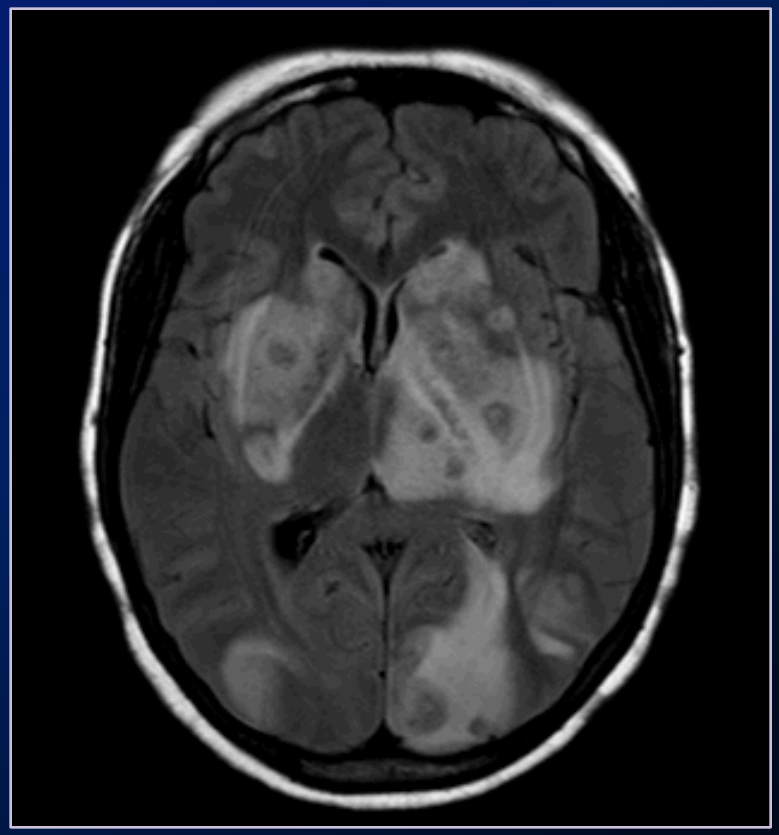
  Maintenance:
  - Fluconazole 200 mg/d, itraconazole less effective

Cryptococcal meningitis: management

- Increased ICP is closely linked to mortality
  - Patients with elevated ICP must have serial LPs until pressures are normal
  - Patients who either do not tolerate daily LPs or deteriorate neurologically despite serial LPs should undergo CSF shunting
  - Steroids, mannitol and acetazolamide are not effective in treating increased ICP
- Up to 30% of patients with cryptococcal meningitis have shown signs of IRIS on initiation of cART
- Current guidelines recommend delaying cART for ~5-6 wks
- Discontinue maintenance therapy w hen CD4 >200 for > 6 months
- No environmental recommendations or primary prophylaxis are recommended

Case 4

- 32 year old woman from Ethiopia
- Presents with gradually progressive headache, nausea/vomiting, weakness (global)
- Newly diagnosed with HIV, CD4 = 6, VL 110,000



Space occupying CNS lesions in AIDS: broad differential

- Toxoplasmosis
- Primary CNS lymphoma
- Brain abscess
- Septic emboli
- Tuberculoma
- Cryptococcoma
- Nocardia
- Rhodococcus
- Syphilitic gumma
- Neurocystercercosis
- Metastatic or primary brain neoplasm

Toxoplasmosis

- *T. gondii* is a ubiquitous intracelluar protozoan, definitive host is the cat
- Humans may become infested either through direct contact with cat feces or ingesting cysts in undercooked meat
- Seroprevalence varies greatly (10-40% US, >70% France and developing countries)

Cat courtesy of Steve Raffanti, MD

Toxoplasmic encephalitis (TE)

- Reactivation disease
- 30% of AIDS patients with positive baseline serology will develop TE if not given prophylaxis
- Most clinical disease occurs at CD4 <100, though may occur at higher CD4
- Pathology ranges from localized granulomatous process to diffuse necrotizing encephalitis

Toxoplasmic encephalitis (TE)

- Clinical presentation includes focal neurologic deficit (50-89%), seizures (15-20%), fever (56%), neuropsychiatric abnormalities
- Diagnosis presumptive based on characteristic lesions (multiple, enhancing, edema), clinical course, risk strata and positive serology
- Patients should show some clinical response by 14 days

Brain Biopsy

- Given broad differential, brain biopsy should be considered
  - In presumptive TE when empiric therapy fails
  - In rapidly progressing single lesion disease
  - In patients with a clinical picture of TE but a reliable history of sulfa-based PCP prophylaxis
  - In patients receiving corticosteroid therapy

Treatment of toxoplasmic encephalitis

- **Acute:** Sulfadiazine (4-8 gm/d) **or** Clindamycin (600 mg q6h)

  Plus

  - Pyrimethamine (200 mg load then 50-75mg/d) with folinic acid (10-20 mg/d) for at least 6 weeks

  - Less proven regimens: macrolides (azithromycin, clarithromycin) or atovaquone (750 mg QID) **plus** pyrimethamine and folinic acid

- **Maintenance:** dose is lower for sulfadiazine therapy (50%), same dose for clindamycin, pyrimethamine 25-50mg/d

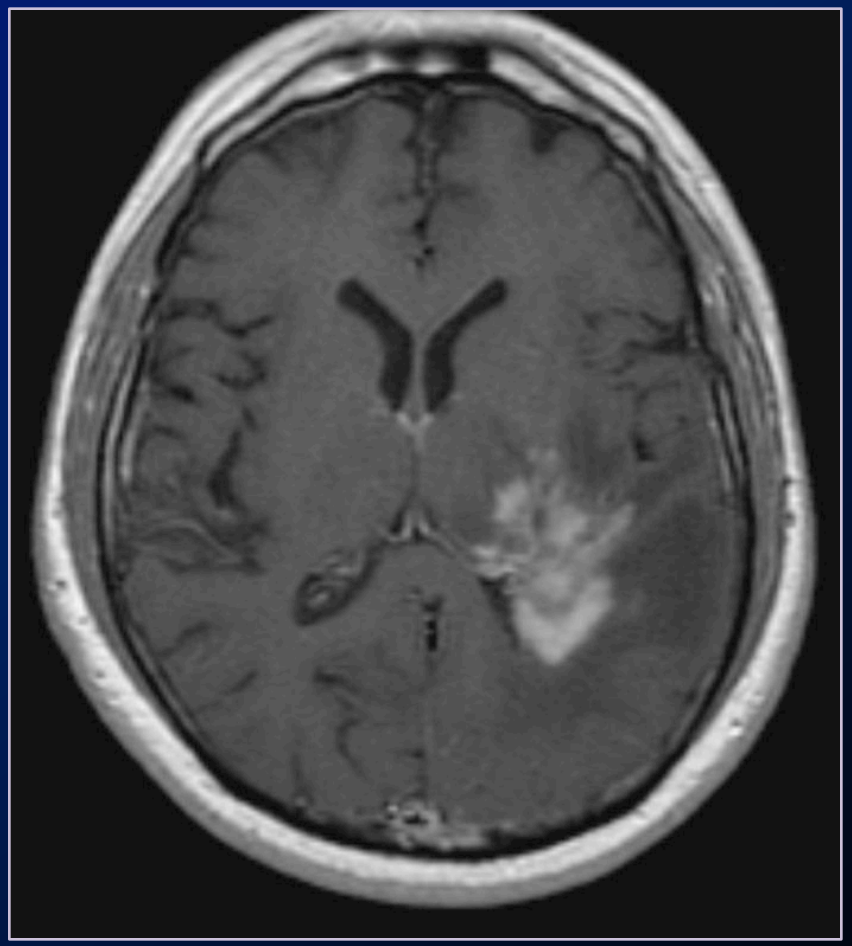
- Maintenance therapy may be discontinued if CD4>200 x 3 mos and patient is stable.

Prevention of toxoplasmic encephalitis

- Patients should be advised to avoid high-exposure situations: avoid eating or handling uncooked or raw meat; avoid changing cat litter or wash hands after changing
- Primary prophylaxis:
  - Baseline IgG serology and f/u when CD4 below 200 cells/mm^3
  - Sulfa-based PCP prophylaxis regimens effective
  - In sulfa-intolerant patients, dapsone + pyrimethamine/folinic acid or atovaquone + dapsone/folinic acie

Primary CNS Lymphoma

- B-cell origin, high-grade
- Reactivation of EBV
- Common signs include focal neuro deficits (38-78%), altered sensorium (57%), seizures (21%), cranial nerve defects (13%)



Primary CNS Lymphoma

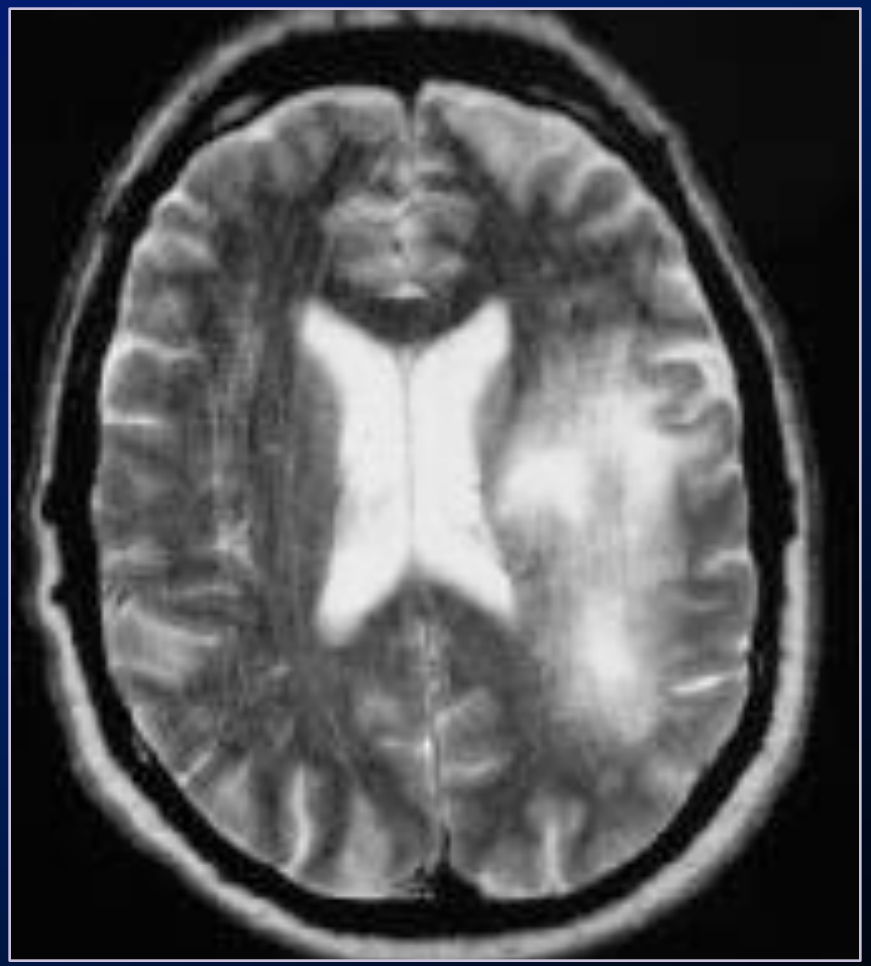
- 50% of patients will have single lesions, usually in the gray matter
- Toxoplasma lesions are usually multiple, smaller and associated with basal ganglia but the two entities cannot be distinguished by imaging alone
- Diagnosis is based on clinical presentation, neuroimaging, CSF studies and brain biopsy
- CSF PCR for EBV is sensitive (66-99%) and specific (60-99%) but not diagnostic
- Treatment is ART +/- chemoradiation

Progressive Multifocal Leukoencephalopathy (PML)

- Demyelinating disease of CNS caused by JC virus infection
- By childhood 40-60% of the population has antibodies to JCV
- Disease only in the severely immunocompromised
- Pathology shows multifocal demyelination with hyperchromatic enlarged oligo-dendroglial nuclei and enlarged bizarre astrocytes.

PML

- Lesions can occur anywhere but are typically found in the white matter, most often in the parietal-occipital regions
- Clinical presentation includes cognitive changes, focal neurologic findings, seizures, altered mental status, coma
- No specific treatment



Herpesvirus Infections

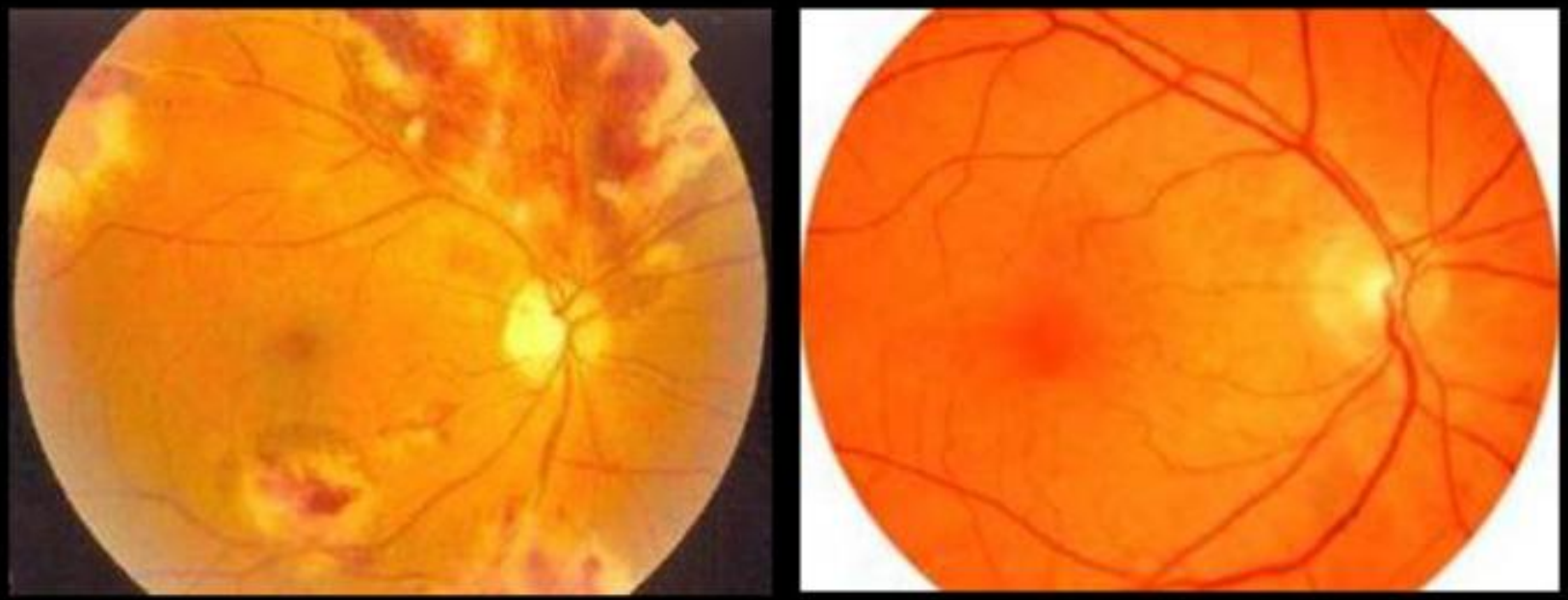
- Herpes Simplex
- Herpes Zoster
- CMV (cytomegalovirus)
- HHV-8
  - Kaposi sarcoma
  - Primary effusion lymphoma
  - Castleman's disease

CMV Disease

- Disseminated viral infection which causes disease in advanced (CD4 <50 cells/mm^3) AIDS
- Usually reactivation disease
- Several reports of IRIS-related disease
- Clinical manifestations are related to end-organ damage:
  - Retinitis (30% of AIDS patients)
  - Colitis (5-10% of AIDS patients)
  - Esophagitis (<10% of AIDS patients)
  - Neurologic disease (<5% of AIDS patients)

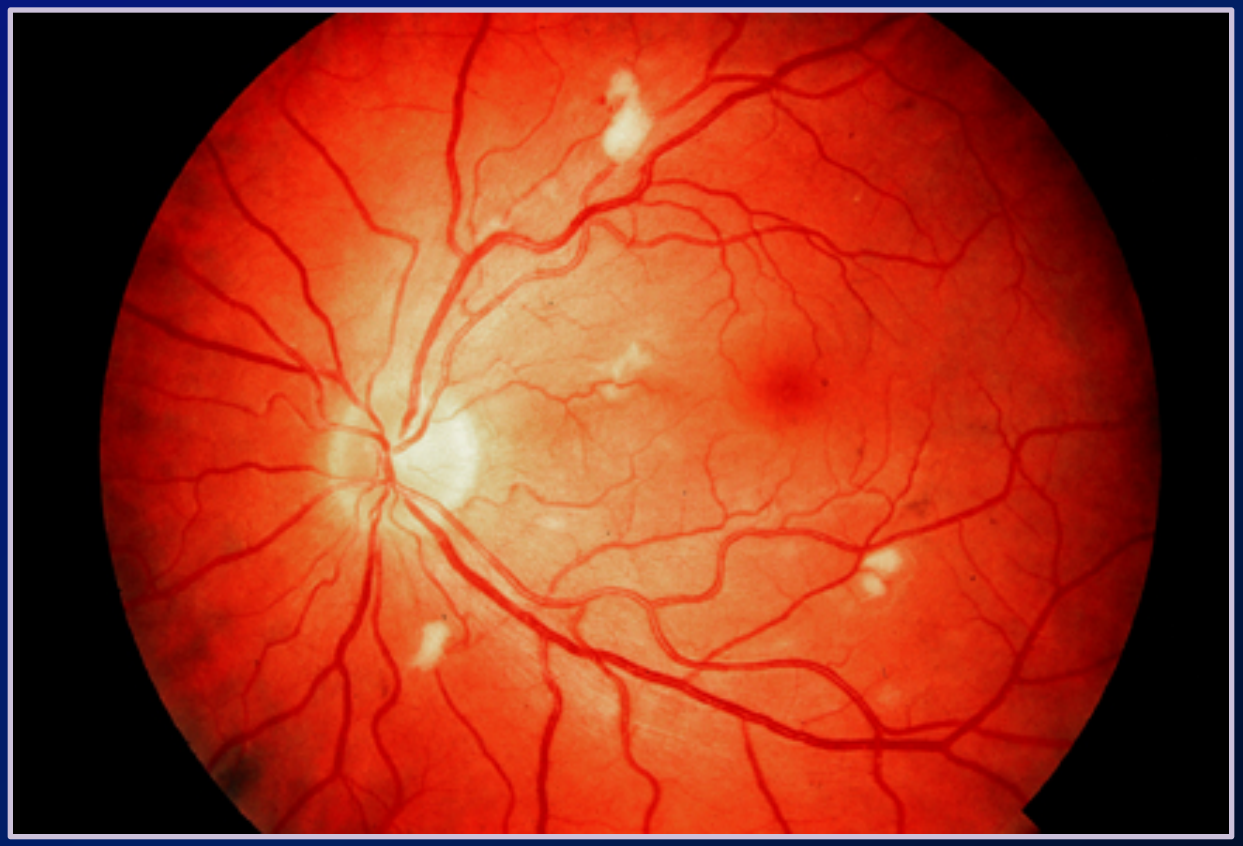
CMV Retinitis

- Most common presentation of CMV infection
- >60% with unilateral disease; will progress to second eye if untreated
- Symptoms include floaters, scotomata, field cuts, decreased acuity
- Progresses rapidly, can be sight threatening in 24 hours
- Painless, rarely associated with new systemic symptom



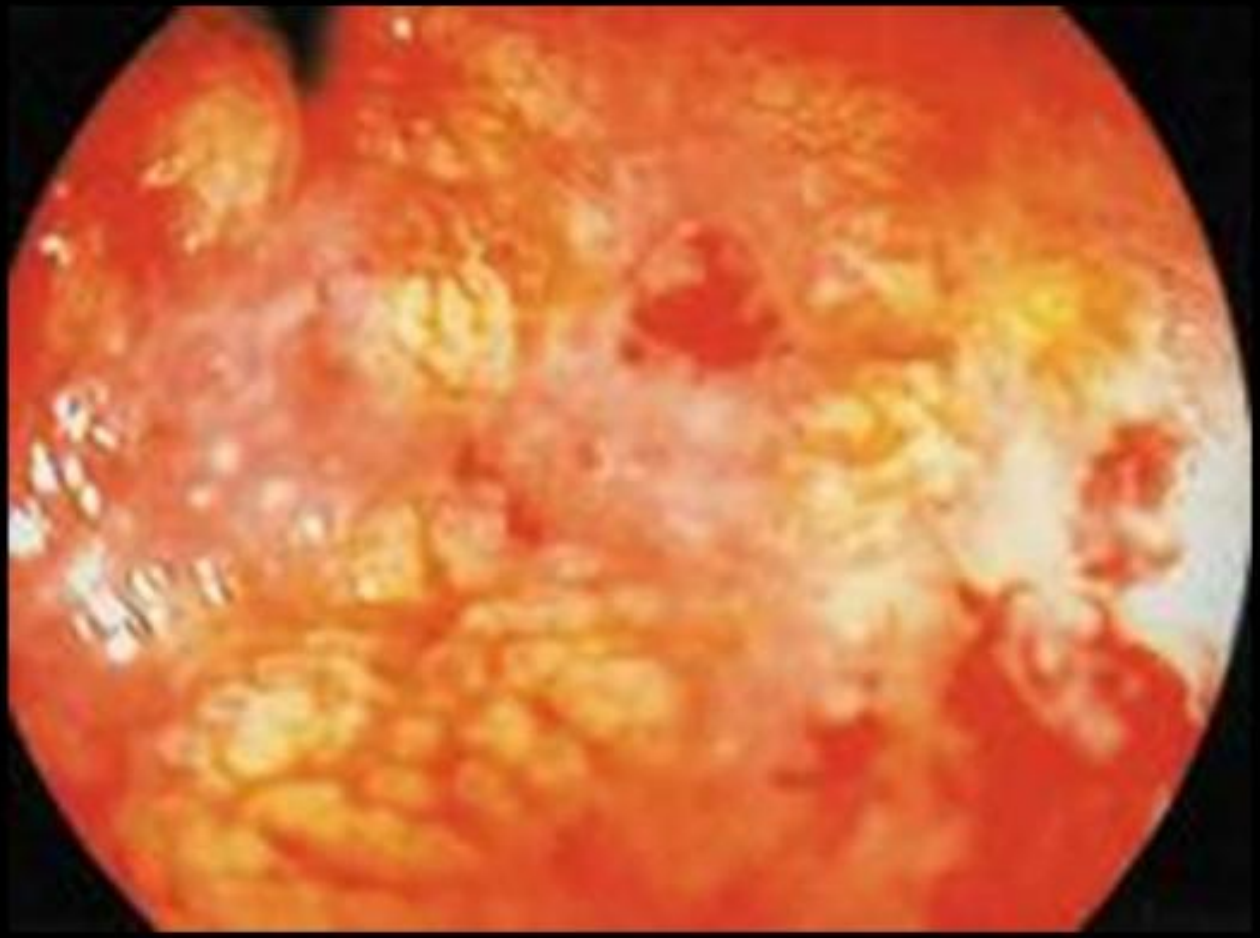
CMV retinitis (left), compared to a normal retina (right)

Benign cotton wool spots



CMV Colitis

- Symptoms may mimic advanced AIDS
  - Fever, anorexia, **abdominal pain**, diarrhea (bloody), weight loss, malaise
- Complications can include perforation
- Pathology shows extensive hemorrhagic inflammation

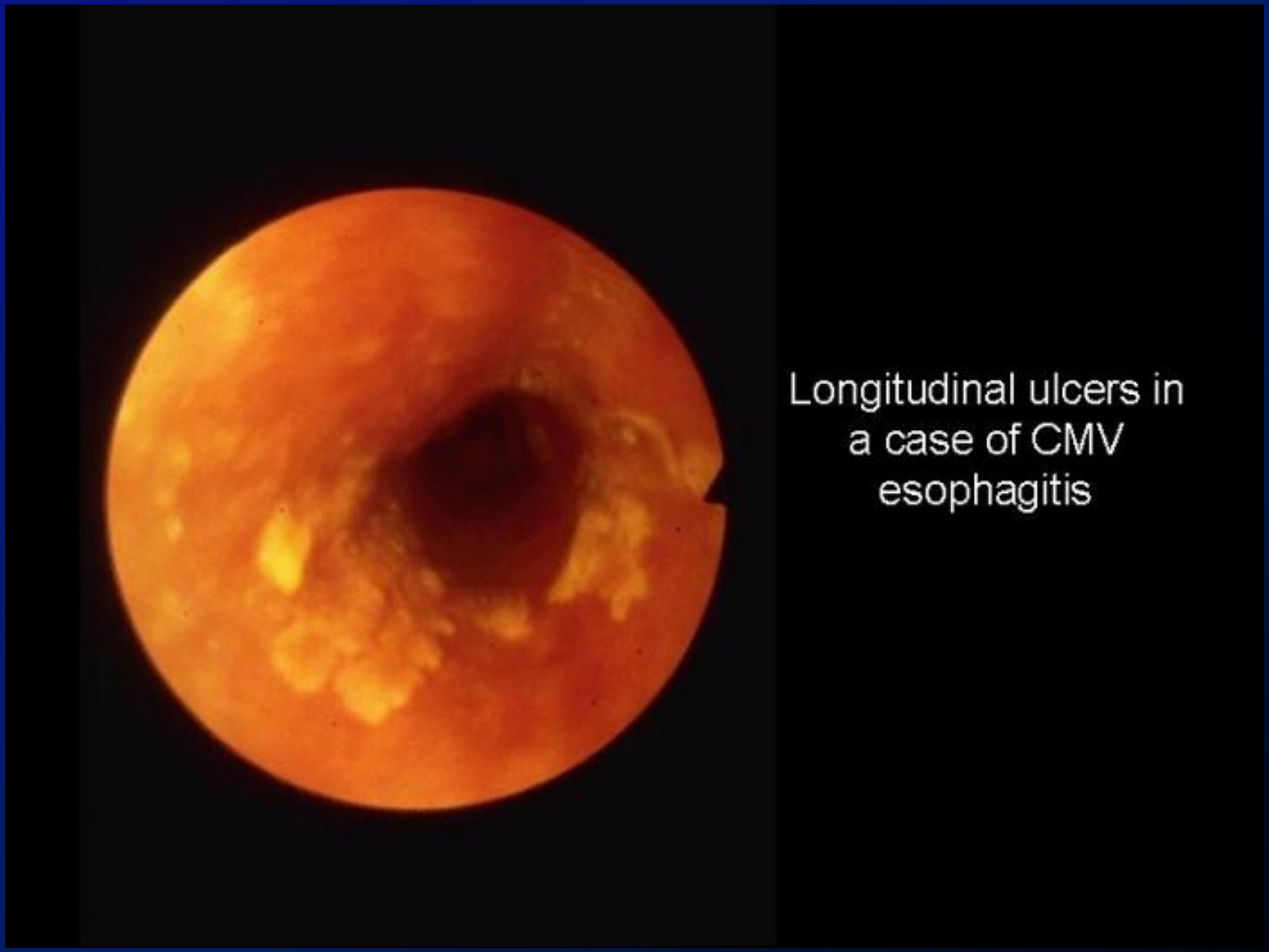


CMV colitis; colonoscopy showing ulcers, bleeding, and pus.

www.aids-images.ch

CMV Esophagitis

- Symptoms:
  - Fever, odynophagia, retrosternal pain, weight loss, nausea
- Included in differential for dysphagia/odynophagia:
  - Candidal disease
  - HSV esophagitis
  - Idiopathic ulcerative disease (aphthous)
  - Other (histoplasmosis, lymphoma, KS)
- Perforation and mediastinitis has been reported



Longitudinal ulcers in a case of CMV esophagitis

CMV Neurologic Disease

- Dementia, ventriculoencephalitis, ascending polyradiculopathy
- Incidence of all these presentations have decreased significantly since advent of cART
- Usually devastating complication of very advanced HIV disease

CMV Ventriculoencephalitis

- Differs from AIDS-associated dementia by steep slope of neurologic decline
- May include fever, delirium, somnolence and cranial nerve involvement
- Imaging may reveal meningeal and periventricular enhancement
- Concurrent evidence of CMV disease may be helpful in making diagnosis
- Course is rapidly fatal if not treated

CMV Ascending Polyradiculopathy

- CMV polyradiculopathy is a rare (<2%) disease presenting in patients with advanced AIDS as rapidly progressive flaccid paralysis of lower extremities which includes back pain, urinary/fecal retention, sensory abnormalities
- Diagnosis is based on clinical features, characteristic CSF and MRI findings and evidence of CMV disease (retinal, PCR in blood or CSF)
- Most patients were described in the pre-cART era and survival was poor with variable response to therapy

CMV Disease: diagnosis

- Retinal disease: recognition of classic findings in at-risk patient
- GI disease: biopsy with histology demonstrating intranuclear inclusion bodies with inflammatory reaction at edge of ulcer
- Culture results are not adequate to demonstrate active disease
- Neurologic disease may depend on CSF findings or brain biopsy

CMV retinitis: treatment

- Various treatment options are available including IV ganciclovir, oral valganciclovir, IV foscarnet, intravitreal ganciclovir implants and injections, IV cidofovir
- Choice of treatment is based on location and severity of disease, point in HIV treatment, predicted adherence of patient, available resources, and concurrent diagnoses
- Critical elements are IV induction phase 14-21 days with close ophthalmologic follow up
- Secondary prophylaxis regimens are equally varied

CMV Disease: treatment

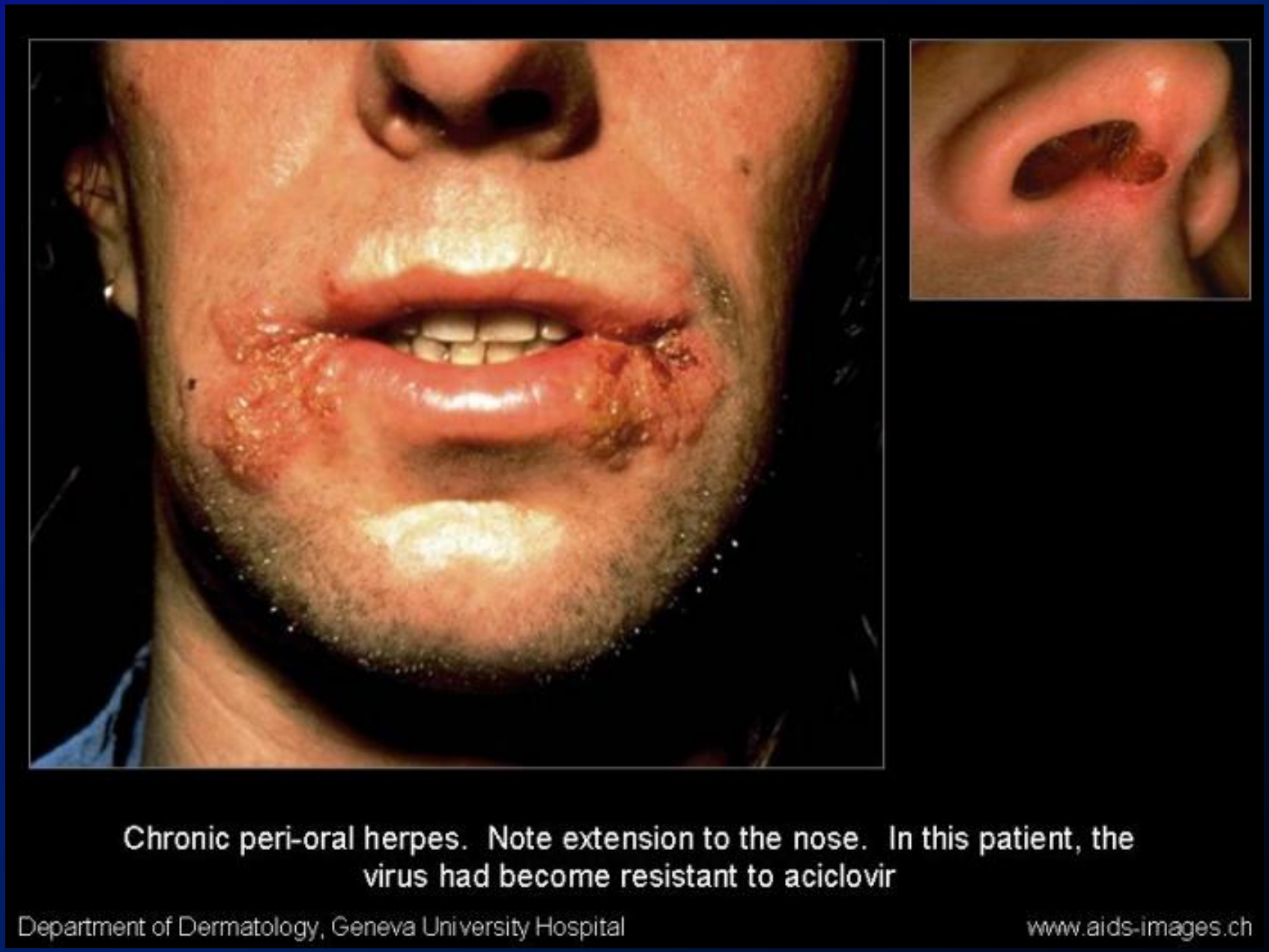
- Colitis or esophagitis:
  - IV ganciclovir for 21 to 28 days or until symptoms resolve
- Neurologic disease:
  - Prompt initiation of IV ganciclovir/foscarnet regimen may be most effective option, AE's are significant
- CMV viremia without evidence of end organ disease:
  - Treatment not recommended
- Although IRIS is an issue in CMV disease, prompt initiation of HAART in patients with active CMV disease is still recommended; CMV neurologic disease may be a situation when cART could be delayed

CMV Disease: prevention

- Best prevention is maintaining CD4 count >50 cells by effective use of cART
- Although oral valgancyclovir has been shown to decrease occurrence of retinal disease, it is not recommended due to expense, potential for resistance and lack of survival benefit
- Discontinuing secondary prophylaxis for retinitis can be considered after CD4 >100 cells for 3-6 months, close collaboration with ophthalmologist

Herpes Simplex

- Clinical Presentations
  - Oral-labial disease
  - Genital and peri-rectal disease
  - Esophagitis
- HSV keratitis, encephalitis, hepatitis present similarly to presentations in HIV-negative persons



Chronic peri-oral herpes. Note extension to the nose. In this patient, the virus had become resistant to aciclovir

Department of Dermatology, Geneva University Hospital

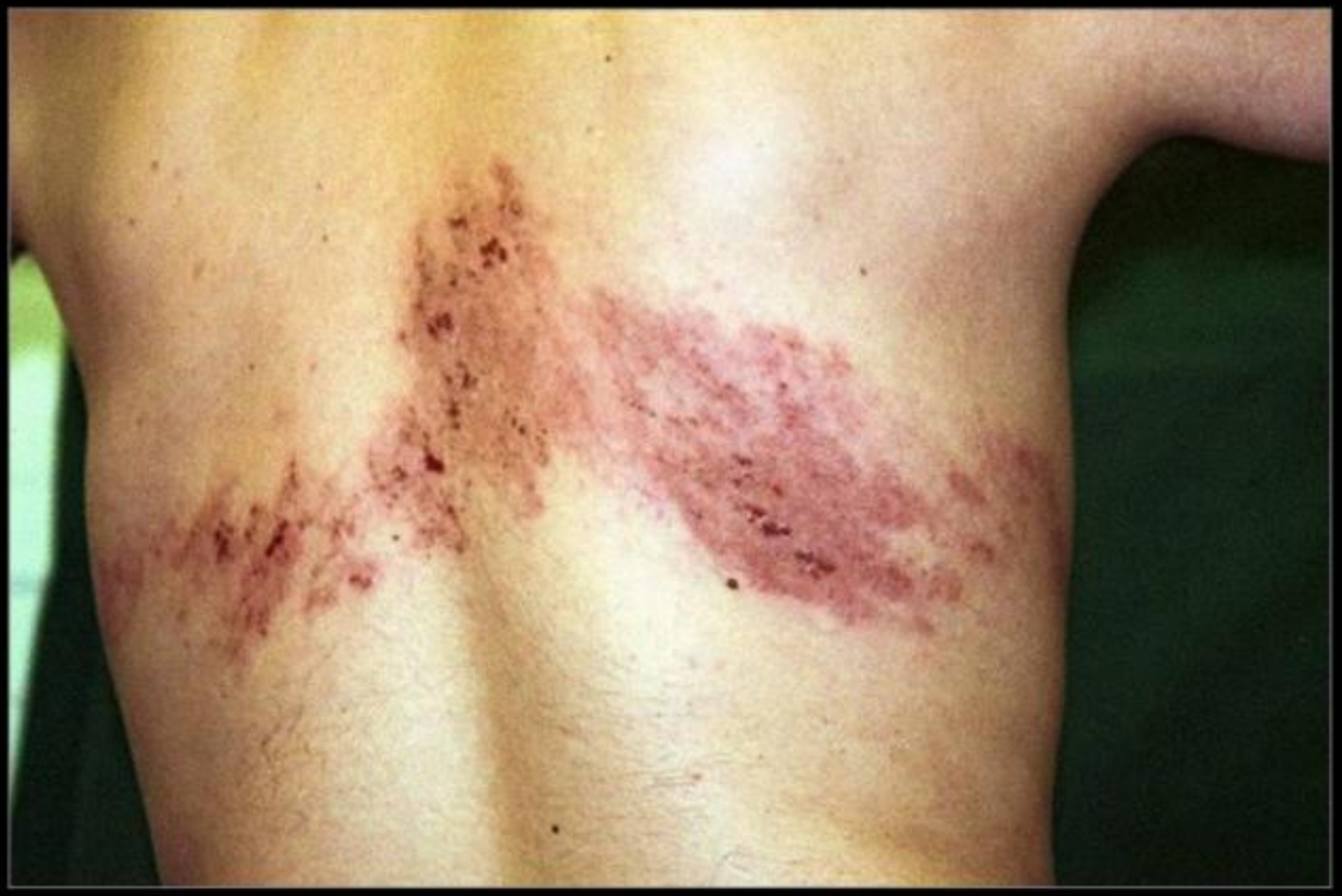
www.aids-images.ch

Varicella-Zoster Virus

- Over 95% of adults have had primary VZV infection
- >15-fold increased incidence in matched HIV-uninfected controls
- VZV can occur at all stages of HIV disease, higher incidence with CD4<200 cells/mm^3
- Use of HAART has not greatly reduced incidence

Varicella-Zoster Virus

- Clinical Presentation:
  - Painful cutaneous eruption in dermatomal distribution:
    - Thoracic (40-5%)
    - Cranial nerves (20-25%)
    - Cervical (15-20%)
    - Lumbar (15%)
    - Sacral (5%)
  - Prodromal hyperesthesia followed by maculopapular to vesicular lesions
  - New lesions develop over 3-5 days, 30-50% cutaneous dissemination, pustules, scabbing and crusting last several weeks



Paricularly in HIV-infected patients, more than one dermatome may be involved

Picture credit: Barts Hospital, London

www.aids-images.ch

Varicella-Zoster Virus

- Sequelae
  - 10-15% of patients will report post herpetic neuralgia
  - Rare cases of encephalitis, meningitis, ventriculitis, and myelitis in advanced HIV disease
- Retinal disease
  - Acute retinal necrosis (ARN), rare complication of VZV infection
  - Progressive outer retinal necrosis (PORN) seen in AIDS patients only

Esophageal candidiasis

- Usually presents with dysphagia (“food sticking”), less frequently odynophagia (retrosternal burning)
- Diagnosis is made either by response to empiric therapy or by endoscopic evaluation
- Common reason for presenting to the ED
- Often co-exists with multiple OIs in advanced patients
- Treatment choice may be based on multiple factors: history of recurrence, history of clinical or microbiological resistance (c. glabrata or kruzeii), prior toxicities and insurance/availability status

Odynophagia/Dysphagia Protocol

- IF patient is not acutely sick and is at risk for OIs:
  - Check for any non-oral HSV lesions
  - Check fundi if appropriate
  - Start oral fluconazole 200- 400 mg daily
  - If no improvement in 24 hours, start HSV treatment
  - If no improvement in 24 hours arrange EGD

Case 5

- 46 yo with poor adherence to ART and prophylaxis
- CD4 = 23 cells/mm^3 3 months ago
- Notes intermittent fevers to 101°, night sweats, 15# weight loss, abdominal discomfort, frequent loose stool, malaise and fatigue
- Initial labs in clinic demonstrate
  - WBC 2.8, hemoglobin 6, platelets 132
  - Alkaline phosphatase 483, total bilirubin 1.8, ALT 90

Fever: other considerations

- Disseminated MAI
- Histoplasmosis
- Other endemic fungi
  - Blastomycosis
  - Coccidiodomycosis

Mycobacterium avium

- Environmental organism found in soil and water
- Disseminated infection common when CD4 <50 cells/mm^3 and in persons colonized
- Spectrum of illness: fever, night sweats, wasting, diarrhea, abdominal pain, intra-abdominal adenopathy, hepatosplenomegaly, skin lesions
- May cause pancytopenia and liver function test elevation
- Diagnosis rests on isolation from sterile site (blood, lymph node, bone marrow)

Mycobacterium avium

- Treatment
  - Two or three drug regimen is recommended: clarithromycin (azithromycin) and ethambutol are first line medications
  - Rifabutin may be added as a third drug (shown to improve survival in one study, decrease emergence of resistance in two studies)
  - Fourth drug (amikacin or streptomycin) may be considered in severe disease
- Prevention (with CD4 < 50 cells/mm^3)
  - Clarithromycin or azithromycin are effective in preventing active disease
  - Rifabutin can be used in patients who do not tolerate clarithromycin or zithromycin
  - Screening for active disease (including blood culture) should be done before starting prophylaxis.

Histoplasmosis

- Caused by *Histoplasma capsulatum,* soil mold associated with bird droppings
- Symptoms include fever, adenopathy, couth, shortness of breath, pancytopenia, hepatosplenomegaly
- Most always disseminated
- May have CNS, gastrointestinal, mucosal or cutaneous involvement
- May present with sepsis syndrome with multi-organ failure

Histoplasmosis: diagnosis

- Urine Ag 95%, serum Ag 80%, BAL Ag 70%, CSF Ag 50%
- Blood and bone marrow cultures 85%
- Organisms have been seen in the peripheral blood smear, skin biopsies, esophageal biopsies
- Serologic tests are positive in the majority of patients with disseminated disease but may not reflect current clinical disease
- Histoplasmin skin tests are not useful and should not be performed

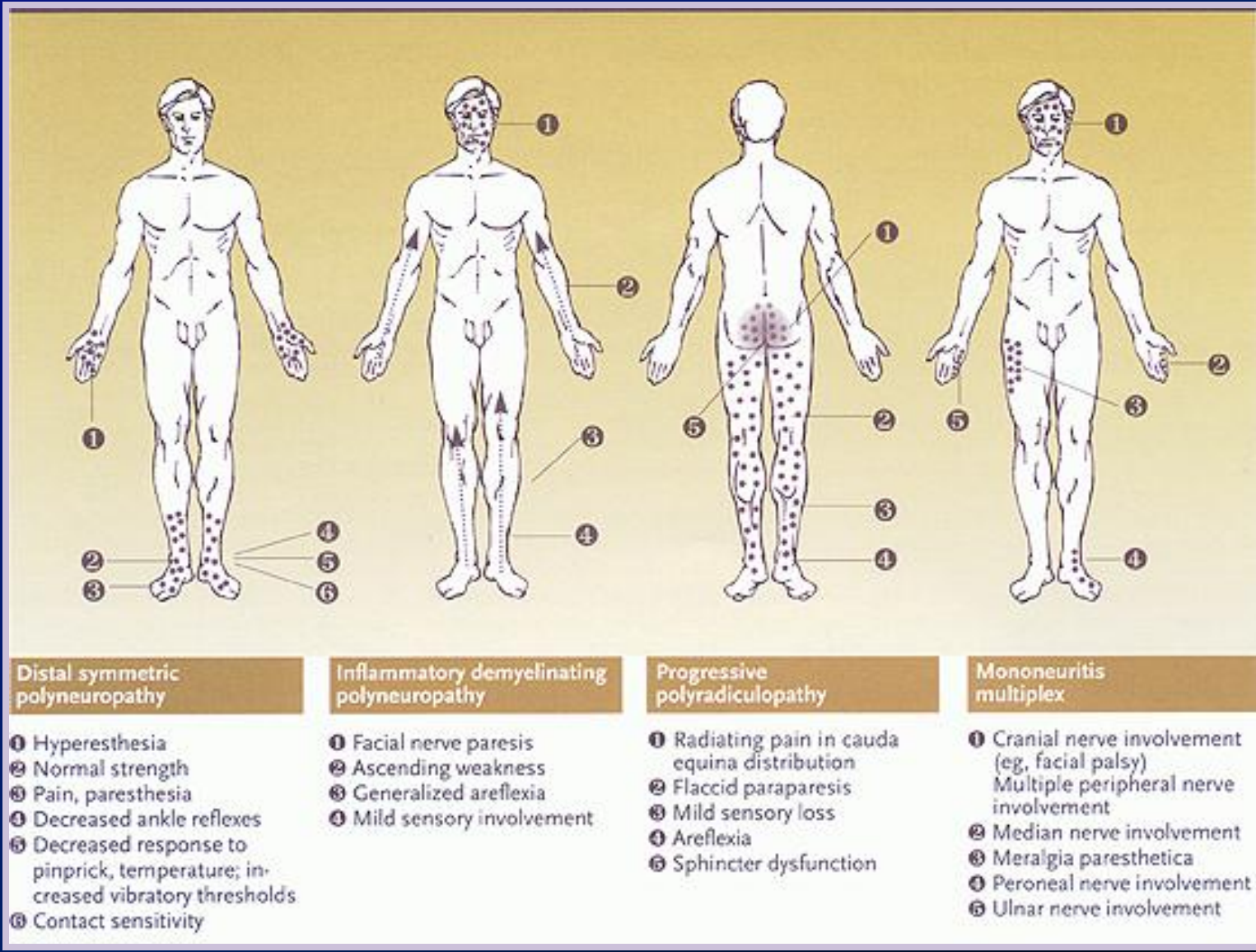
Histoplasmosis: treatment

- Acute management: lipid prep of ampho (3-5 mg/kg) daily for at least 2 weeks followed by itraconazole 200 mg TID for 3 days then 200 mg BID for at least a year
- Treatment of CNS histoplasmosis requires longer ampho induction and possibly higher maintenance dosing of itraconazole
- Less severe disseminated disease can be treated with itraconazole alone
- Drug interactions between itraconazole and ritonavir-boosted PIs, PPIs and other acid blockers
- Secondary prophylaxis can be discontinued in patients with > 1 year of itraconazole therapy, low antigen, CD4> 150 cells/mm^3 and on effective HAART for at least 6 months

Diarrhea in HIV-infection

- Evaluation for acute diarrhea similar to that for non-immunocompromised (stool culture, *C. difficile* toxins, ova/parasite)
- CMV PCR
- For chronic diarrhea, also send *Cryptosporidium* and *Giardia* antigens, *Microsporidia* stain (modified trichrome); consider medication-induced diarrhea
- May need endoscopy if diagnosis unclear

HIV-associated neuropathies



Distal symmetric polyneuropathy

❶ Hyperesthesia
❷ Normal strength
❸ Pain, paresthesia
❹ Decreased ankle reflexes
❺ Decreased response to pinprick, temperature; increased vibratory thresholds
❻ Contact sensitivity

Inflammatory demyelinating polyneuropathy

❶ Facial nerve paresis
❷ Ascending weakness
❸ Generalized areflexia
❹ Mild sensory involvement

Progressive polyradiculopathy

❶ Radiating pain in cauda equina distribution
❷ Flaccid paraparesis
❸ Mild sensory loss
❹ Areflexia
❺ Sphincter dysfunction

Mononeuritis multiplex

❶ Cranial nerve involvement (eg, facial palsy) Multiple peripheral nerve involvement
❷ Median nerve involvement
❸ Meralgia paresthetica
❹ Peroneal nerve involvement
❺ Ulnar nerve involvement

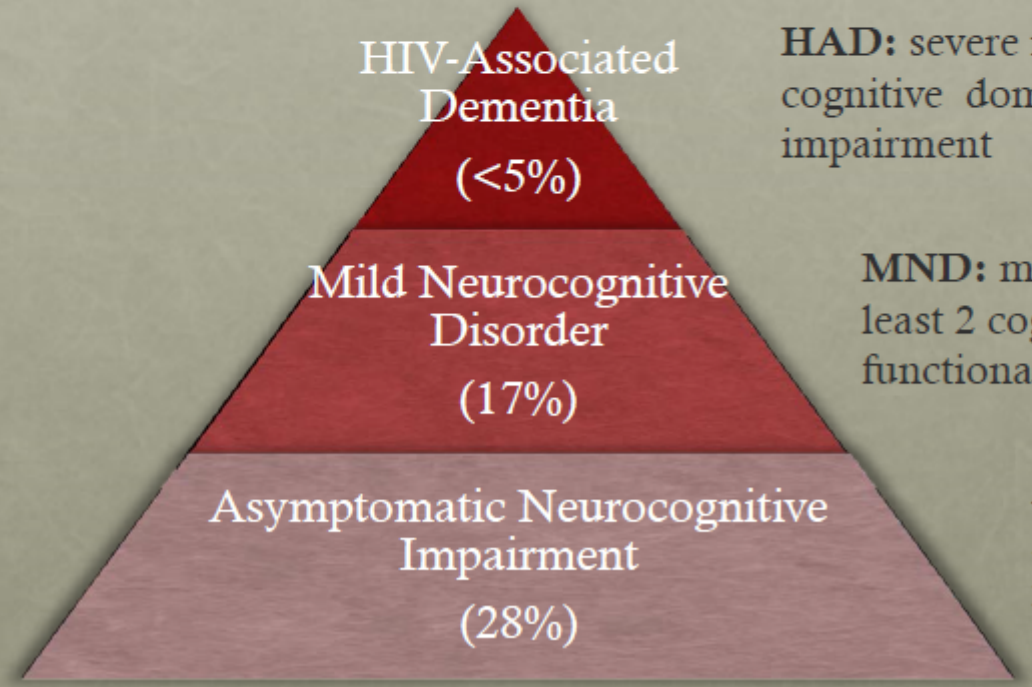
HIV-Associated Neurocognitive Disorder (HAND)

- Spectrum: mild neurocognitive impairment->dementia
- Nadir CD4 count predicts development
- High rates of mild neurocognitive impairment persist at all stages of HIV infection
- Pre-cART had more impairment in motor skills, cognitive speed, and verbal fluency
- cART era involves more memory (learning) and executive function impairment.
- Support for earlier Rx of HIV

Heaton et al. J Neurovirol 2011

HIV-associated neurocognitive disorder (HAND)

- Prevalence of HIV-associated neurocognitive disorder (HAND): 50% of HIV+ adults



HAD: severe impairment in at least 2 cognitive domains + severe functional impairment

MND: mild to mod impairment in at least 2 cognitive domains + mild to mod functional impairment

ANI: any impairment in at least 2 cognitive domains + no functional impairment

Valour VG. *Top Antivir Med.* 2013;21:119-23.

Myelopathy

- HIV associated myelopathy is a rare (<4%) manifestation of advanced disease which presents with leg stiffness, falling, slowness of gait and slowly progresses to bowel/bladder dysfunction, paraplegia
- Hyperreflexia and spasticity are common
- Imaging and CSF are normal except for mildly elevated protein
- Pathology shows vacuolar myelopathy with little inflammation
- Treatment is supportive and rehabilitative

AIDS-defining malignancies are related to chronic viral infections and immunodeficiency

- Include:
  - Kaposi sarcoma (HHV-8)
  - Non-Hodgkin's lymphoma (EBV, HHV-8)
  - Cervical cancer (HPV)
- Decreasing incidence over time in cART era
- Remain the most common malignancies

Non-AIDS-defining malignancies

- Incidence has increased slightly in cART era
- Several malignancies occur more commonly in HIV-infected patients in several studies:
  - Anal
  - Lung
  - Hodgkin disease
  - Liver
  - Oropharyngeal
- Will continue to increase as HIV population ages
- Screening is essential for early diagnosis

Lung cancer in persons with HIV infection

- Increased incidence of lung cancer in persons with HIV (2- to 10-fold)
- Majority have smoking as risk factor
- Disease occurs at younger age
- More aggressive locally and metastatic disease
- Poor response to therapy

Cardiovascular disease (CVD) and HIV

- Rates of CVD higher in HIV-infected persons vs. general population
- HIV associated with a 50% increased acute MI risk
  - after adjustment for traditional risk factors
  - remained among those with well-treated HIV
  - impact of HIV on risk comparable to traditional risk factors
- Greater than 4-fold increased risk of sudden cardiac death

Freiberg MS, et al. JAMA Int Med 2013;173:614-622
Tseng ZH, et al. J Am Coll Cardiol. 2012;59:1891-1896

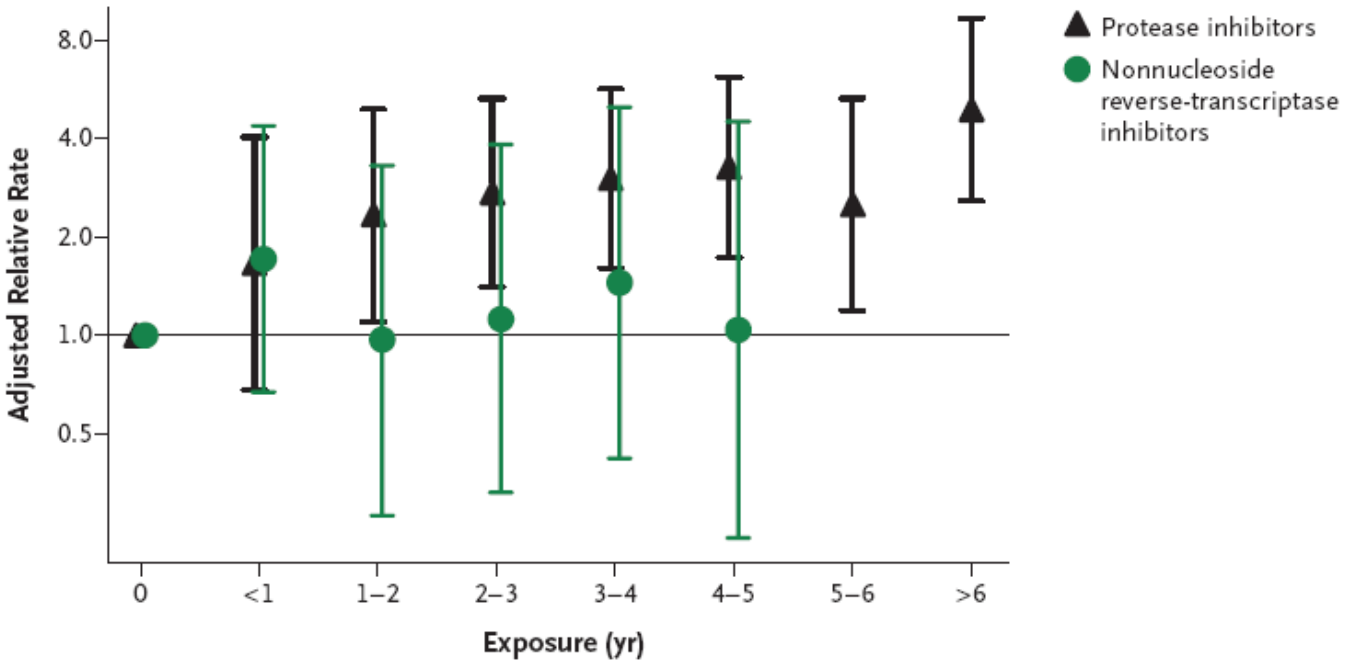
Cardiovascular disease (CVD) and HIV

- Many classic risk factors exist in HIV-positive patients
  - Smoking
  - Diabetes , insulin resistance
  - Hyperlipidemia
  - Hypertension
  - Central obesity
- Chronic inflammation due to HIV infection likely a factor and does not always correlate with viral load
- ART may contribute
- Frequency will increase as HIV population ages

The NEW ENGLAND JOURNAL of MEDICINE

Class of Antiretroviral Drugs and the Risk of Myocardial Infarction

The DAD Study Group*



- Overall adjusted MI risk increased 16% per year ART exposure
- Increase in PI-exposed, not in NNRTI-exposed
- Risk with PIs increased ~10% per year after adjusting for lipids

N Engl J Med 2007;356:1723-35

Antiretrovirals and Effects on Lipids

TDF

RAL
DTG

RPV
ETV

ABC

EFV

ATV/RTV or ATV/COBI
DRV/RTV or DRV/COBI
EVG/COBI

Clinical Care Options

Managing CVD Risk in HIV infection

- CVD risk can be assessed by considering
  - Traditional risk factors
  - HIV-related factors
- Risk calculators underestimate events
  - Framingham, DAD, ACC/AHA
- Higher levels of inflammatory biomarkers (IL-6, hsCRP, D-dimer) are associated with risk of CVD and remain elevated in ART-treated HIV-infected patients; no guidelines for use in routine clinical care

Managing CVD Risk in HIV infection

- Starting ART early can mitigate CV risk even though certain ART drugs may increase lipids
- DHHS guidelines caution re: abacavir and LPVr use in patients with CVD
- Statins have been shown to be effective in reducing CV risk in general population and should be used as indicated in HIV-infected persons
- Ongoing REPRIEVE study

Drug–drug interactions with first-line ART and lipid-lowering therapy

Antiretroviral	Contraindicated	Titrate Dose	No Dose Adjustment
EFV		Atorvastatin Simvastatin Pravastatin Rosuvastatin	Pitavastatin
RPV			Atorvastatin Pitavastatin
ATV/RTV ATV/COBI	Lovastatin Simvastatin	Atorvastatin Rosuvastatin	Pitavastatin
DRV/RTV DRV/COBI	Lovastatin Simvastatin	Atorvastatin Pravastatin Rosuvastatin	Pitavastatin
EVG/COBI/TDF/ FTC	Lovastatin Simvastatin	Atorvastatin Rosuvastatin	
DTG			
RAL			

DHHS Adult Guidelines. April 2015

Bone complications

- 67% of HIV-infected individuals had reduced BMD and 15% had osteoporosis in a meta-analysis
- ART associated with 2-6% decrease in BMD over first 2 years
- HOPS study of nearly 6,000 patients found that 233 had incident fractures with following risk factors:
  - Old age
  - Substance abuse
  - CD4+ nadir < 200
  - HCV infection
  - DM
  - Neuropathy

Young et al. CID 2011
McComsey et al., CID 2010

Kidney disease

- Occurs commonly in HIV infection, due to
  - Other co-morbidities- diabetes, HTN, HCV infection
  - HIV itself or immune activation (HIVAN)
  - Medication-related (tenofovir, sulfa, ampho, etc)
  - Genetic (AA race, family history kidney disease)
- Viral suppression may slow progression
- ACE inhibitors useful for proteinuria

Liver disease

- Most frequently due to chronic hepatitis B or C infection, though hepatic steatosis increasingly common
- Patients with elevated AST on stable ART found to have significant rates of NASH and bridging fibrosis
- Insulin resistance, obesity and presence of two SNPS in the PNPLA3 gene were associated with

Morse et al. CID 2015

Resources

http://www.seaetc.com
www.vanderbilthealth.com/vccc
www.aidsinfonet.org
www.aidsetc.org
https://aidsinfo.nih.gov/guidelines (DHHS guidelines)
http://hab.hrsa.gov/deliverhivaidscare (HRSA Guide for HIV/AIDS care)
http://www.idsociety.org/Organism/#HIV/AIDS
www.niaid.nih.gov
www.AIDS.medscape.com
www.hopkins-aids.edu
www.iapac.org
www.ucsf.edu/medical

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